

CONFIDENTIAL-CONFIDENTIEL and s. 87 *Patent Act* Privilege

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. Qualifications.....	1
II. Mandate and Issues to be Addressed	4
III. Materials Considered.....	6
IV. Summary of Opinions.....	6
<i>The Price of Drugs for Rare Diseases</i>	<i>6</i>
<i>Pharmaceutical Price Regulation in Canada</i>	<i>7</i>
<i>Board Staff's Alternative Models</i>	<i>8</i>
V. The Price of Drugs for Rare Diseases	10
The Costs of Pharmaceutical Innovation: Research and Development	10
<i>Timeline for Drug Development.....</i>	<i>10</i>
<i>Risks in Drug Development.....</i>	<i>12</i>
<i>Challenges in Drug Development for Rare and Ultra-Rare Diseases</i>	<i>14</i>
Profitability, Cost Recovery, and Price Regulation	16
Factors Impacting Pricing and Recovery of Costs for Rare Disease Drugs	17
Potential Effects of Pharmaceutical Price Regulation on R&D Incentives	17
<i>The Impact of Price Regulation on Investment in Pharmaceutical R&D</i>	<i>17</i>
<i>Incentivizing R&D for Rare Disease Drugs: The Orphan Drug Act</i>	<i>19</i>
<i>Challenges in Applying Pharmacoeconomic Models to Rare Disease Drugs</i>	<i>20</i>
VI. Pharmaceutical Price Regulation in Canada: a Reference-Based Pricing Model ...	24
Reference Pricing under the PMPRB Compendium.....	24
<i>External Reference Pricing and the Median International Price Comparison Test</i>	<i>25</i>
<i>Application of the Median International Price Comparison Test to PROCYSBI.....</i>	<i>28</i>
<i>Therapeutic Reference Pricing and the Therapeutic Class Comparison Test</i>	<i>29</i>
Ex-factory Prices vs Net Prices in Canada	34
VII. Board Staff's Alternative Models	34
Same Medicine Comparison Test.....	35
Premium Comparison Test	38
Market Share Comparison Test	40
VIII. Conclusion	45
Appendix A. Curriculum Vitae of Dr. Joel Hay, Ph.D.	
Appendix B. Testimony Experience of Dr. Joel Hay, Ph.D.	
Appendix C. Expert Witness Declaration	
Appendix D. Scope of Review	
Appendix E. Background: Commercialization of PROCYSBI	
Appendix F. Details of Financial Economic Analysis	
Appendix G. Schedules to Financial Economic Analysis	

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

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

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

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

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.

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.

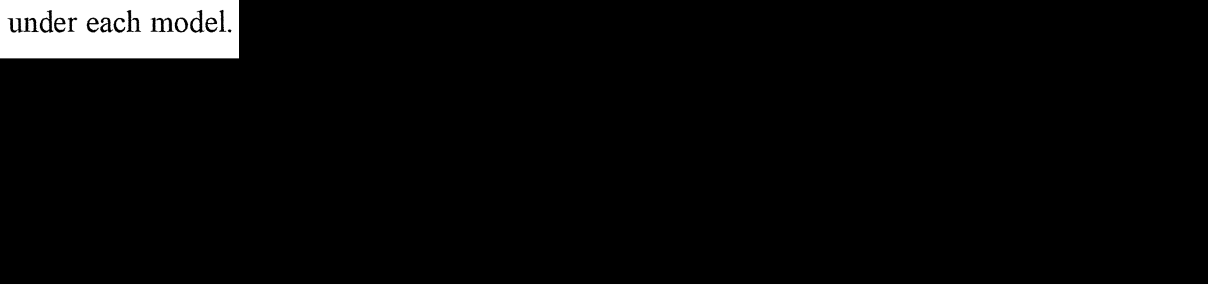
Many countries around the world use reference-based pricing methods to limit the prices of pharmaceutical products or reimbursement for expenditures on these products. Two of the most prominent reference-based pricing methods are Therapeutic Reference Pricing and External Reference Pricing. Therapeutic 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.



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

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.

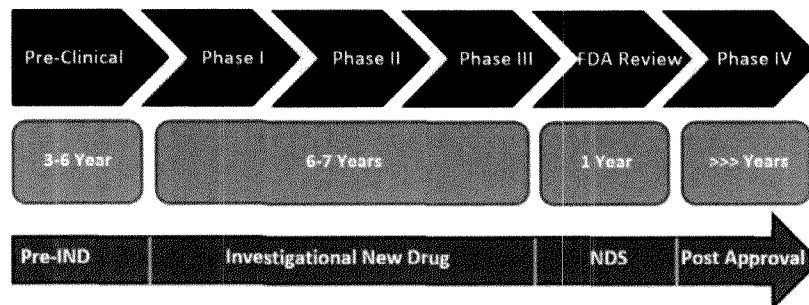
Timeline for Drug Development

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

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

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+Nephroathic&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+Nephroathic&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+Nephroathic&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

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

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

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.

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.

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 Waldfoegel (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

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 Waldfoegel, 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

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 adjusted 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

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

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 precisely 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

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

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 PMPRB7 provide a similar set of countries against which Canada can reasonably use as reference for pharmaceutical pricing.⁷⁷

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 and 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

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

Country	Price in CAD\$ as at Apr 2017		Price in CAD\$ as at Dec 2017		Price in CAD\$ as at Jun 2018	
	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

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 <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

Country	Exchange Rate As at Jun 2019 [A]	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	
		25mg [B]	75mg [C]	25mg [D] = [A] x [B]	75mg [E] = [A] x [C]	25mg [F] = [D] ÷ 25	75mg [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	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	No Price	No Price	No Price
Switzerland		No Price	No Price	No Price	No Price	No Price	No Price
Sweden		No Price	No Price	No Price	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

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;

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;

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

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 Class 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 Directors 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 C_{max}, 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

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."

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 PMBRB.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	Same Medicine
		Per Capsule	Comparison Test
		[A]	[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	Price	Price Per	Price Per
		Per Capsule	Per mg	25mg	75mg
		[A]	[B]	[C] = [B] x 25	[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,

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).

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 [A]	PROCYSBI MIP Price per mg [B]	Per mg Premium [C] = $\frac{1}{4} \times ([B] - [A])$	Price per mg Premium Comparison Test [D] = [A] + [C]	Price per Capsule Premium Comparison Test [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 [A]	PROCYSBI MIP Price per mg [B]	Per mg Premium [C] = $\frac{1}{4} \times ([B] - [A])$	Price per mg Premium Comparison Test [D] = [A] + [C]	Price per Capsule Premium Comparison Test [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.

- (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.

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

Drug Product	PROCYSBI		Cystagon		Weighted Average	Price per Capsule
	Price per mg	Market Share	Price per mg	Market Share	Price per mg	Market Share
	[A]	[B]	[C]	[D]	[E] = [A] x [B] + [C] x [D]	Comparison Test
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

Drug Product	PROCYSBI		Cystagon		Weighted Average	Price per Capsule
	Price per mg	Market Share	Price per mg	Market Share	Price per mg	Market Share
	[A]	[B]	[C]	[D]	[E] = [A] x [B] + [C] x [D]	Comparison Test
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.

- (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

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_pr01_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_euprocysapprv1.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]

[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.

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.

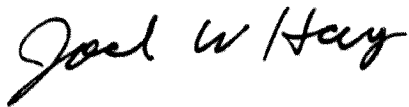
100. As I have explained, the use of the Median International Price Comparison Test in setting the prices of new drugs in Canada has numerous economic benefits. In particular, it ensures that Canadians will, on average, pay no more for a particular drug than individuals in countries of similar socioeconomic 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

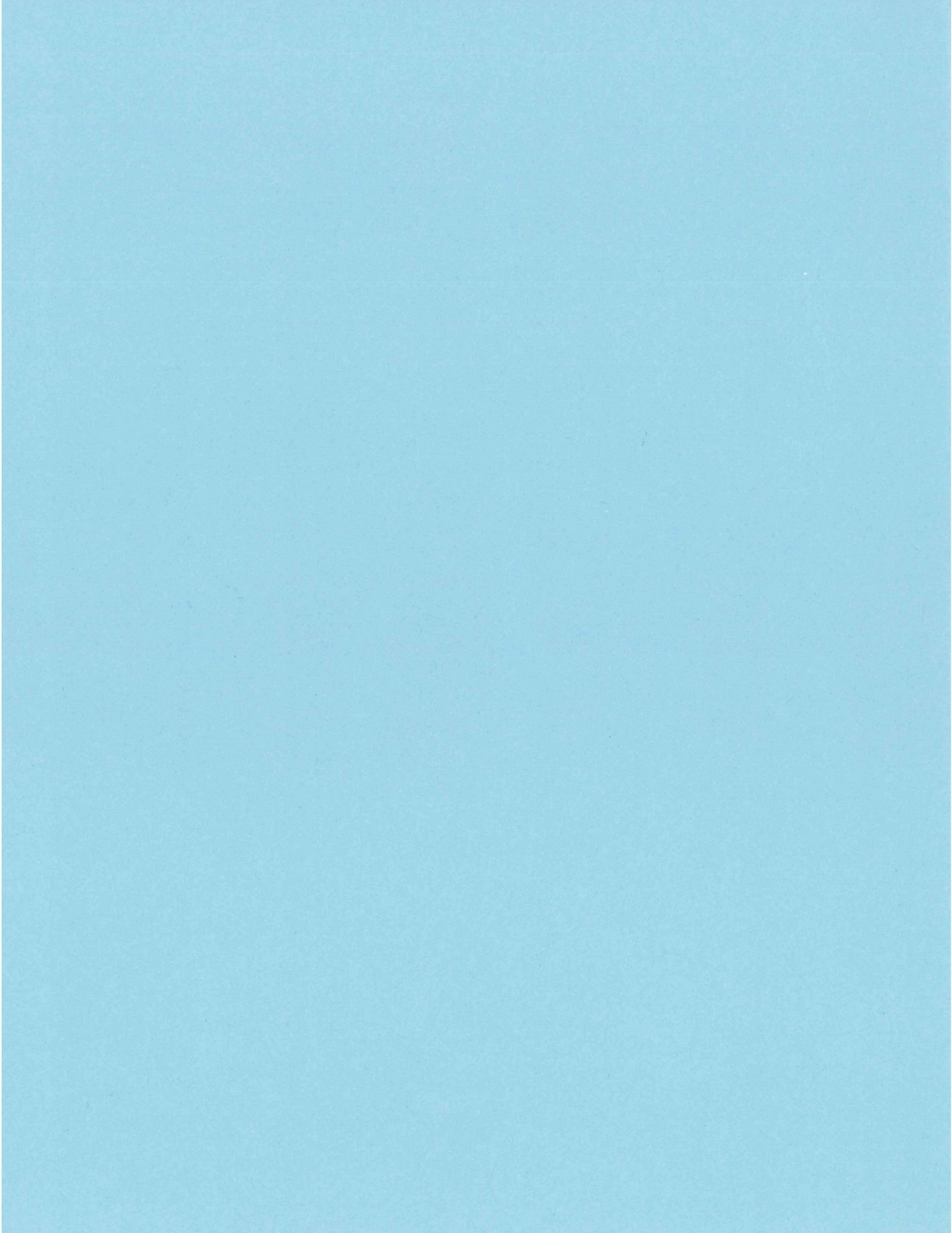
developing and commercializing new rare disease drugs can be expected to have a negative impact on future investment in the development of rare disease drugs like PROCYSBI.

September 9th, 2019

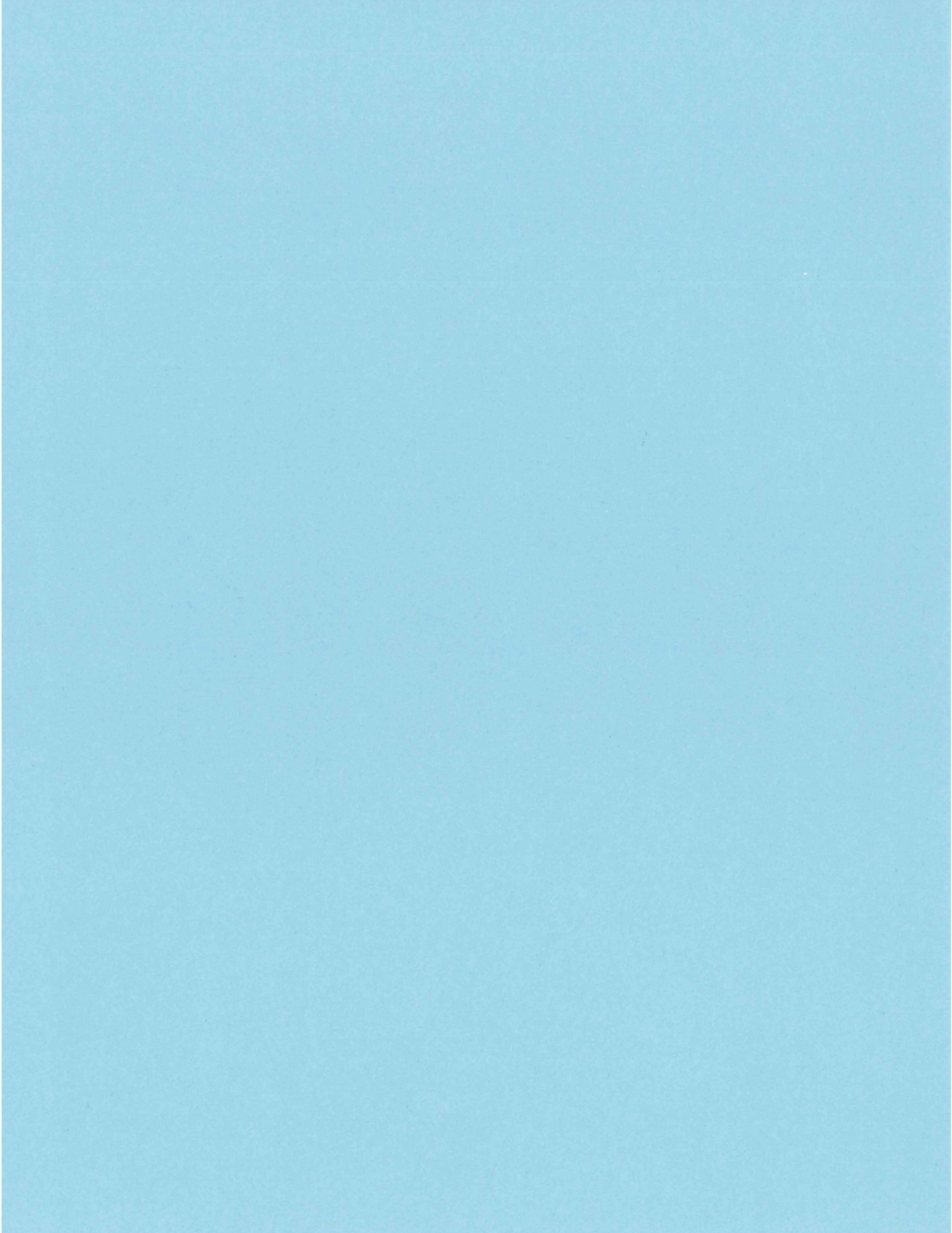
A handwritten signature in black ink that reads "Joel W. Hay". The signature is written in a cursive, flowing style.

Joel W. Hay

APPENDIX A. CURRICULUM VITAE OF DR. JOEL HAY, PH.D.



APPENDIX B. TESTIMONY EXPERIENCE OF DR. JOEL HAY, PH.D.



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**

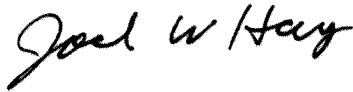
**AND IN THE MATTER OF
Horizon Pharma (the “Respondent”)
and the medicine Cysteamine Bitartrate sold by the Respondent under the trade
name PROCYSBI®**

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.



(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. HNZIP.xlsx (Horizon Financial Information).
- iv. REDACTED
- v. REDACTED
- vi. REDACTED
- vii. REDACTED
- viii. REDACTED

- ix. [REDACTED]
- x. [REDACTED]
- xi. [REDACTED]
- xii. Horizon Pharma PLC, Form 2 - Block 5, January to June 2019.

D. Publicly Available Documents

Scholarly Articles and Book Chapters

- i. 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.
- ii. Adams, C.P. (2006). Estimating the Cost of New Drug Development: Is it Really \$802 million? *Health Affairs*, 25(2): 420-428.
- iii. Asbury, C. H. (1991). The Orphan Drug Act: The First 7 Years. *JAMA: The Journal of the American Medical Association*, 265(7): 893-897.
- iv. 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.
- v. Berdud, M. et al. (2018). *Establishing a Reasonable Price for an orphan drug*. U.K. Office of Health Economics.
- vi. Blackman, G. and Zeckhauser, R. (1992). Fragile Commitments and the Regulatory Process. *Yale Journal on Regulation*, 9(1): 73-103.
- vii. Brennan, M.J. and Schwartz, E.S. (1982). Consistent Regulatory Policy under Uncertainty. *Bell Journal of Economics*, 13(2): 506-521.
- viii. 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.
- ix. Brouwer, W.B. et al. (2006). A Dollar is a Dollar is a Dollar—Or is It? *Value in Health*, 9(5): 341-347.
- x. Cadieux B., Lapidus D. and Greenbaum L.A. (2014) Adherence to Cysteamine and Kidney Outcomes among 224 Cystinosis Patients. Annual Meeting of the American Society of Pediatric Nephrology, Vancouver, 2014.
- xi. 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.
- xii. 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.

- xiii. DiMasi J.A., Mitchell J. and Hay J.W. (1994). The Cost of Drug Development. *Pharmacy and Therapeutics*, 9(1): 68-80.
- xiv. DiMasi, J.A. et al. (2003). The Price of Innovation: New Estimates of Drug Development Costs. *Journal of Health Economics*, 22(2): 151-185.
- xv. 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.
- xvi. 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.
- xvii. Dohil, R. et al. (2006). Understanding Intestinal Cysteamine Bitartrate Absorption. *The Journal of Pediatrics*, 148(6): 764-769.
- xviii. Dohil, R. et al. (2010). Twice-Daily Cysteamine Bitartrate Therapy for Children with Cystinosis. *The Journal of Pediatrics*, 156(1): 71-75.
- xix. Dohil, R. et al. (2010). Long-Term Treatment of Cystinosis in Children with Twice-Daily Cysteamine. *The Journal of Pediatrics*, 156(5): 823-827.
- xx. 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.
- xxi. Drummond, M.F. (2008). Challenges in the Economic Evaluation of Orphan Drugs. *Eurohealth* 14(2): 16-17.
- xxii. 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;
- xxiii. 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.
- xxiv. 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.
- xxv. Ernst, R. (2006). Indirect Costs and Cost-Effectiveness Analysis. *Value in Health*, 9(4): 253-261.
- xxvi. 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.
- xxvii. Gilbert, R.J. and Newbery, D.M. (1994). The Dynamic Efficiency of Regulatory Constitutions. *The Rand Journal of Economics*, 25(4): 538-554.
- xxviii. 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.
- xxix. 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.

- xxx. Grabowski, H. et al. (2012). Does Generic Entry Always Increase Consumer Welfare. *Food & Drug Law Journal*, 67(3): 373-91
- xxxi. 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.
- xxxii. Haffner, M.E. (2006). Adopting Orphan Drugs—Two Dozen Years of Treating Rare Diseases. *New England Journal of Medicine*, 354(5): 445-447.
- xxxiii. Hay, J.W. (2004). Evaluation and Review of Pharmacoeconomic Models. *Expert Opinion on Pharmacotherapy*; 5(9): 1867-1880.
- xxxiv. 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.
- xxxv. 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.
- xxxvi. 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.
- xxxvii. 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.
- xxxviii. Hay, M. et al. (2014). Clinical Development Success Rates for Investigational Drugs. *Nature Biotechnology*, 32(1): 40-51.
- xxxix. 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.
- xl. 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.
- xli. 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.
- xlii. Kanavos, P. et al. (2017). *The Implementation of External Reference Pricing within and across Country Borders*. London School of Economics.
- xliii. Karpman, D. and Höglund, P. (2017). Orphan Drug policies and use in Pediatric Nephrology. *Pediatric Nephrology*, 32(1): 1-6.

- xliv. 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.
- xlv. Krol, M. et al. (2013). Productivity Costs in Economic evaluations: Past, Present, Future. *Pharmacoeconomics*, 31(7), 537-549.
- xlvi. Levy, B. and Spiller, P.T. (1994). The Institutional Foundations of Regulatory Commitment: A Comparative Analysis of Telecommunications Regulation. *The Journal of Law, Economics, and Organization*, 10(2): 201-246.
- xlvii. Lichtenberg, F.R. (2001). Are the Benefits of Newer Drugs Worth their Cost? Evidence from the 1996 MEPS. *Health Affairs*, 20(5): 241-251.
- xlviii. 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.
- xliv. Lichtenberg, F.R. (2004). Sources of US Longevity Increase, 1960–2001. *The Quarterly Review of Economics and Finance*, 44(3): 369-389.
 - i. Lichtenberg, F.R. (2007). Importation and Innovation. *Economics of Innovation and New Technology*, 16(6): 403-417.
 - ii. Lillquist, E. and Green, S. (2010). The Discipline Dependence of Citation Statistics. *Scientometrics*, 84(3): 749-762.
 - lii. Lu, Z.J. and Comanor, W.S. (1998). Strategic Pricing of New Pharmaceuticals. *Review of Economics and Statistics*, 80(1): 108-118
 - liii. Mestre-Ferrandiz, J. et al. (2012). *The R&D Cost of a New Medicine*. U.K. Office of Health Economics.
 - liv. 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. Edward Elgar.
 - lv. Murphy, K M. and Topel, R. H. (2006). The Value of Health and Longevity. *Journal of Political Economy*, 114(5): 871-904.
 - lvi. National Research Council of the National Academies. (2011). *Reference Manual on Scientific Evidence, Third Edition*. National Academies Press.
 - lvii. 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.
 - lviii. Ollendorf, D.A. et al. (2017). *Assessing the Effectiveness and Value of Drugs for Rare Conditions*, Institute for Clinical and Economic Review.
 - lix. 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.
 - lx. 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.

- lxi. Scherer, F.M. (2001). The Link Between Gross Profitability and Pharmaceutical R&D Spending. *Health Affairs*, 20(5): 216-220.
- lxii. Schwartz, L.M. and Woloshin, S. (2019). Medical Marketing in the United States, 1997-2016. *JAMA*, 321(1), 80-96.
- lxiii. 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.
- lxiv. 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.
- lxv. Simoens, S. et al. (2013). Cost-Effectiveness Assessment of Orphan Drugs. *Applied Health Economics and Health Policy*, 11(1): 1-3
- lxvi. Tambuyzer, E. (2010). Rare Diseases, Orphan Drugs and their Regulation: Questions and Misconceptions. *Nature Reviews Drug Discovery*, 9(12): 921-929.
- lxvii. Vernon, J.A. (2005). Examining the Link Between Price Regulation and Pharmaceutical R&D Investment. *Health Economics*, 14(1): 1-16.
- lxviii. 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.
- lxix. Vogler, S. and Martikainen, J.E. (2015). Pharmaceutical Pricing in Europe. In Z. Babar (ed.), *Pharmaceutical prices in the 21st Century*: 343-370. Springer.
- lxx. Yin, W. (2008). Market Incentives and Pharmaceutical Innovation. *Journal of Health Economics*, 27(4): 1060-1077.

Other Publicly-Available Information

- lxxi. 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>.
- lxxii. 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>
- lxxiii. Canadian Agency for Drugs and Technologies in Health, About CADTH, available at <https://www.cadth.ca/about-cadth>.
- lxxiv. Canadian Agency for Drugs and Technologies in Health, Guidelines for the Economic Evaluation of Health Technologies: Canada, 4th Edition, available at https://www.cadth.ca/sites/default/files/pdf/guidelines_for_the_economic_evaluation_of_health_technologies_canada_4th_ed.pdf.

- lxxv. 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>.
- lxxvi. Council of the Federation, “The Pan Canadian Pharmaceutical Alliance”, available at <http://www.canadaspremiers.ca/pan-canadian-pharmaceutical-alliance>.
- lxxvii. CYSTADROPS, Health Canada NOC Database, available at <https://health-products.canada.ca/noc-ac/info.do?lang=en&no=21855>.
- lxxviii. 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>.
- lxxix. Deloitte, *Price Forecast December 31, 2018*, available at https://www2.deloitte.com/content/dam/Deloitte/ca/Documents/REA/ca-en-og-price-forecast-q4-2018-aoda_DC9AAB40.pdf.
- lxxx. 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.
- lxxxi. 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.
- lxxxii. Health Canada Drug Products Database, available at <https://health-products.canada.ca/dpd-bdpp/index-eng.jsp>
- lxxxiii. 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>.
- lxxxiv. Horizon Pharma Annual Report 2016.
- lxxxv. Horizon Pharma Annual Report 2017.
- lxxxvi. Horizon Pharma plc Form 10-Q for the Quarterly Period Ended March 31, 2017.
- lxxxvii. Horizon Pharma plc Form 10-Q for the Quarterly Period Ended June 30, 2017.
- lxxxviii. Horizon Pharma plc Form 10-Q for the Quarterly Period Ended September 30, 2017.
- lxxxix. Horizon Pharma plc Form 10-K for the Fiscal Year Ended December 31, 2017,
- xc. Horizon Pharma Annual Report 2018.
- xc. “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>.
- xcii. “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 <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.

- xciii. Joel Hay – Google Scholar Citations, available at <https://scholar.google.com/citations?user=vKK2BxEAAAJ&hl=en>.
- xciv. 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/raptoru_csdagreement.htm.
- xcv. 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>.
- xcvi. *Patent Act*, RSC 1985, c P-4, available at <https://laws-lois.justice.gc.ca/PDF/P-4.pdf>.
- xcvii. 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>.
- xcviii. 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>.
- xcix. Patented Medicine Prices Review Board, Exchange Rates 2019, available at <https://www.pmprb-cepmb.gc.ca/view.asp?ccid=1426&lang=en>
 - c. 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>.
 - ci. 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>.
 - cii. 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>.
 - ciii. PROCYSBI, Health Canada NOC Database, available at <https://health-products.canada.ca/noc-ac/info.do?lang=en&no=19408>.
 - civ. Raptor Pharmaceuticals Corp. Form 10-K For the Fiscal Year Ended August 31, 2012.
 - cv. Raptor Pharmaceuticals Corp. Form 10-Q For the Quarter Ended March 31, 2013.

- cvi. Raptor Pharmaceuticals Corp. Form 10-K For the Fiscal Year Ended December 31, 2015.
- cvi. Raptor Pharmaceuticals Corp. Form 10-Q For the Quarter Ended June 30, 2016.
- cviii. “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>.
- cix. “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/rptprls_043013.htm.
- cx. “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/rptpr091213_euprocysapprvl.htm.
- cx. “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>.
- cxii. Statistics Canada. Table 18-10-0030-01 - Industrial product price index, by product, monthly, available at <https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1810003001>.
- cxiii. The World Bank, World Development Indicators Databank, available at <https://databank.worldbank.org/source/world-development-indicators>.
- cxiv. 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.
- cxv. U.S. Bureau of Labor Statistics, CPI Inflation Calculator, available at <https://data.bls.gov/cgi-bin/cpicalc.pl>.
- cxvi. U.S. Food & Drug Administration, NDA at the FDA, available at <https://www.fda.gov/media/105012/download>.
- cxvii. U.S. Food & Drug Administration, Orphan Drug Act - Relevant Excerpts, available at <https://www.fda.gov/industry/designating-orphan-product-drugs-and-biological-products/orphan-drug-act-relevant-excerpts>.
- cxviii. U.S. Food & Drug Administration, Orphan Drug Designations and Approvals, available at <https://www.accessdata.fda.gov/scripts/opdlisting/oopd>.
- cxix. 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>.

CONFIDENTIAL-CONFIDENTIEL and s. 87 *Patent Act* Privilege

- cxx. 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>.
- cxxi. World Health Organization, Health Technology Assessment, available at https://www.who.int/medical_devices/assessment/en.
- cxxii. World Health Organization (2015). *WHO Guideline on Country Pharmaceutical Pricing Policies*. Geneva: World Health Organization.

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 Farmaceutici S.p.A. for an upfront payment of USD\$72.5 million, with additional potential milestone payments based certain on sales thresholds.⁵ Horizon

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]

[REDACTED]

[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; HN2P.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 cysteamine 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 HNZIP.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] 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

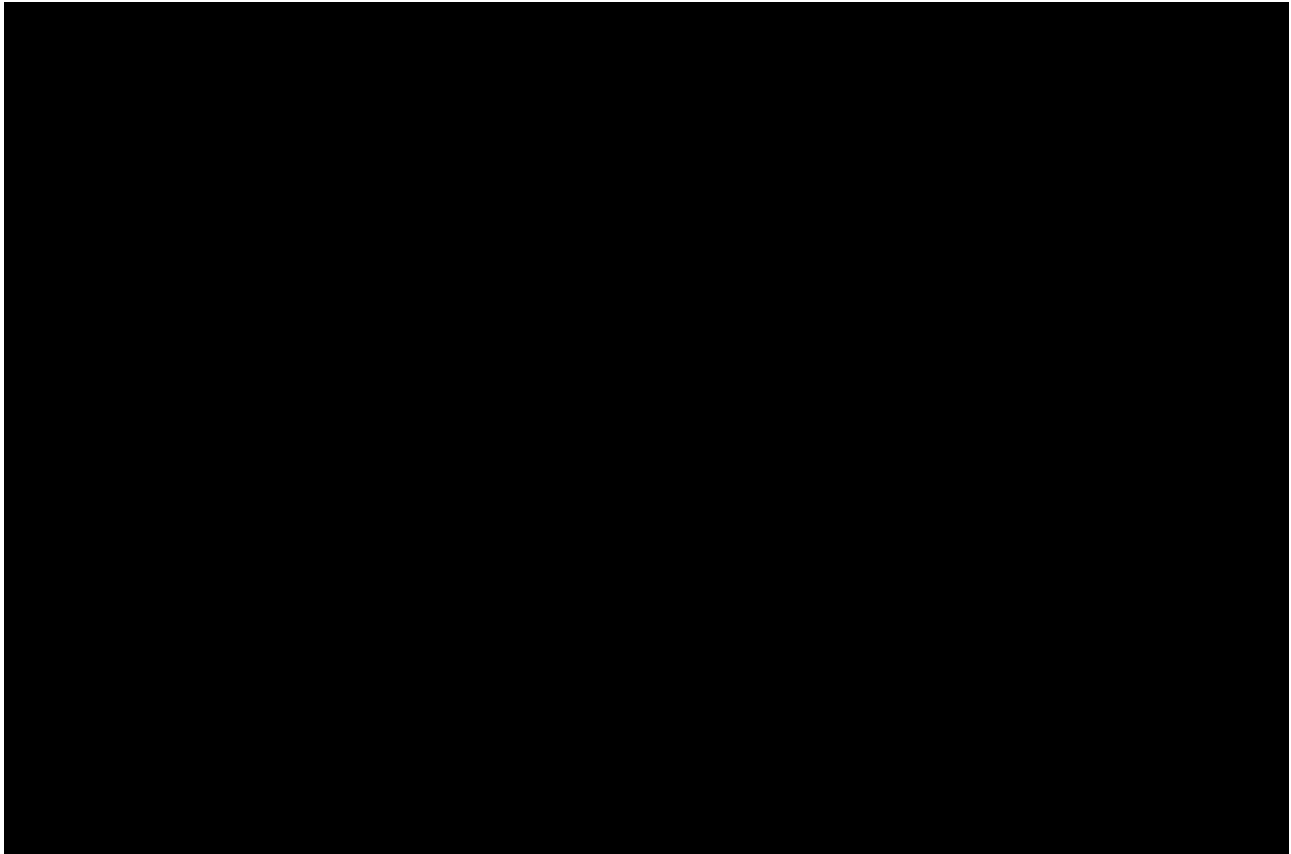
[REDACTED]

5.

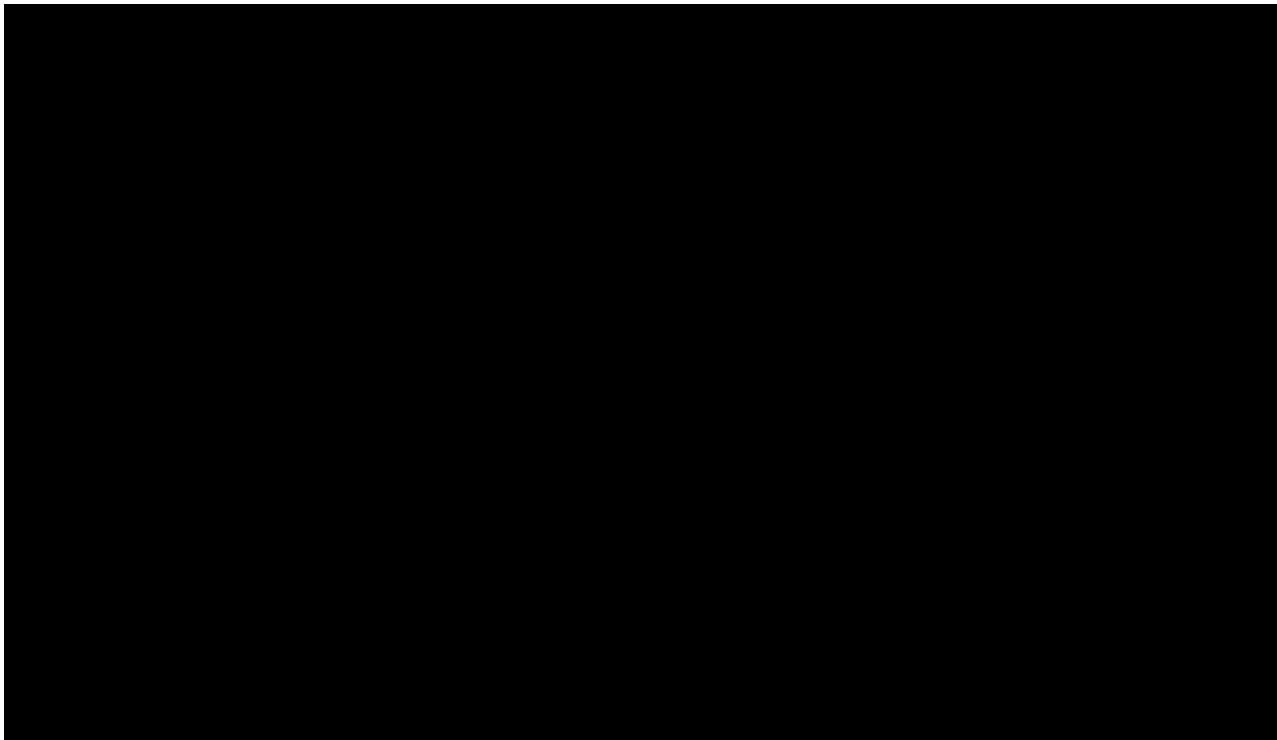
[REDACTED]

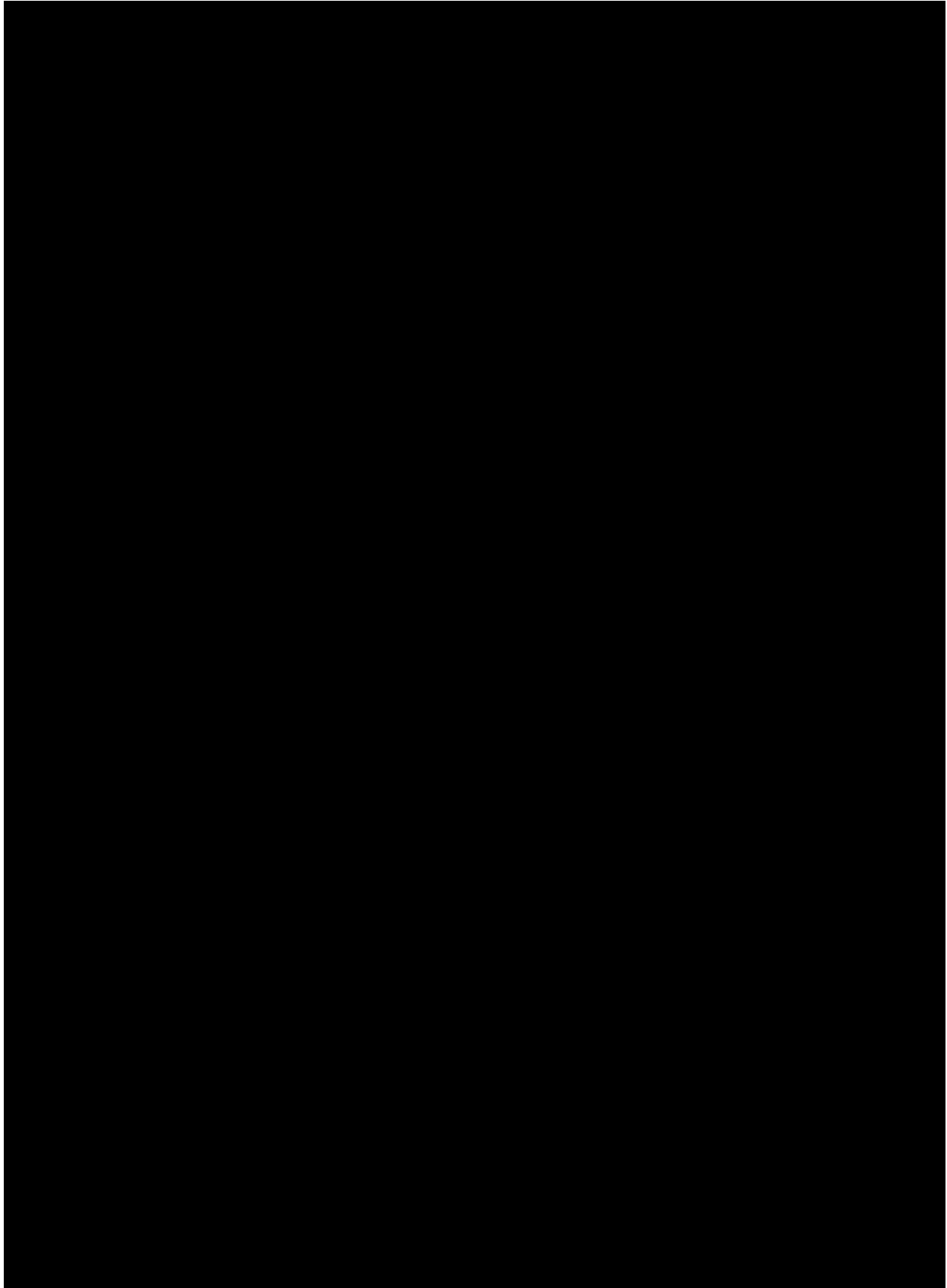
[REDACTED]

[REDACTED]



2. Ex-Factory Prices and Discounts on Sales of PROCYSBI





10. Horizon has indicated that it also provides [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]

[REDACTED]. Horizon has provided me with information on its other cost of sales for PROCYSBI in 2017 and 2018, as well as five-year forecasts [REDACTED] that it has prepared in the ordinary course of business. [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 five-year forecasts [REDACTED]

[REDACTED] that it has prepared in the ordinary course of business. I summarize this information in Exhibit D. [REDACTED]

[REDACTED]

[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.

[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 five-year forecasts [REDACTED] that it has prepared in the ordinary course of business. I summarize this information in Exhibit E. To extend these forecasts out to [REDACTED]

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 Farmaceutici 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

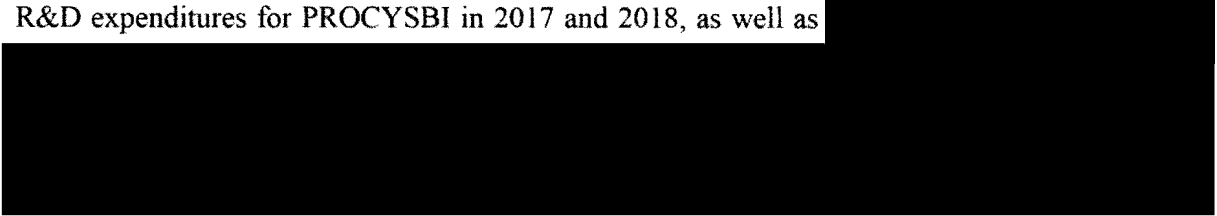
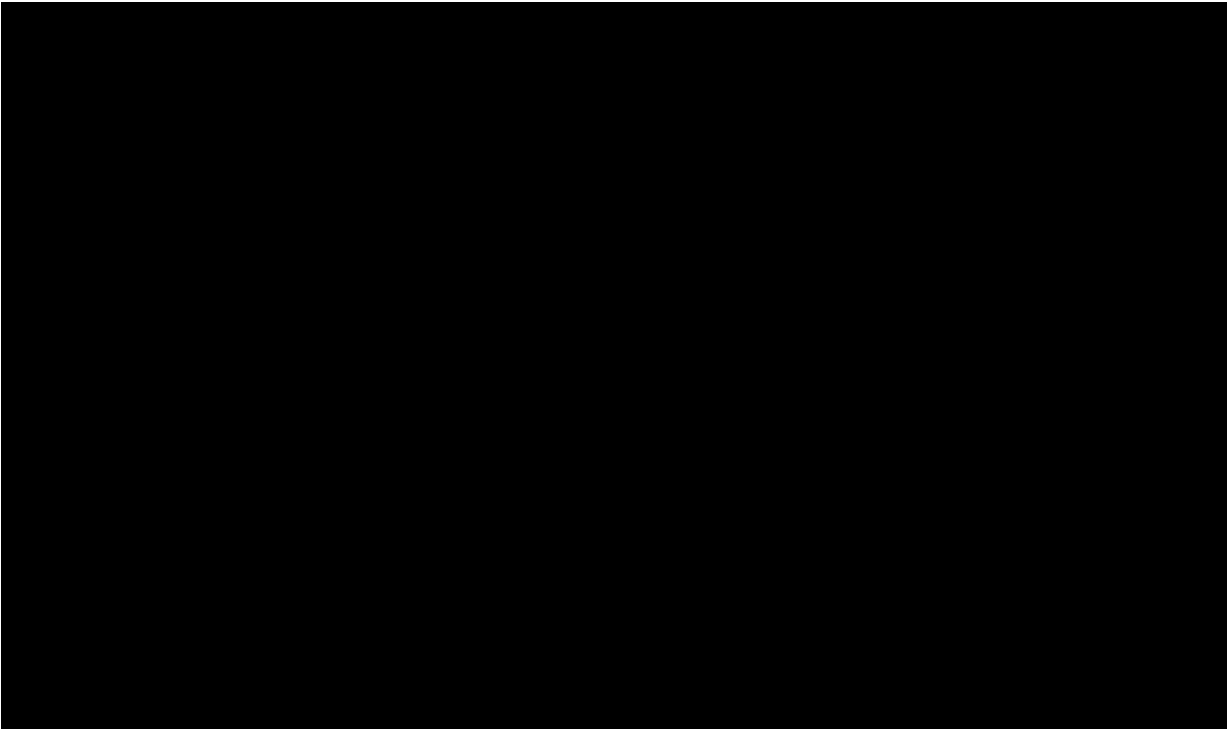
¹⁴ Horizon Pharma Annual Report 2016, F-22-F24; "Horizon Pharma plc Completes Acquisition of Raptor Pharmaceutical Corp." Press Release dated October 25, 2016, available at <https://www.sec.gov/Archives/edgar/data/1070698/000119312516745949/d255637dex99a5ii.htm>

¹⁵ As mentioned in Appendix E, QUINSAIR is not approved for sale in the U.S.

23.



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

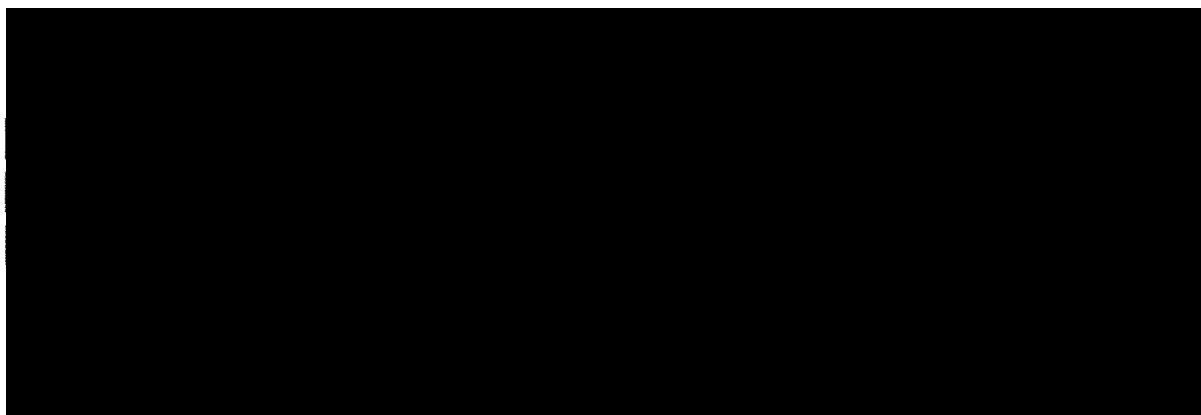
9. Forecasted Net Cash Flows from Sales of PROCYSBI in Canada


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.



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]

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]

[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,

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]
[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]
[REDACTED]

APPENDIX G. SCHEDULES TO FINANCIAL ECONOMIC ANALYSIS

