February 12th, 2020

Mr. Douglas Clark
Executive Director
Patented Medicine Prices Review Board
1400 - 333 Laurier Avenue West
Ottawa, ON K1P 1C1

RE: Roche Canada Input on PMPRB Guidelines Consultation

Dear Mr. Clark:

On behalf of Hoffmann-La Roche Limited ("Roche Canada"), please find enclosed feedback to the Patented Medicines Prices Review Board ("PMPRB") as part of the PMPRB Guidelines Consultation process. As a member of both Innovative Medicines Canada ("IMC") and BIOTECanada, Roche Canada has also contributed to and fully supports the submissions from these industry associations.

As noted in our previous submission, Roche is a science-based company, founded on the principles of innovation and collaboration to enable better health outcomes for patients. We pride ourselves on leading the science and advancing the medical community's understanding of the pathology of disease and its response to medicines. We recognize this mission depends on the long-term sustainability of our healthcare system, which ultimately provides patients with access to our innovations and those of other healthcare companies to support improved health outcomes for all Canadians. Roche plays an active role within our healthcare system and we are keen to partner with all relevant stakeholders to help build a system that is not only equitable, but effective and efficient; a system that is built and integrated for the needs of Canadians today and tomorrow.

Clinical Trials in Canada

Our Canadian affiliate is home to one of five Roche global pharmaceutical Product Development sites. We contribute to all phases of clinical development, including overseeing clinical studies in Canada, the US and around the world. In 2018, Roche invested over $57 million in clinical research in Canada through 442 Roche-sponsored clinical trial sites, which offer Canadians with a variety of medical conditions an opportunity to participate in, and benefit from, the development of potential new treatment options.

Clinical trials are an integral part of the drug or diagnostic discovery and development process as they provide evidence about the safety and efficacy of a medicine and important information about clinical value, cost-effectiveness, and impact on a patient's quality of life. Through clinical trials, Canadians can have access to the latest therapies, and Canadian researchers can play a pivotal role in leading the development of biomedical research and innovation.

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As a general comment, we note that Canada competes with the rest of the world in attracting clinical research investment. The pricing reforms, as proposed by the PMPRB, send a message to Global decision-makers that innovation is not a priority for Canada, thereby putting at risk our ability to compete for clinical research investments on the international stage and potentially limiting Canadian patients' early access to improvements in care.

Incentives for Innovation

The new guidelines expand beyond the excessive price standard. Under the current guidelines, innovative medicines that are improvements to current therapies are able to establish a list price that is higher than an inferior product through the categories of Breakthrough, Substantial Improvement or Moderate Improvement. In the draft guidelines, therapeutic improvement is not recognized. Given that the Maximum List Price (MLP) is set by the lower of the Median International Price (MIP) and domestic Therapeutic Class Comparison (dTCC), prices of newer and more effective products will be the same or less than inferior products and therefore provides no financial incentive for innovation.

The new Maximum Rebated Price (MRP) formula that was introduced in the draft guidelines is problematic for many novel products, and provides a disincentive for any first-to-market products. Case Study 1, enclosed with this submission, illustrates an example where a first-to-market product is penalized (i.e. significantly lower Pharmacoeconomic Price (PEP)/MRP) compared to a second entrant. This case illustrates that although there may be an unmet need for this example (a rare disease), a manufacturer would be disincentivized to become the first entrant to the market.

The risk that MRP may be calculated using transparent publicly available data from CADTH and/or INESSS is a particular concern. Global decisions may be made to deprioritize Canadian launches in order to protect other markets if the risk is perceived to be high. There is research that suggests lower prices have been linked to fewer launches[1] and that aggressive cost-containment measures will delay or prevent the launch of innovative drugs in Canada.

As noted in our October 2016 submission to PMPRB Guidelines Modernization, our focus is continuously advancing science and developing medicines that offer more value than existing therapies. The draft guidelines do not incentivise bringing innovative medicines to Canada or investment in the Canadian healthcare ecosystem. As part of a broader health care system and health policy framework, PMPRB should consider how these significant changes to the guidelines will impact the broader scope of healthcare and the possible unintended consequences to patient outcomes, job growth in the highly skilled, innovative medical sector and the economy.

Predictability

The draft guidelines introduce a significant amount of uncertainty and unpredictability for manufacturers. This is partly because the inputs into the MRP calculations remain unknown during the launch period (e.g. CADTH's re-analysis of the economic analysis). Further, as there is no floor to MRP and some calculations of PEP can produce negative values, manufacturers have no boundaries to work within when assessing whether to launch a product in Canada. If PEP can result in prices close to zero it is important for manufacturers to know this in the context of making business decisions. For multinational companies, product launches are complex, and coordination and collaboration with global regulatory authorities and manufacturers is required. The attractiveness of a market depends on a number of factors, including the healthcare system, prevalence of the disease, the size and market conditions of the country, and the expected return

on investment. The decision to launch and the launch sequence of a new product across the world also takes into consideration market size and reference pricing. The draft guidelines create much uncertainty around all the launch considerations, putting Canada at risk of launch delays.

This significant level of unpredictability associated with new product launches, particularly surrounding product categorization and subsequent indications is illustrated in Case Study 2. Furthermore, the PEP equation is based on inputs from the CADTH/INESSS re-analysis of the manufacturer's submission. In general, the CADTH re-analysis of manufacturer-submitted cost utility models leads to much higher ICERs further increasing the uncertainty. Yin et al have shown that for pCODR, reanalyzed ICERs were 128% higher than the manufacturer submitted ICERs with differing model inputs and data parameters[2]. In addition, ICERs can vary significantly based on relevant comparators as illustrated in Case Study 3. Historically, these differences in perspective were reconciled at the pricing negotiation table, where a mutually acceptable agreement could be reached. However, under the current PMPRB guidelines, (and the inflexible PEP equation) these changes will dramatically and directly affect the MRP, without the ability to discuss the different perspectives and reach a mutually acceptable agreement.

In the draft guidelines, disease prevalence is an important determinant of product categorization and relevant indication; however, there is often limited Canadian specific data. For many diseases, especially rare diseases, there is also variability in epidemiological estimates of prevalence based on the methods used in the study. There may be further variability depending on the testing used to identify disease subtypes. Regardless of the methods used to estimate prevalence, from the guidelines it is unclear at what level of the patient population prevalence will be determined. For example, would prevalence be assessed based on the number of patients with a particular type of cancer? Or would it be limited to those patients with a specific biomarker? Or would it be limited to the number of patients eligible for the treatment based on the approved indication (including line of therapy)? Additionally, for many cancers, there are estimates for one-year, five-year and ten-year prevalence which could lead to different results for categorization and relevant indication. The draft guidelines provide very limited details on what is considered robust and relevant prevalence estimates and therefore manufacturers cannot accurately predict the implications to their launch products.

The PMPRB does not make decisions on patient access to treatment. As a result, the proposed changes to the guidelines are problematic because there is no expectation that reduced prices will lead to improved access. This differs from other markets that formally use cost-effectiveness analyses in the assessment process such as the UK and Australia. In these markets, price reductions which lead to improved estimates of the overall incremental cost-effectiveness ratio also directly lead to improved access via government funding. In other words, there is predictability that by reducing prices, there will be a benefit to patients, physicians, and the manufacturer. In contrast, the PMPRB proposes to use any cost-effectiveness analysis published by a public agency to set a price threshold, irrespective of whether the HTA agency recommends funding or not, or if funding is actually achieved. Not only does this create challenges in terms of implementation, it also creates added uncertainty around the access potential in the Canadian market for manufacturers to consider.

Pricing of pharmaceuticals is established at the global level. In cases where the manufacturer perceives that an innovative product provides value that is not recognized in the pricing policies of a given market, there is a disincentive to prioritize launching or investing in that market. There is aversion to taking a risk on price as a result of price referencing (with no certainty that there will be a corresponding improvement in access) which will inevitably lead to delays. This is especially

true in cases where there is uncertainty of the outcome of the health technology assessment conducted by agencies such as CADTH and INESSS.

PMPRB Implementation and Reporting

The draft guidelines create implementation challenges and unnecessary administrative burden, which the new guidelines purport to avoid. One major challenge in fully assessing the impact is the absence of the *Patentee Guide to Reporting/Online tool*.

Maximum List Price (MLP)

Under the draft guidelines, newly launched products are subject to annual list price re-assessments. The iMLP during the first 3 years (or filings for 5 PMPRB11 countries, whichever comes first) would require patentees to change list prices annually until the MLP is set for any product that falls under this category and therefore causes increased administrative burden. Furthermore, the new guidelines allow for MLP re-benching should the median PMPRB11 (MIP) increase or decrease by over 10%. It is unclear why 10% is used for the reassessment; re-assessments based on MLP changes will be more frequent than under the current guidelines where patentees are subject to the highest PMPRB7.

Given the capital-intensive nature of the pharmaceutical industry, Roche would like to encourage the PMPRB staff to consider transitional measures for grandfathered products that would allow patentees to decrease list prices of existing medicines, which are subject to PMPRB jurisdiction, over a period of 2 or 3 years.

Maximum Rebated Price (MRP)

In addition to the challenges with the predictability of PEP/MRP as noted above, there is a particular concern in the continual reassessment of PEP after every new indication. For example, the first indication may require a large rebate based on the PEP/MRP calculation and this rebate is negotiated with the pCPA; however, the second indication may have a larger prevalence and therefore becomes the new relevant indication for assessing the price. If the new PEP is higher than the old PEP, it would be difficult to negotiate this second indication within the context of the existing healthcare system (i.e. pCPA).

There are many concerns with the market size adjustment factor from both a fundamental and implementation perspective. According to PMPRB, units sold include any product that leaves the manufacturer's warehouse. This includes free goods given away through bridging programs even though the manufacturer does not actually 'sell' these free goods. Case Study 4 illustrates how this new market size adjustment factor will disincentivize manufacturers from providing free goods and creating bridging programs since it will artificially inflate volume of sales and ultimately decrease MRP. It is also noted in the draft guidelines that, "After the initial market size adjustment, a patented medicine's MRP will only be readjusted following an increase in annual units sold. A patented medicine's MRP will not be readjusted following a decrease in annual units sold, or if its realized revenues fall into a lower tier." (PMPRB Draft Guidelines, Page 32). This is an unreasonable rule and may further penalize first-to-market medicines and curative medicines (refer to Case Study 1). It is also important to consider that due to criteria differences, not all patients in a bridging program will be covered once a product is funded.

The process for the guidelines consultation has been particularly difficult, especially with the number of challenges that the new guidelines introduce. The overall consultation period (Nov 21st, 2019 - Feb 14th, 2020) has not allowed enough time to consult on such significant changes to the guidelines. Furthermore, the lack of clarity on several factors including the absence of the amended *Patentee Guide to Reporting/Online tool* does not allow for adequate assessment. As a result of the significant impact on product launches and the lack of clarity, complexity, and operational feasibility of the guidelines, Roche Canada recommends working groups be formed to address some of these challenges before the implementation of guidelines.

Regards,

David Shum
Director, Market Access and Pricing
Hoffmann-La Roche Limited

References

1 http://individual.utoronto.ca/grootendorst/pdf/theta%20drug%20launch%20delays.pdf
2 http://cc-arcc.ca/wp-content/uploads/2015/01/136-Yin-Sunday.pdf

CASE STUDIES

Case Study 1: Similar Products with different MRPs

Impact of Proposed 2019 Guidelines

- Wide and uncertain ICER range as well as uncertainty around subpopulation prevalence complicates the determination of the MRP
- Second-to-market product receives higher PEP despite similar net benefit
- Uncertainty in cost-effectiveness estimates not considered in PEP calculation

Product: Drug X (first to market)
Launch price: $120,000 per vial (one vial per year)
Indication at launch:

Treatment for a rare genetic disorder with several subpopulations
(<1/2000 prevalence for total population)

- Reduces mortality in subpopulation 1
- Improves function in subpopulation 2
- Improves or maintains function in subpopulation 3 (uncertain due to limited evidence)

Drug X is administered in a hospital setting and requires a healthcare practitioner which contributes to the overall cost.

Assessment based on 2019 PMPRB Guidelines:

Current estimate of proportion of patients in each subpopulation can be seen in the table below. Note that there is limited clinical data in Subpopulation 3 and proportion of prevalent population in each subpopulation is expected to shift due to treatment benefits in some subpopulations.

Manufacturer ICERs vs current standard of care, BSC (means of probabilistic analysis) can be seen below:

Subpopulation	Proportion of patients	Incremental Effects (QALYs)	Incremental Costs ($)	Treatment Costs ($)	ICER
1	15%	5	$3.2M	$3.1M	$650K/QALY
2	47%	3.5	$7.5M	$8.8M	$2.0M/QALY
3	38%	1.5	$4.5M	$11.9M	$3.0M/QALY*

*Significant uncertainty in estimate

CADTH ICERs versus current standard of care, BSC (means of probabilistic analysis) and the associated PEP can be seen below. Note: the PEP values were calculated based on the formula in the PMPRB draft guidelines (PEP = [($60,000 x incremental effects) - incremental costs + treatment costs] x (list price/treatment cost)).

Subpopulation	Proportion of patients	Incremental Effects (QALYs)	Incremental Costs ($)	Treatment Costs ($)	ICER ($/QALY)	PEP	% Rebate
1	15%	0.25	$2.0M	$2.2M	$9.0M/ QALY	$11,727	90%
2	47%	0.3	$7.0M	$8.1M	$25.0M/ QALY	$16,563	86%
3	38%	0.6	$4.0M	$11.9M	$7.0M/ QALY*	$80,027	33%
					Weighted PEP	$39,954	66%

*Significant uncertainty in estimate

Market size estimated to be >$12.5M and <$25M at MRP after 1st year of sales
Therefore **MRP = PEP = $39,954** (66% rebate)

Product: Drug Y launching 2nd to market
Launch Price: $120,000 per vial (one vial per year) (same as Drug X)
Indication at launch: Similar to Drug X

Drug Y can be administered at home and therefore the overall cost is lower compared to Drug X.

Assessment based on 2019 PMPRB Guidelines:

Based on results of an indirect treatment comparison conducted to support the cost-effectiveness analysis, Drug Y provides small incremental benefit over Drug X at a slightly lower overall cost . This cost difference is due to savings associated with the mode of administration. The manufacturer submitted ICERs vs current standard of care (Drug X) can be seen below.

Subpopulation	Proportion of patients	Incremental Effects	Incremental Costs	Treatment Costs	ICER
1	15%	0.1	-$0.5M	$3.1M	Dominant
2	47%	0.2	-$2.0M	$8.8M	Dominant
3	38%	0.25	-$1.0M	$11.9M	Dominant

CADTH ICERs vs current standard of care (Drug X) can be seen below:

Subpopulation	Proportion of patients	Incremental Effects	Incremental Costs	Treatment Costs	ICER	PEP	% Rebate
1	15%	0.01	-$0.25M	$2.2M	Dominant	$133,639	0%
2	47%	0.02	-$1.0M	$8.1M	Dominant	$134,832	0%
3	38%	0.03	- $0.5M	$11.9M	Dominant	$125,060	0%
					Weighted PEP	$130,940	0%

Market size estimated to be >$12.5M and <$25M at MRP after 1st year of sales
Therefore **MRP = PEP = $120,000** (0% rebate)

Summary:

Although this example is a rare disease, it can expand beyond rare disease for any products where the first product is compared to standard of care and the following products are compared to the first. Drug X and Drug Y both evaluated as Category 1 drug with similar cost, indication, and efficacy however:

- There is a lack of clarity prior to launch as to price ceiling due differences in estimates
- There is uncertainty in the proportion of patients in each subpopulation and the weighting of the subpopulation over time is not accounted for
- Discounts >85% for subpopulations 1 and 2 although subpopulation 1 has greatest clinical impact and certainty
- Less discount in subpopulation 3 where there is the greatest uncertainty in the estimate of incremental QALYs for Drug X
- Comparator differs for Drug Y because 2nd to market resulting in higher PEP
- PEP calculated based on mean estimates of incremental QALYs and costs however, due to small differences for Drug Y vs Drug X, some estimates may result in opposite scenario for a proportion of the probabilistic analysis (i.e. from > QALYs and < cost to < QALY and > costs depending on uncertainty in the input parameters)

Case Study 2: Multiple Indications and Re-Assessments

Impact of Proposed 2019 Guidelines

- Products with multiple indications may not launch in all indications based on the risk to the PEP
- There may be a discrepancy between the discount for two DINs treating the same disease

Product: Drug Y
Launch Price: $4,700 per vial
1st Indication at Launch: **Indication A** for a population with high unmet need
Classification: Category 1

Assessment based on 2019 PMPRB Guidelines:

Indication	Incremental Effects	Incremental Costs	Treatment Costs	ICER	PEP	% Rebate required
Indication A	0.46	$123,558	$105,930	$268,604	$446.5136	**91%**

Market size estimated (PEP * units) to be <$25M.
Therefore MRP = PEP = $446.5136 (plus future market size adjustment)

Manufacturer chooses NOT to launch in Indication A because the manufacturer cannot provide a 91% discount.

Product: Drug Y (same product as above)
Launch Price: $4,700 per vial
2nd Indication at Launch: Indication B
Classification: Category 1

- **If the manufacturer chose NOT to launch Indication A, Indication B would be assessed for an MRP using the information below:**
  - CUA is not available for Drug Y, therefore, MRP will be calculated based on the lower of Lowest International Price (LIP), domestic Therapeutic Class Comparison (dTCC), international Therapeutic Class Comparison (iTCC) and further adjusted for market size.
  - Note: Drug Y is available in a grandfathered strength for a different indication. The grandfathered DIN is not subject to calculating an MRP.

Assessment based on 2019 PMPRB Guidelines:

Indication	LIP	iTCC	dTCC	Lower of LIP, iTCC, dTCC
Indication B	$3,540	$4,088	$4,794	**$3,540**
Effective Discount				**25.7%**
Calculation based on grandfathered strength (assuming linear relationship) No published prices in Australia and Japan Comparators are all grandfathered DINs in Canada				

The lowest of the LIP, iTCC and dTCC is LIP in this scenario.
Therefore, MRP = LIP = $3,540 (plus future market size adjustment)

Summary:

- For products with multiple future indications, some launches may be delayed or never launch in Canada based on the risk of lowering MRP with newly calculated PEPs and additional market size adjustments.

Case Study 3: Submission to CADTH includes multiple comparators

Impact of Proposed 2019 Guidelines

- Depending on what is considered the most relevant comparator, the value for PEP (and subsequently the MRP) will be different
- There is a lack of predictability in estimating the PEP

Product: Drug X
Launch Price: $30,000 (per vial), one vial per year
Indication: A therapeutic area with multiple comparators, lack of data on market shares especially if some comparators are used/indicated for other therapeutic areas
Sales: Less than $25M

Treatment Cost (in PEP): *$230,000 (discounted 1.5% over lifetime of the treatment based on CADTH model)*

Assessment based on 2019 PMPRB Guidelines:

There are situations where a new therapy may be compared to multiple comparators in the cost utility model. The ICERs and the associated PEP calculation will be different for each comparator. In some scenarios, drug X may be dominant. In other scenarios, drug X may be dominated. The results below refer to deterministic results.

Comparator	Incremental effect (X - Comparator)	Incremental costs (X - Comparator)	ICER	PEP	% Rebate
A	-0.39	-$93,199	$236,546/QALY (X is dominated)	-	-
B	0.13	$42,446	$326,548/QALY	$25,481	15%
C	0.60	$29,924	$50,040/QALY	$30,777	-3%*
D	0.55	-$6,393	-$11,709/QALY (X is dominant)	$35,107	-17%*
E	0.70	$66,558	$95,452/QALY	$26,773	11%
F	-0.20	-$125,834	$632,332/QALY (X is dominated)	-	-
G	0.36	$77,654	$215,706/QALY	$22,689	24%

A PEP is not calculated for comparators A and F since Product X offers less benefits. Even though PEP > launch price, PEP will be set to launch price and therefore 0% rebate.

Summary:

This is an example of how PEP can be significantly different based on relevant comparator and the lack of clarity on how this will be approached. In this case, the rebate required to reach MRP varies from **0% to 24%** for Product X.

Case Study 4: Market Size Adjustments

Impact of Proposed 2019 Guidelines

- There is a disincentive for manufacturers to provide free goods and create bridging programs that artificially increase volume of sales
  *Note: not all indications covered by free goods will be converted to commercials sales

Product: **Drug Y**

In the initial launch of a product, patient assistance programs may provide free goods to patients. As outlined in Figure 1, the forecasted units "sold" for Drug Y during the time period before public funding is from the compassionate program (i.e. free goods). Based on PMPRB's definition of units sold, these units are considered "sold" and therefore used to determine the market size adjustment required even though the manufacturer provided the units at no cost.

Figure 1: Reporting Total Units "Sold" for Drug Y

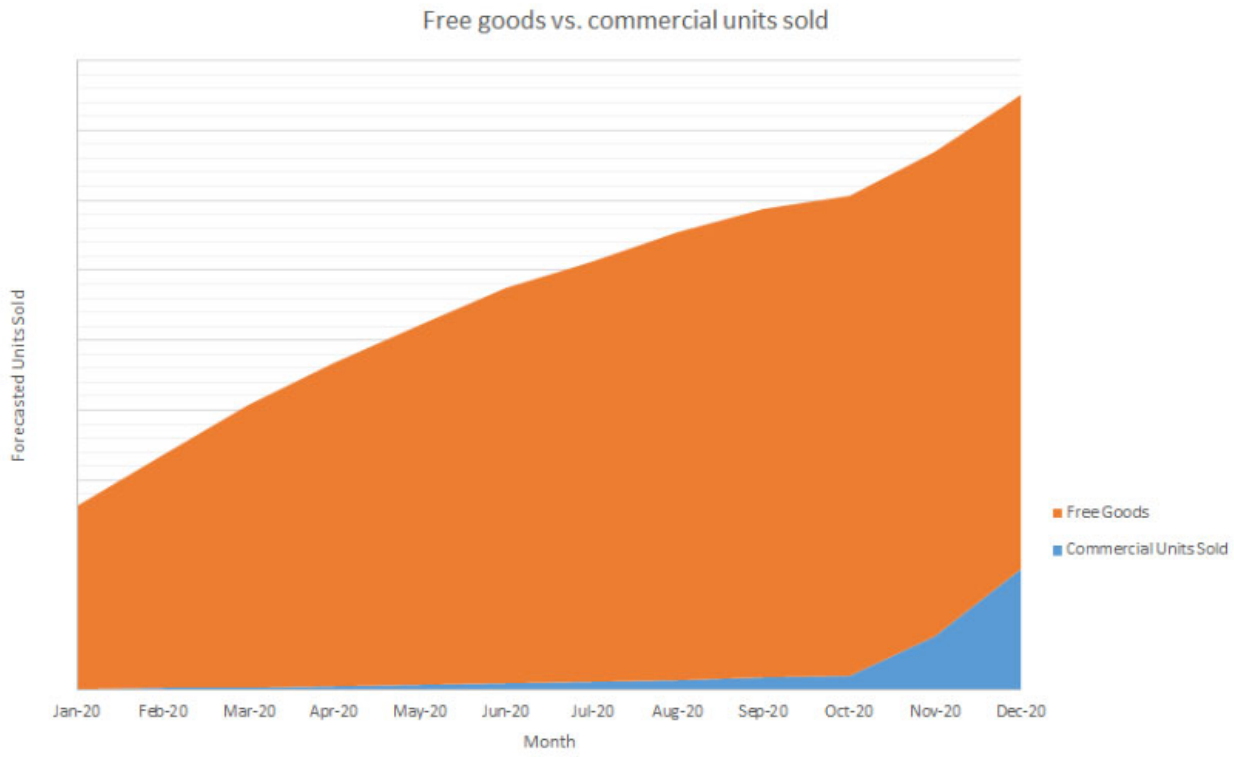

Table 1: Market Size Adjustment for Category 1 medicines

Tier	Annual Revenues	Incremental Adjustment Factor
1	<$25M	0%
2	$25M-$50M	-10%
3	$50M-$75M	-20%
4	$75M-$100M	-30%
5	$100M-$125M	-40%
6	$125M+	-50%

Summary:

- Based on the new PMPRB guidelines, the new definition of sale includes all products that leave the manufacturer warehouse. Based on this definition and the market size adjustment calculation outlined in the PMPRB draft guidelines, Drug Y (illustrated above) would be adjusted to Tier 3 because of the large volumes anticipated from free goods instead of Tier 0 based on actual commercial goods sold (See Table 1 above).

- This would disincentivize manufacturers from creating compassionate or bridging programs and giving away free goods.

- Although the argument is that free goods will translate into future commercial goods sold, historical sales may not accurately reflect future anticipated goods sold especially for products that do not treat chronic diseases, ex. one time use treatments or seasonal treatments.