REDACTED PUBLIC VERSION

PATENTED MEDICINE PRICES REVIEW BOARD

IN THE MATTER OF the *Patent Act*,
R.S.C., 1985, c. P-4, as amended

AND IN THE MATTER OF
Horizon Pharma (the "Respondent")
and the medicine Cysteamine Bitartrate sold by the Respondent under the trade name Procysbi

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MOTION RECORD OF BOARD STAFF

(Motion to Bifurcate, Strike Evidence, and for the Inspection and Production of Documents)

DATED November 28th, 2019

PERLEY-ROBERTSON, HILL & MCDOUGALL LLP
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Lawyers for Board Staff

INDEX

INDEX

TAB1

PATENTED MEDICINE PRICES REVIEW BOARD

IN THE MATTER OF the *Patent Act*,
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NOTICE OF MOTION

Board Staff will present a motion before the Panel on a date to be scheduled at the Board's offices in Ottawa.

THE MOTION IS FOR:

1. An order bifurcating the hearing in this matter.

2. An order striking portions of the Expert Report of Professor Joel Hay.

3. In the alternative, an order directing Horizon Pharma (the Respondent) to produce various documents and to allow Secretariat to conduct an on-site inspection.

4. Such further and other relief as Board Staff may request and the Panel deem appropriate.

THE GROUNDS FOR THE MOTION ARE:

5. Board Staff alleges that the Respondent is selling the medicine Cysteamine Bitartrate under the trade name "Procysbi" ("Procysbi") at a price that is excessive. Board Staff seeks an Order from the Panel under s. 83 of the *Patent Act*, RSC 1985, c.P-4 ("the Act").

6. Section 85(1) of the Act sets out the factors to be considered by the Panel in determining whether a medicine is being sold at an excessive price.

7. Section 85(2) of the Act sets out additional factors that the Panel may take into consideration in determining whether a medicine is being sold at an excessive price. However, such additional factors may only be taken into consideration if the Panel is unable to determine whether the medicine is being sold at an excessive price pursuant to the factors set out in s. 85(1) of the Act.

8. Board Staff submits that the Panel will be able to determine whether or not the price of Procysbi is excessive having regard to the factors set out in s. 85(1) of the Act.

9. The Respondent has served Board Staff with two expert reports. The expert report of Dr. Craig Langman, a pediatric nephrologist, sets out his evidence and opinions regarding the factors set out in s. 85(1) of the Act. (It is not in issue for the purposes of this motion.) The expert report of Professor Joel Hay, a pharmaceutical economist, sets out evidence and opinions regarding the factors set out in both s. 85(1) and s. 85(2) of the Act.

10. The evidence of Professor Hay under s. 85(2) relates to the cost of making and marketing Procysbi.

11. The evidence and opinions of Dr. Hay regarding the cost of making and marketing Procysbi is complex and is not intertwined with his evidence and opinions regarding the factors in s. 85(1). It will lead to a significantly lengthier hearing.

12. Bifurcation of the hearing will lead to a more just and expeditious determination of the matter.

13. In the event that the hearing is not bifurcated, Board Staff seeks the production and inspection of various records from the Respondent in order to respond to the evidence and opinions of Professor Hay in regard to the s. 85(2) factors. Board Staff also seeks an order allowing Secretariat to conduct an on-site inspection at Horizon's offices and to have access and to make copies of all books, records, documents, accounts, and other forms of records necessary to verify the cost of making and marketing Procysbi, including the research costs and total world sales.

14. S. 85, 96, and 97of the Act.

15. Rules 5, 25, 6, and 24 of the *Patented Medicine Prices Review Board Rules of Practice and Procedure*, SOR/2012-247 ("the Rules").

THE FOLLOWING DOCUMENTARY EVIDENCE is being relied upon:

a) The pleadings herein;

b) The expert reports filed by Board Staff and the Respondent; and

c) The Affidavit of Howard Rosen, sworn November 28, 2019.

DATED November 28, 2019

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Lawyer for Her Majesty the Queen in Right of the Province of British Columbia, as represented by the Minister of Health Representative for the Intervenors, the Provinces of Manitoba, Ontario, and Newfoundland and Labrador

TAB2

PATENTED MEDICINE PRICES REVIEW BOARD

**IN THE MATTER OF the *Patent Act*,
R.S.C., 1985, c. P-4, as amended**

**AND IN THE MATTER OF Horizon Pharma (the "Respondent")
and the medicine Cysteamine Bitartrate sold by the Respondent
under the trade name Procysbi**

AFFIDAVIT OF HOWARD ROSEN

I, Howard Rosen, of the City of Toronto, in the Province of Ontario,

MAKE OATH AND SAY:

1. Secretariat International ("Secretariat") has been asked by Perley-Robertson, Hill & McDougall LLP, on behalf of Board Staff of the Patented Medicine Prices Review Board ("Board Staff"), to review a report prepared by Dr. Joel Hay dated September 9, 2019 ("Hay Report") for the Respondent in connection with the above-noted proceeding.

2. In order to analyze, test, verify and potentially respond to all of the assumptions, calculations and conclusions contained in the Hay Report, Secretariat requires copies of and access to certain documents that will assist Secretariat and Board Staff in their review of (and potential response to) the Hay Report.

3. Attached collectively at Exhibit A to this affidavit are copies of both my curriculum vitae and my colleague Julius Koo's curriculum vitae outlining our qualifications. Attached at Exhibit B to this affidavit is a memorandum outlining Secretariat's request for documents that are necessary for the purposes of Secretariat's review and analysis

of the assumptions, calculations and conclusions contained in the Hay Report ("Request for Documents").

4. In order to effectively analyze and validate the documents which Secretariat anticipates receiving in response to the Request for Documents, Secretariat also requests the ability to conduct an on-site inspection at the Respondent's offices, distribution facilities and/or manufacturing facilities as necessary. For the purposes of performing this inspection, Secretariat would require the following:

- Access to and the right to make copies of books, records, documents, accounts and other forms of records as Secretariat considers appropriate to verify the revenues earned and costs incurred by the Respondent, as well as its forecasted revenues and costs, whether in paper, electronic, or digital form and whether recorded and maintained in a computer or storage facilities in possession of the Respondent; and,
- Access to the Respondent's in-house knowledgeable staff to respond to Secretariat's questions regarding the Respondent's accounting processes and documentation.

5. I make this Affidavit in support of a Motion by Board Staff for the production and inspection of documents and for no other or improper purpose.

SWORN BEFORE ME in the City of Toronto, in the Province of Ontario, on Wednesday, the 28th day of November, 2019.

Howard Rosen

(A Commissioner of Oaths)

STUART CHARLTON

TABA

THIS IS EXHIBIT "A" TO THE AFFIDAVIT OF HOWARD ROSEN SWORN BEFORE ME THIS 28TH DAY OF NOVEMBER, 2019.

A Commissioner, etc.

STUART SLOMER

Secretariat
INTERNATIONAL

Curriculum Vitae

Contact Details
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Professional History
- Secretariat International
- FTI Consulting (2009-2018)
- LECG (2004-2009)
- LRTS (1998-2004)
- Arthur Andersen (1992-1998)
- Berenblut & Rosen (1981-1992)
- Coopers & Lybrand (1979-1981)

Education
- Certified Fraud Examiner, 1992
- Accredited Senior Appraiser, 1988
- Chartered Business Valuator, 1984
- Chartered Accountant, 1981
- Bachelor of Business Administration, 1979

Professional Associations
- Swiss Arbitration Association
- Arbitrators Institute of Canada
- Canadian Institute of Chartered Accountants
- Canadian Institute of Chartered Business Valuators
- Institute of Chartered Accountants of Ontario
- National Association of Certified Fraud Examiners
- London Court of International Arbitration

Certifications
- Chartered Professional Accountant/Chartered Accountant, 1981
- Chartered Business Valuator, 1984

Languages
- English

Howard Rosen

Managing Director

Professional Experience

Howard Rosen has over 38 years' experience of advising on all aspects of business valuations, damages quantification, and corporate finance related matters. He has acted as an advisor to private and public companies, regulatory bodies, and all levels of government on a wide variety of industries. His work experience covers assignments across North and South America, Europe, the Middle East, Africa, and Asia. Howard has testified in damages quantification and valuation matters on over 100 occasions.

Howard has acted as court appointed administrator, monitor and inspector and sat as a member of an Arbitral Tribunal and sole Arbitrator. He is the co-author of two texts, a number of chapters and articles on the quantification of economic damages and has lectured extensively to professional interest groups. Howard has acted as instructor at the NITA and FIAA Expert Witness Trial Practice Programs, the MIDS Program at the University of Geneva, and as an MBA instructor at York University's Schulich School of Business in Toronto. Howard has been listed as one of the leading valuations and damages experts in Canada by Lexpert, and internationally by Who's Who Legal as one of the top experts in international commercial arbitration worldwide, every year since the inception of the list in 2011.

Howard is recognized consistently by Who's Who Legal annually in a number of key listings, most recently including: Thought Leaders – Arbitration 2019, Arbitration Expert Witness 2019, Thought Leaders Global Elite 2019, Consulting Experts – Financial Advisory and Valuation – Quantum of Damages 2019, WWL Canada - Arbitration Expert Witnesses 2018, Thought Leaders – Arbitration 2018, Consulting Experts – Financial Advisory and Valuation – Quantum of Damages 2018, and as an expert in the Mining 2019 Industry listing (inception of this list). In the 2016 Who's Who Legal: Consulting Experts, a one-of-a-kind guide to the leading consulting experts across the globe, Howard was listed as one of the top five experts in North America.

Howard has also acted as advisor on transactions in a wide variety of businesses, for both public and private equity investors, conducting strategic due diligence, valuations and deal structuring for both buyers and sellers. Howard has advised independent committees of boards of directors on non-arm's length transactions and has also acted as the chair of independent committees of boards of directors for non-arm's length transactions.

Howard's corporate finance experience extends to private equity investments, and managing investments through liquidity transactions, including sale to strategic buyers and IPO. Howard currently sits on the advisory committee of an institutional investor. Howard's past board positions have included a global Agriculture trading business (Vice-Chair and Lead Independent Director), a Junior resource company (Gas and Mining), a Medical Software and Devices company where he served as Chair of the Audit Committee, as well as a Specialty Manufacturer.

Howard is also a Qualified Valuator under the Canadian CIMVAL standards.

Pharmaceutical and Intellectual Property Experience

- Recent cases related to the pharmaceutical industry and intellectual property that Howard has worked on as the testifying expert or signatory of a valuation opinion include the following:

- Expert reports in connection with patent infringement cases in Canada – Expert opinion reports providing quantification of damages and/or accounting of profits relating to the alleged patent infringement of certain pharmaceutical drugs.

- Reply reports providing comments on reports prepared by other experts and quantifying the impact of different issues on lost profits calculated by other experts.

- Reports also provided financial analysis on the impact of generic entry into the market; commentary on transfer pricing issues; addressing the appropriateness of expenses and deductions in an accounting of profits; analysis of the costs and profitability of manufacturing an active pharmaceutical ingredient and finished drug product using a non-infringing process; addressing pre-judgment interest and appropriate measures of the return realized on the funds retained from infringing profits.

- Reports have been filed in connection with the following cases in the Federal Court of Canada:
    - AstraZeneca Canada Inc., Aktiebolaget Hässle, and AstraZeneca AB v Apotex Inc. (T-1409-04 and T-1890-11) relating to Omeprazole (Oral expert evidence provided at trial in February 2017)
    - ADIR and Servier Canada Inc. v Apotex Inc. and Apotex Pharmachem Inc. (T-1548-06) relating to Perindopril (Oral expert evidence provided at trial in November 2014)
    - H. Lundbeck A/S v Apotex Inc. (T-1407-09) relating to Escitalopram (Oral expert evidence provided at trial in December 2012)
    - Sanofi-Aventis Canada Inc. et al v Apotex Inc. (T-161-07) relating to Ramipril (Oral expert evidence provided at trial in February 2009)
    - Merck & Co. et al v Apotex Inc. et al (T-1272-97) relating to Lovastatin
    - GlaxoSmithKline Inc. et al v Apotex Inc. (T-14-09) relating to Valacyclovir
    - Merck & Co., AstraZeneca UK Limited et al v Apotex Inc. (T-2792-96) relating to Lisinopril

- Expert reports in connection with Section 8 damages proceedings under the Patented Medicines (Notice of Compliance) Regulations – Expert opinion reports providing quantification of damages as a result of commencements of proceedings pursuant to Canadian Patent Regulations which sought prohibition orders to prevent the Minister of Health of Canada from issuing Notices of Compliance for certain pharmaceutical drugs.

- Reply reports providing comments on reports prepared by other experts and quantifying the impact of different issues on lost profits calculated by other experts.

- Reports have been filed in connection with the following cases in the Federal Court of Canada:
    - Apotex Inc. v AstraZeneca Canada Inc. (T-389-11) relating to Esomeprazole (Oral expert evidence provided at trial in May 2017)
    - Apotex Inc. v AstraZeneca Canada Inc. (T-2300-05) relating to Omeprazole (Oral expert evidence provided at trial in February 2017)
    - Apotex Inc. v Merck Frosst Canada (T-1144-05) relating to Alendronate (Oral expert evidence provided at trial in September 2012)
    - Apotex Inc. v Pfizer Canada Inc. (T-825-06) relating to Azithromycin
    - Apotex Inc. v Abbott Laboratories, Limited (T-1396-07) relating to Clarithromycin
    - Apotex Inc. v Merck Frosst Canada (T-411-01) relating to Norfloxacin
    - Apotex Inc. v Ferring Inc. (T-1954-08 and T-165-07) relating to Desmopressin
    - Apotex Inc. v Servier Canada Inc. (T-1783-08) relating to Gliclazide

- Expert report in connection with a dispute under NAFTA – Expert opinion report providing a quantification of damages of a Canadian generic pharmaceutical company as a result of the alleged violations under NAFTA by the U.S. Government and the alleged actions of the U.S. Food and Drug Administration.

- Affidavit in connection with an application for leave to appeal to the Supreme Court of Canada – In connection with a Section 8 damages proceeding under the Patented Medicines (Notice of Compliance) Regulations, which was being appealed to the Supreme Court of Canada. Affidavit providing comments on the concept of "loss" (past losses and future losses) in the context of quantifying damages, and how the concept of "loss" accords with generally accepted accounting principles and business valuation. The affidavit also provided comments on the specific issues regarding damages sought in the claim for lost sales and permanent market share under the Regulations.

- Affidavit in connection with an application for leave to appeal to the Supreme Court of Canada – In connection with a Section 8 damages proceeding under the Patented Medicines (Notice of Compliance) Regulations, which is being appealed to the Supreme Court of Canada. Affidavit providing a calculation of the profits earned during a period when there was no generic competition compared to profits that would have been earned in the presence of generic competition and to Section 8 damages amounts.

- Expert report in connection with a pharmaceutical drug supply agreement dispute under the Ontario Superior Court of Justice – Preparation of an expert opinion report providing a quantification of damages based on analysis of historical sales and market share related to a pharmaceutical drug under a supply agreement.

- Expert report in connection with a pharmaceutical drug supply agreement dispute under the Arbitrations Act, Ontario, Canada – Expert opinion report providing a quantification of damages based on lost market share related to a pharmaceutical drug under a supply agreement.

- Expert report in connection with a dispute under the International Centre for Dispute Resolution of the American Arbitration Association – Preparation of an expert opinion report with respect to the net present value of a branded drug product related to a contract dispute between two pharmaceutical companies based in the U.S.A. and Japan, respectively, for a drug expected in Japan.

- Advisor to a Claimant in connection with an arbitration in Israel – Provided advisory services related to damages issues, critique of the opposing expert reports, and development of questions for cross-examination. This matter related to a contract dispute between two pharmaceutical companies based in Israel.

- Advisor to a pharmaceutical distribution and services company in Canada – Provided advisory services for the purpose of assisting in the assessment of potential claims between a major pharmaceutical distribution and services company and a pharmacy chain in respect to their prime vendor relationship in Canada.

- Expert report in connection with a failed initial public offering case in Canada – Expert report with an analysis of damages relating to the loss of goodwill to a parent company resulting from an alleged conspiracy causing failure of an IPO. The case relates to a national mail order pharmacy.

- Valuation report for corporate reorganization – Valuation of a company which manufactures soft gel capsules, provides encapsulation services, and manufactures pharmaceutical packaging (including bottling and blister packing). The company is based in Canada and services customers worldwide.

- Valuation report for corporate reorganization – Valuation of the intangible assets of a company which markets and distributes sports nutrition, weight loss, and health nutrition supplement products. The company is based in Canada and distributes products worldwide.

Publications (Last Five Years)

» Co-author, "Evaluating Your Business: What Is It Really Worth?", 2019.

» Featured expert article for the King & Spalding Quantum Quarterly Damages Newsletter, 2019.

» Co-author, "Restoring Faith in the Party-Appointed Expert", NYSBA Dispute Resolution Lawyer, 2019.

» Co-author, "Expert Evidence" the Guide to Energy Arbitrations, 2018

- Co-author, "Expert Evidence" the Guide to Energy Arbitrations, 2015.
- Co-author, "Trends in International Arbitration", FTI Journal, 2015.
- Co-author, "Trends in International Arbitration", The European, Middle Eastern and Africa Arbitration Review 2015.
- Co-author, "Going Concern versus Liquidation Valuations, the Impact on Value Maximization in Insolvency Situations", Evergreening and the transfer of patent value", The Asia-Pacific Arbitration Review 2015.
- Author, "How Useful are Party-Appointed Experts in International Arbitration", International Council for Commercial Arbitration (ICCA) Paper, 2014.
- Co-author, "The Valuation of Minority Interests in Forced Takings", The Arbitration Review of the Americas 2014.

Professional Presentations and Speaking Engagements, Seminars and Training (Last Five Years)

- **Prospectors & Developers Association of Canada (PDAC) Annual Conference.** Technical Program speaker on the topic, "Valuation of Damages in International Arbitration Cases". (2019)
- **Vienna International Arbitration Days.** Panelist on the topic, "Juggling the Numbers: Mathematics and Economics in Arbitration". (2019)
- **2018 Summit on Global Dispute Resolution** hosted by Cravath, Swaine & Moore LLP in conjunction with Fordham University, Centre for International Commercial and Investment Arbitration, Georgetown Law, NYU Law and the Engelberg Center on Innovation Law & Policy. Co-presenter on topic of Data Trends in International Disputes. (2018)
- **MCIA: The Changing Landscape of Arbitration in India.** Panelist on the topic, "Role of Experts in Arbitration". (2017)
- **Foundation for International Arbitration Advocacy (FIAA) (2012-2017).** FTI Consulting lead in coordinating our participation in the FIAA workshops. Authored materials conducted workshops and acted as an expert witness and instructor in three-day mock trial in a program that draws counsel from all over the world.
- **Northwind's 2016 Mining Invitational Forum, Modern Management for 21st Century Resource Companies.** Panelist on the topic, "International Arbitration: Its Effects on the Mining Industry and What Can We Do About It". (2016)
- **GAR Live Energy Disputes.** Panelist on the topic, "Recent BIT Cases and the Damages Fog". (2015)
- **Fourth Annual Damages in International Arbitration Conference.** Participant in Mock Arbitration – "Should country Risk Premiums be included in Determining a Discount Rate? Shades of Gold Reserve v. Venezuela and Exxon Mobil v. Venezuela". (2015)

Secretariat
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Curriculum Vitae

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Professional History

- Secretariat International
- FTI Consulting
- Deloitte
- Arthur Andersen

Education

- Master of Accounting, University of Waterloo, 1999
- B.A. in Arts – Accounting, University of Waterloo, 1998

Professional Associations

- Chartered Business Valuator – Canada, 2007
- Chartered Professional Accountant/Chartered Accountant – Canada, 2001

Julius Koo

Director

Professional Experience

Julius Koo is a Director at Secretariat International and is based in Toronto, Canada. He is a Chartered Professional Accountant, Chartered Accountant (CPA, CA), and a Chartered Business Valuator (CBV).

Since 2004, he has practiced exclusively in the areas of business valuation and damages quantification related to international arbitrations and Canadian domestic litigation.

His work experience includes a wide range of industries including pharmaceuticals and healthcare, mining, oil and gas, consumer products and services, manufacturing, and financial institutions.

Mr. Koo has prepared independent business valuation reports for public and private companies, and has prepared independent expert reports on damages related to disputes arising in North America, South America, Europe, Asia, and Africa.

He has prepared numerous expert reports filed in various courts, including the Federal Court of Canada and the Ontario Superior Court of Justice. He has also been involved in preparing expert reports for international arbitrations in various arbitral institutions, including the International Centre for Settlement of Investment Disputes, the ICC International Court of Arbitration, the International Centre for Dispute Resolution of the American Arbitration Association, and the International Arbitral Centre of the Austrian Federal Economic Chamber.

Mr. Koo has acted as an instructor at the Foundation for International Arbitration Advocacy (FIAA) Expert Witness Questioning Training Programs held internationally, as well as at advocacy training programs conducted for law firms. He has also been involved in the education and training of Chartered Business Valuators.

Representative Engagements

<u>Canadian Domestic Litigation</u>

- **Expert reports in connection with patent infringement cases in Canada** – Preparation of numerous expert opinion reports providing quantification of damages and/or accounting of profits relating to the alleged patent infringement of certain pharmaceutical drugs. Preparation of reply reports providing comments on reports prepared by other experts and quantifying the impact of different issues on lost profits calculated by other experts.
- **Expert reports in connection with Section 8 damages proceedings under the *Patented Medicines (Notice of Compliance) Regulations*** – Preparation of numerous expert opinion reports providing quantification of damages as a result of commencements of proceedings pursuant to Canadian Patent Regulations which sought prohibition orders to prevent the Minister of Health of Canada from issuing Notices of Compliance for certain generic pharmaceutical drugs. Preparation of reply reports providing comments on reports prepared by other experts and quantifying the impact of different issues on lost profits calculated by other experts.
- **Affidavit in connection with an application for leave to appeal to the Supreme Court of Canada** – In connection with a Section 8 damages proceeding under the *Patented Medicines (Notice of Compliance) Regulations*, which was being appealed to the Supreme Court of Canada. Assisted in the preparation of an affidavit providing comments on the concept of "loss" (past losses and future losses) in the context of quantifying damages, and how the concept of "loss" accords with generally accepted accounting principles and business valuation. The affidavit also provided comments on the specific

issues regarding damages sought in the claim for lost sales and permanent market share under the *Regulations*.

- **Affidavit in connection with an application for leave to appeal to the Supreme Court of Canada** – In connection with a Section 8 damages proceeding under the *Patented Medicines (Notice of Compliance) Regulations*, which is being appealed to the Supreme Court of Canada. Assisted in the preparation of an affidavit providing a calculation of the profits earned during a period when there was no generic competition compared to profits that would have been earned in the presence of generic competition and to Section 8 damages amounts.
- **Expert report in connection with a pharmaceutical drug supply agreement dispute under the Ontario Superior Court of Justice** – Preparation of an expert opinion report providing a quantification of damages based on analysis of historical sales and market share related to a pharmaceutical drug under a supply agreement.
- **Expert report in connection with a pharmaceutical drug supply agreement dispute under the Arbitrations Act, Ontario, Canada** – Preparation of an expert opinion report providing a quantification of damages based on lost market share related to a pharmaceutical drug under a supply agreement.
- **Advisor to a pharmaceutical distribution and services company in Canada** – Provided advisory services for the purpose of assisting in the assessment of potential claims between a major pharmaceutical distribution and services company and a pharmacy chain in respect to their prime vendor relationship in Canada.

International Arbitration

- **Pharmaceutical – Canada/USA** – Preparation of an expert opinion report providing a quantification of damages of a Canadian generic pharmaceutical company as a result of the alleged violations under NAFTA by the US Government and the alleged actions of the US Food and Drug Administration.
- **Pharmaceutical – USA/Japan** – Preparation of an expert opinion report with respect to the net present value of a branded drug product related to a contract dispute between two pharmaceutical companies based in the USA and Japan, respectively, for a drug expected in Japan. This dispute was under the International Centre for Dispute Resolution of the American Arbitration Association.
- **Pharmaceutical – USA/South Korea** – Preparation of a preliminary damages report with respect to the lost profits of a specific brand of parenteral nutrition products for markets worldwide. This dispute is in relation to a contemplated arbitration under ICC Rules between two pharmaceutical companies based in the USA and South Korea, respectively, for alleged breach of a license and distribution agreement.
- **Pharmaceutical – Israel** – Assisted in advising a Claimant in connection with an arbitration in Israel. Provided advisory services related to damages issues, critique of the opposing expert reports, and development of questions for cross-examination. This matter related to a contract dispute between two pharmaceutical companies based in Israel.
- **Gold – Venezuela** – Assisted in the preparation of expert reports on valuation and damages for an ICSID case related to the alleged expropriation of a gold and copper mining operation by the government.
- **Gold – Romania** – Assisted in the preparation of a preliminary report on valuation for a contemplated ICSID claim related to the alleged expropriation of a mining operation by the government.
- **Dimension Stone – South Africa** – Assisted in the preparation of an expert report on valuation and damages for an ICSID case related to a change in government policy and the alleged effect on the value of a dimension stone mining operation.
- **Oil Pipeline – Turkey** – Assisted in the preparation of expert reports on damages for an ICC arbitration related to a commercial dispute of the alleged breach of terms of the contracts that existed between the owners and the operator of an oil pipeline in Turkey.

- **Fuel Additive – USA/France** – Assisted in the preparation of expert reports on damages and manufacturing costs for an ICC arbitration related to a commercial dispute of a pricing mechanism between a manufacturer and a distributor of a specialty fuel additive.
- **Banking – Kazakhstan** – Assisted in the preparation of an expert report on valuation for an ICSID case to provide an opinion of the fair market value of the Claimant's interest in one of the largest banks in Central Asia.
- **Beverages – Uzbekistan** – Assisted in the preparation of an expert report on valuation for an arbitration, under the Vienna Rules of the International Arbitral Centre of the Austrian Federal Economic Chamber, to provide an opinion of the fair market value of the Claimant's interest in a soft drink bottling operation in Uzbekistan.

Other

- **Valuation report for mediation** – Preparation of a calculation report relating to the fair market value of a chain of long-term care pharmacies located in the U.S.
- **Valuation report for mediation** – Preparation of a calculation report relating to the fair value of a digital technology solutions company based in Canada, in relation to a shareholder oppression dispute in Ontario.
- **Valuation report for corporate reorganization** – Assisted in the valuation of a company which manufactures soft gel capsules, provides encapsulation services, and manufactures pharmaceutical packaging (including bottling and blister packing). The company is based in Canada and services customers worldwide. The valuation was used for a contemplated corporate reorganization.
- **Valuation report for corporate reorganization** – Assisted in the valuation of the intangible assets of a company which marketed and distributed sports nutrition, weight loss, and health nutrition supplement products. The company was based in Canada and distributed products worldwide. The valuation was used for a contemplated corporate reorganization.
- **Valuation reports related to goodwill and intangible assets for financial statement reporting purposes** – Assisted in the valuation of goodwill and intangible assets for financial statement reporting purposes related to the following industries: aerospace and defence electronic products, security technology products, and restaurant chains.
- **Software – Canada** – Assisted in the preparation of an expert report on valuation for the Canada Revenue Agency, related to an investigation under the Income Tax Act and Criminal Code, to provide an opinion of the fair market value of a collection of children's software and clip art software programs.
- **Pet Retail – Canada** – Advisor to the management group of a pet specialty retailer franchise with over 170 stores in Canada, with respect to a management buy-out transaction. Advised on the fair market value of the shares traded on the TSX Venture Exchange.
- **Medical Devices – USA/Switzerland** – Provided advisory services to a private equity firm in relation to the acquisition of a diagnostic systems manufacturer focusing in the diabetes market, specifically blood glucose monitoring systems. Advised on variable and fixed costing, cost of goods sold analysis, cost allocations of centralized costs, and profitability by country/region.
- **Interest Rate Class Action – Canada** – Class action over claims of excessive interest rates on rental agreements for furniture, appliances and home electronics. Engaged by Defendant to analyze the implicit interest rate charged (including administrative and late fees) on rental agreements for a sample of the Class. Also analyzed the difference between early pay-out option amounts and the cash price of merchandise.
- **Interest Rate Class Action – Canada** – Class action over claims of excessive interest rates on monthly satellite TV bills. Engaged by Defendant to analyze the implicit interest rate charged (including administrative and late fees) on monthly accounts for a sample of the Class.

TABB

THIS IS EXHIBIT "B" TO THE AFFIDAVIT OF HOWARD ROSEN SWORN BEFORE ME THIS 28TH DAY OF NOVEMBER, 2019.

A Commissioner, etc.

STUART SVONKIN

MEMORANDUM

FROM: Secretariat International – Howard Rosen, Julius Koo

DATE: November 28, 2019

SUBJECT: PMPRB v Horizon Pharma – PROCYSBI
Request for Documents

Introduction

We have been requested by Perley-Robertson, Hill & McDougall LLP, on behalf of Board Staff of the Patented Medicine Prices Review Board, to review the report prepared by Dr. Joel Hay dated September 9, 2019 (the "Hay Report") for Horizon Pharma in connection with the above-noted proceeding.

The following represents a listing of information and documents which we require in order to analyze, test, verify, and potentially respond to all of the assumptions, calculations, and conclusions contained in the Hay Report.

A. Documents related to Horizon Pharma's Canadian subsidiary – HZNP Therapeutics Canada Limited (also known as Horizon Therapeutics Canada):

1. HNZP.xlsx (Horizon Financial Information) – listed in the Hay Report, Appendix D – Scope of Review, item C.iii. – in Excel format
2. Audited or unaudited annual financial statements – from the fiscal year ended 2015 (2 years prior to the launch of PROCYSBI in Canada in September 7, 2017) to the current fiscal year
3. Unaudited quarterly financial statements – from the first fiscal quarter of 2015 to the current fiscal quarter
4. Financial statements (balance sheet, income statement, statement of cash flows) prepared for internal reporting purposes/consolidation purposes – from the fiscal year ended 2015 (2 years prior to the launch of PROCYSBI in Canada in September 7, 2017) to the current fiscal year
5. Detailed monthly profit & loss/income statements – from the first fiscal month of 2015 to the current month

6. Detailed monthly profit & loss/income statements specifically for PROCYSBI, or any other documents that report profit & loss related to PROCYSBI sales in Canada – from September 2017 to the current month
7. Business plans, marketing plans, forecasts, budgets, and management presentations that contain information on sales, expenses, and profit & loss of PROCYSBI in Canada – from prior to the launch of PROCYSBI in Canada in September 7, 2017 to the current date
8. Business plans, marketing plans, forecasts, budgets, and management presentations that contain information on conversion of patients from Cystagon to PROCYSBI in Canada – from prior to the launch of PROCYSBI in Canada in September 7, 2017 to the current date
9. Data from IQVIA (formerly IMS Health) used by Horizon Pharma to analyze market share of PROCYSBI relative to Cystagon in each country – from January 2015 to the current month
10. Federal and provincial corporate income tax returns and schedules, specifically including the reconciliation of taxable income with accounting income – from the taxation year 2015 to current

B. Documents related to PROCYSBI sales:

1. Detailed listing of all PROCYSBI sales transactions in Canada (from the sales subledger) from launch to the current date – detailing actual sales in units for all stock keeping units ("SKU") (i.e. 25 mg 60 capsule bottles and 75 mg 250 capsule bottles) and unit price for each sale
2. The above listing should include sales units provided free-of-charge ("free goods"), sales returns, and any other sales credit or debit transactions
3. A sample of purchase orders, sales invoices, credit notes, and debit notes for each type of sales transaction, for each SKU
4. Documents that support the assumption that [redacted] of Horizon's patients will be covered by provincial and territorial drug benefit plans and [redacted] will be covered by private insurance plans[1]
5. Documents that support Horizon's copay discount of [redacted] of covered costs to patients covered under private-insurance plans[2]

[1] The Hay Report, page F-4, para. 9.

[2] The Hay Report, page F-5, para. 10.

C. Documents related to PROCYSBI expenses:

1. All agreements and amendments related to royalties to the Regents of the University of California, including but not limited to:
   - Amended and Restated License Agreement, dated May 31, 2017, by and between Horizon Orphan LLC and The Regents of the University of California
   - Amendment No. 1 to Amended and Restated License Agreement, dated September 11, 2018, by and between Horizon Orphan LLC and The Regents of the University of California
2. Documents that support the calculation of royalties payable from sales of PROCYSBI in Canada and the payment of the royalties
3. Documents supporting reported cost of goods sold and per unit standard cost for PROCYSBI Canada for both SKUs (figures contained in the Hay Report, Exhibit B)
4. Purchase orders and invoices for all PROCYSBI units purchased for sale in Canada
5. Documents supporting cost of goods sold for PROCYSBI Global (figures contained in the Hay Report, Exhibit C)
6. Documents that support each expense item under other cost of sales and supply chain (figures contained in the Hay Report, Exhibit C), including but not limited to:
   - Expense subledgers
   - Internal reports used to analyze these expenses
   - Allocations of these costs to specific products, geographic regions, or countries
7. Documents that explain what "manufacturing operations" expenses[3] relate to and whether any of these costs are imbedded in the standard cost/cost of goods sold for PROCYSBI sold in Canada
8. Documents that explain what "inventory adjustments"[4] relate to and whether any inventory adjustments were specific to PROCYSBI sold in Canada
9. Documents that explain what "supply chain" and "freight & warehouse" expenses[5] relate to and whether any of these expenses were specific to PROCYSBI sold in Canada

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[3] The Hay Report, Exhibit C.

[4] The Hay Report, Exhibit C.

[5] The Hay Report, Exhibit C.

10. Documents that explain what each "sales and marketing expense" item (and "medical affairs")[6] relates to and support how each item should be allocated to PROCYSBI sold in Canada
11. Documents that explain what each "general and administrative" expense[7] item relates to and support how each item should be allocated to PROCYSBI sold in Canada
12. Documents relating to executive and managerial salaries and bonuses, and other employee costs that support how these expenses should be allocated to PROCYSBI sold in Canada
13. Documents that detail selling, general and administrative expenses that should be specifically excluded from an allocation to PROCYSBI sold in Canada, [redacted]
14. Documents that explain what "ongoing research and development" expenses[8] relate to and support how these expenses should be allocated to PROCYSBI sold in Canada
15. Documents that support why a growth rate of [redacted] is reasonable for continuing R&D expenditures for PROCYSBI sold in Canada[9]
16. Documents that support Horizon Pharma's acquisition of the worldwide marketing rights to PROCYSBI through its acquisition of Raptor Pharmaceutical Corp. in October 2017 ("Raptor Acquisition Cost" or "Raptor Development Costs")[10] and the allocation of the development and commercial expenditures for PROCYSBI to PROCYSBI sold in Canada, including but not limited to:
    - Documents that supported the due diligence of all research and development, regulatory, and quality costs
    - Valuation reports done by external third party consultants or internally by Horizon Pharma relating to this acquisition transaction, and other related documents used in the allocation of the purchase price into tangible and intangible assets and liabilities

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6 The Hay Report, Exhibit D.

7 The Hay Report, Exhibit E.

8 The Hay Report, Schedules 1-3, Exhibit F.

9 The Hay Report, page F-9, para. 24, footnote 18.

10 The Hay Report, Schedules 1-3, Exhibit F.

- Detailed costing documents that provide a build-up of historical research and development expenditures, and regulatory and quality costs spent prior to the Raptor transaction
- Any internal analysis comparing these past costs to those spent by Horizon Pharma after the acquisition

17. Documents that detail which Horizon Pharma legal entity holds and records the intellectual property/intangible assets (the developed technology) associated with PROCYSBI
18. Documents which support Horizon Pharma's impairment tests relating to PROCYSBI

D. Documents related to PROCYSBI transfer pricing:

1. Corporate organizational charts that present all Horizon Pharma legal entities and third parties globally that are involved with all economic activities associated with PROCYSBI, including but not limited to entities that:
   - Manufacture the active pharmaceutical ingredient ("API") cysteamine bitartrate
   - Purchase and receive the API
   - Supply the excipients
   - Manufacture the finished product (capsulation of the PROCYSBI capsules), including the application of PROCYSBI's enteric coating, delayed release formulation
   - Package and label the finished SKUs for the Canadian market
   - Warehouse and distribute the finished SKUs in the Canadian market
   - Provide other services such as arranging for the above activities, accounting services such as invoicing, managing intercompany relationships
   - Hold the rights to the intellectual property (intangible assets) related to PROCYSBI
   - Hold the distribution rights for the Canadian market
2. All agreements and amendments between Horizon Pharma legal entities involved with PROCYSBI, and other related documents to understand transfer pricing arrangements, price adjustment mechanisms, profit adjustment mechanisms, any mark-ups and fees charged, and intercompany arrangements
3. All agreements and amendments with third parties involved with PROCYSBI, including but not limited to:

- API Supply Agreement, dated November 3, 2010, by and among Cambrex Profarmaco Milano, Horizon Orphan LLC (as successor in interest to Raptor Therapeutics Inc.) and Horizon Pharma Europe B.V. (as successor in interest to Raptor Pharmaceuticals Europe B.V.), as amended April 9, 2013
- Any other raw materials supply agreements
- Manufacturing Services Agreement, dated November 15, 2010, by and among Patheon Pharmaceuticals Inc., Horizon Orphan LLC (as successor in interest to Raptor Therapeutics Inc.) and Horizon Pharma Europe B.V. (as successor in interest to Raptor Pharmaceuticals Europe B.V.), as amended April 5, 2012 and June 21, 2013
- Any other contract manufacturing services agreements
- Any distribution agreements and amendments with Innomar Strategies Inc.
- Any other warehousing, logistics, or co-distribution agreements

4. For all Horizon Pharma legal entities that are involved with the economic activities associated with PROCYSBI, financial documents including but not limited to:
   - Audited or unaudited annual financial statements – from the fiscal year ended 2015 (2 years prior to the launch of PROCYSBI in Canada in September 7, 2017) to the current fiscal year
   - Unaudited quarterly financial statements – from the first fiscal quarter of 2015 to the current fiscal quarter
   - Financial statements (balance sheet, income statement, statement of cash flows) prepared for internal reporting purposes/consolidation purposes – from the fiscal year ended 2015 (2 years prior to the launch of PROCYSBI in Canada in September 7, 2017) to the current fiscal year
   - Detailed monthly profit & loss/income statements – from the first fiscal month of 2015 to the current month
   - Detailed monthly profit & loss/income statements specifically for PROCYSBI, or any other documents that report profit & loss related to PROCYSBI sales globally – from the first fiscal month of 2015 to the current month
   - Business plans, marketing plans, forecasts, budgets, and management presentations that contain information on sales, expenses, and profit & loss of PROCYSBI globally – from prior to the launch of PROCYSBI in each country/market to the current date

- Business plans, marketing plans, forecasts, budgets, and management presentations that contain information on conversion of patients from Cystagon to PROCYSBI globally – from prior to the launch of PROCYSBI in each country/market to the current date
- Data from IQVIA (formerly IMS Health) used by Horizon Pharma to analyze market share of PROCYSBI relative to Cystagon in each country – from prior to the launch of PROCYSBI in each country/market to the current date
- Income tax returns and schedules, specifically including the reconciliation of taxable income with accounting income for each jurisdiction – from the taxation year 2015 to current

5. Documents relating to the actual cost of API supplied by Cambrex Profarmaco Milano that was used in PROCYSBI sold in Canada, including but not limited to purchase orders, invoices, and debit/credit memos
6. Documents relating to the actual cost of excipients used in PROCYSBI sold in Canada, including but not limited to purchase orders, invoices, and debit/credit memos
7. Documents relating to the actual cost of manufacturing (capsulation) by Patheon Pharmaceuticals Inc. for PROCYSBI sold in Canada, including but not limited to purchase orders, invoices, and debit/credit memos
8. Documents relating to the actual cost of packaging and labelling of finished SKUs for PROCYSBI sold in Canada, including but not limited to purchase orders, invoices, and debit/credit memos
9. To the extent that Horizon Pharma performs any manufacturing (capsulation, application of PROCYSBI's enteric coating, delayed release formulation), packaging and/or labelling, and supply chain (freight, distribution, warehouse, logistics) functions for PROCYSBI sold in Canada, documents relating to the actual cost of performing these functions, including but not limited to:
   - Master formula card/recipe sheets
   - Internal cost sheets
   - Calculations of standard cost (by month)
   - Tracking of actual costs and cost variances
   - Physical process diagram of all machinery used in each process (including the location and cost of each asset owned or leased)
   - Information regarding the annual theoretical capacity and actual usage for each machine (by dosage/capsule/SKU)

- Physical process diagram of all supply chain functions used globally (including the location and cost of each warehouse, distribution centre, logistics fleet owned or leased)

10. The documents above should cover all cost categories, including but not limited to:
    - Raw material costs (including API, excipients, other)
    - Packaging material costs
    - Direct labour costs (including set up, clean up, other)
    - Direct overhead costs
    - Direct quality assurance and quality control costs
    - Direct regulatory affairs costs
    - All indirect overhead costs (including indirect labour, allocated general and administrative expenses)
    - Other cost of sales (including manufacturing operations costs, inventory adjustments)
    - Supply chain costs (including freight distribution, warehouse, logistics)
    - Sales and marketing expenses (including medical affairs)
    - All research and development costs, past and ongoing
11. Documents relating to the actual cost of distribution by Innomar Strategies Inc. for PROCYSBI sold in Canada, including but not limited to invoices and debit/credit memos
12. Documents related to the calculation of transfer prices between all Horizon Pharma legal entities involved with PROCYSBI sold in Canada, and any adjustments to transfer prices, from the date of launch in Canada to the current date
13. Documents related to any intercompany transfers of funds and/or product between all Horizon Pharma legal entities with respect to PROCYSBI sold in Canada, including but not limited to purchase orders, invoices, debit/credit memos, intercompany payables/receivables, payment of dividends, payment of fees, and profit adjustments
14. Any correspondence with income tax authorities in any jurisdiction regarding the transfer price of PROCYSBI
15. Any correspondence with income tax authorities in any jurisdiction regarding income taxes (income tax assessments) related to the sales of PROCYSBI
16. Any transfer pricing studies or reports done by external third party consultants or internally by Horizon Pharma relating to PROCYSBI

17. Any breakeven analysis or analysis of internal rate of return ("IRR") done by Horizon Pharma regarding the sales of PROCYSBI globally, by region, by country

E. In order to analyze and validate the documents which we anticipate receiving and reviewing, we request for the opportunity to conduct an on-site inspection at the offices of Horizon Pharma (and manufacturing and distribution facilities) as necessary. For the purposes of performing this inspection, we would require access to the documents requested herein and access to Horizon Pharma's in-house knowledgeable staff to discuss and respond to our questions regarding Horizon's accounting processes and documentation, including but not limited to:

1. Documents that outline the economic relationships and activities of all Horizon Pharma legal entities and third parties globally that are involved with all economic activities associated with PROCYSBI
2. Documents that detail the actual and forecasted revenues and costs of PROCYSBI earned/incurred by Horizon Pharma
3. Documents that detail the nature of the actual cost of goods sold, standard cost of goods sold, and transfer pricing of PROCYSBI, and how the profits from the sales of PROCYSBI in Canada flow through all related Horizon Pharma legal entities for financial reporting purposes and for income tax purposes
4. Documents that detail the nature of the Raptor Acquisition Cost
5. Documents that detail the nature of Ongoing R&D Expenses
6. Documents that detail the nature of each expense item under Other Cost of Sales and Supply Chain that are recorded on a global basis
7. Documents that detail the nature of Sales and Marketing (and Medical Affairs) expenses that are recorded on a Canada wide basis
8. Documents that detail the nature of General and Administrative expenses that are recorded on a global basis

F. Upon our review, analysis, and validation of the requested documents that we anticipate receiving, we expect that we will have follow up questions and additional requests for information and documents. We reserve the right to make such requests after our document review and on-site inspection.

TAB3

TABA

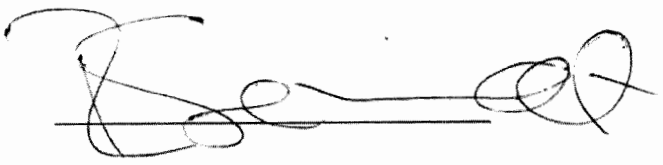
IN THE MATTER OF the *Patent Act*, R.S.C. 1985, c. P-4, as amended

AND IN THE MATTER OF Horizon Pharma (the "Respondent")
and the medicine Cysteamine Bitartrate
sold by the Respondent under the trade name "Procysbi"

I, Richard Schwindt, resident in Abbotsford, in the province of British Columbia, declare that

a) I have been retained Perley-Robertson, Hill & McDougall LLP to provide evidence in the matter of the *Patent Act*, R.S.C. 1985, c. P-4, as amended and in the matter of Horizon Pharma (the "Respondent") and the medicine Cysteamine Bitartrate sold by the Respondent under the trade name "Procysbi";
b) it is my duty to provide evidence in relation to this proceeding as follows:
   i) to provide opinion evidence that is impartial,
   ii) to provide opinion evidence that is related only to matters that are within my area of expertise, and
   iii) to provide any additional assistance that the Board may reasonably require to determine a matter at issue.
c) I acknowledge that the duties referred to above take precedence over any obligation which I may owe to any party by whom or on whose behalf I am engaged.

Dated at Abbotsford, British Columbia this 6 day of September, 2019.



Richard Schwindt

PATENTED MEDICINE PRICES REVIEW BOARD

IN THE MATTER OF the *Patent Act*, R.S.C. 1985, c. P-4, as amended

AND IN THE MATTER OF
Horizon Pharma (the "Respondent")
and the medicine Cysteamine Bitartrate
sold by the Respondent under the trade name "Procysbi"

I, RICHARD SCHWINDT, hereby certify that:

The attached report titled "Opinion Regarding Appropriate Methodologies for Determining Excessive Patented Medicine Prices: the Case of Procysbi," dated September 6, 2019 and signed on September 6, 2019 is my testimony pursuant to Rule 8 of the Patented Medicine Prices Review Board Rules of Practice and Procedure.

Sept 6, 2019

Richard Schwindt — Date

SWORN BEFORE ME in the City of Abbotsford, in the Province of British Columbia, on

September 6, 2019

Name and Signature

PAUL ANTHONY WILLIAMS
Notary Public
100 - 3240 Mt. Lehman Rd., Abbotsford, B.C., V4X 2M9
604.381.2000
NO ADVICE SOUGHT NOR GIVEN.
ATTESTED ONLY BUT NOT DRAWN BY
PAUL ANTHONY WILLIAMS

OPINION REGARDING APPROPRIATE METHODOLOGIES FOR DETERMINING EXCESSIVE PATENTED MEDICINE PRICES: THE CASE OF PROCYSBI

Professor R. Schwindt

I have been asked by counsel to the Staff of the Patented Medicine Prices Review Board (PMPRB) to provide an opinion, from an economic perspective, on an appropriate methodology (or methodologies) to determine whether the price of Procysbi is excessive. This report proceeds by setting out relevant background information and then addressing counsel's issues.

A. CREDENTIALS

The focus of my training, research and teaching is the applied microeconomics field of industrial organization economics. The emphasis has been on competition (anti-trust) policy and regulation of statutory monopoly. I have provided expert opinion to: the Competition Tribunal, Court of Queen's Bench of Alberta, the National Transportation Agency of Canada, Ontario Court, General Division, the Ontario Energy Board, and the PMPRB. My curriculum vitae is attached as Appendix 1 to this report

B. BACKGROUND

To provide context, this section sets out my understanding of the role of the PMPRB and describes the medicine at issue.

1. The Role of the PMPRB

The 1987 amendments to the *Patent Act* significantly strengthened the property rights of pharmaceutical patent holders. This raised fears that the changes would lead to appreciably higher medicine prices to the detriment of the Canadian public interest. To allay these fears the government of the day included in the amendments provision for the establishment of the PMPRB to protect against excessively high prices. [1] The *Act* directs the PMPRB to consider specific factors in its determination of whether a price is excessive.

> *85. (1) In determining under section 83 whether a medicine is being or has been sold at an excessive price in any market in Canada, the Board shall take into consideration the following factors, to the extent that information on the factors is available to the Board:*
>
> *(a) the prices at which the medicine has been sold in the relevant market;*

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[1] Margaret Smith, *Patent Protection for Pharmaceutical Products*, Background Paper 354-E, Law and Government Division, Parliamentary Research Branch, Library of Parliament, November 1993, available at: http://publications.gc.ca/collections/Collection-R/LoPBdP/BP-e/bp354-e.pdf.

(b) the prices at which other medicines in the same therapeutic class have been sold in the relevant market;
(c) the prices at which the medicine and other medicines in the same therapeutic class have been sold in countries other than Canada;
(d) changes in the Consumer Price Index; and
(e) such other factors as may be specified in any regulations made for the purposes of this subsection.

Additional factors

(2) Where, after taking into consideration the factors referred to in subsection (1), the Board is unable to determine whether the medicine is being or has been sold in any market in Canada at an excessive price, the Board may take into consideration the following factors:

(a) the costs of making and marketing the medicine; and
(b) such other factors as may be specified in any regulations made for the purposes of this subsection or as are, in the opinion of the Board, relevant in the circumstances.

Research costs

(3) In determining under section 83 whether a medicine is being or has been sold in any market in Canada at an excessive price, the Board shall not take into consideration research costs other than the Canadian portion of the world costs related to the research that led to the invention pertaining to that medicine or to the development and commercialization of that invention, calculated in proportion to the ratio of sales by the patentee in Canada of that medicine to total world sales.

The *Act* identifies what factors are to be considered by the PMPRB in its determination but does not provide a definition of what constitutes an excessive price. Nor does the *Act* stipulate how the PMPRB is to implement its consideration of the identified factors. This was left to the PMPRB to address on the specific facts of each individual case.

Economists do have tools to deal with the identification and quantification of excessive prices. In essence, from an economics standpoint prices are excessive when they are above the competitive level (i.e., the price that would exist in a competitive market), and the difference between the two prices (i.e., the competitive price and the non-competitive price) is a measure of the degree of excessiveness.

Highly competitive markets are characterized by: a large number of buyers and sellers; low barriers to entry to and exit from the market; homogenous products (i.e., little or no differentiation between products); and symmetrically well informed buyers and sellers. Under these conditions the equilibrium market price just covers the costs of all inputs to the production process, including a normal return to entrepreneurial effort (i.e.,

profits). Inputs are paid at a level that just keeps them in their current employ as they can do no better elsewhere.

However, when the characteristics of a competitive market are not satisfied, it is possible for the market price to rise above the competitive level and become excessive. This can be particularly problematic in unilateral or collusive monopoly situations. When a firm or group of firms exercises market power (i.e., the ability to raise price meaningfully above the competitive level without attracting market entry) there is a redistribution of economic benefit from consumer to producer and an inefficient allocation of resources that is contrary to the public interest.

Public policy addresses the market power problem through several avenues. Where demand side and supply side characteristics allow for competition, competition policy (antitrust policy) addresses extant or emerging market power through constraints on the abuse of dominance, control of mergers leading to dominance, and deterrence of the creation and exercise of collective market power (e.g., cartelization). When competition is not feasible as is the case when economies of scale are so large relative to demand that there is only room for a single efficient supplier, public policy involves direct regulation of price and product or service characteristics. Examples include the direct regulation of utilities (e.g., natural gas and electricity distribution).

The PMPRB does not directly regulate the prices of patented medicines in the way that utilities are regulated. There are no rate hearings where demand and supply characteristics are examined in detail. Rather, the PMPRB has developed a set of non-binding and general guidelines to help operationalize the *Act's* directions in most situations as to what factors to consider in the determination of whether a new medicine's price is excessive. The methodology is tied to the effectiveness of the medicine as compared to other medicines. A simplified schematic of the link between the efficacy of the new medicine and the application of the factors to be considered is shown in Table 1. The methodologies are set out in detail in the PMPRB's *Compendium of Policies, Guidelines and Procedures* (the *Guidelines*).[2]

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[2] Patented Medicine Prices Review Board, Canada, *Compendium of Policies, Guidelines and Procedures,* Updated February 2017, available at: http://www.pmprb-cepmb.gc.ca/CMFiles/Compendium_Feb_2017_EN.pdf

Table 1

Level of therapeutic improvement	*New medicine price test (constraint)*
Slight or No Improvement: A drug product offering slight or no improvement is one that, relative to other drug products sold in Canada, provides slight or no improvement in therapeutic effects.	Price is constrained by the price(s) of medicines in the same therapeutic class, i.e., the Therapeutic Class Comparison (TCC) test.
Moderate Improvement: A drug product offering moderate improvement is one that, relative to other drug products sold in Canada, provides moderate improvement in therapeutic effects.	Price is constrained by the higher of: a. The highest non-excessive price determined by the TCC test b. The midpoint between (a.) and the median international price, i.e. the Median International Price Comparison (MIPC) test.
Substantial Improvement: A drug product offering substantial improvement is one that, relative to other drug products sold in Canada, provides substantial improvement in therapeutic effects.	Price is constrained by the higher of: a. The highest non-excessive price determined by the TCC test b. The median international price as determined by the MIPC test
Breakthrough: A breakthrough drug product is the first one to be sold in Canada that treats effectively a particular illness or addresses effectively a particular indication.	Price is constrained by the median international price as determined by the MIPC test.

Clearly, these price tests are not equivalent to the tests used by economists in evaluating market power or by public utility regulators when dealing with rate making. Nonetheless, they are consistent with an economics approach to defining excessive pricing in the context of competitive and non-competitive prices. This is not surprising. Prior to the 1987 revisions to the *Act*, and establishment of the PMPRB, "Canada sought to moderate the prices of patented medicines by means of compulsory licenses to increase competition."[3] Absent this competition, the PMPRB was tasked with protecting the same public interest through the imposition of price ceilings. Including elements that characterize competitive markets in its setting of price ceilings makes economic sense.

Emphasis in the *Guidelines* on the Therapeutic Class Comparison (TCC) test is a case in point. In essence, this test focuses on the price of substitute medicines. From an economics perspective, the role of substitutes is critical to competitive markets. For any supplier in an unregulated market, pricing is constrained by the prices of substitutes. For homogenous (i.e., identical) products, a supplier simply cannot price above substitutes. In other words, when products are identical, their prices will be the same. However,

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[3] Patented Medicine Prices Review Board, Canada, *Compendium of Policies, Guidelines and Procedures,* Updated February 2017, page 6, available at: http://www.pmprb-cepmb.gc.ca/CMFiles/Compendium_Feb_2017_EN.pdf

when products are differentiated, prices can diverge as buyers value the different characteristics of one product more or less than substitute products. Generally it is true that the greater the extent of differentiation, the greater the possible price divergence. In the context of the *Guidelines*, the introductory price of a medicine that is slightly or no better than existing medicines is strictly constrained by the price of those existing medicines. In other words, the introductory price is bound by the prices of substitutes. At the extreme, when there are no substitutes, as is the case with breakthrough medicines, the TCC test is not operative.

The other core test in the *Guidelines* is the median international price comparison (MIPC) test. While not as closely aligned with an economics approach as the TCC, this test is nonetheless consistent with that perspective. Comparison with the price charged for the new medicine in other jurisdictions provides the PMPRB with valuable information. First, the price charged in a market similar to Canada discloses the patentee's willingness to supply. Generally, willingness to supply suggests that the price is covering the patentee's costs which would include a competitive profit level. Second, constraining the domestic price by foreign prices serves as a proxy for international arbitrage. Absent regulatory constraints to trade in patented medicines, arbitragers in a free, competitive market environment would buy product in low-priced jurisdictions and resell in high-priced jurisdictions. This would put downward pressure on prices in the high-priced market.

2. Procysbi

In its 2018 annual report filed with the U.S. Securities Exchange Commission (SEC), Horizon Pharma PLC described Procysi as follows.

PROCYSBI is indicated for nephropathic cystinosis, or NC, a rare and life-threatening metabolic disorder.PROCYSBI capsules contain cysteamine bitartrate in the form of innovative microspheronized beads that are individually coated to create delayed and extended-release properties, allowing patients to maintain consistent therapeutic systemic drug levels over a twelve-hour dosing period. The enteric-coated beads are pH sensitive and bypass the stomach for dissolution and absorption in the more alkaline environment of the proximal small intestine. Randomized controlled clinical trials and extended treatment with PROCYSBI therapy have demonstrated consistent cystine depletion as monitored by levels of the biomarker (and surrogate marker), white blood cell cystine.

PROCYSBI is differentiated by its ability to control cystine concentration continuously over twelve hours. Older therapies require administration of medicine every six hours. By taking PROCYSBI, patients have to dose only twice a day, leaving them greater control over their medication schedule and lifestyle. Additionally, because PROCYSBI can be administered through a feeding tube or mixed with approved food and

beverages, the patient can choose a more flexible dosing regimen. PROCYSBI also has fewer known side effects, such as less severe body odor, than older-generation therapies.

We estimate that there are approximately 500 patients diagnosed with cystinosis living in the United States. NC comprises ninety-five percent of known cases of cystinosis. In these patients, elevated cystine can lead to cellular dysfunction and death; without treatment, the disease is usually fatal by the end of the first decade of life. Cystinosis is progressive, eventually causing irreversible tissue damage and multi-organ failure, including kidney failure, blindness, muscle wasting and premature death. NC is usually diagnosed in infancy after children display symptoms to physicians, including markedly increased urination, thirst, dehydration, gastrointestinal distress, failure to thrive, rickets, photophobia and kidney symptoms specific to Fanconi syndrome. Management of cystinosis requires lifelong therapy.

In addition to patients who have already been identified, we believe that a number of patients with atypical phenotypic presentation and end-stage renal disease have their condition as a result of undiagnosed late-onset NC and would benefit from treatment with PROCYSBI.

Other than PROCYSBI, we are aware of two pharmaceutical products currently approved to treat cystinosis, Cystagon® and Cystaran®. Cystagon, an immediate-release cysteamine bitartrate capsule, is an older-generation systemic cystine-depleting therapy for cystinosis in the United States marketed by Mylan N.V., and by Orphan Europe SARL in markets outside of the United States. Cystagon is PROCYSBI's primary competitor. Cystaran, a cysteamine ophthalmic solution, is approved in the United States for treatment of corneal crystal accumulation in patients with cystinosis and is marketed by Leadiant Biosciences, Inc.

We believe that PROCYSBI will continue to be well received in the market and continue to expect Cystagon to be the primary competitor for PROCYSBI for the foreseeable future.

Our strategy for PROCYSBI is to drive conversion of patients from Cystagon to PROCYSBI, increase the uptake of diagnosed but untreated patients, identify previously undiagnosed patients who are suitable for treatment and increase awareness of label expansion to position PROCYSBI as first line of therapy.[4]

Horizon clearly states that that Cystagon is the primary competitor for Procysbi. In economic terms, Horizon Pharma views Cystagon as a substitute for Procysbi. It follows that in a competitive market, the price of the competing product, Cystagon, would directly affect the pricing of Procysbi.

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[4] Horizon Pharma PLC, U.S. Securities and Exchange Commission, FORM 10-K, Annual Report for the fiscal year ended December 31, 2018, p. 7, available at: https://www.sec.gov/Archives/edgar/data/1492426/000156459019004667/hznp-10k_20181231.htm#ITEM_1_BUSINESS

Raptor Pharmaceutical Corp., the original developer of Procysbi, held the same view. In its 2015 annual report to the U.S. SEC it names Cystagon as a direct competitor.

Competition

Cystinosis

Other than PROCYSBI, we are aware of two pharmaceutical products currently approved to treat cystinosis. Cystagon® (immediate-release cysteamine bitartrate capsules), is a systemic cystine-depleting therapy for cystinosis in the United States manufactured by Mylan N.V., and by Orphan Europe SARL in markets outside of the United States. Cystagon was approved by the FDA in 1994 and by the EC in 1997. Cystaran® (cysteamine ophthalmic solution) was approved by FDA in 2012 for treatment of corneal crystal accumulation in patients with cystinosis and is marketed by Sigma Tau Pharmaceuticals, Inc.

While we believe that PROCYSBI will continue to be well received in the market, Cystagon remains on the market and we expect it will compete with PROCYSBI for the foreseeable future.[5]

C. THE PRICING OF PROCYSBI IN CANADA

Procysbi was first sold in Canada in the Fall of 2017. It was provided in two formats, 25mg capsules and 75mg capsules. Introductory prices are set out in Table 2. It is my understanding that Canadian prices of Procysbi have not been changed since its introduction.

Table 2
Introductory Price of Procysbi in Canada

Format	Price/capsule CAD	Price/mg CAD
25 mg capsule	10.35	.4140
75 mg capsule	31.05	.4140

[5] Raptor Pharmaceutical Corp., U.S. Securities and Exchange Commission, FORM 10-K, Annual Report for the fiscal year ended December 31, 2015, p. 12, available at: https://www.sec.gov/Archives/edgar/data/1070698/000156459016013558/rptp-10k_20151231.htm#N1_BUSINESS

D. THE APPROPRIATE METHODOLOGY FOR DETERMINING EXCESSIVE PRICING IN THE CASE OF PROCYSBI

In my view there exist a number of unique challenges in the determination of a non-excessive introductory price for Procysbi. These will be identified in what follows.

1. The TCC Test

As noted earlier, the price of substitutes is a critical datum in the generation of a market driven competitive price. It is also a critical datum in the determination of a non-excessive price in the PMPRB's *Guidelines*, which provide general approaches for applying the mandatory considerations of the *Act* in many common circumstances. At issue is whether Procysbi has close substitutes.

There are a number of indicators that assist in the determination of substitutability. The actual physical characteristics of the medicines being considered and their end-use are obvious indicators, and these are properly evaluated through a pharmacological review. Other important indicators include the views and behavior of suppliers and consumers.

My understanding is that the metabolic disorder, nephropathic cystinosis can be treated with Cysteamine Bitartrate, an aminothiol salt. According to Horizon Pharma PLC, besides its product Procysbi, there are two other medicines that deliver Cysteamine Bitartrate to address the disorder cystinosis. These are Cystagon and Cystaron. The latter is limited to ophthalmic applications. Cystagon has been available since the 1990s in both the United States and Europe.

As noted above, in its financial reporting Horizon Pharma views Cystagon as the primary competitor for Procysbi; in other words a substitute. In these proceedings, Board Staff view Cystagon as a close substitute for Procysbi in terms of physical characteristics and end use.[6] Horizon Pharma takes the position that Cystagon and Procysbi are not close substitutes in terms of physical characteristics and end use. Moreover, Horizon Pharma states that Cystagon cannot be viewed as a comparator to Procysbi in Canada because Cystagon has only been available through the Special Access Program.[7]

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6 Patented Medicine Prices Review Board, in the matter of the Patent Act, R.S.C., 1985, c. P-4, as amended, and in the matter of Horizon Pharma (the "Respondent") and the medicine Cysteamine Bitartrate sold by the Respondent under the tradename Procysbi, *Statement of Allegations of Board Staff*, page 2.

7 Patented Medicine Prices Review Board, in the matter of the Patent Act, R.S.C., 1985, c. P-4, as amended, and in the matter of Horizon Pharma (the "Respondent") and the medicine Cysteamine Bitartrate sold by the Respondent under the tradename Procysbi, *Response of Horizon Pharma (*dated February 18, 2019*)*.

Whether Cystagon and Procysbi are close substitutes in terms of physical characteristics and end-use is a pharmacological question, not an economic question. Whether Cystagon can be viewed as a comparable (i.e., a substitute) given that it has only been authorized for use in Canada through the Special Access Program, is a legal question, not an economic question.

From an economics perspective, however, if the two products have similar if not identical physical characteristics and end-use, then Cystagon should be used as a comparator. As a matter of course, the PMPRB takes into consideration (indeed it is instructed to do so by the *Act*) the price of a medicine and the prices of medicines in the same therapeutic class in foreign countries. Those medicines are not available in Canada via international trade because of regulatory barriers. Nonetheless, they provide the PMPRB with information about what prices could be in a more competitive environment. Similarly, the price of Cystagon in Canada under the Special Access Program and its price in foreign countries inform the PMPRB in a comparable fashion.

In the result, it is my opinion that if the PMPRB Hearing Panel determines that Cystagon is a close substitute for Procysbi, then the TCC test is appropriate for determining the NEP for Procysbi. If the Hearing Panel agrees with Board Staff's position that Cystagon and Procysbi are the same medicines, this leads to the same conclusion. My understanding is that there is significant variation in the price of Cystagon between Canada and the comparator countries and among the comparator countries. Under the circumstances it is worthwhile to perform the TCC test using the Canadian price and again using a measure of the international price.

2. The MIPC Test

It is my understanding that Board Staff have rejected the application of the median international price comparison (MIPC) test and that Horizon Pharma has supported its application in the case of Procysbi.

As noted in Table 1, the *Guidelines* suggest a consideration of the MIPC test when a new medicine is classified as a moderate or substantial improvement over existing medicines or qualifies as a breakthrough medicine. The determination of the degree of improvement, if any, of a new medicine relative to existing substitutes, if they exist, is a pharmacological issue. In any case, the use of the MIPC test does raise economic issues.

Comparison of the introductory price of a new medicine in Canada with its price elsewhere is a form of external reference pricing (ERP). The use of ERP models is very common, albeit there are a myriad of variations. However, a common thread is that the reference countries should have similar demand and supply conditions to the jurisdiction

implementing the policy. For example, on the demand side it is common to choose countries with similar income levels. It is known that pharmaceutical companies often price discriminate in favour of poorer countries and therefore it would be unreasonable for a high-income country to use them as references.

Herein lies the fundamental problem with respect to applying the MIPC test to the introductory price of Procysbi. In all of the reference countries Cystagon has been and continues to be available. The availability of Cystagon will condition the buyers' willingness to purchase Procysbi at the transaction price. From the payers' perspective there is an aggregate demand for cysteamine (be it in the form of Cystagon or Procysbi) derived from the size of the cystinosis patient population. If the majority of that demand can be satisfied with Cystagon it implies a small volume of Procysbi would be required. A basic economic tenet is that the smaller the share of the consumer's budget allocated to a product, the less sensitive the consumer will be to price. It follows that, everything else equal, in markets where Cystagon was freely available payers would be less sensitive to the price of Procysbi because the volume of purchases of Procysbi would be very limited.

Horizon Pharma's Form 2 filings list publicly available prices for Germany, the U.K. and the U.S. Cystagon has been and is available in all three of these comparator countries. Hence the market for cysteamine is fundamentally different from Canada in this regard; there are two cysteamine products available abroad, instead of just one. Additionally, there appears to be no publicly available data showing actual volumes of Procysbi purchased. If volumes are very small relative to Cystagon, this would suggest that Procysbi plays a minor role in the treatment of cystinosis and that consequently payers would be less sensitive to its price.

The utility of using this small set of comparator countries is further complicated by the unique orphan drug pricing regime in Germany.

For orphan drugs, additional therapeutic benefit is assumed by virtue of marketing authorisation without reference to an appropriate comparator in Germany for as long as annual SHI expenditure for the entire population treated with the drug remains below EUR 50 million (Bouslouk, 2016). Manufacturers are exempted from the requirement of submitting data to support additional therapeutic benefit for as long as the threshold is not exceeded but the G-BA assesses the magnitude of the additional therapeutic benefit for relevant patient groups in order to create the basis for price negotiations. Once the EUR 50 million threshold is exceeded, manufacturers are required to submit data on additional therapeutic benefit and orphan drugs are evaluated and prices renegotiated in the same manner as for all other drugs.[8]

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[8] Wenzl, Martin and Paris, Valerie (2018), *Pharmaceutical Reimbursement and Pricing in Germany*, OECD, Paris, p. 6, available at: https://www.oecd.org/health/health-systems/Pharmaceutical-Reimbursement-and-Pricing-in-Germany.pdf

In other words, as long as expenditures on an orphan drug fall below 50 million euros per 12 month period, German health authorities do not negotiate price. Apparently when an orphan drug accounts for a small portion of the German health care budget, public payers are not just less sensitive, but are insensitive to price[9]. This clearly sets the German market apart from others, including the Canadian market for cysteamine.

These fundamental differences in the market for cysteamine between Canada and the comparator countries leads me to have misgivings about the use of the MIPC test in the case of Procysbi. However, if the Hearing Panel chooses to integrate this test in its pricing decision some adaptation is in order. As it stands, the *Guidelines* do provide some guidance. The Human Drug Advisory Panel (HDAP) concluded that Procysbi provided a moderate improvement over Cystagon. The *Guidelines* suggest a methodology for determining the maximum non-excessive price (MNE price) for a new medicine that represents a moderate improvement over an existing medicine. The MNE price is constrained by the higher of the highest non-excessive price determined by the TCC test, and the midpoint between the MIPC and the highest non-excessive price determined by the TCC test (hereafter the "moderate improvement test"). At issue is whether this is an appropriate methodology in the specific case of Procysbi. To address this, an understanding of the genesis of this guideline is in order.

The *Guidelines* have evolved over time to address new issues confronting the PMPRB. For example, the 2008 version of the Guidelines did not use the taxonomy set out in Table 1 above. Instead there were just three categories of new medicines:

Category 1, A new DIN of an existing or comparable dosage form of an existing medicine.
Category 2, A new DIN of a non comparable dosage form of an existing medicine, or the first DIN of a new chemical entity that is a breakthrough or provides a substantial improvement over comparable existing DINs.
Category 3, A new DIN of a non comparable dosage form of an existing medicine, or the first DIN of a new chemical entity that provides moderate, little or no therapeutic advantage over comparable existing DINs.[10]

At that time medicines that provided a moderate improvement were classed with those that provided little or no therapeutic advantage over existing medicines: they were all grouped together into Category 3 medicines. The introductory price of this class of medicines was constrained by the TCC test. There were complaints from the

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9 Fifty million euros represents something less than 1/10th of 1 percent of German expenditures on pharmaceuticals. See OECD Data, *Pharmaceutical Spending*, available at: https://data.oecd.org/healthres/pharmaceutical-spending.htm

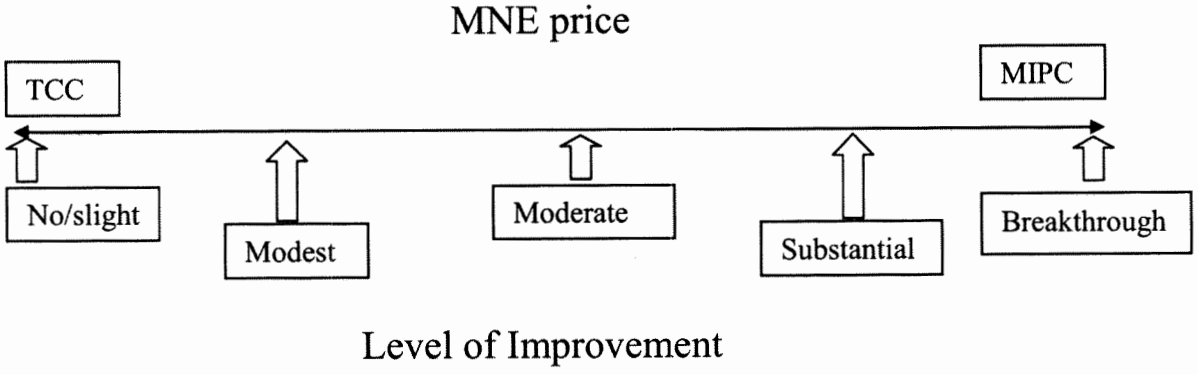
10 Patented Medicine Prices Review Board, Canada, *Compendium of Guideline, Policies and Procedures,* Revised March 2008, page 9, available at: http://www.pmprb-cepmb.gc.ca/CMFiles/comp08-e38NBY-3182008-1638.pdf

pharmaceutical industry that this categorization provided no reward for medicines that contributed modest or moderate improvements over existing medicines.[11]

These complaints were addressed in the 2009 revisions to the *Guidelines* that came into effect in 2010. Moderate improvement became a class onto itself, and the "moderate improvement test" was introduced. From an economics perspective, what PMPRB Hearing Panels and *Guidelines* revisions have done is to provide finer gradations on the spectrum of improvement. At one extreme is a new medicine that is no better than existing ones (i.e., there are substitutes that are as good as, or even superior to, the new medicine). At the other extreme are breakthrough medicines that simply have no substitutes. The task of the Panel is to place a new medicine on this spectrum.

Figure 1 sets this out schematically. As the *Guidelines* now stand, specific tests for excessive prices are suggested for four classes of medicines based on their level of improvement relative to existing medicines. These are (1) no or slight improvement, (2) moderate improvement, (3) substantial improvement and (4) breakthrough medicines. Of course additional gradations could be added if, in a specific case, a PMPRB Hearing Panel found the extant gradations inappropriate. For example, intuitively the moderate category seems to fall midway between no improvement and the breakthrough category. Certainly there are medicines that provide something less than a moderate improvement but more than a slight improvement. Call this a modest improvement; a potential fifth category.

Figure 1



Returning now to the question of whether the *Guidelines'* "moderate improvement test" is appropriate for the specific circumstances of Procysbi, it is helpful to look at how this test would be applied.

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[11] PMPRB, "Review of the Excessive Price Guidelines, Notice and Comment – Draft Revised Excessive Price Guidelines" (March 2009) available at: http://www.pmprb-cepmb.gc.ca/view.asp?ccid=1044#4

Tables 3 and 4 set out the ex-factory prices of Procysbi for the three international comparator countries as reported by Horizon Pharma in its filings with the PMPRB.[12]

Table 3
International Reference Prices at Introduction
2017 (25 mg capsule), CAD

	per capsule	per mg
U.S.	105.34	4.2136
Germany	10.45	0.4179
U.K.	10.29	0.4115
Median	10.45	0.4179

Table 4
International Reference Prices at Introduction
2017 (75 mg capsule), CAD

	per capsule	per mg
U.S.	105.34	1.4045
Germany	31.34	0.4179
U.K.	30.86	0.4115
Median	31.34	0.4179

Board Staff state that at the time of introduction of Procysbi in Canada, the Canadian price of Cystagon, the therapeutic class comparator, was $0.0077 per mg, or $0.58 per 75 mg. The *Guidelines*' suggested methodology for calculating the MNE price in this case is to compute the midpoint between the median international price and the therapeutic class comparator. The results of this exercise are shown in Figure 2. The mechanical application of the *Guidelines'* formula leads to the unexpected outcome that a moderate improvement can result in a price 2,652% greater than the therapeutic class comparator.

To put this in context, consider the case that led to the mid-point formula. In Adderall XR, the PMPRB Hearing Panel found that the extant *Guidelines* did not provide a fine enough gradation in improvement classes and therefore introduced the mid-point

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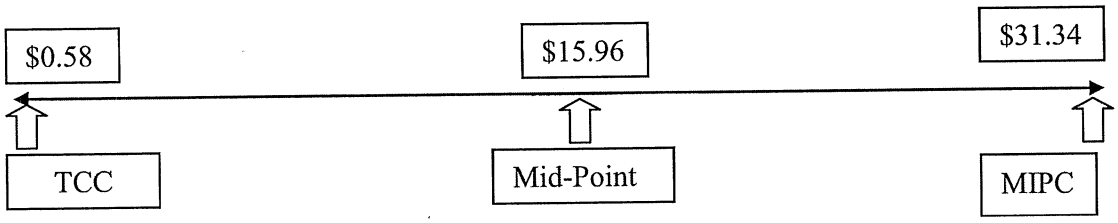
[12] Prices are taken from the Form 2, Block 5 report for the second half of 2017. Domestic currency has been converted to Canadian dollars using the *Guidelines*' methodology (i.e., a 36 month rolling average ending 4 months before the first sale of the medicine in Canada). The U.S. price is the simple average of the wholesale and FSS (Federal Supply Schedule) prices. There is no explanation for the very substantial differential between the U.S. per mg price for the 25 mg capsule and the 75 mg capsule.

formula.[13] In effect, the Panel introduced a fourth category to deal with the specific facts of the situation before it. Application of this new mid-point formula in that particular case resulted in MNE prices for the three dosages involved that ranged from 8% to 100% greater than the most expensive therapeutic class comparator. In my view it is very unlikely that the Adderall Hearing Panel or the authors of the revised *Guidelines* that included the mid-point formula envisaged a situation where the formula would allow a 2,652% premium for a moderate improvement. Note that a 100% premium over the TCC (the largest premium in the Adderall XR case) would result in a MNE price of $1.16 for a 75 mg capsule in the case of Procysbi..

Figure 2

Price per 75 mg



The placement of Procysbi on the spectrum set out in Figures 1and 2 will involve an assessment on the part of the Hearing Panel. Following the Adderall precedent, a 100% premium for Procysbi over the price of Cystagon might be in order. Alternatively, following Board Staff's premium comparison methodology would allow for an increase of 1,340% over the price of the comparator. Candidly, in my experience I cannot identify any other product that is a modest or even moderate improvement over an existing product that commands a 1,000% price premium, let alone a 2,652% premium.

3. Board Staff's Market Share Comparison

Board Staff have suggested a methodology for identifying the NEP by using market share data. The underlying objective is to price Procysbi so that total Canadian expenditures on cysteamine would be at the level that would exist if Cystagon were freely available here. If Cystagon were not available in Canada, Procysbi would have 100% of the cysteamine market. If Cystagon were available, the experience in comparator countries suggests that Procysbi would have a minor share. The procedure is to first estimate what total expenditures on cyteamine would be if Cystagon were available in

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[13] PMPRB, April 10, 2008 Decision: PMPRB-06-D3-ADDERALL XR – Merits IN THE MATTER OF the Patent Act R.S.C. 1985, c. P-4, as amended AND IN THE MATTER OF Shire BioChem Inc. (the "Respondent") and the medicine "Adderall XR", available at: http://www.pmprb-cepmb.gc.ca/view.asp?ccid=808&lang=en

Canada and Procysbi were sold at its introductory price. The second step is to estimate a price for Procysbi that would generate the same total revenues assuming it had 100% of the market. This is best seen by example.

Board Staff suggest that if Cystagon were available, Procysbi could expect a market share of 18.25% (derived from comparator countries). Assume for simplicity that the total demand for cysteamine in Canada is 1,000 mg. Table 5 shows the logic of the calculations. The second column shows the situation with Cystagon in the market, the third, without Cystagon in the market. Total revenues (or expenditures on cysteamine) in both cases are $82. In order to achieve this, Procysbi would have to be priced at $0.0819/mg in the without Cystagon scenario (i.e., in a situation where Procysbi had all of the market). Its revenues would be greater ($82 compared to $76), but its volumes would be much larger (1,000 mg compared to 183 mg).

Table 5
Market Share Methodology

	w/Cystagon	w/o Cystagon
Market Share Procysbi	18.25%	100.00%
Market Share Cystagon	81.75%	0.00%
Volume Procysbi (mg)	183	1,000
Volume Cystagon (mg)	817	0
Price/mg Procysbi	$0.4140	$0.0819
Price/mg Cystagon	$0.0077	na
Revenue Procysbi	$76	$82
Revenue Cystagon	$6	0
Total Revenue	$82	$82

This would reflect an outcome, from the payers' perspective, of a more competitive market (i.e., a market where Cystagon was freely available). While in a sense the outcome is fair to payers, in order for it to be fair to the supplier it would be necessary to ensure that the additional revenues covered the additional costs associated with additional volumes.

4. Conclusion

It remains then for the Hearing Panel to choose an appropriate placement of Procysbi on the spectrum set out in Figure 1. From an economics perspective the appropriate price is one that both adequately rewards the patentee for the improvement (assuming there is an improvement) provided by the product and at the same time protects the public interest in not going beyond that.

As noted earlier, establishing an MNE for Procysbi raises several unique challenges for the Hearing Panel. In my view these can be grouped into two main issues. First, is there a therapeutic class comparator for Procysbi? Second, if it is found that Procysbi is more than a slight improvement over a therapeutic class comparator (if there is one), is the *Guidelines*' "moderate improvement test" appropriate in the specific circumstances of this case?

With regard to the first issue, it is worth reiterating that in their financial reporting both Horizon Pharma and the developer of Procysbi, Raptor Pharmaceutical Corp., identify Cystagon as a competitor. The United States SEC requires reporting companies in their 10-k filings to describe the state of competition in the subject industry (in this case the market for cysteamine) and to identify principal competitors. The concept of a competitor in this context has a clear economic meaning. A competitor provides a substitute product (or products).

Beyond this the Hearing Panel can look to evidence from other sources. This would include scientific evidence on the composition and end use of the two medicines, and the views and behavior of other payers. My understanding is that with respect to both these sources of information there is considerable evidence that Procysbi and Cystagon are comparable which is consistent with the view that they are substitutes in an economic context. In light of this, emphasis should be placed on the price of Cystagon, both in Canada and elsewhere, in establishing the MNE for Procysbi. Put differently, there should be an emphasis on the TCC test.

It is worth noting that earlier versions of the *Guidelines* directly addressed the introductory price of modified release formulations of existing medicines. The MNE price was constrained by the prices of comparable medicines.[14] My understanding is that Procysbi is a modified release formulation of cysteamine bitartrate, a medicine that was introduced as Cystagon more than 20 years ago.

If the Hearing Panel accepts that Procysbi offers something more than a slight improvement to Cystagon, then an MNE price above the price of Cystagon would be called for. However, the extant "moderate improvement test", as set out in the *Guidelines*, is, in my opinion, inappropriate in this case. As discussed above, a mechanical application of this test would result in an MNE price so much higher than the price of the comparator that it would be difficult to defend on economic grounds. In my opinion, the facts in this case (an unreliable median international price that is so much higher than the comparator's price) require a departure from the *Guidelines*. This has happened before as the *Guidelines* cannot possibly foresee every potential contingency.

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[14] Patented Medicine Prices Review Board, Canada, *Compendium of Guideline, Policies and Procedures,* Revised March 2008, page 9, available at: http://www.pmprb-cepmb.gc.ca/CMFiles/comp08-e38NBY-3182008-1638.pdf

Indeed, when first created and applied by a Panel, the "moderate improvement test" deviated from the *Guidelines* of that period.

Ultimately, what is called for is placement of the MNE price on the spectrum set out in Figure 1. If it is concluded that the improvement is modest, then the MNE price should be proximate to the TCC price. How proximate depends upon the extent of the improvement. Once this is decided, the allowable differential between the MNE price and the TCC test price must be determined. Board Staff suggest an MNE price more than 1,000% greater than the TCC test price.

Board Staff have used three alternative methodologies for determining the MNE price at introduction for Procysbi. The results are shown in Table 6. There is a significant range in values. Clearly the TCC test using the Canadian price of Cystagon results in the lowest maximum price, and the highest excess revenue estimate. The modified "moderate improvement test" using the PMPRB[7] price of Cystagon yields the highest allowable introductory price and the lowest estimate of excess revenues. There is no clear best methodology as this will depend upon the Hearing Panel's conclusion with regard to the degree of improvement, if any, that Procysbi offers. If the conclusion is not more than "slight", the TCC test is most appropriate. If the conclusion is something more than "slight" but less than "moderate" the modified "moderate improvement test" would appear to me to be the best choice, albeit this would lead to a MNE price very much greater than the comparator's price.

Table 6
Board Staff Results

	25mg/ capsule	150mg/ capsule	Total excess revenues (millions $)
TCC (using price of Cystagon in Canada)	$0.19	$0.57	3.1543
TCC (using price of Cystagon in PMPRB[7])	$0.46	$1.39	3.0693
Market share methodology (excluding Germany)	$0.81	$2.43	2.9625
Market share methodology (including Germany)	$2.05	$6.14	2.5779
Modified "moderate improvement test" (using price of Cystagon in Canada)	$2.76	$8.27	2.3582
Modified "moderate improvement test" (using price of Cystagon in PMPRB[7])	$2.96	$8.88	2.2945

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"The Organization of Vertically Related Transactions in the Canadian Forest Products Industries," (with S. Globerman), *Journal of Economic Behavior and Organization*, Vol. 7, 1986, pages 199-212

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"Structural Change in the Canadian Pacific Salmon Fishery," *The Canadian Journal of Regional Science*, No. 2, Autumn, 1984, pages 195-210

"Structure of the British Columbia, Washington and Oregon Hotel Industries--A Comparative Analysis," (with T. Var) *Journal of Travel Research*, No. 1, Summer, 1980, pages 2-8

"Advertising, Direct Foreign Investment and Canadian Identity," (with B. Schoner), *Canadian Review of Studies in Nationalism*, No. 1, Spring, 1980, pages 127-150

"The Pearse Commission and Industrial Organization of the British Columbia Forest Industry," *B.C. Studies*, No. 41, Spring, 1979, pages 3-35

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"Bank Act Revision in Canada: Past and Potential Effects on Market Structure and Competition," (with James W. Dean) *Banca Nazionale del Lavoro--Quarterly Review*, No. 116, March 1976, pages 19-49

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Consultancy

A. Expert Testimony

Competition Tribunal, *Director of Investigation and Research and Chrysler Canada* Ltd. (testified for the Crown)

Court of Queen's Bench of Alberta, *Ed Miller Sales & Rentals Ltd. v. Caterpillar Tractor Co. et al.* (testified for the plaintiff)

National Transportation Agency of Canada, Review of the proposed acquisition of Purolator Courier Ltd. by Canada Post (testified for Canada Post)

Competition Tribunal, *Director of Investigation and Research and Air Canada et al.* (testified for The Gemini Group)

Ontario Court, General Division, *Polaroid Canada Inc. and Continent-Wide Enterprises Ltd.*, (testified for the respondent)

Competition Tribunal, *Director of Investigation and Research and Tele-Direct (Publications) Inc.* (testified for the Crown)

Ontario Energy Board, *E.B.O 177-17*, (testified for Union Gas)

Competition Tribunal, *Competition Commissioner and Superior Propane Inc.* (testified for the Crown)

Ontario Energy Board, *RP-2000-0078*, (testified for Union Gas)

Ontario Energy Board, *EB-2005-0551*, (testified for Union Gas)

Patented Medicine Prices Review Board, *In the Matter of Sanofi Pasteur and the Mediciens Quadracel and Pentacel* (testified for Board Staff)

Patented Medicine Prices Review Board, *In the Matter of Ratiopharm Inc. and the Medicine Ratio-Salbutamol HFA* (testified for Board Staff)

Patented Medicine Prices Review Board, *In the Matter of Alexion Phrmaceuticals Inc. and the medicine Soliris* (testified for Board Staff)

B. Consulting engagements

Government of Canada, Competition Bureau. Advised the Crown with respect to investigations involving the following industries.

Plywood manfacture	Automobile parts distrb.	Computer maintenance
Dairy processing	Coffee services	Distilling
Petroleum refining	Flour milling	Book retailing
Gasoline distribution	Sanitary tissues	Propane distribution
Newsprint manufacture	Directory advertising	Newspaper publishing/t.v
Oilfield cleanup service	Grain handling	Photocopier maintenance
Railroads	Lumber manufacture	Semiconductors

Private Antitrust Consultancy. Advised clients engaged in the following industries.

Heavy equipment distrb.	Small parcel express services	Natural gas distribution
Rail freight forwarding	Photographic film distribution	Automobile parts distrb.
Pesticide distribution	Brewing	Electronics retailing
Tug & barge transportation	Feed additives	Electricity generation
Natural gas appliance rentals	Natural gas storage	Mining wear-parts mfg.
Real estate brokerage	Specialty TV channels	Fish processing
Dredging	Automobile distribution	Bleaching chemicals
Coastal ferry service	Dental Services	Tobacco products
Annuity brokerage	Shipbuilding/repair	Baking

Government of Canada, Patented Medicine Prices Review Board Staff, Advised Board Staff with respect to investigations involving:

Vaccines	Multi-dose inhalers

Government of British Columbia, Ministry of Forests, Lands and Natural Resource Operstions, Advised Staff with respect to:

Woodlands mergers	Public timber auctions	Harvesting transfers

TABB

IN THE MATTER OF the *Patent Act*, R.S.C. 1985, c. P-4, as amended AND IN THE MATTER OF Horizon Pharma (the "Respondent") and the medicine Cysteamine Bitartrate sold by the Respondent under the trade name "Procysbi"

I, Dr. Julian P. Midgley, resident in Calgary, in the province of Alberta, declare that

a) I have been retained Perley-Robertson, Hill & McDougall LLP to provide evidence in the matter of the *Patent Act*, R.S.C. 1985, c. P-4, as amended and in the matter of Horizon Pharma (the "Respondent") and the medicine Cysteamine Bitartrate sold by the Respondent under the trade name "Procysbi";
b) it is my duty to provide evidence in relation to this proceeding as follows:
   i) to provide opinion evidence that is impartial,
   ii) to provide opinion evidence that is related only to matters that are within my area of expertise, and
   iii) to provide any additional assistance that the Board may reasonably require to determine a matter at issue.
c) I acknowledge that the duties referred to above take precedence over any obligation which I may owe to any party by whom or on whose behalf I am engaged.

Dated at Calgary, Alberta this 9 day of September, 2019.

Dr. Julian P. Midgley

ZUREEN KAZMI
BARRISTER AND SOLICITOR

A COMMISSIONER FOR OATHS IN AND FOR ALBERTA
NOTARY PUBLIC IN AND FOR ALBERTA BY VIRTUE OF STATUS AS A LAWYER UNDER S. 3(1)(b) of *NOTARIES AND COMMISSIONERS ACT* OF ALBERTA. MY COMMISSION DOES NOT EXPIRE.

IN THE MATTER OF the *Patent Act*, R.S.C. 1985, c. P-4, as amended AND IN THE MATTER OF Horizon Pharma (the "Respondent") and the medicine Cysteamine Bitartrate sold by the Respondent under the trade name "Procysbi"

I, DR. JULIAN P. MIDGLEY, hereby certify that:

The attached report titled "Expert Report – Julian Midgley" dated September 9, 2019 and signed on September 9, 2019 is my testimony pursuant to Rule 8 of the Patented Medicine Prices Review Board Rules of Practice and Procedure.

Dr. Julian P. Midgley

September 9, 2019

SWORN BEFORE ME in the City of Calgary, in the Province of Alberta, on

September 9, 2019

(A Commissioner of Oaths)

ZUREEN KAZMI
BARRISTER AND SOLICITOR

A COMMISSIONER FOR OATHS IN AND FOR ALBERTA
NOTARY PUBLIC IN AND FOR ALBERTA BY VIRTUE OF STATUS AS A LAWYER UNDER S. 3(1)(b) of *NOTARIES AND COMMISSIONERS ACT* OF ALBERTA. MY COMMISSION DOES NOT EXPIRE.

Expert Report – Julian Midgley

Nature of Clinical Practice

As an associate professor at the Cumming School of Medicine and Staff paediatric nephrologist at the Alberta Children's Hospital (ACH), Calgary for 25 years I have been involved in the care of patients with cystinosis since 14 September 1994. Currently I am the primary nephrologist, for cystinosis care, for 18 patients. The first patient was seen nearly 25 years ago and the most recent patient to the clinic was first seen 6 months ago. The duration of care at the ACH cystinosis clinic has been for an average of 12.3 years with a total of 221 patient-years. In addition I have been involved in the care of a patient who has primarily been followed by one of my colleagues at ACH for 13.6 years. Three other patients have been seen for an average of 2.2 years but are no longer followed because of death, followed in their own province (although due to be seen later this year at ACH) and a move to a different province. Of the 18 patients that I currently follow 13 have been followed from their initial diagnosis and 10 are adults (>18 years of age).

Patient Demographics

	All patients ever seen at ACH	Currently followed by me	Followed Since Diagnosis
Number	22	18	13
Median (range) age at diagnosis (years)	1 (0.1 – 11)	1 (0.1 – 11)	1 (0.1 – 2.7)
Average current age (years)*	21.5 (1.3 – 54.1)	21.1 (4.2 – 52.7)	15.9 (4.2 – 28.5)
Average duration of follow up (years)+	11 (0.2 – 24.9)	12.3 (0.5 – 24.9)	14.6 (3.2 – 24.9)

For the three patients no longer seen at ACH

*age of death or age when followed elsewhere used

+duration until death or followed elsewhere used

Cysteamine Preparation Currently Used

Of the 18 patients currently followed 8 take immediate release (IR) cysteamine and 10 delayed release (DR) cysteamine.

Of the 10 who currently take DR cysteamine 5 switched from IR cysteamine after enrollment in a clinical trial and the other 5 have started taking DR cysteamine since the medication has been available in Canada.

Of the 8 who currently take IR cysteamine 7 have never switched medication while one switched to DR cysteamine after enrolling in a clinical trial but converted back to IR cysteamine because of worse gastrointestinal adverse effects.

Those taking IR cysteamine are younger with an average age of 10.6 years (4.2 to 18.8) compared to those taking DR cysteamine who are on average 29.4 (17.3 to 52.7) years old.

Two patients, followed from diagnosis at ACH, started DR cysteamine after enrolment into a clinical trial. Thus the longest duration of use of DR cysteamine, amongst the 10 taking this medication, is 9 years for these two patients.

Therapeutic Effect of IR Cysteamine compared to DR Cysteamine

The therapeutic effect of cysteamine is primarily assessed by white blood cell (WBC) cystine levels. WBC cystine levels have been similar before and after a change from IR cysteamine to DR cysteamine. Four patients at ACH that have switched directly from IR to DR cysteamine, since the latter was available in Canada, have had WBC cystine levels measured by the ACH laboratory before and after the switch. These have all continued to be below the target for WBC cystine. Average levels (of 3 measurements taken at 3 monthly intervals) before and after the switch were somewhat higher in one patient and somewhat lower in three patients.

Before	0.24	0.38	0.21	0.23
After	0.14	0.43	0.07	0.18

Average (n=3) WBC cystine levels before and after a switch from DR to IR cysteamine for 4 patients (nmol ½cystine/mg protein). Target level using the ACH laboratory assay is <0.5 nmol ½cystine/mg protein.

Of these four patients that have switched directly from IR to DR cysteamine the dose (in mg/day) has not been decreased except in one patient, with a 17% dose reduction, after a recent kidney transplant.

An advantage of DR cysteamine, reported by patients, is that it is only taken twice a day rather than the four times a day for IR cysteamine. This is likely to be an advantage for teenagers and adults who are more likely to miss doses rather than younger children who have their medication regimen controlled by their parents.

There has been no clear difference, either in the self-report by patients or clinical observations in clinic, of the halitosis/body odour of patients taking DR cysteamine versus when they were taking IR cysteamine.

A significant disadvantage of DR cysteamine, reported by patients, is the number of capsules that have to be swallowed at any one time. This is four times the number compared to IR cysteamine as the medication is taken half the number of times in the day and the largest capsule (content in mg of cysteamine) is half that of IR cysteamine.

From my observations clinical outcomes are not different when taking DR cysteamine compared to IR cysteamine. For cystinosis patients the clinical outcomes that are very important are the onset of end stage kidney disease requiring dialysis or a kidney transplant and the onset of other significant organ dysfunction such as pancreatic insufficiency (diabetes mellitus), hypothyroidism, muscle weakness (myopathy) or hypogonadism (in males). The time taken for these clinical outcomes to occur are long compared to the length of time that I have observed patients taking DR cysteamine. Therefore, not surprisingly, there have been no new occurrences of these four important clinical outcomes in the patients at ACH taking DR cysteamine. Although one patient who was in a clinical trial and therefore has taken DR cysteamine for 9 years had normal kidney function up until the time of switch to DR cysteamine but had a significant progressive decrease in glomerular filtration rate that started coincident with the switch (however this could be the natural progression of the disease just happening to coincide with the switch).

Given the relatively short period of observation the patients taking DR cysteamine a difference in prognosis or life expectancy compared to taking IR cysteamine cannot be anticipated and I would not offer this as a definite advantage or disadvantage when discussing a switch.

Adherence to Treatment

It is generally recognized that adherence to long-term medication is difficult and that medications that require less frequent dosing during a day to achieve a desired effect are preferred because of improved adherence to the regimen. IR cysteamine should be ingested every 6 hours and this is even more difficult than four times a day because a dose is taken during the usual hours of sleep. Patients with cystinosis are usually diagnosed at about a year of age and four times a day dosing of electrolyte supplements as well as

IR cysteamine is onerous for families but, with administration via a G-tube and the almost invariable determinedness of parents, this regimen for medications works well in almost all families. One family we follow in Calgary were very keen, many years ago, to change to an every 8 hour administration of IR cysteamine which, although likely less optimal, seemed to work reasonably well. This family switched to DR cysteamine once it was available in Canada.

The every 12 hour administration of DR cysteamine is, from the experience in Calgary, desirable for teenagers and adults and is demonstrated by the observation that 9 of the 10 patients now over 18 years of age (one converted back to IR cysteamine) are currently taking DR cysteamine and that 7 of the 8 patients under 18 years of age continue to take IR cysteamine (one taking DR cysteamine is a younger brother of a 24 year old taking DR cysteamine).

The increased adherence from an every 12 hour regimen of DR cysteamine theoretically may result in clinically meaningful difference in outcomes. This has not been observed in the cohort of patients in Calgary although there are relatively few patients treated for a relatively short time (in most patients) with DR cysteamine to observe these longer term outcomes. Whether the possibly more consistent depletion of WBC cystine levels below target levels, given enough time, will be associated with better outcomes may only become apparent over 10 to 15 or more years.

While WBC cystine levels are a surrogate marker for the clinical outcomes of importance they likely only reflect the adherence to the use of cysteamine over the previous days (or perhaps a week). However when measured every 3 months WBC cystine levels may act as a periodic (but not particularly frequent) reminder of the reasons for adherence to cysteamine treatment.

Many other factors, in addition to the frequency of medication administration, likely contribute to adherence to treatment. These include parent/family motivation, support for families including that from the clinic as well as peer support. Clinical observation of the cohort of patients in Calgary suggests a better than usual outcome for the 13 patients that have been followed exclusively in Calgary from the time of diagnosis. Only one has received a kidney transplant before 18 years of age and two others received a transplant at 20 and 24 years of age; the three other adults have decreased but reasonable native kidney function. This experience, of a generally good outcome, has occurred mostly during the time of use of IR cysteamine and certainly the families believe that the consistent care at ACH with several patients with cystinosis has contributed to these good outcomes likely by several factors increasing adherence to treatment.

Administration of IR Cysteamine and DR Cysteamine

The administration of IR cysteamine and DR cysteamine capsules to adolescents and adults is similar in that the capsules are fairly equal in size. The main difference in the administration is the 4 fold increase in the number of capsules taken at any one time (doubled by the fact that the largest capsule size (in mg of cysteamine) for DR cysteamine is half that of IR cysteamine and doubled again by the every 12 hour administration rather than every 6 hours).

The administration requirements in the monograph for DR cysteamine are several: taking DR cysteamine on an empty stomach/spacing in time from food and bicarbonate or carbonate containing medications. This is different to IR cysteamine administration which has no special administration requirements although we recommend taking the medication, when possible, with the same food each time. These requirements for DR cysteamine are perceived by some families as a barrier to a switch from IR cysteamine to DR cysteamine especially in those who are using liquid medications in children who also receive food supplements to achieve adequate growth.

In younger children a G-tube is often used for medication administration. This is possible for DR cysteamine but we have not had the clinical experience of this in Calgary as all the patients taking DR cysteamine are old enough to swallow capsules. The description in the product monograph of mixing DR cysteamine granules with applesauce to administer the medication via a G-tube seems relatively complex and specifically prohibits the mixing of granules in batches e.g. for a day. Recently, when describing this procedure to a parent with a younger child taking IR cysteamine, as laid out in the monograph with 6 separate steps, their reaction was that it seemed much more complex than their current G-tube administration of IR cysteamine. The six steps describe the mixing of the granules in applesauce with a flush of orange juice using a different syringe. This is different to the practice that we have adopted for decades of preparation of a mixture of a day's worth of IR cysteamine capsule contents in water (enough for four doses or a day's medication requirement).

Access to IR Cysteamine

In Canada access to IR cysteamine has always been and continues to be through the Heath Canada Special Access Program (SAP). Prior to the marketing of DR cysteamine access to IR cysteamine via SAP was not at all difficult. For up to 20 years periodic, 6 monthly, Special Access Requests were completed for each patient to ensure a continued supply of IR cysteamine. Funding for IR cysteamine obtained through SAP used to be somewhat problematic as private insurers would rarely cover the costs of the medication without a DIN but this has not been a substantial issue for many years in Alberta because of the Short Term Exceptional Drug Therapy (STEDT) program.

When DR cysteamine received a NOC access to IR cysteamine immediately became problematic as SAP started denying Special Access Requests despite the fact that the commercial DR cysteamine product was not yet available in Canada. Even when available the fact that DR cysteamine could not be funded (no family, without private drug insurance, could possibly afford to pay for the medication and no provincial funding mechanism was initially in place) was not a sufficient reason to allow access to IR cysteamine through SAP. In Calgary we were able to maintain uninterrupted access to IR cysteamine through SAP using legitimate clinical reasons although, at least initially, special phone conversations with SAP staff and limits to the length of the approval of a SAP request were also required.

Adverse Effects

In clinical use there does not appear to be a substantial difference in adverse effects between IR cysteamine and DR cysteamine. Clinically the most important adverse effects are gastrointestinal (GI) symptoms of vomiting, anorexia, diarrhea, nausea and abdominal pain/discomfort. Individual patients generally seem to tolerate either preparation of cysteamine similarly with variation of more or less adverse effects among patients. However there are exceptions. One patient with adolescent onset cystinosis historically had not been able to tolerate IR cysteamine and now tolerates the required dose of DR cysteamine. One patient, who has recently started to come to the Calgary cystinosis clinic, started DR cysteamine in a clinical trial but was unable to continue in the longer-term and switched back to IR cysteamine because of increased GI adverse effects. Most patients that have switched to DR cysteamine generally have tolerated IR or DR cysteamine similarly. Some patients with more GI symptoms prior to the switch continue with similar GI symptoms after the switch while others, with relatively few GI symptoms on IR cysteamine, continue likewise after the switch.

Clinically halitosis is not substantially different although some patients believe there has been an improvement. However an improvement may not be sufficient as one older patient has discovered. They have not been able to find continued employment after training as a dental assistant with the reason given that the dental patients dislike their halitosis/body odour.

Julian Midgley BM BCh, MRCP(UK), FRCPCH, DCH
Paediatric Nephrologist
Alberta Children's Hospital
Associate Professor
Department of Paediatrics
Cumming School of Medicine

August 2019

TAB4

TABA

PATENTED MEDICINE PRICES REVIEW BOARD

IN THE MATTER OF the *Patent Act*,
R.S.C., 1985, c. P-4, as amended

AND IN THE MATTER OF
Horizon Pharma (the "Respondent")
and the medicine Cysteamine Bitartrate sold by the Respondent under the trade name PROCYSBI®

EXPERT REPORT OF DR. CRAIG B. LANGMAN

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Counsel to Respondent,
Horizon Pharma

TABLE OF CONTENTS

Page

PATENTED MEDICINE PRICES REVIEW BOARD

IN THE MATTER OF the *Patent Act*,
R.S.C., 1985, c. P-4, as amended

AND IN THE MATTER OF
Horizon Pharma (the "Respondent")
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EXPERT REPORT OF DR. CRAIG B. LANGMAN

I, Craig Bradford Langman, M.D., of the City of Chicago in the State of Illinois in the United States of America, provide the following statement of the evidence that I propose to present at the trial of the above referenced proceeding.

QUALIFICATIONS

1. I am the Division Head, Kidney Diseases at the Northwestern University Medical School and the Northwestern Memorial Hospital. I have previously served as the Associate Chair of Pediatrics for Research Program Development in the Department of Pediatrics at Northwestern University Medical School. I am also currently the head of the Senior Thesis Program at the Feinberg School of Medicine (called Area of Scholarly Concentration).

2. I am a Board Certified Pediatric Nephrologist. I received my certification for the National Medical Boards in 1978, from the American Board of Pediatrics in 1982.

3. I maintain privileges as Senior Attending Physician in the Division of Nephrology at the Ann and Robert H Lurie Children's Hospital of Chicago and as an Associate Physician in the Department of Pediatrics at Northwestern Memorial Hospital.

4. I have been interested in cystinosis since my residency, when I encountered for the first time a patient with cystinosis. I have treated or consulted upon dozens of patients with

nephropathic cystinosis[1] since the early 1980s. There are few pediatric nephrologists in the United States who have treated as many cystinosis patients as I have, including with PROCYSBI® and Cystagon and, prior to the availability of PROCYSBI® and Cystagon, phosphocysteamine.

5. I was the lead investigator on the first clinical trial involving the drug PROCYSBI, entitled Study RP-103-03. (As I discuss in more detail below, Study RP-103-03 was also the first time that the drug Cystagon was the subject of a formal clinical trial in a population of patients with cystinosis).

6. My background and qualifications are set out in my *curriculum vitae*, a copy of which is attached as **Exhibit "1"** to my report.

MANDATE AND ISSUES TO BE ADDRESSED

7. I understand my obligations as an expert witness in this proceeding. A copy of my signed declaration attesting to my acknowledgement of and adherence to these obligations is attached as **Appendix "A"**.

8. Counsel for Horizon has asked me to provide background information relating to:

(a) cystinosis;

(b) the effects of the disease, if untreated;

(c) the various historical and current treatment options for cystinosis patients, including:

(i) dialysis;

(ii) kidney transplant;

(iii) Cystagon; and

(iv) PROCYSBI.

[1] In this report, I refer to nephropathic cystinosis as "cystinosis" for simplicity. However, there are other types of cystinosis that have different manifestations and treatments.

9. I have also been asked to provide my views with respect to each of these treatment options.

10. I have also been asked to provide Counsel to Horizon with my comments on the literature that was discussed, and the statements made in the following documents:

(a) CADTH Clinical Review Report, dated February 2018

(b) CADTH Pharmacoeconomic Report, dated February 2018;

(c) CADTH Final Report, dated January 2018;

(d) New Medicine Scientific Review, dated January 12, 2018;

(e) HDAP New Medicine Review, dated February 26, 2018;

(f) New Medicine Review Issue Paper, dated April 27, 2018; and

(g) HDAP New Medicine Review, dated May 7, 2018.

11. In order to answer the questions above, I have reviewed the following materials:

(a) The Clinical Review, Pharmacoeconomic, and Final Reports prepared by CADTH;

(b) New Medicine Scientific Review, dated January 12, 2018;

(c) HDAP New Medicine Review, dated February 26, 2018;

(d) New Medicine Review Issue Paper, dated April 27, 2018; and

(e) HDAP New Medicine Review, dated May 7, 2018.

12. I was also asked whether I agree with the following statements:

(a) Treatment with cysteamine bitartrate significantly delays the need for kidney transplant and substantially increases patients' lifespans, even after transplant.

(b) There is no therapeutic advantage between PROCYSBI and Cystagon: neither is inferior to the other in terms of efficacy of treatment, and both lead to the same therapeutic outcome.

(c) PROCYSBI offers no clinical therapeutic advantage -- its only advantage is a reduction in dosing schedule, which may result in increased compliance rates.

13. I have also been asked to provide a summary of my opinions, which I provide in the following section.

SUMMARY OF OPINIONS

Scientific Background

14. ***Cystinosis.*** Cystinosis is caused by a genetic deletion or mutation in the patients' DNA. DNA is the genetic code responsible for making proteins and other biological components required by the body to sustain life. In patients with cystinosis, a part of the required genetic code is missing (an irreparable condition) or (in a smaller percentage of patients) mutated, meaning that the body cannot make the components necessary for the sustenance of life. In the case of cystinosis, this means that the body is incapable of clearing out cysteine, a non-essential amino acid which accumulates in the cell organelle[2] called a lysosome, among others. This cysteine build-up occurs throughout the body, but is particularly hard on the kidneys, as it causes both the filtering portion of the kidney (termed the glomerulus) and the resorbing part of the kidney (termed the proximal tubule) to fail and, absent treatment, inevitably results in end stage renal failure and kidney transplantation.

15. The disease most commonly presents itself in the early years of life. Cystinosis generally presents with several symptoms, including vomiting, failure to thrive, recurrent fevers and episodes of dehydration. The diagnosis is confirmed with biochemical tests (glucose in the urine; cysteine crystals in the eyes; elevated white blood cell cystine ("WBC cystine") levels). If left untreated, cystinosis inevitably results in end stage renal disease, requiring dialysis and/or kidney transplantation. Even when treated, because of its systemic prevalence throughout the body, cystinosis often ends in early death, usually from muscular myopathy. (In addition to impacting major organs and particularly the kidneys, the disease adversely impacts major muscle groups,

[2] An organelle is a cellular structure that performs specific functions within a cell.

including those required for breathing and swallowing). Death can occur as early as the third decade of life.

16. ***The history of treatment options.*** Over the course of my career, I have seen the development of the treatment of cystinosis, from no treatment to the current standard of care using PROCYSBI. When I say "no treatment," I mean precisely that. In the early days of treatment, we were literally watching babies die: because these infants had a life-long condition which inevitably led to a short life and death, they were not considered candidates for dialysis or kidney transplant.

17. Dr. Thoene was the first to show that the administration of cysteamine, in a lab setting (*i.e.*, not in humans), was able to remove cysteine from the lysosome.[3] Ultimately, a novel compound called phosphocysteamine was developed and made available for administration to patients. This was a noxious compound with serious side effects, including side effects relating to the intense bad smell of the compound, and, subsequently in patients. Although this was an undesirable drug, it was the only alternative to no treatment, and certain death.

18. Immediate release cysteamine bitartrate (known commercially as Cystagon) was made available in 1994. In clinical practice, Cystagon had limitations. Its administration required strict adherence to a dosing regimen such that it had to be administered every six hours around the clock. The drug generated a foul-smelling by-product, meaning the patients smelled like rotten eggs and suffered bad breath (halitosis). (In my clinic, we would have to fumigate a treatment room after seeing a patient with cystinosis on Cystagon in order to see another patient). These patients suffered from social isolation, stigma, and sleep deprivation. On this latter point, patients on Cystagon are never able to sleep through the night. This is also true of parents and caregivers, who must also be up in the night with their young children.

19. Further, Cystagon is associated with significant gastrointestinal (GI) issues, as it is released and absorbed in the stomach. It causes nausea, ulcers and vomiting (a serious concern, given the importance of adhering to a strict dosing regimen where missed doses are serious). This adds to the burden of the disease itself, which is itself associated with emesis.

[3] The "lysosome" is an organelle in the cytoplasm of cells containing enzymes, all enclosed in a membrane.

20. All these negative effects—the rotten egg smell, the halitosis, the GI effects—lead to non-adherence. The effect on the patient and the family unit is severe. Even in the case of children whose parents can strictly adhere to the treatment protocol, by the teenage years, the adherence rates among patients fall off dramatically. There is substantial literature that shows that, over time, the vast majority of patients will not adhere to the strict every six-hour regimen around the clock.[4] Lack of adherence means poor clinical outcomes: over time, WBC cystine levels (the common biomarker used to assess the level of cysteine build-up) increase for patients.[5]

21. In part because of the significant problem with adherence, patients on Cystagon generally experience a steady decline in kidney function, which progresses as patients mature into young adults. There is emerging literature that sleep deprivation and interrupted sleep in adults exacerbates the progression of chronic kidney disease.[6] I would expect that there would be no reason for this data to be any different in children. If the goal of treatment in cystinosis is the maintenance of kidney function, these patients were not going to realize this goal. Indeed, there is no literature showing that Cystagon leads to stable kidney function in the majority of patients in the long term. The literature shows that, even with the administration of Cystagon, kidney function worsens over time, in the overwhelming majority of patients.[7]

22. ***Studies of PROCYSBI.*** I was the lead investigator in the Clinical Trial RP-103-03 which was the clinical trial conducted as part of the approval process of PROCYSBI in the United States (and, I believe, elsewhere in the world, including Europe). In this clinical trial, I studied

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[4] Levtchenko, E.N. *et al.,* (2006) Strict cysteamine dose regime is required to prevent nocturnal cystine accumulation in cystinosis, Pediatr Nephrol 21:110-113; Ariceta, G. *et al.,* (2015) Cysteamine (Cystagon) adherence in patients with cystinosis in Spain: successful in children and a challenge in adolescents and adults, Nephrol Dial Transplant 30:475-480.

[5] Levtchenko, E. *et al.,* (2006) Strict cysteamine dose regimen is required to prevent nocturnal cystine accumulation in cystinosis, Pediatr Nephrol 21(1):110-113; Brodin-Sartorius, A. *et al.,* (2012) Cysteamine therapy delays the progression of nephropathic cystinosis in late adolescents and adults, Kidney Int 81(2):179-189; Ariceta, G. Cysteamine (Cystagon®) Adherence in patients with cystinosis in Spain: Successful in Children and Challenge in Adolescents and Adults, Nephrol Dial Transplant 30(3):475-480.

[6] Yamamoto, R. *et al.,* (2018) Sleep quality and sleep duration with CKD are associated with progression to ESKD, Clin J Am Soc Nephr 13:1825-1832; Ricardo, A. *et al.,* (2017) The association of sleep duration and quality with CKD progression, J Am Soc Nephrol 28:3708-3715; Turek, N. *et al.,* (2012) Sleep Disturbances as Nontraditional Risk Factors for Development and Progression of CKD: Review of the Evidence, Am J Kidney Dis 60(5):823-833.

[7] Nesterova, G. *et al.,* (2015) Cystinosis: renal glomerular and renal tubular function in relation to compliance with cystine-depleting therapy, Pediatr Nephrol 30:945-951; Nesterova, G. *et al.,* (2008) Nephropathic cystinosis: late complications of a multi-systemic disease, Pediatr Nephrol 23: 863-878; Markello T.C. *et al.,* (1993) Improved renal function in children with cystinosis treated with cysteamine, N Engl J Med 328:1157-62.

the efficacy of Cystagon compared to the efficacy of PROCYSBI for the control of the biomarker of the disease, WBC cystine. This study is referred to as a non-inferiority study, and its purpose was not to show that PROCYSBI was better than Cystagon. Rather, the study was only designed to determine whether PROCYSBI was inferior to Cystagon in terms of efficacy and in terms of control of the WBC cystine biomarker. The study was designed with this endpoint in mind.

23. For the trial, we took patients who were well controlled on Cystagon (those with the highest rates of adherence, and whose glomerular filtration rate (GFR)[8] was >30 at the outset) and, using a randomized controlled crossover study, exposed each of these patients to both drugs in different arms of the study. We felt it unethical to do a placebo-controlled study for these purposes, as we know that the absence of a cystine depleting agent would produce steady and irreversible damage to the patient's kidney function and other organs.

24. The patients who were enrolled in RP-103-03 were offered the opportunity of continuing treatment with PROCYSBI in an extension study. In the extension study, called RP-103-04, patients were given the choice of staying on PROCYSBI for two years or returning to Cystagon therapy. 40 out of 41 patients from RP-103-03 chose to remain on PROCYSBI and entered RP-103-04.[9] The study demonstrated, over two years, that PROCYSBI was able to maintain the

[8] Glomerular filtration rate (GFR) is a measure of the function of the kidneys. This test measures the level of creatinine in the blood and uses the result in an estimating formula to calculate a number that reflects how well the kidneys are functioning. Glomerular is a term that relates to the glomeruli, the filters in the kidneys that allow waste products to be removed from the blood. Healthy kidneys filter about 200 quarts of blood every day and produce about 2 quarts of urine. The GFR refers to the amount of blood filtered by the glomeruli per minute. As a person's kidney function declines due to damage or disease, the filtration rate decreases, and waste products begin to accumulate in the blood.

[9] A "crossover study," or crossover trial, is a study in which subjects receive a sequence of different treatments (or exposures) over time. Crossover designs are common for experiments in medicine. Patients are randomized between treatment arms. A cohort of patients will begin with Drug A (or placebo), while the alternate randomly assigned cohort begins with Drug B (or placebo). After a period of time (and after a washout period in some cases) the patients continue taking the drug administered in the opposite arm: *e.g.*, those taking Drug A now take Drug B; those taking Drug B continue with Drug A. In a randomized clinical trial, the subjects are randomly assigned to different arms of the study which receive different treatments. Nearly all crossover trials are designed to have "balance," whereby all subjects receive the same number of treatments and participate for the same number of periods. In most crossover trials each subject receives all treatments, in a random order. A crossover study has two advantages. First, the study has its own internal control: each crossover patient serves as their own control. In statistical terms, the influence of confounding covariates is reduced, whereas in a randomized non-crossover study it is often the case that different treatment-groups are found to be unbalanced on some covariates. In a controlled, randomized crossover design such imbalances are implausible (unless covariates were to change systematically during the study). Second, optimal crossover designs are statistically efficient, and require fewer subjects than do non-crossover designs.

WBC cystine biomarker in an ideal range and was associated with statistically significant improvements on quality of life (using a standardized test).

25. Aside from the fact that RP-103-03 was the first time that Cystagon had ever gone into a formal clinical trial, that study and RP-103-04 showed that PROCYSBI was able to control WBC cystine levels and, in addition, deliver improvements in quality of life and other important benefits. Additionally, we have shown that PROCYSBI is able to control the biomarker WBC cystine over time and (particularly in young children naïve to cysteine-depleting therapy) is thereby able to prevent the inhibition of maturation of kidneys seen in patients with cystinosis and patients initially treated with Cystagon.[10]

26. If I were asked to do a clinical trial comparing Cystagon with PROCYSBI, I would decline to do so. I would find it unethical to administer Cystagon to a patient given the superiority of PROCYSBI simply for the purposes of performing an evaluation which does not need to be conducted: PROCYSBI is at least as effective as Cystagon as demonstrated in our studies, and much more so given our recent data, mentioned above. It would be even more problematic to give cystinosis patients a placebo for the reasons I have explained above. Further, there is no need to extend the RP-103-04 study, given the statistically significant improvements shown in that study.

27. ***My clinical experience with Cystagon.*** These improvements are corroborated by real-world experiences. I currently treat or consult upon approximately 40 patients with cystinosis and switched patients from Cystagon to PROCYSBI when it became available. Where I have done so, none of my patients have switched back to Cystagon.

28. In my view, PROCYSBI is superior to Cystagon for several reasons:

As I discuss in more detail later in my report, it was not possible to use placebo or washout periods in the crossover trial that I refer to as RP-103-03. To do so such would require the cessation of therapy to patients that cannot, at any time, go off therapy, which would be unethical.

[10] Vaisbich, M. *et al.,* (2018) Maturation of Renal Function in Young Children with Nephropathic Cystinosis Treated A Priori With Delayed-Release Cysteamine Bitratrate, (Poster 385); Langman *et al.,* (2012) A randomized controlled crossover trial with delayed-release cysteamine bitartrate in nephropathic cystinosis: effectiveness on white blood cell cystine levels and comparison of safety, Clin J Am Soc Nephrol 7:1112-1120; Langman *et al.,* (2014) Quality of Life is improved and kidney function preserved in patients with nephropathic cystinosis treated for 2 years with delayed-release cysteamine bitartrate, J Pediatr 156(3):528-533 e521; Markello T.C. *et al.,* (1993) Improved renal function in children with cystinosis treated with cysteamine, N Engl J Med 328:1157-62.

(a) ***Improved pharmacokinetics.*** PROCYSBI has different release characteristics than Cystagon. It is delivered to the small intestine, as opposed to being released and absorbed in the stomach. This is beneficial, as it lessens the likelihood of ulcers in the stomach and leads to the ability to administer it only every twelve hours, therefore eliminating the need for a nighttime dose.

(b) ***Reduced side effects.*** PROCYSBI is associated with a reduction in GI adverse events and the elimination of sleep deprivation. PROCYSBI's pharmacokinetic profile also eliminates or significantly diminishes the halitosis and "rotten egg" gas associated with the elevated peak serum concentration of immediate release cysteamine bitartrate. Additionally, cystinosis is associated with bone wasting disease and it is not uncommon for cystinosis patients to have bone fractures, even when those patients are on Cystagon. None of my patients have yet had a single bone break while taking PROCYSBI.

(c) ***Reduced dose:*** PROCYSBI is also effective at lower doses than Cystagon. An effective dose of PROCYSBI is generally 20-30% lower than Cystagon.[11]

(d) ***Improved adherence.*** PROCYSBI is a significant improvement over Cystagon in terms of patient adherence given the twice-daily dosing, thus alleviating the sleep deprivation associated with Cystagon for both patients and caregivers. PROCYSBI's facilitation of adherence to an every-twelve-hour (Q12) dosing regimen leads directly to improved therapeutic efficacy.

(e) ***Reduced use of concomitant therapies.*** With PROCYSBI, patients can often avoid the concomitant use of gastric acid reducers (such as proton pump inhibitors (PPIs)), which are associated with bone fractures and kidney issues unrelated to PROCYSBI or cystinosis.[12]

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[11] Langman *et al.*, (2012) A randomized controlled crossover trial with delayed-release cysteamine bitartrate in nephropathic cystinosis: effectiveness on white blood cell cystine levels and comparison of safety, Clin J Am Soc Nephrol 7:1112-1120.

[12] Hart, E. *et al.*, (2019) Proton Pump Inhibitors and Risk of Acute and Chronic Kidney Disease: A Retrospective Cohort Study, Pharmacotherapy Apr;39(4):443-453; Arora, P. *et al.*, (2016) Proton Pump Inhibitors are Associated with Increased Risk of Chronic Kidney Disease, BMC Nephrol Aug 3;17(1):112; Devraj, R. *et al.*, (2019) Demographic and health-related predictors of proton pump inhibitor (PPI) use and association with chronic kidney disease (CKD) stage in NHANES population, Res Social Adm Pharm, Aug 19 pii: S1551-7411.

(f) ***Maintenance of kidney function.*** Studies have shown that patients on PROCYSBI are able to maintain kidney function (as measured by glomular filtration rate, or GFR). Further, one study has shown normal kidney maturation and maintenance of physical growth in 80% of patients taking PROCYSBI in the first two years of life.[13] This has never been shown with Cystagon: to the contrary, Cystagon has only been shown to slow reduction in kidney function over time.

(g) ***Avoidance of more invasive therapies.*** PROCYSBI is the first drug that effectively shows potential for treating cystinosis in the long term with the hope that a patient's need for dialysis or kidney transplant will be substantially delayed or even avoided.

29. To date, I have seen clinical success with PROCYSBI in an overwhelming majority of my patients whereas, with Cystagon, my patients devolved to end stage renal failure and transplantation. Importantly, there are no data of WBC cystine increasing over time in PROCYSBI patients. Indeed, we are seeing now data that suggests that PROCYSBI has a benefit in stabilizing kidney function.[14]

30. As a physician, I aim to provide the best medical care to my patients. It is for this reason that I will not prescribe Cystagon to patients. In my professional judgement, there is no comparison between the two drugs: PROCYSBI is simply superior. Accordingly, I do not view PROCYSBI and Cystagon as equivalent.

31. ***Reviews of PROCYSBI.*** I have reviewed the following documents and have been asked to provide my opinion on them:

(a) The Clinical Review, Pharmacoeconomic, and Final Reports prepared by CADTH;

(b) New Medicine Scientific Review, dated January 12, 2018;

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[13] Vaisbich, M. *et al.*, (2018) Maturation of Renal Function in Young Children with Nephropathic Cystinosis Treated A Priori With Delayed-Release Cysteamine Bitratrate, (Poster 385).
[14] Vaisbich, M. *et al.*, (2018) Maturation of Renal Function in Young Children with Nephropathic Cystinosis Treated A Priori With Delayed-Release Cysteamine Bitratrate, (Poster 385).

(c) HDAP New Medicine Review, dated February 26, 2018;

(d) New Medicine Review Issue Paper, dated April 27, 2018; and

(e) HDAP New Medicine Review, dated May 7, 2018.

32. In my view, these reviews of PROCYSBI ignore important data about PROCYSBI and its benefits and misunderstand the purpose of the non-inferiority study that compared PROCYSBI to Cystagon.

33. ***Questions posed by Counsel.*** The statements posed by Counsel to me are either fundamentally wrong or require more context. In my view, there is no comparison between Cystagon and PROCYSBI: PROCYSBI is simply superior. Accordingly, I do not view PROCYSBI and Cystagon as equivalent. Cystagon cannot be taken on a 12-hour dosing schedule. Further, the literature demonstrates that Cystagon cannot, and does not, fully arrest the degradation in kidney function for the vast majority of patients. Since I began prescribing PROCYSBI in 2013, none of my patients have required dialysis or renal transplantation. Patients also experience less adverse events, which leads to greater compliance and improves the efficacy of cysteamine therapy. These are significant improvements when compared to patients treated with PROCYSBI over Cystagon.

SCIENTIFIC BACKGROUND

Nephropathic Cystinosis

34. Nephropathic cystinosis is a rare genetic disease caused by a genetic deletion in the patients' DNA. DNA is the genetic code responsible for making proteins and other biological components required by the body to sustain life. In cystinosis patients, a part of the required genetic code is missing (an irreparable condition) or (in a smaller percentage of patients) mutated, meaning that the body cannot make the components necessary for the sustenance of life. In the case of cystinosis, this means that the body is incapable of clearing out cysteine, a non-essential amino acid which accumulates in the cells. This cysteine build-up occurs throughout the body but is particularly hard on the kidneys because it causes the filtering portion of the kidney (the glomerulus) and the resorbing part of the kidney (the proximal tubule) to fail.

Absent treatment, cystinosis inevitably results in end stage renal failure and kidney transplantation.

35. ***Diagnosis.*** Cystinosis is diagnosed early in a child's life in children who present with delayed growth, rickets, a failure to thrive, glucosuria (sugar in the urine) and proteinuria (proteins in the urine), dehydration (by virtue of polyuria (large urine volumes)), and an inability to concentrate the urine. The diagnosis is confirmed with biochemical tests, including a test for elevated WBC cystine levels. WBC cystine is a biomarker of the disease that is thought to represent the load of cysteine in white blood cells. Patients are treated with cysteine depleting agents to lower the level of WBC cystine to values seen in unaffected patients.

36. If left untreated, cystinosis ends in end stage renal disease, requiring kidney transplantation. Even when treated, because of its prevalence throughout the body, cystinosis often ends in early death, usually from muscular myopathy. (In addition to impacting major organs and particularly the kidneys, the disease adversely impacts major muscle groups, including those required for breathing). Cystinosis is generally incurable, and death can happen as early as the third decade of life.

37. ***Patient Population.*** Cystinosis is a rare disease, often classified as an ultra-rare disease. Cystinosis affects approximately 1 in 100,000 to 200,000 newborns worldwide. The incidence of cystinosis is higher in some areas of the world, including in Brittany, France,[15] and Quebec.[16] The manner in which clinical trials and studies can be conducted are constrained by patient size, ethical concerns and the fact that these patients are very ill, undergoing various treatment therapies in addition to the use of an agent to reduce cystine accumulation.

38. ***Pathology of Cystinosis.*** Early work on cystinosis confirmed that the disease impacts the entire body. On autopsy, in bone marrow aspirates from living cystinosis patients, it was seen that cystine crystals had accumulated throughout the body. Early investigators realized that the

[15] Langman *et al.*, (2019) Oh Cystinosin: Let me Count the Ways, Kidney Int 96, 275-277.
[16] De Braekeleer, M. (1991) Hereditary Disorders in Saguenay-Lac-St-Jean (Quebec, Canada), Hum Hered 41(3):141-146.

cystine generation and accumulation occurred within the lysosomes[17] within the cell.[18] In normal tissue, cystine is formed in the lysosomes and thereafter reduced to cysteine, and thereafter eliminated through normal transport. Because cystine was accumulating in patients with cystinosis, it was thought that the transporter to get cystine out of the lysosome was not functional. Early researchers felt that the most likely cause of the accumulation of cystine in the cell was a transporter defect localized to the lysosomal membrane. Specific transporters exist on the lysosomal membrane that carry specific amino acids from the lysosome to the cytoplasm of the cell. It was hypothesized, and later proven, that the transporter mechanism for cystine was either missing or dysfunctional.[19]

The Treatment of Cystinosis

Treatment Options Prior to Cysteamine Bitartrate Therapy

39. Before the advent of cysteamine bitartrate therapy, treatment options for cystinosis patients were limited to replacing orally what patients lost in their urine. By nine or ten years of age, however, the kidneys in these patients would fail. Prior to cysteamine bitartrate therapy, neither dialysis nor transplantation (discussed in more detail below) were generally viewed as available options for these patients, and therefore cystinosis was viewed as a fatal disease. The disease was very much a death sentence, with patients often dying before the second decade of life.

The Development of Cysteamine Therapy

40. Cysteamine occurs naturally in humans, but only in very low concentrations. In 1976, Dr. Jess Thoene found that cysteamine removed cystine from cystinotic cells in culture and then in patients.[20] Researchers next discovered that cysteamine works in the cystinotic lysosome by

[17] In 1974, a Belgian scientist, Christian de Duve, shared the Nobel Prize in Medicine for the discovery of lysosomes, an intracellular organelle that digests proteins and other cellular molecules.
[18] Gahl, W.A. *et al.*, (2007) Nephropathic Cystinosis in Adults: Natural History and Effects of oral Cysteamine Therapy Ann Intern Med 147:242-250.
[19] Gahl W.A. *et al.*, (1982) Cystine transport is defective in isolated leukocyte lysosomes from patients with cystinosis, Science 217:1263-1265; Gahl, W.A. *et al.*, (2007) Nephropathic Cystinosis in Adults: Natural History and Effects of Oral Cysteamine Therapy, Ann Intern Med 147:242-250.
[20] Thoene, J.G. *et al.*, (July 1976) Intracellular Cystine Depletion by Aminothiols *in vitro* and *in vivo*, J. Clin Inv, Vol 58:180-89.

reacting with cystine to form a mixed disulfide of half cystine, called cysteine. The cysteamine/cysteine complex would be transported out of the cell via a novel transporter not otherwise active in the patient. This discovery led to the first effective treatment to help delay cysteine build-up in patients with cystinosis. Experts slowly began deploying different formulations of cysteamine to patients through the 1980s and 1990s.

41. ***Cysteamine hydrochloride.*** The success in treating cystinosis with cysteamine was reported in 1987. At that time, early investigators used cysteamine hydrochloride. Cysteamine hydrochloride was not stable as a solid and had to be distributed as a liquid, making its administration at home quite difficult. It was also associated with a horrible smell and taste.

42. ***Phosphocysteamine.*** Investigators next used phosphocysteamine, an odorless compound that was virtually impossible to obtain in a pure form in a way that would make it easy for patients to take. It was therefore not a long-term viable candidate for further development for the treatment of cystinosis patients.

43. ***Cysteamine bitartrate.*** In the late 1980s and early 1990s, cysteamine bitartrate became the formulation used for treating patients with cystinosis. This drug was commercialized in some countries as Cystagon. While the development of a stable form of cysteamine was a welcome development, Cystagon had several important drawbacks:

(a) ***Strict dosing regimen:*** Early on, studies showed that cysteamine bitartrate had to be taken every six hours to be effective.[21] Notwithstanding the importance of strict adherence to the dosing regime, Cystagon's dosing frequency, combined with its significant adverse effects, made adherence challenging. One study indicated that adherence among the study population was less than 25%.[22] Failure to adhere to the regimen results in a more rapid deterioration of kidney function as WBC cystine levels rise.[23]

[21] Levtchenko, E.N. *et al.*, (2006) Strict cysteamine dose regime is required to prevent nocturnal cystine accumulation in cystinosis, Pediatr Nephrol 21:110-113.
[22] Levtchenko, E.N. *et al.*, (2006) Strict cysteamine dose regime is required to prevent nocturnal cystine accumulation in cystinosis, Pediatr Nephrol 21:110-113.
[23] Levtchenko, E.N. *et al.*, (2006) Strict cysteamine dose regime is required to prevent nocturnal cystine accumulation in cystinosis, Pediatr Nephrol 21:110-113.

(b) ***Side effects:*** Patients experience several significant treatment emergent adverse events while taking Cystagon, including nausea, vomiting, emesis, body odor and halitosis. The extent and severity of these adverse effects depends on the blood concentration levels of the product, which depends on the blood concentration of cysteamine (the reagent that drives the dimethylsulfide generation in the stomach which causes many of these side effects).[24]

These side effects can have social implications for patients. In particular, the body odor and halitosis associated with this therapy drive the social isolation suffered by patients, particularly in school age years.[25] These social issues can in turn have an impact on adherence, which is discussed below.

(c) ***Decreased sleep for patients and caregivers:*** The strict six-hour dosing schedule has significant impacts on caregiver and patient sleep patterns. A study by Levtchenko has shown that, if a patient allowed eight hours to lapse between doses (to accommodate a night's sleep), cystine accumulation would reach unacceptably high levels by hour six.[26] This means that patients and caregivers can never have a full night's sleep when using Cystagon. This is particularly problematic for patients, as there is emerging literature establishing a link between sleep and the maintenance of kidney function in adult patients (who already have decreased kidney function).[27] For example, Ricardo and colleagues conducted a study which explored the relationship between habitual sleep duration and quality with chronic kidney disease progression in 431 study participants with chronic kidney disease. Greater sleep fragmentation was

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[24] Cairns, D. *et al.,* (2002) Cystinosis and its Treatment, The Pharmaceutical Journal 269:615-616; Besouw *et al.,* (2007) "The Origin of Halitosis in Cystinotic Patients due to Cystinosis Treatment" Mol Genet Metab 91(3):228-233; Arieceta *et al.,* (2015) Cysteamine (Cystagon®) adherence in patients with cystinosis in Spain: successful in children and a challenge in adolescents and adults, Nephrol Dial Transplant 30(3):475-480.

[25] Cassiman *et al.,* (2016) Clinical relevance and patient relevance of delayed-release cysteamine bitartrate for patients with nephropathic cystinosis, Expert Procedures on Health, Clinical, Economic, and Patient Relevance; Levtchenko, E.N. *et al.,* (2006) Strict cysteamine dose regime is required to prevent nocturnal cystine accumulation in cystinosis, Pediatr Nephrol 21:110-113.

[26] Levtchenko, E.N. *et al.,* (2006) Strict cysteamine dose regime is required to prevent nocturnal cystine accumulation in cystinosis, Pediatr Nephrol 21:110-113.

[27] Yamamoto, R. *et al.,* (2018) Sleep quality and sleep duration with CKD are associated with progression to ESKD Clin J Am Soc Nephr 13:1825-1832; Ricardo, A. *et al.,* (2017) The association of sleep duration and quality with CKD progression, J Am Soc Nephrol 28:3708-3715; Turek, N. *et al.,* (2012) Sleep Disturbances as Nontraditional Risk Factors for Development and Progression of CKD: Review of the Evidence, Am J Kidney Dis 60(5):823-833.

associated with an increased risk of end stage renal disease, and greater sleep fragmentation was associated with a decline in kidney function (as measured by eGFR).[28]

(d) ***Convenience of administration.*** The regular use of Cystagon produces a very bad smell and taste, which causes difficulties in successfully administering the drug. This, of course, makes compliance more difficult, particularly as patients enter their teenage years.[29]

44. ***Dialysis and kidney transplantation.*** As a practical matter, and in large part due to the need for every six-hour administration, it is very difficult for Cystagon to entirely arrest the build-up of cysteine and the concomitant loss of kidney function. The literature shows that immediate release cysteamine bitartrate delays end-stage renal failure, but it does not entirely prevent it.[30] As a result, all my patients who have taken Cystagon required dialysis (a machine-based process of removing excess water, solutes, and toxins from the blood in people with renal failure) and/or kidney transplantation. As I describe in more detail below, since I started treating patients with PROCYSBI in 2013, none have yet required a transplant.

The Development of PROCYSBI

45. PROCYSBI is a delayed release formulation of enterically-coated, microspheronized beads of cysteamine bitartrate. The modified release formulation was developed to solve the serious efficacy, side effects, and adherence issues experienced with immediate release cysteamine. In the section that follows, I discuss very briefly the basic concepts animating the formulation of drugs so that they can be delivered safely and effectively to patients.

46. ***Pharmaceutical Formulation.*** Pharmaceutical formulation is the process whereby a drug is prepared for delivery to a patient in a form which is (1) stable; (2) manufacturable; and (3)

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[28] Ricardo, A. *et al.,* (2017) The association of sleep duration and quality with CKD progression, J Am Soc Nephrol 28: 3708-3715.

[29] Levtchenko, E.N. *et al.,* (2006) Strict cysteamine dose regime is required to prevent nocturnal cystine accumulation in cystinosis, Pediatr Nephrol 21:110-113.

[30] Nesterova, G. *et al.,* (2015) Cystinosis: renal glomerular and renal tubular function in relation to compliance with cystine-depleting therapy, Pediatr Nephrol 30:945-951; Nesterova, G. *et al.*, (2008) Nephropathic cystinosis: late complications of a multi-systemic disease, Pediatr Nephrol 23: 863-878; Markello T.C. *et al.,* (1993) Improved renal function in children with cystinosis treated with cysteamine, N Engl J Med 328:1157-62.

acceptable to the patient who will use it. Formulation is necessary to prepare a drug delivery mechanism that is both stable and acceptable to a patient (including ensuring that it is safe and effective for the patient).

47. Both the properties of a compound (the active ingredient) and its formulation can impact the ability of the drug product to be delivered to a patient. As a result, drug development often involves addressing obstacles in delivering a drug to a patient to ensure that it is safe and effective. Bioavailability is a measure of the ability of the drug to be absorbed to effectively treat the patient.

48. ***Bioavailability.*** Bioavailability is one of the primary pharmacokinetic properties of a drug. It measures the fraction of the dose of an unchanged drug product that reaches the patient's systemic circulation when dosed to a patient. It is essential that a drug reach the systemic circulation in order for the drug product to be delivered to the relevant area of the body.

49. Drugs that are administered intravenously have a bioavailability of 100%. However, many drug products are not convenient to administer intravenously, and other methods of delivery must be developed. However, these routes of administration can significantly reduce the bioavailability of the drug product.

50. To enter a patient's systemic circulation and have appropriate bioavailability, an orally administered drug must be released from its dosage form, successfully undergo the dissolution process, and be solubilized in the fluid of the gastrointestinal tract. Absorption of an oral drug is dependent upon several characteristics of both the drug and the dosage form.

51. Several parameters are commonly used to measure the bioavailability of a drug product, including:

(a) **Area Under the Curve** ("AUC"): AUC measures the total amount of a drug product present in the blood over time;

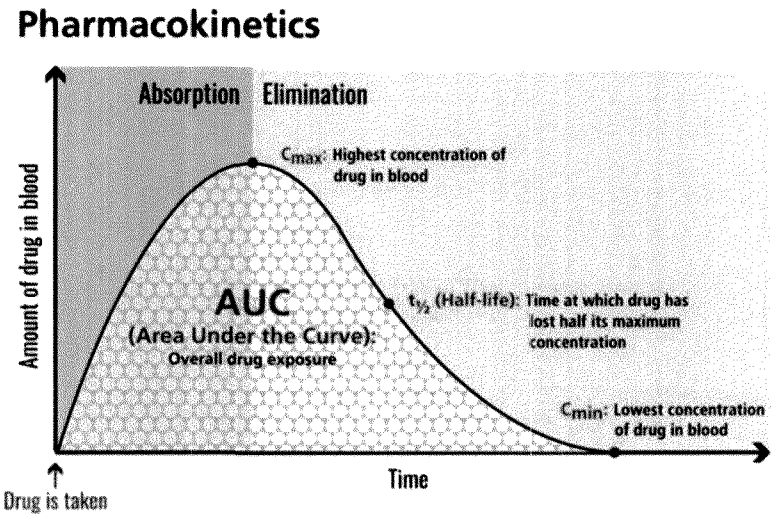
(b) **Peak Serum Concentration** ("C_{max}"): The C_{max} measures the highest concentration of drug in the blood (measured in nanograms per millilitre). C_{max} can be an important factor in adverse events, as adverse events (including GI

tolerability, nausea, vomiting, and headaches) often arise due to the level of drug concentration. Because C_{max} reflects the maximum dose that the patient receives at the systemic level, the higher the C_{max}, the more likely that a patient will experience adverse events;

(c) **Minimum Serum Concentration** ("C_{min}"): the C_{min} is the lowest concentration of the drug in the blood achieved after repeated dosing; and

(d) **Half Life** ("t1/2"): the half-life describes the time at which the drug has lost half of its maximum concentration.

52. Many of these concepts are illustrated in the figure below:[31]



53. ***Modified release formulations.*** In the course of developing a drug, developers may also look to address the inherent properties of a drug compound through formulation techniques. This can include changes to the method of delivery (for example, oral solution, capsule, or tablet) or the development of formulations that affect the release of the drug (immediate or delayed release formulations), or its site of release in the body.

54. The active ingredient in immediate-release medications is usually released within minutes of when a patient has ingested the drug. As a result, in order to ensure that the drug is effective throughout the day, some immediate release medications need to be taken three or four times a

[31] National Institutes of Health. Online at: www.nih.gov

day. In the case of Cystagon, as I have set out above, it is essential that the drug is taken every six hours around the clock.

55. In contrast, however, in many delayed release formulations, the active ingredients of a drug are released over a much longer period of time. This longer release period means that the drug needs to be taken less frequently (for example, once or twice a day). In the case of PROCYSBI, the delayed release characteristics of the drug were shown to allow for dosing on a Q12 hourly basis, rather than every six hours as with Cystagon. Further, immediate absorption of large concentrations of Cystagon in the stomach is associated with increased nausea, emesis and other GI adverse events. Because PROCYSBI, a delayed release formulation, is absorbed by the body, bypassing the stomach, over a longer time period, it is associated with a lower incidence of GI-related adverse events.[32]

56. Furthermore, PROCYSBI's Q12 hourly dosing schedule improves the body odor and halitosis experienced with previous cysteamine therapies, including Cystagon. As set out above, the halitosis and body odor experienced by cystinosis patients appears to be related to the fact that cysteamine eventually metabolizes into a volatile sulphur compound called dimethyl sulphide. The highest concentrations of this compound (and therefore, the worst halitosis and body odor side effects) occur at the drug's C_{max}.[33] With Q6 hourly dosing (as in Cystagon), patients have four separate peak serum concentrations at which these side effects will be more pronounced.[34] PROCYSBI's slower rate of absorption, delayed C_{max}, and overall fewer C_{max} peaks are the likely cause of the reduced body odor and halitosis experienced with PROCYSBI (when compared with immediate release cysteamine bitartrate).[35]

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[32] Langman *et al.*, (2012) A randomized controlled crossover trial with delayed-release cysteamine bitartrate in nephropathic cystinosis: effectiveness on white blood cell cystine levels and comparison of safety, Clin J Am Soc Nephrol 7:1112-1120; Langman *et al.*, (2014) Quality of Life is improved and kidney function preserved in patients with nephropathic cystinosis treated for 2 years with delayed-release cysteamine bitartrate, J Pediatr 156(3):528-533 e521.

[33] Cairns, D. *et al.*, (2002) Cystinosis and its Treatment, The Pharmaceutical Journal 269:615-616; Besouw *et al.*, (2007) The Origin of Halitosis in Cystinotic Patients due to Cystinosis Treatment, Mol Genet Metab 91(3):228-233; Arieceta *et al.*, (2015) Cysteamine (Cystagon®) adherence in patients with cystinosis in Spain: successful in children and a challenge in adolescents and adults, Nephrol Dial Transplant 30(3):475-480.

[34] Besouw *et al.*, (2007) The Origin of Halitosis in Cystinotic Patients due to Cystinosis Treatment" Mol Genet Metab 91(3):228-233.

[35] Ahlenstiel-Grunow *et al.*, (2016) Switching from immediate- to extended-release cysteamine in nephropathic cystinosis patients: a retrospective real-life single-center study, Pediatr Nephrol 32(1):91-97.

57. PROCYSBI's improved pharmacokinetic profile has been demonstrated in our published work on PROCYSBI and my clinical experience with the drug. In the sections that follow, I discuss that work.

My role in the early testing of PROCYSBI: RP-103-03 and RP-103-04

58. I was the lead investigator on the pivotal clinical trial RP-103-03 in which the efficacy of PROCYSBI was established in a head-to-head randomized controlled clinical trial against Cystagon. Additionally, this is the first time that Cystagon was ever evaluated in a formal clinical trial.

RP-103-03

59. ***Study design.*** RP-103-03 was an open-label, randomized, controlled crossover trial which was designed to assess whether delayed-release cysteamine bitartrate (PROCYSBI, then known as "RP-103") was non inferior to Cystagon for maintenance of WBC cystine at levels associated with optimal outcomes in the disease.[36]

60. We recruited 43 patients in eight sites around the world—five in Europe and three in the United States. We used a randomized, controlled, crossover design. Eligible patients entered a two-week run-in period, during which we were able to establish WBC cystine baselines. The reason we had a two-week run-in period was because we wanted to ensure that we selected patients who were well-controlled on their current drug (Cystagon). We wanted patients with optimally controlled disease as measured by WBC cystine biomarkers. Following the run-in period, eligible patients were randomly assigned to one of two treatment arms—either Cystagon or (what was then known as) RP-103. After three weeks, the patients were switched into the other treatment arm.[37]

[36] Langman *et al.*, (2012) A randomized controlled crossover trial with delayed-release cysteamine bitartrate in nephropathic cystinosis: effectiveness on white blood cell cystine levels and comparison of safety, Clin J Am Soc Nephrol 7:1112-1120.
[37] Langman *et al.*, (2012) A randomized controlled crossover trial with delayed-release cysteamine bitartrate in nephropathic cystinosis: effectiveness on white blood cell cystine levels and comparison of safety, Clin J Am Soc Nephrol 7:1112-1120.

61. The study is inherently controlled by its crossover design. A crossover design is a repeated measurements design such that each experimental unit (patient or subject) receives different treatments during the different time periods (*i.e.*, the patients "crossover" from one treatment arm to another during the course of the trial). A crossover study is a controlled study in that each subject serves as his or her own matched control. The fact that each subject serves as his or her own control is a strength of crossover studies, as it reduces the potential for confounding (*i.e.*, the inability to eliminate plausible alternative explanations for an observed relationship between an independent variable and a dependent variable).[38]

62. It was neither possible nor ethical to use a placebo (*i.e.*, administer a pill devoid of any medication in lieu of treatment) or to blind the study (*i.e.*, give patients a pill without its identifying marks). First, the strengths and dosing of the drug products differed, so patients would take different amounts of the drug at different times. Second, the increased halitosis and body odor associated with immediate-release cysteamine (*i.e.*, Cystagon) was readily apparent. With respect to the administration of a placebo, it would have been unethical to withhold treatment for a group of patients who require it to prevent irreversible kidney damage. Because we know the role that cysteamine bitartrate plays in preventing cysteine buildup and thereby reducing renal damage, this is essentially what prescribing a placebo would have amounted to.

63. ***Use of PPIs and Other Concomitant Medications.*** In the Cystagon arm, proton pump inhibitor (PPI) therapy was taken at the discretion of the patient and/or the attending physician. The use of PPIs was voluntarily discontinued initially in the RP-103 arm, although PPIs could be restarted by the physician or the patient. We did this because we thought that a patient on RP-103 did not need PPIs; we believed that PROCYSBI would be released once it passed through the stomach, thereby avoiding the most serious GI effects. PPIs are associated with bone fractures and kidney issues unrelated to PROCYSBI or cystinosis.[39] We hypothesized that PROCYSBI

[38] Williams and Wilkins, *Designing Clinical Research*, 4th ed. (Philadelphia: Lippincott, 2013), p. 156.
[39] Hart, E. *et al.*, (2019) Proton Pump Inhibitors and Risk of Acute and Chronic Kidney Disease: A Retrospective Cohort Study, Pharmacotherapy Apr;39(4):443-453; Arora, P. *et al.*, (2016) Proton Pump Inhibitors are Associated with Increased Risk of Chronic Kidney Disease, BMC Nephrol Aug 3;17(1):112; Devraj, R. *et al.*, (2019) Demographic and health-related predictors of proton pump inhibitor (PPI) use and association with chronic kidney disease (CKD) stage in NHANES population, Res Social Adm Pharm, Aug 19 pii: S1551-7411.

would allow patients with already compromised kidney function to avoid PPIs, and therefore these undesirable side effects.

64. Only five out of eighteen patients in the initial Cystagon arm resumed use of PPIs in the RP-103 arm.[40] We interpreted the fact that some patients went back on PPIs in the RP-103 arm to suggest that some of the GI effects from the Cystagon arm continued on even after the drug had been switched. After all, the GI problems that these patients suffer from take time to resolve themselves. On the other hand, all the patients who started in the RP-103 arm continued in that arm without PPI use.[41] In the patients whom I now treat with PROCYSBI, the minority are on gastro-protective medications. The majority are not.

65. Except for PPIs, all concomitant medications were continued unchanged during both crossover arms of the study. Cystinosis patients are often taking a series of other drugs for symptomatic treatment of many other manifestations of the disease. These include but are not limited to potassium salts, alkali agents such as citrate or bicarbonate, and many other medications.

66. ***Study results.*** RP-103-03 demonstrated that there was no statistical difference in the mean peak plasma concentration (C_{max}) between the two drugs. In the study report, the P-values are reported to be <0.0001 and <0.001. The study showed a longer t_{max} for the delayed release formulation, which was to be expected.[42]

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[40] Langman *et al.*, (2012) A randomized controlled crossover trial with delayed-release cysteamine bitartrate in nephropathic cystinosis: effectiveness on white blood cell cystine levels and comparison of safety, Clin J Am Soc Nephrol 7:1112-1120.

[41] As we reported in the paper, because the protocol asked for cessation of PPI use and because we did not randomize the patients for PPI use in either arm, we did not evaluate, statistically, what otherwise looked like an 87% reduction in PPI use because of PROCYSBI. Indeed, all patients in the Cystagon treatment arms received PPIs. Had they not received PPIs, I expect that their AE reports would have been higher. Arguably, had the PPI use increased in the RP-103 treatment arms, the AE reports would have been less. Again, it is notable that only five patients resumed use of PPIs although all had them available for administration.

[42] Langman *et al.*, (2012) A randomized controlled crossover trial with delayed-release cysteamine bitartrate in nephropathic cystinosis: effectiveness on white blood cell cystine levels and comparison of safety, Clin J Am Soc Nephrol 7:1112-1120; RP-103-03 Clinical Study Report.

67. We measured endpoints both on an intent to treat (ITT) basis[43] and a per-protocol basis.[44] It is important to note that:

(a) Three different patients in the Cystagon arm exceeded the three-day average WBC cystine level and were thus not considered well-controlled on Cystagon[45];

(b) Two siblings had to withdraw because of a prior-planned surgery unrelated to cysteamine treatment (and the parents took both children out of the study because of travel difficulties);

(c) When we did the statistical analysis in the ITT population, we determined that RP-103 was not only non-inferior but also superior to Cystagon in terms of cystine clearance; and

(d) The outcome of non-inferior WBC cystine levels was achieved at a lower dose of RP-103 compared to Cystagon on a body mass basis.[46]

68. Patients in RP-103 were able to tolerate higher total single doses twice a day without using concomitant PPIs and to maintain an effective treatment regime (without the sleep interruption necessitated by Q6 hourly dosing), as compared with patients taking immediate release cysteamine bitartrate. We also stressed that our patients in this study were optimally controlled patients—they were the best controlled patients on Cystagon. We suggested that patient adherence would be improved, based on the convenience of the twice-daily dosing regimen and the results of the study, which showed that such a regimen can effectively keep WBC cystine levels in an optimal range for patients with cystinosis.[47]

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[43] An ITT analysis is one where the results are analyzed based on the initial treatment assignment and not on the treatment eventually received.

[44] A per-protocol analysis compares treatment groups that include only those patients who completed the treatment originally allocated.

[45] In this study, we were looking for well-controlled Cystagon patients—and those who could swallow their doses. Put simply, we were looking to go head-to-head in the best controlled patients.

[46] On average, the daily dose of RP-103 was 82% of that of Cystagon: Langman *et al.*, (2012) A randomized controlled crossover trial with delayed-release cysteamine bitartrate in nephropathic cystinosis: effectiveness on white blood cell cystine levels and comparison of safety, Clin J Am Soc Nephrol 7:1112-1120; RP-103-03 Clinical Study Report.

[47] Langman *et al.*, (2012) A randomized controlled crossover trial with delayed-release cysteamine bitartrate in nephropathic cystinosis: effectiveness on white blood cell cystine levels and comparison of safety, Clin J Am Soc Nephrol 7:1112-1120; RP-103-03 Clinical Study Report.

69. Overall, no unexpected side effects were seen with PROCYSBI compared to Cystagon, and no patient stopped the study due to side effects while on the RP-103 arm. Some patients experienced GI side effects, although, as we noted, this may have been the result of the reduction in PPI use.[48]

70. Based on our results, we felt comfortable that patients who were already well-controlled on Cystagon could be switched to RP-103. We deemed it reasonable that long-term patient adherence would be improved, based on the convenience of twice-daily dosing and on our observations that a delayed release form of cysteamine-bitartrate did effectively keep WBC cystine levels in an optimal range for patients with cystinosis. We concluded that, if such adherence benefit is proven in subsequent real-world use, the deleterious effects of cystinosis on both kidney function and extrarenal organ impairment may be substantially ameliorated.

71. As I discuss below, the 41 study subjects who completed the crossover study were provided with the opportunity to enroll in an extension study to continue treatment with RP-103. All but one chose to do so.

The Extension Study: RP-103-04

72. Following the completion of the RP-103-03 study, patients were offered the choice to continue in a planned extension study, RP-103-04. This study was designed to study the effect of PROCYSBI on quality of life, maintenance of kidney function, and to evaluate growth in order to provide more real-world data on the use of PROCYSBI in cystinosis. Forty of the forty-one patients (97.6%) in the crossover study continued in the extension study. (Patient 41 declined to continue treatment due to other conditions unrelated to cystinosis; the patient had an obsessive-compulsive disorder that did not allow much change in daily routines). While 97.6% of patients electing to continue with the new delayed release is remarkable on its own—suggesting that people wanted to stay on RP-103 when given the choice—the study results themselves

[48] Langman *et al.*, (2012) A randomized controlled crossover trial with delayed-release cysteamine bitartrate in nephropathic cystinosis: effectiveness on white blood cell cystine levels and comparison of safety, Clin J Am Soc Nephrol 7:1112-1120; RP-103-03 Clinical Study Report.

demonstrated statistically significant improvements in quality of life, as well as maintenance of kidney function and preservation of growth over two years.[49]

73. ***Study design.*** Inherent to the design of the short-term crossover study, we recognized the inability of that study to evaluate the effect on maintenance of optimal WBC cystine, native kidney function, somatic growth, and the impact on quality of life. Therefore, the extension study was designed to evaluate these clinically meaningful patient-centric outcomes over a two-year period. The design of the study can be described as a prospective, controlled, open label, single-arm study of delayed release cysteamine bitartrate in 40 patients to assess efficacy in depletion of white blood cell cystine, to assess the dose required to maintain WBC cystine <1nmol half cystine/mg protein, to measure quality of life using a standardized test, to measure the change in estimated GFR and the change in height Z-score.[50]

74. This is the first time that anybody had done a prospective, long-term controlled study using cysteamine bitartrate—whether as Cystagon or as PROCYSBI. Over the course of this 24-month study, we maintained WBC cystine below target level while decreasing the dose of RP-103 at all-time points measured. We also measured significant improvement in social function, school function and total function, all the while maintaining kidney function (GFR) and growth.

75. ***Study population.*** The patients in our study were mostly children or adolescents, all of whom had previously been on Cystagon. We know from the literature that the age at which cysteamine therapy was initiated is a determinant in the progression of the disease. Put another way, the longer a patient's cystinosis remains untreated, the earlier it will be that the patient will suffer kidney failure.[51] In our study, one patient withdrew from the study with a decline in GFR and was placed on dialysis. (That patient had the lowest GFR at the start of the study, so this was not an unexpected result). One other patient went on to transplantation at 17 months, which was

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[49] Langman *et al.*, (2014) Quality of Life is improved and kidney function preserved in patients with nephropathic cystinosis treated for 2 years with delayed-release cysteamine bitartrate, J Pediatr 156(3):528-533 e521.

[50] A Z-score is used because we are dealing with children who are growing over time. In order to see changes in growth, their height is measured in relation to an age-related norm. The technique for doing this is called a Z-score. The Z-score is the standard deviation (SD) above or below the mean. A Z-score of 0 means that the child's height is the same as a 50th percentile in population. A Z-score of plus or minus one means the child is at either at the 15th or 85th percentiles. A Z-score of plus or minus 2 tracks to the 3rd or 97th percentiles. As a result, one can observe improvement in growth over time with changes in a Z-score.

[51] Brodin-Sartorius, A. *et al.*, (2012) Cysteamine therapy delays the progression of nephropathic cystinosis in late adolescents and adults, Kidney International 81:179-189

not unexpected by the treating physician.[52] In my own clinical experience to date, I have yet to transplant a patient who is being treated with PROCYSBI.

76. ***Study results.*** Quality of life was measured using the PedsQL model, which measures health related quality of life in children and adolescents with acute and chronic health conditions. The PedsQL model measures four multidimensional scales (which are broken down into 23 further scales): (1) physical function; (2) emotional function; (3) social function; and (4) school function. Total function is also assessed.[53] We documented a significant change in the patients as they switched from immediate-release to RP-103 in social function (P=0.049), school function (P=0.004) and total function (P=0.048) over a 24-month period. In other measures, physical function and emotional function, there were no significant losses in quality of life. [54]

77. We also observed that there were no unexpected or serious safety concerns during the two-year study. Indeed, we saw a reduction in the incidence of adverse events: 0.059 adverse events per individual per month on RP-103 versus 0.3 adverse events per individual per month on Cystagon (as per our previous study).[55]

78. We were pleased with our results, as optimal control of cystinosis (in terms of maintenance of WBC cystine at the desired level) had never been reported in a clinical trial. This is in large part due to the well-documented[56] difficulties in having patients adhere to the strict every six-hour dosing regimen. For example, in an observational study reporting on 76 children treated with Cystagon over a 32-year period, Markello reported that even with adequate treatment, most patients show renal decline.[57]

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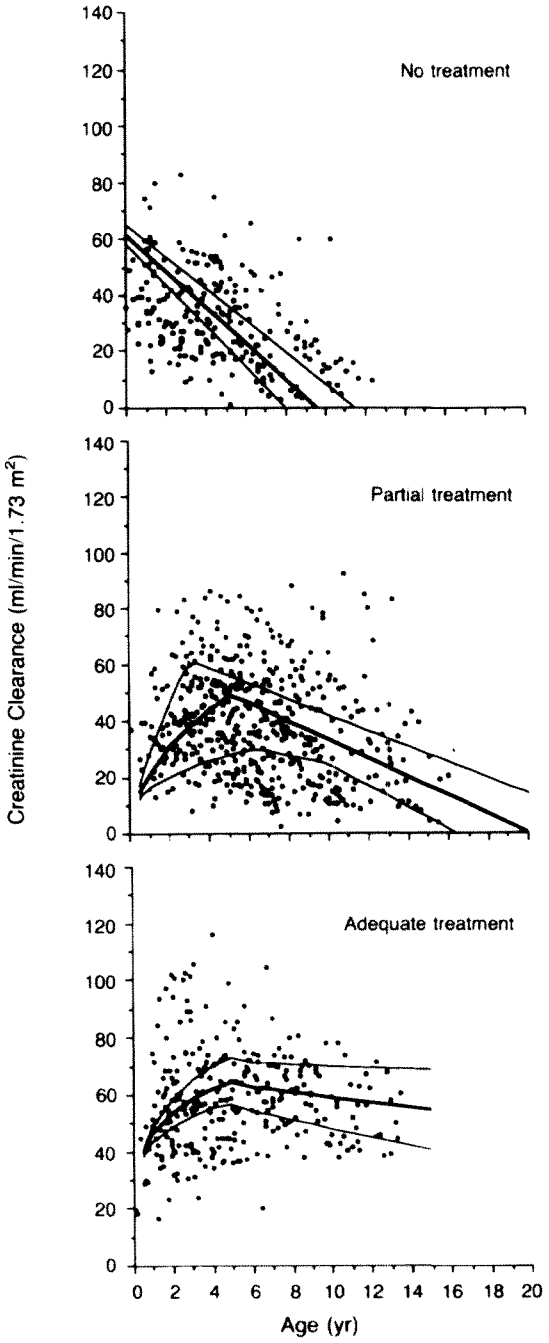
[52] Langman *et al.,* (2014) Quality of Life is improved and kidney function preserved in patients with nephropathic cystinosis treated for 2 years with delayed-release cysteamine bitartrate, J Pediatr 156(3):528-533 e521; RP-103-04 Clinical Study Report.
[53] Varni, J.W., Seid, M. & Kurtin, P.S. (2001). PedsQL 4.0: Reliability and Validity of the Pediatric Quality of Life Inventory Version 4.0 Generic Core Scales in Healthy and Patient Populations, Medical Care 39(8):800-812.
[54] Langman *et al.,* (2014) Quality of Life is improved and kidney function preserved in patients with nephropathic cystinosis treated for 2 years with delayed-release cysteamine bitartrate, J Pediatr 156(3):528-533 e521.
[55] Langman *et al.,* (2014) Quality of Life is improved and kidney function preserved in patients with nephropathic cystinosis treated for 2 years with delayed-release cysteamine bitartrate, J Pediatr 156(3):528-533 e521; RP-103-04 Clinical Study Report.
[56] See Levtchenko C.N. *et al.,* (2006) Strict cysteamine dose regimen is required to prevent nocturnal cystine accumulation in cystinosis, Pediatr Nephrol 21:110-113.
[57] Markello, T.C. *et al.,* (1993) Improved Renal Function in children with cystinosis treated with cysteamine. N Engl J Med 328:1157-1162.

79. Below, I have copied Figure 1 from Markello's article showing the decline in renal function. You will see that in each of the graphs (showing untreated, partially treated and adequately treated patient cohorts) the slope of the line decreases, indicating that, over time, kidney function is declining in the patients treated with Cystagon.

80. In the graphs below, the authors depict visually corrected creatinine clearance according to age in children who had: (1) not received treatment, (2) received partial treatment with

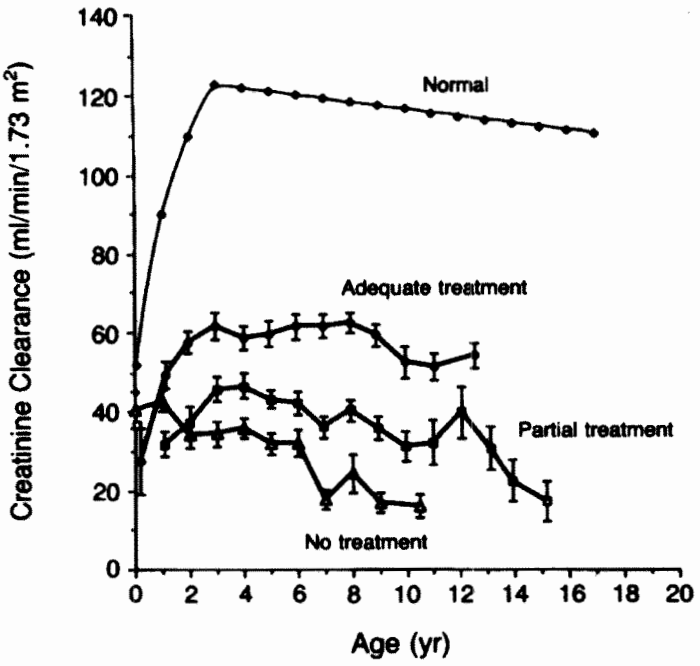
cysteamine, and (3) received adequate treatment with cysteamine.[58]



[58] Markello, T.C. *et al.*, (1993) Improved Renal Function in children with cystinosis treated with cysteamine, N Engl J Med 328:1157-1162.

81. As described in the legend, each point represents the value during one admission, based on 24-hour urine collections. In the top panel, the heavy (middle) line was determined by linear regression analysis; in the middle and bottom panels, it was determined in a log-log fashion up to the age of five years and by linear regression after the age of five (see the Methods section for details). The thin lines are 95 percent confidence intervals.[59]

82. Figure 2 shows mean creatinine clearance as a function of age in normal subjects, patients with cystinosis who had received adequate treatment with cysteamine, patients who had received partial treatment, and patients who had not received treatment:[60]



83. My conclusion from these graphs is that no one getting treatment achieved normal kidney function. Put another way, these graphs show that Cystagon only slows of the decline of kidney function – it does not completely arrest it.

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[59] Markello, T.C. *et al.*, (1993) Improved Renal Function in children with cystinosis treated with cysteamine, N Engl J Med 328:1157-1162.

[60] Markello, T.C. *et al.*, (1993) Improved Renal Function in children with cystinosis treated with cysteamine, N Engl J Med 328:1157-1162.

84. In contrast, in our two-year study, we presented two years of data showing optimal control of the biomarker of the disease – WBC cystine – under a controlled protocol, with preservation of kidney function, stable growth, improved quality of life and an overall decrease in adverse events. We demonstrated that kidney function could be maintained on PROCYSBI. As stated in the paper which published the results, we did not see "a downward slope change in eGFR during the 2 years of treatment" with PROCYSBI,[61] in contrast to the data published by Markello cited above.

85. In my view, there are two chief reasons for these positive results. First, optimal control of a low WBC cystine biomarker was important in this disease. In the Markello retrospective study, the target WBC cystine for the "adequate treatment group" was less than 2 nmol half cystine/mg protein.[62] In our study, we were able to control to less than 1, meaning we were targeting a better performance. Second, we suggested that adherence was superior with RP-103, which was attributed to the modified dosing regimen (every 12 hours with PROCYSBI versus every six hours with Cystagon). Increased adherence also led to not only optimal control but also improved measures of quality of life, preservation of growth, and improved stability of Body Mass Index.[63]

86. As I discuss below, one of the criticisms raised against our study is that we did not do a head-to-head comparison with Cystagon. We addressed this in our paper which reported the results of the study: we deliberately did not do a head-to-head trial because we had already established non-inferiority in RP-103-03.[64] We noted that it had been well-documented many times that patients in clinical trials have outcomes based on adherence levels that are higher than would be seen in real world care. Given the ability to dose every 12 hours and avoid a middle-of-

[61] Langman, C.B. *et al.*, (2014) Quality of Life is Improved and Kidney Function Preserved in Patients with Nephropathic Cystinosis Treated for 2 Years with Delayed-Release Cysteamine Bitartrate, J Pediatr 165(3):528-533; RP-103-04 Clinical Study Report.
[62] Markello, T.C. *et al.*, (1993) Improved renal function in children with cystinosis treated with cysteamine, N Engl J Med 328:1157-1162.
[63] Langman, C.B. *et al.*, (2014) Quality of Life is Improved and Kidney Function Preserved in Patients with Nephropathic Cystinosis Treated for 2 Years with Delayed-Release Cysteamine Bitartrate, J Pediatr 165(3):528-533; RP-103-04 Clinical Study Report.
[64] Langman, C.B. *et al.*, (2014) Quality of Life is Improved and Kidney Function Preserved in Patients with Nephropathic Cystinosis Treated for 2 Years with Delayed-Release Cysteamine Bitartrate, J Pediatr 165(3):528-533; RP-103-04 Clinical Study Report.

the-night dose, we believed that we would get better adherence, and that our study would more closely mimic what would happen in the real-world use of PROCYSBI.

87. Now that I have completed RP-103-04, I would not put Cystagon in a head-to-head trial against PROCYSBI. Given the drastic improvement of PROCYSBI in the control of kidney function, I could not justify—and I doubt that any ethics board would ever permit—a trial of which included an inferior drug.

Corroboration of results seen in RP-103-03 and RP-103-04

88. My views on adherence are not only my own. They are shared by many others in the field.

89. ***Greenbaum and Cadieux.*** For example, in 2014, Greenbaum and Cadieux presented their analysis on the role of adherence to Cystagon therapy (referred to as IR-C) on outcomes, based on a review of the healthcare claims of 224 patients between 2002 and 2013.[65] These investigators mined the data of health claims (prescriptions initiated and refilled) to study whether adherence with the dosing regimen had any effect on disease control. They were able to determine the duration of therapy, whether the treatment had been discontinued, and whether there were any gaps in treatment to arrive at a Medication Possession Ratio (MPR). For these authors, the MPR was a measure of adherence: the higher the MPR, the greater the adherence. The authors found two things:

(a) ***Adherence decreases as patients age.*** First, adherence drops off as the patient ages. This can be seen in the following table, in the middle row, where the average MPR decreased over time:[66]

[65] Cadieux, B. *et al.*, (2014) Adherence to Cysteamine Therapy and Renal Outcomes in Cystinosis, Pediatric Nephrology, Emory Univ, Atlanta, GA.
[66] Cadieux, B. *et al.*, (2014) Adherence to Cysteamine Therapy and Renal Outcomes in Cystinosis, Pediatric Nephrology, Emory Univ, Atlanta, GA.

Table 2. **MPR for IR-C by Decade of Life.**

	Age 0-10	Age 11-20	Age 21-30	Age > 30
N	57	72	51	24
Avg MPR	88%	80%	68%	66%
Range MPR	14% - 167%	14% -112%	1% - 168%	13% - 120%

This result is expected based on our anecdotal understanding of patient adherence. The parents of small children, facing a life-altering disease will observe strict adherence to the dosing regimen. As the patient ages towards adolescence, the social factors associated with adhering to the dosing regimen (including social isolation arising from body odor and halitosis) will all affect adherence.

(b) ***Adherence is critical to delaying end stage renal failure.*** Second, patients with a MPR of less than 80% were more likely to have end stage renal disease than patients with a MPR of greater than 80%. While these findings did not take into account the age of onset of the Cystagon therapy, these data[67] suggest that adherence is critical. These investigators concluded that "[e]fforts to improve adherence [to Cystagon] in this population are needed."[68]

90. Other experts have also noted the importance of adherence in ensuring efficacy:

(a) In 2014, a conference entitled the ***KDIGO (Kidney Disease: Improving Global Outcomes) Controversies Conference*** that included all the leading cystinosis treatment centers worldwide was convened to review the disease and its treatments. The conference was convened in Lisbon, Portugal and brought together 49 leading experts in the field of cystinosis and representatives from patient support groups. KDIGO is the global organization developing and implementing evidence based clinical practice guidelines in kidney disease. Its mission is to "improve the care and outcomes of patients with kidney disease worldwide through the development and implementation of global clinical

[67] These data were reported with a P value of p=0.0053, meaning that these data are statistically significant.
[68] Cadieux, B. *et al.*, (2014) Adherence to Cysteamine Therapy and Renal Outcomes in Cystinosis, Pediatric Nephrology, Emory Univ, Atlanta, GA.

practice guidelines."[69] That conference, which I co-chaired, resulted in a paper that states that the issue of adherence with Cystagon in adolescents and adults continues to be a significant issue facing these patients.[70]

(b) ***Levtchenko, 2006*** demonstrated that long-term cysteamine treatment is very hard with 6-hour dosing, with only 23% patients fully adherent in that study. Levtchenko also observed that, during puberty, it often becomes difficult to convince patients to continue to follow the Q6 hourly dosing schedule required for Cystagon, especially because of the side effects of the drug (breath odor and gastrointestinal discomfort).[71]

(c) In ***Cassiman et al., 2016***, it is noted that immediate-release cysteamine bitartrate (Cystagon) demonstrates three major issues:

(i) a bothersome tolerance profile;

(ii) a strict 6-hourly dosing regimen which forces patients to get up at night; and

(iii) non-adherence as a result of (i) and (ii).

Cassiman explains that the abnormal skin odor, halitosis and gastro-intestinal side-effects impose a significant burden on daily social life, leading to regularly skipping doses in more than 50% of the patients older than 11 years old.[72]

Cassiman further notes that adherence in cystinosis treatment is a non-negotiable prerequisite: "[h]owever, despite the knowledge about all this, compliance in adults still remains low due to the significant side-effects and the unfeasible strict 6-hourly dosing regimen that forces patients to get up at night every night of their

[69] KDIGO online: https://kdigo.org/mission/
[70] Langman C.B. *et al.*, (2016) Controversies and research agenda in nephropathic cystinosis: Conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference. Kidney Int 89(6):1192-203.
[71] Levtchenko, C.N. *et al.*, (2006) Strict cysteamine dose regimen is required to prevent nocturnal cystine accumulation in cystinosis, Pediatr Nephrol 21:110-113.
[72] Cassiman *et al.*, (2016) Clinical relevance and patient relevance of delayed-release cysteamine bitartrate for patients with nephropathic cystinosis, Expert Procedures on Health, Clinical, Economic, and Patient Relevance.

life. In children the compliance is higher due to parents and caregivers being strict guardians of cysteamine intake."[73]

(d) ***Medic, 2017*** points out that patients, caregivers and doctors have expressed the need for new treatments with fewer side-effects and a more feasible dosing schedule.[74]

(e) ***Elmonem, 2016*** states that the current strict dosing regimen and significant adverse effects associated with Cystagon impose a significant burden on cystinosis patients. Estimates say only one-third of patients are able to adhere to that schedule:

> "In patients with poor compliance to frequent dosing formulation, the administration of the newly developed delayed-release formulation is likely to improve patient compliance resulting in fewer long-term complications of cystinosis and improved quality of life."[75]

(f) ***Cherqui, 2012*** states that "[t]he most significant impact of the every-6-H dosing schedule is that cystinosis patients never sleep through the night."[76]

(g) In ***Langman, 2012***, I stated that "[b]ecause Cystagon must be taken every 6 hours around the clock based on pharmacoefficiency of cystine depletion, patients must be awakened in the middle of the night to be fully adherent...[t]here is evidence that failure to adhere to this strict Q6H dosing regimen results in more rapid deterioration of kidney function as WBC cystine levels rise."[77]

My Clinical Experience with PROCYSBI

91. The improvements we observed in RP-103-03 and RP-103-04 are also corroborated by real-world experiences. I currently treat or consult upon approximately 40 patients with

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[73] Cassiman *et al.*, (2016) Clinical relevance and patient relevance of delayed-release cysteamine bitartrate for patients with nephropathic cystinosis, Expert Procedures on Health, Clinical, Economic, and Patient Relevance.
[74] Medic, G. *et al.*, (2017) A systematic literature review of cysteamine bitartrate in the treatment of nephropathic cystinosis, Current Medical Research and Opinion, DOI: 10.1080/03007995.2017.1354288.
[75] Elmonem, M.A. *et al.*, (2016) Cystinosis: a review, Orphanet Journal of Rare Diseases 11:47.
[76] Cherqui, S. (2012) Cysteamine therapy: a treatment for cystinosis, not a cure. Kidney International 81:127-129.
[77] Langman, C.B. *et al.*, (2012) A Randomized Controlled Crossover Trial with Delayed-Release Cysteamine Bitartrate in Nephropathic Cystinosis: Effectiveness on White Blood Cell Cystine Levels and Comparison of Safety, Clin J Am Soc Nephrol 7:1112-1120.

cystinosis and switched patients from Cystagon to PROCYSBI when it became available. Where I have done so, none of my patients have switched back to Cystagon.

92. In my view, PROCYSBI is superior over Cystagon for several reasons:

(a) ***Improved pharmacokinetics.*** PROCYSBI has different release characteristics than Cystagon. It is delivered to the small intestine, as opposed to being released and absorbed in the stomach. This is beneficial, as it lessens the likelihood of ulcers in the stomach and leads to the ability to administer it only every twelve hours, thereby bypassing the need for a middle of the night dose as with Cystagon.[78] Further, PROCYSBI capsules can be opened and the enteric-coated microspheronized beads sprinkled into food or dispersed into liquids, which provides a more convenient administration for young patients and those with difficulty swallowing.

(b) ***Reduced side effects.*** PROCYSBI is associated with a reduction in GI adverse events and the elimination of sleep deprivation. As set out above at paragraph 56, PROCYSBI's pharmacokinetic profile also eliminates or significantly diminishes the halitosis and "rotten egg" gas associated with the elevated peak serum concentration of immediate release cysteamine bitartrate. Additionally, cystinosis is associated with bone wasting disease and it is not uncommon for cystinosis patients to have bone fractures, even when those patients are on Cystagon. None of my patients have yet had a single bone break while taking PROCYSBI.

(c) ***Reduced dose.*** PROCYSBI is also effective at lower doses than Cystagon. An effective dose of PROCYSBI is generally 20-30% lower than Cystagon. As a result of our findings in RP-103-03, we recommended that patients who were already well controlled under a stable daily dose of Cystagon be switched to an

[78] Langman, C.B. *et al.,* (2012) A Randomized Controlled Crossover Trial with Delayed-Release Cysteamine Bitartrate in Nephropathic Cystinosis: Effectiveness on White Blood Cell Cystine Levels and Comparison of Safety, Clin J Am Soc Nephrol 7:1112-1120.

initial RP-103 total daily dose equal to 70% of the Q6H total daily dose of Cystagon.[79]

(d) ***Improved adherence.*** PROCYSBI is a significant improvement over Cystagon in terms of patient adherence given the twice-daily dosing, thus alleviating the sleep deprivation associated with Cystagon for both patients and caregivers. PROCYSBI's facilitation of adherence to an every-twelve-hour (Q12) dosing regimen leads to improved therapeutic efficacy because strict adherence to the dosing schedule is required in order to prevent nocturnal cystine accumulation and thereby prevent the inevitable consequences of the disease.[80]

(e) ***Reduced use of concomitant therapies.*** As set out above, treatment with PPIs has been shown to control the GI side effects arising from Cystagon.[81] However, because it is associated with increased bone fractures and kidney issues in adults, it is generally recommended that PPIs not be taken long-term. [82] Long-term PPI therapy can also lead to cellular changes in the GI system, thereby causing increased GI symptoms.[83] PROCYSBI ameliorates these side effects without requiring concomitant use of PPIs. In RP-103-03, we asked patients to stop their anti-ulcer medications when taking PROCYSBI. None needed to go back on their

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[79] Langman, C.B. *et al.,* (2012) A Randomized Controlled Crossover Trial with Delayed-Release Cysteamine Bitartrate in Nephropathic Cystinosis: Effectiveness on White Blood Cell Cystine Levels and Comparison of Safety, Clin J Am Soc Nephrol 7:1112-1120.

[80] Ahlenstiel-Grunow, T. *et al.,* (2017) Switching from immediate- to extended-release cysteamine in nephropathic cystinosis patients: a retrospective real-life single-centre study, Pediatr Nephrol 32(1):91-97; Levtchenko C.N. *et al.,* (2006) Strict cysteamine dose regimen is required to prevent nocturnal cystine accumulation in cystinosis, Pediatr Nephrol 21:110-113; Brodin-Sartorius, A. *et al.,* (2012) Cysteamine therapy delays the progression of nephropathic cystinosis in late adolescents and adults, Kidney Int 81(2):179-189; Ariceta, G. Cysteamine (Cystagon®) Adherence in patients with cystinosis in Spain: Successful in Children and Challenge in Adolescents and Adults, Nephrol Dial Transplant 30(3):475-480.

[81] Dohil, Fidler *et al.,* (2005) Esomeprazole therapy for gastric acid hypersecretion in children with cystinosis, Pediatr Nephrol 20(12):1786-1793.

[82] Hess, Hoenderop *et al.,* (2012) Systematic review: hypomagnesaemia induced by proton pump inhibition, Aliment Pharmacol Ther 36(5):405-13; Khalili, Huang *et al.,* (2012) Use of proton pump inhibitors and risk of hip fracture in relation to dietary and lifestyle factors: a prospective cohort study, BMJ 344:e372; Martinez, F.D., (2012) Children, Asthma, and Proton Pump Inhibitors: Costs and Perils of Therapeutic Creep, JAMA 307(4):406-407; Fraser, LA., Leslie, W.D., Targownik, L.E. *et al.,* (2013) The effect of proton pump inhibitors on fracture risk: report from the Canadian Multicenter Osteoporosis Study, Osteoporos Int 24:1161; Tamura *et al.,* (2012) Omeprazole- and Esomeprazole-associated Hypomagnesaemia: Data Mining of the Public Version of the FDA Adverse Event Reporting System, Int J Med Sci 9(5):322-326; Toh, Ong *et al.,* (2014) Hypomagnesaemia associated with long-term use of proton pump inhibitors, Gastroenterology Report Vol 3(3) August 2015:243-253.

[83] Heidelbaugh, J. (2012) Overutilization of proton-pump inhibitors: what the clinician needs to know, J Intern Med 248(5):387-396.

anti-ulcer medication. With PROCYSBI, patients can often avoid the concomitant use of gastric acid reducers (such as proton pump inhibitors (PPIs)). PROCYSBI allows patients with already compromised kidney function to avoid PPIs, and therefore these undesirable side effects.

(f) ***Improved Quality of Life.*** As is set out in more detail below, PROCYSBI's Q12 hourly dosing schedule is also associated with significant improvements in quality of life. Patients and caregivers now sleep through the night. This is a significant benefit, as there is significant evidence to support a relationship between sleep quality and cognitive performance, behavior, and quality of life.[84] We showed in RP-103-04 that treatment with PROCYSBI significantly improved quality of life as compared to patients switched from Cystagon.[85] Further still, incidences of halitosis and body odor are vastly diminished.

(g) ***Maintenance of kidney function.*** Studies have shown that patients on PROCYSBI are able to maintain kidney function (as measured by glomular filtration rate, or GFR). Further, one study has shown normal kidney maturation and maintenance of physical growth in 80% of patients taking PROCYSBI in the first two years of life.[86] This has never been shown with Cystagon: to the contrary, Cystagon has only been shown to slow reduction in kidney function over time.

(h) ***Avoidance of more invasive therapies.*** PROCYSBI is the first drug that effectively shows potential for treating cystinosis in the long term with the hope that a patient's need for dialysis or kidney transplant will be substantially delayed or even avoided.

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[84] Kutner, Zhang *et al.,* (2007) Association of Sleep Difficulty with Kidney Disease Quality of Life Cognitive Function Score Reported by Patients Who Recently Started Dialysis, CJASN 2(2) 284-289; Astill, R. G., Van der Heijden, K. B., Van IJzendoorn, M. H., & Van Someren, E. J. W. (2012) Sleep, cognition, and behavioral problems in school-age children: A century of research meta-analyzed, Psychological Bulletin 138(6):1109-1138.
[85] Langman, C.B. *et al.,* (2014) Quality of Life is Improved and Kidney Function Preserved in Patients with Nephropathic Cystinosis Treated for 2 Years with Delayed-Release Cysteamine Bitartrate, J Pediatr 165(3):528-533.
[86] Vaisbich, M. *et al.,* (2018) Maturation of Renal Function in Young Children with Nephropathic Cystinosis Treated A Priori With Delayed-Release Cysteamine Bitratrate, (Poster 385).

93. My personal clinical experience with PROCYSBI is corroborated by the reports of other patients, and their families, published by other scholars and practitioners. It is important to understand that the literature relating to Cystagon and PROCYSBI is limited, for a few reasons:

(a) Cystagon was approved in the early 1990s without a single clinical trial, and based on the clinical experience of physicians who had administered the drug before approval;

(b) PROCYSBI was approved in the United States in 2013. I understand it was approved in Canada in 2017;

(c) PROCYSBI is the first and only cystine depleting drug that has been subjected to a randomized clinical trial for the purposes of FDA approval;

(d) As a rare disease, the patient population is exceedingly small; and

(e) The patient population is exceedingly vulnerable, and it would be unethical to conduct placebo-controlled studies in a very sick population.

94. Given that the duration of the course of treatment is over a lifetime, these gains in adherence and reduction of serious side effects are significant for cystinosis patients.

95. To date, I have seen clinical success with PROCYSBI in an overwhelming majority of my patients whereas, with Cystagon, my patients devolved to end stage renal failure and transplantation. The literature does show that a small minority of patients on Cystagon do not require dialysis or kidney transplant, but these patients are in the extreme minority. It is for this reason, among others, that I no longer prescribe Cystagon to patients.

96. Importantly, there are no data of WBC cystine increasing over time in PROCYSBI patients. Indeed, we demonstrated that PROCYSBI has a benefit of stabilizing kidney function in patients who changed from Cystagon to PROCYSBI.

97. Further, in data that we presented at the Kidney Week 2018 conference of the American Society of Nephrology in San Diego in October 2018, we were able to show that maturation of kidney function in 80% of the study population – the youngest of children with cystinosis who were taking PROCYSBI, who were naïve to treatment for cystinosis – matched that of healthy

patients who did not have cystinosis.[87] This is significant, as the literature had established that cystinosis results in an inhibition of maturation of kidney function.[88] This means that the kidney of a cystinosis patient (even a patient treated with Cystagon), at age two will never be at the same level of function as the kidney of a two year old child who does not have cystinosis. In our recent study, we saw no differentiation between the maturation in 80% of patients taking PROCYSBI and patients without cystinosis.[89]

98. I will not prescribe Cystagon to patients. In my professional judgement, there is no comparison between the two drugs: PROCYSBI is simply superior. Accordingly, I do not view PROCYSBI and Cystagon as equivalent.

Reviews of PROCYSBI

99. As mentioned above in my mandate section, I have been asked to comment on the literature that was discussed:

(a) by CADTH, in its Clinical Review Report dated February 2018, the scientific/medical/clinical issues (and only those) addressed in its Pharmacoeconomic Review Report, and its final Report dated January 2018; and

(b) in documents entitled:

(i) New Medicine Scientific Review, dated January 12, 2018;

(ii) HDAP New Medicine Review, dated February 26, 2018;

(iii) New Medicine Review Issue Paper, dated April 27, 2018; and

(iv) HDAP New Medicine Review, dated May 7, 2018.

100. I was also asked to provide my comments in the above-noted documents that pertain to my expertise.

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[87] A copy of the poster we presented is attached as **Exhibit "2"** to my report.
[88] Thoene, J.G. *et al.*, (July 1976) Intracellular Cystine Depletion by Aminothiols *in vitro* and *in vivo*, J Clin Inv, Vol 58:180-89; Markello T.C. *et al.*, (1993) Improved renal function in children with cystinosis treated with cysteamine, N Engl J Med 328:1157-62.
[89] Vaisbich, M. *et al.*, (2018) Maturation of Renal Function in Young Children with Nephropathic Cystinosis Treated A Priori With Delayed-Release Cysteamine Bitratrate, (Poster 385).

CADTH Clinical Report

101. I have reviewed the Clinical Review Report dated February 2018.

102. Under "Results and Interpretation" there is a subheading, "Included studies" which discusses the "[o]ne study that met the inclusion criteria for this review." This is a reference to RP-103-03, the crossover study discussed above. This suggests to me that the reviewer considered only this one study in the clinical review. This is a very limited view given the literature available on cystinosis, the use of Cystagon, and the burgeoning data that is available on PROCYSBI.

103. On page 7, "several weaknesses" have been identified with respect to the study's design: that it was not blinded and that the minimal clinically important difference for WBC cystine had not been established. As to blinding, as we discussed in our paper, this was not possible (given the different dosing regimens and given the body odor and halitosis issues associated with Cystagon). As to the WBC cystine biomarker, this standard was selected as the level at which optimal patients were being controlled. Moreover, this comment ignores the results showed in RP-103-04, where we demonstrated that controlling to this WBC cystine biomarker standard resulted in the long-term (two year) maintenance of kidney function and growth.

104. RP-103-03 was designed specifically to show non-inferiority of PROCYSBI to Cystagon in terms of the biomarker WBC cystine. By design, its duration was too short to show any of the outcomes listed under efficacy. Under the heading "Efficacy" it is noted that no data were available for some outcomes, including a long laundry list of outcomes that RP-103-03 was neither intended nor designed to measure: patient growth, time to renal transplant, kidney function, growth hormone usage, cognitive function, impact on thyroid function, pulmonary dysfunction, incidence of myopathy, cholesterol levels, retinopathy, vascular/cerebral calcifications, glucose control, and hypergonadotropic hypogonadism. Again, none of these outcomes were measured as an outcome in RP-103-03. Stated another way, the study was not designed to detect differences in these outcomes. What the study was designed to assess was whether, on the critical control parameter (biomarker WBC cystine), PROCYSBI was inferior to Cystagon. Indeed, that was one of the reasons behind RP-103-04: to start looking at some of these outcomes—kidney function, growth, quality of life—in a long-term study.

105. Under "Harms" the reviewer discusses the reported incidence of adverse events. While the study was not designed to study adverse events, the reviewer does not note that the Cystagon cohorts were maintained on PPI therapy, whereas on the RP-103 arm the PPI use was stopped. I have discussed this above in paragraphs 63-65.

106. On page 8, under "Potential Place in Therapy" the reviewer states that the clinical expert consulted for the review noted that RP-103-03 "really only addresses the reduction of whole WBC levels." I do not understand what is meant by the use of the word "whole," but I assume that it means biomarker WBC cystine levels, as we have been discussing. The report further states that "there remains uncertainty about the relative effects of PROCYSBI on other outcomes" but that statement is limited to RP-103-03. There is no mention of RP-103-04 or any of the other literature which shows improvement in quality of life with PROCYSBI. Further, as discussed above, we have shown PROCYSBI to be superior to Cystagon in control of the biomarker WBC cystine, using less drug.[90]

107. Under "Conclusions" the reviewer makes the point, again, that RP-103-03 was only intended to study noninferiority based on WBC cystine levels and that it was not designed to measure other outcomes (including quality of life). Yet, the reviewer seeks to make conclusions on adverse effects based on the data reported in the study. Again, we established significant improvement in quality of life in an extension study in which all but one patient chose to stay on PROCYSBI as opposed to reverting back to Cystagon. Further, in that study, adverse events per patient decreased over the life of the study.

108. On page 11 of the report, the reviewer refers, in the last paragraph, to phosphocysteamine. I am not aware that this precursor to Cystagon is still available. I have not administered this compound to a patient in more than 20 years. With the advent of Cystagon

[90] Langman, C.B. *et al.,* (2012) A Randomized Controlled Crossover Trial with Delayed-Release Cysteamine Bitartrate in Nephropathic Cystinosis: Effectiveness on White Blood Cell Cystine Levels and Comparison of Safety, Clin J Am Soc Nephrol 7:1112-1120; Langman, C.B. *et al.,* (2014) Quality of Life is Improved and Kidney Function Preserved in Patients with Nephropathic Cystinosis Treated for 2 Years with Delayed-Release Cysteamine Bitartrate, J Pediatr 165(3):528-533; RP-103-04 Clinical Study Report; Langman, C. *et al.,* Implications of Renal Impairment on Dosing of Delayed-Release Cysteamine Bitartrate (Presented at the American Society of Nephrology Conference, San Diego, CA, October 23-28, 2018, TH-PO736); Langman C. *et al.,* (2018) Implications of Renal Impairment on Dosing of Delayed-Release Cysteamine Bitartrate, J Am Soc Nephrol 29:310.

(immediate release cysteamine bitartrate), the use of phosphocysteamine ceased. As noted above at paragraph 42, this was a noxious compound with serious side effects.

109. ***Criticisms of RP-103-03.*** Between pages 15 and 30, there is a discussion of RP-103-03. On page 21, under "Critical Appraisal" the report comments on the following issues:

(a) ***Blinding.*** It is impossible to blind a trial in a case such as this, where the dosing schedules are different and patients have experience with the comparator drug.

(b) ***Washout.*** The report appears to indicate that RP-103-03 is less reliable because it did not have a "washout" period, where patients did not receive medication prior to switching over to the other arm of the study. We considered a washout period but determined that it was neither possible nor ethical to have a washout period on a drug which is required to be delivered on a continuous basis according to a strict dosing regimen in order to avoid irreversible kidney damage.[91]

(c) ***Four patient exclusions.*** This comment makes no sense to me. The p-values reported show that whether ITT (intention to treat) or per-protocol, the statistical significance of our studies was exceptionally high: p=0.0001 and 0.001, respectively.

(d) ***Non-inferiority margin.*** The non-inferiority boundary set out in the study had been accepted by multiple health regulatory agencies, including the Food and Drug Administration in the United States, by Health Canada and by the corresponding authority in Europe. Once we established non-inferiority to this margin, we (as treating physicians) felt comfortable administering PROCYSBI to patients on a long-term basis.

(e) ***GI events.*** I agree with the comment that, based on RP-103-03 alone, it is difficult to interpret the increase in GI adverse events observed during RP-103-03. However, the reviewer notes the PPI usage in both arms, which as I have discussed above, may account for the increase in GI adverse events in RP-103-03.

[91] Levtchenko C.N. *et al.,* (2006) Strict cysteamine dose regimen is required to prevent nocturnal cystine accumulation in cystinosis, Pediatr Nephrol 21:110-113.

(f) ***Erratum.*** This errata relates to a trivial change in the presentation of the data. This criticism is meaningless. It also ignores the results found in RP-103-04. In RP-103-04, the extension study, we took the basic teaching of RP-103-03 and extended it to show optimal control as well as improvements in quality of life and maintenance of growth and kidney function over a two-year period.

(g) ***WBC cystine levels.*** I agree with the clinical expert's assessment that a target of 1 nmol half cystine/mg protein is appropriate, based on RP-103-04. For the purposes of establishing non-inferiority, the benchmark we used in RP-103-03 was appropriate. I disagree with the comment on page 28 of the report that controlled individuals generally have levels between 0.2 and 0.5 nmol half cystine/mg protein. There is no data to support these levels. Moreover, this is not my experience, and it does not appear to be the experience of the clinical expert who stated that a threshold of 1nmol half cystine/mg protein is appropriate.

(h) ***Age discrepancy.*** The criticism that there appears to be a minor disconnect between the main study publication and the clinical study report,[92] is of no moment. Regardless of the age[93] and disease stage of the patients—with the exception that we were enrolling the best controlled patients for this study—RP-103-03 showed non-inferiority over Cystagon.

110. ***Limitations of immediate release cysteamine and benefits of PROCYSBI.*** On page 29, under "Potential Place in Therapy" the report states that the clinical reviewer noted that immediate-release cysteamine is "fraught with several limitations:"

(a) The Q6 hourly strict dosing schedule, mandating a middle-of-the-night dose;

(b) Higher serum peak levels following administration, leading to halitosis and "the sulphurous odor that impacts social functioning of those affected";

(c) Nonadherence to this medication occurring at a high frequency, which the reviewer identifies as a considerable issue, due to the difficulty in administering

[92] The clinical study report described three adults older than 18 (26, 23 and 20) whereas the study publication stated that there was only one patient older than 21.
[93] The ages of all patients were reported.

the drug in the middle of the night and because of the "sulphurous odor" in sweat and saliva that arises from the administration of immediate release cysteamine;

(d) The prevalence of GI side effects associated with the medication, which may limit the ability to achieve the necessary therapeutic dose.

111. I agree that all of these limitations are present with respect to Cystagon, for the reasons which I have discussed above. As the literature indicates, lifelong adherence to Cystagon is extremely poor.

112. The clinical expert further states:

> Identification of a medication that allows for twice-daily administration with stable drug levels is expected to have beneficial effects on the side effect profile and adherence, and ultimately may facilitate easier attainment of reductions of whole WBC cystine levels to within therapeutic targets. The quality of life of the families caring for a patient with cystinosis is similarly likely to be positively impacted through improved sleep and simplification of the therapeutic regimen.

I agree with this statement. Moreover, we have demonstrated these exact effects, and had done so by the time of the review. This hypothesis was borne out in RP-103-04. As a result, I was surprised to see the conclusion of this review (based solely on RP-103-03 and none of the information set forth by the clinical expert) that there remains uncertainty about the relative effect of PROCYSBI over Cystagon. In my view, this is an unfounded conclusion.

113. ***Failure to Consider RP-103-04.*** I also note that the reviewer had information relating to RP-103-04 but does not appear to rely on it in reaching the conclusions from that later study.[94] Presumably, the reviewer chose to ignore them because, as the title of the Appendix suggests, these were studies alleged to have been done without control groups. On page 59, the criticism was raised that RP-103-04 included "a select population which elected to continue treatment with RP-103." I would not have put these patients back on Cystagon, although they could have switched if they had so elected (again, 97% elected not to switch back to Cystagon). The study was designed to determine whether the same-controlled patients from the crossover study could

[94] See Appendix 5, CADTH Clinical Report.

be controlled over time simulating real world use. There is but one way to do that study, which is to use the same patients.

114. In the next paragraph, the review criticizes RP-103-04 on the basis that it was not a controlled or blinded trial. I do not understand this criticism. It is not possible to do a study like this with placebo, and I would not have extended the crossover study for two years. The benefit of RP-103 became evident to a statistically significant degree. In my view, the criticism of the sample size as being too small is not valid given the epidemiology of cystinosis as noted above. It is an ultra-rare disease. This was one of the largest studies, if not the largest, done to date. There are no published controlled studies other than this one.

115. In the summary on page 60, the reviewer notes that the majority of the patients in RP103-04 (97%) experienced adverse events. As noted, this is very likely related to the other symptoms that are associated with cystinosis and the other medications that have to be taken. What is not discussed is the fact that compared to the Cystagon treatment arm in RP-103-03 there were markedly fewer adverse events associated with PROCYSBI. But, the number of adverse events went down over time, as shown in RP-103-04.

116. ***Review of Brodin-Sartorius Study.*** In Appendix 6, there is a discussion of a retrospective analysis[95] conducted by Dr. Albane Brodin-Sartorius. In 2012, Dr. Brodin-Sartorius, of the Department of Nephrology of the Necker-Enfants Malades Hospital in Paris, reported on the long-term effects of 86 patients suffering from cystinosis and on Cystagon. At the end of her ten-year period of evaluation, only 8 out of 86 patients in the study (9%) did not have end stage renal disease. Of those 8, only 3 were in their late 20s. This is shown in Figure 1 of the article:[96]

[95] "Retrospective" means that at some point in time you go back and look to see what happened to the patients.
[96] Brodin-Sartorius, A. *et al.*, (2012) Cysteamine therapy delays the progression of nephropathic cystinosis in late adolescents and adults, Kidney International 81:179-189.

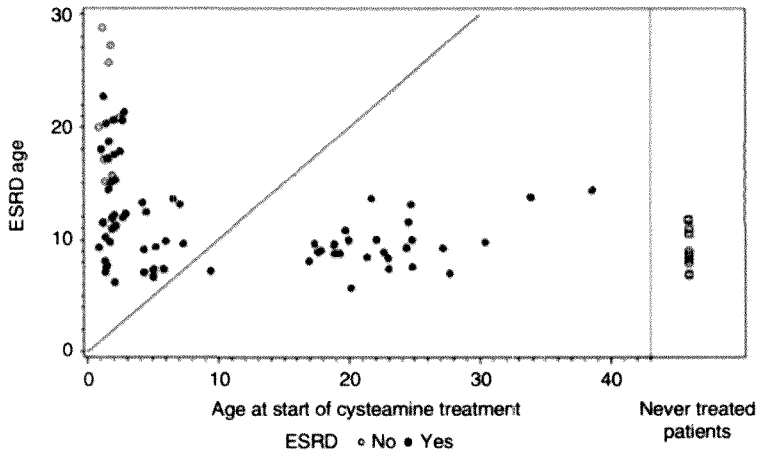

Figure 1 | The age at which end-stage renal disease (ESRD) developed according to the age at which cysteamine therapy was introduced. The $X = Y$ line separates the patients who started cysteamine before ESRD onset ($n = 40$), on the left, and, on the right, the patients who started cysteamine after ESRD onset ($n = 27$). The eight patients without ESRD are displayed with unfilled circle with their age at last follow-up. Patients who were never treated are displayed on the right part of the graph ($n = 11$).

117. The open circles in the figure above indicate that the patient has not (yet) reached end stage renal failure. However, the figure demonstrates that the majority of patients do end up with kidney failure (the solid circles), even on Cystagon.

118. In her paper, Dr. Brodin-Sartorius noted that:

> When compliance is consistent, Cysteamine [Cystagon] achieved leukocyte cystine depletion of up to 95%. However, because of inconvenient dosing requirements and barely tolerable side effects, cysteamine compliance is challenging.[97]

119. She also notes that:

> Adherence to cysteamine treatment is poor for two reasons. First, the pharmacokinetics of the drug imposes the need for oral dosing every 6 h[ours]. Second, side effects such as nausea and halitosis are frequent.[98]

[97] Brodin-Sartorius, A. *et al.*, (2012) Cysteamine therapy delays the progression of nephropathic cystinosis in late adolescents and adults, Kidney International 81:179-189 at 179.
[98] Brodin-Sartorius, A. *et al.*, (2012) Cysteamine therapy delays the progression of nephropathic cystinosis in late adolescents and adults, Kidney International 81:179-189 at 186-187.

120. The study also indicates that leukocyte cystine level was optimal in only 28% of patients,[99] suggesting that lack of adherence is a real-world reality with this medication.

121. The conclusion from this long-term retrospective study is that optimal control conditions were realized in Cystagon in less than 30% of patients and, even then, 91% of adult patients developed end stage renal failure.[100] I was disappointed in reviewing Appendix 6 to see that these important conclusions were missed or ignored. Of course, Dr. Brodin-Sartorius did not have available to her any data on PROCYSBI. As I have discussed above, with PROCYSBI, we are not seeing a decline in kidney function over time. Rather than transplanting 91% of patients (the percentage in Dr. Brodin-Sartorius' study who ended up with renal failure), it is the rare exception for a patient on PROCYSBI who requires a transplant.

CADTH Pharmacoeconomic Review Report

122. I am not a pharmacoeconomist. However, I did review the Pharmacoeconomic Review Report and have the following comments on scientific/medical/clinical issues which fall within my expertise.

123. On page 6, in Table 1, there is a section entitled "Key Limitations." As I have discussed above, the conclusion that PROCYSBI has improved effectiveness was based on expert opinion but was discounted or ignored because the conclusion was not supported by RP-103-03. I have discussed my response to this criticism above.

124. Under the heading "CDR Estimates" the report states that "[t]he efficacy of delayed-release cysteamine was revised to be equivalent to that of immediate-release cysteamine." I disagree with that assumption. The efficacy of PROCYSBI is not the same as that of Cystagon, for the reasons we have shown in our studies and as I have set out above.

125. Everything else suggested by the clinical expert (the benefits that come from better adherence) was rejected. On page 19, in the last paragraph, there is a report from Dr. Brodin-

[99] Brodin-Sartorius, A. *et al.*, (2012) Cysteamine therapy delays the progression of nephropathic cystinosis in late adolescents and adults, Kidney International 81:179-189 at 187.
[100] Brodin-Sartorius, A. *et al.*, (2012) Cysteamine therapy delays the progression of nephropathic cystinosis in late adolescents and adults, Kidney International 81:179-189.

Sartorius that roughly 75% of her patients had adherence rates that could be described as good (35%) or quite good (41%). In my view, these levels are not demonstrative of good adherence amongst the patient population. This is borne out by her data: many of her patients on Cystagon needed a kidney transplant. Thus, I do not view this adherence level as good or quite good.

126. Rejection of the expert evidence can be seen again on page 20, in Table 10, under the heading "Efficacy." In the last half of the comment field, the report states: "Feedback from the clinical expert consulted by CADTH indicated that the biologic plausibility of the assumption of an increased incremental benefit of delayed-release cysteamine over immediate-release cysteamine is rational; greater adherence will hopefully lead to delayed morbidity. **However, the magnitude of the incremental benefit, if any, is not known.** Therefore, the assumption of equivalent effectiveness in the model is acceptable" (**emphasis added**). In my view, this is a troubling and erroneous conclusion based on the available evidence (including the evidence obtained by CADTH from the clinical expert it consulted). PROCYSBI and Cystagon are not equivalently effective.

CADTH Final Report

127. ***DNA Testing.*** In the Final CADTH Report, the first item I noted was that PROCYSBI was recommended for use if the following "criterion" was met:

> For use in patients with an established diagnosis of infantile nephropathic cystinosis with documented cystinosin, lysosomal cystine transporter gene mutation.[101]

128. This recommendation means that, in order to qualify for PROCYSBI, the patient has to have been diagnosed with cystinosis and must have a documented gene mutation. It is not the standard of care to require (or even consider) demonstration of a gene mutation in determining whether to use PROCYSBI.

129. Cystinosin, a lysosomal cystine transporter is a protein that functions to transport cystine out of the lysosomes of cells. This protein is made in the body by a gene coding for this protein. Mutations (or defects) in the gene that codes for this protein cause this disorder. The disorder

[101] CADTH Final Report, pp. 1, 3.

results in this transport mechanism being ineffective with the result that cystine accumulates in the lysosome.

130. CADTH's recommendation of requiring a "documented" mutation disorder means that patients would have to undergo DNA testing. This is surprising to me, as most of my patients never get tested for the DNA abnormality. It is not common practice to demonstrate the presence of an abnormality in the gene in order to make a diagnosis of cystinosis.

131. ***Drug-related adverse events.*** In the second discussion point on page 3 of the report, the expert committee indicates that delayed-release cysteamine (PROCYSBI) was associated with "significant adverse effects, although the relative contribution of the medication and the underlying disease was not clear." I will discuss adverse effects below. Putting this issue to one side, I agree that one cannot draw the conclusion that adverse events were caused by the drug or were symptoms of other medications that these patients were taking. In addition to a cysteamine agent, these patients often take several additional therapies, many of which are toxic to the GI tract.[102]

132. ***PPIs.*** The discussion goes on to note that "patients who received delayed-release cysteamine had lower use of proton pump inhibitors..."[103] Patients taking Cystagon often require medications that reduce acid-secretion, such as proton pump inhibitors, or PPIs, to reduce GI side effects. The patients on the PROCYSBI arm of the study were given the choice of using PPIs if they felt it was necessary.

133. While the PROCYSBI product monograph cautions against concomitant use of PPIs, this is likely because of the known risk to the kidneys of taking PPIs long term. I am not aware of any specific concern about taking PROCYSBI with a PPI (as opposed to taking Cystagon with a PPI). If the PPI is not needed, then it is best not to administer it, so as to reduce the amount of potential damage to the kidneys.

134. ***Conclusion.*** The discussion concludes: "Therefore, one of the manufacturer-proposed benefits with delayed-release cysteamine ... (*i.e.,* reduced adverse effects including

[102] Cairns, D. *et al.,* (2002) Cystinosis and its Treatment, The Pharmaceutical Journal 269:615-616.
[103] CADTH Final Report, pp. 3-4.

gastrointestinal adverse effects) was not supported by data from the reviewed pivotal study."[104] It must be stressed that RP-103-03 was not designed to test side effects. It was intended to show that PROCYSBI's performance could match that of Cystagon in the best patients we had. It did that. That is why we did RP-103-04.

135. I note here that there is no reference in the CADTH Final Report to anything other than "**the** reviewed pivotal study."[105] There is no reference to the extension study (RP-103-04). These conclusions are incomplete without reference to the long-term study: over time there were fewer adverse events. If the reviewer had considered the long-term study RP-103-04, the reviewer would have concluded that, over time, the adverse events were in fact reduced.

136. Under the heading "Clinical Trials" on page 4, the report states that: "[n]o trials were available comparing delayed-release cysteamine to placebo or any other treatments." This statement shows a lack of understanding of the treatment of cystinosis. It is impossible to give a cystinosis patient a placebo, since we know that any delay in treatment causes irreversible damage.[106] No ethics board would ever approve such an unethical study and I would not conduct one. Further, there is no other primary treatment for cystinosis other than Cystagon (other than no treatment which, as set out above, would also be an unethical study to run). We had already completed a comparison of Cystagon in RP-103-03.

137. ***Purported limitations of RP-103-03.*** The report also sets out purported limitations to the study. Each of these purported limitations is incorrect:

(a) ***Small sample size.*** The RP-103-03 study has a sample size of 43 patients and evaluated the patients on an intent-to-treat and a per protocol basis. This was not a small sample, given the very small patient population. Moreover, it was adequately powered for our purposes. We demonstrated non-inferiority in the per-protocol group with a P-value of less than 0.0001 and in the intent-to-treat

[104] CADTH Final Report, p. 4.
[105] CADTH Final Report, p. 4.
[106] Gahl, W. *et al.,* (2002) Cystinosis, N Engl J Med 347(2):111-121; Gahl W. *et al.,* (2007) Nephropathic cystinosis in adults: natural history and effects of oral cysteamine therapy, Ann Intern Med 147(4): 242-250; Brodin-Sartorius, A. *et al.,* (2012) Cysteamine therapy delays the progression of nephropathic cystinosis in late adolescents and adults Kidney Int 81(2):179-189; Levtchenko C.N. *et al.,* (2006) Strict cysteamine dose regimen is required to prevent nocturnal cystine accumulation in cystinosis, Pediatr Nephrol 21:110-113.

population with a P-value of less than 0.001. (P-values of less than 0.05 confirm that results are statistically significant). Thus, I disagree that the sample size was small. It was more than adequately powered to prove the study's pre-defined endpoint.

(b) ***Short duration.*** As I have indicated above, putting a patient on a three-week regimen of a drug that either had to be dosed every six hours (in the Cystagon arm) or twice a day (in the PROCYSBI arm) was more than sufficient for the purposes of demonstrating non-inferiority.

(c) ***Noninferiority design.*** A non-inferiority design is entirely appropriate, was approved as such by the ethical review panel, and ultimately relied upon by the FDA in approving PROCYSBI. Its crossover design is internally controlled (in that the drug products are crossed-over in the same patients).

(d) ***Surrogate primary outcome (WBC cystine levels).*** The biomarker WBC cystine assay is acknowledged as the gold standard for disease control in cystinosis. The point of our study was to show that PROCYSBI maintained WBC cystine levels in the same manner that Cystagon maintained WBC cystine levels in this population of well-controlled patients.

138. Under the heading "Outcomes" on page 5, the report states that:

> [t]he WBC cystine level at which progressive renal failure and extra-renal complications can be prevented is unknown. The minimally clinically important reduction in WBC cystine in patients … has not been established.

139. This statement misunderstands cystinosis and the available literature. The goal of cysteamine therapy is to prevent cystine accumulation. Clearly, the lower one can drive the number, the better. But, there is no absolute level to drive to. The disease causes the accumulation of cystine in the lysosome. There is literature which demonstrates that, on Cystagon, WBC cystine does nothing but increase over time, leading ultimately to end stage renal disease.[107] The fact that we ran an extension study for two years and maintained kidney

[107] Nesterova, G. *et al.*, (2015) Cystinosis: renal glomerular and renal tubular function in relation to compliance with cystine-depleting therapy, Pediatr Nephrol 30:945-951; Markello, T.C. *et al.*, (1993) Improved renal function in children with cystinosis treated with cysteamine, N Engl J Med 328(16):1157-1162.

function in our patients shows that the level we chose was a good level of the biomarker (WBC cystine).

140. Under "Efficacy" on page 5, the first bullet states that:

> There was no statistical testing performed on the health-related quality of life data and there did not appear to be any differences between delayed-release cysteamine and immediate-release cysteamine in study RP103-03.

141. RP-103-03 was an efficacy study, the end-point of which (non-inferiority) was achieved to a high degree of statistical significance. RP-103-03 was not geared to measure health-related quality of life. However, as mentioned above, the subjects of RP-103-03 were given the opportunity to enroll in the extension study, RP-103-04. This paper was published in 2014 in a peer review journal.[108] The extension study conclusively demonstrated the following in patients who took PROCYSBI over a two-year period:

(a) WBC cystine was maintained at less than target value;

(b) The dose of cysteamine was reduced to 82% of the Cystagon dose to achieve these effects;

(c) Statistically significant improvement in social function, school function and total function (P-values of 0.049, 0.004 and 0.048, respectively) was observed; and

(d) GFR was maintained at 24 months **compared with the baseline values.**[109]

142. ***Importance of Adherence.*** On page 6, the report states that:

> [t]he assumption of better clinical outcomes for delayed-release cysteamine compared with immediate-release cysteamine based on feedback from one clinical expert as a result of better adherence to treatment was not appropriate. Given the importance of this parameter in the model, anecdotal evidence provided by one expert was not an appropriate method to justify this assumption and may have overestimated the magnitude of benefit associated with delayed-release cysteamine.

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[108] Langman *et al.*, (2014) Quality of life is improved and kidney function preserved in patients with nephropathic cystinosis treated for 2 years with delayed-release cysteamine bitartrate, J Pediatr 156(3):528-533 e521.
[109] "Compared with baseline" means that the control of kidney function was maintained in these patients at pre-enrolment levels.

143. I do not know the identity of the "clinical expert" being referred to, but I disagree with the report's apparent dismissal of the importance of adherence. As discussed above, there is wide agreement amongst experts in the field that adherence is critical. This point is well supported in the literature and my clinical experience.

144. ***Increased healthcare costs associated with greater life expectancy.*** In its closing paragraph, the Final Report states as follows:

> While delayed-release cysteamine may increase life expectancy compared with no treatment, it is also associated with a high rate of complications since patients live longer, which increases the total health care costs.

145. As a treating physician, I find this an astounding statement. Withholding treatment from a patient leads to death. Treating the underlying disease hopefully means that a patient is going to live longer: this is the goal that physicians strive for when they treat patients with serious ailments. Patients may also experience other complications as they age. From a physician's point of view, this is not a reason not to treat a patient or to prefer less effective therapies.

146. In any event, the preliminary data suggests that some health care costs associated with caring for these patients would be avoided. While we do not have more than six years of data with PROCYSBI, the information that we do have shows much better control of WBC cystine and better adherence with patients taking PROCYSBI. For once, unlike in the real-world experience with Cystagon where we see a decline in kidney function, ultimate kidney failure, need for transplantation, and bone breaks, with PROCYSBI I have seen:

(a) Maintenance of kidney function;

(b) In treatment naïve patients (patients who had never been treated before), a reversal of inhibition of maturation of kidney function, meaning that the kidneys in cystinosis patients at two years of age cannot be differentiated from those of two-year old children without cystinosis; and

(c) Restoration of normal sleep function.

147. These data suggest to me that these individuals and their caregivers should be much better able to live out normal lives, in which case the costs of dialysis and kidney transplants can

be avoided (or deferred). Moreover, society should benefit from the return to a better state of productivity of patients and their caregivers.

HDAP and New Medicine Review Papers

148. I was also asked to review and provide my comments on the HDAP and New Medicine Review Papers, which are summarized below.

New Medicine Scientific Review, dated January 12, 2018

149. ***Inappropriate focus on RCTs.*** On page 12, under "Clinical Trials" the author states that only one of several studies located by the reviewer was a randomized controlled trial. This was the crossover study. Other identified trials were not included because they were mainly single-arm, non-randomized trials, or results were unavailable. Other studies, by Ranjan Dohil, were identified but not included. The reluctance to consider anything other than a randomized clinical trial shows a lack of awareness of the medical literature related to rare diseases and ultra-rare diseases. The patient populations are very small and the number of researchers willing to pursue these diseases equally limited. For this reason, there are very few clinical trials on which to rely.

150. ***Comments on Ariceta.*** Pages 18 to 21 contain a discussion of the work of Dr. Ariceta, which reports that 8% of highly motivated patients had adherence problems on Cystagon. These data are different from what I have observed and the literature supports: because Cystagon must be taken every 6 hours around the clock based on the pharmacoefficiency of cystine depletion, patients must be awakened in the middle of the night to be fully adherent. One study demonstrated that less than 25% of patients were adhering to this regimen. There is evidence that failure to adhere to this strict Q6H dosing regimen results in more rapid deterioration of kidney function as WBC cystine levels rise.[110]

151. It is important to note that 57% of Dr. Ariceta's patients (reported to be 56 cystinosis patients in Spain) had a kidney transplant. As I have discussed above, and as Dr. Ariceta states, all cysteamine therapy can do is slow down the decline in kidney function—even in adherent

[110] Levtchenko, E.N. *et al.*, (2006) Strict cysteamine dose regime is required to prevent nocturnal cystine accumulation in cystinosis, Pediatr Nephrol 21:110-113.

patients.[111] In my view, however, the issue of adherence is much greater than Dr. Ariceta presents. That said, Dr. Ariceta does point out the challenges associated with adherence and she stresses the need for improvements in adherence in cystinotic patients:

> … risk factors for non-compliance with cysteamine therapy include: dosage schedules, problems with tolerance, side effects and the requirements of several medications for the control of the clinical manifestations of the disease. Moreover, other risk factors which are not exclusive to cystinosis are: limited knowledge of the disease, lack of motivation, inadequate transition of patients to adult care units and impact of the disease on quality of life.
>
> …Therefore in order to improve adherence in cystinotic patients, the recommended strategy is to correct risk factors for non-compliance …[112]

152. Putting that last sentence into practice would require waking patients on Cystagon in the middle of the night for their entire lives.

153. ***Limited review of the literature.*** Pages 27 to 29 of the Report contain a discussion about PROCYSBI, relying on a limited set of articles:

(a) Elmonem (2016), cited for the point that PROCYSBI has the "potential to improve compliance through its better dosing regimen."[113]

(b) Medic (2017), cited for the point that skipping the night time dose reduces the patient and caregiver burden of constantly interrupted sleep, and to raise the incidence of GI-related adverse events in RP-103-03 (which I have addressed above).[114]

(c) Cherqui (2012), cited with the author's question, "the patients' quality of life will be improved, but will the impact on the disease also be improved?" As discussed above, I believe that PROCYSBI does have an improved impact on cystinosis.[115]

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[111] Ariceta, G. *et al.,* (2015) Cystinosis in adult and adolescent patients: Recommendations for the comprehensive care of cystinosis, Nefrologia 35(3):304-321 at 315.
[112] Ariceta, G. *et al.,* (2015) Cystinosis in adult and adolescent patients: Recommendations for the comprehensive care of cystinosis, Nefrologia 35(3):304-321 at 315.
[113] Elmonem, M.A. *et al.,* (2016) Cystinosis: a review, Orphanet J Rare Dis 11:47.
[114] Medic, G. *et al.,* (2017) A systematic literature review of cysteamine bitartrate in the treatment of nephropathic cystinosis, Curr Med Res Opin 33(11):2065-76.
[115] Cherqui, S. (2012) Cysteamine therapy: A treatment for cystinosis, not a cure. Kidney Int 81(2):127-9.

(d) Our 2016 Controversies paper in which we report on participants' conclusions regarding the advent of PROCYSBI. We state that "further studies are needed" and that "the impact of long-acting cysteamine on adherence on side effect profile should be further evaluated." Here, we are merely stating the obvious: that, as of 2014, we had seen improvements with PROCYSBI which warrant further investigation because "adherence issues are often associated with depression, anxiety, and psychosocial issues, and at times memory function defects may also alter patient adherence. All of these factors may have an impact on education, employment, and quality of life."[116]

(e) Ahlenstiel-Grunow (2017), cited for the proposition that improvements in halitosis were seen with PROCYSBI, although the pill burden was higher. It is important to note that his paper reported that, on PROCYSBI, GFR remained stable and WBC cystine remained low (as opposed to the decrease in GFR and increase in WBC cystine seen with Cystagon).[117]

(f) Veys (2016),[118] cited (presumably) for the point that halitosis may occur in both PROCYSBI and Cystagon patients. As explained above, there is a lower incidence of halitosis and body odor associated with PROCYSBI over Cystagon – and a scientific rationale for this.[119] When I had patients on Cystagon, I would have to fumigate the treatment room after an appointment. I do not have to fumigate my treatment rooms following patients taking PROCYSBI.

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[116] Langman C.B. *et al.,* (2016) Controversies and research agenda in nephropathic cystinosis: Conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference. Kidney Int 89(6):1192-203.
[117] Ahlenstiel-Grunow, T. *et al.,* (2017) Switching from immediate to extended-release cysteamine in nephropathic cystinosis patients: A retrospective real-life single-center study, Pediatr Nephrol 32(1):91-7.
[118] Veys K.R.P. *et al.,* (2016), Cystinosis: A new perspective. Acta Clin Belg 71(3):131-7.
[119] Cairns, D. et al., (2002) Cystinosis and its Treatment, The Pharmaceutical Journal 269:615-616; Besouw et al., (2007) The Origin of Halitosis in Cystinotic Patients due to Cystinosis Treatment, Mol Genet Metab 91(3):228-233; Arieceta et al., (2015) Cysteamine (Cystagon®) adherence in patients with cystinosis in Spain: successful in children and a challenge in adolescents and adults, Nephrol Dial Transplant 30(3):475-480; Besouw et al., (2007) The Origin of Halitosis in Cystinotic Patients due to Cystinosis Treatment" Mol Genet Metab 91(3):228-233; Ahlenstiel-Grunow et al., (2016) Switching from immediate- to extended-release cysteamine in nephropathic cystinosis patients: a retrospective real-life single-center study, Pediatr Nephrol 32(1):91-97.

New Medicine Scientific Staff Summary, dates February 15, 2018

154. I have been advised by Counsel to Horizon that this document is a briefing document for the Human Drug Advisory Panel. I understand this document and the New Medicine Scientific Review discussed above were given to the HDAP members.

155. On page 15, there is a very cursory discussion of RP-104-03 and RP-103-04, with particular emphasis on the increased GI side effects seen in the RP-103 arm in the crossover study. What is not discussed is the statistically significant improvement in quality of life in controlled patients after two years as reported in RP-103-04, or maintenance of kidney function and growth. While the original articles are said to have been given to the HDAP, the report presents an unbalanced view of the results of our studies (which I discuss above in paragraphs 59-87).

HDAP New Medicine Review, February 26, 2018

156. Under "Primary Factors" there is a discussion of only one study, RP-103-03. On the basis of this study alone, the HDAP recommends that PROCYSBI be classified as a slight or no improvement over Cystagon "as it provides slight or no therapeutic improvement over Cystagon in the treatment of nephropathic cystinosis." I have two comments:

(a) First, it is an error to form this view based on RP-103-03 alone, because that study was specifically designed to show non-inferiority to Cystagon and was not designed to demonstrate superiority.

(b) Second, and more fundamentally, when considered in the context of the extension studies and the literature, I disagree with this conclusion. As I have set out above, PROCYSBI is a vast improvement over Cystagon. PROCYSBI:

(i) Maintains GFR (unlike Cystagon where kidney function declines, as shown by the available literature);

(ii) Controls biomarker WBC cystine (unlike Cystagon in which WBC cystine rises over time);

(iii) Enables age appropriate normal kidney function maturation (unlike Cystagon where we see an inhibition of normal maturation of kidney function) in naïve patients;

(iv) Provides significant improvements in quality of life; and

(v) Enables patients and caregivers to sleep through the night.

157. HDAP recommends that PROCYSBI be considered as a moderate improvement based on what they identify to be the secondary factors. I have two comments on this conclusion:

(a) First, as a practical matter, I would hardly consider PROCYSBI to be merely a moderate improvement. As I have said above, PROCYSBI represents a significant improvement over Cystagon.

(b) Second, I see nine factors listed under the heading "Secondary Factors." In the February 26, 2018 report, I see very little discussion of these factors. Below, I provide my opinion in respect of the factors that apply to PROCYSBI:

(i) **Route of administration:** Both Cystagon and PROCYSBI are oral medications. However, PROCYSBI has been specially formulated to deliver cysteamine bitartrate for absorption in the small intestine. In addition to reducing the dosing schedule for the drug, the benefits of PROCYSBI's formulation include improved bioabsorption of cysteine, reduced inter- and intra-subject variability of bioabsorption, improved GI tolerability, and reduced halitosis and body odor.[120]

(ii) **Patient convenience:** The burden on patients taking Cystagon is significant. Adherence to the strict Q6 hourly regimen is essential for efficacy. However, adherence to this regimen is difficult, with several studies establishing low adherence rates for this regimen.[121] Even in situations where the patient adheres maximally, the patient will never be

[120] Langman, C.B. *et al.*, (2012) A randomized controlled crossover trial with delayed-release cysteamine bitartrate in nephropathic cystinosis: effectiveness on white blood cell cystine levels and comparison of safety, Clin J Am Soc Nephrol 7(7):1112-1120.
[121] Levtchenko C.N. *et al.*, (2006) Strict cysteamine dose regimen is required to prevent nocturnal cystine accumulation in cystinosis, Pediatr Nephrol 21:110-113; Brodin-Sartorius, A. *et al.*, (2012) Cysteamine therapy delays the progression of nephropathic cystinosis in late adolescents and adults, Kidney International 81:179-180.

able to sleep more than six hours. This sleep interruption has been documented to increase the rate of degeneration in kidney function in those with kidney disease.[122] Further, the literature suggests that patients with cystinosis experience a significantly higher risk of unemployment, school/work absenteeism, and reduced productivity compared to their age- and sex-matched peers.[123] Improved patient convenience may help to reduce the extent to which cystinosis patients are affected by these issues.

(iii) **Compliance improvements leading to therapeutic efficacy:** The improvements realized by PROCYSBI referred to above (maintenance of biomarker WBC cystine; maintenance of growth; improvement in quality of life; reversal of inhibition of maturation of kidney function) are each related to the reformulation of cysteamine bitartrate, and, in particular, its ability to be dosed on Q12 hourly basis. The literature strongly suggests that long-term and persistent treatment leads to significantly fewer clinical complications relative to poor, short-term adherence.[124] As a result, we expect that improvement in compliance will lead to greater therapeutic efficacy.

(iv) **Caregiver convenience:** This is the corollary of patient convenience, especially in the case of young children. While studies of caregiver burden have yet to be conducted in the context of cystinosis and end stage renal disease, evidence from the context of end stage renal disease alone suggests that caregivers of patients incur a significant burden. One study

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[122] Yamamoto R. *et al.,* (2018) Sleep Quality and Sleep Duration with CKD are Associated with Progression to ESKD, Clin J Am Soc Nephrol 13:1825-1832; Ricardo, A.C. *et al.,* (2017) The Association of Sleep Duration and Quality with CKD Progression, J Am Soc Nephrol 28:3708-3715; Turek, N.F. *et al.,* (2012) Sleep Disturbances as Nontraditional Risk Factors for Development and Progression of CKD: Review of the Evidence. Am J Kidney Dis 60(5):823-833.

[123] Theodoropoulos, D.S. *et al.,* (1993) Classic nephropathic cystinosis as an adult disease, JAMA 270(18):2200-2204; Brodin-Sartorius, A. *et al.,* (2012) Cysteamine therapy delays the progression of nephropathic cystinosis in late adolescents and adults, Kidney International 81:179-180; Brodin-Sartorius, A.M. *et al.,* (2012) Cysteamine therapy delays the progression of nephropathic cystinosis in late adolescents and adults, Kidney Int 81(2):179-189.

[124] Markello, T.C. *et al.,* (1993) Improved renal function in children with cystinosis treated with cysteamine, N Engl J Med 328(16):1157-1162; Kimonis, V.E. *et al.,* (1995) Effects of early cysteamine therapy on thyroid function and growth in nephropathic cystinosis, J Clin Endocrinol Metab 80(11):3257-3261; Kleta, R. *et al.,* (2004) Long-term follow-up of well-treated nephropathic cystinosis patients, J Pediatr 145(4):555-560.

showed that caregivers of patients receiving hemodialysis or peritoneal dialysis had significant impacts on their quality of life (measured using the SF-36, caregiver burden scale,[125] and cognitive index of depression).[126] Among other things, this study showed that 32% of caregivers had signs of depression.[127] In the case of PROCYSBI, parents who once had to wake up in the middle of the night to administer a dose of Cystagon to their children no longer need to do so. This has obvious practical impact on the lives of caregivers, who can now sleep through the night.

(v) **Duration of usual course of treatment:** Both Cystagon and PROCYSBI have to be taken for life, even after kidney transplantation. Our hope is that, even though PROCYSBI will have to be taken for life, transplantation can be avoided, or markedly delayed. As the reviewer noted in the Pharmacoeconomic Study, "[...] delayed release may increase life expectancy," which means that cystinosis patients will take this drug longer than they would Cystagon.

(vi) **Success rate:** I have moved all of my current patients onto PROCYSBI because, in my view, it is more successful than Cystagon in delaying progress to end stage renal failure. Now that we have seen the results with PROCYSBI – particularly as they pertain to maintenance of stable kidney function, maintenance of growth, improvements in quality of life, reversal of an inhibition of maturation of kidney function – it cannot be said that Cystagon achieves *optimal* therapeutic effect.

(vii) **Percentage of affected population treated effectively**: The number of cystinosis patients who are being effectively treated has increased with the advent of PROCYSBI. In RP-103-04, we demonstrated that, over two

[125] The SF-36 is a scale that assesses caregiver burden. In this study, caregiver emotional aspect, vitality, and mental health were most affected.
[126] Belasco, A.D. *et al.*, (2006) Quality of life of family caregivers of elderly patients on hemodialysis and peritoneal dialysis, Am J Kidney Dis 48(6):955-963.
[127] Using the cognitive index of depression: Belasco, A.D. *et al.*, (2006) Quality of life of family caregivers of elderly patients on hemodialysis and peritoneal dialysis, Am J Kidney Dis 48(6):955-963.

years, we were able to control the WBC cystine biomarker, maintain kidney function, and use less drug over time.

(viii) **Disability avoidance/savings:** As set out above, PROCYSBI enables patients and their caregivers to sleep through the night, and to thereby avoid the impact of sleep deprivation. PROCYSBI also reduces the need for PPIs, which as I have discussed can cause further kidney, bone, and GI issues for an already vulnerable population. These benefits suggest that PROCYSBI helps avoid health issues that are both detrimental to patients and caregivers and costly for the health care system.

Further, PROCYSBI delays the time to end stage renal failure, and therefore delays the need for dialysis and transplantation. Dialysis, alone, is extremely expensive, accounting for approximately 1-2% of the NHS budget in the United Kingdom (which is a large share, given that this cost relates to 0.05% of the UK population).[128] Transplantation is also extremely expensive, costing hundreds of thousands of dollars in the United States.[129] Delaying the need for these procedures saves costs and allows patients to have more years unburdened by end stage renal disease.

158. Based on this report, and without an understanding of all of these factors, a reader would form the erroneous view that PROCYSBI is only marginally better than Cystagon. As I have set out above, in my view, this is not the case.

New Medicine Reviews dated April 2017 and May 2019

159. I have two brief comments on the two additional New Medicine Reviews I was asked to review:

(a) ***Issue Paper, dated April 27, 2017.***[130] This document appears to be a briefing document whereby the HDAP is asked to reconsider is recommendations made in

[128] Sharif, A. and Baboolal K. (2011) Update on dialysis economics in the UK, Perit Dial Int 31 Suppl 2:S58-62.
[129] Milliman (2014) 2014 US organ and tissue transplant cost estimates and discussion.
[130] Although this Issue Paper is dated April 27, 2017, I have been advised by Counsel to Horizon and have assumed that it was written in April 27, 2018.

the February 26 report. On page 3, the report states: "Please see the New Medicine Scientific Review prepared by the Drug Information Centre (DIC) dated January 12, 2018 and the New Medicine Scientific Staff Summary dated February 1, 2018 for a complete review of clinical trials, guidelines and expert opinions on the use of PROCYSBI in patients with nephropathic cystinosis." I have reviewed these documents, as I have discussed above. I would not call this collection of information a "complete review" of the literature or the treatment of cystinosis with PROCYSBI.

(b) ***HDAP New Medicine Review, May 7, 2019.*** In this report, the HDAP confirmed its recommendation set out in the report discussed above at paragraphs 156-158. The summary information given is so short and lacking in detail that it is hard to know what information was considered, or the reasons given for maintaining the recommendation.

Questions Posed by Counsel

160. Counsel for Horizon have posed the following statements to me and have asked me whether I agree with them:

(a) Treatment with cysteamine bitartrate significantly delays the need for kidney transplant and substantially increases patients' lifespans, even after transplant.

(b) There is no therapeutic advantage between PROCYSBI and Cystagon: neither is inferior to the other in terms of efficacy of treatment, and both lead to the same therapeutic outcome.

(c) PROCYSBI offers no clinical therapeutic advantage -- its only advantage is a reduction in dosing schedule, which may result in increased compliance rates.

161. In the section that follows, I provide my views on each of these questions.

162. ***Treatment with cysteamine bitartrate significantly delays the need for kidney transplant and substantially increases patients' lifespans, even after transplant.*** This is a statement that must be treated with much care. For the rare patient who is fully adherent on Cystagon, the statement may read: "for treatment with Cystagon may delay the inevitable need for kidney

transplant and increase patients' lifespan, even after inevitable transplant."[131] For patients taking PROCYSBI, while the treatment history is short (and therefore the scientific literature is not well developed), the statement should read: "treatment with PROCYSBI has significantly delayed the need for kidney transplant and would substantially increase patients' lifespans, even after transplant, if the latter is necessary."[132]

163. ***There is no therapeutic advantage between PROCYSBI and Cystagon: neither is inferior to the other in terms of efficacy of treatment, and both lead to the same therapeutic outcome.*** I strongly disagree. That statement appears to be premised on the fact that RP-103-03 was a non-inferiority study. As I have explained above, RP-103-03 was a comparison, in the best controlled Cystagon patients,[133] so that Horizon could meet these "best in class" results. Because it was not inferior to Cystagon, it was approved.

164. ***PROCYSBI offers no clinical therapeutic advantage -- its only advantage is a reduction in dosing schedule, which may result in increased compliance rates.*** There is no clinical evidence that patients are adherent on Cystagon in the long term. As set out above, the only hope in this therapy is to delay or retard the steady decline to end stage renal failure. As Dr. Brodin-Sartorius showed in 2012, the majority of patients on Cystagon inevitably experience significant degradation in their condition. Moreover, patients who take Cystagon will necessarily have disturbed sleep, which leads to a worsening in kidney function, not to mention the adverse effects that sleep deprivation has on patients and caregivers.

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[131] I note that there is no study of Cystagon being able to maintain WBC levels or normal kidney function. On Cystagon, all the drug is doing is delaying the inevitable.

[132] I note again that we have seen remarkable improvements with PROCYSBI. First, in a recent study, we showed that in the first two years of life, patients on PROCYSBI showed no inhibition of maturation: at two years there was no differentiation between the kidneys of 80% of cystinosis patients treated with PROCYSBI and those of normal patients. Second, we have shown that with PROCYSBI we have been able to maintain WBC and GFR control. We do not have the long-term data to state emphatically that a PROCYSBI patient will never need a transplant, but our hope is that better adherence will help to achieve that outcome.

[133] As I have indicated above, this was the first time that Cystagon had been administered to patients in a formal clinical trial.

CONCLUSION

165. As set out above, to date, I have seen clinical success with PROCYSBI in an overwhelming majority of my patients. In contrast, my patients who were on Cystagon devolved to end stage renal failure and transplantation.

166. As a physician, I aim to provide the best medical care to my patients. As such, I have no professional view on the cost of a drug or treatment. Indeed, I am not qualified to offer such an opinion. My hope in prescribing PROCYSBI is that my patients can avoid the need for dialysis, transplantation and progressive kidney disease exacerbated by sleep deprivation.

167. I will not prescribe Cystagon to patients. In my professional judgement, there is no comparison between the two drugs: PROCYSBI is simply superior. Accordingly, I do not view PROCYSBI and Cystagon as equivalent. Were it true that PROCYSBI is equivalent to Cystagon, Cystagon would be able to be taken every 12 hours. No physician would prescribe Cystagon for use on a 12-hour schedule. Further, the literature demonstrates that Cystagon cannot, and does not, fully arrest the degradation in kidney function for the vast majority of patients. By contrast, since I began prescribing PROCYSBI in 2013, none of my patients have yet required dialysis or renal transplantation. Patients also experience less adverse events, which leads to greater compliance and improves the efficacy of cysteamine therapy. In my clinical experience, these are significant improvements when compared to patients treated with cystinosis over Cystagon.

September 9, 2019

Craig B Langman MD

Craig B. Langman

APPENDIX A – EXPERT WITNESS DECLARATION

PATENTED MEDICINE PRICES REVIEW BOARD

IN THE MATTER OF the *Patent Act*,
R.S.C., 1985, c. P-4, as amended

AND IN THE MATTER OF
Horizon Pharma (the "Respondent")
and the medicine Cysteamine Bitartrate sold by the Respondent under the trade name PROCYSBI®

DECLARATION OF DR. CRAIG LANGMAN

I, Craig Bradford Langman, M.D., of the City of Chicago in the State of Illinois in the United States of America, declare that:

(a) I have been retained by the Respondent to provide evidence in this matter;

(b) it is my duty to provide evidence in relation to this proceeding as follows:

(i) to provide opinion evidence that is impartial;

(ii) to provide opinion evidence that is related only to matters that are within my area of expertise; and

(iii) to provide any additional assistance that the Board may reasonably require to determine a matter at issue.

(c) I acknowledge that the duties referred to above take precedence over any obligation which I may owe to any party by whom or on whose behalf I am engaged.

Dated at Chicago, Illinois, USA
this 9th day of September 2019.

Craig B Langman MD

EXHIBIT "1"

CURRICULUM VITAE

NAME: Craig Bradford Langman

PROFESSIONAL ADDRESS:
Ann & Robert H. Lurie Children's Hospital of Chicago
Division of Kidney Diseases
225 E. Chicago Avenue, #37
Chicago, Illinois 60611
Phone: 312-227-6160
Fax: 312-227-9406
Voice Mail: 312-227-6622

BIRTHPLACE: Philadelphia, Pennsylvania (USA)

EDUCATION:

1970	Honorary B.S. - Central High School, Philadelphia
1973	Temple University, Philadelphia
1977 M.D	Hahnemann University, Philadelphia
1977-1979	Residency in Pediatrics, Children's Hospital of Philadelphia
1979-1981	Fellowship in Pediatric Nephrology, Children's Hospital of Philadelphia and University of Pa.

APPOINTMENTS:

ADMINISTRATIVE:

1995-	Division Head, Kidney Diseases
1991-1996	Associate Director General Clinical Research Center Northwestern University Medical School and Northwestern Memorial Hospital
1989-1993	Associate Chair of Pediatrics Research Program Development, Department of Pediatrics Northwestern University Medical School

ACADEMIC:

2002	Isaac A. Abt, M.D. Professor of Kidney Diseases Northwestern University Feinberg School of Medicine
1993	Tenured Professor of Pediatrics Northwestern University School of Medicine
1989	Member Graduate School Faculty Member Graduate School Faculty Northwestern University
1987-1993	Tenured Associate Professor of Pediatrics Northwestern University School of Medicine
1985-1987	Assistant Professor of Pediatrics Northwestern University School of Medicine
1981-1985	Assistant Professor of Pediatrics, Pritzker School of Medicine, University of Chicago

PROFESSIONAL:

1996 -	Senior Attending Physician, Department of Pediatrics Evanston Northwestern Healthcare
1991 -	Associate Physician, Department of Pediatrics Northwestern Memorial Hospital, Chicago
1985 -	Attending Physician, Division of Nephrology Children's Memorial Hospital, Chicago
1981-1985	Attending Physician, Division of Nephrology Departments of Pediatrics and Internal Medicine Michael Reese Hospital and Medical Center Chicago, Illinois

CERTIFICATION:

1978	Diplomat, National Medical Boards
1982	American Board of Pediatrics
1982	American Board of Pediatrics Sub-board of Pediatric Nephrology
1990	Voluntary Recertification, American Board of Pediatrics and Sub-board, Pediatric Nephrology
2014	Maintenance of Certification, through 2019

RESEARCH and Other SOCIETIES:

Cochrane Collaboration
Society for Pediatric Research
American Federation for Clinical Research
American Society of Nephrology
American Society of Bone and Mineral Research
International Council of Calcium Regulating Hormones
International Society for Renal Nutrition and Metabolism
Association of Clinical Scientists
International Bone and Mineral Society
International Society of Nephrology
International Pediatric Nephrology Association
Midwest Society of Pediatric Research
American Academy of Pediatrics
Research on Calculus Kinetics (ROCK)
Pediatric Academic Society
American Society of Pediatric Nephrology

NATIONAL COMMITTEES (in alphabetical order):

	AMERICAN ACADEMY OF PEDIATRICS, SECTION OF NEPHROLOGY, THE AMERICAN SOCIETY OF PEDIATRIC NEPHROLOGY, AND THE NATIONAL KIDNEY FOUNDATION PATIENT EDUCATION COLLABORATIVE
2018 - 2020	Steering Committee, Writing Panel
	AMERICAN BOARD OF PEDIATRICS
1989-1995	Sub-board of Pediatric Nephrology
1993-1995	Chair, Credentials Committee
1994-1996	**President**, Sub-board of Pediatric Nephrology
	AMERICAN SOCIETY FOR BONE AND MINERAL RESEARCH,
1985-1986	CHAIRMAN, NORTH AMERICAN PEDIATRIC BONE AND MINERAL
1985-1987	WORKING GROUP
1986-1998	EDUCATION COMMITTEE, **ASSOCIATE EDITOR**, PRIMER ON THE METABOLIC BONE DISEASES
	AMERICAN SOCIETY OF PEDIATRIC NEPHROLOGY
1987-1989	NOMINATING COMMITTEE
1989-1991	LONG-RANGE PLANNING COMMITTEE
1992-1997	COUNCIL
1993-1996	CHAIR, PROGRAM DIRECTORS COMMITTEE
1993-1996	CHAIR, PUBLIC POLICY COMMITTEE
1996-1997	**PRESIDENT**

2004 –	**COCHRANE RENAL GROUP** – Referee/Reviewer
	COUNCIL OF AMERICAN KIDNEY SOCIETIES
1995-1997	Councilor
1996-1997	**President**
NATIONAL COMMITTEES (cont'd):	
2002 –	**ILLINOIS MEDICARE PART B**, Carrier Advisory Committee
	INTERNATIONAL PEDIATRIC NEPHROLOGY ASSOCIATION
1994-1997	Publications Committee
1998-1999	National Organizing Committee, Fifth Symposium on Growth and Development in Children with Chronic Renal Failure, New York City, March.
2003-2004	National Organizing Committee, Sixth Symposium on Growth and Development in Children with Chronic Renal Failure, Heidelberg Germany, April 2004.
2017 -	**MAKING DIALYSIS SAFER FOR PATIENTS COALITION** Member
	MIDWEST SOCIETY FOR PEDIATRIC RESEARCH
1992-1993	Council
1993-1994	President-Elect
1994-1995	**President**
	NATIONAL INSTITUTES OF HEALTH
1993-1994	Task Force for 10-year reorganization of the National Center for Research Resources
1986-1989	Special Study Section Reviewer, General Medicine B Reviewers Reserve
	NATIONAL KIDNEY FOUNDATION
1990-2002	Scientific Advisory Board
1991-1994	Young Investigator Grant Review Committee
1995-1998	Research Steering Committee
1995-1998	Public Policy **Chair,** Pediatric K-DOQI Guidelines on Osteodystrophy
2005-2007	K/DOQI Advisory Board Member
2003-2006	**NATIONAL KIDNEY FOUNDATION OF ILLINOIS,** Chairman, Grants Review Committee
1994-1997	**NORTH AMERICAN PEDIATRIC RENAL TRANSPLANT COOPERATIVE STUDY**, Growth Advisory Board
2016 –	**RARE BONE DISEASES NETWORK** MEDICAL ADVISORY COUNCIL MEMBER
2009 -	**RARE BONE DISEASES NETWORK, Chair,** Scientific Advisory Board

2009- **NATIONAL OSTEOPOROSIS FOUNDATION**
EDITORIAL BOARD MEMBER

NATIONAL and INTERNATIONAL CONFERENCES

Organizer and Co-Chair, NIH Workshop on Oxalosis and Stone Disease, Bethesda, MD, 8-9 December 1998.
National Organizer, Workshop on Molecular Disturbances in Growth, International Pediatric Nephrology Association, New York, March, 1999.
Organizer, 1st International Conference on Children's Bone Health, 4-7 May 1999, Maastricht, Netherlands.
Chair, 2nd NIH Workshop on Oxalosis, Columbia, MD 16-17 November 2000.
Organizer, 2nd International Conference on Children's Bone Health, June, 2002, Sheffield, England.
Co-Chair, 3rd NIH Workshop on Oxalosis, Annapolis MD, November 2003.
Organizer, 5th Workshop on Molecular Disturbances in Growth, International Pediatric Nephrology Association, Heidelberg Germany, March 2004.
Co-Director and Invited Speaker, NIH-ASBMR Conference on Effects of Pharmacological Agents on Bone in Children
Vice-Chair, FASEB Summer Research Conference: Calcium and Oxalate in Biology, 2005.
Chair, 4th International Conference on Children's Bone Health (www.ICCBH4.org), Montreal, CA, 21-24, 2007.
Co-Chair, 1st NIH Conference on Rare Bone Disease, Bethesda MD, 2009.
Organizer, 6th International Conference on Children's Bone Health, Rotterdam, June 2013
Chair, 11th International Primary Hyperoxaluria Workshop, Chicago, June 2014
Co-chair, 7th International Conference on Children's Bone Health, Salzburg, Austria June 2015

LICENSURE

Illinois 036063022

MAJOR GRANT SUPPORT:

NIH	Biomedical Research Support Grant (Michael Reese). July 1982-June 1984. "In-vitro studies of the renal 5-hydroxyvitamin D_3-1-hydroxylase"
NIH	New Investigator Award, DK-36821. January, 1985-December, 1987. "Mechanisms of impaired $1,25(OH)_2D_3$ synthesis in acidosis"
NIH	Multipurpose Arthritis Center Grant P60 AR30692 F. Schmid, Program Director, December 1986 - November 1989. "Vitamin D Metabolism in Experimental Arthritis in Rats." C.B. Langman, Principal Investigator
NIH	Nephrolithiasis Program Project, University of Chicago, PO1 DK33949, Fredric L. Coe, Director. September 1987 - August 1991. "Mechanisms of reduced $1,25(OH)_2D_3$ synthesis in acidosis." C.B. Langman, Principal Investigator
NIH	Biomedical Research Support Grant 2 SO7 RR05475, 4/1/89 - 3/31/90, C.B. Langman, Program Director
NIH	General Clinical Research Center, Northwestern University, RR 00048 12/1/90 - 11/30/96, Harry Beatty, M.D., Program Director; Gary Robertson, MD, Director; C.B. Langman, Associate Director
NIH	"Epidemiology of Osteoporosis in Women with Lupus," Renewed through 2005. R. Ramsey-Goldman, MD, Principal Investigator, C.B. Langman, Consultant.
NIH	"Establishing the Precursors of Osteoporosis in Children," 9/30/07-8/31/11, C.B. Langman, Co-Investigator
NIH	"Identification of a Multi-Analyte Profile for Primary Hyperoxaluria," 7/1/09-12/31/14, CB Langman, MD, Principal Investigator
NIH	"Validation of Urine Proteomic Profiling from Primary Hyperoxaluria (PH1) International Registries Compared to Those with Stone Formers of a Differing Etiology," 9/30/09-9/29/11, CB Langman, MD, Principal Investigator
NIH	"Consortium for Hereditary Causes of Nephrolithiasis and Renal Failure," Project 1: Primary Hyperoxaluria, CB Langman, Co-PI. 9/1/09 – 8/31/18.
NIH-NIDDK	"Chronic Kidney Diseases in Children," 3/1/05-7/31/18, CB Langman, MD, Center PI
NIH-NICHD	"Pilot Study: Proteomics of Primary Hyperoxaluria Type I: A Rare Calcium Oxalate Stone Disease" C.B. Langman, co-PI 9/20/14-6/30/18

CMIER	"Bone Mineral Density in Cystic Fibrosis: Effects of Growth Hormone," C.B. Langman, MD, Principal Investigator. 1/03-1/04.
Medical Research Council of South Africa	"Pilot Study of Risk for Development and Progression of Chronic Renal Failure in South African and American Black Children and Adolescents," C.B. Langman, Co-Principal Investigator. 2005-2008.
Altus Pharmaceuticals	"Scientific Directorship of Phase III TheraCLEC Clinical Trials," C.B. Langman, PI (6/06-5/09).
Raptor Pharmaceuticals	"Amendment 5, A Long-Term, Open-Label, Safety and Efficacy Study of Cysteamine Bitartrate Delayed-Release Capsule in Patients with Cystinosis" C.B. Langman, worldwide PI, 1/14/13-6/30/14
Raptor Pharmaceuticals	"Amendment 9, A Long-Term, Open-Label, Safety and Efficacy Study of Cysteamine Bitartrate Delayed-Release Capsule in Patients with Cystinosis" C.B. Langman, worldwide PI, 9/1/10-5/13/17
Alexion	"EVIDENCE – Evaluation of Potential Predictors of Disease Progression in Patients with aHUS, Including Genetics, Biomarkers, and Treatment" C.B. Langman, site PI, 12/1/16-9/30/17
Alexion	"An Observational, non-interventional multi-center, multi-national study of patients with Atypical Hemolytic-Uremic Syndrom (aHUS Registry)" C.B. Langman, site PI, 1/1/14-12/31/17
Alexion	"An Observational, Longitudinal, Prospective, Long-Term Registry of Patients with Hypophosphatasia)" C.B. Langman, site PI, 1/1/2015-12/31/2020

EDITOR:

	Pediatric End-Stage Kidney Disease, issue of *Advances in Renal Replacement Therapy*, 8:155-222, 2001.
	Advances in Pediatric Bone Metabolism, issue of *Clinical Reviews in Bone Metabolism*, April, 2004.
Ongoing-	Pediatric Nephrology textbook, www.medscape.com
	Rare Bone Disease, Current Reports in Osteoporosis

EDITORIAL BOARD MEMBERSHIPS:

Surgeon General's Report on Osteoporosis and Bone Health (2003-2004)
Senior Associate Editor, *American Journal of Nephrology* (2002-2010)
Journal of Renal Nutrition (2002-2005, 2007-2010)
Journal of Bone and Mineral Research (2003-2008)
Associate Editor, *Primer on Metabolic Bone Diseases*, American Society of Bone and Mineral Research (1988-) 1st through 5th (current) editions
Pediatric Endocrinology (1991- 2002)
Pediatric Nephrology (1994-1997)
Advances in Renal Replacement Therapy (1997 - 2003)
Pediatric Nephrology, Section Editor, *"Hereditary disease/Tubular disorders,"* (2006 -
Editorial Board, *European Journal of Pediatrics* (2006-2012)
Internet Journal of Nephrology (2008 -
Clinical Journal of the American Society of Nephrology (2007-2017)
National Osteoporosis Foundation (2009-
Editorial Board, *Journal of Bone and Mineral Research* (January 2016 – December 2018)
Co-Editor, Rare Bone Diseases, *Current Osteoporosis Reports,* 2000-Present

JOURNAL REFEREE:

American Journal of Kidney Diseases
American Journal of Nephrology
American Journal of Physiology Renal; Endocrinology; Regulatory Physiology
Bone
Calcified Tissue International
Clinical Journal of the American Society of Nephrology
Clinical Pediatrics
Critical Care Medicine & Pediatric Critical Care Medicine
European Journal of Endocrinology
European Journal of Pediatrics
Journal of the American Medical Association
Journal of the American Society of Nephrology
Journal of Bone and Mineral Research
Journal of Clinical Investigation
Journal of Pharmacology and Experimental Therapeutics
Journal of Emergency Pediatrics
Journal of Pediatric Gastroenterology and Nutrition
Journal of Pediatrics
Kidney International
Nephron
New England Journal of Medicine
Pediatric Nephrology
Pediatric Annals
Pediatrics
Proceedings of the National Academy of Sciences

LOCAL COMMITTEES:

CHAIR:

2011	Chair, Ad-Hoc Committee on Tenure, Professor of Medicine, Feinberg School of Medicine, Northwestern University
2010	Chair, Ad-Hoc Committee on Tenure, Professor of Medicine, Feinberg School of Medicine, Northwestern University
2008	Chair, Ad-Hoc Committee on Promotion and Tenure, Professor of Urology, Feinberg School of Medicine, Northwestern University
2006	Chair, Ad-hoc Committee on Promotion and Tenure, Professor of Medicine, Gastroenterology, Feinberg School of Medicine, Northwestern University
2004	Chair, Ad-hoc Committee on Promotion and Tenure, Professor of Medicine, Nephrology, Feinberg School of Medicine, Northwestern University

2002-2004	Chair (tri-chair), Search Committee, Stem-Cell Immunobiology, Department of Pediatrics, Children's Memorial Institute for Education & Research, Northwestern University Medical School
2001	Chair, Search Committee, Human and Molecular Genetics, Department of Pediatrics, Northwestern University Medical School
2001	Chair, Ad-hoc Committee on Promotion and Tenure, Professor of Urology, Northwestern Medical School
1998	Chair, Ad-hoc Committee on Promotion and Tenure, Clinical Professorship of Medicine, Northwestern Medical School
1996-1997	Chair, Search Committee, Division Head of Gastroenterology and Liver Diseases, Department of Pediatrics, Northwestern University Medical School and Children's Memorial Hospital
1994	Chair, Schweppe Research Award Committee, Northwestern University Medical School
1991-1992	Chair, Dean's Intramural Research Committee, Northwestern University
1991-1992	Chair, Research Affairs Committee, Northwestern University
1990-1991	Chair, Fellowship Committee, Department of Pediatrics
1989-1991	Chair, Institutional Review Board, Children's Memorial Hospital

MEMBER:

2005- 2010	Children's Memorial Research Committee, Children's Memorial Research Center
2000-	Center for Genetics, Feinberg School of Medicine, Northwestern University Medical School
1999-	Physician Advisor, Utilization Management Committee, Children's Memorial Hospital
1998-	Children's Memorial Hospital, Department of Pediatrics Quality Improvement Steering Group
1995- 2000	Chicago and Illinois Heart Association, Joint Peer Review
1993-1995	Task Force on Research, "Outlook 2000," Northwestern University Medical School
1992-1995	Faculty Advisory Committee, Children's Memorial Institute for Education and Research
1992	Search Committee for Northwestern University Vice President for Research/Dean of Graduate School
1989-1992	General Faculty Committee, Northwestern University
1988-1991	Dean's Research Committee, Northwestern University
1988-2013	Associate Member, Lurie Cancer Center, Northwestern University

1987-1990	Councilor, Medical Faculty Senate Northwestern University School of Medicine
1987-1989	CMIER Research Policy Advisory Committee
1985-1987	Institutional Review Board, Northwestern University

EXTERNAL ADVISORY COMMITTEES

2003-2005	NIH Hyperoxaluria and Dent's Disease Registry
2016-	Chicago Medical Society, Academic Physician Committee

PH.D. COMMITTEES:

1988-	Rita Lucas.
1989	"The role of polyamines in bone resorption"
1989-1991	Geetha Shankar:
	"The role of second messengers in bone resorption"
2009	Nigel David Toussaint:
	"Calcium, calcification and cardiovascular risk in chronic kidney disease"
2016	D. SRI HARI S. KUMAR RAJU
	STUDY OF ATHEROMA, NON ATHEROMA RISK FACTORS AND IMPORTANCE OF MAYO CLINIC QUADRATIC EQUATION IN CHRONIC KIDNEY DISEASE
2018	Emma Brassell
	"Nonsense suppressor therapy of cystinosis"

POST-DOCTORAL TRAINEES (not Fellows)

	Current Position
1989-1990	Susan Paulsen, Ph.D.
	Division Director, Searle
1993	Heloisa Cattini Perrone, M.D. Ph.D.
	Head, Pediatric Nephrology Sao Paolo, Brazil
1997-1999	Bernd Hoppe, M.D
	Head, Pediatric Nephrology
	Cologne, Germany
2000-2001 &	Gema Ariceta, M.D.
2005-2006 (Fullbright	Head, Pediatric Nephrology
Scholar)	Santiago, Spain
2014-2015	Fang Deng, MD, PhD, Anouilh University, China

DOCTORAL DISSERTATION REVIEW

2018	Nokwanda Zamahlubi Gumede Master of Medical Science, University of KwaZulu-Natal

GRADUATE COURSES TAUGHT:

1989-92:	Advanced Topics in Cell Biology: Fundamentals of Neurotransmitter and Endocrine Receptor Pharmacology
1990-95:	Advanced Topics in Cell Biology: Calcium as Second Messenger
1990-1997	Advanced Dental Pharmacology: Bone and Mineral Homeostasis
2017:	Bone Physiology, Department of Pharmacology

ADVISOR:

1991-	Faculty Associate, Shepard Residential College, Northwestern University
1990-	Freshman and Sophomore Advisor, Northwestern University Medical School
1988-	Pediatric Residents, Department of Pediatrics, Children's Memorial Hospital

AWARDS/HONORS:

1997	David Cornfeld Lectureship in Pediatric Nephrology, Children's Hospital of Philadelphia, University of Philadelphia
1997	Listed in *American Men and Woman of Science*
1997	Top 100 Doctors in Chicago, Chicago Magazine
1996	Best Doctors, Pediatric Nephrology, American Health Magazine
1991, 1994, 1998, 2000, 2002, 2004	Listed in *The Best Doctors in America,* Pediatric Stone Disease, Pediatric Nephrology
1992	Society of Pediatric Research Laboratory Scholarship
1999-latest edition (2011)	Listed in *How to Find the Best Doctors: Chicago Metropolitan Area*
1999	Life Member, *Who's Who*, Certificate #114638
2000-	Mary Weston Visiting Professorship University of Natal, Durban, South Africa
2002-	Who's Who in America, Life Member
2016	Demetrius Ellis Endowed Lectureship: University of Pittsburgh

2019	Leighton Hill Lectureship, Texas Children's Hospital
2019	Jose Strauss Visiting Professor Award, 46th Annual Pediatric Nephrology Symposium

COMMUNITY SERVICE:

1992-	Medical Advisory Board, Lincoln Park Zoo
1995-97	Illinois Department of Health Coalition on Osteoporosis
1997-	Chicago Medical Society, #041-09-77-086-3
1998-	Medical Advisory Board, NKF Illinois
2003-	Board of Directors, NKF Illinois
2005-	Reviewer, Project Proposals in Basic Science, Ministry of Science and Environmental Protection of the Republic of Serbia

ORIGINAL ARTICLES

1. Langman CB, Falkner B, Katz S. Renal histopathologic changes in a child with Lawrence-Moon-Biedel Syndrome. J Clin Pathol 30:1077, 1977.
2. Falkner B, Onesti G, Angelakos ET, Fernanades M, Langman CB. Cardiovascular response to mental stress in normal adolescents with hypertensive parents. Hypertension 1:23, 1979.
3. Baumgart S, Engle W, Langman CB, Fox WW, Polin RA. Monitoring radiant power in the critically ill newborn under a radiant warmer. Critical Care Medicine 8:721, 1980.
4. Langman CB, Engel W, Baumgart S, Fox WW, Polin RA. The diuretic phase of respiratory distress syndrome and its relationship to oxygenation. Journal of Pediatrics 98:462, 1981.
5. Baumgart S, Langman CB, Sosulski R, Fox WW, Polin RA. Guidelines for fluid, electrolyte and glucose maintenance in the low birthweight infant. Clinical Pediatrics 21:476, 1982.
6. Langman CB, Mazur A, Baron R, Norman ME. 25-hydroxyvitamin D_3 therapy of juvenile renal osteodystrophy: Beneficial effect on linear growth velocity. Journal of Pediatrics 100:815, 1982.
7. Moore ES, Langman CB, Favus MJ, Coe FL. Secondary hyperparathyroidism in children with idiopathic hypercalciuria. Journal of Pediatrics 103: 932, 1983.

8. Favus MJ, Langman CB. Effects of 1,25(OH)2D3 on colon Ca transport in vitamin D-deficient and normal rats. American Journal of Physiology 246: G268, 1984.
9. Langman CB, Favus MJ, Bushinsky DA, Coe FL. Effects of dietary calcium restriction on 1,25-dihydroxyvitamin D3 net synthesis by rat proximal tubules. Journal of Laboratory and Clinical Medicine 106:286, 1985.
10. Langman CB, Friedman HZ, Favus MJ. Vitamin D metabolism and osteomalacia in cystic fibrosis. Gastroenterology 88: 808, 1985.
11. Moore ES, Langman CB, Favus MJ, Coe FL. Role of fetal $1,25(OH)_2d_3$ production in phosphorus and calcium homeostasis. Pediatric Research 19:566, 1985.
12. Lau YK, Thomas D, Langman CB, Eby B. Pathophysiology of spontaneous hypercalciuria in laboratory rats: Role of deranged vitamin D metabolism. Journal of Clinical Investigation 76:420, 1985.
13. Langman CB, Moore ES, Thoene JG, Schneider JA. Renal failure in a sibship with benign ocular cystinosis. Journal of Pediatrics 107:755, 1985.
14. Bordeau J, Langman CB. Calcium and phosphorus metabolism in the chronically vitamin D-deficient laboratory rabbit. Mineral and Electrolyte Metabolism 12:176-185, 1986.
15. Langman CB, Favus MJ, Coe Fl. Ca and P regulation of $1,25(OH)_2D_3$ synthesis by D replete rat tubules during acidosis. American Journal of Physiology 251 (Renal Fluid Electrolyte Physiology):F911-F918, 1986.
16. Lau YK, Langman CB, Gafter U, Dudeja PK, Brasitus TA. Mechanisms of increased Ca absorption in pre-hypertensive spontaneously hypertensive rat: role of serum $1,25(OH)_2D_3$ levels and intestinal brush border membrane fluidity. Journal of Clinical Investigation, 78:1083-1090, 1986.
17. Bushinsky DA, Favus MJ, Langman CB, Coe FL. Mechanism of chronic hypercalciuria with furosemide: Increased calcium absorption. American Journal of Physiology, 251 (Renal Fluid Electrolyte Physiol): F17-24, 1986.
18. Zikos D, Langman CB, Gafter U, Delahaye B, Lau K. Chronic DOCA treatment increases Ca absorption: Role of hypercalciuria and Vitamin D. American Journal of Physiology, 251 (Endocrinol Metab 14) E279-E284, 1986.
19. Favus MJ, Langman CB: Evidence for calcium-dependent control of 1,25-dihydroxyvitamin D_3 production by rat kidney proximal tubules. J Biological Chemistry, 261:11224-11229, 1986.
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Milliner DS, Monico CG, Bergstralh E, Herges R, Hoppe B, Langman CB, Lieske JC, and IPHR Investigators. Transplantation strategy in primary hyperoxaluria. ASN, Philadelphia, Nov. 2-6, 2008.

Langman CB. Should bisphosphonates be routinely used to treat low BMD with fractures in Children? Pediatric Academic Societies, 2007.

Bobrowski AE, Cohn RA, Brooks ER, Langman CB. Prednisone-free kidney transplantation does not fully eliminate pro-artherogenic serum lipid profiles. Pediatric Academic Societies, 2007.
Asimi NA, Price HE, Langman CB, Dilley KJ. Regulators of osteoclast function in acute lymphoblastic leukemia. Pediatric Academic Societies, 2008.

Grujic D, Salido EC, Langman CB, Margolin AL, Krushinski D, McGrath ME, Patel RJ, Hhalaf N, Hatch M, Shenoy BC. Oral therapy with crystalline oxalate degrading enzyme as a potential therapy for enteric hyperoxaluria. American Society of Nephrolgy, 2008.

Monico CG, Rohlinger AL, Bjornson, BB, Hoppe B, Langman CB, Lieski J, Olson JB, Bergstralh EJ, Milliner DS. Type of AGXT mutation (mistargeting, missense or truncating) correlates with phenotype in Primary Hyperoxaluria Type 1 (PH1). Pediatric Academic Societies, 2008.

Langman CB. Tainted milk: Exposure and kidney disease. American Society of Nephrology, 2009.

Langman CB. Bisphosphonate therapy in glucocorticoid-induced osteopenia. Pediatric Academic Societies, 2009.

Finer G, Arguelles LM, Rausch E, Ariceta G, Langman CB. The bone phenotype of children with idiopathic hypercalciuria. American Society of Nephrology, 2009.

Hanna MG, Daurgirdas JT, Becker-Cohen R, Langman CB. Are children receiving adequate dialysis? The use of surface area normalized clearance in children receiving hemodialysis. Pediatric Academic Societies, 2010.

Langman CB. Melamine-induced stones: What do we know so far? Invited Lecture, Pediatric Academic Societies, 2010.

Langman CB. Rocks in the kidney—Mining new data. Invited Lecture, Pediatric Academic Societies, 2010.

Langman CB. Pathophysiology of early CKD-MBD. Invited Lecture, American Society of Nephrology, 2010.

Edwards BE, Usmani S, Raisch D, McKoy J, Belknap S, Samaras A, Liebling D, Holbrook J, Langman CB, Alfa AA, West DP. Bisphosphonates and acute kidney injury. Safety signal identification in the Good and Drug Administration Adverse Events Reporting System (FDA AERS): A report from the Research on Adverse Drug Events and Reports (RADAR) Project. ASMBR Annual Meeting, 2011.

INVITED SEMINARS AND LECTURES

Selected and Partial Listing

International Pediatric Nephrology Symposia (held every three years)
1986: Hannover, Germany
1989: Tokyo, Japan
1992: Toronto, Canada
1995: Santiago, Chile (also, Chair of Symposium on Bone and Mineral)
1998: London, England
2001: Seattle, WA
2004: Adelaide, Australia
2007: Budapest, Hungary
2010: New York City, United States
2013: Shanghai, China
2016: Brazil

Gordon Research Conference: Bones and Teeth
1989; 1993; 1995; 1997

Growth Failure in Renal Diseases (held intermittently)
1991: Virginia Beach, VA
1995: Heidelberg, Germany
1999: USA (Co-Director of Conference)
2004: Heidelberg, Germany
2009: Oviedo, Spain

European Pediatric Nephrology Association
1994: Amsterdam, Holland
1997: Athens
2011: Dubrovnik.
2015: Brussels

FASEB Summer Research Conference
2002: Session Chair of Oxalate Biology, Medical Connotations

2005: Vice-Chair, Oxalate Biology

Additioanl Invited Lectures (partial listing from 2004...2011).

1. Critical Thinking, Critical Measures in Osteoporosis: Bone Mineral Density, Bone Turnover, Fracture Risk Reduction. Invited E-Lecture, Aug 18, 2004.
2. An Integrated Approach to Metabolic Health in Nephropathic Cystinosis. Keynote Speaker at IPNA Cystinosis Conference, Aug. 2004.
3. Molecular & Cellular Bases for ROD, NCGS National Meeting, Oct. 2004.
4. The Essential Role of Vitamin D in Chronic Kidney Disease. Grand Rounds, Washington University School of Medicine, Dec. 2004.
5. Nutrition in Children with Chronic Kidney Disease and Kidney Transplantation. Keynote Speaker, Cystinosis Mexico, Jan. 2004.
6. Role of Carnitine in Cystinosis. International Cystinosis Conference, Barcelona, July, 2004.
7. Hypercalciuria in Children: Relationships between Kidney and Bone. Leuven University, Sept. 2004.
8. Role for Pre-Emptive Liver Transplantation. 7th International Workshop on Primary Hyperoxaluria, Oct. 2004.
9. Optimal Management of CKD in Cystinosis. Cystinosis Research Network, July 2005.
10. Vitamin D. Endocrine Grand Rounds, Loyola University (Chicago), August 2005.
11. Biology of Bone Formation: Skeletal Health to Disease. Keynote Lecture. ECTS/IBMS Joint International Meeting. June 2005.
12. Hypercalciuria from Bench to Bedside, the Role of Bone. Keynote Lecture. 4th International Congress on Children's Bone Health, May 2005.
13. Pediatric KDOQI and Role of Carnitine in Dialysis. Invited Lectures. Jackson Memorial Pediatric Nephrology Symposium, Feb. 2005.
14. Bone Health in Children with Chronic Kidney Disease. Invited Lecture. Midwest Symposium on Bone Health, April 2005.
15. Bone after Cessation of Alendronate use in Children with Fracturing Osteoporosis. Director, Invited Speaker. NIH/ASBMR Conference on Effects of Pharmacological Agents on Bone in Children, April 2005.
16. Optimizing Care for Patients with Chronic Kidney Disease. URN Course in Transplantation. Oct. 2006.
17. Evidence-Based Medicine Management of Chronic Kidney Disease-Metabolic Bone Disease. Kidney Foundation of Dakotas. Sept. 2006.
18. Bone Turnover and Anti-Resorptive Efficacy. Provident Hospital (Chicago), Sept. 2006.

19. Bone and Cardiovascular Disease in Chronic Kidney Disease-Metabolic Bone Disease. Florida Society of Nephrology, Sept. 2006.
20. Spectrum of Pediatric Metabolic Bone Disease. Medical College of Wisconsin Grand Rounds, Aug. 2006.
21. The Epidemic of Chronic Kidney Disease. Webcast – MedGenMed, Aug. 2006.
22. Bone in Chronic Kidney Disease—Link to Cardiovascular Disease. Mayo Clinic Fellows Course, Aug. 2006.
23. Improving Management of Patients on Dialysis. URN – Innovations in Management of Kidney Disease. July 2006.
24. Medical Management of Stone Disease. NIH/NIDDK Urolithiasis Symposium, March 2006.
25. New Visions of Vitamin D and Osteodystrophy in Children with Chronic Kidney Disease—Bone & Beyond . . . Heart Health. Invited Lecture, Jackson Memorial Hospital/University of Miami, Feb. 2006.
26. Evidence-Based Medicine and Bone in Chronic Kidney Disease. Invited Lecture. ASN Renal Highlights Meeting, Los Angeles, Feb. 2006.
27. Secondary Hyperparathyroidism in Chronic Kidney Disease. Invited Lecture. Nephrologists Advisory Workshop, Atlanta, Feb. 2006.
28. Phosphate & Osteodystrophy in Chronic Kidney Disease and End-Stage Kidney Disease. Invited Lecture, Session Chair. National Kidney Foundation National Meeting, Chicago, April 2006.
29. Renal Bone Disease. 4th International Conference on Cystinosis, Netherlands, July 2006.
30. Classification of ROD. Invited Lecture. Global Conference on Chronic Kidney Disease-Metabolic Bone Disease, Miami, June 2006.
31. Fracturing Bone Disease in Adolescence – An Algorithmic Approach. Invited Lecture. Endocrine Society, Boston, 2006.
32. Bone and Mineral Metabolism in Chronic Kidney Disease. Grand Rounds, University of Toronto Nephrology Division, May 2006.
33. Practical Applications and Implications of KDOQI Guidelines: Bone and Cardiovascular Disease. Chicago, May 2006.
34. Kidney and Bone in Pediatric Chronic Kidney Disease. Invited Lecture. 33rd Meeting, ECTS, Prague, May 2006.
35. Use of Bisphosphonates for Fracturing Osteoporosis in Children. Invited Lecture. PAS Annual Meeting, Toronto, May 2007.

36. Evidence-Based Medicine Approach to Chronic Kidney Disease-Metabolic Bone Disease. Nephrology Grand Rounds, Hershey, May 2007.

37. Chair, 4th International Congress on Children's Bone Health. Montreal, June 2007.

38. Chair and Moderator, ICSD, PDC for Pediatric Bone Densitometry, Montreal, June 2007.

39. Cell Biology of Nephrolithiasis. Session Chair & Invited Speaker. 14th IPNA Meeting, Budapest, Aug. 2007.

40. Hypertensive Urological Emergencies; Update on Nephrolithiasis and Vitamin D and the Heart in Chronic Kidney Disease. Keynote Speaker. Chilean Society of Nephrology Annual Meeting, Pucon, Chile, Sept. 2007.

41. Evidence-Based Medicine Approach to Chronic Kidney Disease-Metabolic Bone Disease. Visiting Professor, Medical College of Wisconsin, Milwaukee, Oct. 2007.

42. Vascular Calcification in Pre-End Stage Kidney Disease; Phosphate Binders in Chronic Kidney Disease, and Pleiotropic Actions of Vitamin D Beyond Bone. Invited Lectures. American Society of Nephrology Annual Meeting, San Francisco, November 2007.

43. Cell & Molecular Biology of Osteoporosis and Hypophosphatemic Rickets—FGF23 as a New Hormone. Endocrine Grand Rounds, University of Illinois, Chicago, Jan. 2007.

44. Evidence-Based Medicine Approach to Chronic Kidney Disease-Metabolic Bone Disease. Grand Rounds, University of Wisconsin, Madison, Jan. 2007.

45. Bones, Stones, Abdominal Groans. Course Director, Pediatric PERLS (CME) and Lecture. Chicago, Feb. 2007.

46. Evidence-Based Medicine Approach to Chronic Kidney Disease-Metabolic Bone Disease. Grand Rounds, Rush Medical College, Chicago, Feb. 2007.

47. Evidence-Based Medicine Approach to Chronic Kidney Disease-Metabolic Bone Disease. Grand Rounds, Loyola Medical School, Chicago, Feb. 2007.

48. Growth in Children with Chronic Kidney Disease. City-Wide Nutrition Conference, Chicago, Feb. 2007

49. The Link Between Bone and Heart in Chronic Kidney Disease. Grand Rounds, Cleveland Clinic, March 2007

50. The Link Between Bone and Heart in Chronic Kidney Disease. Baltimore, March 2007.

51. Heart and Bone in Children with Chronic Kidney Disease. Visiting Professor. Mt. Sinai School of Medicine, New York, March 2007

52. Use of Phosphate Binders in Early Chronic Kidney Disease. Invited Symposium Lecture, National Kidney Foundation Annual Meeting, Orlando, May, 2007.

53. The Link Between Bone and Heart in Chronic Kidney Disease. Nephrology Grand Rounds, University of Pittsburgh, April 2007.

54. Vitamin D – Metabolic Pathway and Novel Therapeutic Considerations. Dermatology Annual Meeting, Alexandria, April 2007.

55. Medical Evaluation and Management. Invited Speaker. NIDDK Urolithiasis Outcomes and Treatment Symposium, Bethesda, Feb. 2008.

56. Renal Osteodystrophy in the Patient on Peritoneal Dialysis. Invited Speaker. 6th National Meeting on Peritoneal Dialysis, Vitoria, Spain, Jan. 2008.

57. Medical Grand Rounds, UCLA, "Mechanisms of Vascular Calcification in CKD and ESKD", Sept 2008

58. Invited Lecture, "Monogenic Disorders of stone formation in childhood: new insights and unanswered questions. 11th International Symposium on Urolithiasis, Nice, Sept 2008

59. Chair, 1st NIH Symposium on Rare Bone Diseases, Oct 22-24 2008

60. Renal Grand Rounds, Wayne State University, November 2008

61. Chairman, American Society of Nephrology Symposium on Vitamin D Deficiency in CKD: Role of Early Repletion, November 2008.

62. Organizer and Speaker, Cystinosis Mexico meeting, January 2009

63. Invited Speaker, Pediatric Nephrology Seminar XXXVI, Miller School of Medicine, February 2009

64. Invited Speaker, 5th International Symposium on Bone & Mineral Disorders, Oviedo, March 2009

65. Invited Speaker, Pediatric Bone Densitometry Course, ISCD Meeting, Orlando, March 2009

66. Invited Speaker, American Urologic Association, Chicago, April 2009

67. Invited Speaker, Lawson-Wilkins Pediatric Endocrine Society at PAS, Baltimore, May 2009

68. Invited Speaker, World Congress of Nephrology, Milan, May 2009

69. Invited Speaker, Chairperson, IPNA Growth Symposium, Oviedo, May 2009

70. Invited Speaker, International Conference on Child Bone Health, Cambridge UK, June 2009

71. Invited Speaker, Cystinosis Foundation, Istanbul Sept 2009

72. Grand Rounds, University of Chicago Medicine & Pediatrics, Oct 2009

73. Invited Speaker, American Society of Nephrology Annual Meeting, San Diego, Nov 2009

74. Invited Speaker, Institute of Medicine panel on Vitamin D, Nov 2009

75. Invited Speaker, 3rd International Urolithiasis Research Symposium, Indianapolis, Dec 2009

76. Invited Speaker, Annual Dialysis Conference, Seattle, March 2010

77. Invited Speaker, PAS Annual Meeting, Vancouver, May 2010

78. Invited Speaker, ERA-EDTA Annual Meeting, Munich, June 2010

79. Invited Speaker, Israeli Society of Nephrology and Hypertension, July 2010

80. Invited Speaker, Organizer, IPNA XV, New York, Sept 2010

81. Co-Chair, Canadian Institute of Health Research Bone Challenge Grant, Ottawa, Sept 2010

82. Invited Speaker, American Society of Nephrology annual meeting, Denver, Nov 2010

83. Invited Speaker, Pediatric Nephrology Seminar XXXVII, Miller School of Medicine, March 2011

84. Invited Speaker, World Congress of Nephrology, Vancouver, April 2011

85. Invited Speaker, LWPES/ASPN meetings at PAS, Vancouver, May 2011

vs. 288.13 ± 95.22 pg/ml, p = 0.018) which was pronounced in patients with cardiac involvement.

Conclusions: Our data suggest an increase in ESL density, and no change in glycocalyx breakdown in patients with Fabry disease. In addition, a rarefication of microvessels was observed. Our findings suggest pathophysiological changes in the microvascular structure of patients with Fabry disease. The enhanced inflammation is not directly related to the microvascular changes.

TH-PO735

Fabry Nephropathy: Transcriptome Sequencing of Microdissected Renal Compartments from Archival Kidney Biopsies at Baseline, and After 5 and 10 Years of Enzyme Replacement Therapy

Oystein Eikrem,[1,2] Philipp Strauss,[1] Miroslav Sekulic,[3] Camilla Tøndel,[4] Arnar Flatberg,[6] Rannveig Skrunes,[4] Lea Landolt,[1] Janka Babickova,[1] Sabine Leh,[4,1] Andreas Scherer,[5] Einar Svarstad,[4,1] Hans-Peter Marti,[1,2] *[1]Department of Clinical Medicine, University of Bergen, Bergen, Norway; [2]Department of Medicine, Haukeland University Hospital, Bergen, Norway; [3]Brigham and Women's Hospital, Boston, MA; [4]Department of Pediatrics, Haukeland University Hospital, Bergen, Norway; [5]Spheromics, Kontiolahti, Finland; [6]Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway.*

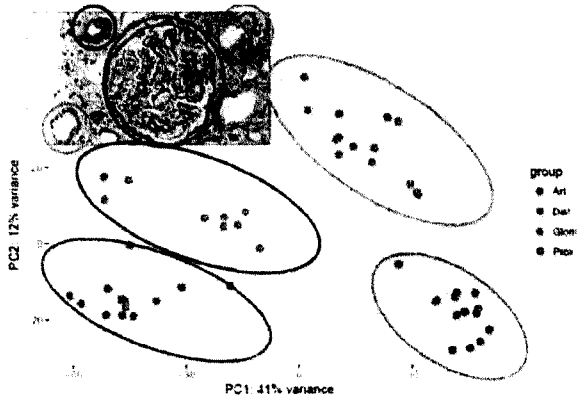
Background: The present study exploited next generation mRNA sequencing from kidney biopsies of Fabry patients with a classical phenotype.

Methods: Kidney biopsies (n=15) were obtained with a 16G needle from Fabry patients (n=5) from 2003-2014. Median patient age at baseline biopsy was 18 years (7-30 y). Control biopsies from peri-tumorous tissue of renal cancer patients (n=32). Formalin-fixed, paraffin-embedded (FFPE) kidney biopsies were obtained: a) baseline prior to enzyme replacement therapy (ERT, n=5), b) after 5y of ERT (n=5), and c) 8-10y of ERT (n=5). Total RNA was extracted from laser-captured, microdissected glomerular, proximal tubular, distal tubular and arterial cross-sections (High Pure FFPET RNA extraction kit, Roche). cDNA libraries were prepared using the TruSeq RNA Access Library Prep Kit[a] (Illumina) and sequenced on an Illumina HiSeq 2500/HiSeq 4000 instrument.

Results: We present the results of the first 42 samples of a larger ongoing series. Several hundred mRNAs were differentially expressed (p-value <0.05, abs. fold change >2) between normal controls and Fabry baseline samples, and between the baseline samples and the two different treatment time points. The samples segregated completely within their own compartment (Fig. 1) in principle component analysis. Gene Set Enrichment Analysis in the glomerular compartment demonstrated enriched gene sets of extracellular matrix, EMT, fibrosis, and immune response in the 10 year biopsies compared to baseline (p<0.05) despite ERT. Several key regulatory inflammatory genes were found to be upregulated in all compartments.

Conclusions: NGS is feasible in archival Fabry disease kidney biopsies, expanding the potential utility of kidney biopsies to detect markers of Fabry nephropathy, chronic kidney disease and therapeutic targets.

Funding: Commercial Support - Sanofi Genzyme, Shire; Government Support - Non-U.S.



TH-PO736

Implications of Renal Impairment on Dosing of Delayed-Release Cysteamine Bitartrate

Craig B. Langman,[1] Saba Sile,[2] Dennis M. Fisher,[2] *[1]Feinberg School of Medicine, Northwestern University, Chicago, IL; [2]P Less Than, San Francisco, CA; [3]Clinical Development, Horizon Pharma Inc, Lake Forest, IL.*

Background: Delayed Release Cysteamine Bitartrate(DRCys) is used to treat nephropathic cystinosis (NC) in order to prolong native kidney function and ameliorate other systemic effects of NC. A biomarker, WBC cystine levels (WBCCys) guides optimal cystine reduction. To date, there are no studies on the effects of impaired renal function, including hemodialysis (HD) on DRCys elimination, and Study RP103-16001 was designed to address these missing data.

Methods: Subjects (all without NC) with mild, moderate, or severe renal impairment, or ESRD requiring hemodialysis, (HD) (8 each; NKF classification based on eGFR) and 32 matched healthy controls were studied. HD subjects received a single 200 mg dose of DRCys twice: 3hr before or 2hr after HD on different days. All remaining subjects received one 200 mg DRCys dose. Blood was sampled for 24h after each dose to determine cysteamine concentrations. Pharmacokinetic analysis was conducted using mixed-effects (population) methods with NONMEM software (ICON Development Solutions, Hanover MD).

Results: Table 1 reports drug clearance relative to healthy controls. For subjects with renal impairment except those on maintenance HD, the effect on DRCys clearance is small, within ±20% of the values in the controls. In HD subjects, clearance fluctuates between successive HD treatments, being maximal post HD and then decreasing.

Conclusions: Although increasing renal impairment is associated with a decrease in the apparent clearance of DRCys, the magnitude is relatively small, and unlikely to necessitate dose reduction. However, the decrease in clearance between HD sessions may cause DRCys efficacy to vary over that time frame. Therefore, biomarker WBCCys results should be interpreted in the context of when patients had the WBCCys sampled relative to HD. Mechanisms for HD-associated clearance changes are unknown but may involve HD improving CYP function.

Funding: Commercial Support - Horizon Pharmaceuticals Inc.

Factors for apparent clearance of DRCys related to residual renal function (eGFR) compared to healthy controls

Degree of impairment	eGFR (ml/min/1.73m2)	Factor
Mild	>80	1.192
Moderate	60-80	0.849
Severe	30-60	0.804
ESRD	Maintenance HD	
Concurrent HD		0.692
Post-HD		0.893

TH-PO737

MAGED2 (Re)wires G-Protein Coupled Receptor Signaling in Renal Collecting Duct Cells

Malte P. Bartram,[1] Björn Reusch,[3] Bernhard Schermer,[1,2] Thomas Benzing,[1,2] Bodo B. Beck,[3] Markus M. Rinschen.[1,2] *[1]University Hospital Cologne, Cologne, Germany; [2]CECAD, Cologne, Germany; [3]University of Cologne Medical Center, Cologne, Germany.*

Background: Recently mutations in MAGED2 were identified as a genetic cause of very severe X-linked polyhydramnios and transient antenatal Bartter syndrome. Since MAGED2 does not code for a transmembrane protein, the molecular mechanisms that contribute to the antenatal Bartter syndrome remain elusive. First results suggest that MAGED2 acts indirectly on ion channels and transporter expression in the kidney tubule system.

Methods: The role of MAGED2 in renal cell culture systems was studied by analyzing the proteome and phospho-proteome after MAGED2 depletion and by analyzing the influence of MAGED2 on vasopressin induced signaling in mouse collecting duct cells using Western Blot, qPCR and proteomic analyses.

Results: We show that MAGED2 ablation in HEK293T cells induced large effects on the phosphoproteome, without affecting protein levels. Since MAGED2 is expressed during development in collecting duct cells of newborn mice, we analyzed the effects of MAGED2 knockdown on vasopressin-dependent signaling in renal collecting duct cells. We found that MAGED2 knockdown altered V2R-induced cAMP-generation kinetics, phosphoproteome rewiring, and blunted phosphorylation on downstream nodes such as phosphorylated CREB. V2R induced ERK inhibition and aquaporin-2 phosphorylation were not affected. Interestingly, these alterations resulted in a marked increase in aquaporin-2 abundance during long-term V2R activation, that was mediated transcriptionally, potentially through the mediator complex.

Conclusions: In conclusion, we show that MAGED2 is a novel modulator of G-protein coupled signaling, that might control important signaling events involved in ion transport and nephron plasticity in the distal nephron. The relevance of these findings needs to be recapitulated in vivo.

TH-PO738

Model of Megalin Trafficking in Differentiated Proximal Tubule Cells and Its Application in Dent Disease

Katherine Shipman, Kimberly R. Long, Youssef Rbaibi, Catherine J. Baty, Ora A. Weisz. *University of Pittsburgh, Pittsburgh, PA.*

Background: The polarized epithelial cells that comprise the proximal tubule (PT) have a specialized, high capacity apical endocytic pathway necessary to maintain a protein-free urine. The multiligand receptor megalin plays an essential role in the binding and uptake of proteins in the ultrafiltrate. The molecular identities of the compartments involved in sorting of ligands and recycling of receptors in PT cells and the kinetics of megalin trafficking through them are unknown. Dysfunctional PT endocytosis results in tubular proteinuria that can progress to renal failure, as is commonly observed in Dent disease, an X-linked disorder caused by mutations in the Cl^-/H^+ exchanger CLC-5. Reduced endocytic uptake in Dent disease is likely due to decreased expression of megalin receptors (without altered mRNA levels); however, the mechanism by which this occurs is unclear.

Methods: We previously discovered that OK cells cultured under continuous fluid shear stress develop morphological and functional features similar to that of the PT *in vivo*, including high apical endocytic capacity and increased megalin expression. Using

TABB

PATENTED MEDICINE PRICES REVIEW BOARD

IN THE MATTER OF the *Patent Act*,
R.S.C., 1985, c. P-4, As Amended

AND IN THE MATTER OF
Horizon Pharma (the "Respondent")
and the medicine Cysteamine Bitartrate sold by the Respondent under the trade name PROCYSBI

EXPERT REPORT OF DR. JOEL HAY

TABLE OF CONTENTS

I, Joel W. Hay, Ph.D., of the City of Los Angeles in the State of California in the United States of America, am providing the following statement of evidence that I propose to present at the hearing of the above referenced proceeding.

I. QUALIFICATIONS

1. I am a tenured Full Professor and Founding Chair of Pharmaceutical Economics and Policy in the School of Pharmacy, with joint appointments in the Department of Economics and at the Schaeffer Center for Health Policy and Economics at the University of Southern California ("USC"). I also served for 15 years as the USC Project Coordinator for the Rand Evidence-Based Medicine Practice Centers of Southern California funded by the U.S. Agency for Health Research and Quality. I am a Health Economics Research Scholar at the UCLA Center for Pediatric Vaccine Research. I am a founding member and founding Executive Board member of the American Society for Health Economics ("ASHEcon") and a founding member and founding Executive Board member of the International Society of Pharmacoeconomics and Outcomes Research ("ISPOR").

2. In 1974, I received my B.A. in Economics, *summa cum laude*, from Amherst College. I then went on to receive my M.A. in Economics in 1975 and my M.Ph. in Economics in 1976 from Yale University. In 1980, I received my Ph.D. in Economics from Yale.

3. From 1978 to 1980, I was an Assistant Research Professor at USC. From 1980 to 1984, I was an Assistant Professor in the Department of Behavioral Sciences and Community Health and in the Department of Economics at the University of Connecticut. I was also a Senior Policy Analyst with Project Hope from 1983 to 1985. From 1985 to 1992, I was a Senior Research Fellow at the Hoover Institution at Stanford University. In 1992, I was recruited by USC to found the Department of Pharmaceutical Economics and Policy. I have been a tenured USC faculty member since that date.

4. I developed and founded the M.S. and Ph.D. graduate programs in Pharmaceutical Economics and Policy at USC in 1994. These programs have grown to become the largest and best-known graduate programs in the field. These programs have graduated over 125 students with advanced degrees in pharmaceutical economics and policy. My graduate students have won

numerous teaching and research awards, including 14 awards for top peer-reviewed research presentations at scientific conferences where I was mentor and co-author.

5. I have authored or co-authored more than 600 abstracts, reports and presentations, including over 200 scientific articles in the fields of pharmaceutical economics, health economics, outcomes research, disease management, statistics, econometrics, epidemiology, healthcare, drug and pipeline valuation, and pharmaceutical markets in journals including: *American Journal of Cardiology*; *American Journal of Health-Systems Pharmacy*; *American Journal of Managed Care*; *American Journal of Public Health*; *Archives of Neurology*; *Cancer*; *CNS Drugs; Haemophilia*; *Health Care Financing Review*; *Health Economics; Health Policy*; *JAMA*; *Journal of AIDS*; *Journal of the American Geriatrics Society*; *Journal of Business & Economic Statistics*; *Journal of Clinical Gastroenterology*; *Journal of Health Economics*; *Journal of Health Politics, Policy and Law*; *Journal of Human Resources*; *Journal of the Royal Statistical Association*; *New England Journal of Medicine; Medical Care*; *Pediatrics*; and *Value in Health*.

6. My scientific citation H-Index is 50, meaning that more than 50 of my scientific peer-reviewed publications have been cited more than 50 times.[1] Moreover, my peer-reviewed scientific publications have been cited in the scientific literature more than 9,700 times.[2]

7. In addition to the hundreds of pharmacoeconomic studies that I have conducted, I have published numerous peer-reviewed scientific articles and abstracts on the cost effectiveness and the economic value of drugs, screening programs, and prevention programs. I recently served as guest editor of a special issue of the *International Journal of the Economics of Business* commemorating 50 years of pharmaceutical economics research.[3]

8. In April 2015, I was one of three invited outside experts who presented to the Directors and Staff of the Office of Medical Policy (Dr. Jonathan Jarow) and the Center for Drug Evaluation

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1 Lillquist, E. and Green, S. (2010). The Discipline Dependence of Citation Statistics. *Scientometrics, 84*(3): 749-762.

2 Joel Hay – Google Scholar Citations, available at https://scholar.google.com/citations?user=vKK2BxEAAAAJ&hl=en.

3 Hay, J.W. (2015). A Special Commemorative Issue Honoring William S. Comanor and 50 Years of Pharmaceutical Economics, *International Journal of the Economics of Business, 22*(2): 165–168.

and Research (Dr. Robert Temple) at the U.S. Food and Drug Administration (FDA) on the regulation of economics claims for pharmaceutical products. In 2016, I was an Invited Forum Participant in the AMCP Partnership Forum: FDAMA Section 114—Improving the Exchange of Health Care Economic Data for the Academy of Managed Care Pharmacy. This forum provided further insights into sharing economic information under FDA regulatory guidelines and led to two conference reviewed publications.[4]

9. I have served as a consultant to the U.S. Centers for Medicare and Medicaid Services, U.S. Agency for Healthcare Research and Quality, U.S. Centers for Disease Control and Prevention, U.S. Public Health Service, FDA, U.S. Environmental Protection Agency, Government of Hungary, Hong Kong Centre for Economic Research, Hong Kong Medical Executives Association, World Bank, California AIDS Commission, California Medi-Cal Drug Advisory Board, County of San Diego Medically Indigent Adult Program, and County of Sacramento Homeless Program.

10. I have also written numerous health-related op-eds published in papers such as the Los Angeles Times, New York Times, Wall Street Journal, San Francisco Chronicle, San Diego Union, Sacramento Bee, Orange County Register and Newsday. I have been interviewed numerous times on television and radio regarding health-related and drug-related policy issues, including media networks such as American Public Media, NPR, PBS, CBS, ABC, NBC, Fox News, C-SPAN, CBC, BBC, and the Australian Broadcast Company.

11. I have served as a member of the Expert Advisory Panel on Drug Utilization Review, United States Pharmacopeial Convention; an Executive Committee member for the federally sponsored Southern California Evidence-Based Medicine Practice Center; and a member of the *JAMA* Web Site HIV/AIDS Editorial Review Panel. I also recently completed a third consecutive two-year term as a Study Section member for the Extramural Grants Review Program for the

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[4] Hay, J.W. (2016). AMCP Partnership Forum: FDAMA Section 114—Improving the Exchange of Health Care Economic Data. *Journal of Managed Care & Specialty Pharmacy, 22*(7): 826–831; Hay, J.W. (2017). AMCP Partnership Forum: Enabling the Exchange of Clinical and Economic Information Pre-FDA Approval. *Journal of Managed Care & Specialty Pharmacy, 23*(1): 105–112.

Agency for Healthcare Research and Quality of the U.S. Department of Health and Human Services.

12. From 2004-2010, I was a founding member of the Health Policy Scientific Council of the International Society for Pharmacoeconomics and Outcomes Research. From 2006-2010, I was founding Co-Chair of the International Society for Pharmacoeconomics and Outcomes Research Drug Cost Task Force. In 2010, this Task Force published six peer-reviewed guideline papers on pharmaceutical costing methodology in the journal *Value in Health*, all of which I edited and co-authored.

13. I served as the Founding Editor-in-Chief of *Value in Health*, the peer-reviewed scientific journal of the International Society for Pharmacoeconomics and Outcomes Research, from its inception in 1998 until 2003. In its first scientific citation impact factor, *Value in Health* was ranked number one in two categories for the year 2004 by the ISI Journal Citation Reports® (JCR) with an impact factor of 3.657. *Value in Health* led all other journals listed in both the Health Care Sciences and Services category in the JCR Science Edition and in the Health Policy & Services category in the JCR Social Sciences Edition. These categories include all journals relating to health economics and pharmaceutical economics.

14. I have served as a legal expert consultant and/or testifying expert witness in hundreds of cases, mostly involving economic valuation of pharmaceuticals. A copy of my *curriculum vitae* and recent legal testimony are attached as **Appendix A** and **Appendix B**, respectively.

15. I understand my obligations as an expert witness in this proceeding. A copy of my signed declaration attesting to my acknowledgment of and adherence to these obligations is attached as **Appendix C**.

II. MANDATE AND ISSUES TO BE ADDRESSED

16. I have been advised by counsel for Horizon that the Patented Medicine Prices Review Board ("PMPRB" or the "Board") has initiated a proceeding to determine whether Horizon is selling or has sold PROCYSBI in Canada at a price that is or was excessive under sections 83 and

85 of the *Patent Act*.[5] In particular, I understand that staff from the PMPRB ("Board Staff") is seeking an order from the Board (i) declaring that the price of PROCYSBI has been excessive since it was introduced in Canada on September 7, 2017, and (ii) requiring Horizon to, among other things, reduce the price of PROCYSBI by approximately 71% to 98% of its current price (the "Proposed Prices").[6,7]

17. Counsel for Horizon has asked me to provide the following:

(a) An explanation of the general considerations that go into the pricing of rare and ultra-rare disease drugs, such as PROCYSBI;

(b) An explanation of the price control models utilized in Canada, including the methodologies set out in the Compendium of Policies, Guidelines and Procedures of the PMPRB (the "PMPRB Compendium");

(c) My opinion on whether the Proposed Prices of PROCYSBI in Canada are reasonable from an economic perspective, namely whether Horizon would be able to recover the costs associated with commercializing PROCYSBI in Canada at the Proposed Prices; and

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5 Notice of Hearing, In the Matter of the *Patent Act* R.S.C. 1985, c. P-4, as amended, and In the Matter of Horizon Pharma and the medicine Cysteamine Bitartrate sold by the Respondent under the trade name "PROCYSBI".

6 Statement of Allegations of Board Staff, ¶68.

As discussed in detail below, Horizon launched PROCYSBI for sale in Canada at an ex-factory price of $10.35 per 25mg capsule and $31.05 per 75mg capsule (*i.e.*, $0.4140 per mg), which it has maintained through to date. In its Statement of Allegations, Board Staff has set out alternative pricing methodologies to reduce the ex-factory price of PROCYSBI from $2.9602 per 25mg capsule and $8.8807 per 75mg capsule (*i.e.*, a reduction of 71.4%) down to as low as $0.1913 per 25mg capsule and $0.5740 per 75mg capsule (*i.e.*, a reduction of 98.15%). [Board Staff Production Tab 98 to Tab 106 (Horizon Form 2 Filings with PMPRB); Horizon Pharma PLC, Form 2 - Block 5, January to June 2019; Statement of Allegations of Board Staff, ¶31 and ¶68]

7 As a pharmaceutical company, Horizon's sales of PROCYSBI are not to patients, but to pharmacies and hospitals, either directly or through a wholesaler. As such, that price at which Horizon sells PROCYSBI to its pharmacy, hospital and wholesaler customers is referred to an ex-factory price because it is the price at which it literally makes sales out of the factory.

(d) An explanation and opinion of the three alternative pricing methodologies set out in the Statement of Allegations (namely, the "Same Medicine Comparison Test," "Market Share Comparison Test," and "Premium Comparison Test").[8]

III. MATERIALS CONSIDERED

18. In preparing this report, I have reviewed information from a variety of sources, including: (i) documents filed with the PMPRB; (ii) documents produced in this matter by Horizon and Board Staff; (iii) discussions with Horizon personnel; and (iv) information from publicly available sources.[9] My understanding of the clinical efficacy and safety of PROCYSBI is derived from my review of its clinical trial results, as well as from the Expert Report of Dr. Craig Langman.[10] In addition, I have relied on my experience and training as a health economist. **Appendix D** provides a complete list of the information that has been reviewed in preparing this report. **Appendix E** sets out key background facts relevant to this matter that I have relied on.

IV. SUMMARY OF OPINIONS

The Price of Drugs for Rare Diseases

19. The costs and risks associated with pharmaceutical innovation play an important role in the pricing of rare and ultra-rare disease drugs. The price of any new pharmaceutical product should enable the manufacturer to recover the costs associated with developing and commercializing the new drug. Because the patient population for a rare disease drug is very small, manufacturers of rare disease drugs must often charge prices that appear high relative to the prices of drugs that serve broader patient populations. This often much higher price is required to provide the manufacturer with the opportunity to recover the costs incurred to develop and commercialize the drug and to generate a return on investment. However, regulatory restrictions that reduce drug prices can also reduce pharmaceutical companies' incentives to engage in research and development (R&D), thereby producing long-term net social losses. This concern is particularly

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8 Statement of Allegations of Board Staff, ¶¶42-61.

9 I have prepared this affidavit with the assistance of other economics professionals from The Brattle Group ("Brattle"). Brattle and I are being compensated for the time we spend on this assignment at our customary hourly rates and are separately reimbursed for reasonable out-of-pocket expenses. No part of my or Brattle's compensation is dependent upon the outcome of this proceeding or the nature of the opinions that I express.

10 Expert Report of Dr. Craig Langman, dated September 9, 2019 ("Langman Report").

pertinent to rare disease drugs, since their small patient populations do not allow R&D costs to be recovered over large sales volumes.

Pharmaceutical Price Regulation in Canada

20. Canada employs "reference-based" pricing methods to cap the ex-factory prices that drug manufacturers can set for new pharmaceutical products.[11] One of the pricing methods used to establish price caps is the Median International Price Comparison Test. The Median International Price Comparison Test is used to determine whether the price of a drug in Canada is excessive relative to international prices; it compares the ex-factory price of the drug under review to the median ex-factory price of the drug across France, Germany, Italy, Sweden, Switzerland, the United Kingdom and the United States (the "PMPRB7").[12] This test has several economic benefits for Canadians. It is based on economic principles that reflect considerations relevant to fair pricing for Canadians, including the principle that Canadians should, on average, pay no more for drugs than individuals in countries of similar socioeconomic status.

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[11] Patented Medicine Prices Review Board, *Compendium of Policies, Guidelines and Procedures, Updated February 2017* ("PMPRB Compendium"), available at http://www.pmprb-cepmb.gc.ca/view.asp?ccid=492.

Notably, in other countries, maximum drug price regulation is focused on reimbursement (*i.e.*, the public payor will not reimburse expenditures on a drug if its price exceeds the price cap). In Canada, however, the drug manufacturer is prohibited from marketing a drug unless its price is first approved by the PMPRB. [See, *e.g.*, Morin, J.F. et al. (2008). Canadian Pharmaceutical Patent Policy: International Constraints and Domestic Priorities. In Y. Gendreau (ed.) *A New Intellectual Property Paradigm*: 81-103, pp. 87-90. Edward Elgar; Kanavos, P. et al. (2017). *The Implementation of External Reference Pricing within and across Country Borders*. London School of Economics.]

[12] PMPRB Compendium, Part C: Guidelines and Procedures and Schedule 5: Median International Price Comparison Test.

Many countries around the world use reference-based pricing methods to limit the prices of pharmaceutical products or reimbursement for expenditures on these products. Two of the most prominent reference-based pricing methods are Therapeutic Reference Pricing and External Reference Pricing. Therapeutic Reference Pricing imposes limits on prices or reimbursement by comparing the price of a new drug to other drugs that are deemed to have comparable clinical effects. In contrast, External Reference Pricing aims to prevent manufacturers from engaging in overt price discrimination across countries by restricting the domestic price of a drug to some measure of the drugs prices in other countries. Therapeutic Reference Pricing is similar to the PMPRB's Therapeutic Class Comparison Test and External Reference Pricing is similar to the PMPRB's Median International Price Comparison Test. [See, *e.g.*, World Health Organization (2015). *WHO Guideline on Country Pharmaceutical Pricing Policies*. Geneva: World Health Organization; Kanavos, P. et al. (2017). *The Implementation of External Reference Pricing within and across Country Borders*. London School of Economics].

21. Had Board Staff followed the Median International Price Comparison Test set out in the PMPRB Compendium, it would have found that the ex-factory price of PROCYSBI in Canada is below the median ex-factory price of PROCYSBI in the PMPRB7 countries in which it is sold. Specifically, the Median International Price Comparison Test would set a price for PROCYSBI between $0.4179 and $0.4289 per milligram.[13] This price range exceeds the ex-factory price of PROCYSBI in Canada ($0.4140 per mg).[14]

Board Staff's Alternative Models

22. Board Staff has argued that applying the methodologies set out in the PMPRB Compendium would be inappropriate unless those methodologies are modified to account for certain unspecified "unusual circumstances."[15] In place of the Median International Price Comparison Test, Board Staff offers three alternative tests, none of which are consistent with the methodologies set out in the PMPRB Compendium and none of which are consistent with the economic principle that the price of a new drug product should enable the manufacturer to recover the costs associated with developing and commercializing the new drug. To the extent there is any basis for departing from the PMPRB Compendium, these models do not provide an economically rational alternative.

23. To evaluate Board Staff's alternative pricing models, I have conducted an analysis of Horizon's anticipated return on investment from PROCYSBI in Canada at the Proposed Prices under each model. [redacted]

[13] The per milligram prices referred to in this report apply to both 25mg and 75mg dosage strengths. For further details see Figure 3 and Figure 4 below.

[14] Statement of Allegations of Board Staff, ¶31.

[15] Statement of Allegations of Board Staff, ¶22.

(a) The Same Medicine Comparison Test sets PROCYSBI's ex-factory price based solely on the price of another drug, Cystagon, and ignores the therapeutic benefit derived from PROCYSBI's patented enterically coated, delayed release formulation.[16] As a matter of economics, a price for PROCYSBI that is based solely on its active pharmaceutical ingredient ("API"), and that does not account for the therapeutic improvement offered by PROCYSBI, would be inappropriate in this case. This method also fails to allow for cost recovery. It would reduce the ex-factory price of PROCYSBI by between 96% and 98%. [redacted]

(b) The Premium Comparison Test provides minimal credit for the significant therapeutic benefit derived from PROCYSBI's enterically coated, delayed release formulation. It arbitrarily sets PROCYSBI's price as the price of Cystagon plus twenty-five percent of the difference between the prices of the two drugs. Board Staff provides no justification for why this "premium" would be appropriate in this case. Given PROCYSBI's improved patient efficacy and side effect profile, as explained by Dr. Langman, I see no reason why this premium would be appropriate in this case. In any event, this premium is *de minimis* given that it fails to allow for any cost recovery. This method would reduce the ex-factory price of PROCYSBI by between 71% and 73%. [redacted]

(c) The Market Share Comparison Test sets PROCYSBI's price based on the weighted average price of each of PROCYSBI and Cystagon, with weights based on their respective market shares in the PMPRB7.[17] However, this methodology relies on a market share comparison between two drugs that are at very different points in their product life cycles. Moreover, in implementing this methodology, Board Staff

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16 Based on my review of Dr. Langman's report, I understand that PROCYSBI's enteric coating and delayed release formulation provide patients with substantial therapeutic benefits, including gains in terms of patient efficacy and reduction in side effects, as well as changed pharmacokinetic parameters realized by delivering enterically coated beads to the small intestine for absorption in the body (lower Cmax, longer duration of action). [Langman Report, ¶¶28, 30, 33, 155-156.]

17 Statement of Allegations of Board Staff, ¶¶46-53.

appears to have included sales of Cystagon in countries where PROCYSBI is not approved for sale. As a result, the market shares used by Board Staff for its calculations are in no way reflective of true marketplace conditions in "the Comparator Countries where PROCYSBI faces competition from Cystagon."[18] Furthermore, like the previous two tests, this method fails to allow for cost recovery. It would reduce the ex-factory price of PROCYSBI by between 80% and 92%. [redacted]

V. THE PRICE OF DRUGS FOR RARE DISEASES

The Costs of Pharmaceutical Innovation: Research and Development

24. A main consideration in the pricing of drugs (including those for rare and ultra-rare diseases) is the cost of innovation or R&D. R&D for pharmaceutical products is a long, complex, and risky process. It is characterized by large, up-front investment costs, the returns of which, if any, will not be realized until many years in the future.

Timeline for Drug Development

25. As illustrated in Figure 1, below, the typical development pathway for a new pharmaceutical drug, from basic research to marketing approval, takes between 10 and 15 years.[19] In the case of rare disease drugs, this process is often longer.[20]

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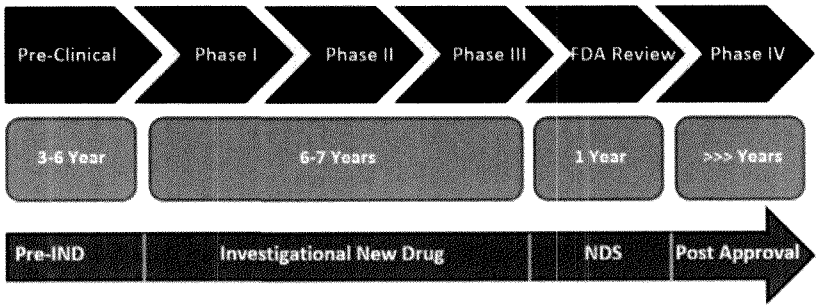
[18] Statement of Allegations of Board Staff, ¶51.

[19] U.S. Food & Drug Administration, NDA at the FDA, available at https://www.fda.gov/media/105012/download; Dickson, M. and Gagnon, J. P. (2004). Key Factors in the Rising Cost of New Drug Discovery and Development. *Nature Reviews Drug Discovery*, *3*(5): 417-429; DiMasi, J.A. et al. (2003). The Price of Innovation: New Estimates of Drug Development Costs. *Journal of Health Economics*, *22*(2): 151-185.

[20] As documented in a recent study, across all phases, the length of time for clinical trials for rare disease drugs is typically longer than that for drugs treating broader populations. [Jayasundara, K. et al. (2019). Estimating the Clinical Cost of Drug Development for Orphan versus Non-Orphan Drugs. *Orphanet Journal of Rare Diseases, 14(*1): 12-22, pp.14-15.]

Figure 1: Timeline of Drug Development



Source: Adapted from U.S. Food & Drug Administration, NDA at the FDA, p. 4.

26. During the pre-clinical phase, scientists conduct laboratory studies to determine whether a potential new biopharmaceutical innovation is suitable for clinical testing. If the innovative drug passes these pre-clinical studies, a company will file a clinical trial application with Health Canada. If Health Canada approves the application, the company may begin testing the drug product in humans, which typically involves numerous clinical trials across multiple phases. Phase I trials test the drug on a small group of volunteers to determine the drug's safety. Drugs that are deemed safe progress to Phase II trials, where they are tested on a somewhat larger group of patients to determine the drug's effectiveness, examine its potential side effects and risks, and identify optimal doses and schedules. Phase III trials test the drug on a larger group of patients to generate statistically reliable information about the drug's safety and efficacy.[21]

27. If the results of the clinical trials indicate that the drug is safe and effective, the company will submit a New Drug Submission to Health Canada, along with all the data collected by the company during its development of the drug. Health Canada will review the submission and evaluate the data on safety, efficacy, and quality to assess the potential benefits and risks of the drug. If Health Canada determines that the benefits of the drug outweigh the risks, the drug is issued a Notice of Compliance (NOC), which allows the company to market the drug in Canada. Even after approval, the drug manufacturer may decide (or, as a condition of approval, may be

[21] Health Canada, Clinical Trials and Drug Safety, available at https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/hl-vs/alt_formats/pdf/iyh-vsv/med/clinical_trails-essais_cliniques-eng.pdf; See also the materials available from U.S. Food & Drug Administration, The Drug Development Process, available at https://www.fda.gov/patients/learn-about-drug-and-device-approvals/drug-development-process.

required) to undertake post-marketing clinical trials to gather information on the long-term benefits and risks of the drug.[22]

28. I understand from Horizon that, in this case, the pre-clinical phase for PROCYSBI began in 1999 and lasted approximately 10 years.[23] The clinical trials phase commenced in May 2009 and lasted over 8 years, with Phase IIIb clinical trials ending in June 2017.[24,25] Health Canada's review of PROCYSBI began in March 2016, while PROCYSBI's Phase IIIb clinical trials were ongoing. Despite having granted PROCYSBI priority review, Health Canada's review took over 15 months to result in a NOC.[26]

Risks in Drug Development

29. R&D is a high-stakes, high risk endeavor in which most drug candidates fail. Over the past two decades, numerous economic studies of the pharmaceutical R&D process have focused on issues such as the probability of success, the cost and time to develop a new medicine, and the

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[22] Health Canada, How Drugs are Reviewed in Canada, available at https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/fact-sheets/drugs-reviewed-canada html.

[23] Response of Horizon Pharma, ¶¶23-26; Dohil, R. et al. (2006). Understanding Intestinal Cysteamine Bitartrate Absorption. *The Journal of Pediatrics, 148*(6): 764-769; Dohil, R. et al. (2010). Twice-Daily Cysteamine Bitartrate Therapy for Children with Cystinosis. *The Journal of Pediatrics, 156*(1): 71-75; Dohil, R. et al. (2010). Long-Term Treatment of Cystinosis in Children with Twice-Daily Cysteamine. *The Journal of Pediatrics, 156*(5): 823-827.

[24] Pilot Study of Safety, Tolerability, Pharmacokinetics/Pharmacodynamics of RP103 Compared to Cystagon in Patients with Cystinosis, available at https://clinicaltrials.gov/ct2/show/NCT00872729?term=RP103&cond=Cystinosis%2C+Nephropathic&phase=0&rank=1; Phase 3 Study of Cysteamine Bitartrate Delayed-release (RP103) Compared to Cystagon in Patients With Cystinosis, available at https://clinicaltrials.gov/ct2/show/NCT01000961?term=RP103&cond=Cystinosis%2C+Nephropathic&phase=2&rank=1; Long-Term Safety Follow-up Study of Cysteamine Bitartrate Delayed-release Capsules (RP103), available at https://clinicaltrials.gov/ct2/show/NCT01197378?term=RP103&cond=Cystinosis%2C+Nephropathic&phase=2&rank=4.

[25] Phase IIIb trials are supplemental Phase III trials (in the case of PROCYSBI, a continuation of the Phase III trial) designed to test additional (*e.g.*, long-term) clinical endpoints. [Horizon Production Tab 41 (Long-Term, Open-Label, Safety and Efficacy Study Of Cysteamine Bitartrate Delayed-Release Capsules (RP103) in Patients with Cystinosis: Interim Clinical Study Report).]

[26] Health Canada granted the New Drug Submission for PROCYSBI Priority Review Status in March 2016, under which reviews of drugs related to the treatment and prevention of serious, life-threatening or severely debilitating illnesses are fast tracked. ["Raptor's PROCYSBI® New Drug Submission Accepted by Health Canada with Priority Review," Press Release dated March 21, 2016, available at https://www.globenewswire.com/news-release/2016/03/21/821869/0/en/Raptor-s-PROCYSBI-New-Drug-Submission-Accepted-by-Health-Canada-with-Priority-Review html.]

economic returns associated with new R&D.[27] These studies highlight the technical and commercial risks associated with the R&D process and the tremendous variability in the economic returns on new drug products.

30. The most obvious risk in drug development is that, despite a long, costly, and uncertain development process, most new drug candidates will not reach the market. Failure can result from toxicity, carcinogenicity, manufacturing problems, inconvenient dosing characteristics, formulation difficulties, inadequate efficacy, adverse events, and economic and competitive factors, among various other problems.

31. For each compound that makes it into clinical trials (*i.e.*, human testing), thousands of compounds are synthesized and examined. Of the compounds that make it into clinical trials, only about 20% survive the development and approval process. This means that four out of five drug candidates that are examined in human subjects are never marketed.[28]

Costs of Drug Development

32. R&D costs typically refer to the costs of a drug from inception through to the post-marketing clinical trials that occur after the drug has been approved (*i.e.*, Phase IV trials).[29]

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[27] See, *e.g.*, the literature surveyed in DiMasi, J.A. et al. (2016). Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs. *Journal of Health Economics, 100*(47): 20-33.

[28] For a discussion of the probability of entering each phase of clinical testing see, *e.g.*, DiMasi, J.A. et al. (2003). The Price of Innovation: New Estimates of Drug Development Costs. *Journal of Health Economics*, *22*(2): 151-185; DiMasi, J.A. et al. (2010). Trends in Risks Associated with New Drug Development: Success Rates for Investigational Drugs. *Clinical Pharmacology & Therapeutics*, *87*(3): 272-277; Hay, M. et al. (2014). Clinical Development Success Rates for Investigational Drugs. *Nature Biotechnology*, 32(1): 40-51; Biotechnology Innovation Organization, BioMedTracker and Amplion (2016). *Clinical Development Success Rates 2006-2015*, available at https://www.bio.org/sites/default/files/Clinical%20Development%20Success%20Rates%202006-2015%20-%20BIO%20Biomedtracker%20Amplion%202016.pdf; DiMasi, J.A. et al. (2016). Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs. *Journal of Health Economics, 100*(47): 20-33.

[29] See *e.g.*, DiMasi J.A., Mitchell J. and Hay J.W. (1994). The Cost of Drug Development. *Pharmacy and Therapeutics, 9*(1): 68-80.

As noted above, even after approval, the drug manufacturer may decide (or, as a condition of approval, may be required) to undertake post-marketing clinical trials to gather information on the long-term benefits and risks of the drug. The manufacturer may also undertake Phase IV studies in order to obtain approval for its drug to treat new indications. [Health Canada, How Drugs are Reviewed in Canada, available at https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/fact-sheets/drugs-reviewed-canada html.]

33. According to a study by Joseph DiMasi, Ronald Hansen and Henry Grabowski published in the *Journal of Health Economics*, the average cost to introduce a new drug in the U.S. was over USD$800 million in 2000 dollars (or the equivalent of almost USD$1,200 million in 2019 dollars).[30] This study examined the representative costs for new drugs for which the mean introduction date was in the late 1990s. The cost estimates incorporated expenditures for drug candidates that failed in the R&D process since these costs must be recouped from the revenues of successful drug candidates. Further, to account for the time value of money, the results of this study were expressed in present value terms at the time of market launch. Subsequent studies have found much higher costs.[31] For example, in 2016, these same authors published an updated study in the *Journal of Health Economics*.[32] This updated study, which was based on drugs with first-in-human testing between 1995 and 2007, found that the average cost to introduce a new drug was USD$2.8 billion in 2013 dollars (or the equivalent of over USD$3 billion in 2019 dollars).[33]

Challenges in Drug Development for Rare and Ultra-Rare Diseases

34. While no standard definition exists, rare diseases (sometimes referred to as "orphan diseases") are generally characterized as serious, debilitating or life-threatening or chronic conditions with extremely low prevalence rates. Both Health Canada and the European Union have adopted a definition of a rare disease as one affecting fewer than 5 in 10,000 people.[34] The U.S. defines an

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30 DiMasi, J.A. et al. (2003). The Price of Innovation: New Estimates of Drug Development Costs. *Journal of Health Economics*, *22*(2): 151-185; U.S. Bureau of Labor Statistics, CPI Inflation Calculator, available at https://data.bls.gov/cgi-bin/cpicalc.pl.

This included both pre-and post-approval R&D costs.

31 See *e.g.*, Adams, C.P. (2006). Estimating the Cost of New Drug Development: Is it Really $802 million? *Health Affairs, 25*(2): 420-428; Paul, S.M. et al. (2010). How to Improve R&D Productivity: The Pharmaceutical Industry's Grand Challenge. *Nature Reviews Drug Discovery, 9*(3): 203–214 Mestre-Ferrandiz, J. et al. (2012). *The R&D Cost of a New Medicine.* U.K. Office of Health Economics.

32 DiMasi, J.A. et al. (2016). Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs. *Journal of Health Economics, 100*(47); 20-33.

33 DiMasi, J.A. et al. (2016). Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs. *Journal of Health Economics, 100*(47): 20-33; U.S. Bureau of Labor Statistics, CPI Inflation Calculator, available at https://data.bls.gov/cgi-bin/cpicalc.pl.

34 Board Staff Production Tab 91 (Report of the Standing Committee on Health, House of Commons Canada, "Canadians Affected by Rare Diseases and Disorder: Improving Access to Treatment", February 2019), pp. 7-9; European Commission, Steering Group on Health Promotion, Disease Prevention and Management of Non-Communicable Diseases, Rare Diseases, available at https://ec.europa.eu/health/non_communicable_diseases/rare_diseases_en.

"orphan disease" as a condition that affects fewer than 200,000 people in America (*i.e.*, a prevalence rate of approximately 7 cases per 10,000 people).[35]

35. Developing treatments for rare and ultra-rare diseases involves all the timing, risk, cost, and other issues described above. However, because rare diseases – by definition – afflict an extremely small patient population, the development of drugs to treat rare diseases poses unique challenges over and above those discussed. These challenges include a lack of data on the natural course of the disease, difficulties in recruiting enough patients to achieve adequately powered statistical analyses of clinical trials, lack of validated clinical end points, logistical difficulties in organizing clinical trials, and low expertise in the medical community.[36] These challenges compound the uncertainties and risks associated with rare drug development, which, in turn, contribute to even higher drug costs, as higher-risk projects need higher profit potential to gain required investor support.[37]

36. Moreover, these costs do not correspond to the size of the drug's potential market. A 2019 study provides the first empirical estimates comparing the cost of development for drugs that treat rare diseases with those of drugs that treat broader patient populations. The results were striking.[38] While the potential market for a rare disease drug is several orders of magnitude smaller than the potential market for a non-rare disease drug, the study found that total development costs for rare disease drugs were still about half as much as those for non-rare disease drugs.[39] For diseases affecting fewer than 5 in 10,000 people, finding and recruiting patients to participate in clinical

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[35] U.S. Food & Drug Administration, Orphan Products: Hope for People with Rare Diseases, available at https://www fda.gov/drugs/drug-information-consumers/orphan-products-hope-people-rare-diseases.

[36] *See, e.g.* the discussion at Rollet, P. et al. (2013). Sustainable Rare Diseases Business and Drug Access: No Time for Misconceptions. *Orphanet Journal of Rare Diseases, 8*(1): 109-118, p. 6.

[37] Tambuyzer, E. (2010). Rare Diseases, Orphan Drugs and their Regulation: Questions and Misconceptions. *Nature Reviews Drug Discovery, 9*(12): 921-929.

[38] Jayasundara, K. et al. (2019). Estimating the Clinical Cost of Drug Development for Orphan versus Non-Orphan Drugs. *Orphanet Journal of Rare Diseases, 14*(1), 12-22.

The difference in cost was $412 million versus $291 million. Note that this study was limited by the fact that it had to rely on publicly available data, unlike previous studies that had access to confidential survey information from pharmaceutical companies. This resulted in lower estimates of the total cost of drug development, a point that the authors of the study themselves acknowledge. [*Ibid*, p. 19.]

[39] The lower cost associated with drugs for rare diseases arises primarily because Phase III study populations are significantly smaller. However, it is important to recognize that this study found that, in all phases, the length of trials for rare disease drugs was longer than for drugs serving broader populations. [*Ibid*, pp. 14-15.]

trials is substantially more costly and complex. For example, based on my experience advising, developing, running, and analyzing randomized clinical trials and teaching statistical power calculations for over three decades in my graduate econometrics and statistics classes, it would be nearly impossible to recruit enough patients to conduct a Canada-only cystinosis clinical trial with adequate statistical power. To be able to detect significant treatment effect differences, one would have to convince essentially every Canadian cystinosis patient to enroll in the trial. In my experience, a substantial number of patients refuse such requests for a variety of reasons, including not wanting to give up their current treatment for an unknown treatment, privacy, costs, and the inconvenience of participating.

Profitability, Cost Recovery, and Price Regulation

37. The costs and risks associated with pharmaceutical R&D play an important role in the pricing of rare and ultra-rare disease drugs. The price of any new pharmaceutical product – including a rare disease drug – should be set so that sales revenues are sufficient to allow the company to recover the drug's R&D, manufacturing, marketing, sales, and general administrative costs from inception to patent expiration.[40]

38. From an economic perspective, a company is unlikely to invest in a project unless it expects to earn a return on investment that provides compensation for the risks involved, as well as for the time value of money. In deciding whether to undertake an investment, a company will consider the return that it will earn if the drug is successfully commercialized. The company will then weigh this return with its assessment of the probability of success. This probability-weighted return is referred to as the expected return. The company's expected return depends on the price that it will be able to charge for its product. If a company believes that, if development is successful, the price it will be able to charge will not allow it to recover its costs, then it is unlikely that the company will invest in commercializing the drug.

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[40] Branded pharmaceutical products rely heavily on the revenues generated before patent expiration in order to earn a return on the R&D investments because (as a result of generic substitution policies) substantially all sales of a drug after patent expiry will be made by low-cost generic companies, which have not made the substantial investments in R&D (and can thus charge lower prices). [Grabowski, H. et al. (2012). Does Generic Entry Always Increase Consumer Welfare. *Food & Drug Law Journal, 67*(3): 373-91.]

39. As a matter of economics, if the company's expected return is below the costs associated with developing and commercializing the drug, the price cannot be viewed as excessive.

Factors Impacting Pricing and Recovery of Costs for Rare Disease Drugs

40. In the case of drugs for rare diseases, it is important to recognize that small patient populations limit the sales volumes over which cost recovery can take place. As discussed in an article published in *Nature Reviews Drug Discovery*, "[u]ltimately, the price of a drug and the corresponding cost per patient is determined by the size of the patient population requiring therapy and by the risk taken to develop the product, which is reflected in the profit potential. Because a drug's average per-unit cost will be inversely related to the volume of sales, a rare-disease drug will typically need to be priced at a much higher level than a non-rare disease drug (all else being equal) for the drug's originator to cover its costs and shareholder returns."[41]

Potential Effects of Pharmaceutical Price Regulation on R&D Incentives

41. Given these market realities, innovators of rare disease drugs must often charge prices that appear high relative to the prices of drugs serving broader populations. If price regulation prevents these innovators from recovering their expenditures on R&D for new rare disease drugs, the incentive to develop future rare disease drugs could be severely curtailed. This concern is particularly acute for companies that seek to produce drugs for rare and ultra-rare diseases.

The Impact of Price Regulation on Investment in Pharmaceutical R&D

42. Economic theory predicts that price regulation can reduce a company's incentive to engage in R&D. It can lower a company's expected profits, which in turn may cause the company to reduce its level of R&D investment. The lowering of the company's expected profits can also increase the cost of financing the development of all drugs in its pipeline, thereby reducing the company's incentive to invest in R&D.

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[41] Tambuyzer, E. (2010). Rare Diseases, Orphan Drugs and their Regulation: Questions and Misconceptions. *Nature Reviews Drug Discovery, 9*(12): 921-929, p. 927. See also Hollis, A. (2006). Drugs for Rare Diseases: Paying for Innovation. In C.M. Beach et al. (eds.) *Health Services Restructuring in Canada: New Evidence and New Directions:* 155-177. Queen's School of Policy Studies; Rollet, P. et al. (2013). Sustainable Rare Diseases Business and Drug Access: No Time for Misconceptions. *Orphanet Journal of Rare Diseases, 8*(1): 109-118.

43. Empirical studies have shown that price regulation reduces pharmaceutical companies' incentive to undertake R&D, consequently leading to a reduction in the number of new drug products that reach the market each year.[42] A leading study that analyzed the R&D expenditures of the top 14 U.S. pharmaceutical companies from 1994 to 1997 found that proposed pharmaceutical price regulations could reduce R&D intensity (*i.e.*, the ratio of R&D expenses to total sales) by as much as 30%.[43] Other studies that looked at the direct effect of price regulations on pharmaceutical industry output have found that, for every 10% reduction in drug prices, pharmaceutical innovation declines between 5% and 6%.[44]

44. The social welfare loss associated with a reduction in R&D stems from the loss of drug products that would no longer be developed. Economic studies have shown that the societal returns on pharmaceutical development are large. For example, a study by Lichtenburg and Waldfogel (2003) investigated the relationship between the health benefits to patients with rare diseases and the increased R&D incentives stemming from the passage of the U.S. Orphan Drug Act (discussed further below). The study found that availability of novel therapies for rare diseases had a statistically significant effect on the longevity of people suffering from these conditions.[45] The

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[42] See, *e.g.*, Scherer, F.M. (2001). The Link Between Gross Profitability and Pharmaceutical R&D Spending. *Health Affairs, 20*(5): 216-220; Kessler, D.P. (2004). The Effects of Pharmaceutical Price Controls on the Cost and Quality of Medical Care: A Review of the Empirical Literature. Mimeo; Vernon, J.A. (2005). Examining the Link Between Price Regulation and Pharmaceutical R&D Investment. *Health Economics, 14*(1): 1-16; Giaccotto, C. et al. (2005). Drug Prices and Research and Development Investment Behavior in the Pharmaceutical Industry. *The Journal of Law and Economics, 48*(1): 195-214; Danzon, P.M., et al. (2005). The Impact of Price Regulation on the Launch Delay of New Drugs—Evidence from Twenty-Five Major Markets in the 1990s. *Health Economics, 14*(3): 269-292; Golec, J.H. and Vernon, J.A. (2006). European Pharmaceutical Price Regulation, Firm Profitability, and R&D Spending. National Bureau of Economic Research, No. w12676; Vernon, J.A. et al. (2006). The Economics of Pharmaceutical Price Regulation and Importation: Refocusing the Debate. *American Journal of Law & Medicine, 32*(2-3): 175-192; Abbott, T.A. and Vernon, J.A. (2007). The Cost of US Pharmaceutical Price Regulation: A Financial Simulation Model of R&D Decisions. *Managerial and Decision Economics, 28*(4-5): 293-306; Lichtenberg, F.R. (2007). Importation and Innovation. *Economics of Innovation and New Technology, 16*(6): 403-417; Eger, S. and Mahlich, J.C. (2014). Pharmaceutical Regulation in Europe and its Impact on Corporate R&D. *Health Economics Review, 4*(1): 23-31.

[43] Vernon, J.A. (2005). Examining the Link Between Price Regulation and Pharmaceutical R&D Investment. *Health economics, 14*(1): 1-16

[44] Scherer, F.M. (2001). The Link Between Gross Profitability and Pharmaceutical R&D Spending. *Health Affairs, 20*(5): 216-220; Giaccotto, C. et al. (2005). Drug Prices and Research and Development Investment Behavior in the Pharmaceutical Industry. *The Journal of Law and Economics, 48*(1): 195-214; Lichtenberg, F.R. (2007). Importation and Innovation. *Economics of Innovation and New Technology, 16*(6): 403-417.

[45] Lichtenberg, F.R. and Waldfogel, J. (2003). Does misery love company? Evidence from pharmaceutical markets before and after the Orphan Drug Act. National Bureau of Economic Research, No. w9750.

literature also shows that pharmaceutical R&D expenditures are more effective in delivering health benefits than other medical expenditures,[46] and that substituting new drugs for older drugs leads to significant improvements in patient health.[47] In fact, economic studies of the U.S. have shown that the increase in health and longevity over the past century has provided the average individual with the equivalent of over $1.2 million in value.[48]

Incentivizing R&D for Rare Disease Drugs: The Orphan Drug Act

45. The relationship between the expected returns from a new rare disease drug and the incentives to invest in the development of these drugs is illustrated by the development of rare disease drugs in the United States following the passage of the Orphan Drug Act in 1983.[49] The Act was passed in recognition of the fact that high R&D costs together with small patient populations create financial barriers to the development of drugs that treat rare diseases. Accordingly, the Act created measures to lower the costs of development (so called "push programs") and to enhance the expected revenues from the commercialization ("pull programs") of drugs that treat rare diseases.[50]

Specifically, Lichtenburg and Waldfogel (2003) found that the percent of individuals dying young for relatively rare illnesses fell from by 6 percentage points between 1979 and 1998, whereas the percent of patients dying young from more common disease conditions had fallen only by 2 percentage points.

46 Lichtenberg, F.R. (2004). Sources of US Longevity Increase, 1960–2001. *The Quarterly Review of Economics and Finance, 44*(3): 369-389.

47 Lichtenberg, F.R. (2001). Are the Benefits of Newer Drugs Worth their Cost? Evidence from the 1996 MEPS. *Health Affairs, 20*(5): 241-251.

48 Murphy, K M. and Topel, R. H. (2006). The Value of Health and Longevity. *Journal of Political Economy, 114*(5): 871-904. See also Nordhaus, W. D. (2005). The Health of Nations: Irving Fisher and the Contribution of Improved Longevity to Living Standards. *American Journal of Economics and Sociology, 64*(1): 367-392.

49 Asbury, C. H. (1991). The Orphan Drug Act: The First 7 Years. *JAMA: The Journal of the American Medical Association, 265*(7): 893-897; Grabowski, H. (2005). Increasing R&D Incentives for Neglected Diseases: Lessons from the Orphan Drug Act. In K. Maskus and J. Reichman (eds.), *International Public Goods and Transfer of Technology Under a Globalized Intellectual Property Regime*: 457-480. Cambridge University Press; Haffner, M.E. (2006). Adopting Orphan Drugs—Two Dozen Years of Treating Rare Diseases. *New England Journal of Medicine, 354*(5): 445-447; Seoane-Vazquez, E. et al. (2008). Incentives for Orphan Drug Research and Development in the United States. *Orphanet Journal of Rare Diseases, 3*(1), 33-39; Yin, W. (2008). Market Incentives and Pharmaceutical Innovation. *Journal of Health Economics, 27*(4): 1060-1077.

50 The preamble to the Orphan Drug Act states "because so few individuals are affected by any one rare disease or condition, a pharmaceutical company which develops an orphan drug may reasonably expect the drug to generate relatively small sales in comparison to the cost of developing the drug and consequently to incur a financial loss." Among its push programs, the Orphan Drug Act includes tax credits on clinical trials, clinical research grants, as well as U.S. FDA counseling for orphan drug sponsors. [U.S. Food & Drug Administration, Orphan Drug Act -

46. The Act has been remarkably successful in encouraging the development of rare disease drugs. In the decade prior to the passage of the Act, an estimated ten or fewer rare disease drugs were approved for sale in the U.S. In contrast, over the past 36 years, there have been over 800 orphan drug approvals through to the end of July 2019, representing over 500 different drugs for almost 600 indications (several drugs have multiple indications).[51] Of course, "[w]hile a simple pre and post ODA time series analyses does not prove causation, the more than tenfold increase in the rate of orphan drug approvals since 1983 is indicative that the Act has indeed been a powerful stimulus to increased R&D investment in drugs for rare illnesses."[52]

47. In Canada, however, rare disease drugs are treated in much the same way as other drugs. Unlike other jurisdictions, such as the U.S. and the European Union, Canada does not have an incentive system or a specific regulatory pathway for rare disease drugs.[53] Accordingly, the incentives for pharmaceutical companies to commercialize rare disease drugs in Canada depend primarily on the ability to secure drug prices that will generate a justifiable and positive return on investment.

Challenges in Applying Pharmacoeconomic Models to Rare Disease Drugs

48. Many countries regulate pharmaceutical prices through a variety of mechanisms, including price caps and, less frequently, rate of return regulation.[54] Another method of price regulation is a

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Relevant Excerpts, available at https://www fda.gov/industry/designating-orphan-product-drugs-and-biological-products/orphan-drug-act-relevant-excerpts.]

[51] U.S. Food & Drug Administration, Orphan Drug Designations and Approvals, available at. https://www.accessdata.fda.gov/scripts/opdlisting/oopd.

[52] Grabowski, H. (2005). Increasing R&D Incentives for Neglected Diseases: Lessons from the Orphan Drug Act. In K. Maskus and J. Reichman (eds.), *International Public Goods and Transfer of Technology Under a Globalized Intellectual Property Regime*: 457-480. Cambridge University Press

[53] See, *e.g.*, Board Staff Production Tab 91 (Report of the Standing Committee on Health, House of Commons Canada, "Canadians Affected by Rare Diseases and Disorder: Improving Access to Treatment", February 2019). pp. 10-13.

[54] See, *e.g.*, World Health Organization (2015). *WHO Guideline on Country Pharmaceutical Pricing Policies*. Geneva: World Health Organization; Vogler, S. and Martikainen, J.E. (2015). Pharmaceutical Pricing in Europe. In Z. Babar (ed.), *Pharmaceutical prices in the 21st Century*: 343-370. Springer; Kanavos, P. et al. (2017). *The Implementation of External Reference Pricing within and across Country Borders*. London School of Economics; U.K. Department of Health and Social Care, *The 2019 Voluntary Scheme for Branded Medicines Pricing and Access - Chapters and Glossary*, available at https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/761834/voluntary-scheme-for-branded-medicines-pricing-and-access-chapters-and-glossary.pdf.

Health Technology Assessment ("HTA"). An HTA encompasses two analyses: (i) an evaluation of the clinical effectiveness of a new drug, and (ii) an evaluation of the cost effectiveness of a new drug, including its impact on both patient health and costs to the health-care system.[55]

49. In a cost-effectiveness analysis (referred to as a cost-utility analysis when the outcomes are valued through health state utilities), the incremental cost-effectiveness of a new drug is assessed based on: (i) the total cost of that therapy, and (ii) the expected quality-adjusted life years ("QALY") provided by that therapy.[56] The result of this comparison is sometimes referred to as a cost per QALY ratio or an incremental cost-utility ratio.[57] However, this ratio is not an end in itself. To be informative for decision making, this ratio must be compared with a "cost effectiveness threshold," which represents society's willingness-to-pay for new drugs.[58]

50. While the use of HTAs may be increasing overall, many pharmacoeconomists believe that they are wholly inappropriate for evaluating prices of (and expenditures on) rare disease drugs. This is because drugs for rare diseases will typically be associated with: (i) higher prices, as discussed above, and (ii) greater clinical uncertainty, as clinical trials with sufficient scale to achieve adequately powered statistical analyses for efficacy and safety are not possible. According to Professor Drummond from the Centre for Health Economics at the University of York:[59]

For a detailed discussion of rate of return regulation in the context of pharmaceuticals see *e.g.*, Drummond, M.F. and Towse, A. (2019). Is Rate of Return Pricing a Useful Approach when Value-Based Pricing is Not Appropriate? *European Journal of Health Economics, 20*: 945-948.

[55] World Health Organization, Health Technology Assessment, available at https://www.who.int/medical_devices/assessment/en.

[56] See, *e.g.*, Grosse S.D., Chaugule S. and Hay J.W. (2015). QALYs and Hemophilia: A Review. *Expert Reviews of Pharmacoeconomics and Outcomes Research, 15*(2): 225-242.

[57] The incremental cost-utility ratio measures the incremental cost of a therapy relative to its incremental quality adjust life years, where incremental is gauged against a baseline standard of care. [See, *e.g.*, Hay, J.W. (2004). Evaluation and Review of Pharmacoeconomic Models. *Expert Opinion on Pharmacotherapy; 5*(9): 1867-1880.]

[58] Ollendorf, D.A. et al. (2017). *Assessing the Effectiveness and Value of Drugs for Rare Conditions*, Institute for Clinical and Economic Review. See also Hay, J.W. (2005). Application of Cost Effectiveness and Cost Benefit Analysis to Pharmaceuticals. In M. Santoro and T. Gorrie (eds.), *The Grand Bargain: Ethics and the Pharmaceutical Industry In the 21st Century*; 225-248. Cambridge University Press.

[59] Drummond, M.F. et al. (2007). Assessing the Economic Challenges Posed by Orphan Drugs. *International Journal of Technology Assessment in Health Care, 23*(1): 36-42, p. 38.

See also Hollis, A. (2006). Drugs for Rare Diseases: Paying for Innovation. In C.M. Beach et al. (eds.) *Health Services Restructuring in Canada: New Evidence and New Directions:* 155-177. Queen's School of Policy

> It is no surprise that orphan drugs fare badly under such procedures. Prices and the corresponding cost-effectiveness estimates are high. First, because of rarity, the development costs have to be recouped from sales to a limited number of patients worldwide, with consequently high acquisition costs per patient. [...] Second, because of the small number of persons suffering from rare diseases, it is often difficult to enroll sufficient patients into a standard randomized controlled trial. This means that, at the time of product launch, there may not be the same breadth and quality of clinical evidence for orphan drugs, compared with those for more common diseases. **In short, if standard HTA procedures were to be applied to orphan drugs, virtually none of them would be "cost effective. [emphasis added]**

51. CADTH's Common Drug Review of PROCYSBI illustrates the issues raised by the application of an HTA to a rare disease drug. Empirical data on the long-term impact of PROCYSBI on health outcomes are not available. CADTH referred to Dr. Brodin-Sartorius, a clinical expert and the lead researcher on the team that conducted the first retrospective clinical trial studies of Cystagon.[60] Although Horizon put forward evidence from Dr. Brodin-Sartorius on how patients' long-term clinical outcomes were impacted by treatment with PROCYSBI, CADTH appears to have ignored her findings.[61]

52. Horizon provided CADTH with a cost-utility analysis. CADTH re-analyzed Horizon's model and reduced the efficacy of PROCYSBI to that of immediate release cysteamine bitartrate, leading to a lower estimate of the cost-effectiveness of PROCYSBI.[62] Moreover, because CADTH's pharmacoeconomic analysis was undertaken from the perspective of the publicly

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Studies; Hughes, D.A. et al. (2005). Drugs for Exceptionally Rare Diseases: Do they Deserve Special Status for Funding? *QJM: An International Journal of Medicine, 98*(11): 829-836; Drummond, M.F. (2008). Challenges in the Economic Evaluation of Orphan Drugs. *Eurohealth 14*(2): 16-17; Tambuyzer, E. (2010). Rare Diseases, Orphan Drugs and their Regulation: Questions and Misconceptions. *Nature Reviews Drug Discovery, 9*(12): 921-929; Simoens, S. et al. (2013). Cost-Effectiveness Assessment of Orphan Drugs. *Applied Health Economics and Health Policy, 11*(1): 1-3; Drummond, M.F. and Towse, A. (2014). Orphan Drugs Policies: A Suitable Case for Treatment. *The European Journal of Health Economics, 15*(4): 335-340; Karpman, D. and Höglund, P. (2017). Orphan Drug policies and use in Pediatric Nephrology. *Pediatric Nephrology, 32*(1): 1-6; Ollendorf, D.A. et al. (2017). *Assessing the Effectiveness and Value of Drugs for Rare Conditions*, Institute for Clinical and Economic Review.

60 Brodin-Sartorius, A. et al. (2012). Cysteamine Therapy Delays The Progression of Nephropathic Cystinosis in Late Adolescents and Adults. *Kidney international, 81*(2): 179-189.

61 These outcomes included survival, as well as the likelihood of developing complications such as end-stage renal disease, diabetes, and neuromuscular disorders. [Board Staff Production Tab 3 (CADTH - Pharmacoeconomic Review Report, February 2018), pp. 7-8, 10, 21-22.]

62 Board Staff Production Tab 3 (CADTH - Pharmacoeconomic Review Report, February 2018), pp. 9, 14-15, 28.

funded health payor, the only costs it considered are those incurred by the payor (cost of therapy and cost of complications) and the only benefit it considered is QALY.[63]

53. Among other limitations, CADTH's approach has the effect of penalizing drugs that extend the life of patients. As acknowledged by CADTH, "[w]hile delayed-release cysteamine may increase life expectancy, this also results in a high rate of complications as patients live longer, increasing the total health care costs."[64] CADTH's approach also ignores the societal benefits generated by patients being able to live healthier and/or longer lives including, for example, the reduced need for parents and/or guardians of young patients to take time off work to accommodate their child's treatment, the additional earning potential of patients over a longer life span, the reduced need for patients and/or caregivers to rely on social assistance, and the possibility of living long enough to have children and raise them.[65]

54. Moreover, a cost-utility analysis itself does not identify the appropriate threshold for how much society is willing to pay for these treatments. A strict utilitarian application of the threshold used to evaluate drugs indicated to treat diseases affecting large patient populations may be seen as conflicting with the principle that all patients have a right of access to healthcare.[66] Indeed, to the extent that society believes that individuals suffering from rare diseases require special consideration, a higher willingness to pay threshold may be more appropriate in the evaluation of rare disease drugs. However, there is currently no established basis for determining how much to

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[63] Board Staff Production Tab 3 (CADTH - Pharmacoeconomic Review Report, February 2018), pp. 7, 10, 21; Canadian Agency for Drugs and Technologies in Health, Guidelines for the Economic Evaluation of Health Technologies: Canada, 4th Edition, pp. 18, 29-31, available at https://www.cadth.ca/sites/default/files/pdf/guidelines_for_the_economic_evaluation_of_health_technologies_canada_4th_ed.pdf.

[64] Board Staff Production Tab 3 (CADTH - Pharmacoeconomic Review Report, February 2018), p. 9.

[65] See, *e.g.*, Sculpher, M.J. (2001). The Role and Estimation of Productivity Costs in Economic Evaluation. In M.J. Sculpher, M. Drummond (eds.) *Economic Evaluation in Health Care: Merging Theory with Practice*: 94-112. Oxford University Press; Ernst, R. (2006). Indirect Costs and Cost-Effectiveness Analysis. *Value in Health, 9*(4): 253-261; Brouwer, W.B. et al. (2006). A Dollar is a Dollar is a Dollar—Or is It? *Value in Health, 9*(5): 341-347; Krol, M. et al. (2013). Productivity Costs in Economic evaluations: Past, Present, Future. *Pharmacoeconomics, 31*(7): 537-549.

[66] Hughes, D. A. et al. (2005). Drugs for Exceptionally Rare Diseases: Do they Deserve Special Status for Funding? *QJM: An International Journal of Medicine, 98*(11): 829-836; Drummond, M.F. et al. (2007). Assessing the Economic Challenges Posed by Orphan Drugs. *International Journal of Technology Assessment in Health Care, 23*(1): 36-42.

pay for a product that is important for the well-being (and possibly survival) of a very small number of individuals.

55. HTA models – including the one applied by CADTH – are a poor fit for evaluating expenditures on rare disease drugs. Countries seeking to control the prices of rare disease drugs must therefore consider other methods. Those other methods include the price controls discussed previously, either in the form of price caps or rate of return regulation. Indeed, health economists have recently put forth proposals adjusting established HTA approaches to explicitly account for drug development costs and/or to evaluate prices based on their associated rates of return.[67] These approaches are appropriate in the case of rare disease drugs preciously because HTAs are "unlikely to be helpful in setting an appropriate price, since the price will be too low, either to encourage manufacturers to launch the products, or, in the long run, to stimulate research into rare conditions."[68]

VI. PHARMACEUTICAL PRICE REGULATION IN CANADA: A REFERENCE-BASED PRICING MODEL

Reference Pricing under the PMPRB Compendium

56. It is my understanding that the origins of Canada's pharmaceutical pricing regulatory framework can be traced back to the 1987 *Patent Act* amendments. These amendments were undertaken in response to concerns about Canada's pending abolition of compulsory licensing. In addition to being contrary to international trade agreements, Canada's policy of compulsory licensing was viewed as providing disincentives for investment in pharmaceutical R&D.[69] The PMPRB was created as a counter balance to mitigate the potential impact of restricting (and later

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[67] Berdud, M. et al. (2018). *Establishing a Reasonable Price for an orphan drug*. U.K. Office of Health Economics; Drummond, M. and Towse, A. (2014). Orphan Drugs Policies: A Suitable Case for Treatment. *The European Journal of Health Economics, 15*(4): 335-340; Drummond, M. F. and Towse, A. (2019). Is Rate of Return Pricing a Useful Approach when Value-Based Pricing is Not Appropriate? *European Journal of Health Economics, 20*: 945-948.

[68] Drummond, M. F. and Towse, A. (2019). Is Rate of Return Pricing a Useful Approach when Value-Based Pricing is Not Appropriate? *European Journal of Health Economics, 20*: 945-948.

[69] PMPRB Compendium, Part A: Legal Framework; Patented Medicine Prices Review Board, Appendix: Historical Context - Background on Federal Regulation of Patented Medicine Prices and the PMPRB's Guidelines for Price Increases, available at http://www.pmprb-cepmb.gc.ca/view.asp?ccid=1086; Morin, J.F. et al. (2008). Canadian Pharmaceutical Patent Policy: International Constraints and Domestic Priorities. In Y. Gendreau (ed.) *A New Intellectual Property Paradigm*: 81-103, pp. 87-90. Edward Elgar.

eliminating) compulsory licensing on generic drug entry and to ensure that monopolistic prices for patented medications were not excessive.[70]

57. Based on my review of the PMPRB Compendium, I understand that Canada relies on price caps to limit the ex-factory prices that drug manufacturers can set for new pharmaceutical products.[71] Like many countries that employ the price cap approach, Canada sets its price caps with reference to drug prices charged in other countries (generally referred to as "reference-based" or "comparative" pricing methods). Two of the most prominent reference-based pricing methods are External Reference Pricing and Therapeutic Reference Pricing (discussed further below). External Reference Pricing aims to prevent manufacturers from engaging in overt price discrimination across countries by restricting the domestic price of a drug to some measure of the drug's price in other countries. In contrast, Therapeutic Reference Pricing imposes limits on prices by comparing the price of a new drug to other drugs that are deemed to have comparable clinical effects.

58. The PMPRB uses both methods: the Median International Price Comparison Test,[72] which is similar to the External Reference Pricing Test, and the Therapeutic Class Comparison Test, which is similar to the Therapeutic Reference Pricing Test.

External Reference Pricing and the Median International Price Comparison Test

59. The Median International Price Comparison Test is used to determine whether the price of a drug in Canada is excessive relative to international prices (*i.e.*, whether Canadians are being

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70 The concern was that removal of compulsory licensing could delay generic drug entry until patent expiry.

71 PMPRB Compendium, Part A: Legal Framework.

As previously mentioned, in other countries, maximum drug price regulation is focused on reimbursement (*i.e.*, the public payor will not reimburse expenditures on a drug if its price exceeds the price cap). In Canada, however, the drug manufacturer is prohibited from marketing a drug unless its price is first approved by the PMPRB. [See, *e.g.*, Morin, J.F. et al. (2008). Canadian Pharmaceutical Patent Policy: International Constraints and Domestic Priorities. In Y. Gendreau (ed.) *A New Intellectual Property Paradigm*: 81-103, pp. 87-90. Edward Elgar; Kanavos, P. et al. (2017). *The Implementation of External Reference Pricing within and across Country Borders*. London School of Economics.]

72 I have been asked to assume that the Median International Price Comparison Test is the appropriate test in this case. I understand that the Board has wide discretion under the *Patent Act* (which does not define any specific tests to be applied). However, I understand that the PMPRB Compendium lists only two tests for drugs that represent a breakthrough or substantial improvement, and these are the tests that I have focused on here. [PMPRB Compendium, Part C: Guidelines and Procedures.]

subject to "price discrimination").[73] For Canadians, the use of this test in setting the prices of new drugs in Canada has numerous economic benefits. As an initial matter, this test ensures that Canadians will, on average, pay no more for a particular drug than individuals in countries of similar socioeconomic status.[74]

60. As discussed, the Median International Price Comparison Test uses the PMPRB7 as the basket of reference countries.[75] From an economic perspective, it is reasonable for Canada to use other major-industrialized nations as comparators in its regulation of ex-factory pharmaceutical prices, as such countries would tend to share similar standards of living.[76] Figure 2, below, shows that Canada ranks at or near the middle of the PMPRB7 (*i.e.*, at the median point) in terms of income, health spending, and life expectancy, which suggests that the PMPBR7 provide a similar set of countries against which Canada can reasonably use as reference for pharmaceutical pricing.[77]

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[73] Price discrimination describes the practice by a seller of charging different prices to different customers. A seller charging different prices to customers in different countries is an example of "third degree" price discrimination.

[74] Patented Medicine Prices Review Board, Appendix: Historical Context - Background on Federal Regulation of Patented Medicine Prices and the PMPRB's Guidelines for Price Increases, available at http://www.pmprb-cepmb.gc.ca/view.asp?ccid=1086; Patented Medicine Prices Review Board, PMPRB Guidelines Modernization – Discussion Paper, June 2016, available at http://www.pmprb-cepmb.gc.ca/en/news-and-events/consultations/current-major-consultations/rethinking-the-guidelines/discussion-paper;

I understand that the Government of Canada has recently amended to the *Patent Act* to, among other things, expand the list of reference countries to 11, in particular, adding Australia, Belgium, Japan, the Netherlands, Norway, and Spain to the list, while removing Switzerland ant the U.S. I understand further that these amendments come into force on July 2020. [Canada Gazette, Regulations Amending the Patented Medicines Regulations, Vol. 153, No. 17, available at http://www.gazette.gc.ca/rp-pr/p2/2019/2019-08-21/html/sor-dors298-eng.html.]

[75] PMPRB Compendium, Schedule 5.

[76] The World Bank, World Development Indicators Databank, available at https://databank.worldbank.org/source/world-development-indicators.

[77] The use of the median in setting prices also makes economic sense. The median of a set of numbers is the middle score for the data arranged in order of magnitude, thus separating the top 50% of the data from the lower 50% of the sample. As compared to the average (*i.e.*, sample mean), one well known advantage of the median is that it is less susceptible to be skewed by outliers. National Research Council of the National Academies. (2011). *Reference Manual on Scientific Evidence, Third Edition.* National Academies Press, pp 238-239, 289-292.

Figure 2: World Bank Development Indicators for Canada and the PMPRB7

	GDP Per Capita (Purchase Power Parity)	Health Expend. Per Capita (Purchase Power Parity)	Life Expectancy (Years)
	Value	Value	Value
Canada	$43,089	$4,718	82.3
PMPRB7			
France	$38,098	$4,782	82.5
Germany	$44,669	$5,463	81.0
Italy	$34,735	$3,427	83.2
Switzerland	$57,610	$7,867	83.6
Sweden	$46,339	$5,387	82.3
United Kingdom	$39,425	$4,178	81.2
United States	$53,632	$9,870	78.5
PMPRB7 Median	$44,669	$5,387	82.3
PMPRB7 Average	$44,930	$5,854	81.8

Source: The World Bank, World Development Indicators Databank.

61. An additional economic rationale for Canada's use of the Median International Price Comparison Test is that each of the PMPRB7 prices can be viewed as the outcome of a bargaining process between a willing buyer (each of Canada's peer countries) and a willing seller.[78]

62. A further economic benefit of the Median International Price Comparison Test is the stable guidance that it provides to potential investors in pharmaceutical R&D. Indeed, as noted in the preamble to the PMPRB Compendium: "[o]ne of the primary objectives of the Compendium of Policies, Guidelines and Procedures (Compendium) is to ensure that patentees are aware of the policies, guidelines and procedures under which Board Staff reviews the prices of patented drug products sold in Canada, and the procedures normally undertaken in the scientific and price review processes and when a price appears to be excessive."[79]

63. The possibility that regulators will deviate *ex post* from policies they committed to *ex ante* can disincentivize investment in pharmaceutical R&D.[80] If a company perceives that there is a risk

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[78] Kanavos, P. et al. (2017). *The Implementation of External Reference Pricing within and across Country Borders*. London School of Economics.; Patented Medicine Prices Review Board, PMPRB Guidelines Modernization – Discussion Paper, June 2016, available at http://www.pmprb-cepmb.gc.ca/en/news-and-events/consultations/current-major-consultations/rethinking-the-guidelines/discussion-paper.

[79] PMPRB Compendium, p. 6.

[80] See, *e.g.*, Brennan, M.J. and Schwartz, E.S. (1982). Consistent Regulatory Policy under Uncertainty. *Bell Journal of Economics, 13*(2): 506-521; Blackman, G. and Zeckhauser, R. (1992). Fragile Commitments and the Regulatory Process. *Yale Journal on Regulation, 9*(1): 73-103; Levy, B. and Spiller, P.T. (1994). The Institutional

that a regulator will change its stated pricing policies after the company has commercialized its product, the company may delay or even forgo sinking its capital into the investment. Economic logic indicates that abrupt deviations from these established guidelines may lead to regulatory uncertainty, the impact of which can be to diminish pharmaceutical companies' R&D incentives and/or raise the cost of financing such R&D.[81]

Application of the Median International Price Comparison Test to PROCYSBI

64. Figure 3, below, which is taken from the Statement of Allegations of Board Staff, provides the prices for PROCYSBI across the countries of the PMPRB7.

Figure 3: Board Staff's Per Milligram Prices for PROCYSBI

	Price in CAD$ as at Apr 2017		Price in CAD$ as at Dec 2017		Price in CAD$ as at Jun 2018	
Country	75mg	25mg	75mg	25mg	75mg	25mg
Canada	$0.4140	$0.4140	$0.4140	$0.4140	$0.4140	$0.4140
PMPRB7						
France	No Price		No Price		No Price	
Germany	$0.4179	$0.4179	$0.4207	$0.4207	$0.4289	$0.4289
Italy	No Price		No Price		No Price	
Switzerland	No Price		No Price		No Price	
Sweden	No Price		No Price		No Price	
United Kingdom	$0.4115	$0.4115	$0.4049	$0.4049	$0.4003	$0.4003
United States	$1.4045	$4.2136	$1.4483	$4.3449	$1.4562	$4.3687
Median	$0.4179	$0.4179	$0.4207	$0.4207	$0.4289	$0.4289

Source: Statement of Allegations of Board Staff, ¶31.

65. This Figure shows that, since launch, the ex-factory price for PROCYSBI in Canada ($0.4140 per mg) has been lower than the median international price for PROCYSBI. Based on the Median International Price Comparison Test, the median international price for PROCYSBI has been between $0.4179 and $0.4289 per mg, depending on the month in which foreign exchange

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Foundations of Regulatory Commitment: A Comparative Analysis of Telecommunications Regulation. *The Journal of Law, Economics, and Organization, 10*(2): 201-246; Gilbert, R.J. and Newbery, D.M. (1994). The Dynamic Efficiency of Regulatory Constitutions. *The Rand Journal of Economics, 25*(4): 538-554.

[81] I understand that, under the *Patent Act*, the costs of making and marketing a drug product, including the portion of the total costs related to the development and commercialization of the drug in Canada, can be a factor considered by the Board in its review of PROCYSBI's ex-factory price. [*Patent Act*, RSC 1985, c P-4, s. 85(2)-(3), available at available at https://laws-lois.justice.gc.ca/PDF/P-4.pdf.]

rates are evaluated. Even at the bottom end of this range, the median international price exceeds the ex-factory price for PROCYSBI in Canada.[82]

66. Figure 4 below provides the most current reported price information for PROCYSBI in Canada and across the countries of the PMPRB7.

Figure 4: June 2019 Price Information for PROCYSBI

		Price Per Cap as at Jun 2019 Local Currency		Price Per Cap as at Jun 2019 Canadian Dollars		Per MG Price as at Jun 2019 Canadian Dollars	
Country	Exchange Rate As at Jun 2019	25mg	75mg	25mg	75mg	25mg	75mg
	[A]	[B]	[C]	[D] = [A] x [B]	[E] = [A] x [C]	[F] = [D] ÷ 25	[G] = [E] ÷ 75
Canada	-	CAD$10.35	CAD$31.05	$10.35	$31.05	$0.4140	$0.4140
PMPRB7							
France		No Price		No Price		No Price	
Germany	CAD$1.49064	€ 7.25	€ 21.76	$10.81	$32.44	$0.4325	$0.4325
Italy		No Price		No Price		No Price	
Switzerland		No Price		No Price		No Price	
Sweden		No Price		No Price		No Price	
United Kingdom	CAD$1.70234	£5.60	£16.80	$9.53	$28.60	$0.3813	$0.3813
United States	CAD$1.30682	USD$76.65	USD$96.58	$100.16	$126.21	$4.0066	$1.6828
Median				**$10.81**	**$32.44**	**$0.4325**	**$0.4325**

Source: Horizon Pharma PLC, Form 2 - Block 5, January to June 2019; Patented Medicine Prices Review Board, Exchange Rates 2019, available at https://www.pmprb-cepmb.gc.ca/view.asp?ccid=1426&lang=en.

67. As shown, the current ex-factory price for PROCYSBI in Canada (which has remained at $0.4140 per mg) remains below the median international price for PROCYSBI, which is now $0.4325.[83] Thus, according to the Median International Price Comparison Test set out in the PMPRB Compendium, the price of PROCYSBI is not excessive.

Therapeutic Reference Pricing and the Therapeutic Class Comparison Test

68. As mentioned above, Therapeutic Reference Pricing is a method used to set a drug's reference price by comparing it to other drugs deemed to be therapeutically equivalent by the relevant authority. The term therapeutic equivalence means that the drug and its comparator achieve comparable clinical effects even if they are not chemically the same. The rationale behind

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[82] Note that the over-time variations in the international prices of PROCYSBI shown in Figure 3 are driven entirely by foreign exchange rate fluctuations. The price of PROCYSBI has remained constant over the above time periods. [Statement of Allegations of Board Staff, ¶31.]

[83] Again, note that the changes in the international prices of PROCYSBI between June 2018 and June 2019 are driven entirely by foreign exchange rate fluctuations.

this approach is that the price of a new drug should reflect its place (*i.e.*, its benefits, or potential drawbacks) vis-à-vis the class of medicines that were previously available to treat the same indication. Put differently, "[t]herapeutic referencing [...] extends the concept of substitutability from generically equivalent products (same molecule) to different molecules for the same indication."[84]

69. As a pharmacoeconomist, I have extensive experience reviewing and applying Therapeutic Reference Pricing models for drugs. For example, I have been a consultant to the U.S. Food and Drug Administration drug approval processes, and to numerous companies seeking U.S. Food and Drug Administration approval for investigational new drug entities, new chemical entities and drug indications. I have also testified in court about U.S. Food and Drug Administration drug approval processes, evidence, and approval decisions numerous times.

70. In practice, drugs subject to Therapeutic Reference Pricing are placed into "clusters" by the relevant authority, usually in consultation with physicians or other medical advisors.[85] The criteria for whether the therapeutic effects of a given set of drugs are sufficiently close to be in the same cluster vary across countries and over time. Once clusters are defined, the Therapeutic Reference Price is set for each cluster according to a variety of calculation methods and other considerations.

71. Canada employs Therapeutic Reference Pricing through the Therapeutic Class Comparison Test. The Therapeutic Class Comparison Test relies on the identification of comparator drugs within the same "therapeutic class" as the drug being evaluated.[86] The drug is evaluated against the comparator class and is identified as belonging to one of the following categories:

(a) Breakthrough: a breakthrough drug is the first one to be sold in Canada that treats effectively a particular illness or addresses effectively a particular indication;

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[84] Danzon, P. M, and Ketcham, K. D. (2004). Reference Pricing of Pharmaceuticals for Medicare: Evidence from Germany, the Netherlands, and New Zealand. In D.M. Cutler and A.M. Garber (eds.) *Frontiers in Health Policy Research, Volume 7*: 1-54, p. 3. MIT Press

[85] *Ibid*, p. 9.

[86] PMPRB Compendium, Schedule 3, 1

(b) Substantial improvement: a drug that provides substantial improvement in therapeutic effects relative to other drug products sold in Canada;

(c) Moderate improvement: a drug that provides moderate improvement in therapeutic effects relative to other drug products sold in Canada;

(d) Slight or no improvement: a drug that provides slight or no improvement in therapeutic effects relative to other drug products sold in Canada.[87]

72. The Therapeutic Class Comparison Test excludes the prices of comparator drugs that the Board has reason to believe are excessive.[88]

73. To determine whether a drug is a breakthrough, substantial improvement, moderate improvement, or slight to no improvement, two groups of factors relating to the therapeutic characteristics of the drug are considered. Both groups of factors are set out in the PMPRB Compendium and have been reviewed and extensively commented upon in Dr. Langman's report.[89]

74. For a breakthrough drug, the Maximum Average Potential Price ("Maximum Price") is the median international price determined by the Median International Price Comparison Test, because such a drug, by definition, has no comparators.[90]

75. For a new drug providing substantial improvement, the Maximum Price is the higher of:

(a) The highest price among comparator drugs identified in the Therapeutic Class Comparison Test;

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87 PMPRB Compendium, C.5.1.

88 PMPRB Compendium, Schedule 3.

89 PMPRB Compendium, C.6.

Primary factors include increased efficacy and reduction in the incidence or grade of adverse reactions. Secondary factors include route of administration, patient convenience, compliance, caregiver convenience, time required to achieve optimal therapeutic effect, duration of usual treatment course, success rate, percentage of affected population effectively treated, and disability avoidance.

90 PMPRB Compendium, C.11.3 and C.8.5.

(b) The median international price from the Median International Price Comparison Test.[91]

76. It is interesting to note that in the case of drugs providing a substantial improvement, the Guidelines permit a price higher than the price yielded by the Median International Price Comparison Test. This is because it does not make sense to deem a drug price as excessive, when the drugs with which it compares (in terms of therapeutic efficacy) are more expensive.

77. For drugs providing moderate improvement, the Maximum Price is the higher of:

(a) The highest price among comparator drugs identified in the Therapeutic Class Comparison Test;

(b) The midpoint between the highest price among comparators from the Therapeutic Class Comparison Test and the median international price from the Median International Price Comparison Test.[92]

78. If no comparator drugs can be identified for the Therapeutic Class Comparison Test, the guidelines dictate that the median international price should be used.[93]

79. For drugs providing slight or no improvement, the Maximum Price is the highest price among comparator drugs identified in the Therapeutic Class Comparison Test.[94] If no comparator drugs are identified for the Therapeutic Class Comparison Test, the Maximum Price is the *lower* of:

(a) The lowest price of the *superior* drugs as identified by HDAP;

(b) The median international price from the Median International Price Comparison Test.[95]

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91 PMPRB Compendium, C.11.4.

92 PMPRB Compendium, C.11.5.

93 PMPRB Compendium, C.11.6.

94 PMPRB Compendium, C.11.7.

95 PMPRB Compendium, C.11.8.

80. Again, if no comparator drugs can be identified for the Therapeutic Clast Comparison Test, the median international price is used.[96]

81. I have reviewed the Expert Report of Dr. Langman and have considered the factors identified as being relevant to determining whether PROCYSBI represents a breakthrough, substantial improvement, moderate improvement, or slight or no improvement. I am comfortable opining on the therapeutic comparisons between PROCYSBI and Cystagon, since my main research and education focus is in developing economic analyses of the trade-offs and relative values of alternative treatments for disease, particularly pharmaceutical treatments. I have over 30 years of experience as a pioneer researcher in the field of outcomes research, a Founding Member of the Board of Directions of ISPOR, the International Society of Pharmacoeconomics and Outcomes Research, and as Founding Editor-in-Chief of ISPOR's official scientific journal, *Value in Health*, which was ranked number 1 when I stepped down as editor and is now ranked number 3 among all scientific journals in Health Economics, Pharmaceutical Economics, Outcomes Research and Health Services Research, and which celebrated its 20th Anniversary this year. Based on precisely these outcomes research issues, PROCYSBI represents at least a substantial improvement over any other drugs in the class (*i.e.*, Cystagon). Dr. Langman's evidence regarding the realizations gained in terms of patient efficacy and reduction in side effects (the Primary Factors), the improvements shown across almost all of the Secondary Factors, and the changed pharmacokinetic parameters realized by delivering enterically coated beads to the small intestine for absorption in the body (lower Cmax, longer duration of action), all reflect a drug that is markedly different from Cystagon. As noted by Dr. Langman, "Procysbi is a vast improvement over Cystagon."[97]

82. To suggest that Cystagon and PROCYSBI should be sold at equivalent prices is to suggest that these two drugs are equivalent. Based on Dr. Langman's Report, they are not. The reverse is also true: to say that the drugs are equivalent is to suggest that the two drugs should be priced the same. This makes no economic sense. Had Horizon known that this product would be priced equivalent to Cystagon, it would not have undertaken the risk and expense of developing a new

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[96] PMPRB Compendium, C.11.9.

[97] Langman Report, ¶155.

drug that, based on Dr. Langman's evidence, has radically altered the treatment landscape for cystinosis sufferers.

Ex-factory Prices vs Net Prices in Canada

83. While the discussion above has focused on how Canada regulates ex-factory prices for new drugs, it is important to recognize that the ex-factory list price is not the final price paid by public and private payors in the Canadian system. Reimbursement prices under public drug coverage plans are set by each provincial and territorial government.[98] A drug company must apply separately to each province and territory to get its new drug product listed on the respective provincial and territorial formularies. These provincial and territorial public drug coverage plans rely on pan-Canadian processes to help decide whether to list the product on their formularies and how much to reimburse the company for the drug.[99] As part of this process, provincial and territorial drug coverage plans obtain price discounts (via rebates) and other concessions as conditions for listing the drug on its public formulary. Thus, a pharmaceutical company's "net price" is its ex-factory price less all the discounts and rebates it has provided on those sales. That is, the effect of these rebates and price concessions is to provide the provincial and territorial public drug plans with net drug prices that are below the ex-factory list price for a new drug.

VII. BOARD STAFF'S ALTERNATIVE MODELS

84. Board Staff has proposed that three alternative pricing tests be applied instead of the approach set out in the PMPRB Compendium: (i) the "Same Medicine Comparison Test," (ii) the "Premium Comparison Test," and (iii) the "Market Share Comparison Test."

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[98] Board Staff Production Tab 91 (Report of the Standing Committee on Health, House of Commons Canada, "Canadians Affected by Rare Diseases and Disorder: Improving Access to Treatment", February 2019), pp. 18-23.]

In addition, I understand that the Federal government administers or facilitates drug coverage for members of the military and veterans, registered First Nations and recognized Inuit people, federal inmates, as well as certain classes of refugees.

[99] Board Staff Production Tab 91 (Report of the Standing Committee on Health, House of Commons Canada, "Canadians Affected by Rare Diseases and Disorder: Improving Access to Treatment", February 2019), pp. 23-30; Council of the Federation, "The Pan Canadian Pharmaceutical Alliance", available at http://www.canadaspremiers.ca/pan-canadian-pharmaceutical-alliance; Canadian Agency for Drugs and Technologies in Health, About CADTH, available at https://www.cadth.ca/about-cadth.

85. None of the alternative tests put forth by Board Staff correspond to the tests in the PMPRB Compendium. [redacted]

86. Below, I review each of these tests and explain how they propose to set ex-factory prices for PROCYSBI in Canada. I then comment on issues specific to the application of each test.

Same Medicine Comparison Test

87. In the Statement of Allegations, Board Staff has made the assumption (with which I disagree) that PROCYSBI and immediate release cysteamine bitartrate are direct therapeutic comparators. Accordingly, under the Same Medicine Comparison Test, the National Average Transaction Price for PROCYSBI is based on the price of cysteamine bitartrate (*i.e.*, Cystagon) in Canada or in the PMBRB7.[100]

88. Figure 5, below, shows Board Staff's Proposed Prices for PROCYSBI under the Same Medicine Comparison Test. Under this approach, Board Staff are seeking a reduction in the price of PROCYSBI from $10.35 per 25mg capsule and $31.05 per 75mg capsule down to either $0.4649 per 25mg capsule and $1.3948 per 75mg capsule (*i.e.*, a 96% decrease) or to as low as $0.1913 per 25mg capsule and $0.5740 per 75mg capsule (*i.e.*, a 98% decrease).

[100] Statement of Allegations of Board Staff, ¶¶42-45.

Figure 5: Board Staff's Same Medicine Comparison Test

Drug Product	Geography	Price Per Capsule [A]	Same Medicine Comparison Test [B]
PROCYSBI 25mg	Canada	10.35	-
Cystagon 150mg	Canada	1.1481	0.1913
Cystagon 150mg	PMPRB7	2.7896	0.4649
PROCYSBI 75mg	Canada	31.05	-
Cystagon 150mg	Canada	1.1481	0.5740
Cystagon 150mg	PMPRB7	2.7896	1.3948

Source: Statement of Allegations of Board Staff, ¶¶44-45.

89. I understand that the price for immediate release cysteamine bitartrate relied on by Board Staff in its Statement of Allegations is based on a formulary listing price published by the Newfoundland and Labrador Department of Health and Welfare in October 2017.[101] Board Staff failed to disclose how the Same Medicine Prices were calculated; however, I was able to replicate the model.[102] As shown in Figure 6, below, Board Staff calculated the maximum price for PROCYSBI using the per mg price of Cystagon multiplied by 25 to obtain the price for 25mg capsules (or by 75 to obtain the price of 75mg capsules).

Figure 6: Calculations of Prices under the Same Medicine Comparison Test

Drug Product	Geography	Price Per Capsule [A]	Price Per mg [B]	Price Per 25mg [C] = [B] x 25	Price Per 75mg [D] = [B] x 75
Cystagon 150mg	Canada	1.1481	0.0077	0.1914	0.5741
Cystagon 150mg	PMPRB7	2.7896	0.0186	0.4649	1.3948

90. There are several issues with this approach. I note the following:

[101] Response of Horizon Pharma, ¶56 and ¶79.

[102] I note that I am unable to precisely replicate Board Staff's calculations under the Same Medicine Comparison Test to the 4th decimal place.

(a) ***Failure to allow for cost recovery***. As discussed above in Section V, from an economic perspective, Horizon needs to charge a price that covers the costs associated with developing and commercializing PROCYSBI (*i.e.*, an enterically coated, delayed release formulation of cysteamine bitartrate), which I understand from Dr. Langman's evidence has led to greatly improved patient outcomes. I have conducted an analysis of Horizon's returns from sales of PROCYSBI in Canada at the Proposed Prices.[103] [redacted]

(b) ***Failure to account for therapeutic improvement***. Board Staff did not disclose how the "Same Medicine Prices" were calculated. This is a significant omission with important consequences. Once one has an understanding of Board Staff's calculations, the error in this approach becomes immediately clear. As shown in Figure 6, above, Board Staff calculated the maximum price for PROCYSBI using the per mg price of Cystagon multiplied by 25 to obtain the price for 25mg capsules, or by 75 to obtain the price of 75mg capsules. I have been advised by counsel for Horizon that the patents in this case relate to the enteric-coated, microspherized formulations of cysteamine bitartrate. I understand it is Dr. Langman's opinion that PROCYSBI is superior to Cystagon as PROCYSBI provides for improved pharmacokinetics, improved adherence to therapy, avoidance of more invasive therapies, reduced side effects, and reduced use of concomitant therapies.[104] Board Staff's proposal ignores these benefits and suggests that PROCYSBI's price be based entirely on its active pharmaceutical ingredient, while ignoring its enterically coated, delayed release formulation. As a matter of economics, a price for PROCYSBI that is based solely on its active pharmaceutical ingredient, and that does not account for the therapeutic improvement offered by the patented invention,

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[103] **Appendix F** describes the details of my analysis. **Appendix G** provides the schedules supporting the analysis.

[104] Langman Report, ¶¶28, 30, 33, 155-156.

namely PROCYSBI's enterically coated, delayed release formulation, is inappropriate in this case.[105].

Premium Comparison Test

91. As an alternative to the Same Medicine Comparison Test, Board Staff posits that, to the extent the PMPRB accepts that PROCYSBI's enteric coating justifies a price premium, "a maximum non-excessive price for PROCYSBI that includes a premium for the value of the enteric coating should not be above the quarter-point between the price of Cystagon and the current price of PROCYSBI."[106] Accordingly, under the Premium Comparison Test, the maximum price of PROCYSBI is equal to the price of Cystagon plus a mark-up equal to 25% of the difference between the current price of PROCYSBI and Cystagon.

92. Figure 7, below, shows Board Staff's calculation for the price of PROCYSBI under the Premium Comparison Test. Under this approach, Board Staff is seeking a reduction in the price of PROCYSBI from $10.35 per 25mg capsule and $31.05 per 75mg capsule down to either $2.9602 per 25mg capsule and $8.8807 per 75mg capsule (*i.e.*, a 71% decrease) or to as low as $2.7550 per 25mg capsule and $8.2651 per 75mg capsule (*i.e.*, a 73% decrease).

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[105] As noted in the literature, new drugs representing important therapeutic advances are priced significantly above their existing substitutes [See *e.g.*, Lu, Z.J. and Comanor, W.S. (1998). Strategic Pricing of New Pharmaceuticals. *Review of Economics and Statistics, 80*(1): 108-118, and the literature cited therein.]

[106] Statement of Allegations of Board Staff, ¶54.

Figure 7: Board Staff's Premium Comparison Test
Based on International PROCYSBI Price in CAD$ as at April 2017
And PMPRB7 Price for Cystagon

Drug Product	Cystagon Price per mg	PROCYSBI MIP Price per mg	Per mg Premium	Price per mg Premium Comparison Test	Price per Capsule Premium Comparison Test
	[A]	[B]	[C] = 1/4 x ([B] - [A])	[D] = [A] + [C]	[E] = [D] x 25 or [D] x 75
PROCYSBI 25mg	0.0186	0.4179	0.0998	0.1184	2.9602
PROCYSBI 75mg	0.0186	0.4179	0.0998	0.1184	8.8807

Based on International PROCYSBI Price in CAD$ as at April 2017
And Purported Price for Cystagon in Canada

Drug Product	Cystagon Price per mg	PROCYSBI MIP Price per mg	Per mg Premium	Price per mg Premium Comparison Test	Price per Capsule Premium Comparison Test
	[A]	[B]	[C] = 1/4 x ([B] - [A])	[D] = [A] + [C]	[E] = [D] x 25 or [D] x 75
PROCYSBI 25mg	0.0077	0.4179	0.1026	0.1102	2.7550
PROCYSBI 75mg	0.0077	0.4179	0.1026	0.1102	8.2651

Source: Statement of Allegations of Board Staff, ¶¶60-61.

93. Here, the key criticisms are similar to those for the Same Medicine Comparison Test. I note the following:

(a) ***Failure to allow for cost recovery***. The Premium Comparison Test provides minimal credit for the significant therapeutic benefits derived from PROCYSBI's enterically coated, delayed release formulation. It disregards the true value of PROCYSBI by providing *de minimis* compensation; even with this premium, Horizon would be unable to recover the costs incurred to commercialize PROCYSBI in Canada. [redacted]

(b) ***Arbitrary compensation for therapeutic benefits***. The Premium Comparison Test also disregards the true value of PROCYSBI's enterically coated, delayed release formulation by arbitrarily setting PROCYSBI's price as the price of Cystagon plus twenty-five percent of the difference between the prices of the two drugs. Board Staff provides no justification for why this premium would be appropriate in this

case, and I see no reason why this premium would be appropriate for PROCYSBI. As a matter of economics, given the superiority of PROCYSBI over Cystagon in terms of (among other things) improved patient efficacy and reduced side effects, as described by Dr. Langman, PROCYSBI should command a premium that is much higher than the arbitrary "quarter-point between the price of Cystagon and the current price of Procysbi" put forward by Board Staff.[107]

(c) ***Failure to account for exchange rates***. Board Staff calculated the price for PROCYSBI using two references for the price of Cystagon: (i) the price of Cystagon based on a formulary listing price published by the Newfoundland and Labrador Department of Health and Welfare in October 2017 ($0.0007 per mg), and (ii) the price of Cystagon in the PMPRB7 of $0.0186 per mg. However, Board Staff considered only the lower median international price for PROCYSBI of $0.4178 per mg based on foreign exchange rates evaluated as at April 2017. Board Staff ignored the higher median international price for PROCYSBI of $0.4289 per mg based on foreign exchange rates evaluated as at June 2018.[108] Had Board Staff considered this alternative price, it would have resulted in a higher price for PROCYSBI under the Premium Comparison Test.

Market Share Comparison Test

94. In proposing the Market Share Comparison Test, Board Staff posits that, to the extent the PMPRB accepts that PROCYSBI's enterically coated, delayed release formulation justifies some higher price relative to immediate release cysteamine bitartrate, the maximum non-excessive price for PROCYSBI in Canada would be the "international market share adjusted price."[109] Accordingly, under the Market Share Comparison Test, the maximum price of PROCYSBI is nothing more than the weighted average price of PROCYSBI and Cystagon, with weights based on their proposed market shares of each of PROCYSBI and Cystagon in the PMPRB7.

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[107] Statement of Allegations of Board Staff, ¶54.

[108] Statement of Allegations of Board Staff, ¶¶60-61.

[109] Statement of Allegations of Board Staff, ¶¶46-53.

95. Figure 8, below, shows Board Staff's calculations of the Proposed Prices for PROCYSBI under the Market Share Comparison Test. Under this approach, Board Staff is seeking a reduction in the price of PROCYSBI from $10.35 per 25mg capsule and $31.05 per 75mg capsule down to either $2.0475 per 25mg capsule and $6.1425 per 75mg capsule (*i.e.*, an 80% decrease) or to as low as $0.8090 per 25mg capsule and $2.4270 per 75mg capsule (*i.e.*, a 92% decrease).

Figure 8: Board Staff's Market Share Comparison Test

Including Germany

	PROCYSBI		Cystagon		Weighted Average	Price per Capsule Market Share
Drug Product	Price per mg	Market Share	Price per mg	Market Share	Price per mg	Comparison Test
	[A]	[B]	[C]	[D]	[E] = [A] x [B] + [C] x [D]	[F] = [D] x 25 or [D] x 75
PROCYSBI 25mg	0.4140	18.25%	0.0077	81.75%	0.0819	2.0475
PROCYSBI 75mg	0.4140	18.25%	0.0077	81.75%	0.0819	6.1425

Excluding Germany

	PROCYSBI		Cystagon		Weighted Average	Price per Capsule Market Share
Drug Product	Price per mg	Market Share	Price per mg	Market Share	Price per mg	Comparison Test
	[A]	[B]	[C]	[D]	[E] = [A] x [B] + [C] x [D]	[F] = [D] x 25 or [D] x 75
PROCYSBI 25mg	0.4140	6.08%	0.0077	93.92%	0.0324	0.8090
PROCYSBI 75mg	0.4140	6.08%	0.0077	93.92%	0.0324	2.4270

Source: Statement of Allegations of Board Staff, ¶¶44-45.

96. As mentioned above, this method is inconsistent with the tests as set out in the PMPRB Compendium. In addition, I note the following:

(a) ***Failure to allow for cost recovery***. Like the previous two tests, the Market Share Comparison Test results in a Proposed Price that does not allow Horizon to recover the costs associated with developing and commercializing PROCYSBI. [redacted].

(b) ***Inappropriate reliance on market share***. This methodology relies on a comparison between the market shares of two drugs that are at very different points in their respective product life cycles. Cystagon has been available for sale in international

markets for many years, having been first approved in the U.S. in 1994.[110] Accordingly, Cystagon would have long ago achieved its steady state market share (and recovered its commercialization costs). Conversely, PROCYSBI first received marketing approval in the U.S. in April 2013 and in the European Union in September 2013.[111] Given the time that it takes for a new drug product to "ramp-up" and penetrate the market to its full potential (on account of the time it takes for the drug to gain formulary listings and broad reimbursement), PROCYSBI's market share in the period after its launch is not reflective of its long-term steady state. Thus, comparing the steady-state market share of one drug that has been on the market for a significant time to the still-developing market share of a new drug would, by construction, bias the results against PROCYSBI. Taking Board Staff's position to the extreme, applying the Market Share Comparison Test to PROCYSBI on the very first day that it launched internationally (when it would have a market share of 0%) would result in a price equal to that of Cystagon, thus completely ignoring the benefits of PROCYSBI (as discussed above).[112]

(c) ***Exclusion of Germany***. In implementing the Market Share Comparison Test, Board Staff further posits that Germany should be excluded as a reference country for the calculation of the maximum price. This is because, in Germany, rare disease

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[110] Cystagon, U.S. FDA Approved Drug Products Database, available at https://www.accessdata fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=020392.

Health Canada has not approved Cystagon for sale in Canada, nor has Mylan Pharmaceuticals (the manufacturer of Cystagon) ever sought approval to market Cystagon in Canada. Nevertheless, patients in Canada have had access to Cystagon since 2000 through the Health Canada's Special Access Programme ("SAP"), which provides patients with access to unapproved medications on an exceptional, case-by case basis for patients with serious or life-threatening conditions. [Board Staff Production Tab 91 (Report of the Standing Committee on Health, House of Commons Canada, "Canadians Affected by Rare Diseases and Disorder: Improving Access to Treatment", February 2019), pp. 13-16; Health Canada Drug Products Database, available at https://health-products.canada.ca/dpd-bdpp/index-eng.jsp; Statement of Allegations of Board Staff, ¶9; Response of Horizon Pharma, ¶13.]

[111] "Raptor Pharmaceutical's PROCYSBI Receives FDA Approval for the Treatment of Nephropathic Cystinosis", Press Release dated April 30, 2013, available at https://www.sec.gov/Archives/edgar/data/1070698/000107069813000018/rptp_prrls_043013.htm; "Raptor Pharmaceutical Receives Marketing Authorization for PROCYSBI in European Union", Press Release dated September 12, 2013, available at https://www.sec.gov/Archives/edgar/data/1070698/000107069813000073/rptp_pr091213_euprocysapprvl htm.

[112] Langman Report, ¶¶28, 30, 33, 155-156.

drugs are presumed to have an additional therapeutic benefit upon receipt of market authorization so long as total annual health insurance expenditures for the drug remain below €50 million. Board Staff states that a cost-effectiveness analysis was not performed for PROCYSBI, and that PROCYSBI was granted reimbursement in Germany without regard to its price. Nevertheless, Board Staff has conducted the Market Share Comparison Test both with and without including Germany.[113] Board Staff's exclusion of Germany from the calculation of PROCYSBI's market share is inappropriate. By definition, accurately calculating PROCYSBI's market share in the "Comparator Countries where PROCYSBI faces competition from Cystagon"[114] requires including all countries where both products are available for sale (but only those countries where both product are available). As a matter of economics, the fact that both prescribers and patients in Germany choose PROCYSBI more frequently (making the average market share substantially greater when Germany is included in the calculation) provides meaningful information on prescribers' and patients' preference for PROCYSBI over Cystagon. By excluding Germany from the calculation, Board Staff ignores this economically relevant evidence.[115]

97. Moreover, Board Staff's application of the Market Share Comparison Test depends on two data points, both of which are problematic:

(a) ***The market share of Cystagon relative to PROCYSBI.*** Although Board Staff indicated that it relied on information from IQVIA (formerly IMS Health), it has not provided the underlying data used in its calculations.[116] As a result, I am unable to independently assess Board Staff's calculations of the relative market share of each of PROCYSBI and Cystagon. [redacted]

[113] Statement of Allegations of Board Staff, ¶¶49-51.

[114] Statement of Allegations of Board Staff, ¶51.

[115] Statement of Allegations of Board Staff, ¶¶44-45.

[116] As of the date of this report, only a redacted pdf-copy of the native dataset used by Board Staff has been produced. See Copy of IQVIA data - Email from Legal forwarding IQVIA data - ATTACHMENT_.pdf.

[redacted] Based on my review of Board Staff's Statement of Allegations, it appears that Board Staff inappropriately included sales of Cystagon in PMPRB7 countries in which PROCYSBI is not approved for sale. In particular, Board Staff states "as per Horizon's filings, PROCYSBI is not sold at all in France, Italy, Switzerland or Sweden, meaning that the market share percentage of Cystagon if available in those countries can be assumed to be 100%."[117] If this is indeed the case, then the "market shares" used by Board Staff for its calculations are in no way reflective of true marketplace conditions in "the Comparator Countries where PROCYSBI faces competition from Cystagon."[118]

(b) ***The prices of PROCYSBI and Cystagon.*** To calculate the weighted average price of both PROCYSBI and Cystagon, Board Staff used the ex-factory price of PROCYSBI in Canada and the price of Cystagon as published by the Newfoundland and Labrador Department of Health and Welfare in October 2017. However, for the calculation of the weighted average price of PROCYSBI and Cystagon to "mirror maximum potential expenditures in the Comparator Countries where PROCYSBI faces competition from Cystagon,"[119] the more appropriate price to use would be the price of PROCYSBI and Cystagon in those Comparator Countries. As shown in Figure 3, the median international price of PROCYSBI (up to $0.4289 per mg) is higher than the ex-factory price of PROCYSBI in Canada ($0.4140 per mg). Likewise, as shown in Figure 6, the median international price of Cystagon ($0.01862 per mg) is higher than the Newfoundland formulary price of Cystagon in Canada ($0.0007 per mg). Had Board Staff used these international prices, the Market Share Comparison Test would have resulted in a higher price for PROCYSBI as compared to the price as determined by Board Staff.

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[117] Statement of Allegations of Board Staff, ¶50.

[118] Statement of Allegations of Board Staff, ¶51.

[119] *Ibid.*

98. Because Board Staff has not produced the data it relied on to implement the Market Share Comparison Test, I am unable to investigate the distribution of relative market shares for both PROCYSBI and Cystagon across the PMPRB7. If warranted and permitted, I will supplement my opinions based on the receipt of additional data or other information, including submissions by Board Staff or experts retained on its behalf.

VIII. CONCLUSION

99. It is my understanding that the Median International Price Comparison Test is the appropriate test for assessing the price of PROCYSBI under the PMPRB Compendium. My application of this test to PROCYSBI demonstrates that PROCYSBI's ex-factory price is not excessive and is, in fact, below the median international price.

100. As I have explained, the use of the Median International Price Comparison Test in setting the prices of new drugs in Canada has numerous economic benefits. In particular, it ensures that Canadians will, on average, pay no more for a particular drug than individuals in countries of similar socioeconomic status. It also provides greater certainty to firms investing in pharmaceutical R&D, thus enhancing their investment incentives.

101. As demonstrated above, none of the alternative models put forward by Board Staff provide an economically rational alternative to the Median International Price Test. In addition to being inconsistent with the methodologies set out in the PMPRB Compendium, none of these models are consistent with the economic principle that the price of a new drug product should enable the manufacturer to recover the costs associated with developing and commercializing the new drug. To the extent that there is any basis for departing from the methodologies set out in the PMPRB Compendium, these models do not provide an economically rational alternative. At Board Staff's Proposed Prices, Horizon would not only fail to generate revenue sufficient to recover its costs of commercializing PROCYSBI in Canada, but it would incur significant financial losses.

102. Manufacturers of rare disease drugs must often charge prices that appear high relative to the prices of drugs that serve broader patient populations. This often much higher price is required to provide the manufacturer with the opportunity to recover the costs incurred to develop and commercialize the drug and to generate a return on investment over a very small patient base. Thus, regulatory restrictions that prevent manufacturers from recovering the costs associated with

developing and commercializing new rare disease drugs can be expected to have a negative impact on future investment in the development of rare disease drugs like PROCYSBI.

September 9th, 2019

Joel W. Hay

Joel W. Hay

APPENDIX A. CURRICULUM VITAE OF DR. JOEL HAY, PH.D.

USCSchaeffer
Leonard D. Schaeffer Center for Health Policy & Economics

8/14/19

CURRICULUM VITAE

PROFESSOR JOEL W. HAY PhD
jhay@usc.edu

PERSONAL INFORMATION

Business/Mail Address	Professor of Pharmaceutical Economics and Policy & Professor of Health Policy and Economics University of Southern California Schaeffer Center for Health Policy and Economics University Park Campus, Verna & Peter Dauterive Hall (VPD 314-K) 635 Downey Way Los Angeles, CA 90089-3333 USA
Business Telephone	Office: (818) 338-5433 Assistant: (213) 821-7940 Fax: (213) 740-3460 (ATTN: Joel Hay)
E-Mail	jhay@usc.edu
USC Websites:	https://healthpolicy.usc.edu/author/joel-w-hay-ph-d/ http://pharmacyschool.usc.edu/faculty/profile/?id=374
USC Graduate Program Website:	http://pharmacyschool.usc.edu/programs/pep/
Schaeffer Center Street Address (Deliveries, e.g. Fedex, UPS)	635 Downey Way Los Angeles, CA 90089-3333 USA Main Phone/Front Desk: (213) 821-7940 J Hay Office: (213) 821-8160 Fax: (213) 740-3460 (ATTN: Caroline) http://healthpolicy.usc.edu

Contact Information for Non-USC Activities

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EDUCATION

1974	B.A., (Summa cum laude), Economics, Amherst College
1975	M.A., Economics, Yale University
1976	M.Phil., Economics, Yale University
1980	Ph.D., Economics, Yale University

PROFESSIONAL EXPERIENCE

November 2018 – Present	Director, Clinical Economics Research and Education Program (CEREP). USC School of Pharmacy and Leonard D. Schaeffer Center for Health Policy and Economics
March 2009 – Present	Full Professor (with tenure), Pharmaceutical Economics and Policy; School of Pharmacy Professor (by courtesy), Department of Economics; University of Southern California, Los Angeles, California.
September 2009-Present	Full Professor, Health Economics and Policy Leonard D. Schaeffer Center for Health Policy and Economics University of Southern California, Los Angeles, California
1992 – 2009	Associate Professor (with tenure), Pharmaceutical Economics and Policy; School of Pharmacy. Associate Professor (by courtesy), Department of Economics; University of Southern California, Los Angeles, California.
September 1985 - May 1992	Senior Research Fellow, Hoover Institution, Stanford University, Stanford, California.
July 1983 - September 1985	Senior Policy Analyst, Project HOPE, Center for Health Affairs, Millwood, Virginia.
January 1981 - June 1983	Visiting Lecturer, M.P.H. Program, Yale University, Department of Epidemiology and Public Health, and Institution for Social and Policy Studies.
June 1980 - September 1984	Assistant Professor, Department of Behavioral Sciences and Community Health, School of Dental Medicine University Connecticut Health Center, Farmington, Connecticut. (from 9/81) Assistant Professor, Department of Economics, UConn Storrs. University of Connecticut Graduate School, Storrs, Connecticut.
June 1978 - June 1980	Assistant Research Professor, Human Resources Research Center, University of Southern California, Los Angeles, California.

ADDITIONAL EXPERIENCE

2018-present	Distinguished Member, European Union Academy of Sciences.
2017-present	External Consultant, Office of the Attorney General, State of California.
2016-2017	Conference Co-Chair and Planning Committee, International Academy of Health Preference Research, North American Conference, Boston MA, June 2017.
2016	Invited Forum Participant, AMCP Partnership Forum: FDAMA Section 114—Improving the Exchange of Health Care Economic Data, Academy of Managed Care Pharmacy.
2016-present	Voting Member, Cochrane Collaboration, www.cochrane.org.
2015	External Reviewer, Italian Ministry of Health, General Direction for Scientific Research and Health Innovation.
2015	Invited Advisor, U.S. Food and Drug Administration Policy on Review of Health Economics Modeling Claims (FDAMA Section 114).
2014-2018	Founding Member, International Academy of Health Preference Research (iahpr.org).
2013-2015	Extramural Reviewer, Healthcare Systems & Value Research Study Section Review Panel, Agency for Healthcare Research & Quality (AHRQ), U.S. Dept. of Health & Human Services.
2012	External Reviewer, Cochrane Tobacco Addiction Research Group, Cochrane Collaboration, www.cochrane.org.
2012	Health Economics Expert Consultant, State Attorneys General Working Group on Pharmaceutical Benefits Management (PBM) Market Competition Issues.
2011-2013	Extramural Reviewer, Healthcare Systems & Value Research Study Section Review Panel, Agency for Healthcare Research & Quality (AHRQ), U.S. Dept. of Health & Human Services.
2011	Extramural Grant Reviewer, Health Services Research Study Section, Agency for Healthcare Research & Quality, U.S. Dept. of Health & Human Services.
2010	Extramural Grant Reviewer, Health Services Research Study Section, Agency for Healthcare Research & Quality, U.S. Dept. of Health & Human Services.
2010	External Grant Reviewer, Netherlands Organisation for Health Research and Development (ZonMw) Health Technology Assessment Methodology Programme.
2010	External Program Contract Reviewer, Agency for Healthcare Research & Quality (AHRQ), U.S. Dept. of Health & Human Services; Developing Evidence to Inform Decisions about Effectiveness-2: The DEcIDE-2 Network.
2007-2013	Leadership Group, International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Disease Management and Prevention Task Force.
2007-2009	Leadership Group, International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Patient Preferences Research Task Force.
2006-2010	Co-Chair, ISPOR Drug Cost Task Force.
2006	Chair, Awards Committee; "The 2006 ISPOR Avedis Donabedian Outcomes Research Lifetime Achievement Award." Presented to Prof. George Torrance at the 11'th Annual International Meeting, Philadelphia, PA.

2005	External Project Reviewer; "The Uninsured and Access to Prescription Drugs in California. The Petris Center on Health Care Markets & Consumer Welfare, University of California, Berkeley.
2005	External Program Reviewer, Agency for Healthcare Research & Quality, Dept. of Health & Human Services; Developing Evidence to Inform Decisions about Effectiveness: The DEcIDE Network.
2004-2010	Health Policy Scientific Council, Intl. Soc. for Pharmacoeconomics & Outcomes Research.
2004-2014	Elected Executive Board Member, American Society of Health Economists (Ashecon.org).
2004-2010	Scientific Advisory Board Member, Disease Management Association of America
2002-2003	Institute of Medicine, National Academy of Sciences. Commissioned Author "Vaccine Reimbursement Policy in the US."
2001-Present	Health Economist, UCLA Center for Vaccine Research, UCLA Harbor Medical Center, Torrance, CA.
2001	Health Plan Reform Consultant, Hong Kong Hospital Authority, Hong Kong.
2000	External Reviewer, National Institute on Aging, NIH Small Grants Program.
1999	External Reviewer, National Institutes of Health, National Institute on Aging,
1999-2011	Co-Investigator, USC Alzheimer Research Centers of California Research Program, California Dept. of Health Services.
1999	Consultant, Univ. Michigan Survey Research Center ADAMS/HRS Dementia Project
1999	External Reviewer, National Inst. of Health, National Institute of Digestive Diseases and Nutrition, Division of Digestive Diseases and Nutrition Hepatitis C Antiviral Long-term Therapy to Prevent Cirrhosis (HALT-C) Ancillary Studies Committee.
1999-2000	Economics Research Consultant, U.S. AHRQ, Southern California Evidence-Based Medicine Practice Project: Deep Vein Thrombosis Treatment in Trauma Surgery Literature Synthesis and Guideline Development.
1999	Member, Long Range Steering Committee Task Force, Harbor-UCLA Medical Center Research and Education Institution, Torrance, CA.
1998-2011	Rand USC Project Coordinator, U.S. Agency for Health Research and Quality, Southern California Evidence-Based Medicine Practice Project.
1998-2002	Founding Editor-In-Chief, Value in Health, Journal of the International Society for Pharmacoeconomics and Outcomes Research.
1998	External Reviewer, Cal Dept of Health Services Alzheimer's Research Fund.
1998-2008	Member, Pharmacy Practice Research Roundtable.
1998-2007	Member, Intl. Working Group on Alzheimer Disease Pharmacoeconomics Research.
1998-2006	Member, Coronary Heart Disease: The Interdisciplinary Council on Reducing the Risk, co-sponsored by the American Heart Association & Bristol-Myers Squibb. Dallas, TX.
1997-98	Co-Chair: ISPOR Working Group on Guidelines for Pharmacoeconomic Research.
1997-98	External Reviewer. Asset and Health Dynamics among the Oldest Old-Dementia Survey Supplement. University of Michigan Inst. for Social Research, Ann Arbor, MI.

1997-2018	Economic Consultant, Rand Corporation, Health Outcome Research Group, Santa Monica, CA
1996-1998	Co-Chair and Primary Organizer: ISPOR Lipid Pharmacoeconomics Conference. Orlando, FL.
1995-1998	Elected Member, Board of Directors, and Founding Member, International Society for Pharmacoeconomics and Outcomes Research (ISPOR), Philadelphia, PA.
1995-2000	Member, Expert Advisory Panel on Drug Utilization Review, United States Pharmacopoeial Convention, Rockville, MD.
1995-96	Research & Graduate Affairs Cmte., American Assoc. Colleges of Pharmacy, Alexandria, VA.
1994-95	Technical Review Study Section, "HIV Costs and Services Utilization Study (HCSUS)," Agency for Health Care Policy & Research, US Dept. Health & Human Serv., Rockville, MD.
1993-94	Member, Research Advisory Panel for Outcome Studies, Wellpoint Pharmacy Management, Blue Cross of Southern California.
1993-1998	Member, Advis. Cmte., American Soc. Consultant Pharmacists Research Foundation
1993	Member, Planning Committee, American Society of Consultant Pharmacists Foundation Pharmacoeconomics Fellowship in Geriatric Long-Term Care
1992-1993	Technical Review Panelist, Drug Utilization Review Demonstration Project Contracts, Health Care Financing Administration, Baltimore, MD.
1992	Member, Council of Advisors, Geriatric Drug Therapy Research Inst., Arlington, VA.
1992	Access to Health Care Task Force Member, American Heart Assoc., Washington, D.C.
1992	Judge, Masters of Innovation Software Competition, Zenith Data Systems, Chicago, IL
1991	Advisor, Hungarian Parliament Health Care Reform Committee, Budapest, Hungary.
1991	Chief U.S. consultant, Hungarian health care reform project, Px Ltd., Budapest, Hungary.
1990-91	Visiting Scholar, Hong Kong Centre for Economic Research, Chinese University of Hong Kong, Shatin, New Territories.
1990	Invited outside reviewer, U.S. Congressional Budget Office Long Term Care Policy Statement.
1990	Invited outside expert, California AIDS Leadership Commission Hearings, Los Angeles, CA.
1989	Proposal Review Consultant, The Smith Richardson Foundation.
1989	Invited outside expert, Select panel on HIV/AIDS estimates and projections. U.S. Public Health Service, Centers for Disease Control.
1989	Consultant, The Henry J. Kaiser Family Foundation, Menlo Park, California.
1988	Consultant, General Assistance Program for the Homeless, Office of the County Counsel, County of Sacramento, CA.
1988	Proposal Reviewer, Special Study Section, National Institutes of Health, U.S. Dept. of Health & Human Services.
1988	Issue Development Participant, "Medication Use in the Elderly," Geriatric Pharmacy Institute, Philadelphia College of Pharmacy and Science.

1988	Consultant, Patient Care/Health Service Delivery Subgroup, Executive Task Force on AIDS, U.S. Public Health Service.
1987	Consultant, Cost-benefit analysis of HIB vaccine, U.S. Food and Drug Administration.
1987	Proposal Reviewer, National Center for Health Services Research, U.S. Dept. of Health & Human Services.
1986, 1989	Proposal Review Consultant, The Henry J. Kaiser Family Foundation, Menlo Park, California.
1984-1986	Principal Investigator, Robert Wood Johnson Foundation; An Incentive Reimbursement Plan for Medicaid Home Health Care Services.
1985	Technical Consultant, Research Projects Approval Committee-Economics, The World Bank.
1985	Technical Advisory Panelist, HCFA Contract No. 500-84-0033; Market Study for Home Health Care Services, Center for Health Policy Studies.
1984	Technical Review Consultant, National Center for Health Services Research, Hospital Care and Utilization Project.
1984	Consultant, County of San Diego; Member of Proposal Review Committee for County Regional Contracts to Provide Care to Medically Indigent Adults.
1983	Visiting Asst. Prof., Inst. for Social Sciences, University of Basel, Basel, Switzerland.
1983	Principal Investigator, U.S. Environmental Protection Agency; Mortality and Air Pollution: A Microanalytic Analysis.
1981 – 1982	Principal Investigator, Connecticut Research Found.; Child Health Status & Cognitive Development. University of Connecticut, Storrs, CT.
1981	Visiting Fellow, Institution for Social & Policy Studies, Yale University, New Haven, CT.
1980	Consultant, National Preventive Dentistry Demonstration Project Evaluation Model, American Fund for Dental Health.
1980	Consultant, National Health Services Corps Personnel Selection Project, Policy Research Inc.
1979 – 1980	Principal Investigator, Doctoral Research Grant, National Center for Health Services Research.
1979 – 1980	Consultant, Cost Benefit Analysis of Outpatient Treatment for Patients from the Psychiatric Ward of L.A. County/USC Medical Center.
1977 – 1978	Instructor, Department of Economics, Yale University, New Haven, Connecticut.
1976 – 1977	Teaching Assistant, Dept. of Economics, Yale University, New Haven, Connecticut.
1974 – 1976	Research Consultant, National Bureau of Economic Research.
1975	Bibliographical Research Project (Russian Language) on Works of Academic Leo Kantorovich for Professor Tjalling Koopmans prior to their joint Nobel Prize Award in Economics.

HONORS AND DISTINCTIONS

2019 Behavioral Science and Policy Association (BSPA) Publication Award for Innovation in Behavioral Policy "Best Paper of 2016-1018;" ***Meeker D, Linder JA, Fox CR, Friedberg MW, Perselle SD, Goldstein NJ, Knight TK, Hay JW, Doctor JN. Behavioral Interventions to Decrease the Inappropriate Use of Antibiotics: A Multicenter Cluster Randomized Trial. JAMA 2016. 315(6):562-570. http://dx.doi.org/10.1001/jama.2016.0275***
This award recognizes research that advances rigorous application and development of behavioral/ social science to policy and practice in public, private and non-profit sectors. Its goal is to encourage work that has potential to improve the quality of life of individuals and/or organizations. The selection committee considered all research published between 2016-2018 in journals or as books. The committee included: Brian Gill (Mathematica), Rick Larrick (Duke University), Anita McGahan (U of Toronto), Dick Nisbett (U of Michigan) and Peter Ubel (Duke University). There were 35 nominations. Each nominee was rated independently by three committee members without COI. Top candidates were then rated by all committee members without COIs to determine the winner.

"Reconstruction after Salvage Total Laryngectomy: A Cost-effectiveness analysis."
Joseph R Acevedo; Jeffery C Yu; Brian Cameron; Margaret Nurimba, Joel W Hay; Neils C Kokot ***3rd Place, 2019 Resident Research Symposium***. USC Caruso Department of Otolaryngology, Head and Neck Surgery.

One of two (out of 1,400 reviews) to receive a ***perfect editorial review score*** (review done with Xiaohan Hu, PhD Cand.). Journal of Allergy and Clinical Immunology: JACI In Practice. 2019. https://www.jaci-inpractice.org/

Distinguished Member (by invitation), European Union Academy of Sciences. January 2018 – present.

"Top Performing Reviewer," Journal of Managed Care and Specialty Pharmacy. 2017.

Western Pharmacoeconomics & Outcomes Research Conference: ***Best Student Poster Award 2017***; Lam J, **Hay JW**, Kenyon N. Cost-effectiveness Analysis of Reslizumab in Patients with Poorly Controlled Eosinophilic Asthma. Invited Poster Presentation, University of New Mexico, October 4, 2017, Albuquerque, NM. (Joel Hay faculty mentor).

Western Pharmacoeconomics & Outcomes Research Conference: ***Best Student Poster Award 2017***; Salcedo J, **Hay JW**. Cost-Effectiveness of Rivaroxaban Versus Warfarin for Treatment of Nonvalvular Atrial Fibrillation in Patients with On-Treatment Worsening Renal Function. Invited Poster Presentation, Western Pharmacoeconomics & Outcomes Research Conference, University of New Mexico, October 4, 2017, Albuquerque, NM. (Joel Hay faculty mentor).

International Society for Pharmacoeconomics and Outcomes Research Mentor: ***Best Student Poster Award 2016***; Nikhil Bhagvandas. Bhagvandas Nikhil, Hay Joel W. Cost Effectiveness of Lurasidone, Quetiapine, and Olanzapine Monotherapy in the Treatment of Bipolar I Disorder Depression. Poster PMH39. ISPOR 21'st Annual International Meeting, May 21-25, 2016; Washington, DC. (Joel Hay faculty mentor).

International Society for Pharmacoeconomics and Outcomes Research Mentor: ***Best Student Podium Presentation Award 2016***; Yifan Xu. Xu, Yifan; Barzi, Afsaneh; Hay Joel W. Comparative Effectiveness of Panitumumab Versus Cetuximab in Patients with Chemo-Refractory Wild-Type Kras Metastatic Colorectal Cancer. Oral Presentation PCN108. ISPOR 21'st Annual International Meeting, May 21-25, 2016; Washington, DC. (Joel Hay faculty mentor).

International Society for Pharmacoeconomics and Outcomes Research Mentor: ***Best Student Poster Award Finalist;*** Shraddha Chaugule, 2015: "Exploring heterogeneity in attribute processing strategies: Use of hybrid random utility maximization-random regret minimization models in a Discrete Choice Experiment." S. Chaugule and J. Hay. (Joel Hay faculty mentor).

International Society for Pharmacoeconomics and Outcomes Research Mentor: ***Best Student Poster Award Finalist;*** Emmanuel Drabo, 2014: "A Cost-effectiveness analysis of pre-exposure prophylaxis (PrEP) for the prevention of HIV among the MSM population of Los Angeles County." (Joel Hay faculty mentor).

Academy of Managed Care Pharmacy Research Mentor, ***Best Student Poster Award***; Kai Yeung, 2011. Yeung K, **Hay JW**. Cost-Utility Analysis of Romiplostim Versus Splenectomy in the Treatment of Chronic Refractory Immune Thrombocytopenic Purpura. Poster presentation at the Academy of Managed Care Pharmacy 23'rd Annual Meeting, March 29, 2011 Minneapolis, MN. (Joel Hay faculty mentor).

International Society for Pharmacoeconomics and Outcomes Research: ***Best New Investigator Podium Presentation Award 2010*** to Dr. Haesun Suh. (Joel Hay faculty mentor).

International Society for Pharmacoeconomics and Outcomes Research: ***Distinguished Service Award, 2009.***

International Society for Pharmacoeconomics and Outcomes Research: ***Outstanding Student Chapter of the Year, Joel Hay Student Chapter Faculty Advisor, 2009.***

Joel Hay was ***Founding Editor-in-Chief of Value in Health*** the peer-reviewed scientific journal of the International Society for Pharmacoeconomics and Outcomes Research until 2003. This journal, started in 1998, became Medline-listed in 2002. In its first impact factor, Value in Health was ranked #1 in two categories for the year 2004, by the ISI Journal Citation Reports® (JCR) with an impact factor of 3.657. ***Value in Health led all other journals listed both in the Health Care Sciences and Services category in the JCR Science Edition and in the Health Policy & Services category in the JCR Social Sciences Edition.***

International Society for Pharmacoeconomics and Outcomes Research Mentor: ***Best Student Poster Award;*** Danielle Zammit, 2004: "Preliminary Economic Analysis of The American Cancer Society Guidelines for Mammography Screening in Average-Risk Women Under 70 Years of Age." D. Zammit and J. Hay. (Joel Hay faculty mentor).

International Society for Pharmacoeconomics and Outcomes Research Mentor: ***Best Student Poster Award;*** Danielle Zammit, 2003: "Economic Analysis of The Use of Angiotensin Converting Enzyme Inhibitors in Patients with Diabetes Mellitus." D. Zammit and J. Hay. (Joel Hay faculty mentor).

International Society for Pharmacoeconomics and Outcomes Research: ***Distinguished Service Award, 2002.***

Founding Member, American Society for Health Economics, San Diego, CA, 2002.

International Society for Pharmacoeconomics and Outcomes Research Mentor: ***Best Student Poster Award;*** Eric Wu, 2001: "Survival & Nursing Home Free Survival (NHFS) of Alzheimer's Disease Patients." E. Wu and J. Hay. (Joel Hay faculty mentor).

International Society for Pharmacoeconomics and Outcomes Research Mentor: ***Best Student Poster Award;*** Jinmei Li, 2000: "Cost Effectiveness of Retinopathy Screening in Pediatric Patients with Type 1 Diabetes Mellitus." J. Li and J. Hay. (Joel Hay faculty mentor).

International Society for Pharmacoeconomics and Outcomes Research Mentor: ***Best Student Poster Award;*** Nishan Sengupta, 2000: "Cost Effectiveness Analysis of Tamoxifen in Breast Cancer Risk Reduction." N. Sengupta and J. Hay. (Joel Hay faculty mentor).

International Society for Pharmacoeconomics and Outcomes Research Mentor: ***Best Student Poster Award;*** Michelle Luo, 1999: "Cost Effectiveness Analysis of Genetic Testing for Breast Cancer." M. Luo and J. Hay. (Joel Hay faculty mentor).

International Society for Pharmacoeconomics and Outcomes Research: ***Health Economics and Outcomes Research Excellence - Methodology Award 1999***

Wallace Lectureship. Idaho State University College of Pharmacy, 1999

International Society for Pharmacoeconomics & Outcomes Research ***Executive Board Recognition Award; 1998***

International Society for Pharmacoeconomics and Outcomes ***Distinguished Service Award; 1998***

Outstanding Speaker Award, American Association for Clinical Chemistry 1996

Founding Member, International Society for Pharmacoeconomics and Outcomes Research (ISPOR), Philadelphia, PA, 1995.

USC School of Pharmacy ***QSAD Centurion Professorship***: 1993-1999

USC School of Pharmacy ***Founding Chair***, Dept. of Pharmaceutical Economics & Policy, 1992

Reviewer, National Science Foundation, 1982: Economics Section, 1987: Economics Section, 1989: Economics Section

Yale University Fellowship, 1974 - 1978

W.T. Akery Prize for Undergraduate Thesis in Economics, 1974

Elected Phi Beta Kappa, 1974

LANGUAGES

French (reading), Russian (reading),
APL, PL/1, FORTRAN, IBM 370 JCL, TSP, SAS, SPSS/X, STATA, LIMDEP, NLOGIT, QUAIL, BMDP, MS DOS, LOTUS 123, SPSS/PC, RATS, SST, VAX/VM.

FIELDS OF GRADUATE TRAINING

Econometrics, Money, Labor

RESEARCH INTERESTS

Pharmacoeconomics, Outcomes Research, Pharmaceutical Care, Health Economics, Econometrics

PROFESSIONAL SOCIETIES

Academy of Managed Care Pharmacy
American Association of Colleges of Pharmacy
American Economic Association
American Public Health Association
American Society of Health Economists
Disease Management Association of America
Eastern Economic Association
Econometrics Society
International Academy of Health Preferences Research
International Health Economics Association
International Society for Pharmacoeconomics and Outcomes Research
International Society for Quality of Life Research
International Society of Technology Assessment in Health Care
Southern Economic Association
Western Economic Association

TEACHING

1976 – 1977	Teaching Assistant, Department of Economics, Yale University, New Haven, Connecticut.
1977 – 1978	Instructor, Department of Economics, Yale University, New Haven, Connecticut.
September - November 1980	Health Economics at the Waterbury Hospital Pediatric Residency Program.
September - November 1980	Social and Behavioral Sciences Seminar "Cost of Illness and Related Topics," Medical/Dental student; Required curriculum, University of Connecticut Health Center.
September 1980 – December 1982	Social and Behavioral Sciences Lecturer "Issues in Health Care Financing and Delivery," Medical/Dental student required curriculum, University of Connecticut Health Center.
September - November 1981	Social and Behavioral Sciences Seminar "Competition in the Health Care Delivery System," Medical/Dental student required curriculum, University of Connecticut Health Center.
September - November 1982	Social and Behavioral Sciences Seminar "HMOs and the Market for Health Care," Medical/Dental Student required curriculum, Univ. of Connecticut Health Center.
December 1980 – January 1983	Introductory Biostatistics Instructor, Medical/Dental student required curriculum, University of Connecticut Health Center.
January 1981 - June 1983	Health Economics, M.P.H. Program, Yale University, Department of Epidemiology and Public Health, and Institution for Social and Policy Studies.
Fall Semester 1982	Graduate Independent Studies Course, Department of Economics, University of Connecticut.
Spring Semester 1982	Undergraduate Health Economics, University of Connecticut, Department of Economics.
Spring Semester 1983	Undergraduate Independent Studies Course, Department of Economics, University of Connecticut.

Fall Semester 1992	The Costs of Drug Abuse, Health Behavior (PSC 439); Economic Assessment of Pharmaceuticals, Contemporary Issues (PSC 551); Health Care Organization in the U.S., Public Health and Social Pharmacy (PSC 437); Department of Pharmaceutical Economics and Policy, USC
Spring Semester 1993	Biostatistics and Literature Evaluation (PSC 331): Co-taught with Prof. McCombs; Department of Pharmaceutical Economics and Policy, USC
Fall Semester 1993	The Costs of Drug Abuse, Health Behavior (PSC 439); Health-related Quality of Life Assessment, Contemporary Issues (PSC 551); U.S. Health Care Finance and Reform, Public Health and Social Pharmacy (PSC 437); Department of Pharmaceutical Economics and Policy, USC
Spring Semester 1994	Biostatistics and Literature Evaluation (PSC 331): Cotaught with Prof. McCombs; Department of Pharmaceutical Economics and Policy, USC
Summer, 1994	Introductory Undergraduate Health Economics (Econ 194BB), University of California, Santa Barbara, Summer Session
Fall Semester 1994	Health Status/Quality of Life Assessment Health Behavior (PSC 439); Contemporary Issues (PSC 551); U.S. Health Care Finance and Reform, Public Health and Social Pharmacy (PSC 437); Department of Pharmaceutical Economics and Policy, USC
Spring Semester 1995	Biostatistics and Literature Evaluation (PSC 331)
Spring Semester 1996	Biostatistics and Literature Evaluation (PSC 331)
Spring Semester 1996	Pharmacoeconomics: Introductory Graduate Course (PMEP 538)
Summer Semester 1996	Pharmacoeconomics: Introductory Graduate Course (PMEP 538)
Spring Semester 1997	Statistics Computer Laboratory (Phar 366)
Summer Semester 1997	Pharmacoeconomics: Introductory Graduate Course (PMEP 538)
Spring Semester 1998	Statistics Computer Laboratory (Phar 366)
Summer Semester 1998	Pharmacoeconomics: Introductory Graduate Course (PMEP 538)
Spring Semester 1999	Statistics Computer Laboratory (Phar 366)
Summer Semester 1999	Pharmacoeconomics: Introductory Graduate Course (PMEP 538)

Spring Semester 2000	Statistics Computer Laboratory (Phar 366)
Spring Semester 2000	Pharmacy Level III Elective: Disease State Management. Pharmacoeconomics (1 Lecture) (Phar 571)
Fall Semester 2000	Pharmacoeconomics Unit on Decision Analysis (Phar 553)
Summer Semester 2000	Pharmacoeconomics: Introductory Graduate Course (PMEP 538)
Fall Semester 2001	Pharmacoeconomics Unit on Decision Analysis (Phar 553)
Spring Semester 2001	Pharmaceutical Econometrics: Graduate Course (PMEP 549)
Summer Semester 2001	Pharmacoeconomics: Graduate Course (PMEP 538)
Fall Semester 2002	Pharmacoeconomics Unit on Decision Analysis (Phar 553)
Spring Semester 2002	Pharmaceutical Econometrics: Graduate Course (PMEP 549)
Summer Semester 2002	Pharmacoeconomics: Graduate Course (PMEP 538)
Spring Semester 2002	Pharmaceutical Econometrics: Graduate Course (PMEP 549)
Spring Semester 2003	Pharmaceutical Econometrics: Graduate Course (PMEP 549)
Summer Semester 2003	Pharmacoeconomics: Graduate Course (PMEP 538)
Fall Semester 2003	Pharmacoeconomics Unit on Decision Analysis (PHRD 553)
Fall Semester 2003	Health Care Policy (PHRD 507)
Spring Semester 2004	Pharmaceutical Econometrics: Graduate Course (PMEP 549)
Fall Semester 2004	Health Care Policy (PHRD 507)
Fall Semester 2004	Pharmacoeconomics Unit on Decision Analysis (PHRD 614)
Summer Semester 2005	Pharmacoeconomics: Graduate Course (PMEP 538)
Fall Semester 2005	Health Care Policy (PHRD 507)
Spring Semester 2006	Pharmaceutical Econometrics: Graduate Course (PMEP 549)
Fall Semester 2006	Health Care Policy (PHRD 507)
Fall Semester 2006	Research Design – Applied Cost Effectiveness Analysis (PMEP 509)

Summer Semester 2007	Pharmacoeconomics: Graduate Course (PMEP 538)
Fall Semester 2007	Health Care Policy (PHRD 507)
Fall Semester 2007	Research Design – Applied Cost Effectiveness Analysis (PMEP 509)
Spring Semester 2008	Pharmaceutical Econometrics: Graduate Course (PMEP 549)
Fall Semester 2008	Health Care Policy (PHRD 507)
Fall Semester 2008	Research Design – Applied Cost Effectiveness Analysis (PMEP 509)
Fall Semester 2008	Pharmaceutical Economics and Policy Graduate Seminar (PMEP 698)
Spring Semester 2009	Pharmaceutical Economics and Policy Graduate Seminar (PMEP 698)
Summer Semester 2009	Pharmacoeconomics: Graduate Course (PMEP 538)
Fall Semester 2009	Health Care Policy (PHRD 507)
Fall Semester 2009	Industrial Systems Engineering Lecturer (ISE 599)
Spring Semester 2010	Pharmaceutical Econometrics: Graduate Course (PMEP 549)
Summer Semester 2011	Pharmacoeconomics: Graduate Course (PMEP 538)
Spring Semester 2012	Pharmaceutical Econometrics: Graduate Course (PMEP 549)
Spring Semester 2012	Health Economics Lecture: Social Work Graduate Course (SOWK 590)
Summer Semester 2013	Pharmacoeconomics: Graduate Course (PMEP 538)
Spring Semester 2014	Pharmaceutical Econometrics: Graduate Course (PMEP 549)
Summer Semester 2015	Pharmacoeconomics: Graduate Course (PMEP 538)
Spring Semester 2016	Pharmaceutical Econometrics: Graduate Course (PMEP 549)
Spring Semester 2017	Economic Analysis of Health Care I: Graduate Course (PMEP 525)
Summer Semester 2017	Economic Analysis of Health Care II: Graduate Course (PMEP 526)
Fall Semester 2017	Economic Analysis of Health Care III: Graduate Course (PMEP 527)
Spring Semester 2019	Economic Analysis of Health Care I: Graduate Course (PMEP 525)

Summer Semester 2019	Economic Analysis of Health Care II: Graduate Course (PMEP 526)
Fall Semester 2019	Economic Analysis of Health Care III: Graduate Course (PMEP 527)

USC UNIVERSITY SERVICE

2018 - Present	Curriculum Committee, School of Pharmacy
2018	American Association of Pharmaceutical Scientists - USC Chapter, Moving Targets Faculty Reviewer
2016	Admissions Committee Evaluation Retreat, School of Pharmacy
2015- 2016	Faculty Position Search Committee, Dept. of Pharmaceutical and Health Economics, School of Pharmacy
2013 – Present	Member, Appointments & Promotions Task Force, School of Pharmacy
2011	External Reviewer, Sol Price School of Public Policy
2009	Chair, Faculty Position Search Committee, Dept. of Clinical Pharmacy, Pharmaceutical Economics and Policy, School of Pharmacy
2006 - Present	Faculty Merit Review Coordinating Committee, School of Pharmacy
2004-2005	Chair, Faculty Position Search Committee, Dept. of Pharmaceutical Economics and Policy, School of Pharmacy
2003 - 2014	Admissions Committee, School of Pharmacy
2003-2006	Chair, Advanced Technology Committee, School of Pharmacy
2002-2004	New Curriculum Development: Course Coordinator, Phar 507: Health Policy for Pharmacists, School of Pharmacy
2002 - 2011	Advanced Technology Committee, School of Pharmacy
2002	Human Subjects Review Policy, USC Faculty Senate Retreat
2000-2001	Computer Committee, School of Pharmacy
2001	Graduate Teaching Assistantship Program Evaluation Committee
2000 – Present	Faculty Advisor, USC ISPOR Student Chapter
1994 - Present	Pharmacy Student Applicant Interview Committee
1992 - 1997	Founding Chair, Dept. of Pharmaceutical Economics & Policy, School of Pharmacy
1993 - 1995	Member, Pharmacy Dean's Search Committee, Office of the Provost.
1992 - 1997	Member, Dean's Executive Committee, School of Pharmacy
1992 - 1997	Member, Appointments & Promotions Committee, Schl of Pharmacy
1993 - 1995	Economic Advisor, East Los Angeles/USC Project on Managed Care for the Medically Indigent; Pacific Center for Health Policy & Ethics
1995 - 1997	Member, Quality/Outcomes Group USC Physicians; Office of Clinical Services
1994 - 1997	Member, Ph.D. Pharmaceutical Economics and Policy Admissions Committee
1994 - 1997	Member, M.S. Pharmaceutical Economics and Policy Admissions Committee
1993 - 1997	Member, University Graduate Studies Advisory Committee, USC Graduate School
1993	Developed Ph.D. Program in Pharmaceutical Economics (Graduate School Approved for Fall 1994)
1993	Proposal Reviewer, Zumberge Research & Innovation Fund Awards
1993	Pharm.D. Candidate Admissions Interviewer, School of Pharmacy

1993	Chair, Graduate Ph.D. Program in Pharmaceutical Economics Curriculum Development, School of Pharmacy
1992/1993	Chair, Junior Faculty Position Search Committee, Dept. of Pharmaceutical Economics and Policy, School of Pharmacy
1994/1995	Chair, Junior Faculty Position Search Committee, Dept. of Pharmaceutical Economics and Policy, School of Pharmacy

OTHER UNIVERSITY SERVICE

2019	External Referee, Promotion and Tenure Committee, Faculty of Medicine, School of Population and Public Health, University of British Columbia, Vancouver, BC, Canada
2019	External Referee, Promotion and Tenure Committee, School of Public Health and Tropical Medicine, Tulane University, New Orleans, LA.
2018	External Referee, Promotion and Tenure Committee, Arnold School of Public Health, University of South Carolina, Columbia, SC.
2018	External Referee, Promotion and Tenure Committee, Department of Medicine, University of Illinois College of Medicine, Peoria, IL.
2016	External Referee, Tenure and Promotions Committee, Department of Pharmacy Practices and Administration, Western Univ of the Health Sciences, Pomona, CA.
2016	External Examiner, Doctoral Thesis Committee, Department of Economics, University of Calgary, Calgary, Alberta, Canada.
2016	External Referee, Tenure and Promotions Committee, Health Services Research Division, College of Pharmacy, University of Iowa, Iowa City, IA.
2016	External Reviewer, School of Pharmacy, Chinese University of Hong Kong, Hong Kong SAR, China.
2015	External Reviewer, School of Medicine, Pennsylvania State University, Hershey, PA.
2015	External Reviewer, Faculty of Pharmacy, University of Toronto, Toronto, Canada.
2014-15	External Reviewer, Pharmacy School, Tianjin University, Tianjin, China.
2014-15	External Reviewer, National University of Singapore, Singapore.

2014	External Reviewer, Faculty of Pharmacy, University of Maryland School of Pharmacy, Baltimore, MD.
2014	External Reviewer, Faculty of Pharmacy, University of Toronto, Toronto, Canada.
2013	External Reviewer, Department of Pediatrics, Harbor-UCLA Medical Center, Los Angeles, CA.
2013	External Reviewer, Dept. of Health Policy and Management, Texas A&M Health Sciences Center, College Station, TX.
2013	External Reviewer, Department of Pediatrics, Division of Neonatology, David Geffen School of Medicine at UCLA, Los Angeles, CA.
2013	External Reviewer, Dept. of Social Pharmacy, College of Pharmacy, Ewha Womans University, Seoul, Korea.
2013	External Reviewer, Department of Pediatrics, Division of Neonatology, David Geffen School of Medicine at UCLA, Los Angeles, CA.
2012	External Referee, School of Nursing, University of Michigan, Ann Arbor, MI.
2011	External Referee, School of Pharmacy, University of Colorado Anschutz Medical Campus, Aurora, CO.
2011	External Referee, University of Wisconsin School of Medicine and Public Health, Department of Population Health Sciences, Madison, WI.
2010	External Referee, Virginia Commonwealth University, School of Pharmacy, Department of Pharmacotherapy and Outcomes Sciences, Richmond, VA.
2010	External Referee, Nelson Mandela Metropolitan University, Faculty of Health Sciences, Port Elizabeth, South Africa.
2010	Outside Examiner, Doctoral Dissertation Committee, College of Pharmaceutical Sciences, Andhra University, Andhra Pradesh, India.
2009	External Referee, Tenure and Promotions Committee, Department of Pharmacy Practice and Science, University of Iowa, Iowa City, IA.

2009	External Referee, Tenure and Promotions Committee, Department of Pharmaceutical Sciences, Oregon State University, Corvallis, OR.
2008	External Referee, Appointments and Promotions Committee, Division of Pharmacy Practice and Administration, College of Pharmacy, Ohio State University, Columbus, OH.
2006	External Referee, Appointments and Promotions Committee, Department of Medicine, Brigham and Women's Hospital; Harvard Medical School, Boston, MA.
2004	External Referee, Appointments and Promotions Committee, Dept. Pediatrics, Harbor-UCLA Medical Center, UCLA School of Medicine, Los Angeles, CA.
2002	External Examiner, Chinese University of Hong Kong Graduate School. Shatin, Hong Kong
2001	External Referee, Appointments and Promotions Committee, College of Pharmacy, University of Iowa, Iowa City, IA.
2000	External Referee, Appointments and Promotions Committee, Depart. of Pediatrics, Harbor-UCLA Med Center, UCLA Schl of Medicine, Los Angeles, CA.
2000	External Referee, Appointments and Promotions Committee, Department of Economics, Rice University, Houston, TX.
1997	External Referee, Appointments and Promotions Committee, School of Dentistry, University of Connecticut, Farmington, CT.
1993	External Referee, Promotions Committee, Department of Medicine, Baylor College of Medicine, Houston, TX.
1993	External Referee, Promotions Committee, Department of Medicine, University of California, San Diego, CA.
1993	External Referee, Promotions Committee, School of Nursing, University of California, San Francisco, CA.
1993	External Referee, Promotions Committee, Department of Economics, University of Hong Kong, Hong Kong.
1992	External Referee, Promotions Committee, School of Nursing, University of California, San Francisco, CA.
1988	External Referee, Tenure and Promotions Committee, Dept. of Economics, Univ. of North Carolina at Chapel Hill, NC.

PENDING GRANT RESEARCH

Sponsor: National Institute on Aging (NIA)
PI: Van Park, PhD
J Hay Role: Co-I Health Economist
Title: **C**ollaborative **A**pproach for Asian Americans and Pacific Islanders **R**esearch and **E**ducation (**CARE**) in Alzheimer's Disease and Related Dementias (ADRD)
Grant #: 1R24AG063718-01
Amount: Total Direct Costs (Y1)- $749,994
Dates: 07/1/2019-06/30/2022

The goal of the proposed project, ***CARE***, is to reduce disparities in ADRD research participation among Asian Americans and Pacific Islanders (AAPI) through the creation of a registry of AAPI who are interested in participating in various types of ADRD research.

Sponsor: Agency for Healthcare Research and Quality (AHRQ)
PI: Mendel, Peter James, PhD
J Hay Role: Co-I Health Economist
Title: Implementation and Evaluation of a Video-based Prospective Feedback Intervention to Improve Antimicrobial Stewardship in Neonatal Intensive Care Units
Grant #: 1 R18 HS026168-01A1
Amount: Total Costs (Y1-Y4)- $1,924,910
Dates: 10/1/2019-06/30/2022

The application proposes to "test the feasibility, acceptability, and clinical and cost-effectiveness of a video-based telehealth learning platform to provide antimicrobial stewardship expertise to front-line providers in real time." We propose to evaluate an innovative, scalable antimicrobial stewardship intervention called ECHO- ASP in NICUs participating in the largest statewide perinatal QI collaborative in the US. The Specific Aims of the project are to: 1) Evaluate the implementation of the ECHO-ASP intervention including barriers and facilitators to implementation, site participation in video-based prospective feedback and audit sessions, dissemination of session results to other local NICU prescribers, perceived acceptability and durability of the intervention, and practice consensus on antibiotic prescribing; 2) Evaluate the effectiveness of the ECHO ASP intervention on patient care outcomes, including antibiotic use, drug-related adverse events, and other clinical complications; 3) Evaluate the cost implications of the ECHO ASP intervention, including implementation costs and effects on costs of care.

ONGOING GRANT RESEARCH

Sponsor: National Institute of Dental and Craniofacial Research
PI: Sharon Cermak, PhD
J Hay Role: Health Economist
Title: Sensory Adapted Dental Environments to Enhance Oral Care for Children (1 U01 DE024978-01)
Amount: $381,201 (First Year Directs)
Dates: 4/01/15-3/31/20

Sponsor: National Institute of Dental and Craniofacial Research
PI: Steve Yen, DMD
J Hay Role: Health Economist
Title: Clinical Effectiveness of Late Maxillary Protraction for Cleft Lip and Palate (U01 DE22937-01A1)
Amount: $3,250,000
Dates: 9/1/13 – 8/31/20

Sponsor: National Institute of Child Health and Human Development T32 HD064578
PI: Florence Clark, PhD
J Hay Role: Co-Investigator
Title: TREET: Training in Rehabilitation Efficacy and Effectiveness
Amount: $102,692
Dates: 04/01/11 - 03/31/22

COMPLETED GRANT RESEARCH (WHILE AT USC)

Sponsor: Agency for Healthcare Research and Quality, US DHHS
PI: Ken Zangwill, MD
J Hay Role: Health Economist
Title: Evaluation and Management of the Young Febrile Infant and Related Healthcare Costs and Morbidities (1 R03 HS024146-01)
Amount: $100,000
Dates: 7/01/15-6/30/16

Sponsor: Baxter International
PI: Joel W. Hay PhD
Title: Economic Evaluation of Hemophilia Inhibitor Bypass Agent Treatment: On Demand Versus Prophylaxis
Amount: $99,000
Dates: 1/1/14 – 12/31/15

Sponsor: Children's Hospital, Los Angeles
PI: Guy Young, MD
J Hay Role: Co-Investigator
Title: Economic Evaluation of Hemophilia Inhibitor Treatments
Amount: $95,000
Dates: 8/1/13 – 7/31/15

Sponsor: Agency for Healthcare Research and Quality, U.S. DHHS
PI: Joel W. Hay PhD
Title: American Society of Health Economists Conference Grant
Amount: $35,000
Dates: 1/1/14 – 2/31/15

Sponsor: US Dept. of Health and Human Services/Asst. Secretary for Policy and Evaluation (DHHS/ASPE)
PI: Shinyi Wu, PhD
J Hay Role: Co-Investigator
Title: Care Management Technology to Facilitate Depression Care in Safety Net Diabetes Clinics
Amount: $1,977,461
Dates: 9/1/10 – 8/31/14

Sponsor: National Institutes of Health (trans agency)
PI: Jason Doctor, PhD
J Hay Role: Co-Investigator
Title: Use of Behavioral Economics to Improve Treatment of Acute Respiratory Infections
Amount: $8,353,371
Dates: 9/1/2010 – 8/31/2014

Sponsor: NIH, National Institute of Aging
PI: Florence Clark, PhD
J Hay Role: Co-Investigator
Title: Lifestyle Redesign for Pressure Ulcer Prevention in Spinal Cord Injury
Amount: $2,111,000
Dates: 9/08 – 8/14

Sponsor: EconoMedRx
PI: Joel W. Hay PhD
Title: Economic Evaluation of the Market for Pediatric Antidepressants
Amount: $99,000
Dates: 8/1/12 – 7/31/14

Sponsor: Baxter International
PI: Joel W. Hay PhD
Title: Economic Evaluation of Hemophilia Inhibitor Bypass Agent Testing Assay
Amount: $99,000
Dates: 8/1/12 – 6/31/13

Sponsor: Auxillium Pharmaceuticals
PI: Joel W. Hay PhD
Title: Economic Evaluation of Dupuytren's Contracture Therapy
Amount: $165,000
Dates: 1/1/11 – 12/31/12

Sponsor: Sunovion Pharmaceuticals
PI: Joel W. Hay PhD
Title: Costs of COPD Treatments
Amount: $85,000
Dates: 3/10 – 8/11

Sponsor: Baxter Pharmaceuticals
PI: Joel W. Hay PhD
Title: Meta-analysis of Hemophilia Patient Inhibitor Therapy Efficacy
Amount: $85,000
Dates: 3/10 – 8/11

Sponsor: Baxter Pharmaceuticals
PI: Joel W. Hay PhD
Title: Economic Evaluation of Hemophilia Patient Inhibitor Therapy
Amount: $80,000
Dates: 9/08 – 8/10

Sponsor: Prolacta Biosciences
PI: Joel W. Hay PhD
Title: Economic Evaluation of Human Milk Fortifier in Necrotizing Enterocolitis
Amount: $80,000
Dates: 9/08 – 8/10

Sponsor: NIH, National Institute of Mental Health
PI: Kathy Ell, PhD
J Hay Role: Co-Investigator
Title: Major Depression in Diabetes Patients
Amount: $678,000
Dates: 9/04 –8/10

Sponsor: NIH, National Institute of Mental Health
PI: Megan Dwight-Johnson, MD
J Hay Role: Co-Investigator
Title: Patient Centered Care in the Public Sector
Amount: $2,642,000
Dates: 7/04 – 6/08

Sponsor: California Dept. of Health Services
PI: Lon Schneider, MD
J Hay Role: Economist
Title: Alzheimer Disease Costs, Quality of Life and Disease Burden
Amount: $600,000
Dates: 1/01 – 12/04

Sponsor: US Centers for Disease Control and Prevention, NIH
PI: Ken Zangwill, MD
J Hay Role: Sub-grant PI
Title: Economic Assessment of Rotavirus Burden of Illness in the Kaiser Southern California Health Plan
Amount: $260,000
Dates: 11/97 – 12/03

Sponsor: US Alzheimer Association, Merck Foundation, Janssen Pharmaceutica
PI: Joel W. Hay PhD
J Hay Role: Economist
Title: Alzheimer Disease Global Burden of Illness
Amount: $200,000
Dates: 6/99 – 12/01

Sponsor: US National Institute on Aging
PI: Florence Clark, PhD
J Hay Role: Project Economist
Title: Well Elderly Occupational Therapy Demonstration Project
Amount: $1.3 million
Dates: 1/96 – 6/98

Sponsor: US PHS Agency for Health Care Policy Research
PI: Paul Schekelle, MD
J Hay Role: USC Project Coordinator
Title: Southern California Evidenced-Based Practice Center
Amount: $420,000
Dates: 3/98 – 9/99

Sponsor: Parke-Davis
PI: Joel W. Hay PhD
J Hay Role: Economist
Title: Economic Assessment of Epilepsy Disease Management Intervention
Amount: $60,000
Dates: 6/95 9/98

Sponsor: US NIH, National Institute on Aging
PI: Mary Mittelman, PhD
J Hay Role: Sub-Grant Co-PI
Title: Economic Evaluation of Alzheimer Disease Caregiver Support Intervention
Amount: $190,000
Dates: 1/96 – 7/98

Sponsor: Bristol Myers Squibb
PI: Joel W. Hay PhD
J Hay Role: USC Project Coordinator
Title: Pharmacoeconomics Fellowship
Amount: $30,000
Dates: 6/96

Sponsor: Bristol Myers Squibb
PI: Joel W. Hay PhD
J Hay Role: USC Project Coordinator
Title: Pharmacoeconomics Training
Amount: $60,000
Dates: 6/96

Sponsor: Parke-Davis
PI: Joel W. Hay PhD
J Hay Role: Economist
Title: Cognitive Function and the Costs of Alzheimer's Disease
Amount: $90,000
Dates: 6/94 8/96

Sponsor: Astra-Merck
PI: Phil Rappa
J Hay Role: USC Project Coordinator
Title: Pharmacoeconomics Training
Amount: $90,000
Dates: 8/94

Sponsor: Allergan
PI: Phil Rappa
J Hay Role: USC Project Coordinator
Title: Pharmacoeconomics Training
Amount: $20,000
Dates: 8/95

Sponsor: Amgen
PI: Phil Rappa
J Hay Role: USC Project Coordinator
Title: Pharmacoeconomics Training
Amount: $30,000
Dates: 7/94

Sponsor: Glaxo-Welcome Pharmaceuticals
PI: Phil Rappa
J Hay Role: USC Project Coordinator
Title: Pharmacoeconomics Training
Amount: $140,000
Dates: 3/93, 3/94

Sponsor: Miles Pharmaceuticals
PI: Joel W. Hay PhD
J Hay Role: Economist
Title: Economic Assessment of Anti-TNF in Treatment of Septic Shock
Amount: $130,000
Dates: 4/94 – 3/95

Sponsor: Kaiser Permanente Southern California Health Care Plan
PI: Jeff McCombs, PhD
J Hay Role: Project Economist
Title: The Kaiser/USC Pharmaceutical Care Demonstration Project
Amount: $860,000
Dates: 3/93 – 9/97

Sponsor: Syntex Roche Pharmaceuticals
PI: Joel W. Hay PhD
J Hay Role: Project Coordinator
Title: Pharmacoeconomics Graduate program development
Amount: $120,000
Dates: 6/92 – 5/93

PEER-REVIEWED PUBLICATIONS

Joel W Hay H-Index: 50
9,800+ citations of JW Hay peer-reviewed articles in the scientific literature.

1. **Hay JW**. "Public Service Delivery in Chicopee, Massachusetts," in *Student Originated Studies Conference Proceedings*, National Science Foundation, 1973, NSF No. 74-33.

2. **Hay JW**. Occupational Choice and Occupational Earnings: Selectivity Bias in a Simultaneous Logit-OLS Model, Ph.D. dissertation, Yale University, New Haven, 1980, published by the *National Technical Information Service*, Rockville, Maryland.

3. Formicola A, Gottsegan R, **Hay JW**. "Commentary on 'Periodontal Disease: Assessing the Effectiveness and Costs of the Keyes Technique'," in *Implications of Cost-Effectiveness Analysis of Medical Technology*, Office of Technology Assessment, U.S. Congress, Washington, D.C., 1981.

4. Yett D, Der W, Ernst R, **Hay JW**. "Blue Shield Plan Physician Participation." *Health Care Financing Review*, June 1981 pp. 9-24.

5. Alvesalo I, Reisine S, **Hay JW**, Bailit H. "Effects of Fluoride and Regular Dental Care on Personal Dental Expenditures of Young Adults in Finland," *Community Dentistry and Oral Epidemiology,* 1982; 10:15-22.

6. Yett D, Der W, Ernst R, **Hay JW**. "A Model of Physician Pricing, Output, and Health Insurance Reimbursement: Findings from Study of Two Blue Shield Plans' Claims Data." in *Essays in Health Economics*, edited by Jacques Van der Gaag, William Neenan and Theodore Tsukahara, Praeger Press, New York, 1982, pp. 197-230.

7. **Hay JW**, Bailit H, Chiriboga D. "The Demand for Dental Health," *Social Science and Medicine*, Volume 16 (1982), pp. 1285-1289.

8. **Hay JW**, Leahy M. "Physician-Induced Demand: An Empirical Analysis of the Consumer Information Gap," *Journal of Health Economics*, Volume 1, 1982; pp. 231-244.

9. **Hay JW**. "A Simultaneous Econometric Model for Physicians' Specialty Choice and Specialty Income," in *Actes du Dixieme Colloque International D'Econometrie Appliquee: Econometrie de la Sant*e, Hospices Civil de Lyon, Lyon, France. 1983, pp. 260-270.

10. **Hay JW**. "The Impact of Public Health Care Financing Policies on Private Sector Hospital Costs." *Journal of Health Politics, Policy and Law*, Volume 7, No. 4 (1983), pp. 945-952.

11. Yett D, Der W, Ernst R, **Hay JW**. "Physician Pricing and Health Insurance Reimbursement," *Health Care Financing Review*, (December 1983), pp. 69-80.

12. **Hay JW**, Leahy M. "Competition Among Health Plans: Some Preliminary Evidence," *Southern Economic Journal* 50 (January 1984), pp. 831-847.

13. **Hay JW**, Mandes G. "Home Health Care Cost-Function Analysis," *Health Care Financing Review* 5(3), (Spring 1984), pp. 111-116.

14. **Hay JW**, Olsen R. "Let Them Eat Cake: A Note on Comparing Alternative Models of the Demand for Medical Care," *Journal of Business and Economic Statistics* 2(3), (July 1984), pp. 279-282.

15. **Hay JW**. "Occupational Choice and Occupational Earnings: A Method for Dealing with Selection Bias Among Economic Activities," in *Research in Population Economics*, Volume 5, edited by T. Paul Schultz and Kenneth Wolpin, JAI Press, Greenwich, Connecticut (1984) pp. 309-329.

16. **Hay JW**. "Variation in Per Capita Pharmaceutical Expenditures: Are Drugs Complements or Substitutes?" In *Pharmaceutical Economics*, Bjorn Lindgren, ed., Liber Forlag Press, Malmo, Sweden, 1985, pp. 21-36.

17. Yett D, Der W, Ernst R, **Hay JW**. "Fee Screen Reimbursement and Physician Fee Inflation," *Journal of Human Resources* 20(2), (Spring, 1985), pp. 278-291.

18. **Hay JW**, Hill WL. "Cost-Effectiveness of Two Transdermal Nitroglycerin Controlled-Release Systems," *Clinical Therapeutics*, 8(1), 1985, pp. 35-40.

19. Sloan F, **Hay JW**. "Medicare Pricing Mechanisms for Physician Services: An Overview of Alternative Approaches," *Medical Care Review*, 43(1), (Spring, 1986), pp. 59-100.

20. **Hay JW**, Ernst R. "The Cost Effectiveness of Home Intravenous Antibiotics," in *Proceedings: Outpatient Parenteral Antibiotic Therapy Symposium*, J.E. Putnam, Ed., IntraMed, New York, NY, 1987 pp. 7-14.

21. Welch B, **Hay JW**, Miller D, Olsen R, Rippey R, Welch A. "The Rand Health Insurance Study: A Summary Critique," *Medical Care*, 25(2), (February 1987) pp. 148-156.

22. **Hay JW**, Daum R. "Cost Benefit Analysis of Two Strategies for Prevention of Haemophilus Influenzae Type B Infection," *Pediatrics*, 80(3) (September 1987) pp. 319-329.

23. **Hay JW**, Leu R, Rohrer P. "Ordinary Least Squares and Sample Selection Models of Health Care Demand: Monte Carlo Comparison," *Journal of Business and Economic Statistics*, 1987; 5(4):499-506.

24. **Hay JW**, Ernst R. "The Economic Costs of Alzheimer's Disease," *American Journal of Public Health*, 77(9) (September 1987) pp. 1-7.

25. **Hay JW**, Anderson G. "The Hospital Services Market: A Disequilibrium Analysis," *Southern Economic Journal*, 54(3) (January 1988) pp. 656-665.

26. **Hay JW**, Osmond D, Jacobson M. "Projecting the Medical Costs of AIDS and ARC in the United States," *Journal of Acquired Immune Deficiency Syndromes*, 1(5) (October 1988) pp. 466-485.

27. **Hay JW**. "Cost-Effectiveness of Three Transdermal Nitroglycerin Controlled-Release Systems," *Clinical Therapeutics*, 10(4), 1988, pp. 450-455.

28. **Hay JW**. "Econometric Issues in Modeling the Costs of AIDS," paper presented at the Johns Hopkins University Conference on The Economic Impact of AIDS: Research Methodology. *Health Policy*, 11(2) (April 1989) pp. 125-145.

29. **Hay JW**. "Projecting the Medical Costs of HIV/AIDS: An Update with Focus on Epidemiology." In *New Perspectives on HIV-Related Illness: Progress in Health Services Research--Conference Proceedings*. National Center for Health Services Research, Pub. No. DHHS (PHS) 89-3449. 1989:84-97. Rockville, MD.

30. **Hay JW**. "The Health Care Cost Crisis," in L. Holland, ed., *Managed Health Care Strategies for the 1990s: Proceedings of a Symposium for Managed Care Professionals*, IntraMed, New York, 1990 pp. 30-39.

31. **Hay JW**. "AIDS Point and Counterpoint." P*riorities; the American Council on Science and Health*, Winter 1990, pp. 35-39.

32. Wittels E, **Hay JW**, Gotto A. "Medical Costs of Coronary Artery Disease." *American Journal of Cardiology*, February 1990, Vol. 65, pp. 432-440.

33. **Hay JW**, Daum R."Cost-benefit Analysis of Haemophilus influenzae Type B Prevention: Conjugate Vaccination at Eighteen Months of Age," *Pediatric Infectious Disease Journal*, April 1990, Vol. 9, pp. 246-252.

34. Gotto A, LaRosa J, Hunninghake D, Grundy S, Wilson J, Clarkson T, **Hay JW**. "The Cholesterol Facts: A Summary of the Evidence Relating Dietary Fats, Blood Cholesterol and Coronary Artery Disease" A Joint Statement of The American Heart Association and the National Heart, Lung and Blood Institute. *Circulation*, May 1990, Vol. 81, No. 5, pp. 1721-1733.

35. **Hay JW**. "Physicians' Specialty Choice and Specialty Income," in G. Duru and J. H. P. Paelinck, eds. *Econometrics of Health Care*, Kluwer Academic Publishers, Amsterdam, Holland, 1990. pp. 95-113.

36. **Hay JW**, Robin E. "Cost-Effectiveness of Alpha-1 Antitrypsin Replacement Therapy in Treatment of Congenital Chronic Obstructive Pulmonary Disease." *American Journal of Public Health*, April 1991, Vol. 81, No. 4, pp. 427-433.

37. **Hay JW**, Wittels E, Gotto A. "An Economic Evaluation of Lovastatin for Cholesterol Lowering and Coronary Artery Disease Reduction," *American Journal of Cardiology*, April 15, 1991, Vol. 67, No. 9, pp. 789-796.

38. **Hay JW**. "Is Hong Kong Ready for Free Market Health Care?" in *Financing Health Care in the 1990s*, Hong Kong Medical Association and Hong Kong Society of Medical Executives, September 1991, pp. 16-21.

39. **Hay JW**. "The Harm They Do to Others: A Primer on the External Costs of Drug Abuse," in E. Lazear and M. Krauss, eds. *Searching for Alternatives: Drug Control Policy in the United States*, Hoover Institution Press, Stanford, CA, November 1991, pp. 200-225.

40. **Hay JW**, Hay AR. "Inflammatory Bowel Disease Costs-of-Illness," *Journal of Clinical Gastroenterology*, 1992, Vol. 14, No. 4, pp. 309-317.

41. Hay AR, **Hay JW**. "Inflammatory Bowel Disease Medical Cost Algorithms," *Journal of Clinical Gastroenterology*, 1992, Vol. 14, No. 4, pp. 318-327.

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15. Langley PC. **Hay JW**, Schwartz JS; Smith SC; McKenney J. From Research into Practice: How Should Healthcare Organizations/Governments Decide About Lipid Therapy and Who Will Pay? Reactor Panel and Open Forum. 4th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, Virginia, May 1999.

16. Li J, **Hay JW**. Cost-Effectiveness of Rentinopathy Screening in Pediatric Patients with Type I Diabetes Mellitus. 5th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, Washington, May 2000.

17. Sengupta N, **Hay JW**. Cost-Effectiveness of Tamoxifen in Breast Cancer Risk Reduction. 5th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, Washington, May 2000.

18. **Hay JW**, Jackson J. Methodological Issues in Conducting Pharmacoeconomic Evaluations-Modeling Studies. 5th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, Washington, May 2000.

19. Sullivan PW, **Hay JW**. Cost-Effectiveness of Rofecoxib Versus NSAIDS in the Treatment of Osteoarthritis. 6th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, Virginia, May 2001.

20. Charles R, **Hay JW**. The Cost-Effectiveness of Lifetime Factor VIII Prophylaxis in the Treatment of Severe Hemophilia A. 6th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, Virginia, May 2001.

21. Yu E, **Hay JW**, Varma R, Globe D. Four Year Cost-Effectiveness of Initial Trabeculectomy Versus Conventional Therapy in Primary Open-Angle Glaucoma (POGA). 6th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, Virginia, May 2001.

22. Mulani P, **Hay JW**. Cost-Effectiveness Model of Thrombolytic Therapy for Acute Myocardial Infraction. 6th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, Virginia, May 2001.

23. Sokolskiy L, **Hay JW**. Cost-Effectiveness Model of Prostate-Specific Antigen (PSA) Screening for Prostate Cancer. 6th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, Virginia, May 2001.

24. Chen K, **Hay JW**. Cost-Effectiveness of "Test &Treat" in Helicobacter Pylori (HP) Infected Dyspeptic Patients in Primary Care Setting. 6th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, Virginia, May 2001.

25. Wu EQ, **Hay JW**. Alternative Management Strategies for Dyspepsia. 6th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, Virginia, May 2001.

26. Bron MS, **Hay JW**. Cost-Effectiveness of Artificial Skin Substitute vs Allograft for Burn Patients. 6th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, Virginia, May 2001.

27. Shi JH, McCombs JS, **Hay JW**, Nichol MB, Chou CP, Hsiao C. Controlling for Biases from Measurement Errors in Health Outcomes Research Using Structural Equation Modeling. 6th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, Virginia, May 2001.

28. Sterling KL, **Hay JW**. Cost-Effectiveness of the Fibrates in the Reduction of Coronary Heart Disease Events. 7th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, Virginia, May 2002.

29. Patel PA, **Hay JW**. The Cost-Effectiveness Analysis of Aspirin for Primary Prevention of Cardiovascular Disease. 7th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, Virginia, May 2002.

30. Etemad LR, **Hay JW**. Cost-Effectiveness Analysis of Pharmaceutical Care in a Medicare Drug Benefit Program. 7th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, Virginia, May 2002.

31. Patel BV, **Hay JW**. Colorectal Cancer Screening: A Cost-Effectiveness Model Comparing Virtual Colonoscopy and Conventional Colonoscopy. 7th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, Virginia, May 2002.

32. Park J, **Hay JW**. Cost-Effectiveness Analysis of Graftskin (Apligraf) and Becaplermin (Regranex) in Diabetic Neuropathic Foot Ulcers. 8th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, Virginia, May 2003.

33. Zammit DC, **Hay JW**. Meta-Analysis of the Effectiveness of Mammography Screening for Breast Cancer. 8th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, Virginia, May 2003.

34. Zammit DC, **Hay JW**. Economic Analysis Of The Use Of Angiotensin Converting Enzyme Inhibitors In Patients With Diabetes Mellitus. 8th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, Virginia, May 2003.

35. Yu YF, **Hay JW**, Yu AP. Cost-Effectiveness Analysis of Long-Term Hormone Replacement Therapy (Estrogen Plus Progestin) in Healthy Postmenopausal Women for Osteoporosis Prevention. 9th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, Virginia, May 2004.

36. Yu AP, **Hay JW**. Cost-Effectiveness Analysis of Dose-Dense Chemotherapy with Filgrastim as Postoperative Adjuvant Treatment of Breast Cancer. 9th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, Virginia, May 2004.

37. Setyawan J, **Hay JW**, Nichol MB. Cost-Effectiveness of Interventions to Improve Patient Medication Compliance in Major Depressive Disorder. 9th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, Virginia, May 2004.

38. Spalding JR, **Hay JW**. Cost-Effectiveness of Tumor Necrosis Factor Alpha (TNF-ALPHA) Inhibitors as First-Line Agents in Rheumatoid Arthritis. 9th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, Virginia, May 2004.

39. Barlev A, **Hay JW**. Cost-Utility of Cochlear Implants a Societal Perspective Analysis. 9th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, Virginia, May 2004.

40. Tonnu IQ, **Hay JW**. The Cost-Effectiveness Analysis Recombinant Human Erythropoietin Growth Factors vs. Transfusion in Chemotherapy Cancer Patients. 9thAnnual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, Virginia, May 2004.

41. Patel V, **Hay JW**. Cost-Effectiveness of Treatment Strategies for Rheumatoid Arthritis Patients with Inadequate Response to Methotrexate. 9th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, Virginia, May 2004.

42. Zhang L, **Hay JW**. Cost-Effectiveness Analysis of Rizatriptan and Sumatripan versus Cafegot in the Acute Treatment of Migraine. 9th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, Virginia, May 2004.

43. Narayan S, **Hay JW**. Cost-Effectiveness of Ratalin® versus Adderall® for First-Line Treatment of Attention Deficit/Hyperactivity Disorder (ADHD) in Children. 9th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, Virginia, May 2004.

44. Zammit DC, **Hay JW**. Preliminary Economic Analysis of The American Cancer Society Guidelines for Mammography Screening in Average-Risk Women under 70 Years of Age. 9th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, Virginia, May 2004.

45. Tencer T, **Hay JW**. The Cost-Effectiveness of Prostate-Specific Antigen Screening for Prostate Cancer Detection. 10th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, Washington, May 2005.

46. Kawatkar AA, **Hay JW**. Cost-Effectiveness of Taxanes as Second Line Agents in Treatment of Metastatic Breast Cancer. 11th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, Philadelphia, May 2006.

47. Vo P, **Hay JW**. Cost-Effectiveness Analysis for Treatments in Ankylosing Spondylitis. 11th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, Philadelphia, May 2006.

48. Suh HS, **Hay JW**. Cost-Effectiveness Analysis of Immunization Strategies for the Control of Meningococcal Infectious disease. 12th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, Virginia, May 2007.

49. Gu NY, **Hay JW**, Gai YW. The Effect of Pharmacist Consultation on Patient Medication Adherence: An Instrumental Variable Approach. 12th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, Virginia, May 2007.

50. Yuan Y, Iloeje U, Parry D, **Hay JW**, Zammit D. Using Decision Simulation Model to Evaluate the Cost Effectiveness of Entecavir Compared to Adefovir Therapy in Lamivudine Refractory Chronic Hepatitis B (CHB) Patients: Analyses from a US Payer Perspective Abstract and poster presentation at the 12th ISPOR Annual International Meeting, Virginia, May 2007.

51. Zammit DC, **Hay JW**, Globe DR, Sugar CA, Gauderman WJ Adjusting for Trial Quality in a Meta-Analysis. Poster presentation at the 10th ISPOR Annual European Congress, Dublin Ireland, October 2007.

52. Zammit DC, **Hay JW**, Globe DR, Sugar CA, Gauderman WJ Framework for The Cost-Effectiveness Analysis Of Mammography Screening For Breast Cancer. Poster presentation at the 10th ISPOR Annual European Congress, Dublin Ireland, October 2007.

53. Ejzykowicz F, **Hay JW**. Cost-Effectiveness Analysis of Lapatinib Plus Capecitabine Vs Capecitabine Alone in the Second Line Treatment for Breast Cancer. Poster PCM 23, 13th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, Toronto, Canada, 2008.

54. An JJ, **Hay JW**. Cost-Effectiveness of Erythropoiesis Stimulating Agent Therapy by Hemoglobin Targets in Chronic Kidney Disease. Poster PSY 15, 13th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, Toronto, Canada, 2008.

55. Ganapathy V, **Hay JW**. Cost-Effectiveness of Once-Daily Stimulant, Non-Stimulant & Combined Stimulant/Behavioral Therapy Interventions in the Treatment of ADHD in Children. Poster PMH 28, 13th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, Toronto, Canada, 2008.

56. Le QA and **Hay JW**. Cost-utility Analysis of Lapatinib (Tykerb®)in 2nd-Line Treatment of HER2-Positive Metastatic Breast Cancer. Poster PCN18, American Society of Clinical Oncology, San Diego, CA 2008.

57. Turpcu A and **Hay JW**. The Cost-Effectiveness of Ranibizumab (Lucentis®) in Treating Patients with Predominantly Classic, Minimally Classic, and Occult Neovascular Age-Related Macular Degeneration (AMD). Poster PSS 15, 13th Annual Meeting, International Society for Pharmacoeconomics and Outcomes Research, Toronto, Canada, 2008.

58. Lescrauwaet B, Nevens F, Zammit D, Yuan Y, **Hay JW**. Modeling Long-Term Mortality and Morbidity with Entecavir Treatment in Chronic Hepatitis B Patients in Belgium. Podium presentation, ISPOR European Conference, Athens, Greece, November 2008.

59. Zammit D, Yuan Y, Intorcia M, **Hay JW**. Using a Decision Simulation Model to Evaluate the Cost-Effectiveness of the Treatment of Nucleoside-Naïve HBe-Antigen Negative CHB Patients in Italy with Entecavir and Tenofovir Abstract and poster presentation at the 11th ISPOR Annual European Congress, Athens, Greece, November 2008.

60. **Hay JW**, Jhaveri M, Tangirala M, Kaliner M. Costs and Resource Utilization Comparisons of Second-Generation Antihistamines vs Montelukast in Treatment of Allergic Rhinitis: Retrospective Analysis of a Large National Insurance Claims Database. American Academy of Allergy, Asthma and Immunology Annual Meeting, March 2009, Washington, DC.

61. Le QA, **Hay JW**. Comparison Between Propensity-Score & Traditional Covariate Adjustment with Logistic Regression Models in Estimating Average Treatment Effects (ATES): Monte Carlo Simulation Results. Poster Session I [PMC10], ISPOR 14th Annual International Conference, May 2009, Orlando, FL.

62. Mark TL, Joish VN, **Hay JW**, Sheehan D, Johnston S, Cao Z. Unintended Consequences of Geriatric Antidepressant Use: Side-Effects, Adherence And Costs. ISPOR 14th Annual American Association of Psychiatry Conference, May 2009, Orlando, FL.

63. Mark TL, Joish VN, **Hay JW**, Sheehan D, Choi JC, Johnston S, Cao Z. Unintended Consequences of Current Antidepressant Use in A Geriatric Population: Drug-Drug Interactions and Their Implications for Adherence. ISPOR 14th Annual American Association of Geriatric Psychiatry Conference, May 2009, Orlando, FL. Am J Geriatr Psychiatry 2009;17(3), Supplement 1:A98.

64. Skrepnek G, Seal B, Tangirala M, **Hay JW**. Adverse Dental Outcomes Associated With Intravenous Versus Oral Bisphosphonate Use In Patients With Osteoporosis. 7th International Symposium on Osteoporosis, April 2009, Washington, DC.

65. Skrepnek G, Seal B, Tangirala M, **Hay JW**. The Association Between Adverse Dental Outcomes And Intravenous Versus Oral Bisphosophonates Within Cancer Patients. European Calcified Tissue Society ECTS 2009, Vienna, Austria, 23-27 May 2009

66. **Hay JW**, Zhou ZY. "APCC Versus RFVIIA In Treatment Of Hemophilia Patients With Inhibitors: A Structured Review Of The Pharmacoeconomic Literature" abstract N° 846 - XXII Congress of the International Society on Thrombosis and Haemostasis, Boston, MA, July 11-16 2009.

67. **Hay JW**, Zhou ZY, Young G. "Economic Comparison Of APCC Vs RFVIIA For Mild-To-Moderate Bleeding Episodes In Hemophilia Patients With Inhibitors" abstract N° 836 - XXII Congress of the International Society on Thrombosis and Haemostasis, Boston, MA, July 11-16 2009.

68. Tangirala M, Jhaveri M, **Hay JW**. "Resource Use in Patients with Allergic Rhinitis (AR) Comorbidities: Oral Second Generation Antihistamines (SGAs) versus Montelukast (MTLK)" Annual Meeting of the American College of Allergy, Asthma & Immunology, Nov. 5-10 2009, Miami Beach, Florida.

69. Colayco D, **Hay JW**. Cost-Effectiveness of Serotonin-Type 3 Receptor Antagonists For Chemotherapy-Induced Emesis In Non-Small Cell Lung Cancer Patients Receiving Cisplatin-Based Chemotherapy. Poster PCN95. ISPOR 15th Annual International Conference, May 2010, Atlanta, GA.

70. Suh H, **Hay JW**. Dealing with Selection Bias in Nonlinear Settings: A Case Of Comparative Effectiveness Of Statin Plus Fibrate Combination Therapy Versus Statin Monotherapy In Type II Diabetes. Podium SB4. ISPOR 15th Annual International Conference, May 2010, Atlanta, GA.

71. Shin J, **Hay JW**. The Cost-Effectiveness of Isotretinoin In Patients With Moderate-To-Severe Acne Vulgaris. Poster PSS6, ISPOR 15th Annual International Conference, May 2010, Atlanta, GA.

72. Ganapathy V, **Hay JW**. Analysis of Necrotizing Enterocolitis Costs Among Extremely Preterm Infants Fed Exclusively Human-Milk Based Diet Vs. Human-Milk Fortified With Bovine-Milk Based Supplements. Poster PIH18, ISPOR 15th Annual International Conference, May 2010, Atlanta, GA.

73. Tran JN, **Hay JW**. Obesity and Health Care Costs And Utilization In The Veteran Affairs Population. Poster PSY34, ISPOR 15th Annual International Conference, May 2010, Atlanta, GA.

74. Soo In Bang, JW Hay. Cost-Effectiveness Analysis of Dutasteride, Tamsulosin and Combination Therapy In The Treatment Of Benign Prostatic Hyperplasia. Poster PUK 11, ISPOR 15th Annual International Conference, May 2010, Atlanta, GA.

75. Chu K, **Hay JW**. Economic Analysis of Endovascular Stenting for Peripheral Arterial Disease In Long Lesions Of The Superficial Femoral Artery. Poster PCV 83, ISPOR 15th Annual International Conference, May 2010, Atlanta, GA.

76. Ding Y, **Hay JW**. Cost-effectiveness analysis of multimodal screening for ovarian cancer. Poster PCN 73, ISPOR 15th Annual International Conference, May 2010, Atlanta, GA.

77. Schwartz E, **Hay JW**. Cost-Effectiveness Analysis in treating Overactive Bladder with Urge Incontinence in Women: A comparison between Oxybutynin and Tolterodine with exploratory analysis of Fesoterodine. Poster PUK 16, ISPOR 15th Annual International Conference, May 2010, Atlanta, GA.

78. Rashid N, **Hay JW**. Cost Effectiveness Analysis of Managing Chronic Gout with Febuoxstat (Uloric) versus Allopurinol (Zyloprim). Poster PMS 20, ISPOR 15th Annual International Conference, May 2010, Atlanta, GA.

79. Suh JK, **Hay JW**. Evaluation of Cost-Effectiveness of Chronic Hepatitis B Treatments: Entecavir And Telbivudine. Poster PGI 22, ISPOR 15th Annual International Conference, May 2010, Atlanta, GA.

80. Poon JL, **Hay JW**. Cost Effectiveness Analysis of Breast Cancer Risk Reduction Therapy: Comparing Tamoxifen and Raloxifene. Poster PCN 71, ISPOR 15th Annual International Conference, May 2010, Atlanta, GA.

81. Wiegand PW, **Hay JW**. Cost-Effectiveness of Statin Therapy for the Primary Prevention of Cardiovascular Events Predicted by the Reynolds Risk Score in Healthy Men and Women Aged 40 to 80 Years of Age. Poster PCV 74, ISPOR 15th Annual International Conference, May 2010, Atlanta, GA.

82. Chang J, **Hay JW**. Cost Effectiveness Analysis of Anti-Epidermal Growth Factor Receptor (Anti-EGFR) Agents for Treatment Refractory Metastatic Colorectal Cancer (mCRC). Poster PCN 84, ISPOR 15th Annual International Conference, May 2010, Atlanta, GA.

83. **Hay JW**, Katon WJ, Ell K, Lee P-J, Guterman JJ. Cost Effectiveness Analysis of Collaborative Care Management of Major Depression among Low-Income, Predominantly Hispanics with Diabetes. Poster presentation at the ICMPE 10'th Workshop on Costs and Assessment in Psychiatry "Mental Health Policy and Economics " March 2011, Venice, Italy.

84. Unützer J, Dwight-Johnson, M, Apesoa-Varano C, **Hay JW**, Hinton L: Older men's preferences for depression care: Preliminary comparison of conjoint survey and qualitative interviews. American Association of Geriatric Psychiatry, March 18-21, 2011, San Antonio TX.

85. Yeung K, **Hay JW**. Cost-Utility Analysis of Romiplostim Versus Splenectomy In The Treatment Of Chronic Refractory Immune Thrombocytopenic Purpura. Poster presentation at the Academy of Managed Care Pharmacy 23'rd Annual Meeting, March 29, 2011 Minneapolis, MN.

86. Ejzykowicz F, **Hay JW**, Sarocco P, Karafilidis J, Walsh J. Hospitalizations, medical management and switch therapy patterns in the COPD Medicare population. Poster PRS 36, ISPOR 16th Annual International Conference, May 2011, Baltimore, MD.

87. Ding Y, **Hay JW**, Zangwill KM, Allred N, Yeh SH. Cost-benefit analysis of postpartum vaccination of birth mothers with influenza vaccine. Poster PIN 19, ISPOR 16th Annual International Conference, May 2011, Baltimore, MD.

88. Zhou Z-Y, **Hay JW**. A systematic review and meta-analysis comparing the efficacy of bypassing agents in hemophilia patients with inhibitors. XXIII Congress of the International Society on Thrombosis and Hemostasis, July 2011, Kyoto, Japan.

89. Ejzykowicz F, Rajagopalan K, Karafilidis J, **Hay JW**. Health Care Costs in a Medicare Population of COPD Patients Treated with Beta-Agonists. American Society of Health System Pharmacists Midyear Meeting, December 2011, New Orleans, LA.

90. Niu, X, **Hay JW**. Cost-Effectiveness Analysis of Nilotinib Versus Dasatinib In Patients with Imatinib-Resistant or Imatinib-Intolerant Chronic Myeloid Leukemia (CML). Poster PCN13, ISPOR 17th Annual International Conference, June 2012, Washington, DC.

91. Villacorta, R, **Hay JW**, Messali A. Cost Effectiveness of Treatment with Etanercept or Ustekinumab For Moderate To Severe Psoriasis. Poster PSY27, ISPOR 17th Annual International Conference, June 2012, Washington, DC.

92. Messali A, **Hay JW**, Villacorta, R. Cost-Effectiveness of Temozolomide in the Adjuvant Treatment of Newly Diagnosed Glioblastoma In the United States. Poster PCN78, ISPOR 17th Annual International Conference, June 2012, Washington, DC.

93. Chagule S, **Hay JW**. Cost Effectiveness of Cetuximab Plus Best Supportive Care (BSC) Versus BSC Alone in Last Line For Kras Wild Type Metastatic Colorectal Cancer Patient Population. Poster PCN64, ISPOR 17th Annual International Conference, June 2012, Washington, DC.

94. Jiang Y, **Hay JW**. Cost-Effectiveness of Denosumab v Alendronate for Prevention of Osteoporotic Fractures in the U.S. Poster PMS27, ISPOR 17th Annual International Conference, June 2012, Washington, DC.

95. Blaylock B, **Hay JW**, Zarchy T. Cost-Effectiveness of Diagnostic Sigmoidoscopy Before Colonoscopy in 40-49 Year-Old Symptomatic Patients. Poster PMD29, ISPOR 17th Annual International Conference, June 2012, Washington, DC.

96. Chaugule S, **Hay JW**. Bypass Therapy Assay Testing as a Strategy to Reduce Treatment Costs for Hemophilia Patients with Inhibitors. Poster PMD18, ISPOR 17th Annual International Conference, June 2012, Washington, DC.

97. Matsuda T, **Hay JW**. Cost-Effectiveness of Bariatric Surgery: Laparoscopic Gastric Bypass and Banding. Poster PSU24, ISPOR 17th Annual International Conference, June 2012, Washington, DC.

98. Ganapathy V, **Hay JW**, Smoot, KJ, Lawler, E, Weber, HC, Grotzinger, KM. Resource Utilization in Thrombocytopenia of Chronic Liver Diseases in the Veterans Affairs Population. Poster PGI14, ISPOR 17th Annual International Conference, June 2012, Washington, DC.

99. Ding Y, **Hay JW**, Zangwill K, Yeh S. Cost-Benefit Analysis of Hospital Based Postpartum Vaccination with Combined Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis Vaccine (Tdap). Poster PMD18, ISPOR 17th Annual International Conference, June 2012, Washington, DC.

100. Chaugule S, **Hay JW**, Young G. Bypass Therapy Assay Testing as a Strategy to Reduce Treatment Costs For Hemophilia Patients With Inhibitors. World Federation of Hemophilia, 2012 World Congress, June 2012, Paris, France.

101. Ding, Y, **Hay JW**, Zangwill, K, Yeh, S. Cost-Benefit Analysis of Hospital Based Postpartum Vaccination with Combined Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis Vaccine (TDAP). Western Pharmacoeconomics Conference, June 2012, Austin, TX.

102. Messali A, **Hay JW**, Villacorta, R. Probabilistic Sensitivity Analysis of the Cost-Effectiveness of Temozolomide in the Adjuvant Treatment of Newly Diagnosed Glioblastoma. Western Pharmacoeconomics Conference, June 2012, Austin, TX.

103. **Hay JW**. Cost Effectiveness Analysis With and Without Stochastic Uncertainty," American Society for Health Economics 4'th Biennial Conference, June 2012, Minneapolis, MN

104. Ejzykowicz F, Rajagopalan K, Bollu V, Karafilidis J, **Hay JW**. Effect of Long Acting Beta Agonist Therapy on Risk of Hospitalization in New Start COPD Patients. Abstract 265134. American Public Health Association 140'th Annual Meeting and Expo, October 29, 2012, San Francisco, CA.

105. Ni W, **Hay JW**, Zangwill K. Potential U.S. Medical Cost Savings Associated With Routine Hospital-Based Use Of A Rapid Diagnostic Tool For Bloodstream Infection. ISPOR 18th Annual International Conference, May 2013, New Orleans, LA.

106. Schwartz E, **Hay JW**. Modeling Diabetes Costs: a comparison of econometric methods using simulated error distributions. ISPOR 18th Annual International Conference, May 2013, New Orleans, LA.

107. Gu NY, Gai Y, Wu J, Raisch DW, **Hay JW**. Predicting healthcare costs in asthma using the EQ-5D health-related quality-of-life (HRQoL) index score with and without adjusting non-random positive spending using a US national representative population. 2nd International Allergen Symposium on Asthma & Economics, July 2013, Sydney, Australia.

108. **Hay JW**, Strylewicz G, Rothfeld A, Chesler R, Doctor J. Provider Preferences for Interventions for Reducing Inappropriate Antibiotic Prescribing. Accepted Podium Presentation, Health Care Applications: Sawtooth Software Conference, October 2013, Dana Point, CA.

109. Gu NY, Gai Y, Wu J, Raisch DW, **Hay JW**. Predicting Health Care Costs In Asthma Using The EQ-5D Index Score. ISPOR 16th Annual European Congress, 2-6 November 2013, Dublin, Ireland.

110. **Hay JW**, Oladapo AO, Epstein JD, Novack AR. Estimating the Potential Cost of Bypassing Agent Prophylaxis Relative to the Cost Of rFVIIa On-Demand Using Actual rFVIIa Doses From the UK NHD Registry. 7th Annual Congress of the European Association for Haemophilia and Allied Disorders, February 2014, Brussels, Belgium.

111. Linder JA, Meeker D, Friedberg MW, Persell SD, Fox CR, Goldstein NJ, Alan Rothfeld, **Hay JW**, Doctor JN. Improving Antibiotic Prescribing for Acute Respiratory Infections using Behavioral Economic Principles: A Cluster Randomized Trial. Society for General Internal Medicine 37'th Annual Meeting, April 2014, San Diego, CA.

112. Grosse SD, Chaugule S, **Hay JW**. Preference-based Measures of Health-related Quality of Life for Adults with Severe Hemophilia: Implications for the Cost-effectiveness of Prophylaxis. World Federation of Hemophilia 2014 World Congress, May 2014, Melbourne, Australia.

113. Chaugule S, Young G, **Hay JW**. Understanding how patients, physicians and the general population value different types of hemophilia therapies and their willingness-to-pay for such therapies: a discrete choice experiment from the US perspective. World Federation of Hemophilia 2014 World Congress, May 2014, Melbourne, Australia.

114. **Hay JW**, Oladapo AO, Epstein JD, Novack AR. Understanding how patients, physicians and the general population value different types of hemophilia therapies and their willingness-to-pay for such therapies: a discrete choice experiment from the US perspective. World Federation of Hemophilia 2014 World Congress, May 2014, Melbourne, Australia.

115. **Hay JW**, Oladapo AO, Epstein JD, Novack AR, Neufeld EJ. Estimating the potential cost of bypassing agent prophylaxis relative to the cost of rFVIIa on-demand using actual rFVIIa doses from multiple US registries. World Federation of Hemophilia 2014 World Congress, May 2014, Melbourne, Australia.

116. McGinnis JJ, **Hay JW**. Cost-Effectiveness of Hepatitis C Treatments in Treatment Naïve Genotype 1 Patients. ISPOR 19th Annual International Conference, May 2014, Montreal, Quebec, Canada.

117. Patel N, **Hay JW**. Management of Spinal Cord Injury-Associated Neuropathic Pain With Pregabalin is Cost-Effective Over Gabapentin. ISPOR 19th Annual International Conference, May 2014, Montreal, Quebec, Canada.

118. Gong C, **Hay JW**. Cost-Effectiveness Analysis of Abiraterone And Sipuleucel-T In Metastatic Castration-Resistant Prostate Cancer. ISPOR 19th Annual International Conference, May 2014, Montreal, Quebec, Canada.

119. Chaugule S, **Hay JW**. Understanding What Patients Value and Their Willingness-To-Pay (WTP) For Hemophilia Therapies: A Discrete Choice Experiment. ISPOR 19th Annual International Conference, May 2014, Montreal, Quebec, Canada.

120. Ding Yao, **Hay JW**. Economic Burden Associated With Patients Diagnosed With Peyronie's Disease in the United States. Poster Tuesday morning, PIH21. ISPOR 19th Annual International Conference, May 2014, Montreal, Quebec, Canada.

121. Ding Yuchen, **Hay JW**. Cost-Effectiveness Comparison of Denosumab and Zoledronic Acid in the Treatment of Postmenopausal Osteoporosis. Poster Monday morning, PMS36. ISPOR 19th Annual International Conference, May 2014, Montreal, Quebec, Canada.

122. Drabo E, **Hay JW**, Vardavas R, Wagner ZR, Sood N. A Cost-Effectiveness Analysis of Pre-Exposure Prophylaxis (Prep) for the Prevention of HIV in the Los Angeles MSM Population. Poster, Wednesday morning, PIN43. ISPOR 19th Annual International Conference, May 2014, Montreal, Quebec, Canada.

123. Chen C, **Hay JW**. Cost-Effectiveness Analysis of Alternative Screening and Treatment Strategies for Familial Hypercholesterolemia in the United States. Poster Monday afternoon, PCV70. ISPOR 19th Annual International Conference, May 2014, Montreal, Quebec, Canada.

124. Chu LH, **Hay JW**, Cohen DJ. A Hybrid Comparison of Cost-Effectiveness of Transcatheter Aortic Valve Replacement Between Randomized Clinical Trials and Real World Practice in Treating Patients With Severe Aortic Stenosis, Poster PCV69. ISPOR 19th Annual International Conference, May 2014, Montreal, Quebec, Canada.

125. Jiao X, **Hay JW**. Cost-Effectiveness of Breast MRI and Mammography for Screening High Risk Populations. Poster Tuesday morning, PHS55. ISPOR 19th Annual International Conference, May 2014, Montreal, Quebec, Canada.

126. Lin CW, **Hay JW**. Cost Utility Analysis of Aflibercept, Ranibizumab, and Bevacizumab for the Treatment of Neovascular Agerelated Macular Degeneration. Poster Wednesday morning, PSS23. ISPOR 19th Annual International Conference, May 2014, Montreal, Quebec, Canada.

127. Massachi S, **Hay JW**. Cost-Effectiveness of Various Clostridium Difficile Infection (CDI) Treatments in Patients with Recurrent Infections. Poster Wednesday morning, PIN50. ISPOR 19th Annual International Conference, May 2014, Montreal, Quebec, Canada.

128. Mehta D, **Hay JW**. Cost-Effectiveness of Adding Bevacizumab to First Line Therapy for Patients with Advanced Ovarian Cancer. ISPOR 19th Annual International Conf., May 2014, Montreal, Quebec, Canada.

129. Ni W, **Hay JW**, Zangwill K. Economics Analysis of Diagnostic Methods for Clostridium Difficile Infection. Poster, Wednesday morning, PIN58. ISPOR 19th Annual International Conference, May 2014, Montreal, Quebec, Canada.

130. Ning N, **Hay JW**. The Cost-Effectiveness of Liraglutide Vs Exenatide for the Treatment of Type 2 Diabetes In The United States. Poster, Wednesday morning, PDB78. ISPOR 19th Annual International Conference, May 2014, Montreal, Quebec, Canada.

131. Thompson CA, **Hay JW**. Evaluating the Impact of Cannabis Use on Metabolic Syndrome Using Data From the Continuous National Health and Nutrition Examination Survey, Poster Tuesday afternoon, PMH13. ISPOR 19th Annual International Conference, May 2014, Montreal, Quebec, Canada.

132. Zhang X, **Hay JW**. Cost-Effectiveness of Fingolimod, Teriflunomide, Dimethyl Fumarate and Intramuscular Interferon Beta-1a In Relapsing-Remitting Multiple Sclerosis. Poster, Monday Morning, PND20 . ISPOR 19th Annual International Conference, May 2014, Montreal, Quebec, Canada.

133. Jiao X, **Hay JW**. Cost-Effectiveness of Breast MRI and Mammography for Screening High Risk Populations. American Society for Health Economics 5'th Biennial Conference, June 2014, Los Angeles, CA.

134. Ding Yuchen, **Hay JW**. Cost-effectiveness Comparison between Generic zoledronic acid and denosumab (Prolia®) in the treatment of Postmenopausal Osteoporosis. American Society for Health Economics 5'th Biennial Conference, June 2014, Los Angeles, CA.

135. **Hay JW**. Behavioral Economics Interventions to Reduce Antibiotic Overprescribing. Organized Session, American Society for Health Economics 5'th Biennial Conference, June 2014, Los Angeles, CA.

136. **Hay JW**, Strylewicz G, Rothfeld A, Doctor J. Provider Preferences for Interventions for Reducing Inappropriate Antibiotic Prescribing. American Society for Health Economics 5'th Biennial Conference, June 2014, Los Angeles, CA.

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150. Drabo E, **Hay JW**. Rolling Out Oral Pre-Exposure Prophylaxis (Prep) is a Cost-Effective HIV Prevention Strategy Among Los Angeles County (LAC) Men Who Have Sex With Men (MSM). Poster PIN54 Tuesday, May 19, 2015. ISPOR 20th Annual International Meeting, May 16-20, 2015; Philadelphia, PA.

151. McGinnis JJ, **Hay JW**. The Cost Effectiveness of a Novel High Priced Combination Therapy For Hepatitis C in Treatment Naïve Genotype 1 Infected Patients. Poster PIN65 Tuesday, May 19, 2015. ISPOR 20th Annual International Meeting, May 16-20, 2015; Philadelphia, PA.

152. Han X, **Hay JW**. Cost-Effectiveness Analysis of Certolizumab, Etanercept, Golimumab and Tofacitinib for the Treatment of Moderately to Severely Active Rheumatoid Arthritis. Poster PMS52 Tuesday, May 19, 2015. ISPOR 20th Annual International Meeting, May 16-20, 2015; Philadelphia, PA.

153. Chaugule S, **Hay JW**. Does Differential Framing of Opt-Out Alternatives in Discrete Choice Experiments (DCES) Matter? Comparison of Random Utility Maximization (RUM) and Random Regret Minimization (RRM) Models. Poster PRM85 Monday, May 18, 2015. ISPOR 20th Annual International Meeting, May 16-20, 2015; Philadelphia, PA.

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172. Gong C, **Hay JW**, Zangwill K, Meeker D, Doctor JN. The Use of Behavioral Economics and Social Psychology to Improve Treatment of Acute Respiratory Infections (BEARI): A Cost-Effectiveness Analysis. Poster PRS24. ISPOR 22'st Annual International Meeting, May 20-24, 2017, Boston, MA.

173. Cohen B, **Hay JW**, Barzi A, Cost-Effectiveness of Short-Course vs. Long-Course Treatment for Stage III Rectal Cancer. Invited Podium Presentation, Western Pharmacoeconomics & Outcomes Research Conference, University of New Mexico, October 4, 2017, Albuquerque, NM.

174. Aliyev E, **Hay JW**. Cost-effectiveness of ustekinumab in adult patients with moderate-severe Crohn's disease (conventional therapy failure and tumor necrosis factor naïve population). Invited Poster Presentation, Western Pharmacoeconomics & Outcomes Research Conference, University of New Mexico, October 4, 2017, Albuquerque, NM.

175. Kim J, **Hay JW**. Cost-Effectiveness Analysis of Regorafenib In Patients with Advanced Hepatocellular Carcinoma. Invited Poster Presentation, Western Pharmacoeconomics & Outcomes Research Conference, University of New Mexico, October 4, 2017, Albuquerque, NM.

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178. Cho S, **Hay JW**. Cost-Effectiveness of Stivarga (Regorafenib) vs. Lonsurf (Trifluridine/Tipiracil) in Refractory Metastatic Colorectal Cancer. Invited Poster Presentation, Western Pharmacoeconomics & Outcomes Research Conference, University of New Mexico, October 4, 2017, Albuquerque, NM.

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180. Bae Y, **Hay JW**. The cost effectiveness analysis of pd-1 and pd-l1 agents compared with docetaxel for second-line treatment of advanced non-small cell lung cancer. Invited Poster Presentation, Western Pharmacoeconomics & Outcomes Research Conference, University of New Mexico, October 4, 2017, Albuquerque, NM.

181. **Hay JW**, Le Q, Wang Y. Cost-Effectiveness of Abaloparatide vs. Teriparatide for Prevention of Osteoporosis-related Fracture: a US Payer Perspective. Invited Poster Presentation AMCP Nexus Conference, October 16-19, Dallas, TX.

182. Mahajerin A, Formica M, **Hay JW**. Cost Analyses of Pediatric Thrombophilia Testing: A report from the Children's Hospital-Acquired Thrombosis Registry. Thrombosis and Hemostasis Societies of North America 4th Biennial Summit, March 8-10, 2018, San Diego, CA.

183. Aliyev E, **Hay JW**, Hwang C. The Cost-Effectiveness of Ustekinumab Compared to Infliximab and Adalimumab in Adult Patients with Moderate-Severe Crohn's Disease (TNF Naïve Population). Research Poster Presentations - Session IV, PGI17: Gastrointestinal Disorders Tuesday, May 22, 2018. ISPOR 23rd Annual International Meeting, May 19-23, 2018, Baltimore, MD.

184. Bae Y, **Hay JW**. The Cost Effectiveness Analysis of PD-1 And PD-L1 Agents Compared with Docetaxel for Second-Line Treatment of Advanced Non-Small Cell Lung Cancer. Research Poster Presentations - Session IV, PCN114 Cancer, Tuesday, May 22, 2018 3:30 PM - 7:30 PM. ISPOR 23rd Annual International Meeting, May 19-23, 2018, Baltimore, MD.

185. Kim J, **Hay JW**. Cost-Effectiveness Analysis of Regorafenib In Patients with Advanced Hepatocellular Carcinoma. Research Poster Presentations - Session IV, PCN107 Cancer, Tuesday, May 22, 2018 3:30 PM - 7:30 PM. ISPOR 23rd Annual International Meeting, May 19-23, 2018, Baltimore, MD.

186. Lam J, **Hay JW**, Salcedo J, Kenyon NJ. An Evaluation of the Cost-Effectiveness of Reslizumab in Poorly Controlled Eosinophilic Asthma. Research Poster Presentations - Session II, PRS29: Respiratory-Related Disorders Monday, May 21, 2018 3:30 PM - 7:30 PM. ISPOR 23rd Annual International Meeting, May 19-23, 2018, Baltimore, MD.

187. Salcedo J, **Hay JW**, Lam J. Cost-Effectiveness of Rivaroxaban Versus Warfarin for Treatment of Nonvalvular Atrial Fibrillation in Patients with Worsening Renal Function. Research Poster Presentations - Session I, PCV49: Cardiovascular Disorders Monday, May 21, 2018 8:30 AM - 2:00 PM. ISPOR 23rd Annual International Meeting, May 19-23, 2018, Baltimore, MD.

188. Innis B, **Hay JW**. Cost Effectiveness Analysis of Evolocumab, a PCSK9 Inhibitor, From the US Societal Perspective. Research Poster Presentations - Session I, PCV46: Cardiovascular Disorders Monday, May 21, 2018 8:30 AM - 2:00 PM. ISPOR 23rd Annual International Meeting, May 19-23, 2018, Baltimore, MD.

189. Cho S, **Hay JW**, Barzi A. Cost-Effectiveness Analysis of Regorafenib and TAS-102 in Refractory Metastatic Colorectal Cancer. Podium Presentation Breakout Session P1: Cost-Effectiveness Studies Monday, May 21, 2018 11:00 AM - 12:00 PM. ISPOR 23rd Annual International Meeting, May 19-23, 2018, Baltimore, MD.

190. Cohen B, **Hay JW**, Barzi A. Cost-Effectiveness of Short-Course Radiotherapy Compared to Long-Course Chemoradiotherapy in the Treatment of Stage III Rectal Cancer Patients from the US Societal Perspective. Research Poster Presentations - SESSION IV PCN129: Cancer Tuesday, May 22, 2018 3:30 PM - 7:30 PM. ISPOR 23rd Annual International Meeting, May 19-23, 2018, Baltimore, MD.

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192. Gong C, Dasgupta-Tsinikas S, Zangwill K, Bolaris M, **Hay JW**. Risk-Based Management of Newborns Exposed to Maternal Intrapartum Fever: A Cost Benefit Analysis. ISPOR 23rd Annual International Meeting, May 19-23, 2018, Baltimore, MD.

193. Barzi A, Jiao X, **Hay JW**, Sadeghi S. Outcomes and utilization of adjuvant chemotherapy (AT) for stage II colon cancer (CC-II) in elderly population. 2019 Gastrointestinal Cancers Symposium (January 17-19, 2019), San Francisco, CA.

194. Salcedo J, Schmaltz C, **Hay JW**, Summers L. The Case for The Inclusion of Human Milk into Georgia State's Medicaid Reimbursement Structure: A Budget Impact Analysis. Poster PIH27: Individual's Health, Monday, May 20, 2019 3:30 PM - 7:00 PM. ISPOR 24th Annual International Meeting, May 21-23, 2019, New Orleans, LA.

195. Zawadzki NK, **Hay JW**, Ahmed CD, Myers K, Gidding S. Cost-Effectiveness of Screening and Management Strategies for Familial Hypercholesterolemia in the United States: An Update. Poster PPM3, Session V PPM: Personalized & Precision Medicine, Wednesday, May 22, 2019 9:30 AM - 2:00 PM. ISPOR 24th Annual International Meeting, May 21-23, 2019, New Orleans, LA.

196. Yu A, **Hay JW**, Zangwill KM. Post-Operative Antibiotic Cost Project: Discontinuation of Antimicrobial Prophylaxis After Surgical Incision Closure. Poster PIN40: Infectious Diseases Tuesday, May 21, 2019 10:30 AM - 2:00 PM. ISPOR 24th Annual International Meeting, May 21-23, 2019, New Orleans, LA.

198. Cho SK, Barzi A, **Hay JW**, Lenz H-J, Ou F-S, Grothey A, Bekaii-Saab TS.Cost-effectiveness of Regorafenib Dose Optimization Schedule in Metastatic Colorectal Cancer. Abstract #269045. ASCO Annual Meeting, June 1-4, Chicago, IL.

199. Barzi A, Xiayu J, Hay JW, Sadeghi S. Total cost of care for patients (pts) with stage II colon cancer (CC-II): a SEER-Medicare analysis. Abstract #272093. ASCO Annual Meeting, June 1-4, Chicago, IL.

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International Journal of the Economics of Business Guest Editor, Special Issue: Commemorating William S. Comanor and 50 Years of Pharmaceutical Economics	2014-2015

JOURNAL REFEREE

Advances in Therapy, AIDS, American Journal of Cardiology, American Economic Review, American Heart Journal, American Journal of Health Economics, American Journal of Managed Care, American Journal of Managed Care and Specialty Pharmacy, American Journal of Public Health, Annals of Pharmacotherapy, Annals of the Rheumatic Diseases, Applied Health Economics and Health Policy, Archives of Pediatrics and Adolescent Medicine, BioDrugs, Blood, BMC Medicine, BMC Health Services Research, BMJ, Breastfeeding Medicine, Canadian Journal of Diabetes, Cancer, Cardiovascular Drugs and Therapy, Chest, Clinical Drug Investigation, Clinical Pharmacokinetics, Clinical Therapeutics, ClinicoEconomics and Outcomes Research, CNS Drugs, Consultant, Critical Care, Current Medical Research and Opinion, Drugs and Aging, Eastern Economic Journal, Econometric Reviews, Epilepsia, European Journal of Health Economics, Evaluation and Expert Opinion on Pharmacotherapy, Expert Opinion on Therapeutic Patents, Expert Review of Pharmacoeconomics and Outcomes Research, Farmeconomia: Health Economics and Therapeutic Pathways, Gerontology, Health Affairs, Health Care Financing Review, Health Economics, Health Professions, Health and Quality of Life Outcomes, International Journal of the Economics of Business, JAMA, Journal of Adolescent Health, Journal of Affective Disorders, Journal of Alzheimer Disease, Journal of the American Statistical Association, Journal of Applied Econometrics, Journal of Cardiovascular Pharmacology and Therapeutics, Journal of Chemotherapy, Journal of Clinical and Experimental Oncology, Journal of Clinical Medicine, Journal of Econometrics, Journal of Environmental Management, Journal of Epidemiology and Community Health, Journal of Gerontology: Social Sciences, Journal of Health Care for the Poor and Underserved, Journal of Health Politics, Policy and Law, Journal of Human Resources, Journal of Managed Care Pharmacy, Journal of Managed Care and Specialty Pharmacy, Journal of Medical Economics, Journal of Medical Education, Journal of Medical Internet Research, Journal of Pain Research, Journal of Perinatology, Journal of Public Economics, Journal of Public Health Dentistry, Medical Care, Medical Decision Making, Milbank Memorial Fund Quarterly, Nature Reviews Drug Discovery, New England Journal of Medicine, Obstetrics & Gynecology, Pediatric Drugs, Pediatrics, PharmacoEconomics, Priorities, Research in Population Economics, Research in Social and Administrative Pharmacy, Review of Economics and Statistics, Social Science and Medicine, SciTechnol, Social Science Journal, Southern Economic Journal, Statistica Sinica, Topics in Hospital Pharmacy Management, Vaccine, Value in Health.

BOOK MANUSCRIPT REFEREE:

2006 Lisa Gordon
Editorial Assistant
Jones and Bartlett Publishers

SCIENTIFIC CONFERENCE ORGANIZATION AND DEVELOPMENT

1996-1998 Co-Chair and Primary Organizer: ISPOR Lipid Pharmacoeconomics Conference. Orlando, FL.

2001-2003 International Health Economics Association 4th World Congress, San Francisco; Local Organizing Committee Member

2004-2005	Scientific Track Evaluation Panel; Disease Management Association of America Annual Conference. Orlando, FL.
2005	Scientific Advisory Committee, Third NIMH Pharmacoeconomics Workshop: MMA03 and Psychotropic Medications
2007	American Society of Health Economics Meeting Organizer, Duke University, Durham, NC.
2009	Western Pharmacoeconomics Conference: Decision Tools for the Health Care Puzzle, Co-Chair and Meeting Organizer; Pasadena CA.
2014	American Society of Health Economists: 4'th Biannual Conference, USC, Los Angeles, CA.
2015	Conference on a Half-Century of Pharmaceutical Economics, University of British Columbia, Vancouver, BC, Canada.
2016-17	Conference Co-Chair, International Academy of Health Preference Research (iahpr.org) North American Conference, Boston, MA.

MEDIA APPEARANCES

October 1989 Time Magazine: "A Recount of AIDS Carriers." Article about J Hay's back calculation model for estimating the number of people infected with HIV/AIDS. October 9, 1989; pg. 103.

June 1992 "Should Marijuana Be Legalized for Medicinal Purposes?" The Dr. Dean Show, NBC, San Francisco.

November 1992 "Prescription Drug Price Inflation: What Should Be Done?" Seniors Speak Out, KPBS, San Diego.

September 1993 "Health Care Reform: Access and Cost" syndicated Public Television show.

June 1994 "Heterosexual AIDS," Diane Crowe/Chuck Whitten Show, KAVL, Lancaster, CA.

September 1994 "Heterosexual AIDS," The Dennis Praeger TV Show, Los Angeles, CA.

October 1994 "Bias in Official Government Projections of HIV/AIDS," FOX Television News Service, New York, NY.

January-March 1995 "Clinicoeconomics" Annenberg Center at Eisenhower Three Part Television Series written by and featuring Joel W. Hay Ph.D., Producer, Chuck Cox. Part 1: Principles of Clinicoeconomics; Part 2: The Outcomes Revolution--Measuring Health Related Quality of Life; Part 3: Practice Variation and Medical Guidelines Development. Rancho Mirage, CA.

September 2000 "Cost Effectiveness of Statins." International Task Force for Prevention of Coronary Heart Disease. Consensus on Statins Conference Webcast: www.chd-taskforce.com

May 2001 "Economic Considerations in Moving Second-generation Antihistamines from Prescription to OTC Status," CNN Headline News interview.

May 2001 "Economics of RU-481." Los Angeles Times interview.

April 2002 "Pharmacy Workforce Effects of Converting from the California to the National Pharmacy Licensure Examination." San Jose Mercury News interview.

December 2002 "National Issues Briefing To Examine Rising Hospital Costs," Washington Press Club Seminar covered by CSPAN http://www.kaisernetwork.org/healthcast/usnews/bcbs/02dec2002 .

October 2005 "Drug Safety in the Aftermath of Vioxx." Investors Business Daily interview.

January 2007	"Democratic Medicare drug plan poised to pass House," McClatchy Newspapers, http://www.mercurynews.com/mld/mercurynews/news/politics/16393085.htm.
January 2007	"House Passes Bill to Require Medicare Part D Price Negotiations". Lou Dobbs Show, CNN.
January 2007	"House Passes Bill to Require Medicare Part D Price Negotiations". Business & Media Institute (http://www.businessandmedia.org/articles/2007/20070112164308.aspx).
January 2007	"Pharmaceutical Industry Profitability, " Investors Business Daily interview.
April 2008	"Merck, Schering Keep Taking Heat For Vytorin Flub." Investors Business Daily interview.
November 2008	"Impact of CVS Generic Drug Pricing Plan." NBC Today Show.
November 2008	"Generic Drug Price Competition." KNBC Evening News.
November 2008	"Gains by Democrats Put Pharma On Edge" Investor's Business Daily interview.
March 2009	J Hay quotations in "Can Marijuana Help Rescue California's Economy?" By Alison Stateman Time Online, March 13, 2009; http://www.time.com/time/nation/article/0,8599,1884956,00.html
July 2009	J Hay interview with Marc Brown on legalizing marijuana KABC TV Channel 7 Evening News. July 28 and July 29, 2009.
July 2009	J Hay interview with Nicole Busch on value of health co-op plans in the health insurance reform legislation. Fox News, July 31, 2009.
August 2009	J Hay interview on KCBS radio newsmaker show: Why marijuana shouldn't be legalized. KCBS August 2.
August 2009	J Hay interview on KNBC-TV Sunday LA, August 2. Why marijuana shouldn't be legalized.
August 2009	J Hay interview on Montel Williams Across America, August 5. Why marijuana shouldn't be legalized.
August 2009	J Hay interview on KCBS Radio news: Should new federal laws be passed to protect pharmacy prescription information from commercial data vendors? August 19.
October 2009	J Hay interview on KCBS Radio news: Medical Marijuana Dispensaries. October 19.

October 2009	Panel discussion on Medical Marijuana and Marijuana Legalization. The Michael Krazny Show, KQED Radio, October 20.
December 2009	J Hay interview on KCBS Radio news: Marijuana Legalization in California, December 18.
December 2009	J Hay interview by Reuters News: Marijuana Legalization in California, December 18.
January 2010	"Recent Advances in Otolaryngology," (www.audio-digest.org).
February 2010	J Hay interview on University of California media release on medical marijuana studies. February 18. http://www.webmd.com/pain-management/news/20100218/medical-marijuana-has-merit-research-shows?page=2
March 2010	J Hay interview on Federal Restrictions on Cost Effectiveness Analysis, NPR's Marketplace; http://marketplace.publicradio.org/display/web/2010/03/16/pm-health-care-costs/#
March 2010	"Orphan Drug Market Catches Pharma's Eye." Investors Business Daily quotes from J Hay.
July 2010	"Bright Future Seen For Vaccine Research." Investors Business Daily quotes from J Hay.
August 2010	"Walgren's Flu Vaccine Gift Cards Don't Make Sense," Interview on KCBS Radio, San Francisco, CA 8/17/10.
September 2010	"Will Drugmakers' Fight To Defer Generics Hit Supreme Court?" Investors Business Daily quotes from J Hay.
November 2010	"Genentech Catching Some Heat For Pushing Expensive Eye Drug," Investors Business Daily quotes from J Hay.
March 2011	"Medical Marijuana Deters Legitimate Medical Cannabinoids" March 13, 2011 Felice J. Freyer, Rhode Island News. http://www.projo.com/news/content/THC_03-13-11_RMMUHVQ_v16.15cf632.html#
April 2011	"Medicare on the table." Marketplace show, NPR 4-13-11, Gregory Warner, http://marketplace.publicradio.org/display/web/2011/04/13/pm-medicare-on-the-table/
June 2011	"World Have Your Say: What would the world look like if all drugs were legalised?" BBC World Service, http://www.bbc.co.uk/programmes/p00gx5gq

August 2011 "Expert Discussion: Prescription For Pot—A Debate on the Merits of Medical Marijuana," MD Magazine: Peers & Perspectives: The Physician's Authority for Debate & Exchange. Podcast.

December 2011 "Lipitor's patent loss is consumers' gain," quotes from J Hay. Los Angeles Times, December 1, 2011.

January 2012 "Excedrin, Gas-X and other Novartis drugs recalled," radio quotes from J Hay. Marketplace Morning Report, American Public Media, January 9, 2012. http://www.marketplace.org/topics/business/health-care/excedrin-gas-x-and-other-novartis-drugs-recalled

January 2012 "FDA: Novartis Recall May Also Affect Painkillers," video quotes from J Hay. AP Video, January 9, 2012. http://youtu.be/dttrjWA_Sn0

March 2012 "Individual mandate under review in Supreme Court," Marketplace show, NPR 3-27-12, Amy Scott, http://www.marketplace.org/topics/economy/health-care/individual-mandate-under-review-supreme-court

June 2012 "Health care reform trajectory won't be stopped by Supreme Court ruling," Southern California Public Radio 6-7-12. http://www.scpr.org/news/2012/06/07/32713/health-care-reform-trajectory-wont-be-stopped/

August 2012 Comment on "As circumcision declines, health costs will go up, study projects," Los Angeles Times, August 21, 2012. http://www.latimes.com/news/science/la-sci-circumcision-health-costs-20120821,0,6266293,print.story

August 2012 Comment on "Study claims decline in circumcision will lead to increase in STDs." Larry Mantle Airtalk, Southern California Public Radio 8-21-12. http://www.scpr.org/programs/airtalk/2012/08/21/27999/study-circumcisions-numbers-drop-std-increase-sex/

August 2012 Comment on "Walmart arms itself with vaccines," NPR Marketplace Morning Report. 8-23-12. http://www.marketplace.org/topics/business/health-care/walmart-arms-itself-vaccines

April 2013 Comment on "Students discuss usefulness of marijuana legalization," USC Daily Trojan, April 9, 2013. http://dailytrojan.com/2013/04/09/students-discuss-usefulness-of-marijuana-legalization/

November 2013 Comment on "Widespread confusion over flu shot insurance benefits," Los Angeles Times, November 7, 2013. http://www.latimes.com/business/la-fi-lazarus-20131101,0,1800506,full.column#axzz2jPZ7iJpn

July 2014	Comment on "Does neurology need a faster FDA?" Lancet Neurology, Vol 13 August 2014; pp. 760-61. www.thelancet.com/neurology
October 2014	Comment on "Why there is no ebola vaccine," NPR Marketplace, October 1, 2014. http://www.marketplace.org/topics/health-care/why-there-no-ebola-vaccine
October 2014	Comment on "Economics of Ebola Vaccine," NPR Marketplace, October 22, 2014. http://www.marketplace.org/topics/health-care/economics-behind-rush-ebola-vaccine
October 2014	Comment on "Big pharma collaborates on Ebola vaccine," Australian Broadcast Company radio interview, October 24, 2014. http://www.abc.net.au/am/content/2014/s4113595.htm
May 2015	Comment on "CVS seeks to buy Omnicare," Marketplace, American Public Media and National Public Radio May 21, 2015. http://www.marketplace.org/topics/business/cvs-seeks-buy-omnicare
September 2015	Comment on "Doctor's attempt to bring lower-price diabetes drug to market thwarted," Los Angeles Times, September 4, 2015. http://www.latimes.com/business/la-fi-lazarus-20150904-column.html
September 2015	"Daraprim Drug Price Hike," Top of Mind with Julie Rose, BYU Radio, September 24, 2015. http://www.byuradio.org/show/e9a84fc9-4bb1-476f-bd5d-0e907b754af8/top-of-mind-with-julie-rose; http://www.byuradio.org/episode/5f014c3f-9e8e-452d-8c30-ba3100d70490?playhead=65&autoplay=true
December 2015	"Drug Pricing and Pharmacies," Top of Mind with Julie Rose, BYU Radio, December 16, 2015. http://www.byuradio.org/episode/80489567-65f0-4c8e-a6b1-bff75c6f2e3f?playhead=63&autoplay=true
January 2016	Comment on "Afrezza patients worry they'll lose access to their insulin," Los Angeles Times, January 8, 2016. http://www.latimes.com/business/la-fi-afrezza-patients-20160108-story.html
January 2016	Comment on "The obscurity of drug spending in Medi-Cal: What do you want to know about State spending on high-cost drugs?" Pauline Bartalone, www.calmatters.org. https://medium.com/california-s-legal-drug-dilemma/the-obscurity-of-drug-spending-in-medi-cal-4ccf1df97392#.v1rgwujib
February 2016	Comment on "The other 'high-cost' drugs: What specialty drugs mean for California." Pauline Bartalone, www.calmatters.org. https://medium.com/california-s-legal-drug-dilemma/the-other-high-cost-drugs-what-specialty-drugs-mean-for-california-df18ddf1e632#.ydyg7zybx

February 2016 Comment on "High Costs For Drugs Used By A Few Are Starting To Add Up," Shots: NPR Health News, http://www.npr.org/sections/health-shots/2016/02/05/465699654/high-costs-for-drugs-used-by-a-few-are-starting-to-add-up

March 2016 Comment on "Voter anger over surging prescription drug costs has generated a campaign issue," Los Angeles Times, March 11, 2016. http://www.latimes.com/politics/la-na-florida-campaign-drug-prices-20160311-story.html

April 2016 Comment on "What's California's prescription for rising drug costs?" Pauline Bartalone, www.calmatters.org. https://calmatters.org/articles/california-takes-measures-to-control-drug-spending-but-costs-soar/

May 2016 Comment on "How Big Pharma Uses Charity Programs to Cover for Drug Price Hikes," Benjamin Elgin, Robert Langreth, Bloomberg Business Week, May 21, 2016. http://www.bloomberg.com/news/articles/2016-05-19/the-real-reason-big-pharma-wants-to-help-pay-for-your-prescription

June 2016 Comment on "U.S. regulator says too many drugmakers chasing same cancer strategy," Reuters, June 14, 2016. http://finance.yahoo.com/news/u-regulator-says-too-many-204549726.html

June 2016 Comment on "Pharma: an industry shaped by shareholder value," Marketplace, American Public Media, June 15, 2016. http://www.marketplace.org/2016/06/08/world/profit-pharma

June 2016 Comment on "Medi-Cal To Spend Nearly $1 Billion On Hepatitis C Drugs Next Year," California Healthline, California Healthcare Foundation, June 21, 2016. http://californiahealthline.org/news/medi-cal-to-spend-nearly-1-billion-on-hepatitis-c-drugs-next-year/

September 2016 Comment on "MannKind developing inhalable epinephrine to challenge Mylan's EpiPen," Los Angeles Times, September 6, 2016. http://www.latimes.com/business/la-fi-mannkind-epipen-20160901-snap-story.html

November 2016 Comment on "Soon adults in California could get a joint delivered faster than a pizza," CBC World November 12, 2016. http://www.cbc.ca/news/world/soon-adults-in-california-could-get-a-joint-delivered-faster-than-a-pizza-1.3848121

November 2016. Comment on "Impacts of Marijuana Legalization for Recreational Purposes in California," The Larry Fedoruk Show, CKTB Radio, November 14, 2016. http://www.iheartradio.ca/610cktb/shows/the-larry-fedoruk-show-1.1816268

February 2017	Comment on "Drug Firm Payouts Under Scrutiny," Boston Herald, February 12, 2017. http://www.bostonherald.com/business/business_markets/2017/02/drug_firm_payouts_under_scrutiny
March 2017	Comment on "Pompe Drug Lauded by Trump Costs $300,000 a Year," New York Times, March 1, 2017. https://www.nytimes.com/reuters/2017/03/01/world/europe/01reuters-usa-trump-drugpricing.html?_r=2
March 2017	Comment on "Patient advocacy groups raking in pharmaceutical dollars, USA Today, March 1, 2017. http://www.usatoday.com/story/news/2017/03/01/patient-advocacy-groups-pharmaceutical-dollars/98593458/
April 2017	Discussion of Joel Hay's Health Reform Proposal "Grasping For The Middle Ground On Obamacare." California Healthline, California Health Care Foundation, April 14, 2017. http://californiahealthline.org/news/grasping-for-the-middle-ground-on-obamacare/
May 2017	Comment on "Amazon would be a disruptor if it sold prescriptions," NPR Marketplace, American Public Media, May 17, 2017. https://www.marketplace.org/2017/05/17/business/amazon-would-be-disruptor-if-it-sold-prescriptions
August 2017	Comment on "If Trump wanted, he could take steps to lower soaring drug prices." David Lazarus, Los Angeles Times, August 1, 2017. http://www.latimes.com/business/lazarus/la-fi-lazarus-drug-price-caps-20170801-story.html
December 2017	Comment on "Less choice, higher prices feared in CVS' takeover of health insurer Aetna." David Lazarus, Los Angeles Times, December 4, 2017. http://www.latimes.com/business/lazarus/la-fi-lazarus-phone-fees-20171205-story.html
February 2018	Comment on "Trump once again vows to lower drug prices, and once again you shouldn't believe him." David Lazarus, Los Angeles Times, February 1, 2018 http://www.latimes.com/business/lazarus/la-fi-lazarus-sotu-trump-drug-prices-20180201-story.html
March 2018	Documentary contributor, "Do No Harm: The Opioid Epidemic Media Project. Narrated by Ed Harris." 4-minute promo. https://vimeo.com/245499897 Available on Amazon Prime, Google Play, iTunes and Vimeo.
May 2018	Radio Interview on "California bill to provide MediCal to all adults, regardless of immigration status," Air Talk with Larry Mantle, KPCC NPR Radio, May 22, 2018. https://www.scpr.org/programs/airtalk/2018/05/22/63062/california-bill-to-provide-medicaid-to-all-adults/

May 2018	Comment on "Pfizer Settles Kickback Case Related To Copay Assistance For $24M," Kaiser Health News, May 24, 2018. https://khn.org/news/pfizer-settles-kickback-case-related-to-copay-assistance-for-24m/
June 2018	Comment on "The FDA Approves the First Drug Derived from Cannabis," American Public Media and National Public Radio June 28, 2018. https://www.marketplace.org/2018/06/25/health-care/fda-considers-approval-drug-cannabis
September 2018	Comment on "When your prescription drug is tainted with a chemical 'used to make rocket fuel'." David Lazarus, Los Angeles Times, September 7, 2018. http://www.latimes.com/business/lazarus/la-fi-lazarus-contaminated-prescription-drugs-20180907-story.html
November 2018	Comment on "Drug giant Pfizer says it will return to 'business as normal,' which means price hikes." David Lazarus, Los Angeles Times, November 2, 2018. http://www.latimes.com/business/lazarus/la-fi-lazarus-drug-prices-pfizer-trump-20181102-story.html
December 2018	Expert appearance and documentary contributor in "DRUG$: THE PRICE WE PAY." Streaming 12/15/18 on Amazon and Youtube. Facebook Trailer: https://www.facebook.com/foxhoundproductions/videos/377465329490173/ Website - www.drugsthefilm.com
January 2019	Comment on "For drug companies, making shareholders happy is more important than treating the sick." David Lazarus, Los Angeles Times, January 8, 2019. https://www.latimes.com/business/lazarus/la-fi-lazarus-lilly-loxo-drug-prices-20190108-story.html
March 2019	Comment on "Lilly unveils a 'generic' insulin and shows how broken our healthcare system really is." David Lazarus, Los Angeles Times, March 6, 2019. https://www.latimes.com/business/lazarus/la-fi-lazarus-healthcare-lilly-insulin-prices-20190308-story.html

PUBLIC HEARING TESTIMONY & PRESENTATIONS

December 1985	"The cost implications of adding Ranitidine to the Medi-Cal Drug Formulary," Medi-Cal Drug and Therapeutics Advisory Commission Hearings, California Department of Health Services, Sacramento, CA.
April 1987	"Cost-Benefit evaluation of Haemophilus influenzae type b capsular polysaccharide vaccine," FDA Workshop on Haemophilus b Polysaccharide Vaccine, US Food and Drug Administration, Rockville, MD.
January 1990	"AIDS Case Projections for California," California AIDS Leadership Committee, California Department of Health Services, Los Angeles County, CA.
August 1990	"A Comparative Analysis of CDC and Other HIV/AIDS Projections and Recent (1990) Regional Cost Projections for California," Northern California Integrated Planning Project: HIV Epidemiology Task Force, Sacramento AIDS Foundation, Sacramento, CA.
September 1991	"Cost-Effectiveness Issues in Cholesterol Treatment of Coronary Artery Disease," Panel on Adult Treatment Guidelines for Established Coronary Artery Disease; the National Institutes of Health, National Heart, Lung and Blood Institute and the American Heart Association, Washington, D.C.
July 1992	"Research and Demonstration Waiver Request for Kaiser-Permanente Enhanced Pharmacy Services Project," California State Board of Pharmacy, Burlingame, CA.
January 1994	"The Impact of the Clinton Health Care Reforms on Small Business," Congressional Testimony held at Diamond Bar, California at the invitation of Hon. Jay Kim, U.S. House of Representatives.
November 1996	"The cost effectiveness of Pravastatin and the Medi-Cal Drug Formulary," Medi-Cal Drug Program, California Department of Health Services, Sacramento, CA.
May 2001	"Economic Considerations in Moving Second-generation Antihistamines from Prescription to OTC Status," presentation to the US Food and Drug Administration Committee on Non-Prescription Drugs, Gaithersburg, MD.
March 2002	"Pharmacy Workforce Effects of Converting from the California to the National Pharmacy Licensure Examination." Presentation to the California Assembly on AB 2165, Sacramento, CA.

February 2010 "Cost-effectiveness of An Exclusively Human-Milk Based Diet Vs. Bovine-Milk Based Diet In The Prevention of Necrotizing Enterocolitis Among Extremely Premature Medicaid Infants (Gestation Age < 28 weeks)" Presentation to the Texas Medicaid Drug Utilization Review Program, Austin, TX.

February 2012 "Competition Issues in the Pharmaceutical Benefits Manager (PBM) Market," Presentation to the Federal Trade Commission Bureau of Economics and the State Attorneys General Task Force on PBM Market Issues, Washington, DC.

CONFERENCES & PRESENTATIONS SINCE 1997

February 1998	"Methodological Issues in Conducting Pharmacoeconomic Evaluation—Modeling Studies," Panel Co-Chair. ISPOR Pharmacoeconomic Guidelines Consensus Development Conference. Crystal City, VA.
May 1998	"Lipid Therapy Cost Effectiveness: Are All Statins Equivalent?" Invited Plenary Session, Association of Managed Care Pharmacy Annual Meeting, Philadelphia, PA.
May 1998	"Alzheimer Disease Pharmacoeconomic Issues," Invited Session, Association of Managed Care Pharmacy Annual Meeting, Philadelphia, PA.
May 1998	"Hong Kong Health Care Reform," Harvard School of Public Health, Cambridge, MA.
June 1998	"Mortality and Hospital Utilization Differences in the Kaiser/USC Pharmaceutical Care Intervention Study," University of Florida College of Pharmacy, Gainesville, FL.
July 1998	"Alzheimer Disease Pharmacoeconomics," Invited Session, First International Conference on Alzheimer Disease Pharmacoeconomics, Amsterdam, Netherlands.
October 1998	"The Future of Pharmacy," Pharmacy Practice Research Roundtable Conference, San Diego, CA.
October 1998	"Lipid Therapy Cost Effectiveness," Calif. Society Health Systems Pharmacy, Anaheim, CA.
December 1998	"The US Pharmacoeconomic Methods Consensus Guidelines," ISPOR First Annual European Conference, Cologne, Germany.
March 1999	"Lipid Therapy Costs and Outcomes," New York University Department of Cardiology Grand Rounds, New York, NY.
April 1999	"Drug Patents and R&D Protection." The Wallace Lectureship, Idaho State University School of Pharmacy. Pocatello, ID.
April 1999	"Survival and Hospitalization in the Kaiser/USC Pharmaceutical Care Demonstration Project." The Wallace Lectureship, Idaho State Univ. School of Pharmacy. Boise, ID.
May 1999	"Cost Effectiveness Analysis of Occupational Therapy for Independent Living Elderly," ISPOR Annual Meeting, Podium Presentation. Washington, DC.

September 1999 "Rotavirus Cost of Illness," Rotavirus Vaccine Advisory Panel, Wyeth-Ayerst, Radnor, PA.

October 1999 "The Cost of Lipid Therapy: A Systems Approach," Interdisciplinary Council on Cardiovascular Risk Reduction, Washington, DC.

October 1999 "Survival and Hospital Utilization in the Kaiser/USC Pharmaceutical Care Study," Kaiser Permanente Research and Evaluation Dept Seminar., Pasadena, CA.

November 1999 "The High Cost of Drugs and What to Do About It," Univ. of California Riverside Life Society Extension Program, Riverside, CA.

November 1999 "Pharmacoeconomics of Epilepsy Medications," American Epilepsy Society, Orlando, FL.

February 2000 "Rotavirus Costs of Illness," Vaccine Research Center, Harbor-UCLA Medical Center, Torrance, CA.

February 2000 "Pharmaceutical Expenditure Growth and Medicare Outpatient Drug Benefits," Mid-Valley Independent Practice Association, Portland, OR.

April 2000 "Alzheimer Disease Cognition Measures and Economic Costs," Invited presentation. 2nd International Alzheimer Disease Pharmacoeconomic Conference, Stockholm, Sweden.

April 2000 "Pharmacoeconomics of Antibiotic Treatment Strategies," 10th Congress of the International Society for Infectious Disease, Buenos Aires, Argentina.

April 2000 "Economic Research Issues in Alzheimer Disease." State of California Alzheimer Research Centers Site Visit. Los Angeles, CA.

September 2000 "Cost Effectiveness of Statin Therapy." International Task Force for Prevention of Coronary Heart Disease. Consensus on Statins Conference. Invited Presentation. Paris, France.

September 2000 "Cost Effectiveness of Statin Therapy." Interdisclipinary Council on Coronary Heart Disease. Invited Presentation. New York, NY.

November 2000 "Pharmacy Retail Price Variation," Pharmaceutical Economics Seminar, UCLA School of Public Health. Westwood, CA.

March 2001 "Choicecare: A Health Insurance Market Plan for Hong Kong. Invited Seminar, Hong Kong Hospital Authority; Hong Kong.

May 2001 "Cost Effectiveness Considerations in Adult/Adolescent Pertussis Vaccination Strategies," Vaccine Health Advisory Group Conference, La Romana, Dominican Republic.

July 2001	"China's Health Care Reform," International Health Economics Assoc. Meeting, York, UK.
September 2001	"Cost Effectiveness of Statins: Implications for the National Cholesterol Education Panel Recommendations." Washington, DC.
November 2001	"Chemotherapy-Induced Neuropathy In Ovarian Cancer Cost Effectiveness." ISPOR European Conference, Cannes, France.
March 2002	"Conjoint Analysis of Alzheimer Disease Treatment Preferences: Preliminary Results." CCH/HSRC Methods Seminar, UCLA/NPI Center for Community Health and Health Services Research Center, Westwood, CA.
March 2002	"Ethics and Economics in Health Care Decision-making." USC Health Sciences Campus Seminar on Moral and Spiritual Issues in Health Care, Los Angeles, CA.
April 2002	"Current Status of Health Economics Checklists and Guidelines." Academy of Managed Care Pharmacy Annual Convention, Podium Presentation, Salt Lake City, UT.
May 2002	"Quality of life effects of chemotherapy-induced neuropathy in ovarian cancer (Abst 886)." "Neuropathy in Chemotherapy: Results of an Oncology Nurse Survey (Abst 2618)." Poster Presentations, American Society of Clinical Oncology Annual Meeting. Orlando, FL.
May 2002	"Vaccine Reimbursement Policy in the United States: Issue Development." Institute of Medicine, National Academy of Sciences. Washington, DC.
September 2002	"Recent Trends in U.S. Lipid Medication Use: 1998-2002. Interdisclipinary Council on Coronary Heart Disease. Invited Presentation. New York, NY.
September 2002	"Drugbusters: How to Manage your Medicine Cabinet." Invited Roundtable Presentation. Los Angeles Times Festival of Fitness and Health. Los Angeles, CA.
October 2002	"Recent Drivers of Hospital Inpatient Expenditure Growth." Media presentation sponsored by the Blue Cross Blue Shield Association, Chicago, IL.
November 2002	"Rising Hospital Costs in California." Panel Discussion sponsored by Blue Shield of California, Univ. of California, Berkeley, CA.
December 2002	"National Issues Briefing To Examine Rising Hospital Costs," Panel Discussion sponsored by U.S. News & World Report. Washington, DC.

January 2003 "What's Behind the Rise in Health Care Costs" Invited Keynote Presentation, Washington Business Group on Health Employer Summit. New York, NY.

March 2003 "High Tide for Benefits Budgets: Rising Healthcare Costs." Invited Keynote Presentation, Illinois BlueCross BlueShield Natl Accounts Conf, San Diego, CA.

April 2003 "Current trends and future directions of Health-Systems in the US," Health Economics and Outcomes Research Invited Presentation, Abbott Laboratories, Evanston, IL.

May 2003 "U.S. Health Care Expenditure Growth: Issues and Solutions." St. Louis Civic Entrepreneurs Organization, St. Louis, MO.

June 2003 "U.S. Pharmaceutical Expenditure Growth:1999-2002" Paper presented at the Intl Health Economics Association 4'th World Congress, San Francisco, CA.

June 2003 "Medical Market Failures and Intellectual Property" Paper presented at the Intl Health Economics Association 4'th World Congress, San Francisco, CA.

August 2003 "Determinants of Survival and Nursing Home Placement for AD Patients." Paper presented at the International Psychogeriatrics Association Annual Meetings, Chicago, IL.

December 2003 "Claritan's Shift to OTC Status: A Lesson for the HMOs." Paper presented at Pharmaceutical Economics And Policy Seminar, UCLA Schl of Public Health, Westwood, CA.

April 2004 "Pharmacoeconomics & Biotech." Invited presentation at PDL Biopharma, Fremont, CA.

July 2004 "Cost Effectiveness Of Pertussis Vaccine In Adults And Adolescents." Invited presentation, Pediatric Vaccine Workshop, New York, NY.

November 2004 "Vaccine Costs and Benefits." Invited presentation, GSK Pediatric Vaccine Advisory Board., Scottsdale, AZ.

February 2005 "Patents, Drug R&D and Protection of Intellectual Property," Invited Panel Presentation: International Trade in Pharmaceuticals, The International Law Society Meetings, Costa Mesa, CA.

May 2005 "Dually Eligible Mentally Ill Population" Session Chair; Third NIMH Pharmacoeconomics Workshop: MMA03 and Psychotropic Medications, NIMH, Bethesda, MD.

May 2005 "How Should Intellectual Property be Rewarded and Protected in the Global Pharmaceutical Industry?" Panel Discussion, USC Law School Intellectual Property Institute, Second Annual Conference. Beverly Hills, CA.

May 2005 "Structure & Design of Pharmacoeconomic Models." With Marc Botteman and Ben Van Hout. ISPOR Short Course presented at the 10th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, Washington, DC.

June 2005 "Implementation and Outcomes of Commercial Disease Management Programs in the United States: the Disease Management Outcomes Consolidation Survey." Nationwide Teleconference presentation with Mark Roberts.

October 2005 "Using Conjoint Analysis to Assess DM Intervention Attributes: Application to Alzheimer's Disease Caregivers." Paper presented at the Disease Management Association of America Annual Meeting, San Diego, CA.

October 2005 "Conjoint Analysis Validation Of The Hui-3 Utility Scale In An Alzheimer Disease Caregiver Population." Abstract 1216 presented at the International Society of Quality of Life Research, San Francisco, CA.

November 2005 "Economic Implication Of Hepatitis B Viral (HbV) Load Reduction For Entecavir In Hepatitis B E Antigen-Positive Chronic Hepatitis B (CHb) Patients" Presented at the 8'th ISPOR European Conference, Florence, Italy.

January 2006 "Methods for Selection Bias Adjustment: Propensity Scores, Instrumental Variables and the Heckman Method. Invited Grand Rounds Presentation, Maveric, Dept. of Veterans Affairs and Harvard Medical School, Boston, MA.

March 2006 "Cost Effectiveness of Entecavir for Chronic Hepatitis B Disease in China." Presented at the ISPOR Asian Conference, Shanghai, China.

March 2006 "Adjusting for Selection Bias in Administrative Health Care Databases." Invited Presentation, China Center for Pharmacoeconomics and Outcomes Research, Peking University, Beijing, China.

April 2006 "Stated Preference Theory (Conjoint Analysis) is the Best Way to Assess Health-Related Quality of Life for Economic Assessment of Drugs and Medical Interventions: An Application in Alzheimer Disease" Invited International Teleconference Presentation, ISPOR Student Chapter Network.

October 2006 "The Value of Biomedical Innovation." Invited Seminar, AstraZeneca Pharmaceuticals, Alderly Park, Cheshire, UK.

October 2006 "Cost Effectiveness of Magnetic Resonance Angiography versus Digital Subtraction Angiography for Peripheral Vascular Disease." Presentation at the 9'th European ISPOR Conference, Copenhagen, Denmark.

January 2007 "Stated Preference Theory in Assessing Health-Related Quality of Life for Economic Assessment in Alzheimer Disease. Invited Seminar; Medical University of South Carolina.

February 2007 "Stated Preference Theory in Assessing Health-Related Quality of Life for Economic Assessment in Alzheimer Disease. Invited Seminar; Tulane University School of Public Health.

October 2007 "Risk-Stratified Medical Costs for Asthma Patients in a Managed Care Organization (MCO)." Presentation at the 10'th European ISPOR Conference, Dublin, Ireland.

October 2007 "Stated Preference Theory in Assessing Health-Related Quality of Life for Economic Assessment in Alzheimer Disease. Invited Seminar; National University of Ireland, Galway, Ireland.

January 2008 "How Should Drug Prices Be Measured?" Invited Seminar, School of Public Health, University of California Los Angeles, Los Angeles, CA.

February 2008 "How Not to Use Health Economics Data: Lessons from the U.S. Health Care Sector" invited presentation at the Hong Kong Hospital Authority Conference "Use of Health Economics Data in the Health Care Environment of Hong Kong The Way Forward." Hong Kong SAR, China.

March 2008 "Cost Effectiveness of Statins and Other Lipid Therapies." Invited presentation at the 3rd International Symposium on Healthy Aging: Meeting the Challenges of an Aging Population, Hong Kong SAR, China.

April 2008 "Pharmacoeconomic Modeling," Invited Lister Hill Seminar presentation, University of Alabama at Birmingham School of Public Health. Birmingham, AL.

August 2008 "Pharmacoeconomics Modeling and Empirical Analysis," Invited Lecture Series, National University of Colombia. Bogota, Colombia.

September 2008 "Issues in Pharmacoeconomic Methods," Invited Lecture, Amylin Pharmaceuticals, San Diego, CA.

November 2008 "Modeling Long-Term Mortality and Morbidity Impact with Entecavir Treatment in Chronic Hepatitis B Patients in Belgium." Benedicte Lescrauwaet, Frederik Nevens, Danielle Zammit, Yong Yuan, Joel Hay. Podium presentation, ISPOR European Conference, Athens, Greece.

December 2008 "Successful Pharmacoeconomic Models," Invited presentation, Mexico ISPOR Chapter, Mexico City, Mexico.

March 2009 "Drugs and Outcomes Research: Where are the Comparative Effectiveness Guideposts Moving To?" Opening Keynote Address, Western Pharmacoeconomics Conference, Pasadena, CA.

April 2009 "Comparative Effectiveness: What Does It Mean and How Do We Do It?" Invited University-Wide Seminar, USC School of Pharmacy, Los Angeles, CA.

April 2009 "Stated Preference Theory (Conjoint Analysis) Assessment of Health-Related Quality of Life for Economic Assessment of Medical Interventions," Invited Seminar, University of Washington School of Pharmacy, Seattle, WA.

April 2009 "Health Economic Evaluation of Oral versus IV Therapy in Oncology." Invited Presentation, Current And Emerging Trends In The Treatment Of Cancer: Pharmacoeconomics And Market Assessment, Guaraja, Brazil.

May 2009 "Comparative Effectiveness Research: What it is and Why We Need it." Invited Podium Presentation, International Society for Pharmacoeconomics and Outcomes Research 14th Annual International Meeting, Orlando, FL.

August 2009 "Outcomes Research, Comparative Effectiveness, Cost Effectiveness: What is Needed Now and Why?" Invited Seminar, Colombia Chapter: International Society for Pharmacoeconomics and Outcomes Research, Bogota, Colombia.

August 2009 "Pharmacoeconomics of Autoimmune Disease Therapy." Invited presentation, XII Colombian Rheumatology Congress, Bogota, Colombia.

October 2009 Debate on the Pros and Cons of Marijuana Legalization. Invited speakers, The Arsalyn Foundation, Duarte, CA.

November 2009 Resource Use in Patients with Allergic Rhinitis (AR) Comorbidities: Oral Second Generation Antihistamines (SGAs) versus Montelukast (MTLK)" Podium Presentation, Annual Meeting of the American College of Allergy, Asthma & Immunology, Miami Beach, Florida.

November 2009 "Impact of Obama's Health Care Reform on Payers" Speaker Panel Moderator; USC School of Pharmacy Board of Councilors Retreat. Los Angeles, CA.

November 2009 "Debate on Obama's Health Care Reform with Prof. Tom Rice, Vice Chancellor, UCLA," at UC Davis Mondavi Center, Davis CA. http://webcast.ucdavis.edu/IGA/2009/Health_Care_Debate_11-17-09.qtl

December 2009 "Resource Use in Patients with Allergic Rhinitis (AR) Comorbidities: Oral Second Generation Antihistamines (SGAs) versus Montelukast (MTLK)" Podium Presentation, Annual Meeting of the American College of Allergy, Asthma & Immunology, Nov. 5-10, Miami Beach, Florida.

January 2010 "Medical Marijuana: The Quack Pot Cure," Research Study Club Invited Presentation, Providence Saint Joseph Medical Center, Los Angeles, CA.

February 2010 "Health Care Reform," Arsalyn Foundation, UCLA, Los Angeles, CA.

March 2010 "Obama's Health Care Reform," USC Executive Master's Program in Health Administration, Lost Angeles, CA.

April 2010 "Obama Health Care Reform," USC Schl. of Pharmacy, Lamda Chi Seminar, Los Angeles, CA.

June 2010 "Economic Comparison of aPCC versus rFVIIa for mild-to-moderate bleeding episodes in hemophilia patients with inhibitors." Invited presentation, 8th Inhibitor Workshop for Opinion Leaders in Hemophilia." Gdansk, Poland.

September 2010 "Pharmacoeconomics & Comparative Effectiveness: A U.S. Perspective." Invited presentation to NECA (National Evidence-based Healthcare Collaborating Agency) Seoul, Korea.

September 2010 "Cost-effectiveness of An Exclusively Human-Milk Based Diet Vs. Bovine-Milk Based Diet In The Prevention of Necrotizing Enterocolitis Among Extremely Premature Infants." Invited presentation to the Cedars-Sinai Dept. of Pediatrics, Beverly Hills, CA.

September 2010 "Marijuana Legalization: No on Proposition 19." Invited presentation, Loyola Marymount University, Los Angeles, CA.

October 2010 "Marijuana Legalization: The Quack Pot Cure to California's Fiscal Woes." Invited presentation UCLA Extension Campus, Westwood, CA.

October 2010 "Marijuana Legalization Debate: Proposition 19." Invited presentation UCLA, Westwood, CA.

October 2010 "Marijuana Legalization Debate: Proposition 19." Invited presentation UCSC, Santa Cruz, CA.

October 2010 "Insurance Innovation: How to Succeed after Reform" Invited presentation, First Annual Schaeffer Center Conference, Leonard Schaeffer Center for Health

Policy and Economics, University of Southern California, Los Angeles, CA. http://www.youtube.com/watch?v=SraGxvHlZWs

October 2010 "Marijuana: Potential Medical Consequences & Societal Issues Related to Legalization," Invited presentation, The Marijuana Conference: A Forum for Discussion of Business, Legal & Health Issues. New York, NY.

October 2010 "Marijuana Legalization: Proposition 19," Invited presentation, The Fell Conversation, School of Policy, Planning, and Development, University of Southern California, Los Angeles, CA.

December 2010 " Econometric Issues in Pharmacoeconomics," Invited presentation, National University of Colombia, School of Pharmacy, Bogota, Colombia.

December 2010 "Comparative Effectiveness Research in the Changing US Policy Environment," Invited presentation, ISPOR Chapter of Colombia, Bogota, Colombia.

December 2010 "Introduction to Pharmacoeconomics," Invited presentation, Universidad del Atlántico, School of Pharmacy, Barranquilla, Colombia.

December 2010 "Comparative Effectiveness and Outcomes Research," Invited presentation, Universidad del Atlántico, School of Pharmacy, Barranquilla, Colombia.

February 2011 "Pharmacy's Changing Roles Under Health Care Reform," Invited presentation, USC Pharmacy Student Industry Association. Los Angeles, CA.

March 2011 "Pitfalls in Comparative Effectiveness Research: From Poison IVs to Uninformed Posteriors." Invited Plenary Presentation, Western Pharmacoeconomics Conference, University of Washington, Seattle, WA.

April 2011 "Medical Marijuana: Therapeutic, Economic and Policy Issues." Invited presentation, Providence Tarzana Medical Center, Tarzana, CA.

April 2011 "Budget Impact Models in MCO Decision Making: Current Practice, Challenges and Insights," Invited Workshop presentation, Academy of Managed Care Pharmacy, 23'rd Annual Meeting, Minneapolis, MN.

May 2011 "Branded Pharmaceutical Markets and Anticompetitive Harm." Invited presentation, UCLA Dept. of Health Services, Graduate Seminar on Pharmaceutical Economics and Policy. Los Angeles, CA.

July 2011 "Health Economics Research Objectives." Invited presentation, UCLA Dept. of Health Services, Health Economics Workshop with Monash Univ., UCLA & USC, Los Angeles, CA.

September 2011 "Optimal Health Care Treatment Allocation With and Without Stochastic Uncertainty." Invited presentation, University of Tennessee College of Pharmacy. Memphis, TN.

October 2011 "Medical Marijuana: Therapeutic, Economic and Policy Issues." Invited presentation, Ventura Community Memorial Hospital, Ventura, CA.

October 2011 "Medicare: Financial, Economic and Policy Issues." Invited presentation, Association of Health Care Journalists, Business of Health Care Workshop, San Francisco, CA.

November 2011 "Meeting the Challenges of US Health Care Reform: Payer and Provider Perspectives for the Biopharmaceutical Market." Invited Panel Discussion, 2011 IMS Life Sciences Strategy Conference, San Francisco, CA.

November 2011 "Health Care Reform: Where Does Pharmacy Fit?" Invited presentation, USC Pharmacy Student Industry Association. Los Angeles, CA.

December 2011 "Health Care Costs in a Medicare Population of COPD Patients Treated with Beta-Agonists." American Society of Health System Pharmacists Midyear Meeting, New Orleans, LA.

December 2011 "Optimal Health Care Treatment Allocation With and Without Stochastic Uncertainty—Part I," Schaffer Center for Health Policy and Economics, USC. Los Angeles, CA.

February 2012 "Optimal Health Care Treatment Allocation With and Without Stochastic Uncertainty—Part II," Schaffer Center for Health Policy and Economics, USC. Los Angeles, CA.

May 2012 "Optimal Drug Treatment Allocation with & without Stochastic Uncertainty," UCLA Seminar on Pharmaceutical Economics and Policy." Los Angeles, CA.

May 2012 "Optimal Personalized Treatment Allocation With & Without Stochastic Uncertainty," Invited seminar, SingHealth Academy Symposium on Health Care Decision-making and Personalized Medicines, Singapore.

May 2012 "Cancer Treatments, Expensive Medications and Cost Effectiveness: Perspectives of a Health Economist," Panel Discussion, SingHealth Academy Symposium on Health Care Decisionmaking and Personalized Medicines, Singapore.

May 2012 "Comparative Effectiveness & Outcomes Research: Where is the U.S. Headed?" National University of Singapore invited seminar, Singapore.

June 2012 "Introduction to Economic Assessment of Drugs, Devices and Medical Interventions," Conference Workshop, American Society for Health Economics 4'th Biennial Conference, Minneapolis, MN.

June 2012	"Cost Effectiveness Analysis With and Without Stochastic Uncertainty," Organized Podium Session, American Society for Health Economics 4'th Biennial Conference, Minneapolis, MN.
October 2012	"U.S. Health Care Reform Issues," Invited presentation, Arsalyn Foundation, Alhambra, CA.
November 2012	"Preparing Drug Review Dossiers for the Academy of Managed Care Pharmacy," Invited presentation, USC Managed Care Pharmacy Student Association, Los Angeles, CA.
February 2013	"Hemophilia Inhibitor Bypass Agents: A Clinical and Economic Review of the Literature," Invited Webinar on Hemophilia Treatment.
February 2013	"Drug Patents, Intellectual Property and Pricing," Invited seminar, Tulane University School of Public Health, New Orleans, LA.
February 2013	"Stated Preferences and Conjoint Analysis: Theory and Applications," Invited seminar, Tulane University School of Public Health, New Orleans, LA.
March 2013	"Accountable Care Organizations and Health Care Reform," Invited Seminar USC Medical and Pharmacy Students Collaboration." USC, Los Angeles, CA.
April 2013	"Optimal Health Care Treatment Allocation with & without Stochastic Uncertainty," Invited Seminar, Veterans Affairs Health Care Program and University of New Mexico PEPPOR Graduate Program, Albuquerque, NM.
April 2013	"The Current State of Comparative Effectiveness & Outcomes Research," Invited Seminar, University of New Mexico PEPPOR Graduate Program, Albuquerque, NM.
September 2013	"The U.S. Societal Costs of Cannabis," Invited presentation. The Marijuana Conference, Rancho Cucamonga, CA.
October 2013	"Conjoint Analysis of Provider Preferences for Interventions for Reducing Inappropriate Antibiotic Prescribing," Invited presentation. BEARI Investigators Meeting. Los Angeles, CA.
November 2013	"Pay-for-Delay Settlements for Pharmaceutical ANDA Cases: Right or Wrong?" Invited seminar, UCLA School of Public Health, Los Angeles, CA.
February 2014	"Why Drugs Should Not Be Legalized," Invited presentation. Arsalyn Foundation Student Conference, El Monte, CA.
March 2014	"Cost-Effectiveness Analysis Under Stochastic Uncertainty," Steven M. Teutsch Prevention Effectiveness Fellowship invited presentation. U.S. Centers for Disease Control and Prevention, Atlanta, GA.

March 2014 "Assessment of Health-Related Quality of Life for Medical Interventions: A Discrete Choice Experiment Application in Alzheimer Disease," Steven M. Teutsch Prevention Effectiveness Fellowship invited presentation. U.S. Centers for Disease Control and Prevention, Atlanta, GA.

March 2014 "Hemophilia Treatments, Costs and Outcomes," invited presentation. National Center on Birth Defects and Developmental Disabilities; U.S. Centers for Disease Control and Prevention, Atlanta, GA.

September 2014 "Current U.S. Trends in Health Technology Pricing and Value," invited presentation. Forum on HTA and Reimbursement, Peking University, Beijing, China.

September 2014 "US Healthcare Financing System & Reforms," invited presentation. Health Care Financing Forum, Party School of the Central Committee of the Communist Party of China, Beijing, China.

September 2014 "U.S. Health Care Reform," invited Plenary Symposium presentation. ISPOR 6th Asia-Pacific Conference, Beijing, China.

February 2015 "Is there a Convergence of Health Economics with U.S. Health Policy?" Panel Discussion Invited Presentation, DePaul University Conference on Health Economics. Chicago, IL.

March 2015 "Pharmaceutical Research & Development: An Economist's Perspective." Invited Lecture, Harbor-UCLA Grand Rounds. Torrance, CA.

April 2015 "Cost Effectiveness Analysis with Stochastic Uncertainty," Invited seminar, Pharmaceutical Outcomes Research and Policy Program, University of Washington. Seattle, WA.

April 2015 "Regulating Health Economics Modeling Claims," Invited presentation to the Office of Medical Policy and the Center for Drug Evaluation and Research, Food and Drug Administration. Silver Spring, MD.

September 2015 "Orphan, Specialty and Low Volume/High-Priced Drugs," Workshop on Pharmaceutical Economics and Policy, Center for Health Economics and Outcomes Sciences, University of British Columbia. Vancouver, BC, Canada.

November 2015 "Cost Effectiveness Analysis with Stochastic Uncertainty," Invited seminar, Dept. of Economics, University of Iowa, Iowa City, IA.

March 2016 "What is Pharmacoeconomic Information Under FDAMA 114?" Invited Panel Discussion, AMCP Partnership Forum, FDAMA 114: Improving the Exchange of Pharmacoeconomic Data, Washington, DC.

March 2016	"Marijuana Legalization: Costs and Medical Harms." Invited discussion, USC Seminar, Preventive Medicine PM547: Public Health Policy and Politics, Los Angeles, CA.
April 2016	"Health Economics: An Introduction for Biomedical Engineers," Invited Keynote Lecture, 20th Annual Grodins Research Symposium, USC Dept. of Biomedical Engineering, Los Angeles, CA.
September 2016	"Enabling the Exchange of Clinical and Economic Data pre-FDA Approval," Invited Panel Discussion, AMCP Partnership Forum, Tysons Corner, VA.
November 2016	"2016 National and California Election Implications for Pharmaceuticals," Invited Seminar, Pharmaceutical Economics and Policy, School of Public Health, University of California, Los Angeles, Los Angeles, CA.
April 2018	"The Value in Aging: Health Economics Applications in Gerontology," Invited Seminar, Université de Sherbrooke Centre de Recherche sur le Vieillissement, Sherbrooke, Quebec, Canada.
October 2018	"Cost-Effectiveness of Screening and Management Strategies for Familial Hypercholesterolemia in the United States: A Markov Model Update," Invited Podium Presentation, 2018 Familial Hypercholesterolemia GLOBAL SUMMIT, Marina Del Rey CA.
January 2019	"Drug Pricing, Patents and Intellectual Property," Invited Seminar, Pomona Student Union, Pomona College, Pomona, CA.
February 2019	"FDA Regulation of Off-Label Medical Information: Policing Renegade Drug Companies or Infringement of Protected Commercial Speech?" John E. Osborn, with Discussion and Counter by Joel W. Hay, PhD, Seminar on Pharmaceutical Economics & Policy, Dept. of Health Policy & Management, University of California, Los Angeles, Los Angeles, CA.
May 2019	"Value in Health at Age 20: Keep Focusing on the Science." Invited Panel Discussion "Back to the Future in Value in Health." ISPOR 24th Annual International Meeting, May 21-23, 2019, New Orleans, LA.
May 2019	"Extensions of the Standard Cost Effectiveness Model: Dealing with Uncertainty, Alternative Decision Maker Perspectives & Worker Productivity." Invited Seminar Presentation, Centre for Health Economics and Policy Analysis (CHEPA), Faculty of Health Sciences, McMaster University, Hamilton, ON, Canada.

RESEARCH CERTIFICATIONS:

5/23/2010 Completion Report

CITI Collaborative Institutional Training Initiative

Human Research Curriculum Completion Report
Printed on 5/23/2010

Learner: Joel Hay (username: jhay@usc.edu)
Institution: University of Southern California
Contact Information CHP 140 J
1540 E Alcazar St
USC Pharmaceutical Economics and Policy
Los Angeles, CA 90089 USA
Department: 330
Phone: 323-442-3296
Email: jhay@usc.edu

Investigators Conducting both Biomedical and SBR Research: This group has been established for investigators conducting both Biomedical and Social & Behavioral Research

University of Southern California

This is to certify that

HAY, JOEL W.

has completed the human subjects education program
"Understanding the Fundamentals -
Responsibilities and Requirements for the Protection of Human Subjects in Research"
07/23/2004

Sponsored by
The Office of the Provost and the Office of Compliance
Your certification is valid for three years from the above date of completion.

Certificate Number: 2341

FISCAL ADMINISTRATION COURSE INFO

Joel Hay has completed
USC's Fiscal administration course
on Wed Jun 28, 2006

Please contact the USC Office of Compliance at (213) 740-8258
if you have any questions.

COLLABORATIVE INSTITUTIONAL TRAINING INITIATIVE (CITI PROGRAM)
COURSEWORK REQUIREMENTS REPORT*

* NOTE: Scores on this Requirements Report reflect quiz completions at the time all requirements for the course were met. See list below for details. See separate Transcript Report for more recent quiz scores, including those on optional (supplemental) course elements.

- **Name:** Joel Hay (ID: 618466)
- **Institution Affiliation:** University of Southern California (ID: 498)
- **Institution Unit:** 330
- **Phone:** 323-442-3296

- **Curriculum Group:** CITI Good Clinical Practice
- **Course Learner Group:** Same as Curriculum Group
- **Stage:** Stage 1 - Basic Course

- **Report ID:** 15187675
- **Completion Date:** 02/02/2015
- **Expiration Date:** N/A
- **Minimum Passing:** 80
- **Reported Score*:** 91

University of Southern California

This is to certify that

HAY, JOEL W.

has completed the

Ethical Conduct in Research Course (Biomedical)

04/21/2004

Sponsored by
The Office of Compliance

Certificate Number: 1018

University of Southern California

This is to certify that

HAY, JOEL W.

has completed the

HIPAA Privacy Education Program
Sunday, March 23, 2003

Sponsored by
The Office of Compliance

Certificate Number: 2853

Human Participant Protections Education for Research Teams

Completion Certificate

This is to certify that

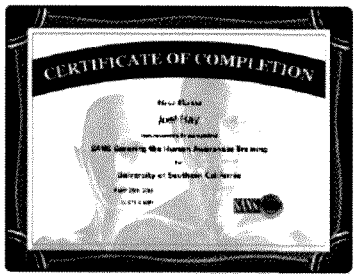
Joel Hay

has completed the **Human Participants Protection Education for Research Teams** online course, sponsored by the National Institutes of Health (NIH) on 03/26/2004

This course included the following:

- key historical events and current issues that impact guidelines and legislation on human participant protection in research
- ethical principles and guidelines that should assist in resolving the ethical issues inherent in the conduct of research with human participants
- the use of key ethical principles and federal regulations to protect human participants at various stages in the research process
- a description of guidelines for the protection of special populations in research
- a definition of informed consent and components necessary for a valid consent
- a description of the role of the IRB in the research process
- the roles, responsibilities, and interactions of federal agencies, institutions, and researchers in conducting research with human participants

National Institutes of Health
http://www.nih.gov



quirements set by:

University of Southern California

CERTIFICATE OF COMPLETION

Joel Hay

Grants Management Training for Faculty Refresher
by the Department of Contracts and Grants

APPENDIX B. TESTIMONY EXPERIENCE OF DR. JOEL HAY, PH.D.

August 14, 2019

Court and Arbitration Cases that Joel W. Hay, Ph.D. has offered reports, declarations, depositions or testimony in the past four years:

United States of America, and State of California, ex rel Bobbette A. Smith and Susan Rogers, Plaintiff-Relators, V. Tom S. Chang, M.D., Tom S. Chang, M.D., Inc., Michael A. Samuel, M.D., Michael J. Davis, M.D., Retina Institute of California Medical Group, California Eye and Ear Specialists, Brett Bruan and San Gabriel Ambulatory Surgery Center, LLP, Defendants. United States District Court
For the Central District of California. Case settled.
I filed a report in March 2019. I was deposed in May 2019.
(I worked for attorneys representing Plaintiff-Relators).

Teva Ltd. vs. Sandoz Inc. and Momenta Pharmaceuticals Inc In Re: Copaxone 775 Patent Litigation. C.A. No. 16-1267-CFC (Consolidated). United States District Court for the District of Delaware. Case settled.
I filed a report in February 2019. I was deposed in March 2019.
(I worked for attorneys representing Defendants).

Allergan USA, Inc., Plaintiff v. Imprimis Pharmaceuticals, Inc., Defendant. Case No. 8:17-cv-01551-DOC-JDE. United States District Court, Central District of California, Southern Division.
I filed reports in December 2018 and January 2019. I was deposed in April 2019.
(I worked for attorneys representing Defendant). Defendants won at trial.

Beckman Coulter Inc, Plaintiff vs Quidel Corp, Defendant, CASE NO: 37-2017-00044865-CU-AT-CTL. Superior Court of California, County of San Diego, Central.
I filed a declaration in November 2018.
(I worked for attorneys representing Defendant).

Attorney General of California (Complainant) vs. Catholic Medical Mission Board (Case No. 2018-13-5602319) (OAH No. 2018050397); Food for the Poor (Case No. 2018-CT086331) (OAH No. 2018050194); MAP International (Case No. 2018-CT103136) (OAH No. 2018050401) (Respondents). Administrative Hearing Before the Attorney General of California Administrative Hearing Office, Los Angeles, CA.
I filed a report in October 2018. I testified at Administrative Hearing in December 2018.
(I worked for Complainant).

United States of America; the States of California, Colorado, Connecticut, Delaware, Florida, Georgia, Hawaii, Illinois, Indiana, Iowa, Louisiana, Massachusetts, Michigan, Minnesota, Montana, Nevada, New Jersey, New Mexico, New York, North Carolina, Oklahoma, Rhode Island, Tennessee, Texas, Virginia, Washington and Wisconsin; The District of Columbia, the Cities of Chicago and New York; ex rel., Charles Arnstein and Hossam Senousy, Plaintiffs and Relators, v. Teva Pharmaceuticals USA, Inc.; Teva Neuroscience, Inc.; and Teva Sales and Marketing, Inc., Defendants. Civil Action No. 13 Civ. 3702 (CM). United States Dist. Court: Southern District of New York.
I filed a report - April 2018, a rebuttal report - June 2018 and was deposed in July 2018.
(I worked for Plaintiffs' and Relators' attorneys).

Devrim Aran (Complainant) v. Ahmet Toksoz, Zafer Toksoz, Comodo Health, Inc., and Arkhe Pharmaceuticals Corporation (Respondents). Reference No. 1425022633. JAMS Arbitration, New York, New York
I filed a report in November 2017. I filed a rebuttal report in December 2017. I testified at Arbitration Hearing in June 2018.
(I worked for Respondent's attorneys).

Teva Pharmaceutical Industries Limited, Plaintiff and Mylan Teoranta Trading as Mylan Institutional, Defendant. Record No. 2017/9398P.
The High Court of Ireland: Commercial.
I filed a report in November 2017. I filed a rebuttal report in December 2017. Defendant won; Judge cited favorably to my opinion.
(I worked for attorneys representing Defendant).

Court File No. T-1409-04 Between: Astrazeneca Canada Inc. and Aktiebolaget Hässle, Plaintiffs/Defendants by Counterclaim -and- Apotex Inc., Defendant/Plaintiff by Counterclaim. Court File No. T-1890-11between: Astrazeneca Ab and Aktiebolaget Hässle, Plaintiffs/Defendants By Counterclaim, -and- Apotex Inc. Defendant/Plaintiff by Counterclaim, Court File No. T-2300-05 Between: Apotex Inc. Plaintiff -and- Astrazeneca Canada Inc. Defendant. Federal Court of Canada.
I filed two reports in November 2016.
(I worked for attorneys representing Defendant/Plaintiff by counterclaim).

Christopher Corcoran, et al. on behalf of themselves and all others similarly situated, Plaintiffs, v. CVS Pharmacy, Inc. Defendant. Case No. 15-civ-03504-YGR. United States District Court for the Northern District of California, Oakland Division.
I filed a declaration in October 2016. I filed a supplemental declaration in November 2016 and a report in December 2016. I was deposed in November 2016 and March 2017. I filed a reply report and a rebuttal report in January 2017. I filed a declaration and addendum in June 2017. I was deposed in June 2017.
(I worked for Plaintiffs' attorneys).

Teva Pharmaceuticals USA, Inc., Teva Pharmaceutical Industries Ltd., Teva Neuroscience, Inc. and Yeda Research and Development Co., Ltd., Plaintiffs, v. Doctor Reddy's Laboratories, Ltd. and Doctor Reddy's Laboratories, Inc., Sandoz Inc. and Momenta Pharmaceuticals, Inc., Synthon Pharmaceuticals Inc., Synthon B.V., Synthon S.R.O. Blansko, and Pfizer, Inc., Mylan Pharmaceuticals Inc., Mylan Inc. and Amneal Pharmaceuticals LLC, Defendants. C.A. No. 1:14-cv-1171-GMS (consolidated). United States District Court for the District of Delaware.
I filed reports in April and June 2016. I was deposed in July 2016. I testified at trial in October 2016. Defendants won on all patents. The court favorably cited to my opinions on commercial success.
(I worked for Defendants' attorneys).

Kowa Company, Ltd. et al., Plaintiffs, v. Amneal Pharmaceuticals LLC, Mylan Inc. et al., Orient Pharma Co., Ltd., Zydus Pharmaceuticals (USA) Inc. et al., Sawai USA, Inc. et al., Apotex, Inc. et al., Lupin Ltd. et al., Defendants. Civil Action No. 14-CV-2760 (PAC). United States District Court for the Southern District of New York.
I filed a report in April 2016 and in September 2016. I was deposed in October 2016. I testified at trial in January 2017. Plaintiffs won.
(I worked for Defendants' attorneys).

Mylan Pharmaceuticals Inc. and Amneal Pharmaceuticals LLC,
Petitioners v. Yeda Research and Development Co. Ltd. Patent Owner. Case No. IPR2015-00643 (8,232,250 B2), Case No. IPR2015-00644 (8,399,413 B2), Case No. IPR2015-00830 (8,969,302 B2). United States Patent and Trademark Office, before the Patent Trial and Appeal Board. I filed a declaration in March 2016 and was deposed in April 2016. Petitioners won.
(I worked for Petitioners' attorneys).

United States of America, ex rel. Beverly Brown, Plaintiff-Relator v. Celgene Corporation, Defendant. Civil Action No. CV10-03165 GHK (SSx). United States District Court Central District of California – Western Division.
I filed reports in September and December 2015. I filed a declaration in October 2015. I filed a report in April 2016. I was deposed in June 2016. Plaintiffs won settlement damages.
(I worked for Plaintiffs' attorneys).

Abbvie Inc., Plaintiff, v. Medimmune, LLC, Defendant. Case No. 11 CH 4176. Circuit Court of the Nineteenth Judicial Circuit, Lake County, Illinois, Chancery Division.
I filed a report in this case in September 2013. I filed a rebuttal report in December 2013. I was deposed in February 2014. I testified at trial in September 2015. The jury awarded plaintiff a complete victory at trial.
(I worked for Plaintiff's attorneys).

Luitpold Pharmaceuticals, Inc., Plaintiff, v. Ed. Geistlich Söhne A.G. Für Chemische Industrie, and Osteomedical Ltd. Defendants. Case No. 11-cv-0681 (KBF) (THK). United States District Court, Southern District of New York.
I filed a report in this case in July 2012. I filed another report in October 2012. I was deposed in October 2012. I filed another report in April 2013. I filed two additional reports in August 2015. Case settled.
(I worked for Plaintiff's attorneys).

Astrazeneca AB, Aktiebolaget Hässle, Astrazeneca LP, KBI Inc. and KBI-E Inc., Plaintiffs and Counterclaim-Defendants, v. Mylan Laboratories Limited and Mylan Inc., Defendants and Counterclaim-Plaintiffs. United States District Court for the District of New Jersey Civil Action No. 3:12-cv-01378-MLC-TJB.
I filed a declaration in July 2015. Defendants won.
(I worked for Defendant's attorneys).

Torrent Pharmaceuticals Limited and Apotex, Inc. and Mylan Pharmaceuticals Inc., Petitioners, v. Novartis AG and Mitsubishi Pharma Corp., Patent Owners. United States Patent and Trademark Office, Before the USPTO Patent Trial and Appeal Board. Case IPR2014-00784, Case IPR2015-00518, Patent 8,324,283 B2.
I filed a declaration in June 2015. Petitioners won.
(I worked for Petitioners' attorneys).

Safeway Inc; Walgreen Co.; The Kroger Co.; New Albertson's, Inc.; American Sales Company, Inc.; and Heb Grocery Company, LP, Plaintiffs; Meijer, Inc. & Meijer Distribution, Inc.; Rochester Drug Co-Operative, Inc.; and Louisiana Wholesale Drug Company, Inc., On Behalf of Themselves and All Others Similarly Situated, Plaintiffs; Rite Aid Corporation; Rite Aid Hdqtrs Corp.; JCG (PJC) USA, LLC; Maxi Drug, Inc D/B/A Brooks Pharmacy; Eckerd Corporation; CVS Pharmacy, Inc.; and Caremark LLC, Plaintiffs; Smithkline Beecham Corporation, d/b/a Glaxosmithkline, Plaintiff; v. Abbott Laboratories, Defendant. United States District Court Northern District of California Oakland Division, Case Nos. C 07-5470 (CW), C 07-5985 (CW) (Consolidated Cases), C 07-6120 (CW), C 07-5702 (CW). All Related per November 19, 2007 Order to Case No. C 04-1511(CW).
I filed a report in March and two reports in July 2010. I was deposed in July 2010. I testified at jury trial in March 2011. I filed a report in February 2015 and another in March 2015. I was deposed in March 2015. Jury found for defendant. Case settled.
(I worked for Defendant's attorneys).

In re Questcor Pharmaceuticals Inc. Securities Litigation, John K. Norton, Individually, the Federal Securities Laws and on Behalf of All Others Similarly Situated, Plaintiffs, vs. Questcor Pharmaceuticals, Inc., Don M. Bailey, Michael Mulroy, Stephen L. Cartt, David Young, David J. Medeiros, and Mitchell I. Blutt, Defendants. Case No. 8: 12-cv-01623-DMG(FMOx). United States District Court, Central District of California Southern Div.
I filed a report in February 2015. Case settled.
(I worked for Plaintiffs' attorneys).

U.S. et al. ex Relator. James Garbe, Plaintiffs, v. Kmart Corporation, Defendant. Case No. 3:12-cv-00881-NJR-PMF. United States District Court, Southern District of Illinois. I filed a report in July 2014 and a declaration in September 2014. I was deposed in September 2014. I filed an additional report in November 2014. I filed a declaration in May 2017. Plaintiffs' received damages in settlement.
(I worked for Plaintiffs' attorneys).

APPENDIX C. EXPERT WITNESS DECLARATION

PATENTED MEDICINE PRICES REVIEW BOARD

IN THE MATTER OF the *Patent Act*,
R.S.C., 1985, c. P-4, as amended

AND IN THE MATTER OF
Horizon Pharma (the "Respondent")
and the medicine Cysteamine Bitartrate sold by the Respondent under the trade name PROCYSBI®

DECLARATION OF DR. JOEL HAY

I, Joel W. Hay, Ph.D., of the City of Los Angeles in the State of California in the United States of America, declare that:

(a) I have been retained by the Respondent to provide evidence in this matter;

(b) It is my duty to provide evidence in relation to this proceeding as follows:

(i) to provide opinion evidence that is impartial;

(ii) to provide opinion evidence that is related only to matters that are within my area of expertise; and

(iii) to provide any additional assistance that the Board may reasonably require to determine a matter at issue.

(c) I acknowledge that the duties referred to above take precedence over any obligation which I may owe to any party by whom or on whose behalf I am engaged.

Dated at Los Angeles, California
this 9th day of September 2019.

Joel W Hay

(SIGNATURE)

APPENDIX D. SCOPE OF REVIEW

In reaching my conclusions, I have reviewed and relied upon the information from the documents listed.

A. Filings with the Patented Medicine Prices Review Board

i. Notice of Hearing, In the Matter of the *Patent Act* R.S.C. 1985, c. P-4, as amended, and In the Matter of Horizon Pharma and the medicine Cysteamine Bitartrate sold by the Respondent under the trade name "PROCYSBI".

ii. Statement of Allegations of Board Staff, dated January 16, 2019.

iii. Response of Horizon Pharma, dated February 18, 2019.

iv. Reply of Board Staff, dated March 11, 2019.

v. Expert Report of Dr. Craig Langman, dated September 9, 2019.

B. Documents Produced by Board Staff

i. Tab 3 (CADTH - Pharmacoeconomic Review Report, February 2018).

ii. Tab 91 (Report of the Standing Committee on Health, House of Commons Canada, "Canadians Affected by Rare Diseases and Disorder: Improving Access to Treatment", February 2019).

iii. Tab 98 to Tab 106 (Horizon Form 2 Filings with PMPRB).

iv. Copy of IQVIA data - Email from Legal forwarding IQVIA data - ATTACHMENT_.pdf.

C. Documents Produced by Horizon Pharma

i. Tab 38 (Preliminary Clinical Study Report: Clinical Study RP103-03 Top-Line Clinical Data).

ii. Tab 41 (Long-Term, Open-Label, Safety and Efficacy Study Of Cysteamine Bitartrate Delayed-Release Capsules (RP103) in Patients with Cystinosis: Interim Clinical Study Report).

iii. HNZP.xlsx (Horizon Financial Information).

iv. REDACTED

v. REDACTED

vi. REDACTED

vii. REDACTED

viii. REDACTED

ix. [redacted]

x. [redacted]

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xii. Horizon Pharma PLC, Form 2 - Block 5, January to June 2019.

D. Publicly Available Documents

Scholarly Articles and Book Chapters

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APPENDIX E. BACKGROUND: COMMERCIALIZATION OF PROCYSBI

1. I am advised by counsel for Horizon that scientific research for PROCYSBI began as early as 1999.

2. In October 2007, Raptor Pharmaceuticals Corp. ("Raptor"), Horizon's predecessor in title, entered into a licensing agreement with the Regents of the University of California for the research, development, and commercialization of enterically coated cysteamine capsules.[1] I understand that, under the terms of this agreement, Raptor agreed to pay royalties of 5.5% of net revenues from sales of PROCYSBI in countries where PROCYSBI is covered by a patent right, in addition to lump sum developmental and regulatory milestone royalties payable under certain conditions.[2]

3. In October 2016, Horizon merged with Raptor and acquired the worldwide marketing rights to PROCYSBI in a transaction valued at USD$860.8 million.[3] As part of the transaction, Horizon acquired the worldwide commercial rights both PROCYSBI and QUINSAIR (another drug marketed by Raptor). I understand that QUINSAIR is not approved for sale in the U.S.[4] In June 2017, Horizon sold the marketing rights to PROCYSBI and QUINSAIR in the Europe, Middle East and Africa regions to Chiesi Farmecutici S.p.A. for an upfront payment of USD$72.5 million, with additional potential milestone payments based certain on sales thresholds.[5] Horizon

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[1] I understand that the license agreement was originally entered into by Encode Pharmaceuticals, which Raptor acquired via merger in December 2017. [License Agreement between Encode Pharmaceuticals and the Regents of California for Case No. SD2006-092 (Enterically Coated Cysteamine), available at https://www.sec.gov/Archives/edgar/data/1203944/000120394408000013/raptorucsdagreement htm; "Raptor Pharmaceuticals Acquires Orphan Clinical Program," Press Release dated December 17, 2007, available at https://www.sec.gov/Archives/edgar/data/1203944/000120394407000053/pressrelease121707.htm.]

[2] Raptor Pharmaceuticals Corp. Form 10-K For the Fiscal Year Ended August 31, 2012, pp. 45-46; Horizon Pharma Annual Report 2018, p. 16; License Agreement between Encode Pharmaceuticals and the Regents of California for Case No. SD2006-092 (Enterically Coated Cysteamine), available at https://www.sec.gov/Archives/edgar/data/1203944/000120394408000013/raptorucsdagreement htm; Amended and Restated License Agreement between Horizon Orphan LLC and the Regents of the University of California, Case NOs. SD2006-092, SD2017-110, SD2017-113 and SD2017-236, available at https://www.sec.gov/Archives/edgar/data/1492426/000119312517298000/d431610dex104.htm.

[3] Horizon Pharma Annual Report 2016, F-22-F24; "Horizon Pharma plc Completes Acquisition of Raptor Pharmaceutical Corp," Press Release dated October 25, 2016, available at https://www.sec.gov/Archives/edgar/data/1070698/000119312516745949/d255637dex99a5ii.htm

[4] Horizon Pharma Annual Report 2016, p. 47.

[5] Horizon Pharma Annual Report 2017, F-23-F23; "Horizon Pharma plc Completes Sale of European Marketing Rights for Procysbi® delayed-release capsules and QUINSAIR™ in Europe, Middle East and Africa (EMEA) Regions to Chiesi Farmaceutici S.p.A.", Press Release dated June 23, 2017, available at

retained the marketing rights for PROCYSBI and QUINSAIR in the U.S., Canada, and Latin America.

4. By the time it merged with Horizon in October 2017, Raptor reported incurring out-of-pocket costs of approximately USD$125 million (and likely closer to USD$175 million when accounting for personnel costs) to develop and commercialize PROCYSBI.[6]

5. Health Canada granted Horizon a Notice of Compliance ("NOC") to market PROCYSBI in Canada on June 13, 2017, at which point in time it was the first and only cysteamine bitartrate product approved for sale in Canada.[7] Horizon made its first sale of PROCYSBI in Canada on September 7, 2017, launching at a price of $10.35 per 25mg capsule and $31.05 per 75mg capsule, (*i.e.*, $0.4140 per mg), where it has remained since introduction.[8] [redacted]

https://www.globenewswire.com/news-release/2017/06/23/1028469/0/en/Horizon-Pharma-plc-Completes-Sale-of-European-Marketing-Rights-for-PROCYSBI-cysteamine-bitartrate-delayed-release-capsules-and-QUINSAIR-levofloxacin-nebuliser-solution-in-Europe-Mi html.

6 Raptor Pharmaceuticals Corp. Form 10-Q For the Quarter Ended March 31, 2013, pp. 24-25; Raptor Pharmaceuticals Corp. Form 10-K For the Fiscal Year Ended December 31, 2015, pp. 59-60; Raptor Pharmaceuticals Corp. Form 10-Q For the Quarter Ended June 30, 2016, pp. 25-26; HNZP.xlsx (Horizon Financial Information).

7 PROCYSBI, Health Canada NOC Database, available at https://health-products.canada.ca/noc-ac/info.do?lang=en&no=19408.

PROCYSBI remains the only cysteamine bitartrate capsule product approved for sale in Canada. On February 11, 2019, Health Canada approved a cystemine hydrochloride ophthalmic solution product (Cystadrops), but this product is indicated only for the treatment of corneal cystine crystal deposits in adults and children from 2 years of age with cystinosis (and not for the treatment of cystinosis). [CYSTADROPS, Health Canada NOC Database, available at https://health-products.canada.ca/noc-ac/info.do?lang=en&no=21855.]

8 Board Staff Production Tab 98 to Tab 106 (Horizon Form 2 Filings with PMPRB); iii. Horizon Pharma PLC, Form 2 - Block 5, January to June 2019.

9 [redacted]

6. I understand that there are two patents at issue in this matter, Canadian Patent No. 2,640,531 ("'531 Patent") and Canadian Patent No. 2,914,770 (the "'770 Patent"). I further understand that the '770 Patent is the later expiring of the two patents and that it is anticipated to expire in June 2034, [redacted]

APPENDIX F. DETAILS OF FINANCIAL ECONOMIC ANALYSIS

1. Based on forecasts prepared in the ordinary course of business by Horizon, I have developed a financial model that calculates the net operating profits (*i.e.*, cash flows) from sales of PROCYSBI in Canada [redacted][1] This appendix provides the details of my financial economic analysis. The schedules and exhibits to the analysis are appended to this affidavit as Appendix G. The exhibits provide the financial information underlying my calculations of Horizon's return on investment on PROCYSBI under Board Staff's Proposed Prices. These exhibits then feed into the schedules, which provide my calculations of Horizon's profits from sales of PROCYSBI under Board Staff's Proposed Prices.

A. CASH FLOWS FROM PROCYSBI BASED ON ITS CURRENT EX-FACTORY PRICE

2. In Exhibit G, I present my calculations of the cash flows from PROCYSBI under the ex-factory price at which Horizon currently sells PROCYSBI to pharmacy and wholesale customers in Canada. The cash flows that Horizon can expect from sales of PROCYSBI in Canada over the product's life cycle are revenues less costs. Thus, quantifying these cash flows requires one to:

- Quantify Horizon's net revenues from sales of PROCYSBI in Canada, based on its forecasted unit sales volume and ex-factory prices, as well as the discounts and rebates it offers on those sales.
- Quantify the costs Horizon is expected to incur in making those sales, all cost of goods sold and other cost of sales, sales and marketing expenses, and general and administrative expenses during PROCYSBI's product life cycle.

1. Forecasted Unit Sales of PROCYSBI Through [redacted]

3. As mentioned in my affidavit, PROCYSBI is available in two dosage strengths: 25mg capsules and 75mg capsules. Horizon sells its 25mg PROCYSBI to its wholesale, pharmacy and hospital customers in bottles of 60 capsules and its 75mg PROCYSBI in bottles of 250 capsules. For the purpose of my analysis, Horizon has provided me with its actual unit sales of PROCYSBI in Canada from launch in 2017 and 2018, as well as forecasts for the number of Canadian patients

[1] HNZP.xlsx (Horizon Financial Information).

Horizon expects to treat during the period from 2019 through to [redacted], which it has prepared in the ordinary course of business. From these patient forecasts, I have constructed estimates of the unit sales for PROCYSBI in Canada from 2019 through to [redacted] I provide these unit sales forecasts in Exhibit A.

4. Specifically, I understand that Horizon's patient forecasts are based on the assumption that [redacted] patients with nephropathic cystinosis will be on PROCYSBI in Canada by the end of [redacted], with net additions of [redacted] patients in [redacted] and [redacted], [redacted] patients in [redacted] and [redacted] and [redacted] patients through to the [redacted]. For my analysis, I have assumed that the age distribution of current patients on PROCYSBI in [redacted] is similar to that found by a 2014 study conducted by Cadieux, Lapidus and Greenbaum, and is as follows:[2]

[redacted]

5. [redacted]

[redacted]

2 [redacted]

3 [redacted].

6. [redacted]

2. Ex-Factory Prices and Discounts on Sales of PROCYSBI

7. [redacted]

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4 [redacted]

5 [redacted]

8. [redacted]

9. [redacted]

REDACTED

[redacted].[7] REDACTED

[redacted]

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6 [redacted]

7 REDACTED

[redacted]

10. Horizon has indicated that it also provides [redacted]

11. [redacted]

3. Royalties Payable on Net Sales of PROCYSBI

12. As mentioned above, I understand that under the terms of the licensing agreement between Horizon and the Regents of the University of California concerning the commercialization of PROCYSBI, royalties of 5.5% of net revenues from sales of PROCYSBI are payable to the University of California in countries where PROCYSBI is covered by a patent right.[8] In computing the cash flows from sales of PROCYSBI, I deduct these royalty payments from Horizon's net revenues of PROCYSBI at row [16] of Exhibit G.

4. Per Unit Cost of Goods Sold for PROCYSBI

13. In Exhibit B.1, I also show the forecasted per-unit cost of goods sold for PROCYSBI. For the purpose of my analysis, Horizon has provided me with its ordinary course of business forecasts for its standard cost of PROCYSBI from 2019 through to [redacted]

14. For 2017 and 2018, Horizon has provided me with its actual total cost of goods sold for PROCYSBI in each of these years. In these years, I understand that Horizon supported patients

[8] Raptor Pharmaceuticals Corp. Form 10-K For the Fiscal Year Ended August 31, 2012, pp. 45-46; Horizon Pharma Annual Report 2018, p. 16; License Agreement between Encode Pharmaceuticals and the Regents of California for Case No. SD2006-092 (Enterically Coated Cysteamine), available at https://www.sec.gov/Archives/edgar/data/1203944/000120394408000013/raptorucsdagreement htm; Amended and Restated License Agreement between Horizon Orphan LLC and the Regents of the University of California, Case NOs. SD2006-092, SD2017-110, SD2017-113 and SD2017-236, available at https://www.sec.gov/Archives/edgar/data/1492426/000119312517298000/d431610dex104.htm.

through a compassionate access program while reimbursement discussions with both the pan-Canadian Pharmaceutical Alliance ("pCPA") and provincial and territorial formularies progressed. As a matter of economics, these units of PROCYSBI provided free-of-charge by Horizon represent an additional cost of goods sold, over and above standard cost for the unit sales Horizon made at its ex-factory price. Accordingly, in Exhibit B.2, I show my calculations for the effective per unit cost of goods sold for PROCYSBI in 2017 and 2018 based on the actual total cost of goods sold relative to the actual sales volume in these years. [redacted].

5. Other Cost of Sales for PROCYSBI

15. As shown in Exhibit C, "other cost of sales" for PROCYSBI include (among other categories of costs) [redacted] Horizon has provided me with information on its other cost of sales for PROCYSBI in 2017 and 2018, as well as [redacted] forecasts [redacted] that it has prepared in the ordinary course of business. [redacted],

16. [redacted]

[9] [redacted]

6. Sales and Marketing Expenditures for PROCYSBI

17. Sales and marketing expenditures for pharmaceutical companies include the cost of physician detailing (*i.e.*, presentations to physician by company salespersons), and other promotional activities such as conference and medical affairs presentations. Such marketing activities serve to, among other things, (i) increase physician awareness about treatment options and the results of clinical studies, and (ii) help inform physicians about the optimal course of therapy for their patients.[10]

18. Horizon has provided me with information on its actual sales and marketing expenses in Canada for 2017 and 2018, as well as [redacted] forecasts [redacted] that it has prepared in the ordinary course of business. I summarize this information in Exhibit D. [redacted]

19. [redacted]

[10] In addition, I understand from my discussions with Horizon business representatives that Horizon has an agreement in Canada with Innomar Strategies ("Innomar") in relation to the distribution of PROCYSBI in Canada, under which Innomar provides Horizon with fulfillment, pharmacy, patient and pharmacovigilance services. I understand that expenses in this regard are also included in Horizon's marketing expenses.

[11] [redacted]

[12] [redacted]

7. General and Administrative Expenditures for PROCYSBI

20. General and administrative expenditures reflect managerial and business-services costs incurred in the day to day operation of pharmaceutical companies. Horizon has provided me with information on its actual general and administrative expenses for 2017 and 2018, as well as [redacted] forecasts [redacted] that it has prepared in the ordinary course of business. I summarize this information in Exhibit E. [redacted]

21. [redacted][13]

8. Cost of PROCYSBI's Development and Commercialization

22. As mentioned above in **Appendix E**, Horizon acquired the worldwide marketing rights to PROCYSBI through its acquisition of Raptor in October 2017, in a transaction valued at USD$860.8 million.[14] This transaction compensated Raptor for its development and commercialization expenditures for PROCYSBI as well as for QUINSAIR, a second drug that was marketed by Raptor. Thereafter, in June 2017, Horizon sold the marketing right to PROCYSBI and QUINSAIR in the Europe, Middle East and Africa regions to Chiesi Farmecutici S.p.A. for USD$72.5 million, but Horizon retained the marketing rights to PROCYSBI and QUINSAIR in Canada, Latin America and the U.S.[15]

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13 [redacted]

14 Horizon Pharma Annual Report 2016, F-22-F24; "Horizon Pharma plc Completes Acquisition of Raptor Pharmaceutical Corp," Press Release dated October 25, 2016, available at https://www.sec.gov/Archives/edgar/data/1070698/000119312516745949/d255637dex99a5ii.htm

15 As mentioned in Appendix E, QUINSAIR is not approved for sale in the U.S.

23. [redacted]

24. For R&D expenses thereafter, Horizon has provided me with detailed statements of its total R&D expenditures for PROCYSBI in 2017 and 2018, as well as [redacted][18] [redacted]

16 [redacted]

17 [redacted]

18 [redacted]

9. Forecasted Net Cash Flows from Sales of PROCYSBI in Canada

25. To calculate Horizon's gross revenues, I rely on the above-mentioned long-term forecasts of its expected unit sales of PROCYSBI multiplied by the corresponding price. I then deduct: (i) the rebates Horizon would expect to provide to public payors under the terms of the provincial and territorial formulary agreements it has entered in respect of PROCYSBI, and (ii) the copay discounts it offers to private insurers. Horizon's net sales revenues from PROCYSBI in Canada are its gross revenues net of these two figures.

26. Horizon's net cash flows for PROCYSBI (before tax) are then calculated on the basis of these net revenues less its costs of goods sold, other cost of sales, sales and marketing expenses, general and administrative expenses, and research and development expenses that it would have incurred to generate those net revenues.

B. Cash Flows from PROCYSBI based on Board Staff's Proposed Prices

27. Next, I use my financial economic model for PROCYSBI in Canada to assess Horizon's return on sales of PROCYSBI under Board Staff's Proposed Prices. Specifically, for the purpose of my analysis, I consider the case of: (i) a 71% price reduction for PROCYSBI, *i.e.*, the lower of the price reductions sought by Board Staff under the Premium Comparison Test; (ii) an 80% price reduction for PROCYSBI, *i.e.*, the lower of the price reductions sought by Board Staff under the Market Share Comparison Test; and (iii) a 96% price reduction for PROCYSBI, *i.e.*, the lower of the price reductions sought by Board Staff under the Same Medicine Comparison Test.

28. [redacted]

REDACTED

29. In determining the effect of a price reduction, my model must address how Horizon would reallocate sales and marketing expenses, as well as general and administrative expenses. [redacted]

[redacted] For example, economic theory indicates that a company would lower its level of marketing activities following a decrease in price, since the value of the sales supported by those activities will be diminished.[19] Likewise, it is reasonable to assume that a company would reduce management and administrative support services in the event of a severe reduction in revenues, especially one that is as substantial as that being proposed by Board Staff.

30. For the purpose of my analysis under a reduced-price scenario, I reallocate expenses so as to maintain a constant ratio of expenses to sales. For example, if the ratio of expenses to sales was initially $50 million in expenses relative to $100 million in sales (*i.e.*, a 1:2 ratio) and revenues from sales of PROCYSBI were to fall to $25 million, then expenses would have to fall to $12.5 million in order to re-establish a 1:2 ratio.[20]

31. In Schedule 1, I show my calculations of Horizon's earnings from PROCYSBI in Canada following a 71% ex-factory price reduction under the Premium Comparison Test. As shown, in the event of a 71% reduction in its ex-factory price, [redacted]

32. In Schedule 2, I show my calculations of Horizon's earnings from PROCYSBI in Canada following an 80% ex-factory price reduction under the Market Share Comparison Test. As shown,

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[19] See, *e.g.*, Bagwell, K. (2007). The Economic Analysis of Advertising. In M. Armstrong and R.H. Porter (eds.) *Handbook of Industrial Organization Volume 3*: 1701-1844. Elsevier.

[20] An alternative approach would be to update the ratio of expenses to sales to reflect the decreased share of total Horizon revenues coming from the sale of PROCYSBI in Canada. For example, suppose $50 million in expenses were initially allocated based on $100 million in sales from PROCYSBI in Canada relative to $1,000 million in Horizon sales overall. Then, if revenues from sales of PROCYSBI were to fall to $25 million, expenses would have to fall to $13.5 million to reflect the decreased share of total Horizon revenues being generated from the sale of PROCYSBI in Canada.

I note that the approach I have taken herein is more conservative than this alternative approach – specifically, more financially severe results are found under a scenario where Horizon would update its ratio of expenses to sales to reflect the decreased share of total Horizon revenues coming from the sale of PROCYSBI in Canada following a reduction in the price of PROCYSBI.

in the event of an 80% reduction in its ex-factory price, [redacted]

33. In Schedule 3, I show my calculations of Horizon's earnings from PROCYSBI in Canada following a 96% ex-factory price reduction under the Same Medicine Comparison Test. As shown, in the event of a 96% reduction in its ex-factory price, [redacted]

APPENDIX G. SCHEDULES TO FINANCIAL ECONOMIC ANALYSIS