2022

Biopharmaceutical Ecosystem Index: *Where Does Canada Rank on its Attractiveness for New Medicine Launch?*

Spring 2022

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Biopharmaceutical Ecosystem Index: Where does Canada Rank on its Attractiveness for New Medicine Launch?

This report was published by PDCI Market Access, A Division of McKesson Canada.

Spring 2022

For questions about this publication, please visit www.pdci.ca or contact John-Paul Dowson at JP.Dowson@pdci.ca.

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FOREWORD

“The global pharmaceutical industry is changing. Science is moving faster, policies are shifting, and new medicines are in greater demand as advancements in science and biotechnology see diseases cured, and their natural histories changed. Even a global pandemic demonstrates how we can change trajectory of disease with effective vaccines in our armamentarium. As Canadians we pride ourselves on punching above our weight when it comes to health technology research, innovation, and the availability of leading-edge medicine, but amid changes in the global pharmaceutical industry and our local ecosystem, we cannot rely solely on our history of being a desirable destination for innovative medicine investment. There are many reasons global pharmaceutical manufacturers would like to launch their new medicines in Canada. Yet, pharmaceutical ecosystems around the globe are continuously evolving to attract the research and innovative medicines that will be needed to stave off our future health challenges. In all this change, questions will naturally be asked about Canada’s readiness to attract future leading-edge treatments. What is and will be Canada’s relative desirability as a future launch destination for the new medicines being researched and developed today? If there is one thing our recent pandemic history demonstrates, it is that despite our personal and collective heartache and challenges over the past two years, Canadians can collaborate, innovate and implement focused health policy solutions with tremendous success.

In 2020 and 2021, Canadian politicians and policymakers took unprecedented measures to engage the global pharmaceutical industry, welcome their innovation, and clear the way for COVID-19 vaccines to arrive on Canadian soil and get into the arms of Canadians. Meanwhile, only a few blocks away from where those decisions were made in Ottawa, other policymakers continued work to implement patented medicine pricing reforms, which were first announced in 2017. Those proposed measures represented the most extensive drug pricing reforms introduced in Canadian history. As that work marched on, Canadian stakeholders repeatedly expressed concerns about how such changes would undermine Canada as a priority launch destination for new medicine manufacturers. Many of us looked to the success of Canada’s collective action to get COVID-19 vaccines into the country, en masse and quickly as evidence of what we can gain when there is a resolve to value and support of biopharmaceutical innovation. Yet, we’ve seen how policies that ignore the link between the price of innovative medicines and global launch decisions seriously risk Canadians’ access to those new treatments.

…Recent changes and uncertainty have left us at a critical juncture: can Canada convey global leadership in attracting launches of innovative biopharmaceuticals? Will global decision-makers continue to see Canada as a worthwhile launch destination? Or will we fall off the priority list entirely?

There is indeed a link between policies affecting patented medicine prices, and our access to those products. According to the much-delayed 2020 Annual Report of the Patented Medicines Prices Review Board (PMPRB), the number of new patented medicines reported to PMPRB dropped almost 30% from 2018 to 2019. While other countries also observed a dip in regulatory approvals over this time, the dip was smaller and short-lived, rebounding by 2020. According to PMPRB’s 2020 annual report, evidence of a rebound remains out of sight.

While there are encouraging signs from policymakers that Canada may well return to greater price certainty, recent changes and uncertainty left us at a critical juncture: can Canada convey global leadership in attracting launches of innovative biopharmaceuticals? Will global decision makers continue to see Canada as a worthwhile launch

destination? Or will we fall off the priority list entirely? To answer these questions, we need to know where Canada stands today; and what risks are threatening our access to new medicines.

PDCI's Biopharmaceutical Ecosystem Index (the Index), which is made possible by the guidance of its Editorial Advisory Board, and contributions of dozens of stakeholders, allows Canadians to examine our current standing and attractiveness among global counterparts as a launch destination for new medicines. The benefits of fostering an attractive environment for innovative drug launches cannot be understated. Again, one only need to reflect upon the pandemic to see what is possible when policymakers engage with the global biopharmaceutical sector, opening doors, not building walls for new medicines to reach Canadians.

A country's strong standing in the Index rankings confers benefits for its citizens. Attracting life sciences innovators within our borders directly benefits personal health and broader economic health. We cannot ignore the interplay between the attractiveness of a market for new medicines, and the overall health of our citizens. This is true now more than ever: In 2021 a record 84 novel active substances were launched globally which is twice as many as five years ago. Among those which were launched in the United States, more than 60 percent were characterized by the FDA as first-in-class and more than half received orphan drug designation.1 Canada cannot afford to fall behind at a time when so many launches are at stake for highly effective specialized treatments, for life-limiting illnesses. In his 2021 mandate letter, Prime Minister Justin Trudeau directs the federal minister of health to "work with the Minister of Innovation, Science and Industry to continue demonstrating leadership in public health." This is a welcome call from the Prime Minister, one that hopefully fosters greater collaboration between those tasked with supporting the discovery of innovative medicines and those tasked with enabling Canadians' access to them.

In his 2021 mandate letter, Prime Minister Justin Trudeau directs the federal minister of health to "work with the Minister of Innovation, Science and Industry to continue demonstrating leadership in public health." This is a welcome call from the Prime Minister, one that hopefully fosters greater collaboration between those tasked with supporting the discovery of innovative medicines and those tasked with enabling Canadians' access to them.

This Index is intended to be a tool to identify where and how policies could most effectively improve Canada's attractiveness for new medicine launch within the global biopharmaceutical ecosystem. It identifies the indicators and ideal conditions considered attractive from the perspective of global biopharmaceutical decision makers; it assesses how countries currently stack up; and it proposes where Canada has opportunities to grow. Ideally, this inaugural edition of the Index will provide a benchmark for future editions to capture how changes in the global biopharmaceutical ecosystem will affect rankings going forward.

John-Paul Dowson
Director, Strategic Consulting & Policy Research at PDCI Market Access

ACKNOWLEDGEMENTS

Editorial Advisory Board

PDCI Market Access would like to thank all members of the Editorial Advisory Board for volunteering their time and expertise to guide development of this index. Without their support this publication would not have been possible.
Please see Appendix A for complete biographies of the Editorial Advisory Board members.

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"This is a strong Advisory Board of Canadian thought leaders. I'm not surprised by the high quality of this report given the experience and insights of the individuals involved."
—Jason Field, President & CEO, Life Sciences Ontario

Authors

Please see Appendix A for complete biographies of the authors.

- Courtney Abunassar, Associate Director, Market Access & Policy Research
- John-Paul Dowson, Director, Strategic Consulting & Policy Research
- Mark Fleming, Strategic Advisor
- Claudia Loschmann, Associate Director, Market Insights
- Veronique Scott, Manager, Policy Insights
- Melissa Burt, Manager, HTA & Clinical Evaluation

Research Support

- Shabna Mohideen, Analyst, HTA & Health Economics
- Hussein El-Kechen, Analyst, HTA & Clinical Evaluation
- Piraveena Sabesan, Associate, HTA & Health Economics

Special Thanks

PDCI Market Access would like to thank all colleagues and stakeholders who supported this project, contributed research advice and commentary and who participated in interviews for the qualitative research portion of this study.

Funding Note

This report is an independent initiative of PDCI Market Access. PDCI, the report authors and the Editorial Advisory Board members received no funding associated with the research, development or writing of this report. Editorial board members were invited by PDCI to participate on a voluntary basis, without monetary compensation for time devoted.

EXECUTIVE SUMMARY

Global biopharmaceutical decision makers have historically considered Canada an important country (among the top tiers) when prioritizing their new medicine launch efforts.[2] However, recent studies show that fewer medicines are submitted for regulatory approval in Canada compared to other countries, and Canadian submissions are often delayed.[3-5] Amid changes in both the Canadian and global biopharmaceutical ecosystems, concerns have been raised about Canada's continued attractiveness for new medicine launches, and in turn, how Canadian patients' access to new medicines may be affected in the years to come.[6]

The objective of PDCI's Biopharmaceutical Ecosystem Index (the Index) is to rank countries according to their attractiveness for new medicine launches.[a] Decisions on whether and when to launch a new medicine in a country are complex and multifactorial. No single decision or decision-maker will follow the same values or approach as another. Business decisions will include subjective viewpoints based on the unique perspectives, experiences and biases of the decision makers and according to the context of the new medicine, the launch decision and information available at the time. However, based on their collective and extensive experience with such decisions, the Index's Editorial Advisory Board agreed on a number of common features that global biopharmaceutical decision markers would typically contemplate when deciding global launch sequencing for new innovative medicines.[b]

Each country's performance in three technical areas was assessed: Development and Commercialization Infrastructure, Regulatory Landscape, and Access Environment. The indicators and measurements under each technical area were selected and weighted by the Editorial Advisory Board according to the magnitude of direct or indirect influence the indicator would have in an average global launch sequencing decision.

Table 1 summarizes the indicators measured in this Index and their relative importance in new medicine launch decisions.

[a] Note throughout this Index the definition of "New Medicines" includes any novel drug products which have not been previously marketed in Canada. All new medicinal ingredients and combinations would be included irrespective of their degree of innovativeness. The definition generally excludes biosimilars or generic medicines which would be subject to different decision-making processes different indicators and indicator weights which would make a country attractive for launch of these products.

[b] For simplicity, indicators and weights were meant to represent an "average" new medicine global launch sequencing decision, however, the authors and editorial advisory board acknowledge that different subsets of innovative medicines (e.g. drugs for rare diseases, oncology products, vaccines, etc.) could have different indicators, measurements and weights contributing to decision-makers perceptions of a country's attractiveness for launch of these specific types of new medicines

Table 1 - Indicators and Weights Summary

Technical Area	Indicator	Weight	Measurement
Development & Commercialization Infrastructure	Late-Stage R&D Activity	**.038**	• Number of Phase 3 Clinical Trials Registered (2020)
	Manufacturing Capability	**.036**	• $ Value of Pharmaceutical Industry Exports (2019)
Regulatory Landscape	Intellectual Property Protection	**.122**	• Years of standard patent life • Years of patent term restoration • Years of data protection • Other IP Incentives
	Market Authorization Process	**.102**	• Standard and prioritized review time (targets and actual 2019) • Existence of specialized and/or prioritized review pathways • Existence of a rolling review pathway
	Price Regulation	**.180**	• Influence of price regulator • Resulting average prices
Access Environment	Market Potential	**.112**	• Share of global pharmaceutical market • Wealth (GDP/Capita) • Share of out-of-pocket spending
	HTA & Reimbursement	**.346**	• Time to reimbursement from market authorization • Existence of sizeable private market • Complexity: Number of payers/ processes • Mechanism for HTA concurrent with regulatory or reimbursement
	Patient Role	**.064**	• Impact of patient participation in HTA
	Total	**1.000**	

Following a literature review on each measurement, each country was evaluated and assigned a score out of 10 points for each of the eight indicators. A score of "0" would indicate – if considering that indicator alone – that the country is not at all attractive for new medicine launch, and a score of "10" would indicate the country has an ideal state of attractiveness for new medicine launch – again if considering that indicator in isolation of all others. After completing all research and scoring for each indicator, each country's scores were weighted according to the relative importance the Board assigned to each indicator. Figure 1 and Figure 2 report the overall composite scores for each country and rankings for Canada and the comparator countries.

Figure 1 Results: Composite Scores & Country Rankings

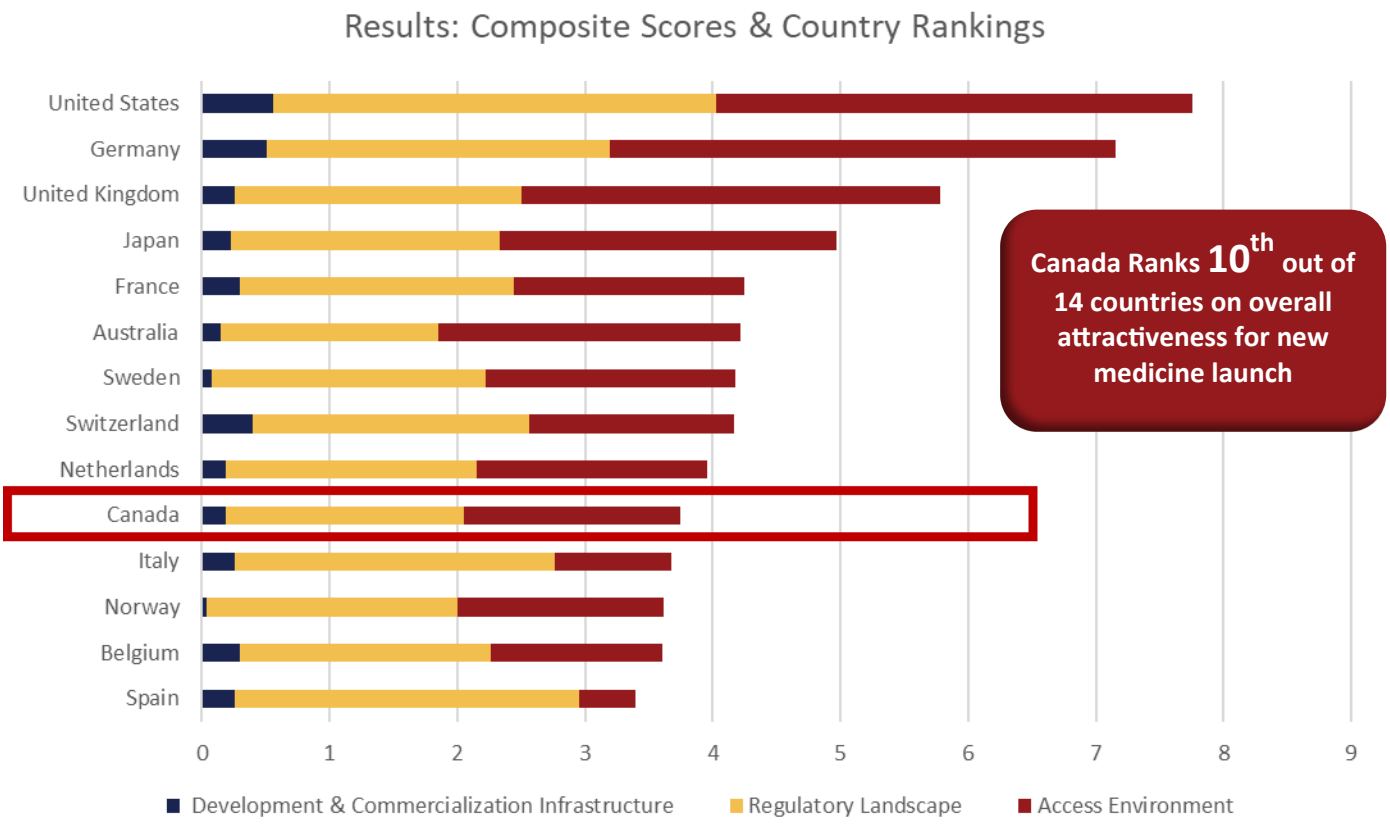
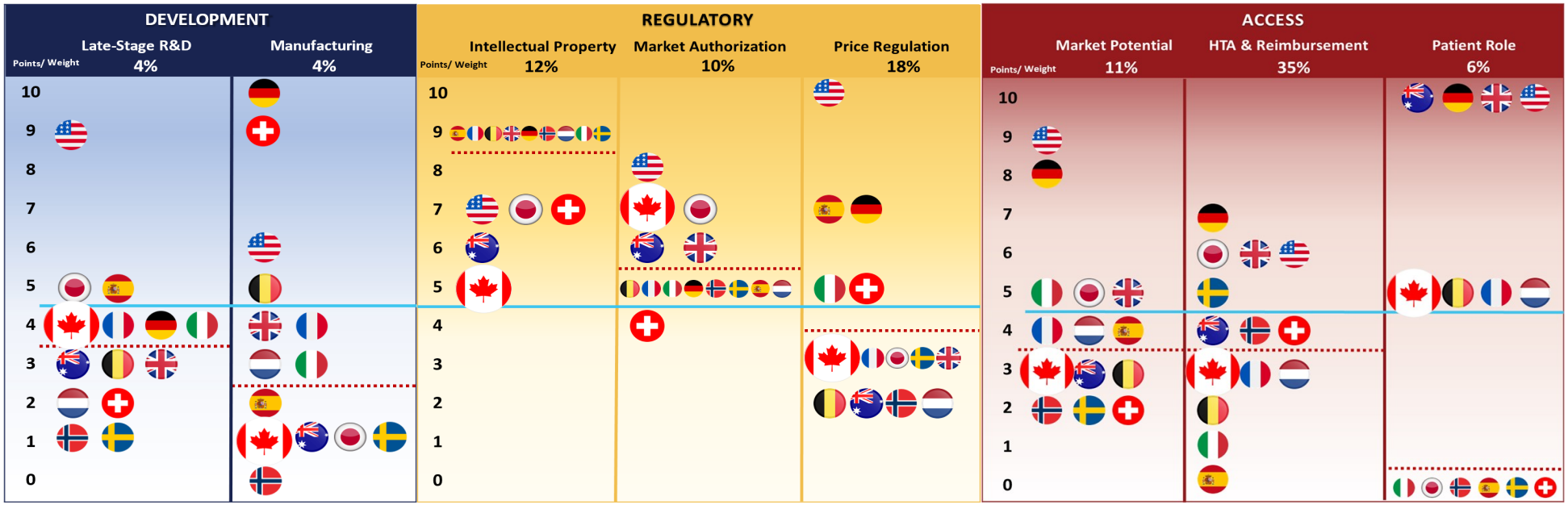


Figure 2 Country Scores by Indicator



Median

5 points line

Canada ranks 10th out of 14 countries assessed on overall attractiveness for new medicine launch. It performed better than Italy, Norway, Belgium, and Spain, but lagged all other countries in the analysis. Canada performed best in market authorization processes: second only to the US, Canada scored 7 out of 10 and shared this 2nd ranking spot with Japan. Canada scored in the middle of the pack concerning late-stage R&D, price regulation, and patient role. Canada found itself in the bottom third of countries when it came to manufacturing, market potential and HTA & reimbursement, and Canada scored last on intellectual property.

Among the 14 countries, Canada ranks:

- **10th overall**
- **10th on Development & Commercialization Infrastructure**
- **13th on Regulatory Landscape**
- **9th on Access Environment**

The US took the top spot overall and in two technical areas: Development and Commercialization Infrastructure and Regulatory Landscape. Germany ranked second to the US overall and edged out the US for top rank in the Access Environment technical area. Rounding out the top three overall was the UK, which also took third rank in the Access Environment technical area. In Development and Commercialization Switzerland ranked third, and in the Regulatory Landscape technical area Spain ranked third.

Canada performed best in market authorization processes: second only to the US, Canada scored 7 out of 10 and shared this 2nd place ranking with Japan. Canada scored in the middle of the pack concerning late-stage R&D, price regulation, and patient role. Canada found itself in the bottom third of countries when it came to manufacturing, market potential and HTA & reimbursement, and Canada scored last on intellectual property.

No country received a perfect score on the attractiveness of its ecosystem for new medicine launch. Each country had aspects that were worth emulating by other countries and opportunities for improvement relative to others. It is important to recognize that each country's commitment to its biopharmaceutical ecosystem has evolved differently: with different histories, values, goals, contexts and expectations.

This Index has identified those areas where Canada excels, competes and falls behind. Some areas - such as how our relatively small population contributes to our lower market potential - are not easily changed through policy. Other aspects such as drug price regulation and time to achieve public reimbursement could effectively be changed with policy tools. When considering changes in these areas, Canadian policy makers must be mindful of Canada's current position among comparator countries and be sensitive to the complex and interconnected factors that influence perceptions of Canada's attractiveness for new medicine launch, among global biopharmaceutical decision makers. In doing so, policymakers can help ensure their efforts are effective in supporting Canadian patients' access to new medicines.

STAKEHOLDER PERSPECTIVES

In addition to consultation with the Index's Editorial Advisory Board, the authors engaged key stakeholders in the Canadian biopharmaceutical ecosystem to capture their perspectives on both the methodology followed and results generated in the index. The goals of the supplementary qualitative research were both to validate the approach undertaken and provide qualitative commentary to assist in interpretation of the results.

The authors secured interviews with representatives of a number of small to large multinational biopharmaceutical companies (Canadian offices), Canadian pharmaceutical industry association leadership, patient organization leaders, life sciences organization leadership and academic/health policy thought leaders. Other stakeholders contacted in Federal and Provincial governments, health technology assessment and payers did not respond or declined participation. Excerpts from the interviews have been included within this report, however please note that the stakeholders were not provided with editorial rights on the content of this report and therefore this report's content and conclusions may or may not align with the stakeholders' perspectives.

Comments on Index Objectives

Overall, the stakeholders interviewed were very supportive of the Index's objective to measure how Canada stacks up against comparator countries as a destination for new medicine launch. They felt there was real value in the evidence-based analysis driven by our Editorial Advisory Board's indicator weightings. Richard Owens, Senior Munk Fellow at Macdonald-Laurier Institute, commented, "I've been trying to encourage the development of policies that would allow us [Canada] to become more productive and innovative, and I think a more fulfilled and interesting country. This report helps to put metrics around an area I've been focused on for years. I thought it was very well done."

We received constructive feedback during our stakeholder interviews. We value all the feedback received, on this first foray into publishing the Index; and, we are open to areas for improvement as we look to repeat this analysis in the future. Durhane Wong-Reiger, President, Canadian Organization for Rare Disorders (CORD) suggested, "…instead of [just] looking at this through the lens of all drugs evaluated by a country and then ranking the countries you should be looking at how individual drugs were handled by these countries in specific therapeutic areas." This is a valuable insight which may lead us to explore case studies of how comparator countries handled specific drugs from a development, commercialization, regulatory and access perspective.

Comments on Technical Areas, Indicators and Weighting

Interviewees recognized that choosing the technical areas and indicators and assigning the weighting to each indicator was the critical component of this publication. They commended our approach to measuring each country's performance on the indicators by basing our scoring on evidence and published data. The technical rankings across the eight indicators for the 14 countries were objectively set by evaluating the literature. Bob McLay, VP, General Manager, Sobi Canada Inc. said, "…I like the objectivity and the scientific methodology of the report. I think it will have some credibility based on that. It is evidence-based and that is important."

Specifically related to the weighting of the various indicators, our stakeholders generally recognized that assigning weightings across the indicators out of a total of 1.00 was a subjective exercise conducted wholly by our Editorial Advisory Board and based upon their varied and significant experience in either managing pharmaceutical products through to launch in Canada or observing the process as a key stakeholder in the biopharma ecosystem. Jason Field, Life Sciences Ontario commented, "… the weightings are probably the most subjective part [of your Index], and you've

recognized that. There will be opposition to a methodology like this, and the detractors will focus on the subjectivity associated with the weightings. However, based on my experience and the expertise you have gathered on your Editorial Advisory Board I am aligned in terms of how they've assigned the weightings. I think it fairly captures the environment within Canada."

Results

Stakeholders expressed little surprise regarding Canada's overall ranking of 10th out of 14 with several indicating the results were consistent with challenges they have faced launching new medicines in Canada.

"I am not surprised by Canada's ranking," said Bob McLay. "…where does most of the world's [biopharma] innovation come from? United States and Switzerland. Those countries have embraced incentives for innovation. I would ask how much innovation is coming out of Canada when it comes to CAR-T gene therapy? Most is coming out of the US because they're incentivized for it."

> "It is one thing to see in your Index that Canada performs well on the speed of Regulatory and HTA processes but what use is it to perform faster on these fronts only to run into a brick wall when it comes to product reimbursement and access for patients? "
> —Frederic Lavoie, Business Lead, Inflammation & Immunology, Pfizer Canada

There are exceptions, however, as noted by Kim Steele, Director, Government and Community Relations and John Wallenburg, PhD, Chief Scientific Officer, Cystic Fibrosis Canada. "We have recently had the experience with [market access] success of a new Cystic Fibrosis medicine moving into the Canadian marketplace. In my 15 years in health policy I've never seen a drug that moved through the system like this," commented Steele. "This was an exceptional circumstance with this new medicine," said Dr. Wallenburg, "We were used to quite the opposite being the norm so perhaps there is hope for a better future here in Canada."

The stakeholders we interviewed generally felt that Canadian policy makers and government decision makers should heed the results of this report and work to identify areas where policy and process changes could be made to help strengthen Canada's ongoing place in the development of innovative biopharmaceutical technologies. Ensuring that Canada and Canadians are leading and not on the trailing edge in terms of accessing innovative medical technologies is critical. If anything, living through the access to medicines experience during the pandemic has reinforced how important it is for Canada to pay close attention to the success factors outlined in the Index.

"We are a wealthy country and how better to spend our money than on our health," commented Richard Owens. "And you know innovative therapies create a lot of wealth, not just through their economic gains but also the well-being and extra years of life that come from them, and the savings they bring to the health care system. But we don't have a perspective that allows us to incorporate these benefits into a holistic assessment of our ecosystem. Instead, we far too often see a narrow-minded focus on price."

Frederic Lavoie, PhD, Business Lead, Inflammation and Immunology, Pfizer Canada commented "I wish we had these kinds of results from three years back because I feel that things have changed for the worse here in Canada in recent years. Agencies such as Health Canada, CADTH and INESSS, to name a few, must be commended for always seeking for more efficient means to deliver on their respective mandates. However, it is one thing to see in your Index that Canada performs well on the speed of regulatory and HTA processes but what use is it to perform faster on these fronts only to run into a brick wall when it comes to product reimbursement and access for patients? Biopharma technologies are evolving rapidly to targeted therapies and products for rare diseases. I am concerned that Canada is on a path that will lead it to being even less likely as a priority launch destination than what is reported here in your Index."

BACKGROUND & OBJECTIVE

"Speaking to pharmaceutical executives over the years from both legal practice and academic context, the consistent reaction I have had is to the negative impacts of price controls and that Canada is a small market consuming a disproportionate share of resources on regulatory processes and market access. "
—Richard Owens, SJD University of Toronto, Senior Munk Fellow, Macdonald-Laurier Institute, University of Toronto, Adjunct Professor, Faculty of Law

The Patented Medicine Prices Review Board (PMPRB) is a quasi-judicial body responsible to regulate the prices of patented medicines sold in Canada. Since 2017, it underwent changes to its governing regulations and pursued guidelines updates which, at one point, threated price decreases up to 30% and represented $19.8 billon over 10 years.[7] In public consultations, stakeholders unequivocally stated the effect such changes could have: Canada would be deprioritized by global medicine manufacturers, meaning substantial delays for Canadians to access new medicines, if they ever launched in Canada at all.[8] Stakeholders argued that with Canada being a relatively small market with a complex drug reimbursement pathway, achieving a Canadian price aligned with comparator countries is a central support post holding up the tent on Canadian patients' access to new medicines. Recent updates in Spring 2022 suggest greater price certainty may be on the horizon, which is promising, as even prior to these price regulatory changes taking effect, Canada has a history of lagging other jurisdictions with respect to timely access to new medicines.

- A 2019 study comparing the number of new active substances launched between 2011 and 2018, found Canada approved 119 out of 243 approved globally, resulting in a rank of 14th among 69 countries.[9] It also found that Canada had a median launch lag time of 11 months after a new medicine's first global launch, ranking Canada 10th among its 15 peer countries.

- A 2020 report from the Centre for Innovation in Regulatory Science examined new medicine regulatory approvals from 2010-2019 across all countries included in this analysis.[c] It showed waves of submissions that manufacturers make to regulatory agencies: first to FDA and EMA, then Health Canada, Switzerland, and Australia, then to Japan. Of the 41 medicines approved in all countries from 2015-2019, the average lag between the first submission and Canadian submission was 91 days.

- When it comes to submission timing, a 2015 study comparing regulatory processing times showed the US to be first priority, as FDA submissions were completed an average of 4 months earlier than EMA submissions and 14 months earlier than Health Canada submissions.[4] Another recent study showed the average difference between Canadian and US approvals was 468 days.[3] Authors identified submission delays accounted for 464 days, and differences in regulatory efficiency accounted for only 4 days of the 468-day average difference. Similarly in the European Union, Canadian approval dates lagged the EMA by an average of 404 days, 395 of which were attributed to later submission dates in Canada, and only 9 days attributable to longer regulatory processing time in Canada.[3]

Several reasons for Canada's lag are hypothesized in the literature, including that:

- Manufacturers have limited resources to direct towards product launches so must prioritize launches in countries with larger markets than Canada in terms of population and pharmaceutical sales.

[c] However, at the time, the UK was included in the EMA.

- Canada's complex regulatory, HTA, and reimbursement infrastructure create lengthy delays between when the manufacturer must begin investing, when sales can start trickling and when market penetration is maximized. Additionally, the complexity may mean achieving sales in Canada is more costly than other countries where these pathways are more centralized or consistent.

- Because Canada is a price reference country (formally or informally) for several other jurisdictions, there is a risk that a low list price achieved in the Canadian market could undermine prices attainable in foreign markets due to the practice of international price referencing.[3,4,9]

Recent research draws more direct correlations between uncertainty with PMPRB changes and Canadians' access to medicines, documenting early warning signs that Canada may have already been deprioritized throughout uncertainty about the future of drug price regulation in Canada.[10] Notwithstanding recent announcements scaling back on the extent of drug price reform expected in Canada (i.e. the federal government announcing it would proceed only with a new basket of reference countries, and not with new economic factors) the study highlights the possibility that even the environment of uncertainty has caused a lag that may become worse before it gets better. Much may depend on what we see with new PMPRB Guidelines.

By the Numbers

- **Canada ranks 14th out of 69 Countries on the number of medicines approved 2011-18 (119 of 243)**
- **Canada ranks 10th out of 14 countries on its median launch lag time (11 months in 2011-18)**
- **468: Average number of days between US FDA and Canadian regulatory approvals**
- **464: Number of days attributable to delayed manufacturer submissions**
- **4: Number of days attributable to regulatory efficiency**

As summarized above, numerous studies examine the number of new medicines launched and the lag times of those launches among countries included in this analysis. They've documented that Canada indeed does not see as many launches or if it does, they significantly lag when those same medicines were approved in other countries. Some studies have explored potential reasons why manufacturers find Canada less attractive, but none have comprehensively evaluated Canada's launch attractiveness relative to comparator countries from the perspective of global biopharmaceutical decision makers. The objective of this index is to identify the most important factors influencing new medicine launch decisions, and to rank Canada with respect to these factors among its peer countries. The goal is to shed light on why past research shows Canada lagging, and potentially identify where actionable policy improvements may make the situation better. [d]

[d] While this report measures attractiveness of a country for new medicine launch, the Index is not designed to correlate attractiveness rankings with the quality of medicine access enjoyed by a country's residents (which has been measured and reported in the literature referenced above). The Index results are offered for policy makers, pharmaceutical decision makers, and patient advocates to reflect upon and consider where correlations may exist, and where further research may uncover connections between a market's attractiveness for launch, and access to new medicines.

THEORETICAL FRAMEWORK & INDICATORS

Understanding the attractiveness of a country's ecosystem for new medicine launch is complex. According to the European Federation of Pharma Industries and Associations, when it comes to commercial decisions of launch sequencing "there are many interconnected factors that could explain unavailability and it is not possible to untangle their impacts with perfect precision."[11] Numerous factors may theoretically or practically contribute to decisions about whether and when to launch a new medicine; and ultimately, the factors affecting an individual launch decision will be unique to the product and sponsoring company. However, through the collective experience of PDCI and the Index's Editorial Advisory Board, several factors were identified that frequently inform global pharmaceutical decision makers when developing a launch sequence strategy.

> "Your Index is an expert consensus… your Board is comprised of experts in various aspects of the ecosystem, so I see your Editorial Board as bringing their experiences in the biopharma ecosystem to the table. "
> —John Adams , Co-founder & CEO of CanPKU and Allied Disorders

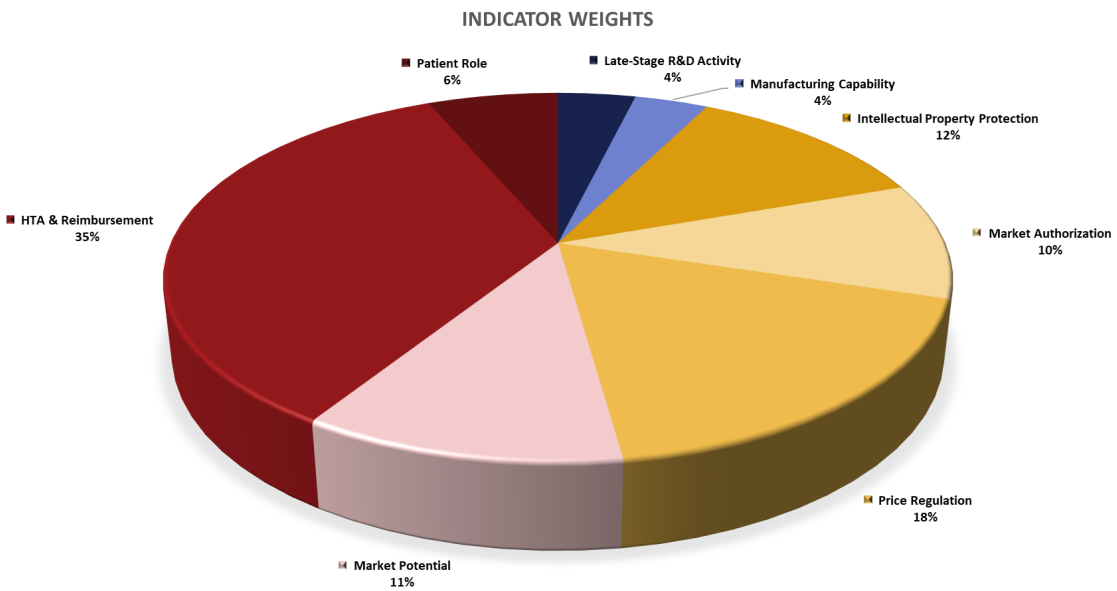
The Index analyzes and compares indicators across 14 countries to produce a composite launch attractiveness score for each country. Indicators in three technical areas were examined:

- Development and Commercialization Infrastructure
- Regulatory Landscape
- Access Environment

The indicators and their appropriate underlying measurements were identified, then selected and weighted by the Editorial Advisory Board based on the influence each would typically have on an average new medicine launch sequencing decision.

Figure 3 summarizes the weight each indicator represents as part of the whole index.

Figure 3 Technical Area & Indicator Weights



Development & Commercialization Infrastructure

A development ecosystem that is welcoming was identified as a technical area that has a small, but potentially important role to attract new medicine launches. A robust research and development community including public universities, research facilities, and public funding or tax incentives can meaningfully draw in early-stage pharmaceutical research and development (R&D) investment. While this may confer substantial economic benefits for a country in the form of high-paying direct and indirect jobs (and it may incentivize pharmaceutical manufacturers to conduct early work in Canada), the experience of the Index's Board advised that locations of early drug development work has little influence on where and in what sequence of countries a new medicine is launched.

> "How do we know that these chosen indicators are in fact those that are most influential in the decision-making process? The real acid test at the end of the day is did the patient get the medication and did the patient get better? "
> —Durhane Wong-Rieger, President, Canadian Organization for Rare Disorders (CORD)

On the contrary, the Board's experience suggested that late-stage R&D activities in a country could influence post-market availability of the product in that country. For example, if a company conducts Phase 3 clinical trials in a country, this investment builds experience with the product in the country among clinical trial investigators and the patients who will eventually use it following approval. Additionally, as a matter of ethics, the World Medical Association Declaration of Helsinki commits companies conducting medical research with human patients to continue ensuring patients are able to access therapy beyond the clinical trial process, assuming it has been beneficial.[12] Therefore, it would not be prudent for a manufacturer to conduct late stage R&D with patients in countries without a viable path towards commercialization.

Another commercialization factor that may sometimes be relevant to global pharmaceutical decision makers in launch sequencing decisions is the ability to manufacture in a country. Manufacturing capability may be extremely important to ensure access for residents of a country in the case of a supply shortage. However, from the perspective of a global decision maker, product manufacturing location is typically of little importance in launch decisions, since exportation and importation – albeit important and complex – are generally not major barriers to achieving market success. Hence why this indicator was assigned only a small weight.

Table 2 lists the performance indicators & measurements selected under this technical area.

Table 2 Development & Commercialization Infrastructure Indicators and Measurements

Indicator	Measurement
Late-Stage R&D Activity	• Number of phase III clinical trials registered in each country
Manufacturing	• Value of global pharmaceutical production exporting from each country

Regulatory Landscape

Regulation is necessary to support access to medicines. It can protect the value of innovation (e.g. through the patent regime) or it can be a barrier to new medicine access if processes are too stringent or time-consuming.

When considering launching new medicines, an ideal regulatory landscape from the perspective of a global biopharmaceutical decision maker would:

- Have a strong intellectual property protection regime. New medicine sponsors must realize a return on their investment. Investing in a country that is perceived to have inadequate intellectual property protection could invite premature competition and risk the company's return on investment.
- Have a regulatory approval process that effectively balances evaluation of safety and efficacy against timely access to new medicines.
- Provides for predictable pricing in the market, which is acceptable to the manufacturer and in line with comparable countries.

Table 3 lists the performance indicators & measurements selected under this technical area.

Table 3 Regulatory Landscape Indicators and Measurements

Indicator	Measurement
Intellectual Property Protection	• Years of standard patent life
	• Years of patent term restoration
	• Years of data protection
	• Other IP Incentives
Regulatory Approval Process	• Standard and prioritized review time (targets and actual 2019)
	• Existence of specialized and/or prioritized review pathways
	• Existence of a rolling review pathway
Price Regulation	• Influence of price regulator
	• Resulting average prices

Additional measurements were considered for this technical area, but were excluded in the quantitative index scoring due to data limitations and/or difficulty to compare the measurements fairly across the countries. Under regulatory approval, these included the complexity or uniqueness of dossiers, the existence of cross-jurisdictional cooperative regulatory reviews. Under price regulation, these included predictability of the price regulatory results, time to complete price reviews and whether sales can be made prior to completion of price regulatory reviews.

Access Environment

A clear and supportive access environment provides predictability for the manufacturer and assurance appropriate patients will be able to access treatment with new medicines. For global pharmaceutical decision makers, an ideal access environment is one where achieving return on research risk and investment is predictable and reliable. The attractiveness of a country's access environment is multifactorial; it includes many issues in the control of Canadian policymakers, such as clear pathways for health technology assessment, reliable and efficient reimbursement pathways, the overall speed of market penetration and treatment uptake. Additionally, the number of potential patients, as well as the ability and the desire of a country to invest in new medicines, including through public and/or private drug insurance infrastructure, provides further confidence in reimbursement infrastructure and opportunities.

Table 4 lists the performance indicators and measurements selected under this technical area.

Table 4 Access Indicators and Measurements

Indicator	Measurement
Market Potential	• % of Global Pharmaceutical Market Revenues
	• Wealth (GDP per Capita)
	• Proportion of Out-of-Pocket spending
Health Technology Assessment & Reimbursement	• Time to Reimbursement (from regulatory approval)
	• Existence of a private market
	• Complexity of Achieving Public Reimbursement (number of payers or formulary listing processes)
	• Mechanism for HTA concurrent with regulatory or reimbursement
Patient Role	• Impact of Patient Input in HTA

Additional measurements were considered for this technical area but were not included in the quantitative Index scoring due to data limitations and/or difficulty to compare the measurements fairly across the countries. Excluded indicators include: the transparency and predictability of HTA or funding processes, the HTA or reimbursement success rate, the level of organization and resources associated with patient involvement with HTA and reimbursement, and capability or infrastructure to negotiate and administer managed access mechanisms (e.g. outcomes based reimbursement agreements).

METHODS & DATA

This Index was developed in accordance with best practices described in the OECD Handbook on Constructing Composite indicators.[13]

Comparable Countries

The countries chosen for comparison purposes are those that have been considered as comparators by the Patented Medicine Prices Review Board for purposes of external price referencing. Under proposed new regulations for the PMPRB, the United States and Switzerland (previously in the basket of seven international reference countries) will be eliminated as comparator countries on the basis that US prices are an outlier and that Switzerland's GDP per capita is almost double that of Canada's.[14] France, Germany, Italy, Sweden and the United Kingdom will be retained from the former PMPRB7 basket, and Australia, Belgium, Japan, Netherlands, Norway, and Spain will be added to result in a new PMPRB11 basket. The PMPRB justified its selection of reference countries based on its opinion that they are aligned with Canada economically (measured by GDP per capita), they conduct price regulation from a consumer protection perspective, and have similar pharmaceutical market characteristics.[15] However, in considering the attractiveness of a country for new medicine launches, Switzerland and the US both matter. Canada is competing against both those countries along with the new PMPRB11 countries for access to new medicines. Hence, this research includes Switzerland and the US, along with the other proposed PMPRB11 countries.

Weighting

Weighting indicators is a necessarily subjective exercise. Launch and sequencing decisions are themselves subjective decisions, made by pharmaceutical decision makers according to their own sets of information, perspectives, opinions and biases. Given the intended goal of this Index is to measure and rank attractiveness of countries for launch, it is necessary to take the perspective of those responsible for making launch decisions – looking at the launch attractiveness of countries from their vantage point. For this reason, we looked to the insight of our Editorial Advisory Board representing extensive, varied and deep real-world lived experiences in this field to make determinations of the appropriate relative weights for this Index.

Following selection of the indicators and measurements appropriate for the analysis, each Board Member had 100 points to allocate over the selected indicators.[e] Each could assign more points to those indicators they felt would be more (or more frequently) influential to a launch decision, and fewer points to indicators they felt would be less (or less frequently) influential to launch decisions.

> "The bulk of our membership are small and medium sized companies in early development stages, mostly before many of the indicators you have identified so the full extent of the ecosystem you describe in your Index may not be relevant to them. It is important to recognize that ecosystem means different things to different companies and priorities are dependent upon where companies are in their product development cycle. "
> —Ron Boch, Vice President, BIOTECanada

[e]Note that the initial weighting exercise included nine indicators as Health Technology Assessment and Reimbursement were considered to be separate indicators. During the course of research, these indicators were amalgamated to better compare and evaluate processes between Canada (where HTA and reimbursement are conducted quite separately) and many of the other countries (where HTA, price negotiations and reimbursement decisions are frequently consolidated within the same organization).

PDCI aggregated all points and calculated so the sum of the weights would equal 1.0. Each indicator has a weight between zero and one, where a "0" would imply the indicator has no bearing on the decision to launch a new medicine in a country and a weight of "1" would suggest it is the sole consideration on which to base decisions about medicine launch in a country. For mathematical simplicity, the sum of weights assigned across the indicators was made to equal "1".[f] Board members combined their collective experience and expertise to arrive at a consensus on the appropriate weight for each indicator.

Table 5 Indicator Weights & Measurements

Technical Area	Indicator	Weight	Measurement
Development & Commercialization Infrastructure	Late-Stage R&D Activity	**.038**	• Number of Phase 3 Clinical Trials Registered (2020)
	Manufacturing Capability	**.036**	• $ Value of Pharmaceutical Industry Exports (2019)
Regulatory Landscape	Intellectual Property Protection	**.122**	• Years of standard patent life • Years of patent term restoration • Years of data protection • Other Incentives
	Market Authorization Process	**.102**	• Standard and prioritized review time (targets and actual 2019) • Existence of specialized and/or prioritized review pathways • Existence of a rolling review pathway
	Price Regulation	**.180**	• Influence of price regulator • Resulting average prices
Access Environment	Market Potential	**.112**	• Share of global pharmaceutical market • Wealth (GDP/Capita) • Share of out-of-pocket spending
	HTA & Reimbursement	**.346**	• Time to reimbursement from market authorization • Existence of sizeable private market • Complexity: Number of payers/processes • Mechanism for HTA concurrent with regulatory or reimbursement
	Patient Role	**.064**	• Impact of patient participation in HTA
	Total	**1.000**	

Overall, the Board felt the most important indicators from the perspective of a global pharmaceutical decision maker were HTA & reimbursement and price regulation, together representing more than half of the Index's weight. The relative importance of these two indicators reflects the business imperative to ensure the manufacturer's investment to launch a new medicine in a country can, at minimum, be recouped. Securing an acceptable list price for the product and ensuring there are customers who will provide payment for the product in a timely fashion were recognized as the two biggest factors contributing to risk reduction of launch investments.

Overall, the Board felt the most important indicators from the perspective of a global pharmaceutical decision-maker were HTA & reimbursement and price regulation, together representing more than half of the Index's weight.

[f]Because all indicators were selected specifically because of their influence on new medicine investment, no indicator received a weight of "0". Additionally, because decisions to conduct new medicine investment in a country are typically complex and multifactorial, no indicator received a weight of "1". It is recognized that each decision about new medicine investment is unique, and therefore there may be cases where individual decisions would be weighted differently, or exclusively on some factors versus others, however, for the purpose of this Index, it is assumed each indicator potentially influence new medicine launch decisions on average.

Slightly less influential, but still significant contributors to launch decisions were intellectual property protection, market potential and the market authorization process. The Board indicated it's important for a country have clear, reliable processes in these areas, and that countries meet a minimum standard concerning these indicators. However they are not often independently "make or break" factors in launch decisions within this sample of countries.

Finally, the Board felt that late-stage R&D, manufacturing capability and patient role indicators could play important roles for some individual new medicine investment decisions but on average would be more likely considered "nice to have" factors that would not substantially influence launch decisions.

"I am aligned with the Advisory Board in terms of how they've weighted [the indicators] based on my experience at Life Sciences Ontario and in working with many companies in the biopharma space. However, I suspect there will be individuals that have a specific ideological view around pricing that will voice opposition to the report's conclusions. "
—Jason Field, President & CEO, Life Sciences Ontario

Research Methods & Data Analysis

Index Data: Search Strategy, Selection and Scoring

This Index provides a snapshot of the global ecosystem for new medicine launch current to December 2021. Data supporting each indicator were gathered by searching for publicly available sources from relevant databases or published reports or papers. Key word searches specific to each indicator were used. An initial search was done through the OECD website and databases, followed by an internet search engine (Google) search. Where appropriate, a targeted grey literature search was completed to supplement missing data (e.g., government, regulatory, or HTA websites).

"The index is an attempt to kind of impose a framework on what would seem to be rational factors in launch decision-making, but is this really what corporate executives follow? Do they use these factors intuitively or more deliberately, to come up with their decisions in terms of where to launch? "
—Durhane Wong-Rieger, President, Canadian Organization for Rare Disorders (CORD)

Data were selected based on relevance to the indicators selected (i.e., direct measure or relevant proxy). OECD data were preferred, followed by peer-reviewed or other reputable sources (e.g., government databases or reports), if possible. The most recent sources were used and if data were older than three years, they were evaluated to determine if still relevant and excluded if considered no longer pertinent to current context. Sources including multiple countries were prioritized and helped to inform additional searches to supplement country-specific data, if possible. All sources used have been listed for transparency. The cut-off date for inclusion in the quantitative research was December 1, 2021.[g]

"I'm struck by the extensive analysis and research that went into this. Concerns about subjectivity in terms of weighting could be somewhat dispelled when your readership looks at the volume of data you have evaluated and integrated into your report. "
—Cate McCready Vice President, BIOTECanada

Following the literature review for each measurement within each indicator, each country was evaluated relative to the

[g]Some discussions in the index reference recent or anticipated changes in the indicators or measurements in the various countries. The qualitative discussion portion of this Index considers the possible impact of recent or anticipated changes. However all scoring is based on the evidence and research available as of December 2021. Future updates to this Index will be able to incorporate whether and/or how anticipated changes in Canada and the comparator countries affect the rankings.

others and assigned a score out of 10 points for each of the eight indicators. The general approach to scoring each measurement was to first identify the range of performance values within the sample of countries for the measurement. The country with the best performance would receive full points, the country with the poorest performance would receive zero points and interceding points were distributed as evenly as possible in between. Specific scoring rationale for each indicator is summarized in the corresponding results section. After completing all research and scoring for each indicator, each country's scores were weighted according to the relative importance the Board assigned to the indicators.

Qualitative Research

The Index methodology results in quantitative scores and rankings for the sample countries; but the data on their own cannot tell the entire story of countries' attractiveness in the global biopharmaceutical ecosystem. For this reason, the authors engaged external stakeholders to assist in interpretation, gather important insights, and provide experiences and qualitative commentary concerning the quantitative Index results.

Participant categories and an initial list of individual participants were identified through PDCI's network. After validation and supplementation by the Editorial Advisory Board members, PDCI recruited 14 interview participants for 45-minute interviews via a web conferencing platform.

The authors made efforts to identify and invite the following stakeholder individuals or groups to participate in the qualitative research:

- Canadian based pharmaceutical company leaders (CEO level, and senior management in market access and medical affairs). Additionally, we connected with senior management in the industry associations, Innovative Medicines Canada and BIOTECanada
- Canadian patient organization leaders
- Canadian and provincial Life Sciences organization leadership
- Federal government officials including PMPRB, Health Canada and ISED
- Provincial payers in Ontario and representatives from the pan-Canadian Pharmaceutical Alliance
- Health technology leadership of the Canadian Agency for Drugs and Technology in Health
- Health Canada and Innovation, Science and Economic Development Canada (ISED)
- Academics and health policy experts

We were successful in securing interviews, with representatives of a number of small to large multinational biopharmaceutical companies (Canadian offices), Canadian pharmaceutical industry association leadership, patient organization leaders, life sciences organization leadership and academic/health policy thought leaders. Each interview was preceded by a detailed pre-read including draft results of the quantitative rankings.

We received no response from the Federal or Provincial government representatives we contacted including PMPRB, ISED nor from the province of Ontario Executive Office of the Ontario Provincial Drug Program (OPDP). We received no response from CADTH. We did receive a response from the office of the pCPA, however, they declined to be interviewed.

Interviews with relevant stakeholders occurred between January 3 and April 7, 2022. Participants were provided with an embargoed draft of the quantitative Index results for review prior to their interview. The interviews were facilitated with use of a discussion guide, with the objective of eliciting insights and commentary about the index results, including any feedback about the rankings, results and scoring which could not be captured by the quantitative indexing exercise. Data collected from the interviews were analyzed using a basic thematic analysis and summarized throughout this report.

RESULTS

Overall

Following research on all the measurements for all indicators in all 14 countries and developing an internally consistent scoring system to assign each country a score out of 10, Table 6 summarizes each country's scores across all eight indicators.

Table 6 - Indicator Scores Summary

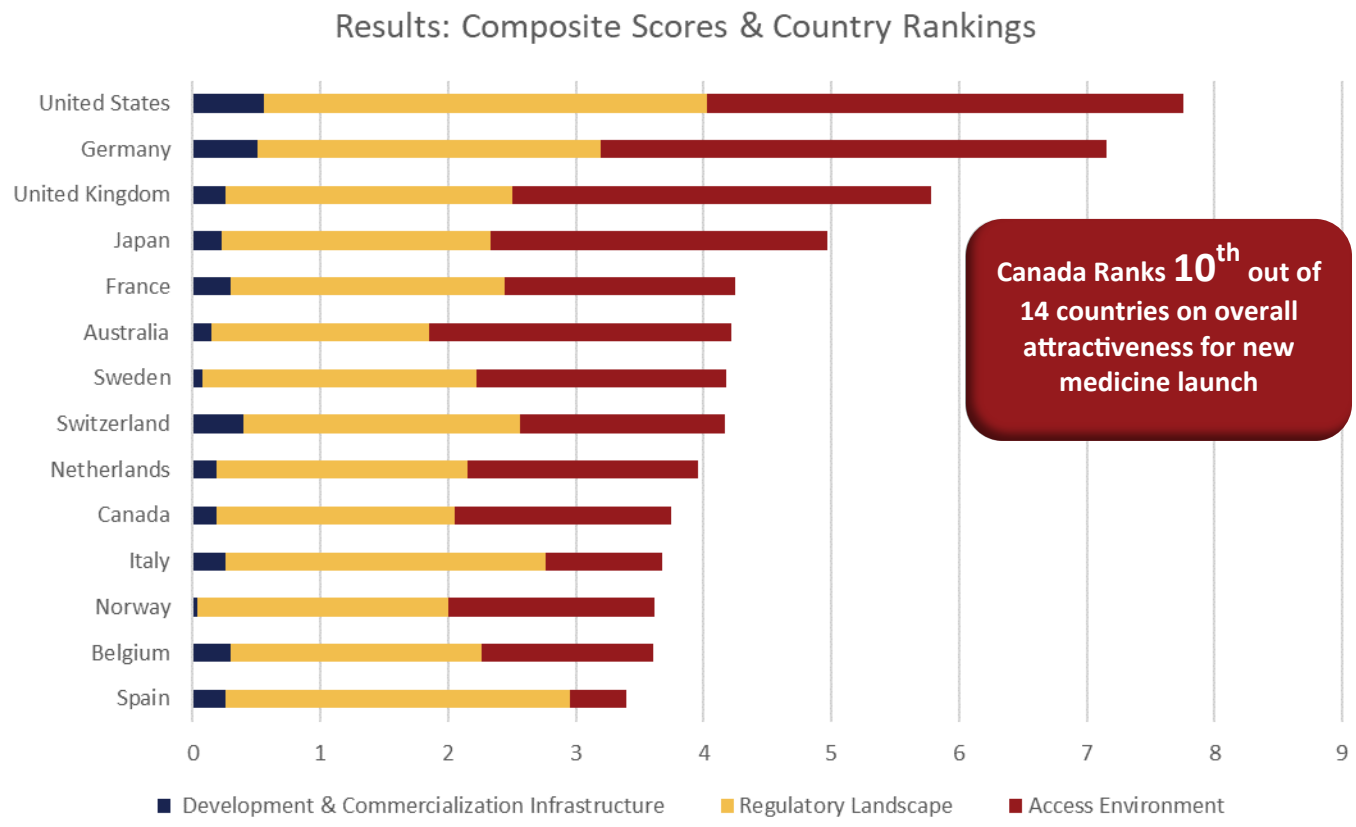
	INDICATOR							
	Development & Commercialization		Regulatory Landscape			Access Environment		
Country	Late-Stage R&D	Manufacturing Capability	IP Protection	Regulatory Approval	Price Regulation	Market Potential	HTA & Reimbursement	Patient Role
Canada	4	1	5	7	3	3	3	5
Australia	3	1	6	6	2	3	4	10
Belgium	3	5	9	5	2	3	2	5
France	4	4	9	5	3	4	3	5
Germany	4	10	9	5	6	8	7	10
Italy	4	3	9	5	5	5	1	0
Japan	5	1	7	7	3	5	6	0
Netherlands	2	3	9	5	2	4	3	5
Norway	1	0	9	5	2	2	4	0
Spain	5	2	9	5	6	4	0	0
Sweden	1	1	9	5	3	2	5	0
Switzerland	2	9	7	4	5	2	4	0
UK	3	4	9	6	3	5	6	10
US	9	6	7	8	10	9	6	10

After weighting the scores reported in Table 6 in accordance with the Board-assigned weights from Table 5, Figure 4 and Figure 5 report the composite scores of how each country performs overall with regards to its attractiveness for new medicine launch.

"One might criticize this as being too heavily weighted on price and reimbursement, but we are for-profit businesses, generally, so that's a big component of launch sequencing. Market opportunity, return on investment and the burden of price and funding regulations impacts greatly on our launch opportunity and decision-making."
—Bob McLay, VP, General Manager Canada, Sobi Canada Inc.

"Canada appears in the lower half of your performance results which I believe reflects what I would have expected. It's helpful, though, that the data supports some favorable evaluations for Canada. It still doesn't argue against improvements in regulatory approval or HTA processes, but it does say you've tried to evaluate this fairly and Canada does perform well in some areas but not so well in others."
—Richard Owens, SJD University of Toronto, Senior Munk Fellow, Macdonald-Laurier Institute, University of Toronto, Adjunct Professor, Faculty of Law

Figure 4 Results:Composite Scores and Country Rankings



The following figures report the results for each of the three technical areas independently.

Figure 5 Results and Rankings: Development and Commercialization Infrastructure

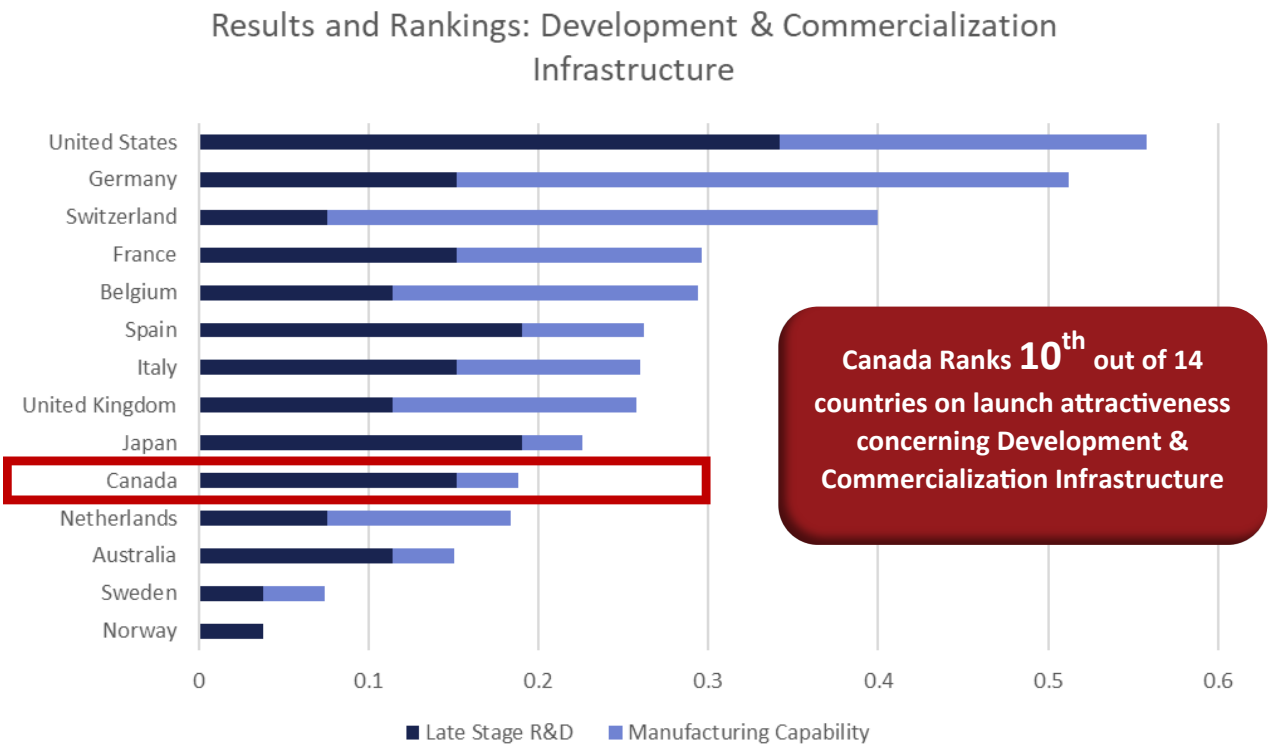


Figure 6 Results and Rankings: Regulatory Landscape

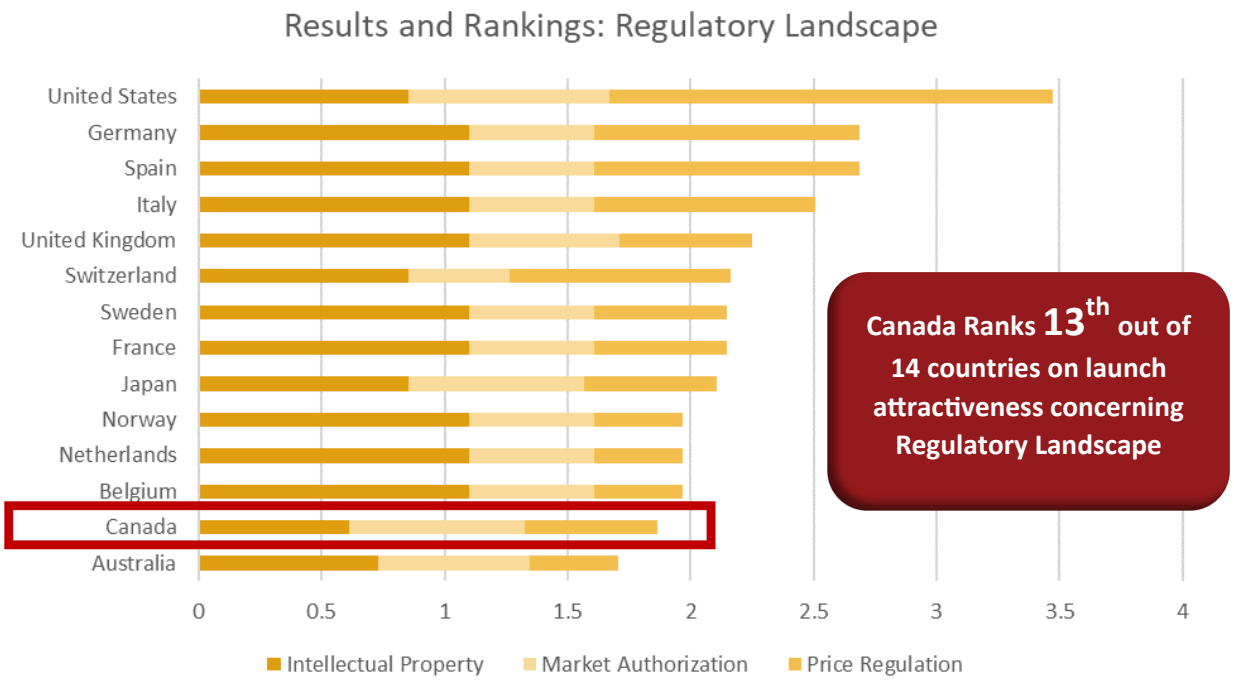


Figure 7 Results and Rankings: Access Environment

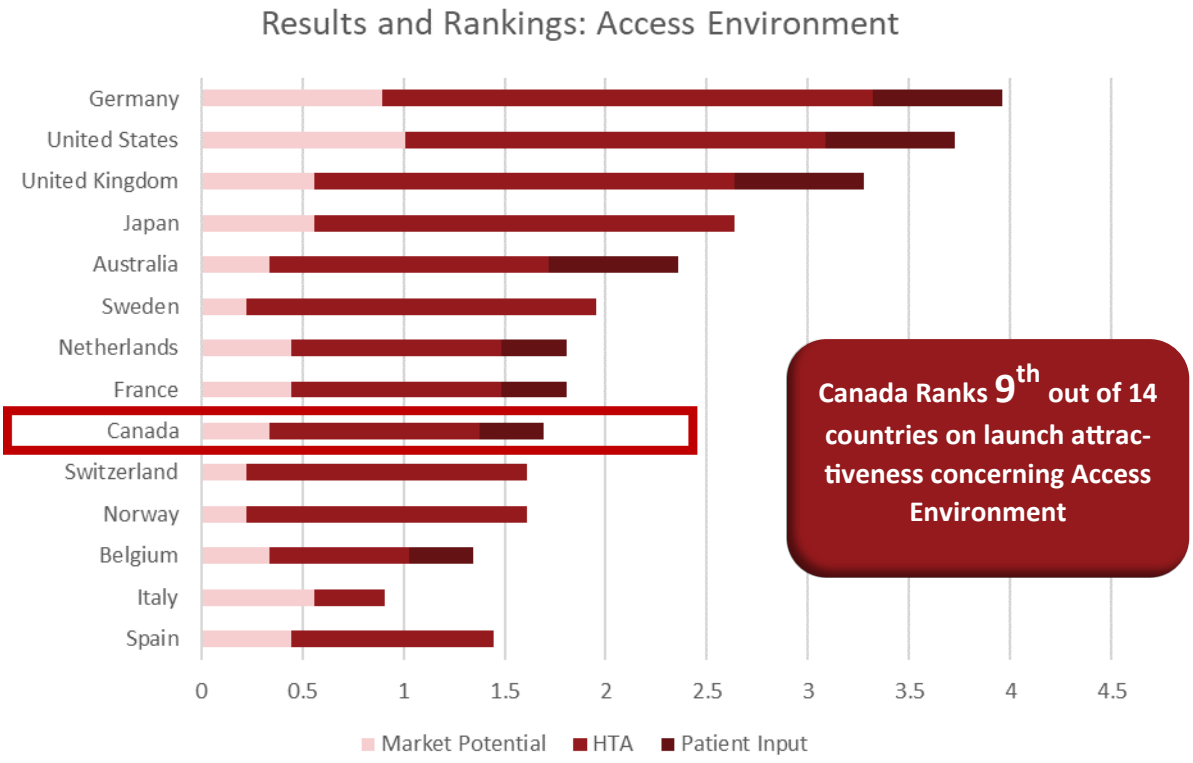
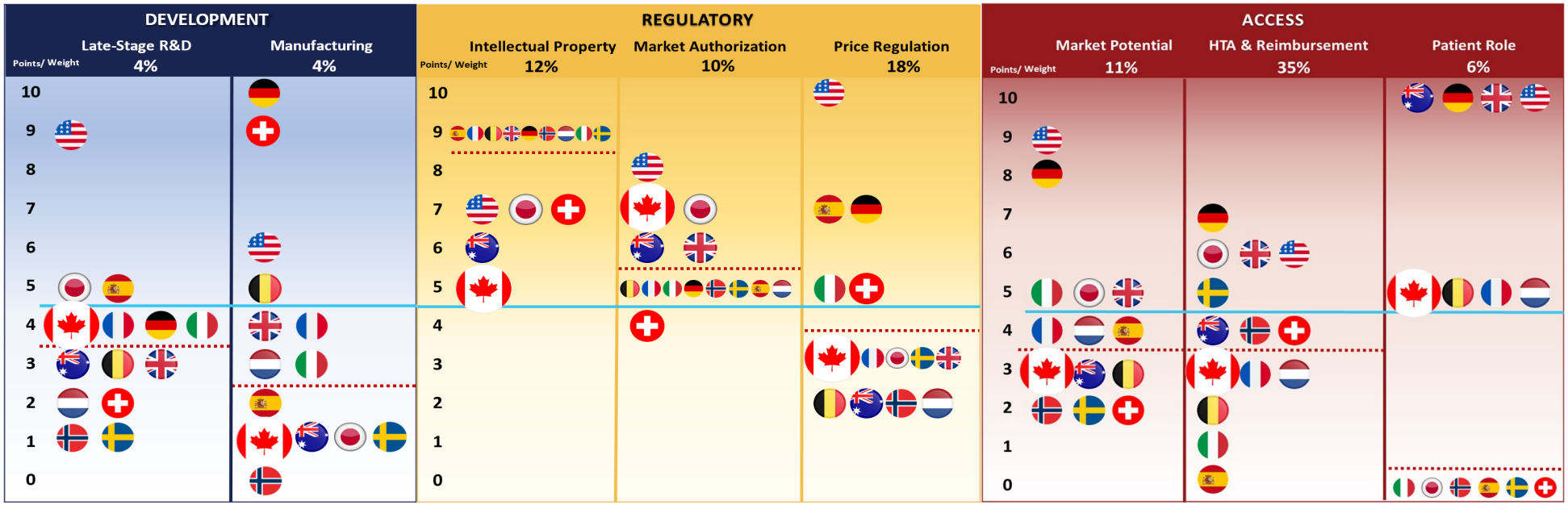


Figure 8 Country Scores by Indicator



Median

5 points line

Development and Commercialization Infrastructure Indicators

Late-Stage Research & Development

Clinical trials are essential to the development of new medicines. To the extent Phase 3 trials take place in Canada, they provide Canadian patients an opportunity to access therapies still under development, which is particularly important in disease areas for which there are no or insufficient treatment options. Besides developing evidence about safety and efficacy, when manufacturers conduct Phase 3 trials in a country, their investment builds the confidence and engagement of the public, health care providers, and policy makers.[2] As referenced earlier, increasing clinical trial activity means opportunities for countries to be global leaders in drug innovation. Clinical trial of new drugs are critically important for attracting research dollars in the short term and improving access to new drugs in the longer term.[3]

For this indicator we measured the number of phase 3 clinical trials registered in 2020 across the countries of interest. The more late-stage clinical trials in a country indicated how desirable the country's infrastructure is perceived as a destination for not only the clinical trials but subsequent launch. The source consulted for this measurement was the World Health Organization (WHO) International Clinical Trials Registry Platform. It is a central database containing trial registration data sets provided by the registries and provides links to the full original records.[7] A clinical trial is any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes.

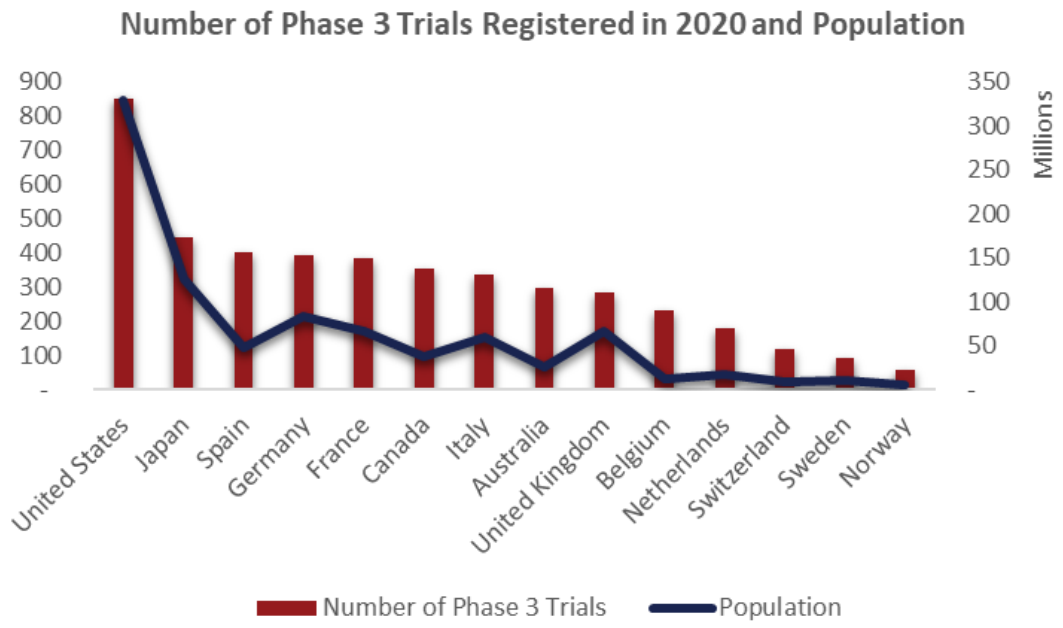
Scoring Rationale

A higher number of phase 3 clinical trials is indicative of a positive environment for late-stage R&D, and manufacturers' confidence that they will eventually successfully launch their product in the country. Ten points are available. One point was given for every 100 trials registered: One point was awarded for 1-99 trials registered, two points for 100-199 registered, and so on. More than 900 trials would have to be registered to achieve all 10 points.

Table 7 Late-Stage Research & Development Summary & Scoring

Country	Phase 3 Trials Registered 2020[16]	Total Population 2020[17] (in thousand)	Score
Canada	354	38,005	4
Australia	299	25,687	3
Belgium	231	11,556	3
France	383	67,392	4
Germany	392	83,241	4
Italy	337	59,554	4
Japan	444	125,836	5
Netherlands	180	17,441	2
Norway	56	5,379	1
Spain	400	47,352	5
Sweden	93	10,353	1
Switzerland	121	8,637	2
United Kingdom	284	67,215	3
United States	850	329,484	9

Figure 9 Number of Phase 3 Clinical Trials Registered in 2020



Canada performs strongly in this measurement (6th) among the comparator countries. Except in the case of the UK, the number of trials registered in a country seems to correlate with the country's population size. Japan performs very well on this measurement given its importance as a market and its requirements that medicines have local clinical trials completed as a condition of market authorization. Note that registration of clinical trials to the registry is not mandatory but is strongly encouraged, therefore data in this indicator is limited by compliance across the countries of interest.

Manufacturing Capability

Drug commercialization involves a strategic, complex, multi-departmental and even multiorganizational effort to achieve market access. This includes empowering sales force readiness, preparing the supply chain, distribution networks and customer support programs to ensure the successful launch and continued use of a new drug.[4] Local manufacturing in a country may be viewed as an asset as it eliminates the need for importation and if manufacturers have an existing presence in the country (whether manufacturing or otherwise) their experience with the local market may make them more inclined to bring a product to market in that country.

As a proxy measure of a country's manufacturing capability, we examined data on the value ($USD) of each country's pharmaceutical exports in 2019.

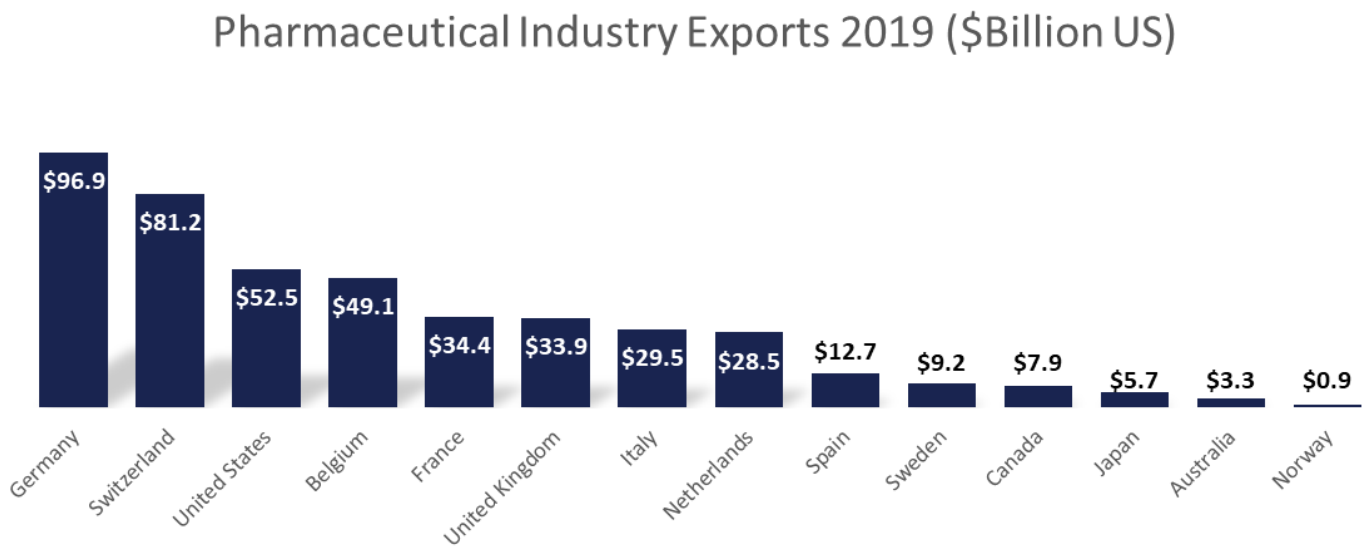
Scoring Rationale

No points were assigned for less than $1 billion USD of exports. One point was assigned for each increment of $10 billion exported, such that $1 billion to $9.9 billion received 1 point, $10 billion to $19.9 billion received 2 points and so forth until $90 billion to $99.9 billion received all 10 points.

Table 8 Manufacturing Capability Summary & Scoring

Country	Pharmaceutical Industry Exports in 2019 ($Million US)[18]	Score
Canada	$7,925.44	1
Australia	$3,297.73	1
Belgium	$49,096.15	5
France	$34,377.73	4
Germany	$96,888.63	10
Italy	$29,519.72	3
Japan	$5,653.99	1
Netherlands	$28,507.95	3
Norway	$925.90	0
Spain	$12,689.44	2
Sweden	$9,242.66	1
Switzerland	$81,188.31	9
United Kingdom	$33,918.28	4
United States	$52,537.48	6

Figure 10 Pharmaceutical Industry Exports 2019 ($ Billion US)



A limitation of this measurement as a proxy for domestic manufacturing capability is its inability to include the value of locally manufactured drugs which were also locally consumed.[h] This is perhaps why we observe smaller markets such as Germany and Switzerland – which are perceived as being high producers – score highest while the US – which is similarly known to be a high producer but also has a very large domestic pharmaceutical market itself – score lower when measuring the exports alone. Additionally, exports include both innovative and generic medicines which could require different production capabilities and infrastructure and therefore this data may not adequately reflect attractiveness in the case of, for example, manufacturers seeking to manufacture complex biologics within the market. Having lots of small-molecule generic production capability would not necessarily be enticing for launch decisions concerning new medicines with more complex manufacturing needs.

[h] For example, the US receives a mid-range score while Germany receives top score. However it's possible the US manufacturing capability is equal or higher than Germany but a much larger value of the US production is consumed domestically than German production would be given the much smaller market and population of Germany compared with the US .

Regulatory Landscape Indicators

Intellectual Property Protection

Intellectual property protection (IPP) allows for pharmaceutical product manufacturers to exclusively market and collect returns on their products in a country. Mechanisms for IPP include patent regimes that provide an incentive to invest in research and development (R&D). An effective patent regime confers a limited period of market exclusivity during which upfront research and launch investments can be recouped. Innovative pharmaceuticals require substantial risk and R&D investments, so by a country creating and upholding a mechanism for market exclusivity, innovators will feel confident they have a reasonable opportunity to earn return on investments, before competing generics or biosimilars may enter the market. The global importance of strong IPP regimes is affirmed through international harmonization that resulted through World Trade Organization's Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS Agreement).

Measurements evaluated for this indicator include the standard patent term available in each country, patent term restoration (PTR) mechanisms which provide time payback for the fact that patent term continues to lapse while regulators evaluate medicines for the purpose of market authorization, and data protection mechanisms, which, albeit separate from patent life, also can serve to restrict generic or biosimilar entrants for a period of time by preventing other manufacturers from referencing data from the innovator's regulatory filing in order to achieve market authorization for itself. In addition, any opportunities for manufacturers to file for extensions to the data protection period are noted. Countries sometimes offer such extensions to incentivize investment and research into certain therapeutic areas.

Appendix B summarizes research concerning the intellectual property indicator measurements in the countries of interest.

Scoring Rationale

Pharmaceutical patents protect innovative pharmaceuticals by ensuring a period of market exclusivity. Patent extension beyond the basic term and data protection provide additional opportunities for market exclusivity and flexibility for pharmaceutical companies. This is particularly important, as the basic patent term of 20 years typically starts well before market authorization for many products. Each country was scored out of 10 based on the potential length of intellectual property protection as achieved through various mechanisms.

- Two points were attainable for the duration of standard patent life: no points for less than 20 years, one point for 20 years or two points for more than 20 years.
- Three points were possible for patent term restoration: 0 points for no PTR, one point for two years or less, 2 points for more than two to four years and three points for more than four years.
- Three points were possible for duration of data protection: no points for no data protection mechanism, one point for up to 5 years of data protection, two points for 6-9 years, three points for 10 years or more.
- Two points were possible for other incentives: no points for no other incentives; one point for one incentive mechanism; two points for multiple special incentive mechanisms.

Table 9 Intellectual Property Protection Summary & Scoring

Country	Patent Term	Patent Term Restoration	Data Protection	Incentives for Innovation	Score
Canada	20 Years	2 years	8 years	+6 months data protection for pediatric	5
Australia	20 Years	Up to 5 years	5 years	N/A	6
European Union & UK	20 Years	Up to 5 Years	8+2+1 years	+6 months data protection for pediatric Orphan Medicines Exclusivity	9
Japan	20 Years	Up to 5 years	8 years	6-10 years re-examination for orphan drugs	7
Switzerland	20 Years	Up to 5 Years	3 years	10 year data protection for significant clinical benefit or pediatric product 15 year data protection for Orphan Drugs	7
US	20 Years	Up to 5 Years	5	+5 data protection for antibiotics, 7 years for orphan, +3 for New Clinical Investigation	7

Canada receives the lowest score on this indicator due to it having a much shorter time offered for patent term restoration. While its data protection offerings are aligned or better than some other countries, it has little in the way of extra IP regime incentives compared to the others.

Regulatory Approval Process

Securing regulatory approval is a mandatory step to successfully marketing a drug. Regulatory approval processes are generally intended to protect residents from using medicines for which the potential harms outweigh potential benefits. The regulator authorizes sale of a medicine only after having taken time to evaluate evidence of its safety, efficacy and quality; but it is important the process be balanced to avoid discouraging or dissuading market entry for new medicines (e.g. taking too long to complete, being too costly, or too complex). For this indicator, we reviewed the following measurements to score and compare countries on the basis of their regulatory approval process:

- Length of review time targets (standard and prioritized)
- Existence of prioritized review pathways
- Average time from submission to authorization
- Application fees
- Existence of rolling review pathway

For this indicator, research sources were primarily published information authored by the regulators in the countries of interest, including procedural guidance documents, performance reviews and annual reports. Published academic literature, such as studies comparing time to regulatory approvals in various countries was also consulted for additional performance analyses and qualitative discussion to explain differences across countries and any underlying practical issues perhaps not obvious in data on regulatory approval timelines supplied from the regulators themselves.

Scoring Rationale

The amount of time a new medicine is undergoing regulatory review is critical to a country's desirability for launch, as each month the marketing authorization is ongoing, represents a month longer until a product can be launched into the market. For this reason, less time between submission and approval was viewed as the most influential factor for launch attractiveness. Lower standard and prioritized review time targets remain very important but so too is the actual recent performance data on time between submission and approval, as actual review time may better capture the effect of clock-stop times, and perhaps indirectly the extensiveness of questions addressed during these periods. The existence of expedited pathways which apply to a larger number or broader definition of new medicines is also important to reducing regulatory approval time on average, and while fees are a quantitative and easily comparable feature of the regulatory review process, given the massive costs of drug development and commercialization generally, regulatory application fees are generally considered an insignificant incremental cost, therefore no points were assigned for application fees.

- Two points were possible for countries concerning standard review times:
  - 0 points for > 300 days
  - 1 point for 200 to 300 days
  - 2 points <200 days of standard review time
- Two points were possible for countries which have prioritized review pathways:
  - 0 points for countries without prioritized review pathways
  - 1 point for prioritized review pathways with narrower definitions of qualifying products
  - 2 points for many pathways for which a broad definition of products may qualify (If 30% or more new medicines approved by the regulatory authority in 2019 qualified for priority review this was considered to be a broad definition)
- Two points were possible for countries concerning prioritized review times:
  - 0 points for countries without prioritized pathways or with times greater than 300 days
  - 1 point for countries with prioritized review times of 201 to 300 days,
  - 2 points for countries with prioritized review times of 200 days or fewer
- Three points were possible for countries based on their actual 2019 median review time:
  - 0 points for greater than 500 days
  - 1 point between 400-500 days
  - 2 points between 300-399 days
  - 3 points for less than 300 days
- One point was possible for countries with rolling review processes: those with rolling review processes receive the point and those without did not receive the point.

Table 10 summarizes the analysis of this indicator and the scores assigned.

Table 10 Regulatory Approval Process Indicator Summary & Scoring

Country	Standard Review Time Target	Prioritized Review Time Target	Review Time Actual 2019 Performance (# NAS, Median days)[5]	Expedited or Other Pathways	Rolling Review[i]	Standard Fees	Score
Canada	300 calendar days	180 or 200 calendar days	N=31, 346 days	• Priority Review • NOC/c	No	CDN $437,009[19] $344,400 USD*	7
Australia	40 + 255 active workdays	40 + 150 active workdays	N=25, 346 days	• Priority Review • Provisional Review	No	$50,300 Application Fee and $201,600 Evaluation Fee[20] $180,930 USD*	6
EMA	210 active calendar days	150 active calendar days	N=27, 423 days	• Accelerated Assessment • Conditional Approval • Exceptional Circumstances	No	€296,500 $339,290 USD*	5
Japan	12 months	6 or 9 months	N=33, 304 days	• Priority Review • Sakigake	Yes	¥533,800 to MHLW ¥30,535,100[j] $180,930 USD*	7
Switzerland	540 days (330 SMC time)	350 days (140 SMC time)	N=28, 520 days	• Fast Track	No	80 000 fr $86,720 USD*	4
US	10 months	6 months	N=47, 243 days	• Fast Track • Priority Review • Breakthrough Therapy • Accelerated Approval	Yes	$3.1M USD[j]	8
UK	150 calendar days	N/A	Data not available[k]	• Early Access to Medicines Scheme	Yes	£92,753[21,l] $1,259,530 USD*	6

** USD conversion with January 2022 exchange rate*

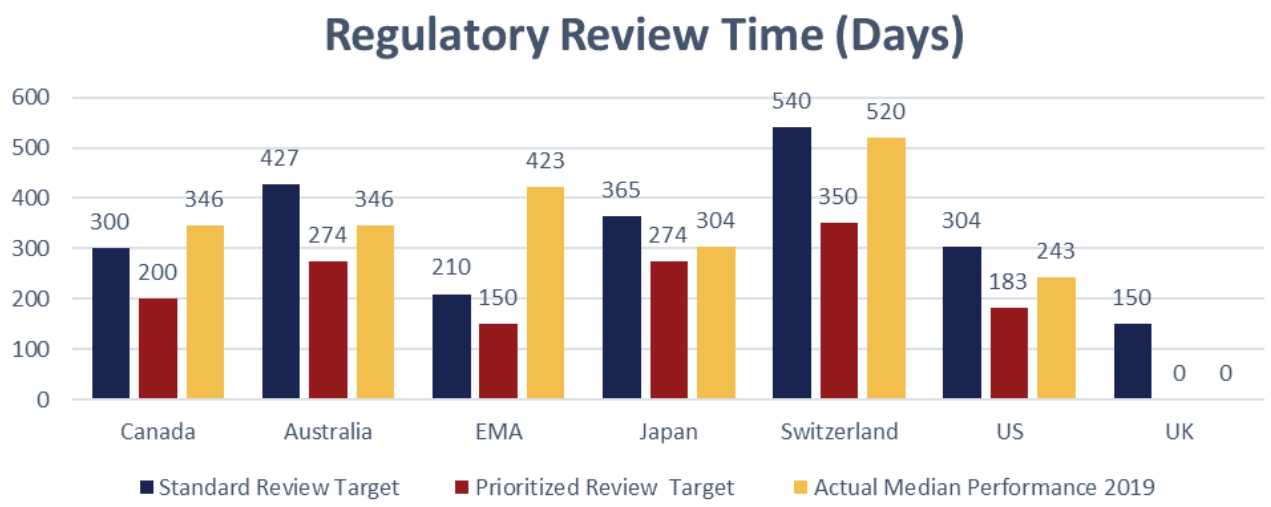
[i] Several countries took unprecedented measures to implement rolling review processes specifically for COVID-19 vaccines and therapeutics. Countries received "Yes" only if they have a rolling review mechanism which is accessible for a broader definition of medicines across therapeutic areas.

[j] Fees waived for designated orphan drugs.

[k] Because actual data is not available we assumed it's actual review time would be aligned with recent EMA data.

[l] Application fees for Orphan drugs authorizations are generally lower at £29,732.

Figure 11 Regulatory Review Time (Days)



Studies have consistently identified that Canada often lags the US and Europe with regards to regulatory approval of new medicines.[3,22] However, the review times summarized in Table 10 shows Canada's regulatory processing times to be in step with other jurisdictions. This suggests the issue is likely not caused by longer regulatory processing times but rather due to delayed submissions to Health Canada by sponsoring manufacturers. Published literature aligns with this finding.

Canada lags the US and Europe with regards to regulatory approval of new medicines… the issue is likely not caused by longer regulatory processing times but by delayed submissions to Health Canada by sponsoring manufacturers, as regulatory performance times are in line with other jurisdictions.

When it comes to submission timing, a 2015 study comparing regulatory processing times showed US to be first priority, as FDA submissions were completed an average of 4 months earlier than EMA submissions and 14 months earlier than Health Canada submissions.[4] Another recent study showed the average difference between Canadian and US approvals was 468 days. Authors identified submission delays accounted for 464 days, and differences in regulatory efficiency accounted for only 4 days of the 468-day average difference. Similarly, in the European Union, Canadian approval dates lagged the EMA by an average of 404 days, 395 of which were attributed to later submission dates in Canada, and only 9 days attributable to longer regulatory processing time in Canada.[3]

Based on the scoring, Canada fares well on this indicator, second only to the US and tied with Japan which had a median review time in 2019 just over 300 days. Japan's target of 12 months for standard reviews seems conservativein light of its actual performance data, likely due to the high percentage of reviewed drugs which qualify for prioritized review. The US received highest marks given its superior commitment to service standards and variety of specialized and accelerated pathways for approval. It does have significantly higher application fees than other jurisdictions, however, given that the fees are formally linked to the service standard, not to mention the sheer size of the US market that is accessed via an FDA approval, it seems relatively insignificant. Switzerland received lowest marks for its actual 2019 review times being longest out of the analyzed countries. This is in large part due to the fact that its review times provide substantial periods for sponsor responses.

Not considered under this indicator but which may have an effect on attractiveness for launch include the complexity or uniqueness of dossier requirements across the regulators (as this may incur greater costs and investments from the manufacturer), the extensiveness of comments or critiques of the regulator (which would contribute to longer

manufacturer times required to respond), and also the risk of not receiving authorization which could hurt the product's potential elsewhere around the globe. Also not considered here is whether regulators engage in cross-jurisdictional alignment, co-operation, information sharing or coordinated reviews. These mechanisms have been proposed in order to minimize the impact of submission lag in jurisdictions which experience significant delays relative to other countries and in which Canada has engaged.[m] Additionally, it seems these programs aren't being optimized by manufacturers. To its credit, Health Canada's processing time is comparable to other jurisdictions and it has been collaborating internationally to facilitate concurrent submissions and cooperative reviews (e.g. FDA portal and Access Consortium (including Australia, Canada, Singapore, Switzerland and UK), but few reviews have been completed via these mechanisms and those which have seemed to have been initiated by regulators.[5] Such processes seem insufficient to overcome the other gaps observed in this index.

Price Regulation

Price and volume are the two key components global pharmaceutical decision makers must assess to forecast their expected revenues for a new medicine launch. Pharmaceutical companies planning global product launches have identified a troubling tension between the time to market and prices that together determine total earnings.[23] Several countries use international price referencing as part of their local price regulation processes. For this reason, companies are sometimes incentivized to launch first in countries where they can secure the higher list prices and later in countries where list prices are lower, so a low price attained in one country does not compromise the price possible in other countries where the product has yet to launch. The following measurements were evaluated to score countries on this indicator:

> "Canada has a lot of assets and we're shooting ourselves in the foot by being outliers in just a very few specific areas like PMPRB regulations. And there is a relatively straightforward fix to that. In terms of getting the regulations done, making sure you're doing it in such a way that doesn't discourage investment and delay product launches in Canada ."
> —Jason Field, President & CEO, Life Sciences Ontario

1. The nature and influence of price regulation:
    - whether regulatory mechanisms are formalized in legislation, or less formal mechanisms to lower drug prices, such as through payer negotiations.
    - the mandate of the price regulator, over which products and sales it has authority to regulate. For example, does the jurisdiction of a price regulator depends on a product's patent or prescription status? Or, does the price regulator's oversight only apply to sales reimbursed by a public drug plan (and prices for off-formulary products are not regulated for the purpose of out-of-pocket sales)?

2. Whether the resulting list prices in a country are acceptable to the manufacturer. We consulted literature comparing prices across the 14 countries included in this analysis. We assumed countries that publish higher list prices (on average or median) are more likely to have processes that result in prices that are acceptable to manufacturers.

[m] Application fees for Orphan drugs authorizations are generally lower at £29,732.

Scoring Rationale

From the perspective of the global pharmaceutical decision maker, less regulation on pricing provides more flexibility to engage with payers, to discuss needs, and to negotiate reimbursement. For this reason, countries with more formal mechanisms that regulate a wider definition of medicines receive lower scores. For whether resulting prices are acceptable to the manufacturer, we consulted literature comparing prices across the countries included in this analysis and have assumed that countries which have higher prices are more likely acceptable to manufacturers to facilitate launch.

- Three points were possible for the influence of the price regulator: no points for regulation of the vast majority of medicines, two points for a large influence (e.g. those medicines covered on the publicly funded formulary), three points for small or only informal influence.
- Seven points were possible for the measurement of resulting prices being acceptable to the manufacturer. This score is based on the median 2018-2020 foreign-to-Canadian price ratios of manufacturer list prices in US$ market exchange rates, reported in Skinner 2021.
    - 0 points for ratio of < 0.8
    - 1 point for ratio of 0.8 - 0.89
    - 2 points for ratio of 0.9 – 0.99
    - 3 points for ratio of 1.0 – 1.09
    - 4 points for ratio of 1.1 – 1.19
    - 5 points for ratio of 1.2 – 1.29
    - 6 points for ratio of 1.3 – 1.39
    - 7 points for ratio of 1.4+

Table 11 Price Regulation Indicator Summary & Scoring

Country	Influence of Price Regulator	Resulting Prices are Acceptable to Manufacturer[24]	Score
Canada	All Canadian sales of patented, prescription and non-prescription medicines = 0 points	1 = 3 points	3
Australia	Formulary drugs only= 2 points	0.75 = 0 point	2
Belgium	All drugs launched in the country=0 points	0.97 = 2 points	2
France	All prescription reimbursable drugs =2 points	0.82 = 1 point	3
Germany	Formulary drugs only= 2 points	1.10 = 4 points	6
Italy	Formulary drugs only= 2 points	1.09 = 3 points	5
Japan	Formulary drugs only= 2 points	0.84 = 1 point	3
Netherlands	Prescription-only medicines = 1 point	0.82 = 1 point	2
Norway	Prescription-only medicines[n]= 1 point	0.85 = 1 point	2
Spain	Formulary drugs only= 2 points	1.17 = 4 points	6
Sweden	Formulary drugs only= 2 points	0.89 = 1 point	3
Switzerland	All patented prescription medicines[o]=1 point	1.15 = 4 points	5
UK	Formulary drugs only= 2 points	0.85 = 1 point	3
US	Payer negotiations in private market only= 3 points	3.84 = 7 points	10

[n]For medicines not eligible or reimbursed by the public program, the manufacturer provides the Ministry of Health with a Notified Price for the product which it may oppose on the basis of protecting public interest.
[o]Only prices of on-formulary products are regulated by the government and subject to price negotiations, but prices of non-listed patented drugs may also be subject to surveillance by the Price Council.

Rising drug expenditures are a concern for patients, employers, states, and government.[25] Canada is currently undergoing unprecedented changes to one segment of its drug pricing regime: the PMPRB drug price regulatory mandate, which operates entirely apart from payer/manufacturer negotiations. Beyond the above measurements, other important features of the price regulatory regime are the predictability of price regulatory results, time to complete price reviews and whether sales can be made prior to completion of price regulatory reviews. In recent years, there has been unprecedented confusion about the future of Canada's price regulatory regime. This high-level of uncertainty has created difficulty for manufacturers to commit to investments in Canada as reported by brand medicine companies in a survey conducted by Life Sciences Ontario.[26] Notwithstanding, because the Index considers the current landscape, we find Canada placing among its peers, in the middle of the pack on this indicator in December 2021.

Access Environment Indicators

Market Potential

Global biopharmaceutical decision-makers prioritize launch in countries where there is strong market potential. A high level of pharmaceutical expenditure and utilization combined with a low-cost impact on patients would indicate lower risk for product launch in a country. To score countries with regards to their market potential, we considered the measurements below.

- Population
- Share of Global Pharmaceutical Market
- Wealth (GDP per Capita)
- Spending per Capita on Medicines
- Share of medicine spending by funding sources (public or private insurance or out-of-pocket)

Scoring Rationale

The most important measurement for this indicator is the share of the global pharmaceutical market that the country represents. This takes into account the country's population, total pharmaceutical spending and pharmaceutical spending per capita. Therefore, high points were assigned for the share of the global pharmaceutical market. The population and the pharmaceutical spending (both total and per capita) are reported here for interest but are not scored, as they are captured within the measurement of the Share of Global Pharmaceutical Market.

- Five points were possible for the Share of Global Pharmaceutical Market: no points for 0.5% or less, 1 point for 0.51%-2.5%, 2 points for 2.6%-4.99% 3 points for 5-10%, 4 points for 10-20% and 5 points for more than 20%.
- Two points were possible for wealth: no points for GDP per capita of less than $40,000. 1 point for $40,000-$60,000, and 2 points for greater than $60,000.
- Three points were possible for the share of out-of-pocket spending: 0 points for >30%, 1 point for 20-30%, 2 points for 10-20% and 3 points for less than 10%.

Table 12 Market Potential Indicator Summary & Scoring (2018 Data)

Country	Population (thousands)	Share of Global Pharmaceutical Market	Wealth (GDP/ Capita)[27]	Pharmaceutical sales (Millions, USD, PPP 2018)	Pharmaceutical spending, per capita $USD	Share of OOP Spending[28]	Score
Australia	25,687	0.8%	$51,812	$10,123	$663.38	23%	3
Belgium	11,556	0.7%	$44,594	$8,733	$607.34	21%	3
Canada	38,005	2.1%	$43,258	$25,542	$859.88	22%	3
France	67,392	2.1%	$39,030	$25,770	$634.66	N/A	4
Germany	83,241	5.0%	$46,208	$60,039	$891.60	6%	8
Italy	59,554	2.7%	$31,676	$32,889	$631.72	N/A	5
Japan	125,836	5.6%	$39,539	$66,608	$811.28	14%	5
Netherlands	17,441	0.5%	$52,397	$5,956	$408.20	N/A	4
Norway	5,379	0.2%	$67,390	$2,865	$477.65	46%	2
Spain	47,352	2.5%	$27,063	$30,057	$524.22	11%	4
Sweden	10,353	0.4%	$52,259	$5,370	$540.98	28%	2
Switzerland	8,637	0.5%	$87,097	$5,604	$843.68	31%	2
UK	67,215	2.5%	$40,285	$29,912	$510.83	N/A	5
US	329,484	40.4%	$63,544	$485,000	$1,308.75	14%	9

*France and United States information were from LEEM-GERS; DREES, comptes de la santé[26] and Statistica[27] respectively. The France information was converted from Euro to USD with the average USD rate in 2018 (1.1811), and to PPP $USD using the OECD chart. World Bank Data is used for the population.[28] The global pharmaceutical sales market share was calculated using the country pharmaceutical sales in 2018 divided by the global pharmaceutical market in 2018 (IQVIA Institute, Dec 2018 Report The Global Use of Medicine in 2019).

Figure 12 Global Pharmaceutical Market Share 2018

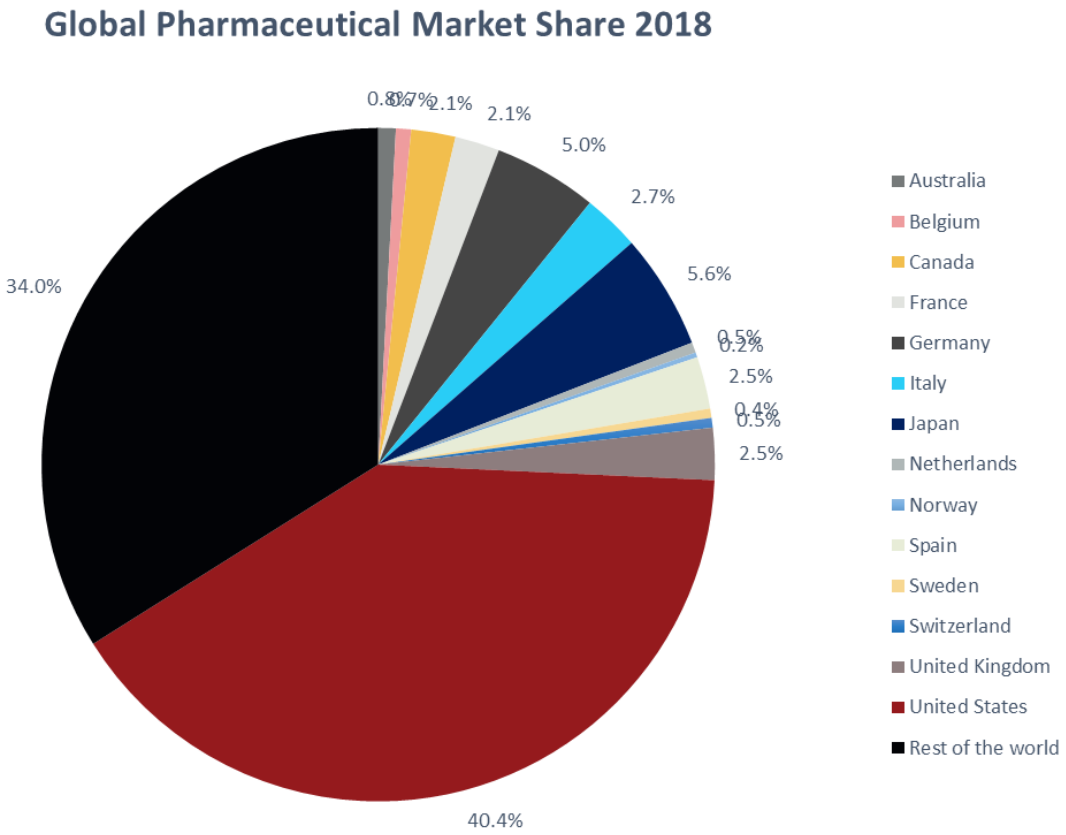
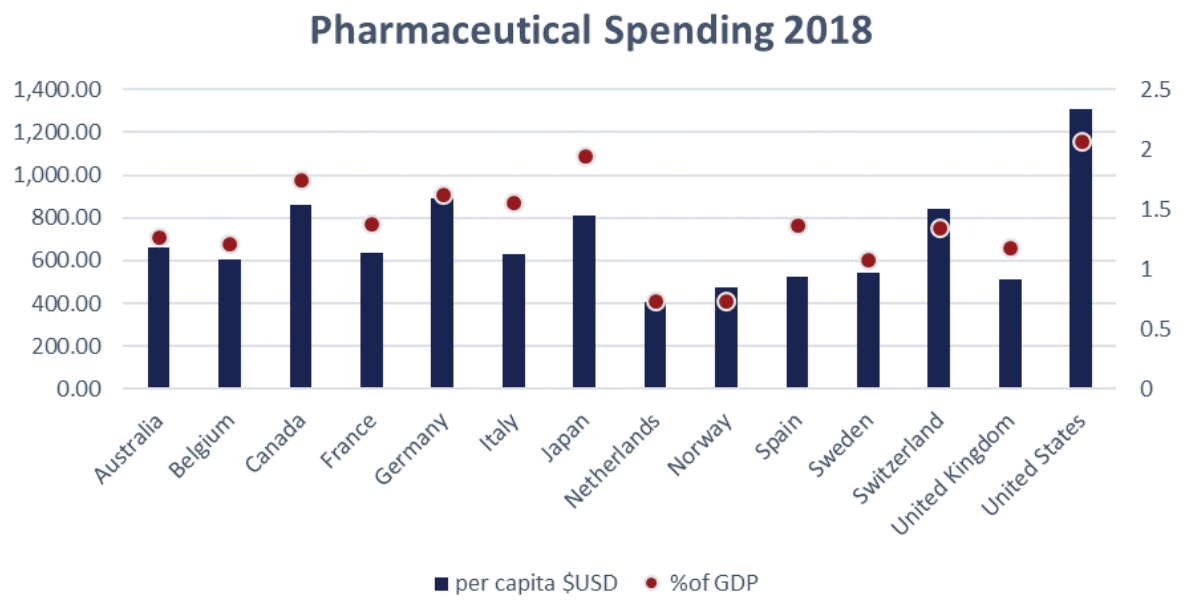


Figure 13 Pharmaceutical Spending in 2018



Health Technology Assessment & Reimbursement[p]

Prescription medicines are funded or reimbursed through various mechanisms across the countries in this analysis. As global expenditure on medicines continues to increase,[31] and the trend towards costly therapeutics for smaller patient populations continues, the role of drug insurance to mitigate risk becomes more important as well. To find a country attractive for launch, given the upfront investment in drug development, global medicine decision-makers will prefer to launch in countries where they can begin earning a return the quickest. For this indicator, we focus on the time to achieving maximum market penetration and the number of payers, processes and degree of complexity in getting a product to its optimized reimbursement state.

To support reimbursement decision-making, many countries have health technology assessment agencies whose mandate is to evaluate medical technologies including new medicines for the purpose of understanding their value for money. Unlike the regulatory processes which evaluate safety, efficacy, and quality of a medicine independent of other therapeutic options, HTA considers value for money relative to the existing standard of care. Elements of the evaluation process differ across agencies, as does the context for assessment (such as health system, availability of comparators, treatment guidelines and practices, population, social factors, and perspective), as well as target audience or customers for HTA, and whether the HTA body is also the payer. This can result in different outcomes of the HTA processes across jurisdictions.

Undergoing HTA as a new medicine sponsor can be arduous and costly depending on the submission requirements and time required to support a product through assessment. Additionally, to the extent HTA stands between regulatory approval of the product and its reimbursement, it can present barriers to the manufacturer's ability to begin realizing return on investment. Therefore, we have conducted a sub-analysis on time attributable to HTA.[q]

[p]Note the main sources relied upon for this indicator was an analysis in the Value in Health Journal, A Synthesis of Drug Reimbursement Decision -Making Processes in Organization for Economic Co-operation and Development Countries.

[q]This sub-analysis is not quantified in the index as it would double count the time required for HTA which is already captured in data sources which compare the time to reimbursement from regulatory approval.

Scoring Rationale

Manufacturers will find a country more attractive on this indicator if it has a shorter time to maximum market penetration, and the process to achieving maximum reimbursement is less complex with fewer payers and more consolidated processes. Despite potentially adding complexity to the achievement of reimbursement, points are also granted for countries which offer a sizeable private drug insurance market, as this may provide pathways for products meeting different needs or populations than those covered by public reimbursement and/or a quicker pathway to reimbursement for a portion of the market.

- Five points are assigned for time to reimbursement from market authorization:
  - 5 points for 0-100 days
  - 4 points for 101-200
  - 3 points for 201-300 days
  - 2 points for 301-400 days
  - 1 point for 401-500 days
  - 0 points for 501+ days
- Two points are assigned for the number of payers or formulary listing procedures[r]
  - 2 points for countries with a single payer and formulary process to achieve listing
  - 1 point for countries with multiple payers but a single formulary or reimbursement pathway
  - 0 points for countries with many payers with individual formularies or reimbursement pathways
- Two points for the existence of a sizeable private payer market[s]
- One point was possible if HTA can be completed in parallel with regulatory review or reimbursement.

Data on the time to reimbursement are sourced from the Innovative Medicines Canada 2021 pCPA Timeline Data analysis using IQVIA International Reimbursement Comparison data. The study identified new medicines approved for sale in each country between 2012-2018 and calculated the average time from marketing approval to public reimbursement (the first public drug plan listing in the case of Canada).

"The challenges in Canada in the rare disease space are clear. The system is deterring us from bringing novel rare disease drugs to Canada. We've done calculations and, in some cases, we take 24 years to get a return on investment by going to CADTH. This is not a viable business model. The Canadian system is rigged in the wrong way for rare disease and this, I believe, helps to explain Canada's relatively poor performance on your Index."
—Bob McLay, VP, General Manager Canada, Sobi Canada Inc.

[r]Note that for simplicity we consider a country to have a single payer if there is a universal, mandatory drug insurance program in place funded primarily by the federal government. Many of these countries also allow for supplementary private health insurance payers to provide services and products not eligible under the public plan. While a high proportion of residents may avail themselves of private health insurance for supplementary medical coverage, in these countries the public program continues to pay the vast majority of drug expenditures in the country.
[s]Sizeable private market is defined as having a private primary insurance provider for at least 20% of the population.

Table 13 HTA and Reimbursement Indicator Summary & Scoring

Country	Time to Reimbursement from Approval[t] (days)[32,33]	Targeted Time between HTA & Listing (days)	Sizeable Private Payer Market	Number of Payers	% Population Covered by Public Insurance	Parallel HTA Review	Score
Canada	632=0 point (N/A)	130[33]	Yes	Many public and private payers with different formularies = 0	61.8%[35,u]	Yes	3
Australia	452=1 points (N/A)	120	No	One public payer and formulary = 2	91%[36]	Yes	4
Belgium	477=1 points (439)	180[37]	No	One public payer and formulary and six private non-profit payers = 1	99%	No	2
France	437= 1 points (566)	90	No	One public formulary = 2	99.9%	No	3
Germany	135= 4 points (127)	0[v]	No	One public exclusion list = 2	88.9%	Yes[w]	7
Italy	543 = 0 points (436)	180[38]	No	One national process and formulary, 21 regional payers = 1	100%	No	1
Japan	99= 5 points (N/A)	60-90	No	One national policy and formulary with many health insurance societies = 1	100%[39]	No	6
Netherlands	368= 2 points (252)	20	No	One national policy regulating many private payers= 1	99.8%	No	3
Norway	242= 3 points (522)	180[40]	No	One national policy and 4 regional health authorities = 1	100%	No	4
Spain	526= 0 points (414)	180[41]	No	One national policy and 17 regional payers = 0	99.1%	No	0
Sweden	286= 3 points (269)	180[41]	No	One public formulary, 21 regions= 1	100%	Yes	5
Switzerland	152= 3 points (158)	60[43]	No	One publicly administered formulary, many private payers = 1	100%	No	4
UK	156= 3 points (349 England, 425 Scotland)	90[44]	No	Single government run program = 2	100%	Yes[45,x]	6
US	180= 3 points (N/A)	90	Yes	Many public and private payers = 0	36%[46]	Yes[47]	6

[t]For a point of comparison where data is available, EFPIA Time to Reimbursement from Approval is provided in parentheses. IQVIA EFPIA Patients W.A.I.T Indicators Survey 2021 . Differences in these numbers are largely explained by different time periods examined in the studies and differences in definitions used.

[u]In Canada this refers to the number of Canadians eligible for public insurance, irrespective of whether they are enrolled. Many Canadians have dual eligibility for public and private plans such that 62% of Canadians are enrolled in private drug insurance plans.

[v]In Germany, the HTA and price negotiation processes are completed within the first year of a new medicine's launch and do not delay funding. Results of the HTA and pricing negotiation take effect after the first year of market access. The HTA process is completed in 6 months and an additional 6 months may be taken for price negotiations after which time they would go to arbitration. Even though the price negotiation process takes 6 months or longer if arbitration is required, the measurement is 0 days because throughout the negotiation time funding of the medicine is already ongoing.

[w]Germany does not conduct HTA concurrently with regulatory approval but it does permit automatic, concurrent funding of new medicines while HTA and price negotiations are ongoing, therefore these processes do not delay access to medicines.

[x]NICE historically completed scoping exercises while approval was pending such that the average submission gap between EMA approval and NICE submission was minimal.

Eight of the 14 countries evaluated score ahead of Canada on this indicator, while Netherlands and France tie Canada, and the trio outscore Belgium, Spain and Italy. Ranking on this indicator is driven largely by the time the process takes between regulatory approval and public reimbursement, with 5 of the 10 points achievable on this indicator allocated to this measurement. Canada is falling behind on this indicator because it earns zero of the five points possible for this measurement and zero of two points possible for its relatively complex and fragmented payer processes and infrastructure.

While Canada's uncommon offering of a sizeable private market may make it attractive for launch in some cases, its existence adds some complexity to the process of achieving maximum market penetration. The existence of a private payer market in Canada provides opportunities for a quicker path to begin achieving return on investment via private drug benefits programs. Generally private payers conduct their own forms of HTA internally to make reimbursement decisions. Because private reimbursement decisions are often made prior to publication of CADTH recommendations and for a different beneficiary population and payer perspective, in most cases CADTH recommendations would not have substantial influence over private drug plan reimbursement decisions. It should be noted, however, that private drug plan insurers in Canada are increasingly referring to publicly available CADTH recommendations to inform reimbursement decisions, especially concerning specialty medicines or those with specific price or budget impact thresholds.[y]

Canada earns points due to the option of completing HTA processes concurrently with regulatory review which could cut down on overall time to reimbursement. This sets Canada apart from several European countries which do not yet have processes to conduct HTA while EMA review is ongoing.

CADTH's pre-NOC HTA pathway – initially allowing a manufacturer to submit its HTA dossier up to 3-months prior to anticipated regulatory approval – was updated in 2018 to allow for submissions 6 months pre-NOC.[48] Additionally, the optional aligned reviews process was launched in June 2018 which, in addition to providing for concurrent regulatory and HTA reviews, also allows for information sharing efficiencies among Health Canada, CADTH and INESSS. Most European countries generally have not had mechanisms to initiate HTA pre-approval because of the regulatory approval happening at a different level than the domestic HTA. Just because EMA approval is pending does not mean the manufacturer will launch in all European countries. Compared to European countries at least, Canada may have more opportunities for collaboration and consolidation among regulatory and HTA bodies and has recently taken advantage of this to improve efficiencies. However, this Canadian advantage is expected to change imminently as the EU adopted regulation in December 2021, which will align clinical evaluation for purposes of HTA under the new European Joint Clinical Assessment (JCA) which will be fully effective in January 2025 and replace the need for individual jurisdiction clinical HTA assessments (reimbursement decisions and pricing negotiations will remain the responsibility of the jurisdictions). [49] Another aspect to consider is program effectiveness in Canada for pre-NOC or aligned reviews. CADTH is offering pre-NOC HTA, however, challenges with uptake for pre-NOC or aligned reviews call into question whether existence of this pathway is sufficient to earn points for attractiveness if it is not being sufficiently used or optimized. Canada performs well due to the ability for HTA to be conducted concurrently with regulatory processing time. However, this mechanism is currently not being optimized. In one study the median submission overlap of regulatory and HTA reviews in Canada is only 30 days.[45]

[y]See for example the Manulife DrugWatch™ Plan

Sub-Analysis on HTA Procedures and Timelines

Because Canadian HTA through CADTH occurs separately from public funding procedures (Federal, Provincial and Territorial Drug Programs decide upon reimbursement at their jurisdiction level), the authors were interested to conduct a sub-analysis to evaluate attractiveness of the HTA component alone.

As shown in Table 14, Canada's time to complete HTA through the CADTH procedures is in line with the comparator countries. In Canada there's fragmentation between CADTH performing HTA, pCPA conducting price negotiations, and jurisdictions managing formularies and being the ultimate decision makers and payers.

"Where I get discouraged is when the organizations responsible for evaluating and adjudicating new medicines don't work together. Health Canada, PMPRB, CADTH, INESSS, pCPA are all critical as we look to bring new medicines to Canada. Unfortunately, there's inadequate collaboration between them and it is patients who end up suffering as a result."
—Bob McLay, VP, General Manager Canada, Sobi Canada Inc.

Table 14 - HTA Comparison

Country	Time to Complete HTA[45,50]
Canada	180 days[51]
Australia	125 days[45]
Belgium	90-180 days[44]
France	155 days[45]
Germany	170 days[45]
Italy	375 days[45]
Japan	60-90 days[45]
Netherlands	70 days[50]
Norway	180 days[52]
Spain	221 days[45]
Sweden	180 days[52]
Switzerland	302 days[53]
UK	224 days[54]
US	6-9 months[55]

Canada may be considered attractive because its HTA has less influence on the market compared to most other countries in the analysis (except US). Canada's national HTA procedures are only bearing on the publicly administered drug programs representing about half of the country's pharmaceutical market. Because of their single payer or universal drug insurance programs in many comparator countries, national HTA is bearing on the entire market and is typically also performed by the payer. In contrast, because the HTA process in Canada is separate from pricing negotiations and reimbursement implementation, the HTA body makes a recommendation to its customers (the public drug program payers) who hold the authority regarding whether and how it will be implemented. In theory, the fact that HTA outcomes are not binding creates flexibility for a manufacturer with regards to appealing outcomes or further negotiating with payers.

While fragmentation causes complexity, it also creates flexibility, which manufacturers experienced in navigating the Canadian market access landscape may value despite the added complexity it introduces in the environment.

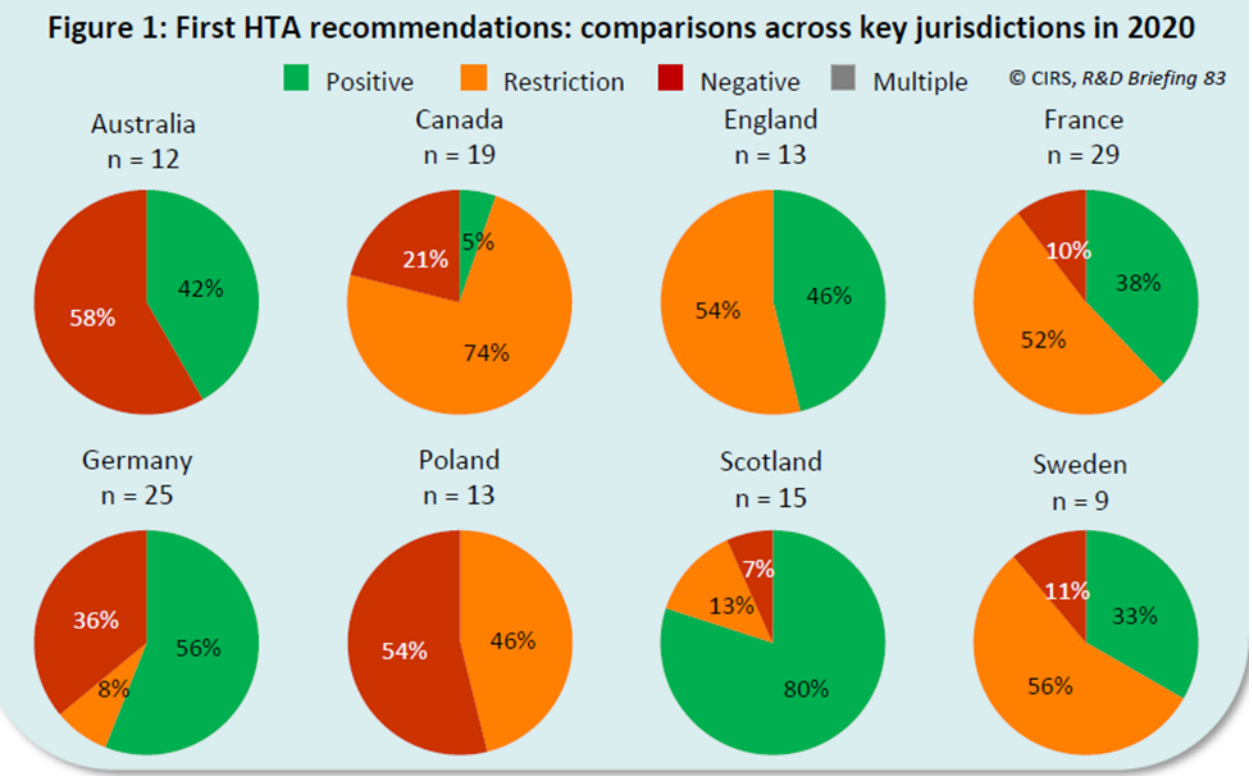
Moreover, there is latitude for individual jurisdictions to implement HTA recommendations in accordance with their individual needs and values. Such latitude could create opportunities for manufacturers knowledgeable in different regional reimbursement priorities to address diverse values and contexts across stakeholders and payers. In Canada, because the HTA process is separate from pricing negotiations and reimbursement implementation, the HTA body makes a recommendation to its customers (the public drug program payers) who hold the authority regarding whether and how it will be implemented. In theory, the fact that HTA outcomes are not binding create flexibility for a manufacturer with regards to appealing outcomes or further negotiating with payers.

That said, there is a very high degree of concordance between CADTH recommendations and reimbursement decisions, so the benefit of a separate non-binding HTA process may be overstated in the case of Canada. However, feedback received via qualitative research interviews highlighted the potential insufficiency of HTA to meet the needs of the implementers given the need to take into account so many different payers and payer contexts. One stakeholder suggested a reason pCPA negotiations and reimbursement implementation takes so long is because the HTA input into the process does not always meet the needs of payers for purposes of implementation. So despite the fact that HTA seems competitive when comparing review timelines and procedural factors, without measuring quality of the HTA output it is not possible to assess how much Canada's low-ranking performance on the HTA and Reimbursement indicator has to do with either the HTA or Reimbursement processes, but the disaggregation of the two pieces.

Another relevant measurement which was not included quantitatively for the index was the likelihood that HTA would produce a positive decision or recommendation. From the perspective of a global decision maker, countries with HTA organizations more likely to produce negative recommendations and thereby deny (directly or indirectly) reimbursement would be less attractive for launch than a country with an HTA body perceived to be more lenient or likely to issue positive decisions. Due to data limitations, the authors of this Index did not quantitatively score likelihood of a positive HTA recommendation but agreed it is worth qualitative discussion.

Considering data that is available, the Centre for Innovation in Regulatory Science has compared eight countries on their percentages of positive, restricted and negative HTA recommendations. Its analysis includes Canada, Australia, England, France, Germany and Sweden – which are pertinent to this index – as well as Poland and Scotland. The CIRS analysis summarized in Figure 14 finds Canada issued by far the lowest percentage of positive recommendations among countries included in this Index: only 5% compared to France and Sweden which had one third or more of their recommendations as positive, and Australia, England and Germany whose positive recommendations approached or surpassed the 50% mark. At 74% Canada had the highest percentage of restricted recommendations, such that its negative recommendations – the only type of recommendation which effectively precludes further pursuit of public reimbursement in Canada – remained at only 21% which is higher than England, France and Sweden but substantially lower than the percentage of negative recommendations in Germany and Australia.

Figure 14 CIRS HTA Outcomes Across Countries[56]



Patient Role

A country's access environment may be shaped by the opportunities for and influence of the patient voice during HTA and reimbursement processes. An environment that meaningfully considers patient insights is considered an attribute because an engaged patient community can provide real world experiences, values, perspectives and data which is becoming increasingly important in many markets.

In a poster for the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) in 2021 called 'Patient Centricity in HTA: Fact or Fable?' by Akbraian, Schmitz, & Allen, the authors aimed to understand how HTA bodies incorporate patient input to inform their decision-making and to determine which approaches are more impactful. They defined:[57]

- High level of impact to include committee meetings with patient participation and the ability to provide comments on draft recommendation
- Medium level of impact to include submissions to agencies via patient advocacy groups
- Low level of impact to include online patient submissions; patient representative committee members

Scoring Rationale

Countries with high-level of impact received 10 points, countries with medium-level impact received 5 points and countries with a low-level of impact received 0 points.

Table 15 Patient Impact on HTA Decision Indicator Summary & Scoring

Country	HTA Agency	Patient Impact on HTA Decision[57]	Score
Canada	Canadian Agency for Drugs ant Technologies in Health (CADTH)	Medium	5
Australia	Pharmaceutical Benefits Advisory Committee (PBAC)	High	10
Belgium	Belgium Health Care Knowledge Centre (KCE)	Medium[58]	5
France	French National Authority for Health/Haute Authorite de Sante (HAS)	Medium	5
Germany	Federal Joint Committee (Gemeinsamer Bundesausschuss – GBA) and the Institute for Quality and Efficiency in Health Care (IQWiG)	High	10
Italy	Italian National Agency for Regional Healthcare Services (AGENAS)	Low	0
Japan	Ministry of Health, Labour and Welfare (MHLW) Medical Technology Evaluation Team	Low[59]	0
Netherlands	Zorginstituut Nederland (ZIN)	Medium	5
Norway	Norwegian Medicines Agency (NOMA)/The Norwegian Knowledge Centre for Health Services	Low	0
Spain	The Spanish Agency for Medicines and Healthcare Products (AEMPS)	Low	0
Sweden	The Dental and Pharmaceutical Benefits Agency (TLV)	Low	0
Switzerland	Swiss Federal Office of Public Health (FOPH/BAG)	Low[60]	0
UK	National Institute for Health and Clinical Excellence (NICE)	High	10
US	Technology Assessment Program AHRQ	High	10

DISCUSSION

Canada's mixed regulatory landscape performance

Canada outperforms most countries on the Regulatory Approval indicator, yet ranks second to last in the technical area with the lowest score on IP protection. In 2021 Canada remained on the Watch List of the U.S. Trade Representative's report concerning the adequacy of countries' ability to protect and enforce IP rights, even despite new provisions undertaken by Canada as part of recent international trade agreements.

> "There are some really positive things that we're doing in Canada, like the Biomanufacturing and Life Sciences strategy and, I hope, a comprehensive rare disease strategy in the near future."
> —Jason Field, President & CEO, Life Sciences Ontario

With regards to regulatory approval, stakeholders reported their perceptions that Health Canada is faultless when it comes to its process efficiencies. Indeed several noted its diligent efforts to collaborate with other national regulators to reduce submission gaps. In terms of potential improvements, stakeholders noted an obvious and continued absence of a specialized orphan drug pathway for the purpose of regulatory approval, despite several movements in that direction over the last two decades. While some such medicines would qualify for expedited review via other existing pathways, a country offering more specialized pathways for regulatory approval received more points than countries which did not have such pathways.

Focus on Biomanufacturing & Life Sciences

In July 2021, the federal government launched Canada's Biomanufacturing and Life Sciences Strategy, with $2.2 billion of investments announced in the 2021 budget. Biomanufacturing has become a high priority for the Canadian government as it aims to rebuild the domestic capacity that would have been critically supportive had it been available and agile early in the COVID-19 pandemic. Given recent experience, the focus on biomanufacturing is a sensible strategy to prepare for future health emergencies. In this study, however, we find that for the average new medicine launch sequencing decision, local manufacturing contributes very little to attractiveness of a country. According to the Editorial Advisory Board, local manufacturing is not a strong influencer of where and when to launch products as generally speaking, drug manufacturing occurs in a country chosen for different reasons than where it will be commercialized. Importing to all other countries where the drug will be sold is typically not considered a hurdle, so much as a logistics task. Similarly, to the extent that life sciences investments committed by the federal government aim to incentivize development activity, if they are to improve Canada's attractiveness for new medicine launch they should focus on late-stage biopharmaceuticals development, which is seen by the Editorial Advisory Board as having some – albeit small – influence on attractiveness for launch. While the Biomanufacturing and Life Sciences Strategy is highly encouraging with respect to developing Canada's capacity to address future health emergencies and growing the sector for its exceptional economic contributions, it cannot be seen as an effective solution to improve Canada's attractiveness for new medicine launches generally given the exceedingly small weight placed on the development and commercialization technical area (7.4% of the index).

As an independent market, Canada faces hurdles not experienced by European Markets of comparable size

Canada is competing as an isolated market relative to European markets which despite being individually small markets, they benefit from geography and shared regulatory processes. As a relatively small market with its own regulatory process, and with patients spread across large geography (which poses unique commercial and distribution challenges) Canada needs to do even more to overcome its competitive disadvantage in size.

"Canada typically is a top 10 market and senior management wants to launch in Canada, but if they have bad experiences like I've had bad experiences, they start to question, is it a viable place to launch? I am hearing this more frequently in recent years despite Canada's relatively healthy market size."
—Bob McLay, VP, General Manager Canada, Sobi Canada Inc.

Canadian policymakers have said there is weak or no correlation between the price of medicines in Canada and the country's attractiveness for launch, claiming other countries have lower prices and comparable or better access to innovative medicines[61]. However, as this research suggests, price alone cannot be an indicator of market attractiveness. Canada appears to have maintained a foothold as an important launch country despite trailing other countries in very important market attractiveness indictors, such as reimbursement and access; we still held reasonable and stable list pricing. EU countries may have equivalent or lower prices in some cases, but they are much larger volume (at least collectively); and the economies of scale of regulatory processes and more consolidated geography make them more efficient to access. Canada is small volume and can be complex to access. If policymakers make the pricing environment more complex or uncertain, decision-makers will question launching here even more.

Snapshot of Attractiveness

This index compares attractiveness of countries at a single point in time, but launch decisions are made at different points over time and are influenced by policy contexts in these markets that constantly evolve. Commercial launch decisions are made based on the existing attractiveness, but also on decision-makers past experience and perceptions of the future market access landscape their drugs will enter. Here are just a few currently evolving policies that could substantially affect country rankings in the years to come:

"The Index is a static evaluation within a very dynamic context, and I wonder if in the commentary section that you could explore trends? The ecosystem is dynamic, and you have captured but a snapshot in time in your report."
—Richard Owens, SJD University of Toronto, Senior Munk Fellow, Macdonald-Laurier Institute, University of Toronto, Adjunct Professor, Faculty of Law

- More than five years after new price ceiling regulations were proposed the Canadian federal minister of health announced the government will only proceed with a new basket of price reference countries[62]. A host of proposed and complex economic factors will not proceed. An interim set of guidelines are expected from the PMPRB as of July 1, 2022, with final guidelines to follow, perhaps up to a year later. While the news signaled to many a favourable government view on the value of the life sciences sector, permanent guidelines operationalizing the new regulations will not yet be in place leaving manufacturers' major questions about viability of launches unanswered.

- Work in Canada proceeds on the Canadian Drug Agency (including its work towards developing a pan-Canadian formulary) and the federal government's National Strategy for Drugs for Rare Diseases.

- UK's establishment of processes independent from EU – it has set ambitious regulatory review timelines of 150 days but so far there is no performance data on whether this relatively quick timeline will be met. France has also committed to significant improvements in time to reimbursement.

- EU implementation of the Joint Clinical Assessment regulation to be fully effective in January 2025 which replaces the need for jurisdiction level clinical assessments for the purpose of HTA and is likely to improve timeliness of HTA in European countries and potentially facilitate clinical HTA evaluation in advance of regulatory approval.

CONCLUSION

Canada continues to be a top 10 market for global pharmaceutical decision makers in terms of pharmaceutical revenues, but amid recent changes in the development, regulatory and market access environments, both here and internationally, we must not rest on our history alone to ensure Canadian patients continue to have early access to new medicines poised to cure and change trajectory of important diseases within our lifetime. There are many aspects of the Canadian market that are not easily changed – such as our market size, geography and independent regulatory infrastructure (e.g. in comparison to the EU with shared regulatory pathway). Yet, when it comes to things we can change – such as price regulation, and the time and complexity of reimbursement, which together make up more than half of the index's weight - Canadian policymakers must make decisions within the context of the entire biopharmaceutical ecosystem to ensure Canadian patients are not left behind. Canada's attractiveness is not measured by one policy alone, be it pricing, intellectual property, regulatory or reimbursement. Rather our appeal as a launch destination is measured through the lens and totality of all policies. If our regulatory process is considered world-leading, what impact does long and cumbersome reimbursement have on attractiveness? And if our reimbursement environment is indeed complex, what is the impact on our attractiveness if our price ceiling regulations become onerous and punitive on biopharmaceutical innovators? Policymaking is about understanding the interplay of policies within a sector; it is about knowing which policies hold greater value for a sector; and above all it is making the right trade-offs to build an attractive environment to do business.

"It's a very big deal when you can move a disease from untreatable to treatable to curable which happened with PKU (phenylketonuria). My son has lived with PKU for much of his life and seeing the direct impact of new medicines on his life has been so important. It's an even bigger deal when you can move a disease from untreatable to curable in the new emerging era of cell and gene therapies. Canada has to evolve to find a way to fairly evaluate the new wave of medicines that is coming forward for rare diseases."
—John Adams , Co-founder & CEO of CanPKU and Allied Disorders

"The real question is what is it that we would ask people to change or countries to change in order for us to get access to drugs quicker? And what are the key things we need to do? Is it speeding up regulatory approval? Is it speeding up patient access? How do policy makers and decision makers view this report, and can they use it to determine what they need to do differently? "
—Durhane Wong-Rieger, President, Canadian Organization for Rare Disorders (CORD)

This research report was conducted with the intent to help clarify the interrelationship between policies affecting biopharmaceutical launch decisions, to shed light on where policies can have the greatest impact on Canada's attractiveness for new medicine launches, and to help policy makers and biopharmaceutical leaders engage in constructive dialogue on the trade-offs that may be required to create the best possible system for accessing new innovative medicines in Canada.

"My work is harder than before as an ambassador of Canada working with global colleagues to have new, innovative medicines launched here. I suspect this will become even more challenging as our portfolios evolve to being more specialized and for smaller patient populations. My concern is that my power of persuasion carries only so much weight as I interact with my global colleagues in determining where Canada fits into launch sequencing. As the aggregated scorecard (for Canada) degrades I am concerned that I won't be able to bring needed innovations here as quickly as I would like. We want to do what is right for patients, but the hurdles continue to rise here in Canada. "
—Frederic Lavoie, Business Lead, Inflammation and Immunology, Pfizer Canada

APPENDICES

APPENDIX A: BIOGRAPHIES

Editorial Advisory Board Members

Wayne Critchley
Senior Associate
Global Public Affairs' Health & Life Sciences practice

Wayne Critchley is Senior Associate with Global Public Affairs' Health & Life Sciences practice, providing counsel to leading biopharmaceutical and medical device corporations and associations along with other health policy stakeholders. Wayne has a long track record of success as a senior executive with over twenty years of experience in government departments, boards and agencies dealing primarily with issues that impact the pharmaceutical sector.

He served as Executive Director of the Patented Medicine Prices Review Board from 1990 to 2005 and as a Vice President of the Canadian Agency for Drugs and Technologies in Health in 2009. From 2007-2009, he was a partner in one of Canada's leading law firms. Wayne is widely recognized as an expert in pharmaceutical pricing, reimbursement and market access and is regularly called upon to write and present on Canadian pharmaceutical issues.

Wayne served as Chair of the Canadian Organization for Rare Disorders from 2015-2019 and currently serves on the Board of Directors of the Macdonald-Laurier Institute. He is also active with the Canadian Club of Ottawa and served as President from 2012-2013.

Martine Elias
Executive Director
Myeloma Canada

Martine Elias is the Executive Director at Myeloma Canada, the only patient-driven, grassroots organization bringing the Canadian myeloma community together and promoting a strong, unified national voice for people living with multiple myeloma. In addition, Martine is Chair of the Collective Oncology Network for Exchange, Cancer Care Innovation, Treatment Access and Education (CONECTed), a Canadian based organisation. She is a Board member of the International Myeloma Foundation. As well, in 2019 Martine was one of three patient representatives on the PMPRB Guideline Development Steering committee.

Martine started her career in clinical research in the pharmaceutical industry and has since dedicated her professional life to patient advocacy, empowering the patient voice, and helping patients gain access to essential medical treatments. She is passionate about ensuring that the patient voice is included in all aspects of health policy decisions.

Previously, Martine was Director Access, Advocacy and Community Relations at Myeloma Canada where she developed, led, and executed all advocacy strategies and programs.

Editorial Advisory Board Members

Brian Jahns

Chief Business Officer
Enthean Biomedical Corp.

Dr Brian E. Jahns is an accomplished pharmaceutical business leader with robust and progressive commercialization experience in the biopharmaceutical industry. Brian works for Entheon Biomedical Corp., as Chief Business Officer. Entheon Biomedical is a clinical stage psychiatry company developing innovative small molecules, drug formulations and biomarkers to improve the care of patients living with addiction and substance use disorder.

Previously, Brian was Vice-President, Global Marketing at ZYUS Life Sciences Inc., a clinical stage phytotherapeutics company working to address chronic and refractory pain. Brian worked as Senior Vice-President, Commercial and Business Development for Trillium Therapeutics Inc. In this role, Brian was responsible for providing commercial direction into the clinical and regulatory strategy, as well as executing business development activities for this clinical stage immune-oncology company.

Earlier in his career, Brian worked at Hoffmann-La Roche, Ltd., in a variety of medical, marketing, and sales leadership roles where he was intimately involved in the successful launch and growth of several antivirals, transplant immunosuppressants and anticancer biologics. He developed a keen interest in factors influencing optimized patient care, including the promise of personalized medicine, the intricacies of how medicines are used and the connection between funding and the ability to improve outcomes. Brian rose to become Vice President of Oncology, and then Vice President of Product Strategy at Roche Canada.

In an era that embraces innovation and patient centricity, Brian's perspective is shaped by his experiences as a healthcare provider, researcher, and business leader. Whether it is his ability to help others reach their professional potential or to help patients affected by life-threatening diseases, Brian is a change agent who is not only in step with the growth of pharmaceuticals - but he is also helping to drive it, to ensure that patients benefit.

Danielle Peters
President
Magnet Strategy Group

Dani Peters is President of Magnet Strategy Group, a consulting firm that manages public affairs strategies in Canada and the United States.

Prior to founding Magnet Strategy Group, Dani held senior roles in public affairs firms in the U.S. and Canada, concentrating on fields that include innovation, health care and life sciences. Over the past 17 years, Dani has worked with groups in the health sector to develop and manage government, public policy, funding, advocacy, and stakeholder strategies. Dani is a Co-Founder of Cross-Border Health, a non-profit organization that fosters dialogue between Canada and the United States around common health priorities. In addition to operating Magnet Strategy Group, Dani serves on the Industry Advisory Board for Bloom Burton & Co., a healthcare investment advisory firm in Toronto. She is also a Health Leader-in-Residence for the World Health Innovation Network (WIN), within the University of Windsor's Odette School of Business.

Dani serves as a Senior Advisor to the Canadian Antimicrobial Innovation Coalition, a non-profit organization committed to preventing the rise in antimicrobial resistance (AMR), by positioning Canada to be a leader in AMR research and product development, economic growth, and investment. She is also a Senior Advisor to the Alliance for Safe Online Pharmacies in Canada. The Alliance for Safe Online Pharmacies is a global non-profit organization dedicated to combatting illegal online pharmacies and falsified medicines to make the internet safer for consumers worldwide.

In 2019, Dani was appointed to the board of the Ontario Arts Council and reappointed as Vice-Chair in 2021.

Editorial Advisory Board Members

Nigel Rawson

Affiliate Scholar at Canadian Health Policy Institute and Senior Fellow with the Fraser Institute

Dr. Nigel Rawson is a pharmacoepidemiologist and pharmaceutical policy researcher based in Saskatoon, Saskatchewan. He is also a Senior Fellow with the Macdonald-Laurier Institute, an Affiliate Scholar with the Canadian Health Policy Institute, and a Senior Fellow with the Fraser Institute. Educated in the United Kingdom, he holds an MSc in statistics and a PhD in pharmacoepidemiology. Dr. Rawson has performed epidemiologic studies of the use of drugs and their outcomes for over 40 years and published more than 140 articles in peer-reviewed journals. He is the author of the monograph "Drug Safety: Problems, Pitfalls and Solutions in Identifying and Evaluating Risk."

Dr. Rawson held academic research positions in the United Kingdom until the end of 1989 and subsequently held professorships at the University of Saskatchewan and Memorial University of Newfoundland in Canada. His research activities focused on population-based studies of the use and safety of drugs using administrative healthcare utilization data and the evaluation of issues impacting access to new medicines in Canada. Dr. Rawson has also been a senior researcher in an independent research centre in one of the United States' largest health insurers where he collaborated with the Food and Drug Administration on drug safety studies, and GlaxoSmithKline's only epidemiologist in Canada providing advice and analysis for the company's medicines and vaccines. Between 2012 and 2020, Dr. Rawson was President of Eastlake Research Group whose mission was to create data-driven responses to pharmaceutical policy issues. He continues this work as an independent researcher.

Jared Rhines

Vice President/General Manager
BioCryst Pharmaceuticals Inc.

Jared Rhines is Vice President and General Manager of Biocryst Canada. With nearly 30 years in the industry focussing on commercial strategy and rare diseases Jared has extensive international experience in launching new medications both Canada and globally.

His experience spans clinical research, regulatory affairs, sales, marketing, market access, and geographic expansion. He has successfully led multiple integrations and scaled organizations from ground-up.

Jared has served as a member of the Board of Directors of Innovative Medicines Canada for nearly 10 years. He has his undergraduate degree from the University of Pennsylvania and earned his Masters of Business Administration from Duke University's Fuqua School of Business.

Victoria Vertesi

Vice President, Biopharma Solutions
McKesson Canada

Victoria Vertesi is a pharmaceutical executive at McKesson Canada with a demonstrated track record of success leading high-performing teams, launching new products, and turning around existing products to new levels of growth and profitability.

Her career is characterized by the ability to capitalize on opportunities, through innovative business solutions, creating competitive advantages and cultivating stakeholder relationships resulting in mutual benefits for the organization.

She has experience in leading strategic plans, life cycle management, account tenders and supporting organizational transformation.

She is committed to creating an organizational culture that fosters a performance mindset, continuous improvements & focus on developing people.

She is passionate about the patient & the healthcare system.

Authors

Courtney Abunassar
Associate Director, Market Access and Policy Research
PDCI Market Access, a division of McKesson Canada

As a member of PDCI's Strategic Consulting and Policy Team, Courtney helps clients make business decisions that will achieve optimal pricing and reimbursement for their products. She has lead dozens of market access assessments, providing insights to clients about the market access landscape and recommending strategies and roadmaps to optimize access in ever-evolving therapeutic and access landscapes. Courtney has assisted clients to prepare for public and private reimbursement negotiations, including assessing points of leverage between negotiating parties and recommending deal structures that anticipate and satisfy payer needs without compromising value. Additionally, Courtney has led dozens of payer research and advisory board projects, broadening her market access knowledge, insights and connections beyond PDCI's in-house expertise, and becoming sensitive to nuances of various payer and other stakeholder perspectives from coast to coast.

A key skill developed in her strategic planning work is conducting stakeholder influence mapping to understand the interests, roles and power of individuals and organizations which may serve barriers or facilitators towards a client achieving its market access goals. This skill has helped clients effectively engage internal and external stakeholders to align interests and/or strategically plan to avoid or mitigate challenges.

Courtney also leads PDCI policy projects in a wide variety of topics of interest to the innovative pharmaceutical industry. In this work, she has conducted primary and secondary research to author reports delivering novel insights on topics such as national pharmacare and the private payer PLA landscape in Canada.

Prior to joining PDCI in 2011, Courtney worked in strategic policy analysis and communications positions with the federal government and not-for-profit health organizations. Courtney holds a Bachelor's degree in Journalism and a Master's degree in Public Administration with a specialization in health policy, both from Carleton University in Ottawa.

John-Paul Dowson
Director, Strategic Consulting & Policy Research
PDCI Market Access, a division of McKesson Canada

John-Paul is Director, Strategic Consulting and Policy Research at PDCI. He brings more than 25 years of experience working in the health and pharmaceutical sectors. Prior to joining PDCI, John-Paul was the Founder and Managing Director of Roubaix Strategies Inc.(RSI), where he built two negotiation development programs: Effective Negotiation Skills (directed to the pharmaceutical industry) and Negotiation Skills for Advocacy Professionals (directed to patient and disease organizations). Prior to launching RSI, he spent the better part of a decade in market access leadership roles, negotiating drug reimbursement agreements for innovative pharmaceuticals in Canada. John-Paul's experience and knowledge in market access and negotiation strategy covers an extensive scope therapeutic and business areas, including strategic insights on how to obtain and maintain product reimbursement in both public and private markets.

John-Paul has led successful reimbursement strategies and negotiated funding agreements for conventional and specialty care products across Canada. He has worked with companies on successful negotiation strategies for the reimbursement of more than 20 drug products (Drugs for Rare Diseases, Oncology and Biomarker Testing, Cardiovascular and Diabetes, Neuroscience, and Consumer Healthcare).

At PDCI, John-Paul leads Strategic Consulting across the business focusing on the development and implementation of market access and negotiation strategies for the reimbursement of pharmaceuticals, devices, and diagnostics in Canada. He oversees the PDCI Pricing and Policy Teams, providing clients with strategic insights and foresights into Canadian pricing strategies for pharmaceuticals and public policies affecting the broader life sciences sector.

A sought-after speaker, strategist, and thought leader, John-Paul brings a keen understanding of the interrelationships between Canada's public and private drug markets, and the emerging reimbursement pathways for negotiated agreements.

Prior to his career in the pharmaceutical industry, John-Paul worked for several years with two major health professional associations in Ontario. This work included the successful negotiation of the first-ever agreement with the Ontario Government for compensation of pharmacies delivering influenza immunization clinics. He also spent several years working as an advisor in Federal and Ontario governments.

John-Paul holds a BA in Political Science from St. Jerome's University (at Waterloo), and an Executive Certificate in Marketing Management from the Schulich School of Business. He is an active member of the Canadian Association for Healthcare Reimbursement, and BioteCanada (BTC), serving on the latter's Health Advisory Board and Orphan Drug Working Group.

Authors

Mark Fleming
Strategic Advisor
PDCI Market Access, a division of
McKesson Canada

Mark was previously the Director of Federal Affairs & Health Policy at Janssen Inc. (Pharmaceutical Companies of Johnson & Johnson). In this role he was responsible for representing Janssen and Johnson & Johnson federally and internationally with elected officials, bureaucrats and other key decision makers.

Mark's leadership in the biopharmaceutical industry spanned over 30 years including roles in government affairs, health policy and strategic pricing, and senior sales and marketing responsibilities at both Janssen and Eli Lilly Canada. Mark trained as a pharmacist, graduating from the Faculty of Pharmacy, University of Manitoba in 1980. He went on to practice as the Director of Pharmacy at the Churchill Health Centre in northern Manitoba. While in Churchill, Mark researched, wrote, photographed and published a book entitled Churchill, Polar Bear Capital of the World which was in print for 22 years selling over 14,000 copies in Canada and around the world.

Mark has held a number of leadership roles within Janssen and with industry associations including Chair, National Parliamentary Affairs Team, Vice-Chair, Biologics Committee at Innovative Medicines Canada, and co-Chair, Subsequent Entry Biologics Task Force, BIOTECanada. As well, he is a volunteer leader in his community and is Chair of the Terry James Honour the Volunteer Youth Scholarship Awards.

Claudia Loschmann
Associate Director, Market Insights
PDCI Market Access, a division of
McKesson Canada

Claudia Loschmann is Associate Director, Market Insights with PDCI. In her current role, Claudia develops Canadian market access and reimbursement strategies, and provides clients with deep strategic insights into the public policy trends affecting the Canadian bio-pharmaceutical market.

With over 15 years of experience in consulting and healthcare reimbursement, Claudia has an in-depth understanding of product/service launches, market access, and reimbursement strategies for pharmaceutical, biotechnology, medical device companies, and works closely on integrated market solutions for clients with McKesson Specialty Distribution and Patient Support Programs. She has developed numerous strategies which include product positioning, market assessments, and tactical support programs for both the public and private payer environments.

Previously, Claudia served as Senior Manager of Reimbursement & Access Services for McKesson Specialty Care Solutions, a business unit of McKesson Corporation, based in Scottsdale, Arizona. While in this position, she had a direct role in the on-boarding of new specialty clients and launch partners, and implementing reimbursement strategies.

Prior to her work for McKesson in the US, Claudia served as a Consultant for Boston Healthcare, Inc., a boutique strategic reimbursement consulting firm in Boston. At Boston Healthcare, she conducted qualitative research with both public and private payers and worked directly with clients on product positioning and reimbursement strategies for specialty products.

Melissa Burt
Manager, HTA and Clinical Evaluation
PDCI Market Access, a division of
McKesson Canada

Dr. Melissa Burt is a Manager, HTA and Clinical Evaluation at PDCI. Her role involves the development of clinical documents and components of reimbursement and pricing submissions, as well as market access and pricing assessments. This involves evaluating and summarizing scientific information and providing strategic guidance based on the Canadian market access landscape.

Melissa joined PDCI in 2017 as an Associate and has worked on a wide range of disease states and products. Prior to joining PDCI, she had over 8 years of preclinical research experience with a strong background in neurodevelopment and neurobiological disorders. She previously worked as a Senior Medical Writer at IC Axon in Montreal, where she developed training materials for pharmaceutical and biotechnology companies including global launch training curriculums and live meetings.

Véronique Scott
Manager, Policy Insights
PDCI Market Access, a division of
McKesson Canada

Véronique Scott is a Policy Insights Manager at PDCI Market Access, a division of McKesson Canada. As a member of the Strategic Consulting and Policy Research Team, she contributes research and analysis to strategic policy projects relevant to life sciences and healthcare sectors, and supports the team's development and implementation of public and private market access strategies. Véronique provides insights into private and public payer markets, drug review processes and reimbursement trends affecting market access.

Prior to joining PDCI in 2021, Véronique was part of the McKesson Canada's Retail Banner Group division where she successfully implemented a communication department for the Quebec pharmacy banners working closely with pharmacist owners in Quebec. Previously Véronique worked in Market Access positions with both Teva Canada Innovation and Sandoz Canada. In those roles she contributed to the development and execution of successful Market Access strategies for innovative and biosimilar medicines in Canada. She has also served in communication roles for hospitals in both Montreal and Kingston.

Véronique holds a bachelor's degree in Communication, with an expertise in Health Care and Social Services Management from the Université du Québec à Montréal and Université de Montréal.

APPENDIX B: INTELLECTUAL PROPERTY PROTECTION

Canada

In Canada, the basic patent term for pharmaceutical agents is 20 years, which was established in 1991. The 20-year term begins from the date patent filing. Canada did not have a patent term restoration mechanism until 2017 when it became a key obligation to reach the EU-Canada Comprehensive Economic Trade Agreement (CETA). Patent term restoration of up to two years became available for medicinal ingredients or new combinations of medicinal ingredients receiving NOC on or after September 21, 2017, through the form of a Certificate of Supplementary Protection (CSP).[63]

In addition to patent protection, Canada provides up to 8 years data protection for innovative drugs from the date of market authorization of the innovative product. For the first six years, other manufacturers (typically generics or biosimilars) are not permitted to file for market authorization by referencing the innovator's data. While other manufacturers may file after six years, the market authorization cannot be granted for an additional two years, resulting in 8 years of data protection. An additional 6 months of data protection is attainable for products which have a pediatric indication, or for which pediatric studies are completed within five years of the initial approval. Subsequent-entry drugs have 6 years of data protection.[64]

Australia

The basic patent term is 20 years from the patent filing date. A patentee can apply for patent term restoration for new products containing pharmaceutical active ingredients. Through this mechanism, patent life may be extended for up to 5 years from the date of marketing approval, provided that it has been five years between the patent filing date and the date of regulatory approval.[65]

European Union & UK

All EU member states (including Belgium, France, Germany, Italy, Netherlands, Spain, Sweden included in this analysis) are under the same patent protection legislation. There are two types of patents in the EU: national patents and European patents. Although European patents are granted by the European Patent Office (EPO), a European patent is in fact a bundle of identical national patents, with each one validated in the relevant European Patent Convention (EPC) contracting state.[66] In 2022, Unitary Patents will be available, which will allow patent protection in up to 25 EU Member States by submitting a single request to the EPO.[67]

Basic patents are effective for 20 years from the date of filing. Supplementary protection certificates (SPC) aim to compensate innovators for loss of patent protection due to a delay caused by the regulatory process and granting of marketing authorization. An SPC provides patent term restoration for up to 5 years after expiry of the patent, or 15 years from the date of the first marketing authorization, whichever is earlier. An additional SPC extension of 6 months is available for pediatric indications.

Since 2005, the EU provides for up to 11 years of regulatory data protection (RDP) (a policy known as 8+2+1). There is a period of 8 years of data protection (during which other manufacturers may not submit for regulatory approval referencing the innovator's data) and an additional 2 years of market exclusivity (during which time evaluation can occur but approval cannot be granted). During this period of 10 years, if the marketing authorization holder obtains another indication, there is an opportunity to extend market exclusivity for 1 more year.[68]

To incentivize orphan drug development, designated drugs are eligible for 10 years of market exclusivity, not only from generic competition but also protection from similar medicines in the same indication.

Japan

As with elsewhere, the standard patent term is 20 years from the date of application. A maximum of five years of patent term restoration is available to innovative drug manufacturers in Japan. Japan does not have a data exclusivity system, but it does have a re-examination period in pharmaceutical regulations which can effectively serve a similar function. This is a post-market surveillance mechanism, during which post-market data is collected to be re-examined. If another applicant wishes to receive market authorization during this time, it is unable to reference the innovator data. The duration of the re-examination period is variable and determined by the Minister of Health, Labour and Welfare upon market authorization. Generally, it is eight years for new active substances, four years for new indications or dosage forms. Orphan drugs can receive between six to 10 years of re-examination.

Switzerland

As with elsewhere, the standard patent term is 20 years from the date of application. A maximum of five years of patent term restoration is available to new drug manufacturers in Switzerland.

United States

The standard patent term in the US is 20 years from the filing date. The 1984 Hatch-Waxman Act provided for a maximum of five years of patent term restoration to be achieved as long as the total effective patent life following market approval of the drug is no more than 14 years.

The duration of data protection in the US is generally five years from the time of approval for new chemical entities. However, orphan drugs are eligible for seven years, drugs with pediatric indications or studies may receive an additional six months, biologics are eligible for 10 years and drugs associated with the Generating Antibiotic Incentives Now (GAIN) initiative may achieve an additional five years. New Clinical Investigation exclusivity can also be achieved for three years which can apply to new indications or patient populations.[69]

APPENDIX C: REGULATORY APPROVAL MARKET AUTHORIZATION

Canada

In Canada, Health Canada's Health Products and Food Branch (HPFB) is responsible for issuing market authorization (called Notice of Compliance or NOC) for new medicines. Its service standard for reviewing a pharmaceutical or biologic New Active Substance (NAS) is an average of 300 calendar days from submission to a first decision.[70] In fiscal year 2019-2020, the average review time reported by HPFB was 267 days for pharmaceutical and 281 days for biologic new active substances. Two expedited review pathways exist through which manufacturers can achieve faster market authorization: Priority Review and Notice of Compliance with Conditions (NOC/c). The Priority Review pathway exists for drugs intended for treatment, prevention or diagnosis of serious, life-threatening or severely debilitating illnesses where there no alternative treatments exist, or where the drug represents a significant improvement versus existing products. Manufacturers must specifically apply to request priority review. A drug submission approved for Priority Review receives a shortened review target of 180 calendar days. The NOC/c review process shortens the review target from 300 to 200 calendar days. Products eligible for this pathway are those with promising evidence of clinical effectiveness to treat serious or life-threatening conditions and for which no alternatives are available, or the new product represents significant improvement, however, the existing clinical evidence for the product would be insufficient to issue a non-conditional NOC. For these products, a conditional market authorization can be granted based on a manufacturer's commitment to complete studies better establishing efficacy. A 2018 study found that between 1995 and 2016, almost 30% of drugs approved by Health Canada were reviewed via these expedited pathways.[4] In 2019, 40% of new active substances were approved by Health Canada via an expedited pathway.[5] Canada does not have a regulatory pathway specifically for orphan drugs.

In September 2020, Canada's Minister of Health signed an Interim Order allowing Health Canada to accept rolling submissions for drugs to be used in relation to COVID-19. Otherwise rolling reviews are not conducted by Health Canada. The fees to apply for Health Canada to review a new active substance submission are $437,009, as of April 1, 2021.[19]

Australia

In Australia the Therapeutic Good Administration (TGA) is responsible for evaluating a new medicine's safety, efficacy, and quality. Products approved for the Australian market are included in the Australian Register of Therapeutic Goods (ARTG). Following review by TGA, a delegate, typically a Medical Officer, makes the decision to register the product with ARTG. The delegate considers all advice provided by evaluators, advisory committees, and the sponsor's comments.

The legislated timeframe for TGA to complete an evaluation for a Category 1 application (registration of a new prescription medicine) is 255 working days (not including weekends or holidays). According to its 2020 Annual Performance Statistics Report, TGA approved 33 Category 1 submissions between July 2019 and June 2020 with an average review time of 190 working days (196 median and 25-247 range).[71]

TGA employs a priority review pathway for medicines representing a major therapeutic advance. The pathway shortens the evaluation time to 150 working days. In 2019-20 Category 1 evaluations approved for priority review (n=6) were evaluated with a mean approval time of 129 active working days. A provisional approval pathway is available for vital and lifesaving prescription medicines based on evaluation of preliminary clinical data. In 2019-2020 4 Category 1 provisional approval registrations

Australia

occurred with a median approval time of 199 active working days. In 2019, 28% of NAS applications were reviewed via these pathways.[5]

For a new chemical entity standard prescription medicine, the TGA applies an application fee of $50,300 and an evaluation fee of $201,600. Fees are waived for designated orphan drugs.

Belgium, France, Germany, Italy, Netherlands, Norway, Spain, and Sweden

In Europe, regulatory approval is generally achieved through the Centralized Procedure overseen by the European Medicines Agency (EMA).[72] Through the centralized procedure, the EMA provides an opinion resulting in a single marketing authorization applicable to countries in the European Economic Area (EEA) which includes the 28 member states of the European Union plus Iceland, Norway, and Lichtenstein.

The Committee for Medicinal Products for Human Use (CHMP) conducts the assessment and provides a recommendation on whether the medicine should be marketed. The European Commission makes the legally binding decision based on the CHMP recommendation. Assessment of a new medicine application can take up to 210 active days (clock stop periods may occur at two occasions within the assessment, during which the applicant responds to CHMP questions). The CHMP opinion is issued by day 210, and the legally binding European Commission decision is issued 67 days thereafter.

Conditional and exceptional approval pathways are available, however, do not have different timelines for completion. In 2019, 26% of NAS applications were reviewed via these pathways.[5] An accelerated assessment pathway exists for products of major interest for public health and therapeutic innovation. The assessment timeframe for accelerated assessments is 150 days of active review. The EMA makes use of a rolling review as a regulatory tool to speed assessments of promising medicines during a public health emergency.[73,z]

Application fees for a new human medicine seeking marketing authorization are $296,500 in 2021. Fee reductions and incentives are possible for small companies, and designated orphan medicine applications.[74]

Japan

The Pharmaceutical and Medical Devices Agency (PMDA) evaluates new drug applications for purposes of granting market authorization in Japan. The Evaluation and Licencing Division within Japan's Ministry of Health and Labour Welfare (MHLW) issues the approval certificates for new medicines.

Generally, drug submissions are reviewed in the order of application. However priority review and conditional accelerated approval are two specialized pathways to achieve market authorization in Japan. Orphan drugs typically qualify for priority review. Additionally, the Strategy of Sakigake is an MHLW initiative introduced in 2015 which includes a rapid authorization mechanism for breakthrough drugs that are developed in Japan and seek first regulatory authorization in Japan. In addition to a shortened review time of 6 months, manufacturers may submit Phase 3 study results following the submission and may be eligible for a premium price.[75] In 2019, 42% of NAS applications were reviewed via these pathways.[5]

Rolling reviews are possible, though they do not ensure a faster review. Generally, the target review time is 9 months for prioritized submission and 12 months for regular submissions. However it may take up to two years to account for manufacturer responses. Fees are ¥533,800 to MHLW and ¥30,535,100 to PMDA (approximately $275,000 USD).

Switzerland

Swissmedic is the regulatory authority that assesses safety, quality and effectiveness of new medicines for marketing in Switzerland. Swissmedic sets administrative time limits for applicants. However these are not legally stipulated time limits. The process allows for up to 540 days from submission until

[z]Rolling reviews have been conducted for drugs used in association with the COVID-19 pandemic but otherwise are not typical.

Switzerland

decision, with 330 being evaluation time by Swissmedic, and 210 days being time for the sponsor to provide information.[76] A fast-track authorization procedure is available in Switzerland with review time limited to a total of 350 days – 140 being evaluation time by Swissmedic and 210 days for sponsor responses. In 2019, 32% of NAS applications were reviewed via these pathways.[5]

At the time of publication, the January 1, 2019, version of the Ordinance on Fees levied by the Swiss Agency for Therapeutic Products remained in effect, with a new active ingredient application having a fee of 80 000 fr. (approximately $87,000 USD). Swissmedic has implemented a rolling review process exclusively for COVID-19 therapeutics.[77]

United Kingdom

Since January 1, 2021, medicines seeking market authorization in the United Kingdom apply to the independently operating Medicines and Healthcare products Regulatory Agency (MHRA). Products previously approved by the EMA for marketing in the UK were provided an automatic grandfathering opportunity to receive a Great Britain Product to continue to be sold following the transition period from the centralized review procedure at the EMA.

The MHRA offers a 150-day accelerated assessment timeline for marketing authorization applications. This accelerated timeline is applicable to all complete and high-quality applications being submitted. It is not reserved for designated prioritized products. The timeline includes an initial 80-day Phase 1 assessment, up to 60-day clock stop period during which the sponsor responds to questions from the initial assessment. Phase 2 of the assessment begins upon the applicants' responses being received. The MHRA has 70 days, during which it will consult with the Commission on Human Medicines and reach its opinion on approvability by day 150.[78] Performance data are not yet available for the 150-day accelerated assessment process.

The early access to medicines scheme (EAMS) aims to provide access to medicines which do not yet have marketing authorization if there is a clear unmet medical need for patients with life-threatening or seriously debilitating conditions. Medicines assigned a promising innovative medicine (PIM) designation may be eligible for EAMS based on its early clinical data. The MHRA offers a rolling review procedure. There are no restrictions with respect to which medicines can be accepted for rolling review.

The national fee for a Great Britain Product Licence major application is £92,753. However these fees are reduced for products previously granted marketing licences via the EU. Additionally, much lower fees (£29,732) are charged for Major Orphan drug applications.

United States

In the United States, the Food and Drug Administration (FDA) is responsible for authorizing new drugs for sale. The Prescription Drug User Fee Act (PDUFA), originally passed in 1992, allows the FDA to collect an application fee from manufacturers to review and authorize new medicines for sale. In exchange, the FDA is required to meet performance benchmarks with regards to its timeliness to complete a review. For fiscal year 2022 the fee for an application with clinical data required is $3,117,218 USD. Under PDUFA VI, the Act's most recent iteration, the FDA is required to review and act on 90% of standard new drug applications (NDA) within 10 months of the 60-day filing date, and 90% of prioritized NDAs within 6 months of the 60-day filing date. For fiscal year 2019, the FDA's PDUFA Performance Report to Congress reported that 100% (n=44) of prioritized NME and BLA submissions were acted upon within 6 months of their filing date and 100% of non-prioritized original NMEs and BLAs were acted upon within 10 months of the filing date (n=33).[79]

The FDA employs several mechanisms for accelerating reviews, including Fast Track, Breakthrough Therapy, Accelerated Approval and Priority Review which each confer special privileges. In 2019, 70% of NAS applications were reviewed via these pathways.[5] Drugs designated through these pathways are frequently eligible for prioritized approval, and therefore are eligible for the shortened review time described above.

APPENDIX D: PRICE REGULATION, HTA & REIMBURSEMENT[aa]

Canada

The Canada Health Act provides the legal authority for Canada's universal healthcare system which is federally regulated and (in-part) funded, but administered by individual provinces. Notwithstanding this approach for universal access to medically necessary hospital and physician services, Canada's system for funding medicines administered outside of hospital is characterized by its many federal, provincial and territorial public programs and numerous private payers who provide insurance to different populations of Canadians. While many Canadians may not access prescription drug insurance programs, according to a 2017 Conference Board of Canada Report, fewer than 2% of Canadians are ineligible for public or private coverage programs across Canada.[35] For the most part, public plans in Canada provide coverage for residents age 65+, those on social assistance, or for whom drug costs exceed a percentage of household income (catastrophic plans). Other provinces (including British Columbia and Quebec) administer universal plans for residents of those provinces, Ontario administers a youth (under age 25) program, and most provinces administer specialized plans for certain populations or diseases. Some provinces have Cancer Agencies which provide funding for all oncology medicines, whether they are administered in hospital outpatient clinics or dispensed at the pharmacy for community use. One study estimated there are more than 100 public plans and 100,000 private plans operating in Canada each with unique beneficiary groups, premiums, deductible, copayment, and annual maximum rules.[80] In 2019, the public drug programs accounted for 43.6% of prescribed drug spending in Canada.[81] In 2021, CIHI forecasted total prescribed drug spending in Canada to be 44.8% from public insurance sources, 35.5% from private insurance, and 19.7% out-of-pocket.[bb]

Aside from market authorization by Health Canada, achieving market access in Canada includes complying with list price regulations, proceeding through health technology assessment, and achieving listing with the various public and private insurers on their formularies, which often requires further reimbursement negotiations.

With regards to price regulations, the Patented Medicine Prices Review Board (PMPRB) is a quasi-judicial agency which was established in 1987. The PMPRB has a formal price regulatory mandate (laid out in the Patent Act) to prevent pharmaceutical patentees from charging excessive prices during the patent protected period. The PMPRB regulates the factory-gate prices of only those medicines which are actively patented and being sold in Canada. It does not set the prices of medicines but regulates the upper limit or ceiling prices for all (prescription and non-prescription) medicines with any active patents (including for-use patents, process patents, etc.). Its mandate does not apply to non-patented generics or biosimilars.

The national HTA agency in Canada is the Canadian Agency for Drugs and Technology in Health (CADTH). It is funded by the federal and provincial public drug programs[cc] to (among other things) provide consistent and coordinated evaluation services and recommendations to the drug programs to inform their reimbursement decisions. While private drug plan insurers in Canada do sometimes refer to publicly available CADTH recommendations to inform reimbursement decisions, they conduct their

[aa] Note several countries in this analysis are members of EUnetHTA. The European Commission established the European Network for Health Technology Assessment (EUnetHTA) as a network across Europe for transparent and transferable information related to HTAs in European countries. The EUnetHTA is reported to include 30 countries and over 80 organizations. The EUnetHTA facilitates collaboration between countries to connect HTA agencies; promoting reuse of HTA reports to avoid duplication and to standardize HTA processes.

[bb] Calculated from data table G.14.2 from CIHI series available here https://www.cihi.ca/en/national-health-expenditure-trends#data-tables

[cc] Excluding Quebec, which relies on its own HTA service called the Institut national d'excellence en santé et services sociaux (INESSS) which provides reimbursement recommendations for the public drug program in that province.

own forms of HTA internally to make reimbursement decisions and because private reimbursement decisions are typically made prior to publication of CADTH recommendations and for a different beneficiary population and payer perspective, they generally do not significantly influence private drug plan reimbursement.

CADTH's Expert Committees - including the Canadian Drug Expert Committee (CDEC) and the pan-Canadian Oncology Expert Committee (pERC) make recommendations to the public drug programs which participate in the CADTH Reimbursement Reviews. These recommendations are not binding on the participating programs – the participating drug programs may choose to implement the recommendations (or not) in accordance with its own health system needs, patient populations and budget considerations. That said, in more recent years, studies have shown a high degree of similarity and harmonization across the participating drug plans with regards to listing status of medicines reviewed via the CADTH Reimbursement Reviews.[51,82,83] One such study showed "moderate to substantial agreement between provincial listing decisions and CADTH reimbursement recommendations."[51,82,83,84]

The review timelines for a standard, tailored, complex review, a resubmission or standard reassessment are targeted to be 180 calendar days. In CADTH's 2019-2020 annual report, it notes 100% of its reimbursement recommendations were issued within the 180 calendar days of receipt of the complete submission.[51] New medicines may undergo HTA processes concurrently with market authorization procedures. CADTH has an aligned review mechanism whereby its HTA can be completed concurrently with Health Canada's regulatory review and the INESSS HTA review in Quebec. Additionally, CADTH administers a pre-NOC review procedure for which submissions may be made for products up to 180 days prior to its anticipated Health Canada approval.

On the public side, there are 14 jurisdictions participating in the CADTH Reimbursement Reviews programs. Because CADTH serves as the central HTA, but healthcare systems are administered at the provincial level in accordance with the Canada Health Act, following receipt of a HTA recommendation, sponsoring manufacturers must still seek reimbursement with the individual payers to decide on reimbursement for the various plans which they administer. In Quebec, a separate HTA process is completed with INESSS, before manufacturers can achieve reimbursement on Quebec's RAMQ formulary.

In addition to the price regulatory function served by the PMPRB, Canadian payers also leverage their purchasing power to negotiate agreements with pharmaceutical manufacturers, which typically include financial rebates. The pan-Canada Pharmaceutical Alliance (pCPA), established in 2010, negotiates confidential reimbursement agreements on behalf of all publicly funded drug plans in Canada. Its leverage applies to sales of prescription medicines that are reimbursed under public drug plan formularies and special drugs programs, irrespective of their patent status. Since 2010, the pCPA has since grown to include Quebec and the federal public drug plans (in addition to the founding FPT public programs). Despite the central procedure for negotiating listing agreements, the pCPA process still results only in a Letter of Intent to list a product, and sponsoring manufacturers must still secure the listing based on that intent letter with each Canadian jurisdiction. While each negotiation is unique and timing is highly dependent on individual circumstances of the product and negotiating company, the pCPA did publish process guidelines in 2018 to provide some transparency and formality to its procedures. Timelines primarily focused on administrative components to initiate and consider engagement, with less formal estimates of times for the active negotiation phase. Based on PDCI's recent experience, manufacturers may expect the process between receiving an HTA recommendation and completing listing agreements (i.e. reimbursement coming online) with individual jurisdictions to take between 18-24 months. A study based on data from drugs reviewed via CADTH in 2015-16 found the average time between regulatory approval and the first provincial listing to be 505 days (increased from 365 days compared with 2013-14 data), and the time to countrywide listing to be 571 days (up from 470 days compared with 2013-14 data).[85] An IQVIA data analysis by Innovative Medicines Canada found that in each year between 2018-2020, completed negotiations took in excess of 300 days on average, with 30% or fewer files being completed each year within the 180-day target timeline

Canada

in pCPA's Brand Process guidelines.[33] The COVID-19 pandemic has caused pCPA processes to become backlogged up to three months between the time of final HTA recommendations and the time pCPA may pick up files to initiate negotiations. A prioritization process and targeted negotiation procedures attempt to alleviate and manage these pressures.

On the private reimbursement side – which CIHI forecasted represented 35.5% of prescribed drug spending in Canada in 2021 – there are more than 160 life and health insurers operating in Canada. A subset provides drug benefits, and among them three make up approximately 56% of the private drug insurance market in Canada.[86] Generally speaking, the time to achieve reimbursement on private drug plans is much quicker than on public, however, this may no longer be true for the most costly products (those costing more than $10,000 per patient per year), for which some private insurers may await CADTH recommendations and the private insurers may engage the manufacturers in their own listing agreement negotiations which can protract the time to achieving any reimbursement in Canada.[86] Private plans generally provide reimbursement for medicines more quickly than public plans. A study based on a sample of drugs from 2015 found average time to reimbursement on private plans being 132 days and 468 days for public plans.[88]

Private payers are not involved with pCPA price negotiations, but several have built their own negotiating capacity in recent years. Many private insurers negotiate and administer their own confidential agreements, similar to pCPA, especially for higher cost specialty drugs (greater than $10,000 per patient per year).[87] However, given each payers' smaller number of lives covered compared to the number represented by the pCPA, it is reasonable to presume private payers may not realize the same financial terms negotiated by the pCPA.

In theory, on the date of Health Canada regulatory approval, a patient could receive a prescription and visit the pharmacy to pay cash out-of-pocket to access a therapy, however, this is not typical practice. Particularly for more costly medicines, prescribers will wait to learn of reimbursement for a product prior to prescribing widely, and stock will not be on pharmacy shelves until launch which typically coincides with more widespread reimbursement. For this reason, manufacturers often complete a product launch closer to when reimbursement is anticipated, and a study showed in Canada launch occurs on average 90 days from the product's Canadian regulatory approval.[89]

Australia

In Australia, the federal government administers a universal healthcare system which includes subsidized access to outpatient medicines for all permanent residents with a valid Medicare card. The Pharmaceutical Benefits Scheme (PBS) is the part of Australia's National Medicines Policy which administers the Schedule of Pharmaceutical Benefits. The Pharmaceutical Benefits Advisory Committee (PBAC) is appointed by the Australian government to conduct health technology assessment and make recommendations to the Minister of Health regarding inclusion of drugs in the Schedule of Benefits.

All new licensed outpatient drugs are eligible to be listed on the Schedule of Pharmaceutical Benefits for general (unrestricted) or restricted reimbursement. Some medicines or uses may be classified as "authority required" indicating that Medicare Australia must pre-approve use of the medicine before it will be reimbursed. Products can be submitted for listing on the Schedule by the manufacturer, sponsor, medical bodies, health professionals, or private individuals and their representatives. A reimbursement decision is made by the Department of Health (Minister or their delegate), based on recommendations by the PBAC[90,dd]. In its review, PBAC considers disease severity/burden of illness, clinical need, availability of alternatives, quality of/uncertainty in the evidence, clinical benefit/effectiveness or comparative effectiveness, cost-effectiveness (based on the list price initially set by the manufacturer) or value for money, extent of use or experience with the drug, affordability or budget impact, and innovativeness.

[dd] Medicines estimated to cost more than $20 million per year must additionally receive Cabinet approval.

Australia

Once PBAC has issued a positive recommendation for inclusion in the PBS, the government may seek to negotiate its reimbursement price. The Pharmaceutical Benefits Pricing Authority (PBPA) is an independent non-statutory body established by the Minister for Health and Ageing. It makes recommendations to the Minister on prices for new pharmaceutical items and vaccines positively recommended by PBAC. The PBPA may also recommend revised prices where the use of drugs is extended or changed.[91] PBPA uses the following methods to recommend price: Cost plus method, internal reference prices and weighted average monthly treatment cost.

Different types of agreements may be negotiated between the government and manufactures. Risk-sharing agreements are increasingly used to contain overall costs of drugs included in the PBS or to manage financial risks for the government. The government has agreed to implement Special Pricing Arrangements (SPAs) as one type of agreement which allows manufacturers to confidentially rebate the price of medicines while maintaining higher published prices.

PBS expenditure is not capped in Australia. However, pharmaceutical prices can be reduced. The price of each drug listed in the PBS is reviewed annually by ATC groupings.[92] PBS also applies a 5% reduction to the PBS Approved Ex-Manufacturer Price (AEMP) for all brands of all pharmaceutical items containing the drugs mentioned in the list.[93]

The Life Saving Drugs Program (LSDP) is a federally administered program outside of the PBS which subsidizes high-cost, specific essential medicines to treat patients with rare and life-threatening diseases and which would generally not be the PBS criteria for cost-effectiveness. The price negotiation for these products may be based on any pricing parameters determined by the LSDP Expert Panel. The arrangements recommended are including outcome-based risk-sharing arrangements.[94] Currently 15 medicines are funded through this program for the treatment of 10 conditions.

Private health insurance providers do operate in Australia to subsidize costs of products and services which are not covered by the universal public program.[95] More than half of the population has private health insurance particularly to access elective or quicker medical care, as in the case of drug spending, PBS covers more than 80% of drug expenditures in the country.[ee,96,97]

According to the industry association Medicines Australia, the time to complete a PBAC review is typically 4 months, and the time to PBS listing takes a minimum of an additional 4 months, during which time price and risk-sharing negotiations are completed.[90] This is aligned with PBAC's published 35-week timeline in its Procedure and Guidelines documents.[98] In Australia, manufacturers can submit to HTA before market authorization is granted on the Australian Register of Therapeutic Goods (ARTG); the median overlap between regulatory and HTA process is 107 days and reviews fairly consistently take 125 days to complete.[45] Medicines Australia reported in its 2021 Facts Book that the average time between a positive PBAC recommendation and successful PBS listing was 285 days or 9.4 months.[99]

Belgium

The Belgian National Institute for Health and Disability Insurance (NIHDI) manages Belgium's compulsory health insurance program. The program includes three systems (for employees, civil servants and the self-employed) and seven pillars. There is one public national sickness fund and six private non-profit insurers. All Belgian residents must register with one of these seven insurers. Residents may choose to register with additional private (for-profit) insurance providers to cover costs not eligible under compulsory health insurance. However the vast majority of health expenses (75%) are covered by the compulsory health insurance.[100]

Compulsory health insurance will only reimburse medicines which are included on the list of reimbursable pharmaceutical specialties. Pharmaceutical companies submit new drugs for reimbursement on

[ee] In 2017-18 PBS spend $11,603 million, which is 88.9% of total PBS prescriptions (patients paid the remaining $1,455 million in co-payments. In the same year, individuals spend $9.4 billon on medicines not subsidized by the PBS which includes over the counter medicines, vitamins and health-related products.

Belgium

the list to the Secretariat of the Commission for Reimbursement of Medicinal Products (CRM) at NIHDI for consideration. The Belgian Health Care Knowledge Centre (KCE), is the institution responsible for HTA in Belgium, with activities commissioned by the Ministry of Public Health and Social Affairs. The KCE has relationships with other scientific institutions (e.g. NICE in the UK, ZIN in the Netherlands, HAS in France, IQWIG in Germany, and the Norwegian Institute of Public Health). The decision to list and reimburse a drug includes 5 criteria: the therapeutic value, market price, clinical effectiveness, budget impact for the National Health Insurance, and cost-effectiveness. The KCE does provide Rapid Reviews (RR) which is a simplified review process to produce information in a short period of time with mention of an 8-week timeline.

The formulary is tiered, such that products reimbursed as Category A vital medicinal products be reimbursed fully (100%), with products in other categories reimbursed at lower percentages. Factors considered in the reimbursement review include disease severity/burden of illness, therapeutic value, clinical benefit/effectiveness or comparative effectiveness, and price and level of reimbursement compared to other jurisdictions. NIHDI's Drug Reimbursement Committee (DRC) makes recommendations to the Minister of Social Affairs to decide on inclusion in the list. The standard procedure includes 150 days for the Commission for Reimbursement of Medicines to provide its advice to the Ministry of Social Affairs, which has 30 days to decide, therefore reimbursement decisions are to be taken within 180 days of submission.

Manufactures submit simultaneously for reimbursement and pricing reviews. The pricing procedure is the responsibility of the Minister of the Economy (Agence fédérale des médicaments et des produits de santé (AFMPS)) which sets the maximum ex-factory price for all products sold in Belgium.[100] Manufacturers submit a dossier justifying the requested maximum ex-factory price and the Minister of Economic Affairs determines the maximum price based on scientific and economic information submitted. Several measures for price control can be applied including the ceiling price measure, internal price referencing (cluster), patent cliff, old drug cliff and biocliff. An increase in use of managed entry agreements to control expenditure has been noticed.

Other initiatives for price regulation include collaborations between the European countries. The Beneluxa Initiative (Belgium, Netherlands, Ireland, Austria and Luxembourg) jointly negotiates prices of new medicines entering these markets, and the International Horizon Scanning Initiative (Denmark, Switzerland, Belgium, Netherlands, Portugal, Norway, Ireland, and Sweden) provides payers with data to leverage in price negotiations for new medicines.[100]

France

In France, health insurance coverage is compulsory and provided to all residents by non-competitive statutory health insurance funds. Some private health coverage operates in France. However this only covers services not covered under the compulsory program (mainly vision and dental care). More than 70% of pharmaceutical expenditure is estimated to be public spending in France.[37] All licensed outpatient and inpatient drugs undergo general reimbursement reviews for decisions by the Ministry of Health and Social Services, based on recommendations from the French National Authority for Health (HAS). HAS is an independent public body mandated to provide the government with evaluation and recommendation of health products for reimbursement by the national health fund. Factors considered in the reimbursement review include disease severity/burden of illness, safety or benefit-harm ratio, clinical benefit/effectiveness or comparative effectiveness, impact on public health, and affordability or budget impact. Individual (case-by-case) or cohort reimbursement exists for different classes of drugs.

The HTA opinion process is targeted to take 90 days, however actual time has been measured at 157 days.[45] In July 2018, the French Prime Minister noted the country's intent to improve its time to reimbursement by 2022. A directive of the European Commission states that both pricing and reimbursement decisions should be completed within 180 days in member countries. However the average time from EMA authorization to publication of reimbursement in France was reported at that time to be 530 days.[102]

France

The Transparency Commission of HAS makes determination for pricing in accordance with the level of value provided by the medicine on a scale called *amelioration du service medical rendu* (ASMR) and its reimbursement rate based on its actual benefit (SMR). Once SMR and ASMR have been determined through concurrent processes, the manufacturer negotiates with the Comité Economique des Produits de Santé (CEPS) to determine the reimbursement price and rate. Reimbursement is assessed throughout the product's lifecycle and may be adjusted every five years.

The Economic Committee for Health Care Products (CEPS), is mainly responsible by law for setting the prices of medicines and the prices of medical devices for individual use, as well as benefits covered by compulsory health insurance.[103] The price for non-reimbursable medicines and most hospital use or OTC products are not regulated. The government applies several measures for price control: price reference system (Tarif Forfaitaire de Responsabilité, TFR), agreements, prescription volumes, generic substitution, performance-based costing system and the clawback system. For hospital products (inpatient), the CEPS fixes a level of reimbursement or concludes a managed-entry agreement. [104]

The government contracts with manufacturers to purchase new medications at a price that reflects their added therapeutic value. The CEPS negotiates a price corridor so that they are neither higher nor lower than the highest or lowest prices in the United Kingdom, Germany, Italy, and Spain.[90] Second, it uses a budget cap to keep national health insurance (NHI) drug spending in line. It requires manufacturers to pay rebates if spending exceeds a national pharmaceutical spending cap set by Parliament. When sales exceed the contract cap, manufacturers pay rebates of between 50 percent and 80 percent. The country also prohibits price increases after a new drug's launch and, after five years, lowers prices and obtains additional discounts based on market competition.[105]

Germany

Health insurance is mandatory in Germany. The vast majority (90%) of the population relies on the government's statutory health insurance program (SHI) while the other 10% are covered by private insurance or special schemes.[106] The basket of goods and services covered by SHI is defined at the national level by law. Private health insurers generally cover a similar basket though they are allowed to extend or restrict benefits.

Pricing and reimbursement policies in Germany are based on the following principles: prescription drugs are automatically eligible for reimbursement by health insurance (unless specifically excluded); manufacturers are free to set their initial price; drugs can be clustered in groups of products considered to be therapeutically equivalent and subject to maximum reimbursement amounts.[106]

The Joint Federal Committee (GBA) is responsible for eligibility of medicines for reimbursement under SHI. Unlike most other markets where the responsible body positively determines inclusion on a formulary (positive listing), in Germany all drugs are automatically eligible for reimbursement by the sickness funds upon market authorization and the GBA makes determinations only on the exclusion of products (a negative list). GBA completes health technology assessment with assistance of the independent Institute for Quality and Efficiency in Health Care (IQWiG) for the purposes of determining whether a medicine provides additional therapeutic benefit. The Arzneimittelmarkt-Neuordnungsgesetz law (AMNOG) implemented in 2011 requires manufacturers to submit evidence concerning their products' comparative benefit. Factors considered in the review include clinical need, availability of alternatives, clinical benefit/effectiveness or comparative effectiveness, cost-effectiveness or value for money, and innovativeness. The outcome of this process informs price regulation for the product in year two and onwards, but access and reimbursement is not delayed until this process has been completed. Effectively, products can be launched as of regulatory approval at the price determined by the manufacturer and funding is effective immediately. Following GBA evaluation, the GBA and manufacturer may enter confidential price negotiations, based on the level of additional benefit assessed by the GBA. If no added benefit is determined, then the product is placed within a reference price cluster with other medicines of similar effect. The AMNOG evaluation and price negotiation process applies to all new patented medicines introduced in the German market, except those

Germany

with annual SHI expenditure below EUR 1 million.[107] The price regulation mechanisms range from price freezing to compulsory rebates, reference prices limit and negotiated reimbursement price.[108] For outpatient medicines, an automatic 7% discount off ex-factory price is required for sickness funds and other health insurers on patented pharmaceuticals that are not clustered in reference price groups.

Within three months of market authorization the GBA and IQWIG complete the assessment of new drugs' additional benefit by law. A resolution on the added benefit assessment is reached by GBA within another three months (a total of 6 months since launch). Price negotiations for drugs with added benefit proceed thereafter between the Central Federal Association of Health Insurance Funds and the pharmaceutical company. Negotiations must be completed within 6 months of the GBA resolution or proceed to arbitration. The price negotiated is effective from the beginning of the second year of sales, irrespective of when the negotiations were actually finalized.[108]

Italy

Italy provides universal healthcare coverage to citizens as a matter of shared jurisdiction between the government's National Health Service (called Servizio Sanitario Nazionale, SSN) and the regions of Italy. SSN does not allow residents to opt out of the universal system. Private insurance is complementary, and approximately 10% of the population has voluntary health insurance. In 2018 SSN funded 77% if Italy's total pharmaceutical spending, with most of the remaining privately funded expenditure being out-of-pocket as opposed to private insurance.[38] Despite the national pricing and reimbursement processes, Italy has 21 regions which each manage their own budgets and formularies adding complexity to the process of achieving reimbursement in all regions.

The Italian medicines agency *Agenzia Italiana del Farmaco* (AIFA) is responsible to review medicines for listing on the National Pharmaceutical Handbook. It manages the pricing and reimbursement negotiations procedures with assistance from its Scientific Technical Committee which assesses the additional benefit of drugs and the Pricing and Reimbursement Committee which negotiations drug prices and reimbursement with manufacturers. The factors considered in the review include disease severity/ burden of illness, clinical need, safety or benefit-harm ratio, clinical benefit/effectiveness or comparative effectiveness, affordability or budget impact and prices in other countries (European countries). The negotiation procedure has a duration of 180 days from applications and may have one interruption period for a maximum of 90 days, but this can be expedited to 100 days for orphan drugs.[38] During negotiation, the medicine is categorized as Class C (0% reimbursement) but can be sold if the manufacturer chooses to launch prior to the coverage determination by AIFA. A 2020 study of 137 new active substances which were approved for marketing and reimbursed in Italy between 2014-19 found a median time to reimbursement of 228 days.[109] In 2021 AIFA published a performance report on authorization timelines for products reviewed between 2018-2020 which showed a general decrease across administrative verification time, review procedure time and time to listing in the Official Journal. It showed the administrative verification time taking 6 days on average in 2020 (compared with 17 days in 2018), 241 days for the review procedure in 2019 (compared with 271 in 2018), and 61 days for listing in 2019 (compared with 78 days in 2018).[110]

Italian law requires that all prices of medicines reimbursed by SSN be negotiated between AIFA and the manufacturer. Pharmaceutical companies are obliged to grant to the National Health Service a cumulative 5% + 5% mandatory manufacturer discount on the ex-factory price of reimbursed medicines. Cancer medicine and other innovative medicines meeting defined criteria can be exempted from the rule. In Italy, an expenditure governance system is in place in case of overspending the national budget ceilings, which are defined on an annual basis, companies have to contribute to paybacks. [111]

New high-priced medicines are often subject to managed-entry agreements (whether financially based such as spending caps, price volume, cost sharing, confidential discounts or performance-based such as Payments by Result, Risk Sharing and Payment at Results) and "appropriateness agreements" that monitor prescribing appropriateness through AIFA Monitoring Registries.

Japan

Japan administers a universal National Health Insurance System for all residents, including coverage for medicines. Various health insurance societies exist which people enroll in based on their employment or residence and age. People not enrolled with a health insurance society are insured directly with the Japan Health Insurance Association. The universal coverage program funds about 70% of all healthcare costs in Japan.

Following obtaining the marketing licence under from the Minister of Health, Labour and Welfare (MHLW) under the Pharmaceutical and Medical Device Act, manufacturers apply to Ministry of Health, Labour, and Welfare (MHLW) to achieve listing in the Drug Price Standard. Based on recommendations from its Drug Pricing Organization (DPO) and consultation with its Central Social Insurance Medical Council (Chuikyo) MHLW drafts listing of the product. Factors considered in the review include availability of alternatives and clinical benefit/effectiveness or comparative effectiveness.

Drug price determinations are calculated through various methods. When there is a comparable drug with same indication in the list, the daily price of a new medicine is to be equal to that of the comparable drug and premiums are not applicable. The price of new pharmaceuticals without similar drugs is determined by the total cost of raw materials, manufacturing, and similar inputs, then premiums (ranging from 5%-125%) are applied for various incentivized features such as Breakthrough Premiums, Usefulness Premium, Orphan Drug Premium, Pediatric Premium, Drugs in Small Markets Premium, among others.[112] Drug prices calculated by Comparative Method (I) and Cost Calculation Method is adjusted if there is a large disparity between average foreign prices (US, UK, Germany and France).[113] [114]

It generally takes 60-90 days from marketing authorization to listing in the Drug Price Standard.[113] A 2016 study found the average time to reimbursement for new molecular entities approved from 2004-2014 was 66 days.[115]

Netherlands

In the Netherlands, the government ensures universal coverage of pharmaceuticals for all residents meets a minimum standard. However it regulates a competitive private health insurance market rather than administering the insurance itself. The social health insurance scheme is regulated by the Ministry of Health, Welfare and Sport (MoH).

In the Netherlands, all new licensed outpatient drugs and inpatient orphan drugs undergo general reimbursement for decisions by the Minister of Health, Welfare, and Sport. The National Health Care Institute (ZIN) is the government agency which conducts the HTA and makes recommendations to the Minister of Health, Welfare and Sport (VWS) concerning reimbursement and the co-payment rates for medicines used outside of hospitals. Factors considered in the review include disease severity/burden of illness, clinical need, therapeutic value, quality of and uncertainty in the evidence, safety or benefit-harm ratio, clinical benefit/effectiveness or comparative effectiveness, cost-effectiveness or value for money, extent of use or experience with the drug, and affordability or budget impact.

The pharmaceutical assessment procedure starts after the marketing authorization. Once the company submission is received ZIN prepares an assessment using evidence from the application and other sources to assess the technology. ZIN has 70 days to prepare advice for the Ministry. The Ministry then has 20 days to make a final decision. The 70 days represents approximately 1 month to write a draft report that is then scheduled into a monthly Committee meeting for discussion before being amended. The process from submission to decision takes 90 days.

The MoH determines the maximum wholesale price set for all outpatient prescription-only medicines; where manufacturers sell their products to a pharmacy directly, they have to restrict the prices to the maximum wholesale price set by the ministry. Medicinal products not subject to prescription are generally not eligible for reimbursement and do not have to comply with maximum prices. Central price setting does not apply to over-the-counter products. [116]

Netherlands

The Dutch Medicine Prices Act sets maximum allowable prices for medicines based on the average of what similar medicines cost in 4 reference countries: currently Belgium, France, Germany and the United Kingdom.[117] For high-cost medicines and orphan medicines, therapeutic value and cost-effectiveness is taken into account. Mostly, medicines are purchased by tendering. For this purpose, hospitals join together in regional purchasing groups. [118]

Other initiatives for price regulation include collaborations between the European countries. The Beneluxa Initiative (Belgium, Netherlands, Ireland, Austria and Luxembourg) jointly negotiates prices of new medicines entering these markets, and the International Horizon Scanning Initiative (Denmark, Switzerland, Belgium, Netherlands, Portugal, Norway, Ireland, and Sweden) provides payers with data to leverage in price negotiations for new medicines.[100]

Norway[118,119]

In Norway, membership in the state-owned National Insurance Scheme (NIS) is mandatory and universal. The NIS covers retirement pensions, disablement benefits, sickness benefits, unemployment benefits and health care, including pharmaceuticals.[40]

The Ministry of Health and Care Services (Helse- og omsorgsdepartementet, HOD) is the legislative authority for NIS. The Norwegian Medicines Agency (Statens legemiddelverk, NoMA) is part of the Ministry of Health and Care Services. NOMA assesses medicines and clinical trials for market authorization and reimbursement for universal access through the National Insurance Scheme. It is also responsible for marketing authorization, classification, vigilance, pricing, reimbursement and providing information on medicines to prescribers and the public.[121] All newly licensed pharmaceuticals go through the general reimbursement pathway for decisions by NoMA. The factors considered in the review include clinical need, clinical benefit/effectiveness or comparative effectiveness, cost-effectiveness or value for money, and solidarity. The executive responsibility of a Single Technology Assessment (STA) resides with The Norwegian Knowledge Centre for Health Services where a review of safety, efficacy, health economics from clinical studies and health economic models submitted by the manufacturer is conducted. The process takes up to 6 months. The Regional Health Authorities have the responsibility of decision-making once the review is complete.

Norway has a statutory pricing policy for prescription-only medicines (POM) for human use. Before entering the Norwegian market, the Marketing Authorization Holder (MAH) has to apply for a maximum price with NoMA. OTC drugs are usually not price regulated. External price referencing is the key mechanism for setting maximum prices, while internal price referencing is used for setting tiered prices, once generic entry provides for interchangeability. For NoMA's assessment, it considers HTA, pharmacoeconomic reviews and horizon scanning. Additional initiatives for cost control include generic substitution and in some cases management entry agreements with confidential prices[121]. Additionally Norway collaborates through the International Horizon Scanning Initiative (Denmark, Switzerland, Belgium, Netherlands, Portugal, Norway Ireland and Sweden) which provides payers with data to leverage in price negotiations for new medicines. [40] NoMA revises the price of the top-selling active ingredients on a yearly basis.

Spain

Spain administers a universal healthcare system for all eligible residents. Healthcare provision in Spain is decentralized and administered and financed by the regions.

Key institutions in reimbursement of new medicines are the Spanish Agency of Medicines and Medical Devices (Agencia Española de Medicamentos y Productos Sanitarios / AEMPS), which is responsible for marketing authorization and for a clinical assessment of the medicine (Therapeutic Positioning Report), and the Ministry of Health (MoH), which takes pricing and reimbursement decisions based on manufacturer submissions and the AEMPS clinical assessment. After market authorization of a new medicine, MoH begins the mandatory process. Manufacturers have up to 15 days to provide submissions which must include cost-effectiveness studies, and whether the sale of the product will benefit Spain's economy. The General Directorate for Pharmacy decides whether it will be reimbursed and the Inter-

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ministeral Committee for Pricing (Comisión Interministerial de Precios de los Medicamentos / CIPM) is the body deciding on the maximum reimbursable price. The CIPM involves national public authorities and the regions, makes decisions on pricing and reimbursement.

The regional network (AETS) evaluates cost of technologies. Local regions and hospitals may conduct further HTA. Despite the centralized HTA process, because the regions allocate budget to fund new medicines, there may be variability in terms of implementation across regions and access may be subject to conditions in manufacturer agreements with individual regions.

The main mechanisms for MoH pricing and reimbursement decisions include external and internal reference pricing as well as price negotiations. Price negotiations apply to new innovative medicines while generics are subject to statutory pricing and mandatory substitutions. External reference pricing applies to new medicines where there is no comparator in the Spanish market; it serves as additional information for the pricing and reimbursement decision- a supplementary pricing policy. Internal reference pricing is used if a comparator exists within Spain (generics), free pricing for non-reimbursable medicines.[116] In the case of high-priced medicines, a managed-entry agreement (either a financially based or a performance-based MEA) can be concluded. In the case of price negotiations, the General Directorate for Pharmacy takes the lead on behalf of the MoH. Spain applies two clawback systems; on mandatory discount for new medicine and orphan medicine and one annual sales payment at the pharmacy level.[122]

The process is intended to take 180 days. However clock stop periods may occur with times of up to 1 year for the process being possible. It is reported that the actual time through HTA is 221 days.

Sweden

Sweden has a universal healthcare system called the Pharmaceutical Benefits Scheme in which all residents are automatically enrolled. The system's regulation is a federal government responsibility under the Ministry of Health and Social Affairs, while its financing and delivery is the responsibility of the regions. Costs for outpatient pharmaceuticals, though formally financed by the regions are almost fully covered by federal transfers to the regions.

The Swedish Dental and Pharmaceutical Benefits Agency (TLV) is the governmental agency responsible for deciding the drugs to include in the national drug benefit scheme. It makes pricing and reimbursement decisions for prescription medicines used in outpatient care. Within the agency the Pharmaceutical Benefits Board makes reimbursement decisions following submissions of manufacturers requesting reimbursement at a specific price. Evaluations use three categories of criteria: human value which is an ethical principle, need and solidarity which is operational in terms of disease severity where the more severe condition is given priority, and cost-effectiveness. Budget impact is not a formal requirement. The HTA process including reimbursement and pricing decisions is completed in 180 days from the receipt of a complete application. While manufacturers may submit HTA submissions up to 90 days before European Marketing Authorization is anticipated, the application will not be considered complete until a market authorization is received.[42] Local regions are to accept the TLV decisions. However implementation may vary across regions. Decisions are legally binding and may be reviewed after 5 years.

Medicines not reimbursed in the public Benefits Scheme can be priced without regulation. For those medicines reimbursed, the pricing decision is based on clinical evidence and health economic documentation. Application is granted by TLV on Value Based Pricing of pharmaceuticals. The reimbursement decision depends on several factors, where one may be the existence of a managed entry agreement between the county councils and the pharmaceutical company. Pharmaceuticals subject to price competition, mainly generics, are substituted at the pharmacy. The preferred product is selected through a monthly auction. A special pricing procedure is applied for pharmaceuticals older than 15 years that have no (or weak) generic competition. International Reference Pricing is not applied in Sweden. TLV may initiate a review of a pharmaceutical's pricing and reimbursement status. A review can be initiated

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to ensure that a group or a single pharmaceutical within the reimbursement scheme still is cost-effective.[123] Sweden is a member of the International Horizon Scanning Initiative (Denmark, Switzerland, Belgium, Netherlands, Portugal, Norway Ireland and Sweden). [124]

Switzerland

Switzerland has a universal and mandatory health insurance system including coverage for pharmaceuticals. The Swiss Federal Office of Public Health (FOPH) which is responsible for public health ensures the insured products and services meet a minimum standard, but it regulates a private insurance market rather than administer and fund the insurance itself as a public payer. More than 50 non-profit insurers compete on cantonal exchanges, providing different policies for children (under 18), youth (18 -25) and adults (26+). All insurers provide the compulsory basic health insurance and may provide supplementary insurance for products, services or features not covered by the basic health insurance. Despite regulation occurring at the federal level, the responsibility to deliver healthcare and fund health insurance is with the catons.

The FOPH makes decisions concerning the products included in the formulary known as the specialty list. In addition to having market authorization provided by Swissmedic, products must demonstrate effectiveness, functionality and economic efficiency in manufacturer applications to FOPH to be reimbursed. The FOPH makes decisions based on recommendations from the Federal Drug Commission (FDC). Factors considered in the review include disease severity/burden of illness, clinical need, availability of alternatives, price and level of reimbursement compared to other jurisdictions, and innovativeness. Individual/case-by-case reimbursement exists for other classes of drugs.

The FOPH also regulates pricing of reimbursed pharmaceuticals. It sets maximum prices for all listed drugs whether on- or off-patent, as well as generic drugs. The government does not regulate prices of drugs that are not included in the formulary. However prices of non-listed patented drugs may be subject to surveillance by the Price Council to prevent abuses from a dominant market position. Prices of non-reimbursed over-the-counter and prescription drugs are freely set by the manufacturers, while reimbursed product prices are negotiated with manufacturers. Though manufacturers can decide not to seek reimbursement and avoid price negotiation, the expected benefits of reimbursement status generally lead them to opt for reimbursement.

Efforts to manage drug expenditures include generic substitution, international price benchmarking, value-for-money evaluation and relative effectiveness. International price benchmarking includes prices in Germany, Denmark, the United Kingdom, and the Netherlands which are first considered. France, Austria and Italy can be considered as subsidiary countries, and other countries may be included in the comparison. Drugs included in the formulary are subject to periodic assessments to confirm that they still offer “value-for-money”; the first one occurs 24 months after their inclusion to check if the entry price was appropriate. Maximum prices are set when the innovator product is placed on the formulary. No price increases are allowed within the first two years and thereafter price increases must have authorization by FOPH. Switzerland is part of the International Horizon Scanning Initiative (Denmark, Switzerland, Belgium, Netherlands, Portugal, Norway, Ireland, and Sweden). [124,125] At patent expiry or 15 years after listing, the innovator product undergoes reassessment. This process establishes a reference price which sets a benchmark for pricing of generic alternatives.

The FOPH actively engages with HTA networks to share knowledge, including the Swiss Network for Health Technology Assessment (SNHTA) sharing Swiss scientific experts and with EUnetHTA. According to FOPH, the process for HTA includes Topic Identification and Pre-scoping (2 months), HTA protocol (5 months), and HTA report or assessment (6-12 months). The Appraisal phase is conducted by extra-parliamentary commissions, and the Decision by the FOPH. The relevant ordinance stipulates that the FOPH issues its final reimbursement decision within 60 days, but the median time has been estimated at 200 days.[126] A 2021 study examined the time to reimbursement for medicines in Switzerland, comparing those with rebates to those without rebates. Authors found the median time between approval and price determination for drugs with rebates to be 302 days and 106 days for drugs without rebates.[53]

United Kingdom

The UK has a universal publicly funded healthcare system including medicines for its four countries, each of which manages its own National Health Service (NHS). The public healthcare system covers 85% of healthcare expenditures with the remaining 15% covered by private insurance or out-of-pocket sources.

The National Institute for Health and Care Excellence (NICE) conducts health technology assessment to provide a reimbursement recommendation to the Department of Health which makes reimbursement determinations for the NHS. Factors considered in the appraisal include disease severity/burden of illness, availability of alternatives, quality of/uncertainty in the evidence, clinical benefit/effectiveness or comparative effectiveness, cost-effectiveness or value for money, and affordability or budget impact. The NHS typically must make a drug available within three months of a positive NICE recommendation. Final decisions for products not selected for appraisal by NICE are made by local Clinical Commissioning Groups. Decisions are legally binding; typically reviewed after 5 years' time.

The Single Technology Appraisal process includes several steps with specific timelines: from information requests to evidence review and publication of the report. A fast-track appraisal process exists at NICE approved by NICE in 2017, as a way for patients to gain access to innovative treatments more quickly. In England, providers can prescribe medicines once it receives marketing authorization, if the drug is not a negative list. NHS will reimburse medicines at 100% of price minus copayments. Evaluations can be initiated when NICE receives notification of proposals for market authorization. A Single Technology Assessment will take 32 weeks at least from initiation to publication of the report. For most drugs, following a NICE recommendation that a medicine be funded by the NHS, Regulations require that the NHS comply within 3 months.[54] A fast-track process is available where medicines can become available one month after receiving marketing authorization. Local payers must reimburse for approved products by NICE.

While NICE HTA is generally focused on England, other countries in the UK consider NICE guidance. Scotland carries out its appraisals by the Scottish Medicines Consortium (SMC) and Wales makes its decisions via the All Wales Medicines Strategy Group (AWMSG).

Prices for prescription drugs in the NHS are currently set through discussion between manufacturers and the Government under the Pharmaceutical Pricing Regulation Scheme (PPRS). The PPRS is a voluntary agreement between the Department of Health (DH) and the pharmaceutical industry. This regulates the profits that companies can make from NHS sales and is typically renegotiated every five years. The PPRS has two main elements for controlling drug prices: profit control using caps and price cuts, usually for older drugs. PPRS placed greater emphasis on the use of Patient Access Schemes (PASs). These are proposed by a pharmaceutical company to improve the cost-effectiveness of a drug. There are two types of schemes: financially based and outcome-based. Expenditure control is also achieved through value-based pricing. PPRS introduced provisions to allow companies to change the price of a drug after it has been marketed.[127] Prices for branded (on-patent) and generic (copies of off-patent brand) drugs are set differently.[128] Generic products price are open to the market forces.

United States

Health insurance and prescription medicine reimbursement in the US is characterized by its high number and mix of public and private payers. More than two thirds of Americans have private drug insurance, typically through employer-subsidized group benefits plans. Medicare and Medicaid are the two main programs jointly funded by federal and state governments to provide health insurance for older and low-income Americans respectively. In 2019 there were 952 companies providing health insurance in the United States.[129]

Medicare Part D is an optional program providing insurance for outpatient prescription drugs for Medicare beneficiaries. In 2019, about three quarters of Medicare enrollees opted in to Part D.[130] Program expenditures were $102 billion which represents approximately one third of retail prescription drug spending in the United States.[131] The Centers for Medicare and Medicaid Services (CMS) requires for products on Medicare Part D the P&T committee reviews a new FDA approved drug product within 90 days and complete a National Coverage Determination within 180 days of its release onto the market.[123] The Agency for

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Healthcare Research and Quality (AHRQ) provides Technology Assessments for the Centers for Medicare & Medicaid Services (CMS), including the Medicare Part D, CMS' prescription drug program. The assessments aid in decision-making for National Coverage Determinations (NCDs). The program is transparent with comments and final reports posted publicly. AHRQ will task its Evidence-based Practice Centers (EPCs) to conduct scientific analysis of high priority for payers. The Food and Drug Administration (FDA) and CMS do have a parallel review process where FDA and CMS will meet with the manufacturer to provide feedback on the proposed clinical trials and results are then reviewed in parallel. Parallel review does not change the standards for review at either agency in addition to CMS' national coverage determinations. Reviews are substantial and may take up to one or two years to complete. Whereas rapid reviews have a shorter process and may take up to six months.

Drug manufacturers freely set their list prices in the US. Most medicine costs are paid for by Medicare/ Medicaid, or by private insurers. The "non-interference clause" prohibits the federal government from "interfering" in negotiations between drug companies and the private plans that deliver Part D coverage, and also prohibits the government from requiring a particular formulary or price structure for drugs. However, in November 2021 the federal government announced a pricing plan that would allow Medicare to negotiate drug prices. The plan will begin negotiating up to 10 drugs per year in 2023 and prices will take effect in 2025. Drugs eligible for negotiation are small molecules which have been marketed for nine years and biologics which have been marketed for 12 years.[132] Private payers typically rely on third-party pharmacy-benefit managers (e.g. Express Scripts, CVS Caremark and OptumRx being the three largest), to negotiate discounts. Often they make exclusive deals with drug makers, which limits the choice of drugs patients have. The private sector relies heavily on "alternative dispute resolution" approaches, including a variety of arbitration organizations, such as the American Arbitration Association for price setting conflict.[132-134]

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