PMPRB Guideline Submission February 14th, 2020

Thank you for the opportunity to provide feedback on the draft Guidelines published in late November 2019.

We, the signatories to this submission, will provide below some background to our deliberations to set the context though which we considered the Guidelines, provide case studies for your review (attached), provide comments about technical areas of concern about the Guidelines, describe substantive issues from an oncology specific perspective with the Guidelines and provide recommendations to remedy those concerns.

Background

We are aware of the challenges of a duel federal/provincial jurisdiction for aspects of healthcare for people across Canada.

We are also aware that there are inequities in coverage for medications across the country due to several factors. Public systems are the responsibility of provinces and territories and of course each has its own economic engine, priorities, demographics and other factors that drive decisions about how much to spend, what to fund and what funding models to implement. In addition, employers, unions and individuals who can afford them have private plans that provide additional access.

Patients understand that this is the construct we have. We understand that public plans cannot afford to provide access to all drugs that we might need although we trust that they will use instruments that will help make fair, objective and evidence-based choices. We want a sustainable system; we want the prices of drugs to permit sustainability. This is no doubt the appeal of a universal single payer pharmacare plan.

Patient groups continue to support health technology assessment agencies, CADTH and INESSS ,and also pCPA. As for PMPRB, over 20 years ago, the Canadian Treatment Action Council , a

national patient driven HIV organization, chaired by Louise Binder, a representative of one of the signatories to this submission, advocated strongly to the PMPRB and the then federal Minister of Health, (including holding a public protest) that the Regulations for PMPRB be amended to remove the U.S. from the basket as an outlier, with high drug prices, and with health policies inconsistent with our health system. Finally, this is happening.

Patient organizations support the reassessment of the current basket of reference countries proposed for PMPRB consideration.

It is also important in our view to remember the history of cancer management in Canada:

- In 2007 the House of Commons Standing Committee on Health heard evidence that cancer treatments required their own health technology assessment process to ensure that value is analyzed based on factors relevant to that complex group of diseases. The Committee agreed with these recommendations. The result of those hearings was the creation of pCODR with a four-part deliberative Framework as its HTA process.
- The federal government also created a cancer strategy stewarded by the Canadian Partnership Against Cancer.
- Provinces have cancer agencies to manage cancer generally, including drug reimbursement, separately from other treatments.

The statistics regarding cancer certainly make the case for this specific focus on cancer:

- It is the number 1 cause of death in Canada.
- It is estimated that 1 of 2 people in Canada will be diagnosed with cancer in their lifetime.
- 1 in 4 will die from it, or 821,000 in Canada.

This is a huge public health issue that requires a discreet policy approach, as the governments have recognized.

In addition, as we know, there is not just one type of cancer, one stage of cancer or one cause of cancer:

- There are cancers that are uncommon and those that are more common.
- There are cancers for which research has found genetic links that inform prevention and treatment and those that have not.
- There are cancers that can be cured.
- There are cancers that can be effectively and have been transformed into chronic illnesses with newer, more effective treatments; yet, there are many that continue to be a certain death sentence within months of diagnosis.

Breast cancer: The most common cancer among women, both young and older people alike, is breast cancer. In 2019, 26,900 women were diagnosed with breast cancer and 5,000 will die of this disease. 230 men will also be diagnosed with breast cancer. Among women, between 5 and 10% of breast cancers are thought to be hereditary. The BRCA1 and BRAC2 have been known to be linked with a higher link of breast cancer. More recently, a study in 2017 found 72 new genetic mutations linked to breast cancer and now under study.

Colorectal cancer: Colorectal cancer is the number 2 leading cause of death from a cancer. 50% of cases are diagnosed at stage III and IV and 9600 died of this cancer in 2019.

Lung cancer: Lung cancer has a 29,300 incidence and 21,000 will die each year in Canada. It is the leading cause of cancer deaths for males and females at 25 % and 26 % respectively. Contrary to public opinion, it is not just a disease of those who smoke. Unlike breast cancer, no genetic links have been discovered related this disease. There are certain "signatures" within the lung cancer cell that determine which oral cancer therapies to use. It has a 19% five year survival rate compared to 93 % in prostate cancer, 88% in breast and 65% in colorectal.

Uncommon cancers: There are also uncommon cancers like gastrointestinal stromal tumours (GIST) with unknown prevalence and incidence levels in Canada but estimated at about 400 cases. Genetic testing is recommended to guide treatment decisions for high risk resected and advanced GIST

Paediatric cancers: In young people, approximately 3,800 children, adolescents and young adults aged 0 to 29 years of age are diagnosed with cancer each year in Canada in 2019. 1,500 children and adolescents aged between 0 and 19 were diagnosed with cancer in Canada. Cancer is the second most common cause of death for children in the developed world, after accidents. 416 Canadian children will die of cancer every year. The five-year survival rate for Canadian children has improved from 71% to 82% due to access to new treatments. Without treatment these cancers are fatal.

In our submission the PMPRB, as another agency of the federal government, must recognize that government policy has determined that oncology is a discreet group of diseases for public policy purposes. The signatories to this submission strongly support public policy in this regard.

Until the Guidelines were issued in late November 2019, patient groups had no defined concrete formula or processes by which to determine whether the planned changes will consider public policy regarding oncology and, therefore, whether it will be a good public policy instrument. We do not want another health technology instrument that is less robust than those we presently have.

In order to ensure an objective, evidence based and expert analysis of the Guidelines, we asked an external consultant to assist us. Specifically we asked him to look at a number of oncology drugs for different types of cancer that have been reviewed by pCODR fairly recently and to compare the outcomes they received through that process with the outcomes we can predict they would have had under the proposed Guidelines with the information available to us.

Case studies

Attached are the six case studies analyzed by the health economics expert. We chose these because they are drugs that have been reviewed recently by pCODR so we have numbers for them – at least those that are in the public domain.

Conclusions

It is clear that oncology needs its own approach in these Guidelines, as the federal and provincial governments have recognized in other health policies. It is clear that this approach must be flexible enough to recognize the differences between uncommon and more common cancers, difference stages of cancer, genetic factors, paediatrics versus adults, comorbidities, Indigenous populations and social determinants of health, to name a few. This blunt instrument may be workable for some diseases. The case study analysis clearly demonstrates that we need a much more nuanced, flexible and pragmatic instrument is required for cancers.

In two cases the impact of the Guidelines is minimal in terms of pricing changes required and probably will not change the decision about whether or when the drug will come to market in Canada.

In the vast majority of cases, however, the use of this one blunt health technology instrument, the single criterion of an ICER, will generally not make it a practical economic business decision to bring this drug to Canada, or at least not to put it high on the list for applications relative to other countries for market entry.

CADTH's deliberative framework for oncology drugs, with four considerations, including clinical benefit, cost effectiveness, patient values and feasibility of adoption, has recognized this nuanced, flexible and pragmatic health technology assessment required for oncology drugs. This is a recognition that there are limitations of using a single outcome measure for economic evaluation, since doing so that important health consequences are excluded. INESSS also takes into account public and patient values into its health technology assessment considerations.

Recommendation #1

The Guidelines be amended to adopt explicitly the CADTH pCODR deliberative framework for oncology health technology assessment and remove any specific reference to an ICER.

Recommendation #2

The Guidelines be amended to provide that PMPRB's public decision will provide information that the analysis has either met the PMPRB threshold and is not excessive or that it has not met the PMPRB threshold or other CADTH analysis and is excessive. No specific economic data or numbers supporting this decision will be made public by PMPRB. This will ensure that the public Canadian price will not put at risk the U.S. market such that companies will decline to enter, or delay, the Canadian market for that reason.

Recommendation #3

The Guidelines be amended to provide for ongoing monitoring and evaluation by a multi-stakeholder Committee and a publicly issued annual report of findings of this Committee. At least two patient group representatives chosen by the patient community, with one from the cancer community, will be included.

Recommendation #4

No Guideline finalization should take place until a full consultation is undertaken with Quebec stakeholders including patient groups and patients with all documents and consultations taking place in both Official languages.

Recommendation #5

No Guideline finalization should take place until a full consultation is undertaken with Indigenous stakeholders *i.e.* First Nations, Metis and Inuit including patient groups and patients following a process of their choosing.

Technical issues to be resolved

1. PMPRB states that it will rely on the base case reanalysis conducted by the public agency (i.e. CADTH and/or INESSS). pCODR does not presently generally do a base case reanalysis and INESSS does one in some cases but not all. This will require coordination amongst the agencies.

2. pCODR builds in the price for companion diagnostics. The manner in which this will be analyzed and taken into account by PMPRB must be clarified and should be described in the Guidelines.
3. pCODR does not do weighted averages for subgroups. PMPRB requires these. This will require coordination between the agencies for resolution.

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PMPRB ceiling price proposed guidelines – November 2019 Oncology Case Studies (2020-02-13 ver1.1)

Introduction

The PMPRB proposed guidelines of November 2019 are used in this analysis to estimate plausible MRPs (maximum rebated prices) of six oncology drugs that have recently been reviewed by CADTH and are now being covered in Canada. These estimates of the MRP these drugs may have gained under the proposed guidelines are compared with plausible estimates of the prices at which these drugs have been covered in Canada (the actual prices at which these drugs are covered are confidential and, thus, estimates of these prices are best guesses). This comparison results in an estimate of the price reduction from our best guess of current prices that would be required for each drug to be considered compliant with the PMPRBs proposed pricing regulations. Depending on the size of these price reductions, we estimate whether or not the drug is very likely, likely, unlikely or very unlikely to have been supplied in Canada had these guidelines been in place when these drugs were considering entering the Canadian market. This judgement has as an underlying assumption that the PEP, and subsequently the MRP, will be, in effect, transparent to the world under the proposed guidelines.

The value of this analysis is to look at drugs that are now currently available and providing real known benefits to Canadians but are very likely to be assessed as providing poor value for money (under a cost effectiveness framework). Their potential loss to the Canadian health system would have tangible and known effects. By comparison, analysis of drugs that are not yet in our market would have unknown effects, effects in principle, and thus, an unknown sense of loss. We believe this assists us in understanding the value to patients (and society) of drugs that appear to be of low value when assessed solely through the Cost Effectiveness Analysis lens.

The six drugs reviewed to date are:

- Vencexta (venetoclax) – a drug for treating chronic lymphocytic leukaemia (CLL) among patients who have failed at least one prior therapy (and, therefore, have no further treatment options);
- Opdivo (nivolumab) – for (among many other indications) adjuvant treatment of fully resected melanoma;
- Darzalex (daratumumab) – for treatment (in combination with other medicines) of multiple myeloma in patients who have failed at least one other prior therapy (and, therefore, have few further options);
- Blincyto (blinatumomab) – for treatment of pediatric patients with Philadelphia chromosome-negative relapsed or refractory B precursor acute lymphoblastic leukemia (a small group of patients - 40 a year - who face no alternatives and a very high likelihood of death);
- Unituxiini (dinutuximab) – for use in combination with other drugs for the treatment of pediatric patients with high-risk neutoblastoma who achieve at least a partial response to prior therapy (a group of around 25 to 35 children a year); and
- Tagrisso (Osimertinib) - for the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (EGFR) mutations (a relatively large group of around 2,000 patients annually).

Venclexta (venetoclax)

Estimation of MRP

Indication (coverage requested): As monotherapy for the treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy and who have failed a B-Cell Receptor Inhibitor (BCRi)

Item	CADTH Base Case	CADTH Best Case	CADTH Worst Case
ICER threshold (a)		60,000	60,000
Incremental QALYs (b)		2.59	0.05
Incremental costs (c)		359,506	69,300
Treatment costs (d)		355,409	62,181
PharmacoEconomic Price - PEP (e*(a*b+d-c)/d) - $/mg		0.289	-0.047
Likely current market price - $/mg		0.476	0.476
Submitted public price (e) - $/mg		0.680	0.680
Percent reduction of likely current price			
At PEP		39%	>100%
Where revenue at $37.5M a year		41%	>100%
Where revenue at $62.5M a year		45%	>100%

NOT AVAILABLE

Assumptions:
- Estimation of MRP would be determined from the stated indication.
- Treatment cost is not reported in the CADTH reports so treatment cost is estimated from reported median treatment duration and dosing regimen for the submitted base case and then used as a proportion of the incremental treatment costs reported for the best and worst cases.
- Likely current market price is estimated at 30% price submitted to CADTH [anecdotally, this is considered conservative].

Interpretation of results

The proposed guidelines intend to use the CADTH Base Case estimates to determine the PEP. Never-the-less, CADTH do not report base case estimates for venetoclax indicating that a base case was not deliberated on or, in essence, adjudicated by an expert committee independent of the PMPRB.

The negative estimate of the PEP under the CADTH Worst Case deliberations indicates that venetoclax would have to be supplied along with a payment from the supplier for it to be considered compliant with the proposed pricing regulations. Clearly, this is not a possible price for a drug in a market and indicates there are some situations where the proposed formula does not work.

The best and worst case deliberations reported by CADTH indicate that the price reduction from best estimates of the current price would need to be somewhere between 39% and near 100% to be compliant with the proposed regulations.

At the mid-point between these estimates – a 70% price reduction from our best guess of the current price or an equivalent internationally visible price at around 80% below the publicly submitted price, we judge that it would be **very unlikely** that venetoclax would have been submitted for consideration of supply into the Canadian market.

Opdivo (nivolumab)

Estimation of MRP

Indication (coverage requested): as monotherapy, for the adjuvant treatment of adult patients after complete resection of melanoma with regional lymph node involvement, in transit metastases/satellites without metastatic nodes, or distant metastases.

Item	CADTH Base Case	CADTH Best Case	CADTH Worst Case
ICER threshold (a)		60,000	60,000
Incremental QALYs (b)		1.31	0.92
Incremental costs (c)		87,974	87,191
Treatment costs (d)		96,062	102,856
PharmacoEconomic Price - PEP (e*(a*b+d-c)/d) - $/mg		17.732	13.538
Likely current market price - $/mg		13.755	13.755
Submitted public price (e) - $/mg		19.650	19.650
Percent reduction of likely current price			
At PEP		0%	2%
Where revenue at $37.5M a year		0%	5%
Where revenue at $62.5M a year		0%	10%

NOT AVAILABLE

Assumptions:
- Estimation of MRP would be determined from the stated indication.
- Likely current market price is estimated at 30% price submitted to CADTH [anecdotally, this is considered conservative].

Interpretation of results

The proposed guidelines intend to use the CADTH Base Case estimates to determine the PEP. Never-the-less, CADTH do not report base case estimates for **opdivo** indicating that a base case was not deliberated on or, in essence, adjudicated by an expert committee independent of the PMPRB.

The best and worst case deliberations reported by CADTH indicate that the price reduction from best estimates of the current price would need to be somewhere between 0 and 10% to be compliant with the proposed regulations.

At the mid-point between these estimates – a 5% price reduction from our best guess of the current price or an equivalent internationally visible price at around 25% below the publicly submitted price, we judge that it would be **likely** that nivolumab would have been submitted for consideration of supply into the Canadian market.

Darzalex (daratumumab)

Indication (coverage requested): In combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy.

In combination with lenalidomide and dexamethasone

Item	CADTH Base Case	CADTH Best Case	CADTH Worst Case
ICER threshold (a)		60,000	60,000
Incremental QALYs (b)		3.76	0.71
Incremental costs (c)		622,746	422,874
Treatment costs (d)		498,197	338,299
PharmacoEconomic Price - PEP (e*(a*b+d-c)/d) - $/mg		1.213	-0.742
Likely current market price - $/mg		4.186	4.186
Submitted public price (e) - $/mg		5.980	5.980
Percent reduction of likely current price			
At PEP		71%	>100%
Where revenue at $37.5M a year		72%	>100%
Where revenue at $62.5M a year		74%	>100%

NOT AVAILABLE

In combination with bortezomib and dexamethasone

Item	CADTH Base Case	CADTH Best Case	CADTH Worst Case
ICER threshold (a)		60,000	60,000
Incremental QALYs (b)		1.72	0.91
Incremental costs (c)		189,690	178,583
Treatment costs (d)		151,752	142,866
PharmacoEconomic Price - PEP (e*(a*b+d-c)/d) - $/mg		2.572	0.790
Likely current market price - $/mg		4.186	4.186
Submitted public price (e) - $/mg		5.980	5.980
Percent reduction of likely current price			
At PEP		39%	81%
Where revenue at $37.5M a year		41%	82%
Where revenue at $62.5M a year		44%	83%

NOT AVAILABLE

Assumptions:
- Estimation of MRP would be determined from the stated indication.
- Treatment cost is not reported in the CADTH reports so treatment cost is assumed to be a constant proportion (80%) of the incremental cost.
- Likely current market price is estimated at 30% price submitted to CADTH [anecdotally, this is considered conservative].

Interpretation of results

The proposed guidelines intend to use the CADTH Base Case estimates to determine the PEP. Never-the-less, CADTH do not report base case estimates for daratumumab indicating that a base case was not deliberated on or, in essence, adjudicated by an expert committee independent of the PMPRB.

The proposed guidelines intend to calculate a weighted average of the PEP for an indication where there are clear sub-populations for which a PEP for each can be determined. However, the CADTH reports do not provide any information to enable a weighted average to be calculated in this instance.

The negative estimate of the PEP under the CADTH Worst Case deliberations for the lenalidomide with dexamethasone combination indicates that daratumumab would have to be supplied along with a payment from the supplier for it to be considered compliant with the proposed pricing regulations. Clearly, this is not a possible price for a drug in a market and indicates there could be some situations where the proposed formula does not work.

The best and worst case deliberations reported by CADTH indicate that the price reduction from best estimates of the current price would need to be somewhere between 39% and near 100% to be compliant with the proposed regulations.

At the mid-point between these estimates – a 70% price reduction from our best guess of the current price or an equivalent internationally visible price at around 80% below the publicly submitted price, we judge that it would be **very unlikely** that daratumumab would have been submitted for consideration of supply into the Canadian market.

Blincyta (blinatumomab)

Estimation of MRP

Indication (coverage requested): For the treatment of pediatric patients with Philadelphia chromosome-negative relapsed or refractory B precursor acute lymphoblastic leukemia (ALL).

And for the treatment of all adult patients with Philadelphia chromosome-negative relapsed or refractory B-precursor acute lymphoblastic leukemia (ALL), including those who have had one prior line of therapy (i.e., adult patients who are refractory or patients who are in first or later relapse)

Item	CADTH Base Case	CADTH Best Case	CADTH Worst Case
ICER threshold (a)		60,000	60,000
Incremental QALYs (b)		1	0
Incremental costs (c)		158,224	158,270
Treatment costs (d)		154,919	154,964
PharmacoEconomic Price - PEP (e*(a*b+d-c/d) - $/vial		757.72	121.33
Likely current market price - $/vial		2,091.08	2,091.08
Submitted public price (e) - $/vial		2,987.26	2,987.26
Percent reduction of likely current price			
Where revenue < $12.5M		46%	91%
Where revenue at $20M		54%	93%
Where revenue at $40M		61%	94%

NOT AVAILABLE

Assumptions:
- Estimation of MRP would be determined from the adult indication given its likely greater prevalence.
- Blinatumomab would qualify as rare and thus its MRP would be adjusted under rules for rare disease drugs.
- Treatment cost is not reported in the CADTH reports but median treatment cycles and cycle cost is reported for the submitted base case. Treatment costs under the best and worst cases are assumed to be the same constant proportion of the incremental cost calculated from the median cycles and cycle costs reported for the submitted base case.
- Likely current market price is estimated at 30% price submitted to CADTH [anecdotally, this is considered conservative].

Interpretation of results

The proposed guidelines intend to use the CADTH Base Case estimates to determine the PEP. Never-the-less, CADTH do not report base case estimates for blinatumomab indicating that a base case was not deliberated on or, in essence, adjudicated by an expert committee independent of the PMPRB.

The best and worst case deliberations reported by CADTH indicate that the price reduction from best estimates of the current price for blinatumomab would need to be somewhere between 46% and near 94% to be compliant with the proposed regulations.

At the mid-point between these estimates – a 70% price reduction from our best guess of the current price or an equivalent internationally visible price at around 75% below the publicly submitted price, we judge that it would be **very unlikely** that blinatumomab would have been submitted for consideration of supply into the Canadian market.

Unituxiini (dinutuximab)

Estimation of MRP

Indication (coverage requested): for use in combination with GM-CSF, IL-2 and Retinoic acid (RA) for the treatment of pediatric patients with high-risk neuroblastoma who achieve at least a partial response to prior first-line multi-agent, multimodal therapy (a very small group of patients numbering around 25 to 35 a year in Canada).

Item	CADTH Base Case	CADTH Best Case	CADTH Worst Case
ICER threshold (a)	60,000		
Incremental QALYs (b)	4.74		
Incremental costs (c)	347,793		
Treatment costs (d)	313,014		
PharmacoEconomic Price - PEP (e*(a*b+d-c/d) - $/vial	10,247.56		
Likely current market price - $/vial	8,995.00		
Submitted public price (e) - $/vial	12,850.00		
Percent reduction of likely current price			
Where revenue < $12.5M	0%		
Where revenue at $20M	0%		
Where revenue at $40M	0%		

Assumptions:
- Dinutuximab would qualify as rare and thus its MRP would be adjusted under the rules for rare disease drugs.
- Treatment cost is not reported in the CADTH reports but the individual costs of the combination treatment are itemised for a full 6 cycles of treatment. Thus the proportion that dinutuximab (90%) makes up of these costs (less isotretinoin) is used to estimate treatment costs as a proportion of incremental costs.
- Likely current market price is estimated at 30% price submitted to CADTH [anecdotally, this is considered conservative].

Interpretation of results

The base case reanalysis by CADTH indicates that the submitted public price would be below the MRP (assuming market size falls below $12.5M as estimated) and, therefore, compliant with the PMPRB regulations.

Given no price reductions would have been required to be compliant with the PMPRB regulations, we judge that it would be **very likely** that dinutuximab would have been submitted for consideration of supply into the Canadian market.

Tagrisso (osimertinib)

Estimation of MRP

Indication (coverage requested): For the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (EGFR) mutations.

Compared with gifitinib

Item	CADTH Base Case	CADTH Best Case	CADTH Worst Case
ICER threshold (a)		60,000	60,000
Incremental QALYs (b)		0	0
Incremental costs (c)		142,401	141,598
Treatment costs (d)		131,147	130,408
PharmacoEconomic Price - PEP (e*(a*b+d-c/d) - $/vial		0.48	0.36
Likely current market price - $/vial		2.58	2.58
Submitted public price (e) - $/vial		3.68	3.68
Percent reduction of likely current price			
At PEP		87%	90%
Where revenue $200M		88%	91%

NOT AVAILABLE

Compared with ofatinib

Item	CADTH Base Case	CADTH Best Case	CADTH Worst Case
ICER threshold (a)		60,000	60,000
Incremental QALYs (b)		0	0
Incremental costs (c)		138,459	137,686
Treatment costs (d)		130,882	130,152
PharmacoEconomic Price - PEP (e*(a*b+d-c/d) - $/vial		0.53	0.42
Likely current market price - $/vial		2.58	2.58
Submitted public price (e) - $/vial		3.68	3.68
Percent reduction of likely current price			
At PEP		86%	89%
Where revenue $200M		87%	90%

NOT AVAILABLE

Assumptions:
- Treatment cost is not reported in the CADTH reports but median treatment duration is provided for the submitted base case. Together with estimated monthly cost, a cost of treatment with osimertinib is estimated. This cost, as a proportion of incremental costs in the submitted base case, is assumed to be constant in all other cases.
- Likely current market price is estimated at 30% price submitted to CADTH [anecdotally, this is considered conservative].
- Market size is assumed to be significant for this drug because of the incidence and the duration and price of treatment.

Interpretation of results

The proposed guidelines intend to use the CADTH Base Case estimates to determine the PEP. Never-the-less, CADTH do not report base case estimates for osimertinib indicating that a base case was not deliberated on or, in essence, adjudicated by an expert committee independent of the PMPRB.

The proposed guidelines intend to calculate a weighted average of the PEP for an indication where there are clear sub-populations for which a PEP for each can be determined. However, the CADTH reports do not provide any information to enable a weighted average to be calculated in this instance.

The best and worst case deliberations reported by CADTH indicate that the price reduction from best estimates of the current price for osimertinib would need to be somewhere between 86% and 91% to be compliant with the proposed regulations.

At the mid-point between these estimates – a 88% price reduction from our best guess of the current price or an equivalent internationally visible price at around 91% below the publicly submitted price, we judge that it would be **very unlikely** that osimertinib would have been submitted for consideration of supply into the Canadian market.

Administrative and technical observations

- The guidelines anticipate that the cost effectiveness analysis required to make the PEP and MRP calculations will be available from recognised public authorities (i.e. the public HTA bodies used by Canadian jurisdictions) in the form required to make the calculations. Currently, not all the information required to make the calculations is available in the public records from CADTH (note: information from INESSS was not reviewed in this project). While the information may be available in information shared between these public bodies and the PMPRB, these case studies illustrate that the missing information will not have been deliberated on by CADTH's expert committees unless its assessment processes are changed. Thus, unless the assessment processes change, it won't be able to be claimed that all the information used to calculate the PEP has, in effect, been adjudicated by the recognised public HTA body.

- Similarly, the guidelines anticipate calculating a weighted average PEP within an indication where there are multiple treatment sub-groups. Where this occurs, the information to make these weighted averages is not discussed in the CADTH expert committee reports and, thus, is not currently adjudicated by the public HTA body.

- These case studies indicate that there are some circumstances under which the calculated PEP can be negative. While these situations have been encountered in these case studies as a consequence of having to make assumptions about the treatment cost (as this information is frequently missing), it is not valid to conclude that this is an artefact of the assumptions used here. There are realistic scenarios under which the current formula can result in negative numbers being those where the treatment cost makes up a relatively low proportion of the incremental cost. These situations are likely to arise when a new drug is used in combination therapies - which are not uncommon in oncology.