Canada's Drug Agency
L'Agence des médicaments du Canada

Industry Task Force Summary Report

August 2024

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Executive Summary

Background

Canada's Drug Agency was involved in collaboratively developing the strategic framework for Canada's use of real-world evidence (RWE) to support decision-making and has engaged several impacted groups to support and provide guidance on the optimal use of RWE.

RWE has increasingly been incorporated and considered, where appropriate, in Reimbursement Reviews, and has become an important tool in evaluating drugs across the drug life cycle when limited clinical trial data are available.

This is especially true for rare diseases and specific indications in oncology, looking at secondary outcomes, and assessing the effectiveness and safety of drugs in the real world. Canada's Drug Agency has increasingly been adopting RWE in its programs to better respond to customer queries.

The Post-Market Drug Evaluation (PMDE) program was launched in September 2022 to answer queries from senior health care decision-makers about the safety and effectiveness of marketed drugs using RWE. PMDE established and funds CoLab, which is a network of experts in applied research, scientific methods, and data analysis.

Issue

Manufacturers and commercial developers of pharmaceuticals and biologics (industry) are increasingly collecting and sponsoring the generation of real-world data (RWD). They have expressed interest in sharing evidence that they have generated from their RWD, where permissible, with health technology assessment (HTA) agencies to aid in further understanding the value of their treatments. The PMDE program offers an ideal initial platform to explore the targeted sharing of RWE from industry-sponsored data to expand the availability of evidence for decision-makers.

The PMDE program offers an ideal initial platform to explore the targeted sharing of RWE from industry-sponsored data to expand the availability of evidence for decision-makers.

Substantial work is needed to effectively operationalize access to and use of industry-sponsored RWE. Constructive dialogue between industry and payers through HTA bodies can help improve the understanding of data available and inform decision-making.

Approach

To address the issue, we convened an industry task force (ITF) for the first time, with representation from pharmaceutical and biologics manufacturers (n = 10), Health Canada (n = 1), and staff from Canada's Drug Agency (n = 5). We co-led the ITF with industry representatives, with deliberation led by an independent facilitator.

While we have worked collaboratively over the years with several impacted groups to define optimal use of RWE in decision-making, and have increasingly been incorporating RWE into our programs, the ITF represents a milestone as a first-of-its-kind, time-limited working collaboration and deliberation on sharing of industry-sponsored RWE with Health Canada and our organization.

The ITF demonstrates an innovative approach to improving access to evidence within the Canadian landscape. It discussed agreed-upon topics and themes (scope, transparency, operational requirements, privacy and intellectual property, and overall integration), over the course of 3 virtual meetings and 1 face-to-face meeting, to address various aspects of the existing PMDE query process. The ITF also deliberated on a collaboration model for sharing of evidence that could be implemented in the future.

Purpose

The purpose of the ITF was to provide formal advice to the PMDE program on questions related to operationalizing access to and use of industry-sponsored RWE.

This document is intended to capture the conversations and opinions of ITF members and does not represent an approved plan moving forward from our organization. Additional steps will be required —

The ITF demonstrates an innovative approach to improving access to evidence within the Canadian landscape.

including extensive feedback from patients, health decision-makers, and data holders, as well as an internal review — with consideration for how these proposed actions could be implemented.

This initiative contributes to a broader goal of understanding how industry-sponsored evidence could support postmarket decision-making.

Additional work toward this goal includes the development of a framework, which will include consultations with impacted groups, and identifying potential pilots to confirm the feasibility and utility of using industry-sponsored RWE. The aim is to incorporate some of the following considerations into the current PMDE process before the end of the year.

Considerations for Industry Engagement

Sharing RWE between manufacturers and the PMDE program appears to be feasible and desirable, and may be appropriate under certain conditions. Key considerations identified by the ITF are described according to each theme in Table 1.

Table 1

Summary of Considerations

Key considerations	Description
What types of RWE can be shared?	• A variety of RWE sources were identified. • There is a lack of consistency among datasets and availability will largely depend on the therapeutic area being studied. • An agreement between Canada's Drug Agency and manufacturers will be developed in advance of data-sharing to ensure timeliness.
Implications of ownership of RWE	• RWD is not always held or generated by industry; sharing requires clear articulation of the goals of how RWE will be used and consent from all data holders. • Regardless of the type of evidence shared, patient privacy will be a primary consideration throughout the process. With some data holdings, such as from PSPs, patients will often not have consented to have their data used to generate evidence for payer policies.

Key considerations	Description
What level of transparency is required?	• It is reasonable for our organization to report that evidence was requested from a manufacturer but could not be shared with us. We should also be clear about who was contacted and the rationale. • To ensure that the level of detail is acceptable to all parties, and similar to the previous Reimbursement Review process, manufacturers would like to retain the ability to redact information from PMDE reports. Our mandate is toward greater transparency. • Manufacturers indicated that evidence will only be shared if there is an adequate level of transparency around a research question and protocols used for PMDE queries as well as clarity on intended use of evidence and outcomes.
What are the operational requirements for sharing RWE?	• We already host a secure platform that allows confidential information to be transferred that is currently used for Reimbursement Reviews, and this appears to be a viable solution; direct sharing between manufacturers and research teams is challenging. • Confidentiality agreements will need to be in place between our organization, manufacturers, and research teams who will be accessing manufacturer-sponsored RWD, shared as RWE.
Refining the PMDE process	• Manufacturers have indicated interest in being involved throughout the PMDE query process from start to finish to reduce barriers to participation. • Depending on the customer's needs, consideration must be given to creating flexibility in PMDE timelines as they may impact the manufacturer's ability to participate.
Collaborative evidence generation for postmarket evaluation and decision-making	• There is a willingness by manufacturers to generate postmarket RWE collaboratively, between payers, our organization, Health Canada, and industry. • Collaborative evidence generation would need to be patient focused and enable appropriate access to pharmaceuticals; it will be difficult for manufacturers to engage in any process where PMDE customers cannot be transparent about the objectives and ultimate use of the evidence. • Reimbursement Reviews could be a good starting point to provide clear signals for manufacturers to collect RWD for future decision-making purposes.

PMDE = Post-Market Drug Evaluation; PSP = patient support program; RWD = real-world data; RWE = real-world evidence.

Proposed Actions

The ITF identified several actions that can inform how to operationalize access to and use of industry-sponsored RWE in the PMDE program described in Table 2.

Table 2

Proposed Actions for Operationalizing Use of Industry-Sponsored RWE

1. Strategies for sharing evidence

Action	Rationale	Who leads
1.1 We should provide manufacturers with multiple-use cases to describe hypothetical or real questions and responses to requests for evidence.	Multiple-use cases will contribute to a broad understanding of the types of questions and format of the evidence that may be useful to our organization.	Canada's Drug Agency
1.2 We should consider establishing optional upstream processes that involve exchanges between our organization, payers, and manufacturers as part of establishing an evidence-generation plan.	Early exchanges will lead to the most relevant industry–HTA interaction. This may require modifying processes outside of PMDE.	
1.3 We should outline expectations regarding legal requirements, data ownership and evidence publication plans, and other important factors that can help companies understand potential use requirements.	A thorough understanding of expectations can avoid unnecessary delays.	
1.4 Create specific wording within industry protocols and patient informed consent procedures (or other formal study documentation and legal agreements) about the potential of evidence-sharing with Canadian authorities beyond Health Canada (which may be status quo).	Pre-emptive clauses in industry-sponsored RWD can reduce barriers to access downstream.	Individual companies

2. Implications of using industry-sponsored evidence

Action	Rationale	Who leads
2.1 We should consider a process that involves manufacturers and alignment between all impacted groups when analyzing industry-sponsored evidence.	If different methodological approaches are used to analyze data, the rationale should be clear.	Canada's Drug Agency
2.2 We will need to consider revised timelines and feasibilities depending on the types of RWD sources (e.g., PSPs vs. chart reviews) required.	Not all evidence can be shared in a similar time frame.	
2.3 Explore and implement changes to the governance of data sources not initially intended for decision-making.	Some evidence may be valuable to decision-makers but require appropriate attention to privacy concerns.	Individual companies

3. Transparency

Action	Rationale	Who leads
3.1 A customizable template that addresses confidentiality and transparency should be developed to inform evidence-sharing agreements. This should outline a clear understanding of the scope and framework of evidence that will be required and its intended dissemination and use.	Understanding what terms are preferred will provide clear expectations and reduce delays.	Canada's Drug Agency
3.2 Revisit PMDE process timelines to consider how early and to what extent queries and associated PMDE query research protocols can be shared with industry partners.	Sharing of PMDE query research protocols will provide clear expectations and reduce delays.	
3.3 An agreed-upon list of reasons for not contacting or not sharing should be co-developed and approved by our organization and manufacturers participating in the PMDE process.	Transparency is important to bolster legitimacy but the reasons for contacting and sharing must be factual, clear, and free of judgment.	Canada's Drug Agency and individual companies
3.4 A process of redaction, similar to that used in the former Reimbursement Review process will be discussed further.	Manufacturers would like to retain the ability to redact information pertaining to evidence in PMDE reports. Our mandate is toward greater transparency.	
3.5 A publication process should be developed that outlines the involvement of industry as either reviewers or contributors in alignment with our existing authorship guidelines.	Adhering to a principle of transparency will aid in accountability and support the legitimacy of the process.	

4. Operationalization

Action	Rationale	Who leads
4.1 These issues should be further explored through discussion across impacted groups and within the activities of the Drug Data Services and Analytics team.	Specific details will require more highly specialized perspectives.	Canada's Drug Agency
4.2 Industry should consider sharing its own surveillance work and RWE activities before a Reimbursement Review.	Understanding what activities are under way will help us understand Canadian inventories of RWE assets and initiatives and where future queries may be addressed.	Canada's Drug Agency and individual companies

5. Refining the PMDE process

Action	Rationale	Who leads
5.1 Given the nature of the PMDE program, the process should be refined regularly.	Ensure these processes are impactful and are a means of continuous improvement.	Canada's Drug Agency
5.2 We should explore mechanisms to better anticipate future RWE queries that involve manufacturers, payers, and our organization at earlier stages of the drug review life cycle. Alternatively, this could happen after a recommendation is issued.	Anticipating queries will aid our organization and industry in being prepared to respond to payers.	

6. Additional opportunities for collaboration

Action	Rationale	Who leads
6.1 A standardized approach to creating questions for RWE studies should be considered.	This is a necessary starting point for prioritizing collaborative RWE studies.	Canada's Drug Agency
6.2 Feasibility and initiation of a pilot program with ongoing advice from manufacturers is recommended.	There is willingness to engage in a pilot program by both our organization and industry.	Canada's Drug Agency and industry

PMDE = Post-Market Drug Evaluation; PSP = patient support program; RWD = real-world data; RWE = real-world evidence.

The implications for the overarching PMDE process are outlined in Figure 1.

Figure 1

Considerations for Industry-Shared RWD in PMDE Query Process

Step	Description	Key considerations for Canada's Drug Agency and industry-sponsored RWE collaboration
1 Query submission	Query submission by senior health care decision-makers though a direct connection via email or through our request form. Entered in Central Intake.	Legal agreements addressing confidentiality, intended use and publication in place with participating manufacturers. Manufacturers will be involved with scoping to better understand purpose of sharing, feasibility, and availability of evidence.
2 Scoping and refinement	PMDE conducts initial scoping and refinement (2-6 weeks).	Manufacturers may not be able to participate for various reasons (e.g., timelines); we would publicize who was or was not contacted and the rationale for non-participation.
3 Query response team engagement and feasibility assessment	Kick-off meeting with PMDE, CoLab response team, and customer (feasibility assessed in advance / in parallel).	Collaboration focused on the research approach, objective of the query, research plan, and so on, between or across manufacturers facilitated by us. PMDE will determine if industry-sponsored RWE has added value beyond existing available evidence.
4 Delivery of draft protocols and plans	Protocol/statistical analysis plan (protocol posted for feedback through our online feedback process).	Patient consent and global approval will be challenging when it comes to sharing evidence and will depend on ownership of data.
5 Evidence generation and analysis	CoLab response team conducts the work.	Our existing secure transfer platforms will be used to share evidence between manufacturers, our organization, and CoLab.
6 Interpretation of evidence and findings	CoLab response team drafts report (draft posted for feedback through our online feedback process).	Manufacturers will review reports for accuracy and shareability of content. The goal is to follow the joint position statement between our organization, ICER, and NICE on redacting clinical evidence for publication.
7 Knowledge dissemination	Report is delivered to the customer and posted on our website. Additional visual summaries / tools created.	Involvement of manufacturer, including approach and scope of involvement will be publicized. The intent from our organization is to avoid redaction in final reports, with a mandate towards greater transparency.
8 Follow-up for impact	Follow-up with customer(s) and impacted groups.	Follow-up with customer(s) and impacted groups regarding how the evidence was used to inform decision-making.

ICER = Institute for Clinical and Economic Review; NICE = National Institute for Health and Care Excellence; PMDE = Post-Market Drug Evaluation; RWE = real-world evidence.

Further Considerations Beyond PMDE

The ITF provided key considerations for expanding opportunities to provide evidence from manufacturers. However, the task force recognized that the use and sharing of RWE could be further enhanced outside of the current PMDE process. Currently, private sector companies plan RWD generation much earlier to increase scientific knowledge and scientific exchange, as well as to meet the needs of internal teams (e.g., commercial teams) and a variety of externally impacted groups (e.g., health care providers and administrators, regulators, and private and public payers in Canada).

Discussions about evidence-generation considerations could take place during engagement in our Early Scientific Advice program and after the release of the Reimbursement Review recommendations report. We could consider creating a new forum such as a postsubmission meeting to address feedback from the process and prepare manufacturers and payers for addressing future PMDE queries.

Overall, the ITF agreed that a more streamlined approach to discussing evidentiary uncertainty beyond the Reimbursement Review process with our organization would be helpful for manufacturers. Currently, this is done on a case-by-case basis during a Reimbursement Review.

The task force recognized that the use and sharing of RWE could be further enhanced outside of the current PMDE process.

Terminology Used in This Report

Some terminology used in this report could be interpreted in different ways. The following concepts were discussed by the ITF.

RWD Versus RWE

"Data" has been defined as "information considered collectively, typically obtained by scientific work and used for reference, analysis, or calculation."[1] This definition does not distinguish between information from individuals or grouped observations, the analysis of this information, or even descriptive information about information (i.e., metadata).[2]

The ITF recognized that the term "real-world data" (RWD) could have multiple meanings even when it is more specifically defined as "data collected outside of traditional clinical trials."[3]

When referring to "data" or "real-world data" within this Summary Document, the ITF agreed that this encompasses industry-sponsored patient-level data. Sharing of individual patient data can be problematic due to the potential identification of patients.

When these data or RWD have been anonymized, aggregated, or summarized, this precludes individual patient identification. Once shared with our organization, it is deemed "real-world evidence" (RWE) and is termed as such throughout the document. The ITF agreed that neither raw data nor individual patient data would be requested or stored by our organization, nor would the data be shared by manufacturers.

Industry, Manufacturers, and Commercial Innovators

The ITF was asked to provide a perspective of private life-science companies that market medicines that are ultimately reimbursed through Canada's public insurance programs.

The term "manufacturers" is sometimes used synonymously with "industry" although it is recognized that not all companies manufacture the medicines they market (i.e., they may have licensing arrangements with other manufacturers).

Similarly, companies under the umbrella term "industry" may have other distinguishing characteristics such as ownership (public versus private), use of patents, type of medicines marketed (e.g., large versus small molecule, blood products, recombinant genes), and representation (member versus independent companies). Proposed actions for "industry" refer to all companies that may market medicines through public insurance programs, not simply the ITF.

Background

Context

RWE is playing an increasingly important role in health care policy and practice decision-making. Canada's Drug Agency was involved in developing the strategic framework for Canada's use of RWE to support decision-making, serving as chair of the collaborative Real-World Evidence Steering Committee. We have engaged with several impacted groups to support and provide guidance on the optimal use of RWE and have been adopting RWE in our programs to better respond to customer queries. RWE has increasingly been incorporated and considered, where appropriate, in Reimbursement Reviews, and has become an important tool in evaluating drugs across the drug life cycle when limited clinical trial data are available — especially for rare diseases and specific indications in oncology — and in assessing the effectiveness and safety of drugs in the real world.

As we continue to provide support and guidance on the optimal use of RWE in decision-making, and increasingly incorporate RWE into a variety of our programs, eliminating barriers to gain access to evidence is a necessary step to better respond to customer queries.

RWE and observational studies are a pillar in the postmarket space and have continued to gain interest in recent years, particularly in therapeutic areas with limited clinical trial data, to assess the effectiveness and safety of drugs.

The use of RWD in evaluating drugs is expected to be a key component for the future of drug evaluation at all stages.

The PMDE program was launched within our organization in September 2022. It is intended to provide evidence in response to queries from senior federal, provincial, and territorial decision-makers about the safety and effectiveness of drugs that have received regulatory approval and are broadly available to people in Canada.

PMDE queries are answered through CoLab, a network of experts in applied research, scientific methods, and data analysis. RWE is a key source of evidence that informs postmarket drug evaluations.

Recent international initiatives and research on the use of RWD and RWE in health care decision-making highlight the need for developments in data governance to enable appropriate sharing and usage of data, aggregate data, and evidence.[4-7] This includes data standardization and interoperability standards, as well as cross-sector collaboration to develop these.

Issue

Manufacturers and commercial developers of pharmaceuticals and biologics ("Industry") use and collect RWD for specific purposes, such as regulatory compliance. However, they are increasingly collecting and sponsoring the generation of RWD. The RWD may come from a variety of sources including chart reviews, clinical registries, longitudinal surveys, observational studies, and patient support programs (PSPs). Health data are often collected, analyzed, and stored in different ways — with different ownership arrangements and needs for patient privacy protection and patient consent — which can create barriers to sharing.

Despite this, manufacturers have expressed an interest in sharing aggregate data and evidence, where permissible, with HTA agencies and decision-makers to aid in further understanding the safety and effectiveness of their new treatments.

The PMDE program offers an ideal initial platform to explore the targeted sharing of RWE from industry-sponsored data to expand the availability of evidence for decision-makers.

Substantial work is needed to effectively operationalize access to and use of industry-sponsored RWE by health care decision-makers in Canada, who require data about utilization, safety, and effectiveness to inform public policy issues and health care decision-making. A starting point is constructive dialogue between industry and payers through HTA bodies, which can help improve public policy by bringing payers evidence from valuable industry data.

Approach

To address the issue, we convened an ITF for the first time, with representation from pharmaceutical and biologics manufacturers (n = 10), Health Canada (n = 1), and staff from Canada's Drug Agency (n = 5). We co-led the ITF with industry representatives, with deliberation led by an independent facilitator. While we have worked collaboratively over the years with several impacted groups to define optimal use of RWE in decision-making, and have increasingly been incorporating RWE into our programs...

...the ITF represents a milestone as a first-of-its-kind, time-limited working collaboration and deliberation on sharing of industry-sponsored RWE with Health Canada and Canada's Drug Agency.

It demonstrates an innovative approach to improving access to data and evidence within the Canadian landscape.

The ITF discussed agreed-upon topics and themes (scope, transparency, operational requirements, privacy and intellectual property, and overall integration), over the course of 3 virtual meetings and 1 face-to-face meeting, to address various aspects of the existing PMDE query process. The ITF also deliberated on a collaboration model for sharing of evidence that could be implemented in the future.

Purpose

The purpose of the ITF was to provide formal advice to the PMDE program on the questions related to operationalizing access to and use of industry-sponsored RWE.

This document is intended to capture the conversations and opinions of ITF members and does not represent an approved plan moving forward from our organization. Additional steps will be required — including extensive feedback from patients, health decision-makers, and data holders, as well as an internal CDA-AMC review — with consideration for how these proposed actions could be implemented.

This initiative contributes to a broader goal of understanding how industry-sponsored evidence could support postmarket decision-making. Additional work toward this goal includes the development of a framework, which will include consultations with impacted groups, and identifying potential pilots to confirm the feasibility and utility of using industry-sponsored RWE.

The aim is to incorporate some of the following considerations into the current PMDE process before the end of the year.

Approach to Deliberation and Advice

The approach to deliberation is reported according to guidance for terms of reference outlined in the Deliberative Processes for HTA Checklist.[8]

Need for Deliberation

The goals of the ITF were primarily to probe and explore underlying manufacturer perspectives, including how these may vary across organizations.

Ultimately the purpose of deliberation is to better understand what a collaborative approach between industry and our organization looks like and to provide feasible and relevant recommendations to Canada's Drug Agency and our PMDE Advisory Committee, a

multidisciplinary group that provides credible, strategic PMDE advice and expertise to our organization on queries, strategic initiatives, and key priority areas. The meetings primarily focused on how companies would interact with the PMDE process, although an additional meeting was held to discuss collaboration more broadly, including feasible interaction beyond the provision of data.

Guiding Principles

Meetings were held under the guiding principles of timeliness and inclusivity. The Chatham House Rule[9] was imposed to facilitate open discussion.

Who Was Involved?

The membership of the ITF included representatives from 10 private-sector life-science companies ("manufacturers"); 8 of these are active members of Innovative Medicines Canada and BIOTECanada, and 2 others are independent. Five representatives from Canada's Drug Agency and 1 representative from Health Canada also served on the ITF. The meeting was facilitated by an independent third-party facilitator with a history of working for both public-sector and private-sector life-science organizations. Co-leads from our organization and from industry were designated to help design meetings and review initial meeting summaries (refer to Table 3).

Representatives

- 10 representatives from private-sector life-science companies
- 5 representatives from Canada's Drug Agency
- 1 representative from Health Canada

Selection and Representation of Members

The ITF is a fixed-term membership. Independent companies responded to a public call on our website and underwent review and an interview process, while member companies were nominated by their respective industry associations. Each participant was asked to represent the views of their individual companies.

Meeting Format

Meetings were closed to the public and occurred both virtually and face-to-face. Questions were developed by the co-leads and facilitator before each meeting. ITF representatives could discuss answers to questions at the meeting and afterward through a postmeeting survey. Findings were then summarized and discussed further at each subsequent meeting.

No formal voting system was used to establish consensus. The consultation allowed for collaborative discussion about process beyond the provision of aggregate data as it pertained to PMDE queries. The process is outlined in Figure 2.

Table 3

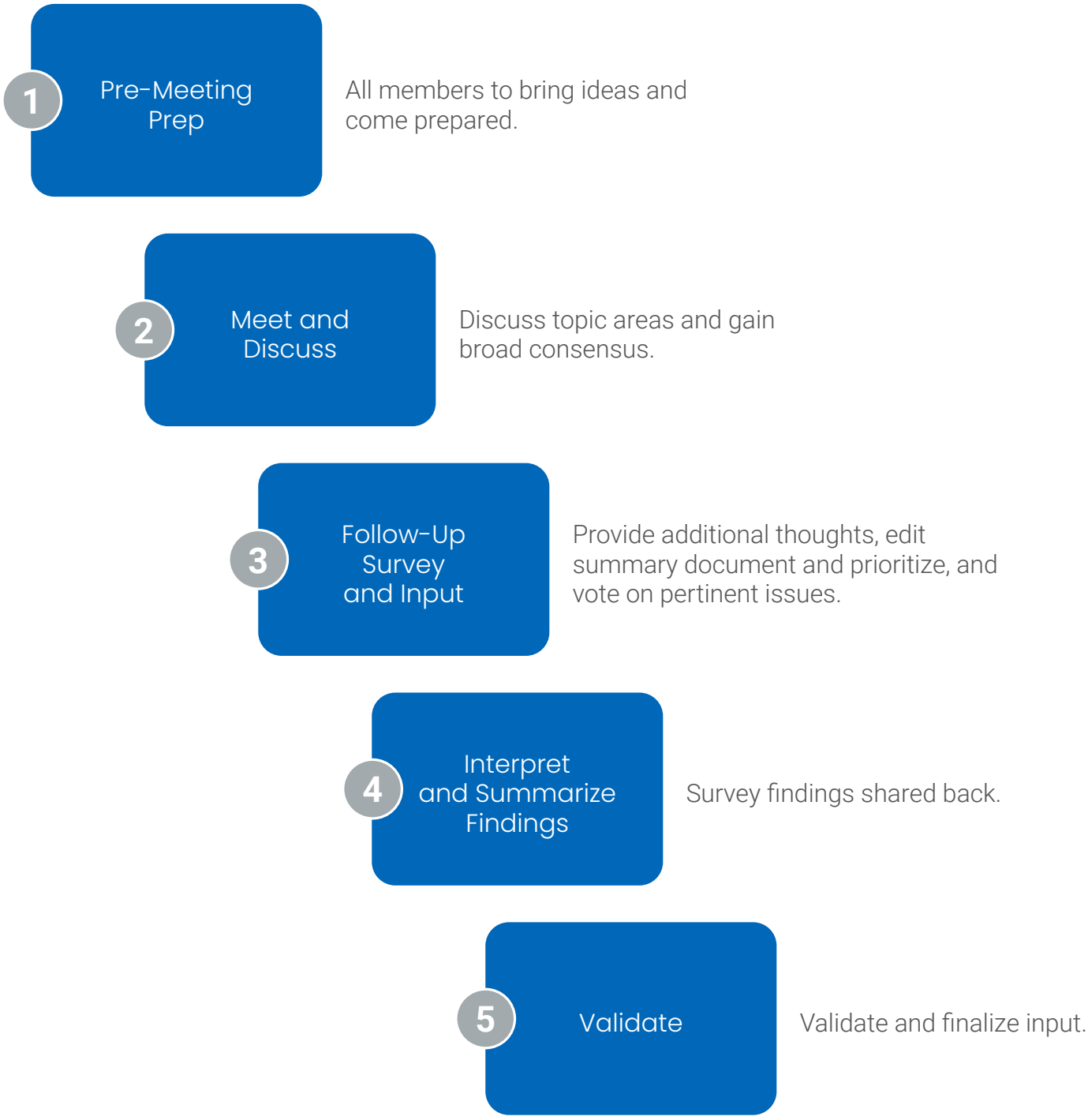
Composition of the ITF

ITF	Representatives	
Facilitator	• Don Husereau, Adjunct Professor, School of Epidemiology and Public Health, University of Ottawa	
IMC and BIOTECanada companies	• Jefferson Tea, Vice-President Medical and Scientific Affairs, Takeda • Jennifer Wu, Health Data Strategy Lead, Roche (meetings 1 to 3) • David Shum, Director, Strategic Access and Pricing, Roche (meeting 4) • Kevin Pollock, Director of Real-World Evidence, International Markets, Bristol Myers Squibb	• Jennifer Glass, RWE Lead Canada, Eli Lilly • Maria Luckevich, Health Economics Associate Director, Novo Nordisk • Nikolas Goyert-Stephens, Senior Manager, Market Access, Biogen • Subra Seshadri, Manager Access for Anti-Virals and Hospital Business, Pfizer • Virginie Giroux, Director, Health Economic and Outcomes Research, Merck (Co-lead)
Independent industry representatives (not IMC or BIOTECanada)	• Jason Lee, Head of Market Access and Stakeholder Relations, Amylyx	• Véronique Gaudet, Senior Manager, Real-World Evidence, Bausch Health, Canada Inc.
Health Canada	• Kelly Robinson, Director General, Marketed Health Products Directorate	
Canada's Drug Agency	• Tarry Ahuja, Director, PMDE (Co-lead) • Nadine Sulatycky, Manager, PMDE • David Stock, Scientific Advisor, PMDE	• Brendan McIntosh, Senior Drug Program Advisor, Pharmaceutical Reviews • Farah Husein, Director, Science and Methods
Other contributors from Canada's Drug Agency (as required)	• Heather Logan, Vice-President, Strategic Relationship Initiatives • Trish Caetano, Director, Drug Data Services and Analytics	• Peter Dyrda, Director, Pharmaceutical Policy and HTA

HTA = health technology assessment; IMC = Innovative Medicines Canada; ITF = industry task force; PMDE = Post-Market Drug Evaluation.

Figure 2

Approach to Deliberation of the Industry Task Force



Development and Organization of This Report

Meeting and survey summaries were developed by a member of our staff (Nadine Sulatycky, Manager, PMDE) and shared with ITF co-leads and the facilitator for comment before sending to the rest of the ITF for review before subsequent meetings.

Meeting and survey finding summaries were also shared with the ITF for feedback regarding accuracy and updated accordingly. Meeting and survey summaries were then used by the facilitator (Don Husereau) to develop the first draft of the report, which was in turn reviewed by co-leads, the PMDE Manager, and then ITF members for accuracy and completeness.

This report represents the findings of individual meetings, organized by report chapter.

Some of the language used to describe report chapter headings and questions has been modified from the original language used to improve clarity of understanding without altering meaning. Throughout the report, the terms "private-sector life-science companies," "manufacturers," "drug manufacturers," and "industry" are used interchangeably.

The report is organized as follows:

Chapter 1 explores what types of RWE are feasible to share.

Chapter 2 describes ownership of RWE and its implications for the PMDE process.

Chapter 3 explores what level of transparency is required and acceptable to industry.

Chapter 4 outlines operational requirements, including sharing platforms and conditions required for effective RWE sharing.

Chapter 5 proposes a new PMDE process that considers findings from sections 1-4.

Chapter 6 explores additional opportunities for collaboration between manufacturers and payers to generate RWE outside of the PMDE process.

Chapter 1

What Types of RWE Can Be Shared?

Summary

1. A variety of RWE sources were identified.
2. There is a lack of consistency among datasets and availability will largely depend on the therapeutic area being studied.
3. An agreement between Canada's Drug Agency and manufacturers will be developed in advance of data sharing to ensure timeliness.

Background

Manufacturers and commercial developers of pharmaceuticals and biologics ("industry") have an increasing interest to collect and use RWD.

These RWD may come from a variety of sources, including chart reviews, clinical registries, longitudinal surveys, primary data collection observational studies, and patient support programs. RWD are used to generate evidence for specific purposes, such as regulatory compliance. However, manufacturers are increasingly collecting and sponsoring the generation of RWD for research and market access purposes. The PMDE program is open to consider any RWE which could be of value to answer a specific query. These health data are often collected, analyzed, and stored in different ways and with different ownership and patient consent arrangements, which create barriers to sharing.

To facilitate an understanding of how aggregate data could be shared between industry partners and our organization, initial discussion centred on what types of data might be available, whether they are collected in a consistent manner, and whether they adhere to our (or other) guiding principles.

Specifically, ITF members discussed answers to the following questions:

1. What RWD sources are available to local (i.e., Canadian) affiliates?
2. What are barriers to and potential enablers for accessing the data?
3. Is there consistency across data sources for factors such as core outcomes, data structure, and governance?
4. Is there awareness of our RWE guiding principles?

1. What RWD Sources Are Available to Local (i.e., Canadian) Affiliates?

Several types of industry-specific sources of RWD were discussed and include:

Patient Support Programs

Patient support programs (PSPs) have been developed to help patients access specialized, often high-cost, medicines. PSPs in Canada are typically run by private third-party life-science organizations and funded by drug manufacturers. They may collect information required by insurers and regulators related to patient demographics, disease types, treatment patterns, patient-relevant outcomes, and discontinuation, but there are no standards for how they are structured and information is typically centred around a single therapeutic intervention. PSPs can also aid reimbursement navigation, administrative work for physicians, and injection services (including education on device use), and provide financial assistance or even

compassionate access to new drugs. PSPs are not routinely designed for research purposes. There are estimated to be more than 400 PSPs currently in place in Canada.[10,11]

Open-Label Extension Studies

Open-Label Extension Studies (OLEs) have been developed to aid long-term monitoring of safety and persistence. They are similar to the idea of phase IV clinical trials, although "extension" is usually offered to those who have successfully completed the follow-up period of a phase III trial.[12-14] Unlike PSPs, these studies are typically run globally, and local recruitment will depend on sites of the original phase III study.

Routine or Mandated Pharmacovigilance of Adverse Events

Harms data may be collected through a Health Canada– or EU-mandated risk management plan (in the US through a risk evaluation and mitigation strategy [REMS]) or simply through routine pharmacovigilance activities, which rely on spontaneous reporting to detect important signals of harm.[15]

Data Collected for Observational Studies

De novo observational studies are typically led by medical affairs or patient access departments of manufacturers. Primary data collection for these studies can generate evidence. They can aid in understanding drug effectiveness and safety issues not well addressed by clinical trials, either due to the exclusion of key factors (populations or procedures) not generalizable to local health care systems.[16-20] Observational studies may be prospective or retrospective in nature and refer to any noninterventional design including chart reviews and registries.

Data Summaries from Unpublished Reports

Manufacturers may conduct analyses and generate study reports from clinical trials, OLEs, or observational studies that contain aggregated summaries of data collected for these research purposes that are potentially informative for PMDE activities, but unavailable publicly.

Chart Reviews and Other Sources of Data

Manufacturers may also rely on data from paper or electronic medical records (i.e., chart reviews) or disease registries, to aid in understanding aspects of the disease not specifically related to use of their marketed drugs such as natural history, current or former treatment patterns, and discontinuation rates. While these studies are still "observational" in an epidemiologic sense, they may require less scrutiny by manufacturers because the clinical impact on patients is not in scope.

Registries

Patient registries may be local or global, and funded privately or publicly by any combination of patient, clinical, academic, or life-science organizations.[21,22] Observational studies intended to examine the impact of a new intervention may rely on data from patient registries.

2. What Are Barriers to and Potential Enablers for Accessing These Data?

Any access to data will require internal processes that relate to consent and privacy, contracting, permissions, costs, and manufacturer priorities. Depending on the size of the project (and budget involved) there could still be a need to obtain approval from the corporate executive team; however, for smaller initiatives, only approval at the country level may be required. Manufacturers may not have access to raw data but rather results of preplanned analyses. Importantly, the ITF agreed that neither raw data nor individual patient data would be requested or stored by our organization, nor would it be shared by manufacturers. Several themes emerged related to barriers and potential enablers of sharing data (see Table 4.)

Table 4

Barriers and Enablers to Sharing Aggregate Data or Evidence

Theme	Description of barrier	Solution
Consent and privacy	Data access must adhere to privacy laws and ethical frameworks in research; access is governed by strict SOPs and approval processes, and may only be available if anonymized and aggregated, and if no re-identification risk is posed (i.e., population size is sufficient).	Canada's Drug Agency would not be requesting raw, patient-level data, but instead aggregated or summarized data tables. If consent is required, it would need to be established a priori. This would likely require agreement between our organization, payers, and manufacturers around the time of (or before) a new drug submission.
Report availability	Manufacturers may have aggregate analyses in the form of private, commercial reports or draft or preprint publications. Some data (e.g., AEs) are routinely reported, but may not be analysed in aggregate by companies. Other data sources may not be report-ready and require new inquiry (e.g., postmarket databases) or will have results available at a set future date.	Reports will require company authorization to share; attempts should be made to engage manufacturers as early as possible in the query process and to partner with industry on solutions for timely and complete data reporting.
Variability of data	Evidence-generation programs will often have highly variable data quality, size, and follow-up. The amount of data may also depend on the resources available to (and size of) a manufacturer. Some data (such as dose adjustments) may not be captured by any source. Evidence-generation plans are reviewed and approved annually and cannot easily be modified once approved. Our organization indicated that a potential barrier is the confidentiality of certain requests received from the customer.	Providing companies with research questions as soon as possible can facilitate the timeliness of a response by providing manufacturers time to examine the feasibility of the request.
Cost to purchase	Companies may be faced with charges for commercial or government health care data, particularly if linking data about utilization, patients, and outcomes. Larger manufacturers may be better able to support data collection plans than smaller manufacturers.	Responsibility for associated costs related to data access will need to be addressed before company participation. Our organization has access to some government health care data.
Legal and rights	Companies may not own all data or analyses that are privy to them, as accessibility may be due to partnership agreements or through nondisclosure arrangements (e.g., manuscripts for submission to commercial publications).	Legal and rights issues will need to be addressed before company participation. Even awareness before an inquiry may improve the timeliness of a request.

HTA = health technology assessment; IMC = Innovative Medicines Canada; ITF = industry task force; PMDE = Post-Market Drug Evaluation.

3. Is There Consistency Across Data Sources for Factors Such as Core Outcomes, Data Structure, and Governance?

Like the secondary use of health care administrative datasets, many data sources available to manufacturers and their associated patient access teams were not designed to answer specific research questions.[23]

Due to the general inability to anticipate all potential research questions at the outset, even data sources developed for research purposes may also vary in their suitability to address specific PMDE-oriented objectives. As such, our organization should anticipate there may be inconsistent outcomes, data structures, or data governance across manufacturers.

The ITF indicated that data availability would be highly dependent on therapeutic areas or products being studied. Even clinical registries, which can be an important source of information about clinical outcomes of therapies, lack national operating principles to support registry best practice design, development, and implementation (as observed in the US and Australia).[22,24]

4. Is There Awareness of Our RWE Guiding Principles?

While there was awareness of our organization's RWE guiding principles, manufacturers indicated that these largely overlapped with Guidance for Good Pharmacoepidemiology Practices (GPP), developed by the International Society for Pharmacoepidemiology,[25] and other similar guidelines used as industry standards.

Table 5

Proposed Actions and Rationale for Chapter 1

Action	Rationale	Who leads
1.1 We should provide manufacturers with multiple-use cases to describe hypothetical or real questions and responses to requests for evidence.	Multiple use cases will contribute to a broad understanding of the types of questions and format of the evidence that may be useful to our organization.	Canada's Drug Agency
1.2 We should consider establishing optional upstream processes that involve exchange between our organization, payers, and manufacturers as part of establishing an evidence-generation plan.	Early exchange will lead to the most relevant industry-HTA interaction. This may require modifying processes outside of PMDE.	Canada's Drug Agency
1.3 We should outline expectations regarding legal requirements, data ownership and evidence publication plans, and other important factors that can help companies understand potential use requirements.	A thorough understanding of expectations can avoid unnecessary delays.	Canada's Drug Agency
1.4 Create specific wording within industry protocols and patient informed consent procedures (or other formal study documentation and legal agreements) about the potential of evidence-sharing with Canadian authorities beyond Health Canada (which may be status quo).	Pre-emptive clauses in industry-sponsored RWD can reduce barriers to access downstream.	Individual companies

HTA = health technology assessment; PMDE = Post-Market Drug Evaluation; RWD = real-world data.

Chapter 2

Implications of Ownership of RWE

Summary

1. RWD is not always held or generated by industry; sharing requires clear articulation of the goals of how RWE will be used, as well as consent from all data holders.
2. Regardless of the type of evidence shared, patient privacy will be a primary consideration throughout the process. With some data holdings, such as from PSPs, patients will often not have consented to have their data used to generate evidence for payer policies.

Background

Clinical trials for new drugs are typically sponsored by private-sector life-science companies; because registrational trials often represent innovation in medicine, the findings and existence of these trials are more often publicized.[26]

In addition to financing, clinical trial sponsors are responsible for trial design, ensuring high-quality conduct, safety of patients, and adherence to the International Good Clinical Practice (CGP) Standards, which include provisions for data governance that outline the rights and responsibilities of data holders.[27] This guidance seeks to balance the interests of impacted groups, ensuring scientific knowledge can be used by society to advance our understanding of medicine, while protecting patient privacy through protection of trial participant data.

Canada's Drug Agency describes RWD as information about the health of individuals or the delivery and/or outcomes of health care that is collected outside of traditional clinical trials, including routinely collected health care data or data collected specifically for study as outlined in chapter 1. Unlike clinical trials, studies based on RWD are less likely to be published[28] and there are no widely recognized international frameworks for RWD governance.[29] Instead, these frameworks tend to be country-specific and address risk management for health care stewards.[30] As interest in the use of RWD to inform policy decision-making is increasing, so have proposals to improve data governance strategies for RWD.[31,32]

Issues specific to ownership of data were explored, including the impact of ownership on the PMDE process, and to what extent these aggregated data, and subsequently RWE, can be analyzed using different approaches by our organization.

Specifically, ITF members discussed answers to the following questions:

1. What are the privacy issues to be considered for data-sharing and/or using data for purposes outside of the original intent?

   Can data or aggregated data be used for a PMDE query?

   What if different questions are asked than originally intended?
2. What is the role of patient rights and consent?
3. Who owns and has the right to share data?

1. What Are the Privacy Issues to be Considered for RWD-Sharing and/or Using Data for Purposes Outside of the Original Intent?

Our organization has indicated that we do not intend to request patient-level data; therefore, privacy and protection of individual patients should be less of an issue. Nonetheless, identifiability may still be a concern, particularly in disease areas such as oncology and rare diseases, due to the relatively small patient populations, even with aggregate data. Any requests for data

will still require manufacturers or data holders to determine the nature of our request (i.e., for what purpose) and level of risk before sharing. In some cases, data holders may suppress data when minimum patient sample thresholds are reached, for purposes of avoiding the risk of identification.

In Canada, protection of a patient's personal information by a private entity is governed by jurisdictional and federal privacy acts, such as the Personal Information Protection and Electronic Documents Act (PIPEDA) and Personal Health Information Protection Act (PHIPA). The Acts also contain provisions for the use of private data with knowledge or consent, including for research and consent when confidentiality is ensured and it is impracticable to obtain consent. Some RWD assets (such as data registries) may be owned by third parties (who determine access), with manufacturers either owning or co-owning research protocols, while others (e.g., observational studies, OLEs, PSPs) are typically industry-sponsored with manufacturers also making data-access decisions.

PSP Data

PSPs have been developed to help patients access specialized, often high-cost, drugs. These programs were not initially intended to collect data that could additionally benefit patients, but many companies have more recently explored approaches to doing so. As such, while a PSP program may collect necessary data, patients will often not have consented to have their data used for payer policies. Currently, industry may be unable to share PSP data (patient-level or aggregate) due to patient consent and global manufacturer approval issues. The intended use by PMDE will likely need to align with what was prespecified at the time of PSP establishment to receive internal approval for data-sharing. The ITF agreed that neither raw data nor individual patient data would be requested or stored by Canada's Drug Agency, nor would it be shared by manufacturers.

Analysis of Data by Canada's Drug Agency

The methodology of the data analysis would need to be shared with the manufacturer; similarly, industry data analysts may need to be involved with the analysis or in consultation with the PMDE Scientific Advisor. A necessary part of a PMDE approach involving industry would be for Canada's Drug Agency to be clear that findings are based on our approach to interpreting evidence and that we assume responsibility for our approach to analysis and our findings. Ideally, we work toward a process that involves manufacturers and alignment between all impacted groups when analyzing evidence shared by industry, so that any differences in analytic judgments (and their implications) are transparent and understood by those using the information.

2. What Is the Role of Patient Rights and Consent?

Retrospective observational study and chart reviews may not involve patient consent. In general, private-sector organizations may or may not have informed consent procedures related to the prospective collection of data, provided risks of identification are addressed. Historically, PSPs have had specific statements asking for patient consent, mainly for drug utilization purposes. For data registries, patients' rights need to be addressed on a case-by-case basis. Thus far, there has been significant variability in the use of data registries for PMDE queries, depending on the needs of the jurisdictions.

3. Who Owns and Has the Right to Share Data?

Internal approval for industry-owned and industry-sponsored data (i.e., OLEs, observational studies, PSPs) is protocol-driven and peer-reviewed. For most manufacturers, observational study concepts must first be reviewed, approved, and funded by global teams based on priority of the evidence gaps and available resources, then a detailed protocol must be internally peer-reviewed and approved ahead of study initiation. An important caveat is that all analyses and intended use (including dissemination plan) must be prespecified in the protocol.

The timeline of this could be long (> 6 months) and may not fit the PMDE query process. The approvals will also depend on who is analyzing the evidence, what the data analysis entails, and how critical the PMDE query is for the drug(s) of interest. Similarly, if data are co-owned, all involved parties would have to sign for the ownership, including the PMDE program, the manufacturer, and our organization. If the data are already in the public domain, there are no issues. If industry hires a vendor to do a landscape or horizon analysis, then industry either owns these data or has approval to share through a licensing agreement.

Table 6

Proposed Actions and Rationale for Chapter 2

Action	Rationale	Who leads
2.1 We should consider a process that involves manufacturers and alignment between all impacted groups when analyzing industry-sponsored evidence.	If different methodological approaches are used to analyze data, the rationale should be clear.	Canada's Drug Agency
2.2 We will need to consider revised timelines and feasibilities depending on the types of RWD sources (e.g., PSPs vs. chart reviews) required.	Not all evidence can be shared in a similar time frame.	Canada's Drug Agency
2.3 Explore and implement changes to the governance of data sources not initially intended for decision-making.	Some evidence may be valuable to decision-makers but require appropriate attention to privacy concerns.	Individual companies

PSP = patient support program; RWD = real-world data.

Chapter 3

What Level of Transparency Is Required?

Summary

1. It is reasonable for Canada's Drug Agency to report that evidence was requested from a manufacturer but could not be shared with us. We should also be clear about who was contacted and the rationale.
2. To ensure that the level of detail is acceptable to all parties, and similar to our previous Reimbursement Review process, manufacturers would like to retain the ability to redact information from PMDE reports. Our mandate is toward greater transparency.
3. Manufacturers indicated that evidence will only be shared with an adequately provided level of transparency around a research question and protocols used for PMDE queries as well as clarity on intended use of evidence and outcomes.

Background

There has been a more recent movement toward transparency and accountability in both government[33] and science.[34]

While open science and open government are intended to reduce falsification and enhance the legitimacy of decisions, there are still tangible barriers to achieving openness. Complete transparency by manufacturers may be seen as a barrier to competitiveness; complete transparency by government may create unnecessary political interference or security concerns for manufacturers. Sharing of evidence by publicly owned companies may also be considered a trade secret that can influence shareholder decisions to invest. However, many countries have already acknowledged the need for public over commercial interests in access to information laws.

We have expressed our commitment toward a guiding principle of transparency in our assessment of evidence to aid policy-makers. We have also committed to enhancing opportunities for partnership with industry and other key health care system contributors.

As the level of transparency is a key issue in sharing information between manufacturers and our organization, a more fulsome discussion on what level of transparency is desirable was undertaken.

Specifically, ITF members discussed answers to the following questions:

1. How do we ensure all required evidence is shared?
2. How do we report what data exist and are eligible for sharing?
3. How do we report reasons for not sharing data?
4. What level of detail is acceptable in a final PMDE report?

1. How Do We Ensure All Required Evidence Is Shared?

What Needs to Be Shared?

What needs to be shared will relate directly to the research questions developed by our organization to inform the policy questions posed to us through the PMDE Program. This would include RWD study protocols and analysis plans, as well as aggregated results in the form of tables or reports that do not risk identifying individual patients. There was general agreement that individual patient data will not be requested, nor would they be shared. It was also noted that sharing the rationale and objective of the query and policy questions will be helpful in defining the scope of what needs to be shared.

The majority of participants confirmed that they have internal policies that results are made public or shared whether they are positive, negative, or inconclusive. Not all results will be shareable or helpful because in some

cases, studies provide inconclusive results due to unanticipated low numbers, data quality issues, or other reasons. In some cases, the objective of these studies is purposefully exploratory.

Manufacturers indicated that RWE generated specifically to address a PMDE query would require sharing the PMDE query response draft protocol and the statistical analysis plan. However, there may also be additional circumstances (e.g., investigator-initiated studies where release of findings is not company-led) for which guarantees of nondisclosure will be necessary to enable sharing. It was suggested that these circumstances should be managed case-by-case, exploring the manufacturer's ability to share with our organization, asking investigators directly if this is not feasible.

The PMDE query process timeline can vary significantly, from 3-18 months, depending on the needs of the query. The delivery timelines are not self-imposed by the PMDE program; they are requested by the query customers so that they can make decisions in a timely manner. Members indicated that there may be challenges to sharing industry data within the query process timeline.

Protocols and Analysis Plans

Protocols and analysis plans are proprietary and typically not shared outside of those involved in the evidence generation. In a similar fashion to managing other sensitive pieces of information, if confidentiality of proprietary material can be guaranteed, approval to share study protocols can be more easily obtained. As indicated in chapter 1, manufacturers may follow internationally recognized good publication practices for pharmacoepidemiologic studies, which necessitate a "description of plans for disseminating and communicating study results, including the presence or absence of any restrictions on the extent and timing of publication."[35]

2. How Do We Report What Data Exist and Are Being Shared?

Transparency can refer to the existence of information, its properties, or the information itself.[36] Within manufacturers, there will be instances in which the existence of evidence can be shared but its details cannot be shared. Manufacturers indicated that sharing the information that a study exists, and the nature of the study (i.e., its design and objectives), should not be a problem.

There will be instances in which the existence of a study is not easily known without manufacturer engagement. Studies presented or published are in the public domain and can typically be identified in a systematic literature review if appropriate questions (stemming from a PMDE query) are asked; however, the existence of RWD studies that are unfinished,

unpublished, inappropriately indexed, or not registered may be difficult to ascertain without sponsor identification. Our organization indicated that even knowledge of a study's existence may be helpful, as it may prevent unnecessary scoping or duplication.

Transparency about study findings from manufacturers, in turn, will depend on several factors. As drug manufacturers may not be data owners, information that can be shared will depend on existing licensing agreements. There may also be constraints to releasing information to local affiliates, given the global nature of governance of multinational pharmaceutical companies. In some cases, manufacturers may have conducted studies that have dissimilar objectives to the questions being posed by PMDE customers and may judge the content of their study as not appropriate.

Similarly, manufacturers indicated that sharing will be hampered by imprecise or nontransparent research questions and protocols stemming from PMDE queries. Most companies indicated that internal approvals for sharing will depend on a clear statement of intended use and dissemination of information governed by a well-defined process. If study findings were unpublished and the dissemination to our organization had not been prespecified, companies would need to seek internal approval for protocol amendments that could take several months.

3. How Do We Report Reasons for Not Sharing Data?

It is reasonable for our organization to report that evidence was requested from a manufacturer but could not be shared. Some reasons why requested evidence may not be shared include availability being limited by licensing or intellectual property; no confidentiality guarantees; use of evidence for this purpose not being prespecified in the study protocol; perceived risk to countries outside of Canada, and requested timelines not being able to be met. Publicity regarding communication as to whether or not a company has shared evidence with PMDE should be communicated with context (i.e., beyond a simple yes or no). Additionally, manufacturers indicated that sharing of data will in part be dependent on the transparency of the research questions and protocols used for PMDE queries. There must also be clarity on intended use and dissemination of information governed by a well-defined process.

4. What Level of Detail Is Acceptable in a Final PMDE Report?

The primary intent of the PMDE query process is to produce a scientific report for policy-makers in Canada as soon as possible for decision-making; there is also a desire to make queries and reports publicly available on our website. Once policy-makers have used the report, CoLab researchers may optionally want to publish their work in academic journals. There may also be instances in which our organization conducts queries in conjunction with

another HTA body (such as the Institute national d'excellence en santé et en services sociaux [INESSS]), with the intent of having simultaneous co-publication.

While concerns have been raised in the past about premature data disclosure jeopardizing the ability to publish results in influential peer-reviewed journals,[37] these rules have more recently been exempted for the purpose of reporting to payers and regulators.[38] Additionally, our organization, along with the National Institute for Health and Care Excellence (NICE) and the Institute for Clinical and Economic Review (ICER), has more recently created a joint position statement on confidentiality of clinical evidence informing HTA decision-making. When this is applied to RWD, then "data from real-world evidence studies that has not been made publicly available and for which there is no plan for the data to become publicly available" can remain confidential.

If data provided by a manufacturer are shared in confidence and there is no intent by the manufacturer to publish (i.e., for commercial competitive purposes), there may be a desire by the manufacturer to have RWE used in confidence or its details redacted, to limit public disclosure of detailed findings by Canada's Drug Agency. This will be considered further by our organization, while maintaining that our mandate is toward greater transparency.

For manufacturers, publishing nonpublic data is often subject to a whole new set of internal checks and reviews. There is still interest from industry to publish results as collaborators and co-authors, following good publication practices.[39] Manufacturers would prefer to have the ability to review the content of publication and have PMDE acknowledge any contributing authors. Industry has suggested that our organization act in accordance with any decision made by the manufacturer, which may determine that industry-sponsored evidence should not be published.

If our organization intends to share data not already in the public domain, these data will be subject to far greater levels of scrutiny before being released by a sponsor. This is particularly true if information is shared that does not directly address the PMDE query, which points to the need for our organization to create well-defined requests for evidence with clear nonmodifiable study objectives. Some requests (e.g., utilization data), may be perceived as providing competitor intelligence. Anything that is in the public domain would be fair to include. If we are willing to keep confidential information out of the public domain, it will be much easier for sponsors to share it. Still, information that risks manufacturer competitiveness (e.g., international presentations) may be difficult to release, even if confidentiality agreements are in place.

To ensure that the level of detail is acceptable to all parties, and similar to our Reimbursement Review process, manufacturers would like to retain the ability to redact information from PMDE reports. This may be especially relevant when companies do not own the top-level rights to share aggregated findings from a RWD study.

Table 7

Proposed Actions and Rationale for Chapter 3

Action	Rationale	Who leads
3.1 A customizable template that addresses confidentiality and transparency should be developed to inform evidence-sharing agreements. This should outline a clear understanding of the scope and framework of evidence that will be required and its intended dissemination and use.	Understanding what terms are preferred will provide clear expectations and reduce delays.	Canada's Drug Agency
3.2 Revisit PMDE process timelines to consider how early and to what extent queries and associated PMDE query research protocols can be shared with industry partners.	Sharing of PMDE query research protocols will provide clear expectations and reduce delays.	Canada's Drug Agency
3.3 An agreed-upon list of reasons for not contacting or not sharing should be co-developed and approved by our organization and manufacturers participating in the PMDE process.	Transparency is important to bolster legitimacy but the reasons for contacting and sharing must be factual, clear, and free of judgment.	Canada's Drug Agency and industry
3.4 A process of redaction, similar to that used in the former Reimbursement Review program, will be discussed further.	Manufacturers would like to retain the ability to redact information pertaining to evidence in PMDE reports. Our mandate is toward greater transparency.	Canada's Drug Agency and individual companies
3.5 A publication process should be developed that outlines the involvement of industry as either reviewers or contributors in alignment with our existing Authorship Guidelines.	Adhering to a principle of transparency will aid in accountability and support the legitimacy of the process.	Canada's Drug Agency and industry

PMDE = Post-Market Drug Evaluation.

Chapter 4

What Are the Operational Requirements for Sharing RWE?

Summary

1. Canada's Drug Agency already hosts a secure platform that allows confidential information to be transferred, which is currently used for Reimbursement Reviews, and this appears to be a viable solution; direct sharing between manufacturers and research teams is challenging.
2. Confidentiality agreements will need to be in place between Canada's Drug Agency, manufacturers, and research teams who will be accessing manufacturer-sponsored RWD, shared as RWE.

Background

Sharing confidential or sensitive data between industry and our organization has practical challenges that relate to who has access, how data are transferred, where these data will be stored, and what safeguards need to be in place.

Once the scope (types of studies and level of transparency) for sharing has been agreed to, these operational challenges must be addressed to fully integrate manufacturers into the PMDE process. While much progress has been made in the last decade with regard to the sharing of clinical trial data, sharing protocols may be less developed but benefit from similar underlying principles.

In Canada, both Health Canada and Canada's Drug Agency have extensive experience with the receipt of confidential commercial information from the pharmaceutical industry. There are also significant advances in information technology and communication solutions to aid in safeguarding sensitive information. Understanding exactly how evidence can be shared is an important aspect of developing a PMDE process that involves manufacturers. To address this, a discussion regarding operational requirements was undertaken.

Specifically, ITF members discussed answers to the following questions:

1. How have databases been structured and who has access?
2. How will data be shared and where will the data be held?
3. What safeguards need to be in place?
4. How long will it take to access the data?

1. How Have Databases Been Structured and Who Has Access?

In Canada, RWD governance and stewardship are typically managed by an independent third-party data holder with the manufacturer providing oversight assets. Manufacturers often work with data holders who have limited funding and may also partner with for-profit and not-for-profit organizations. These arrangements will vary by drug and therapeutic area. Internationally, this will differ country by country. Data holders or owners will adhere to their own infrastructure and legal requirements.

2. How Will Data Be Shared and Where Will the Data Be Held?

Our organization already hosts a secure platform that allows confidential information to be transferred for Reimbursement Reviews. This platform has already been approved by manufacturers for this purpose. Although we work with vetted, third-party research teams, direct sharing between manufacturers and research teams is challenging. For some manufacturers,

it is preferable for our organization to hold industry evidence with our current safeguards and, in turn, provide access to research teams; however, other manufacturers suggested that the facilitation of data transfer by our organization will not reduce the number of necessary approvals.

3. What Safeguards Need to Be in Place?

Confidentiality agreements will need to be in place between our organization and research teams who will be accessing the evidence shared by the manufacturer(s). To facilitate sharing, we would (at minimum) also need to be responsible for vetting these teams throughout each query. We will need to explore whether our current contracts with these teams require changes. While the sharing of individual patient-level data would heighten these requirements, there was general agreement that individual patient data will not be requested, nor would the data be shared; in addition, neither PMDE nor the manufacturers believed sharing these data was currently feasible.

Patient consent and the risk of identification is another important consideration for evidence-sharing. The risk of patient re-identification is a particular challenge in smaller patient populations, such as oncology and rare diseases, even when aggregate data are shared. Manufacturers or data holders may need to determine the level of risk before sharing. Some governments are now requiring routine surveillance of patient data for safety, regulatory purposes, or policy-making, and we are currently exploring ways in which we could access this evidence, which may minimize challenges with access to industry-sponsored data.

4. How Long Will It Take to Access the Data?

The vetting process for most manufacturers is unlikely to be completed within PMDE query timelines. The ability to transfer data in a timely fashion will depend on who owns the data, the volume of data, how frequently the data will be shared (periodically versus 1 time), geographic restrictions (e.g., some data owners require the data to be held within the region the data originated from), and type of data (e.g., aggregate versus individual-level data, text versus images, and so on). In most scenarios, technical infrastructure challenges are solvable, but legal and compliance issues will be a larger issue.

As the timeline surrounding the query process may create limitations in being able to access shared evidence, earlier industry engagement will assist in creating efficiencies in this process. Our Horizon Scan efforts will likely create awareness of policy priorities and the potential for future queries and will allow identification of emerging issues that could be addressed by PMDE. This, in turn, may allow time to ensure agreements with appropriate safeguards are already in place. Typically, stewardship and safeguards surrounding RWD holdings are

influenced by a variety of factors, including number of patients, number of variables collected, and length of studies. Larger assets may have more procedures in place and require more time to access. This means access times for new queries could vary from weeks to years.

Table 8

Proposed Actions and Rationale for Chapter 4

Action	Rationale	Who leads
4.1 These issues should be further explored through discussion across impacted groups and within the activities of the Drug Data Services and Analytics team.	Specific details will require more highly specialized perspectives.	Canada's Drug Agency
4.2 Industry should consider sharing its own surveillance work and RWE activities before Reimbursement Review.	Understanding what activities are under way will help our organization understand Canadian inventories of RWE assets and initiatives and where future queries may be addressed.	Canada's Drug Agency and individual companies

RWE = real-world evidence.

Chapter 5

Putting It All Together: Refining the PMDE Process

Summary

1. Manufacturers have indicated interest in being involved throughout the PMDE query process from start to finish to reduce barriers to participation.
2. Depending on a customer's needs, consideration must be given to creating flexibility in PMDE timelines, as they may impact the manufacturer's ability to participate.

Background

The mandate of the PMDE program is to provide evidence to decision-makers and regulators in Canada through commissioned research partners in Canada.

Central to the PMDE program are not-for-profit RWD research teams (which make up the CoLab research network) that have their own data or have direct access to data (e.g., jurisdictional administrative data).

The teams are further divided into core network partners (granted) and collaborators (contracts). PMDE also accesses data from holders such as the Canadian Institute for Health Information (CIHI), Merative MarketScan, and Clinical Practice Research Datalink (CPRD). Currently, CoLab comprises 4 core network partners and 4 network collaborators (additional information available on the CoLab website).

The PMDE query process can be broken down into 8 steps (Figure 3).

Specifically, ITF members discussed answers to the following questions:

1. When in the postmarket evaluation process could industry be involved and what role could they play?
2. What are perceived risks from a manufacturer's perspective?
3. How can decision-maker needs be better anticipated?

Figure 3

The PMDE Query Process

Step		Description
Query submission	1	Query submission by senior health care decision-makers though a direct connection via email or through our request form. Entered in Central Intake.
Scoping and refinement	2	PMDE conducts initial scoping and refinement (2 to 6 weeks).
Query response team engagement and feasibility assessment	3	Kick-off meeting with PMDE, CoLab response team, and customer (feasibility assessed in advance or in parallel).
Delivery of draft protocols and plans	4	Protocol and statistical analysis plan (protocol posted for feedback through our online feedback process).
Evidence generation and analysis	5	CoLab response team conducts the work.
Interpretation of evidence and findings	6	CoLab response team drafts report (draft posted for feedback through our online feedback process).
Knowledge dissemination	7	Report is delivered to the customer and posted on our website. Additional visual summaries and tools created.
Follow-up for impact	8	Follow-up with customer(s) and impacted groups.

PMDE = Post-Market Drug Evaluation.

There are 2 streams of PMDE queries: proactive and reactive. Reactive queries are those submitted by decision-makers, whereas proactive queries are identified by PMDE. Proactive queries are identified through drug pipeline evaluation and horizon scanning. They are intended to anticipate downstream policy questions facing health system decision-makers whose feedback is solicited to inform topic prioritization.

The types of queries submitted to PMDE vary greatly but can include questions around utilization (better understanding of uptake), formulary management, health economics or budget impact analysis, and evidence reviews. Year 1 of the program was a proof-of-concept period and, as query reports are completed and shared, it is anticipated this will drive further demand.

1. When in the Postmarket Evaluation Process Could Industry Be Involved and What Role Could They Play?

Given the potential for delays, due to manufacturer internal processes and the risk of timeliness being a barrier to participation, there was general consensus that industry should be involved as early as possible, ideally at the scoping and refining phase. However, it was recognized that earlier engagement (e.g., at the presubmission or early advice stage) would be better.

Industry members suggested involving industry from start to finish of the query process. This includes during the preliminary phases, when it would also allow industry to do an internal assessment of feasibility and what RWD are available, all the way to dissemination of findings, when they can be involved in the review process. A summary of considerations is provided in Figure 4.

Figure 4

Considerations for Industry-Shared RWD in PMDE Query Process

Step	Key considerations for Canada's Drug Agency and industry-sponsored RWE collaboration
Query submission	1 Legal agreements addressing confidentiality, intended use and publication in place with participating manufacturers. Manufacturers will be involved with scoping to better understand purpose of sharing, feasibility, and availability of evidence.
Scoping and refinement	2 Manufacturers may not be able to participate for various reasons (e.g., timelines); we would publicize who was or was not contacted and the rationale for nonparticipation.
Query response team engagement and feasibility assessment	3 Collaboration focused on the research approach, objective of the query, research plan, and so on, between or across manufacturers facilitated by us. PMDE will determine if industry-sponsored RWE has added value beyond existing available evidence.
Delivery of draft protocols and plans	4 Patient consent and global approval will be challenging when it comes to sharing evidence and will depend on ownership of data.
Evidence generation and analysis	5 Our existing secure transfer platforms will be used to share evidence between manufacturers, our organization, and CoLab.
Interpretation of evidence and findings	6 Manufacturers will review reports for accuracy and shareability of content. The goal is to follow the joint position statement between our organization, ICER, and NICE on redacting clinical evidence for publication.
Knowledge dissemination	7 Involvement of manufacturer, including approach and scope of involvement will be publicized. The intent from our organization is to avoid redaction in final reports, with a mandate towards greater transparency.
Follow-up for impact	8 Follow-up with customer(s) and impacted groups regarding how the evidence was used to inform decision-making.

ICER = Institute for Clinical and Economic Review; NICE = National Institute for Health and Care Excellence; PMDE = Post-Market Drug Evaluation; RWE = real-world evidence.

2. What Are Perceived Risks From a Manufacturer's Perspective?

Some perceived risks could include unclear research plans, lacking sufficient detail on data handling, misaligned proposed analyses, or unclear intentions around publication of results. These may result in lengthier manufacturer approval processes and/or hesitancy in providing data that may be sensitive or complex.

Clearly articulated processes and expectations pertaining to use and dissemination of RWE is crucial to promote effective RWE partnership between industry and our organization.

There was consensus that manufacturers have the right to refuse to participate in our projects for a multitude of reasons, and there was general agreement that we would share the refusal and an agreed-upon rationale of the refusal in its reports. While manufacturers may be concerned about the reputational impact of refusing to participate, this would also likely depend on the reason for refusing or not providing a rationale; ultimately, there are no tangible repercussions for manufacturers who cannot or will not participate in the process.

Manufacturers also suggested some consideration is needed regarding the flexibility of PMDE timelines, as they may be unrealistic and impact a manufacturer's ability to participate. Timing and ability to participate will also be influenced by the resources available to manufacturers, with some manufacturers not being able to prioritize resources for participation, particularly smaller companies. It is acknowledged, however, that these timelines are ultimately dictated by the needs of policy-makers; based on experience, however, the PMDE team believed there could be flexibility if valuable additional data could be made available.

Manufacturers may also know other entities with published work in the specific therapeutic area and could direct our organization to these resources. Manufacturers also suggested it would be helpful for them to know what the historical challenges have been for our other processes, as they may be similar to the PMDE program. Industry will also need to better understand the outcomes and impacts of PMDE work as this further develops so they can better gauge the risks of engagement.

3. How Can Decision-Maker Needs Be Better Anticipated?

Engaging industry about postmarket evidence needs at the presubmission stage for Reimbursement Reviews would likely allow for better opportunities to collect evidence of relevance. Industry has concerns about the impact of sharing evidence with PMDE in the event that this evidence could be leveraged for reimbursement reassessment, which could impact initial recommendations. Another suggestion was made to have these conversations after Reimbursement Review but with the involvement of payers, which would be more compelling for getting approvals for participation. Some of this is explored further in chapter 6.

Table 9

Proposed Actions and Rationale for Chapter 5

Action	Rationale	Who leads
5.1 Given the nature of the PMDE program, the process should be refined regularly.	This ensures that these processes are impactful, and a means to continuous improvement.	Canada's Drug Agency
5.2 We should explore mechanisms for better anticipating future RWE queries that involve manufacturers, payers, and our organization at earlier stages of the drug review life cycle. Alternatively, this could happen after a recommendation is issued.	Anticipating queries will aid our organization and industry in being prepared to respond to payers.	Canada's Drug Agency

PMDE = Post-Market Drug Evaluation; RWE = real-world evidence.

Chapter 6

Collaborative Evidence Generation for Postmarket Evaluation

Summary

1. There is a willingness by manufacturers to generate postmarket RWE collaboratively, between payers, Canada's Drug Agency, Health Canada, and industry.
2. Collaborative evidence generation would need to be patient-focused and enable appropriate access to pharmaceuticals; it will be difficult for manufacturers to engage in any process in which PMDE customers cannot be transparent about the objectives and ultimate use of the evidence.
3. Reimbursement Reviews could be a good starting point to provide clear signals for manufacturers to collect RWD for future decision-making purposes.

Background

As outlined in chapters 1 to 5, the PMDE process seeks to involve manufacturers in identifying and sharing RWE that may be useful for postmarket decision-making.

There may be barriers to meaningful participation due to the process and timelines. Additionally, the PMDE approach assumes that private-sector manufacturers may be collecting data for their own purposes that also happen to align well with the needs of health care systems and policy-makers.

A more optimal approach would be to align data generation requirements for private companies and public health care programs by design rather than happenstance. That is, private and public sector health care contributors would engage in a collaborative approach to RWD generation. The ITF was asked to explore what factors might enable collaborative data generation in a postmarket space.

Specifically, ITF members discussed answers to the following questions:

1. Is there a willingness to generate postmarket RWD collaboratively?
2. What factors would enable collaborative RWD generation?
3. What alternative pathways or programs may help generate RWD collaboratively?
4. What are some barriers or instances in which collaborative data generation will be challenging or unfeasible?
5. Are there opportunities to trial development of postmarket RWD collaboratively?

1. Is There a Willingness to Generate Postmarket RWD Collaboratively?

ITF participants stated a willingness to generate postmarket RWD collaboratively, between payers, Canada's Drug Agency, Health Canada, and industry. However, private-sector companies will need to have a clear understanding of what the goals, process, and ultimate use of RWD findings are. There may be particular therapeutic areas where collaborative data generation makes more sense for all interested groups including common disease areas, given common uncertainties that, if resolved, could lead to more benefits for patients.

2. What Factors Would Enable Collaborative RWD Generation?

Collaborative RWD generation will need to be patient-focused.[40] Some key factors suggested to enable collaborative RWD generation include:

- formal agreements (e.g., nondisclosure agreements [NDAs], as well as terms and conditions for internal review toward contracts)
- adoption of scientific standards or frameworks that dictate the judgment that will be used to interpret analyses from RWD, such as NICE standards[41]

- collaborative assessment of feasibility
- ensuring consent was obtained for intended usage of data
- query plans and clear assignment of roles (i.e., who is conducting the analysis; if from an academic database, then the specific institution may need to be engaged to do analyses and reporting; if from a PSP database, the PSP vendor may need to conduct analysis or agree to a third-party vendor)
- collaborative query-related research protocol development
- operational processes for data-sharing and analyses
- alignment on how findings will be publicized (including redaction)
- alignment on whether our organization and/or decision-makers will accept an analysis report or aggregated and/or analyzed data, or require patient-level data or ability to audit individual records (e.g., for quality assurance). Our mandate is toward greater transparency.

3. What Alternative Pathways or Programs May Help Generate RWD Collaboratively?

Early understanding of the gaps in evidence would be the most beneficial from industry's perspective; there may be a need for postmarket data during drug pricing negotiations. Our Drug Data and Analytics team is working on proactively identifying patient registries, particularly for rare diseases. The team is also helping patient registries become useful for pricing negotiations by positioning the registries to collect data prospectively.

Manufacturers may also have opportunities to broaden PSP patient consent procedures, include data-sharing specifically for postmarket evaluation.

A recurring theme in discussing how to expand the current PMDE process was the need to establish patient consent a priori, based on agreements between our organization, payers, and manufacturers around the time of (or before) a submission for a new drug enters Reimbursement Review.

Further work between Canada's Drug Agency and the ITF could help map the current pathways for RWE development and look for opportunities to involve payers in the process. Exchange with patients during a PMDE query process or new collaborative process was seen as a way of improving the capture of RWD and the generation of evidence.

Discussions regarding considerations for evidence generation could occur during engagement in the Early Scientific Advice program and at the stage of writing recommendation reports in Reimbursement Reviews. The presubmission meeting was also suggested but it may not be as helpful to have discussions, as it may be too early for producing postmarket evidence.

During these discussions, it was further suggested that co-created plans to generate RWE at the time of Reimbursement Review may be a pragmatic approach to our current time-limited

recommendation process. The current process leaves patients without access to potentially valuable therapies due to evidentiary uncertainty, but at the same time Canadian RWD cannot be generated without coverage. RWD generation with the intent of satisfying time-limited recommendations may be a natural solution. Comprehensive summaries of if and how RWE could reduce uncertainty in Reimbursement Reviews could be a good starting point and provide clear signals for manufacturers.

A multidisciplinary postrecommendation meeting, when appropriate, could then better facilitate alignment of the evidence-generation strategy with the uncertainties identified by our organization and payers. If relevant questions in the PMDE space could be anticipated, industry could remove barriers to sharing generated evidence a priori by prespecifying intended use and audience in study protocols. Understanding how aligned the PMDE reactive queries are to the identified areas of uncertainty in our recommendations report could be a good place to start when trying to assess feasibility or attractiveness of a postrecommendation meeting. The process would be aided by agreement across all impacted groups regarding the reimbursement outcomes that could be achieved, depending on the results of evidence-generation activities.

There may also be lessons from other jurisdictions including the use of federated analyses (e.g., DARWIN[42] and EHDEN[43,44]), the use of agreed-upon third parties to conduct analyses, and the use of RWD to inform coverage with evidence development[45] or time-limited recommendations.

4. What Are Some Barriers or Instances in Which Collaborative Data Generation Will Be Challenging or Unfeasible?

Beyond availability and feasibility of providing data at all or within a certain period, a key barrier will be intent of use; it will be difficult for manufacturers to engage in any process where PMDE customers cannot be transparent about the objectives and ultimate use of the data. Ultimately, RWD generation is an investment by industry partners intended to satisfy clinical, regulatory, or payer policy objectives. RWD generation must be undertaken with a clear understanding about how the data will be used or disclosed. These are necessary details for collaborative data generation.

Other commonly mentioned barriers include legal concerns (this will be problematic at some companies, and global approvals may be a limiting factor); the potential for technical disagreements on study design, protocol, and methods; lack of resources to participate or costs of participating; corporate or research ethics challenges; historical reliability and lack of accountability for academic or clinical stewards for timely deliverables; and how information will be publicized. One participant suggested that even if collaborative generation of RWD in Canada is a good idea, there may be other international jurisdictions where RWD generation is met with fewer barriers.

5. Are There Opportunities to Trial Development of Postmarket RWD Collaboratively?

Given the breadth of therapeutic areas and different manufacturers in this space, creating innovative pilot programs in this space should be feasible. Selection of companies should be based on a transparent process, with companies presented with an opportunity to opt in to a pilot project, as either core participants or advisors. Considerations should be given to how the learnings from a trial project can be disseminated to other contributors in the ecosystem, and how the process can be adapted from the insights gained.

Queries focused on ensuring equity of access, especially to traditionally marginalized populations, were identified as priority areas where RWE would provide benefit and opportunity. RWE could help with expanding access to these populations under the condition of collecting data to better understand uptake or utilization and impact. Many of these subpopulations are not well represented in randomized controlled trials; so, potentially, the only way to study this is through RWE generation.

For industry, any research collaboration that improves access or streamlines reimbursement criteria for a product will be much easier to implement and commit resources to versus collaborative projects that have no impact on how patients are treated. This means studies of testing or diagnosis rates, or health resource utilization, may be far less attractive than those that look at outcomes related to access to therapy.

A good starting point would be for industry to leverage our drug review process, where guidance and feedback could be provided on specific study questions that could be addressed by RWE. Given the current federal focus on rare diseases, and associated uncertainties with these, there may be more willingness for manufacturers to collaborate and commit resources to RWD projects if this allowed for special market access for the study.

Table 10

Proposed Actions and Rationale for Chapter 6

Action	Rationale	Who leads
6.1 A standardized approach to creating questions for RWD studies should be considered.	This is a necessary starting point for prioritizing collaborative RWD studies.	Canada's Drug Agency
6.2 Feasibility and initiation of a pilot program with ongoing advice from manufacturers is recommended.	There is willingness to engage in a pilot program by both our organization and industry.	Canada's Drug Agency and industry

RWD = real-world data.

References

1. <eref>Oxford English Dictionary. Data. 2012; https://www.oed.com/dictionary/data_n?tl=true. Accessed 2024 Apr 28.</eref>
2. <jrn>Maclure M, Schneeweiss S. Causation of bias: the episcope. *Epidemiology*. 2001;12(1):114-122. Medline</jrn>
3. <eref>Real-world evidence: a primer. Ottawa (ON): CADTH; 2024: https://www.cadth.ca/real-world-evidence-primer. Accessed 2024 Apr 28.</eref>
4. <jrn>Husereau D, Nason E, Ahuja T, Nikaï E, Tsakonas E, Jacobs P. Use of Real-world data sources for Canadian drug pricing and reimbursement decisions: stakeholder views and lessons for other countries. *Int J Technol Assess Health Care*. 2019;35(3):181-188. Medline</jrn>
5. <jrn>Capkun G, Corry S, Dowling O, et al. Can we use existing guidance to support the development of robust real-world evidence for health technology assessment/payer decision-making? *Int J Technol Assess Health Care*. 2022;38(1):e79. Medline</jrn>
6. <jrn>Hogervorst MA, Pontén J, Vreman RA, Mantel-Teeuwisse AK, Goettsch WG. Real world data in health technology assessment of complex health technologies. *Front Pharmacol*. 2022;13:837302. Medline</jrn>
7. <jrn>Makady A, Ham RT, de Boer A, et al. Policies for use of real-world data in health technology assessment (HTA): a comparative study of six HTA agencies. *Value Health*. 2017;20(4):520-532. Medline</jrn>
8. <jrn>Oortwijn W, Husereau D, Abelson J, et al. Designing and implementing deliberative processes for health technology assessment: a good practices report of a joint HTAi/ISPOR Task Force. *Value Health*. 2022;25(6):869-886. Medline</jrn>
9. <eref>Chatham House. Chatham House Rule. 2022; https://www.chathamhouse.org/about-us/chatham-house-rule. Accessed 2024 Mar 04.</eref>
10. <jrn>Wills A, Mitha A, Cheung WY. Data collection within patient support programs in Canada and implications for real-world evidence generation: the authors' perspective. *J Pharm Pharm Sci*. 2023;26:11877. Medline</jrn>
11. <jrn>Sarp S, Reichenbach R, Aliu P. An approach to data collection in compassionate use/managed access. *Front Pharmacol*. 2022;13:1095860. Medline</jrn>
12. <jrn>Hemming K, Hutton JL, Maguire MJ, Marson AG. Open label extension studies and patient selection biases. *J Eval Clin Pract*. 2008;14(1):141-144. Medline</jrn>
13. <jrn>Weatherall M, Burgess C, Taylor W. Open-label extension studies. *Int J Pharm Med*. 2007;21(2):115-120.</jrn>
14. <jrn>Taylor GJ, Wainwright P. Open label extension studies: research or marketing? *BMJ*. 2005;331(7516):572-574. Medline</jrn>
15. <eref>About good pharmacovigilance practices (GVP) inspections. Ottawa (ON): Health Canada; 2016: https://www.canada.ca/en/health-canada/services/inspecting-monitoring-drug-health-products/drug-health-product-inspections/about-good-pharmacovigilance-practices-gvp-inspections.html. Accessed 2024 Feb 28.</eref>
16. <jrn>Black N. What observational studies can offer decision makers. *Horm Res*. 1999;51 Suppl 1:44-49. Medline</jrn>
17. <jrn>Robinson H. Re: "Causality inference in observational vs. experimental studies: an empirical comparison." *Am J Epidemiol*. 1989;130(1):206-209.</jrn>
18. <jrn>Concato J. Observational versus experimental studies: what's the evidence for a hierarchy? *NeuroRx*. 2004;1(3):341-347. Medline</jrn>
19. <jrn>Kunz R, Khan KS, Neumayer HH. Observational studies and randomized trials. *N Engl J Med*. 2000;343(16):1194-1195; author reply 1196-1197. Medline</jrn>
20. <jrn>Dunn G. Can we obtain credible estimates of the causal effects of interventions from non-randomized trials (observational studies or so-called quasi-experiments)? *Crim Behav Ment Health*. 2005;15(2):123-125. Medline</jrn>
21. <bok>Brooke EM, World Health Organization. The current and future use of registers in health information systems. Geneva (CH): World Health Organization; 1974: https://iris.who.int/handle/10665/36936. Accessed 2024 Jun 04.</bok>
22. <edb>Gliklich RE, Leavy MB, Dreyer NA, editors. Registries for evaluating patient outcomes: a user's guide. 4th ed. Rockville (MD): Agency for Healthcare Research and Quality; 2020: https://www.ncbi.nlm.nih.gov/books/NBK562575/pdf/Bookshelf_NBK562575.pdf. Accessed 2024 Jun 04.</edb>
23. <jrn>Sarrazin MSV, Rosenthal GE. Finding pure and simple truths with administrative data. *JAMA*. 2012;307(13):1433-1435. Medline</jrn>
24. <eref>Simmonds F, Jones L, Berger M, Tazelaar-Molinia J, Zhang M. Australian clinical quality registries project for ACS&QHC: final report Wollongong (AU): Centre for Health Service Development, University of Wollongong; 2009: https://ro.uow.edu.au/ahsri/494/. Accessed 2024 Jun 04.</eref>
25. <eref>International Society for Pharmacoepidemiology (ISPE). VII. Archiving. In: Guidelines for good pharmacoepidemiology practices (GPP), revision 3. 2015; https://www.pharmacoepi.org/resources/policies/guidelines-08027/#6. Accessed 2024 Mar 04.</eref>
26. <jrn>Siena LM, Papamanolis L, Siebert MJ, Bellomo RK, Ioannidis JPA. Industry involvement and transparency in the most cited clinical trials, 2019-2022. *JAMA Netw Open*. 2023;6(11):e2343425. Medline</jrn>

27. <eref>ICH harmonised guideline: good clinical practice E6(R3) draft version Geneva (CH): International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; 2023: https://database.ich.org/sites/default/files/ICH_E6%28R3%29_DraftGuideline_2023_0519.pdf. Accessed 2024 Mar 03.</eref>

28. <jrn>Baudart M, Ravaud P, Baron G, Dechartres A, Haneef R, Boutron I. Public availability of results of observational studies evaluating an intervention registered at ClinicalTrials.gov. *BMC Med.* 2016;14:7. Medline</jrn>

29. <jrn>Cole AM, Garrison LP, Mestre-Ferrandiz J, Towse A. Data governance for real-world evidence: cross-country differences and recommendations for a governance framework. *Value Health.* 2016;19(3):A290-A291.</jrn>

30. <jrn>Oderkirk J, Ronchi E, Klazinga N. International comparisons of health system performance among OECD countries: opportunities and data privacy protection challenges. *Health Policy.* 2013;112(1-2):9-18. Medline</jrn>

31. <jrn>Solà-Morales O, Sigurðardóttir K, Akehurst R, et al. Data governance for real-world data management: a proposal for a checklist to support decision making. *Value Health.* 2023;26(4S):32-42. Medline</jrn>

32. <eref>Workshop on the application of the General Data Protection Regulation (GDPR) in the area of health and Secondary Use of Data for Medicines and Public Health Purposes: Meeting with the EMA Patient and Consumers' Working Party (PCWP) and Healthcare Professionals' Working Party (HCPWP). Amsterdam (NL): European Medicines Agency; 2020: https://pink.citeline.com/-/media/supporting-documents/pink-sheet/2020/07/gdpr-patients.pdf. Accessed 2024 Mar 03.</eref>

33. <jrn>Wirtz BW, Weyerer JC, Becker M, Müller WM. Open government data: a systematic literature review of empirical research. *Electron Mark.* 2022;32(4):2381-2404. Medline</jrn>

34. <jrn>Danchev V, Min Y, Borghi J, Baiocchi M, Ioannidis JPA. Evaluation of data sharing after implementation of the International Committee of Medical Journal Editors data sharing statement requirement. *JAMA Netw Open.* 2021;4(1):e2033972. Medline</jrn>

35. <eref>International Society for Pharmacoepidemiology (ISPE). II. Protocol Development. In: Guidelines for good pharmacoepidemiology practices (GPP), revison 3. 2015; https://www.pharmacoepi.org/resources/policies/guidelines-08027/#1. Accessed 2024 Mar 01.</eref>

36. <jrn>Gillman D. Achieving transparency: a metadata perspective. *Data Intell.* 2023;5(1):261-274.</jrn>

37. <jrn>Angell M, Kassirer JP. The Ingelfinger Rule revisited. *N Engl J Med.* 1991;325(19):1371-1373. Medline</jrn>

38. <eref>Recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals. Philadelphia (PA): International Committee of Medical Journal Editors; 2024: https://www.icmje.org/icmje-recommendations.pdf. Accessed 2024 Mar 03.</eref>

39. <eref>Defining the role of authors and contributors. In: Recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals. Philadelphia (PA): International Committee of Medical Journal Editors; 2024: https://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html. Accessed 2024 Apr 25.</eref>

40. <jrn>Maruszczyk K, McMullan C, Aiyegbusi OL, et al. Paving the way for patient centricity in real-world evidence (RWE): qualitative interviews to identify considerations for wider implementation of patient-reported outcomes in RWE generation. *Heliyon.* 2023;9(9):e20157. Medline</jrn>

41. <eref>NICE Decision Support Unit, The University of Sheffield. Real world data. 2022; https://www.sheffield.ac.uk/nice-dsu/methods-development/real-world-data. Accessed 2024 Mar 04.</eref>

42. <eref>DARWIN EU® welcomes first data partners. Amsterdam (NL): European Medicines Agency; 2022: https://www.ema.europa.eu/en/news/darwin-eur-welcomes-first-data-partners. Accessed 2024 Mar 04.</eref>

43. <eref>European Health Data Evidence Network (EHDEN). 2022; https://www.ehden.eu/. Accessed 2024 Mar 04.</eref>

44. <jrn>Voss EA, Blacketer C, Van Sandijk S, et al. European Health Data & Evidence Network—learnings from building out a standardized international health data network. *J Am Med Inform Assoc.* 2023;31(1):209-219. Medline</jrn>

45. <jrn>Hampson G, Towse A, Dreitlein WB, Henshall C, Pearson SD. Real-world evidence for coverage decisions: opportunities and challenges. *J Comp Eff Res.* 2018;7(12):1133-1143. Medline</jrn>

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