Real World Evidence Workshop
Industry Input – IMC/BIOTECanada Working Group

This document represents the consolidated input of member companies representing both Innovative Medicines Canada (IMC) and BIOTECanada. Appropriate to the subject matter, it has been developed through the collaboration and input of a diverse group of industry experts with responsibilities for Health Technology Assessment, Regulatory Affairs, Market Access, Medical Affairs, and other functions implicated by the generation and application of Real-World Data (RWD) and Real-World Evidence (RWE). [1]

EXECUTIVE SUMMARY:

IMC and BIOTECanada appreciative the opportunity to engage with Health Canada, CADTH, CAPT, IHE and other agencies on this important subject. Appropriate access to healthcare data in Canada is a growing and valuable resource that can be leveraged for varying research and policy purposes.

The RWE workshop planned for October 21st will be an important opportunity to begin working through these important questions. The scope implied by the range of questions provided in advance of this workshop is a good start to what we expect to be a much longer process of RWE policy development and implementation in Canada. The industry recommends a multi-stakeholder working group be established to address key policy questions going forward.

It will be critical going forward to acknowledge and recognize that the RWE have both local (domestic) and global dimensions. Developing and instituting regulatory and HTA policies on the use of RWE requires broad collaboration from various public and private sector actors. Canada is not pursuing RWE policy in isolation. Indeed, our associations and member companies are already engaging with the challenges and opportunities related to RWE as part of other international initiatives on this basis, and we would encourage the Canadian agencies to do the same. We would specifically highlight both the Duke-Margolis Real-World Evidence Collaborative in the United States and the IMI GetReal Initiative in the European Union as instructive examples in this regard.

We propose the following approach based on some key principles on this important topic:

A. International Alignment where appropriate and possible

International alignment will continue to be critical in all aspects, especially for effective evidence evaluation framework design and implementation. Canada should take note of and contribute to the global conversation on data quality standards, study methods, and all other critical aspects of appropriately deploying RWE for regulatory, HTA and payer purposes. Equally, given the size of our market, Canada cannot afford to fall out of alignment with emerging global RWE approaches and standards. Although a

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[1] *For the purpose of this document, we would generically use RWE going forward but would note that RWD and RWE could be perceived as different types of information by stakeholders.*

"made-in-Canada" solution may be desirable to some, we encourage leveraging the work done by international groups where appropriate instead of 'reinventing the wheel' on every aspect of definitions, quality standards and implementation aspects.

B. Lifecycle management, including the principle of timely adoption of innovative medicines in areas of unmet medical need

Industry is supportive of the lifecycle management approach being pursued by the government or government funded stakeholders such as the health technology management agenda put forward by CADTH, which should not be limited by therapeutic area (e.g. oncology) or product classification. RWE can support and/or inform lifecycle management and the adoption of innovative medicines in areas of unmet need. The guiding principle should be one of collaboration on the practical implications and appropriate use of different forms of evidence.

C. Acceptable data quality and study methods

Issues of data quality and methods is important across this entire discussion. In order to transform RWE into valuable and actionable input for decision-making, we need to develop a better shared understanding and alignment around these issues.

D. Learn by doing – project-based learning

We suggest moving forward quickly with collaborative pilots or demonstration projects in priority areas where we can find common ground among stakeholders. This will allow all stakeholders to gain insights into the practical challenges as well as opportunities for using RWE to gain better understanding of drug effectiveness and safety. Given the complexity of this evolving area, there may be a risk in getting stuck if we wait for definitive answers to all questions.

We are eager to start working with the Canadian agencies, government stakeholders, academics and research center experts on a forward-facing approach which encompasses sound policy principles, focused strategies based on key priorities in the beginning of this process and solutions meant to address anticipated operational changes. This is a complex topic, and we should all be prepared to assess outcomes and adjust our approaches as may be warranted.

Accordingly, we would strongly recommend that a more permanent, adequately resourced forum or table be established in order to align on issues and priorities, manage consultations, and sequence activity plans going forward. A formalized working group of stakeholders to continue the dialogue and framework development is critical to ensure some accountability and continued forward momentum.

Questions for Discussion – RWE Use and "Decision-Grade" Quality Standards

Please provide responses to the following questions:

1. **WHERE TO USE: Where should RWE be considered to support regulatory and HTA/payer decision-making in Canada across the pharmaceutical product lifecycle (e.g., to support new indications, to assess in-market cost-effectiveness)?**

- RWE has a role across the entire product lifecycle and across therapy areas. Its value and impact may vary based on the quality of data, the nature of the evidence being generated, and the purpose for which it is generated.
- As an illustration of the range of specific examples, RWE could be used as follows during different lifecycle stages:
  - **Pre-approval**
    - Research/trial planning (patient selection, endpoint, comparator and surrogate marker selection, trial design factors, etc.).
    - Support new or expanded indications and populations.
  - **Access and reimbursement**
    - Inform disease characteristics (e.g. prevalence/incidence, economic burden of disease, current treatment patterns, natural history, etc.
    - De-risk or limit risk for uncertain reimbursement decisions (e.g. the coverage with evidence development approaches, pay for performance risk sharing models, etc.).
    - Support for HTA decisions that must be made based on a body of evidence that falls outside the typical study designs and level of evidence that we know CADTH typically expects (i.e. the phase 2 trials, novel study designs etc.). In these situations, the body of evidence might not mature any further than what was provided for regulatory approval and thus, RWE could be a mechanism through which payers can mitigate against clinical or cost-effectiveness uncertainty.
    - Validate surrogate endpoints and support link to product efficacy.
    - Support indirect treatment comparisons to support cost-effectiveness analyses where it would otherwise be impossible to do so.
    - Support Canadian-specific reimbursement decisions with Canadian population characteristics and clinical practice patterns.
  - **Post-access**
    - Regulatory actions (e.g. changes to conditional approval status, safety monitoring, expanded labels, etc.).
    - Real world clinical effectiveness/cost-effectiveness and health technology management.
    - Support clinical guidelines development.
    - Optimize reimbursement criteria to maximize patient health outcomes and minimize inefficient health spending.

2. **WHAT IS OUR EVIDENTIARY 'BAR': What is the quality and level of data/evidence that should be considered in Canada for reimbursement and regulatory decision-making?**

- Quality of data and level of evidence, while loosely related, are entirely distinct issues which are non-correlative and as such should be approached with care.
- The levels of evidence required for reimbursement and regulatory decision-making are highly variable and dependent on many factors, including but not limited to:
  - Therapeutic and clinical characteristics (e.g. patient population, relevant prior evidence, availability of comparators).
  - The decision context and scope, including the specific regulatory or reimbursement question to be addressed with RWE (compared to an HTA perspective). For example, a regulatory decision to revise a monograph/label to include new safety data might require a different level of evidence than a regulatory decision to expand the product's labelled indication.
  - Ethical considerations (i.e. disease burden/severity, lack of available alternatives).
  - Alignment between Health Canada and CADTH is key and needs further clarity.
- Improved data quality through the use of common standards should be a shared objective across the system.
  - Improved data collection will support the development of more complete and accurate datasets.
  - Moving toward data standards across regions in Canada, therapeutic areas, etc.
  - Innovative tools and technical approaches to improve data quality such as better missing data imputation, machine-learning data correction, etc.
- All RWE used for regulatory and HTA/payer decision-making, regardless of study result, should meet high standards of validity (especially when used in the regulatory context).
  - In cases where RWE appears to conflict with prior RCT results, additional scrutiny and context will be required in order to understand why the results diverged.
  - Contextual information is therefore highly relevant for determining the quality and level of the real-world data or real-world evidence required for reimbursement and regulatory decision-making.

   a. **Has industry encountered models internationally where the use and quality of RWE across the life cycle is well-defined? What can Canada learn from that experience?**

- There is a general and growing international acceptance that there is a role for RWE across the lifecycle. But frameworks for incorporating RWE in regulatory and HTA/payer decisions in a prescription drug context are still in development, and there are several international efforts to consider the most appropriate model(s) and implementation approaches.
- Some key international activities include:
  - **Regulators:**
    - European Union
      - The EMA Senior Medical Officer, Hans-Georg Eichler and co-authors have stated: *"Even with these advances in clinical trial designs, randomized clinical trials (RCTs) will always leave significant uncertainty about benefits, risks, real-life utilization and performance of new drugs; RCTs are often designed to*

remove confounding factors such as comorbidities or exclude elderly, frail patients. 'Confounder cleansing' increases the ability to detect a drug effect if it is there but reduces external validity. Progressive reduction of those uncertainties will need to be achieved by way of the use of data from observational studies."[2]

- The EMA's Adaptive Pathway concept has opened the door to greater use of RWE during drug development and in early launch for innovative products to treat diseases with significant unmet need.

- United States
  - There is a move towards imminent regulatory RWE policy development in the United States. The 21st Century Cures Act and the sixth Prescription Drug User Fee Act require the US FDA to establish a draft "framework" by the end of 2018 for how the agency will evaluate the potential use of RWE to support the approval of a new indication for an approved drug and to support or satisfy post-approval study requirements. By the end of 2021, FDA must develop draft guidance on the circumstances in which sponsors, and the agency, may rely on RWE for these purposes. This guidance also will address standards and methodologies for the collection and analysis of real world data.
  - FDA is currently sponsoring or supporting several demonstration projects that are intended to elucidate further insights into the acceptability of RWE for regulatory decision-making and inform the development of the guidance. FDA Commissioner Scott Gottlieb has stated that, "there's nothing in our statute or regulations that prevent the FDA from using a broad range of information sources of evidence" (September 2017), indicating that the FDA will continue to evolve its use of RWE.
  - USFDA has issued guidance for the industry regarding the use of Electronic Health Record Data in Clinical Investigations which may serve as a good supplementary resource.[3]

- **HTA**:
  - Canada is uniquely placed with two experienced HTA agencies (CADTH and INESSS) as well as provincial level expertise that can be used to provide implementable recommendations to the funders.
    - In particular, there is an opportunity to broaden the scope of the CDR and pCODR recommendations and work with stakeholders and the committees (CDEC, pERC and HTERP) to address key policy questions where it has been noted that the clinical evidence used for marketing authorization is premature or based on surrogate outcomes.
  - In the United States, MCOs (managed care organizations) and PBMs (pharmacy benefit managers) are currently using certain types of RWE to inform formulary decisions, especially as they revisit conditional access. These organizations are also

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[2] *Clin Pharmacol. Ther. 2015; 97(3): 234-246.*
[3] *https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM501068.pdf*

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using their own RWE to compare treatment outcomes and associated costs of care, estimate a treatment's budget impact, monitor the quality of their services on an ongoing basis, identify high risk patients, and benchmark themselves versus competitors.

▪ In Europe, HTA bodies use RWE to understand disease burden, natural history of disease, and treatment patterns, but do not systematically or consistently use product-specific RWE in evaluations of medicines' effectiveness. However, HTA agency use of RWE is expected to continue to evolve in the next few years and bears monitoring.

- Italy continues to be a leader in the generation and use of RWE, having mandated registries in certain therapeutic areas and maintained longitudinal patient databases.
- In the UK, NICE is assessing current guidance on the use of RWD and identifying areas where further research or guidance is required by offering case studies of where RWE has played a role in decision making. This is especially important as payers seek to understand the differences among drugs in highly competitive markets.
- Other European jurisdictions such Italy and France are making some use of RWE in payment decisions, although this remains relatively uncommon.

o **RWE Consortiums**:
   ▪ In the United States, the Duke-Margolis RWE Collaborative is a multi-stakeholder consortium – comprised of the FDA, pharmaceutical companies, research organizations, data vendors, patient organizations, and academia – working to advance consensus on the use of RWE to support applications for regulatory label revisions and expansions. The Collaborative, launched in December 2017, has recently developed baseline principles and a framework for assessing the quality of RWD sources for RWE generation[4] and is currently exploring how observational research could contribute to a totality of evidence approach for regulatory decision-making.[5]
   ▪ In the EU, the Innovative Medicines Initiative (IMI) GetReal Initiative, launched in July 2018, is building on the foundational efforts and framework of the original Get Real project (2013-2017). That project created an environment for stakeholders – patients, industry, academia, HTA bodies and regulators – to dialogue, build trust, and co-develop methodological approaches, analytical tools, best practice guidelines, and educational programs to support implementation and appropriate adoption of RWE in drug development and health care decision-making. The new GetReal Initiative will refine and promote the adoption of tools and programs developed in the original project, develop new solutions to outstanding challenges, and through a new "think tank" of global RWE experts provide thought leadership on RWE generation and use.[6]

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[4] *Characterizing RWD Quality and Relevancy for Regulatory Purposes, available at*
https://healthpolicy.duke.edu/sites/default/files/atoms/files/characterizing_rwd.pdf
[5] *More information about the Collaborative is available at https://healthpolicy.duke.edu/real-world-evidence-collaborative.*
[6] *Resources from this group could inform work in Canada and can be found at https://rwe-navigator.eu/*

- The Duke-Margolis RWE Collaborative and the GetReal Initiative offer models, both in participation and objectives, for the kind of sustained multi-stakeholder effort that industry believes is needed to advance the appropriate use of RWE in regulatory and HTA/payer decision-making in Canada.

b. **Should the evidentiary bar/type/quality of evidence differ by:**
    i. **Product line?**
    ii. **Type of submission across the life cycle?**
    iii. **Other?**

- In short, yes. The credibility of RWE must be assessed as being "fit for purpose". The Duke-Margolis RWE Collaborative has set out a four-part framework for this assessment in regulatory decision-making, which we would offer as a starting point for further discussion – and potential application to HTA/payer decision-making – in a Canadian context:
    o Regulatory Context (what is the specific decision under consideration);
    o Clinical Context (disease state, treatment effect, etc.);
    o Data Considerations (relevance, standards, quality, etc.); and
    o Methods Considerations (credibility, applicability).

c. **Are there products /indications/populations that are better suited to the use of RWE, and if so do they reflect appropriate starting points?**

- Canadian policy and data infrastructure development efforts should not unduly limit the applicability or use of RWE to specific sectors or therapeutic areas. There are current opportunities available in certain areas – but also the potential for greater generation and use of RWE across a wide range of current and emerging therapy areas. This must be acknowledged and addressed by any Canadian framework.
- There are many illustrative examples where RWE can offer valuable knowledge:
    o Diseases and conditions that disproportionately impact diverse populations that might be underrepresented in clinical trials (e.g., individuals with co-morbidities, the elderly, minority populations, geographically isolated populations);
    o Rare diseases and other conditions where studies cannot be conducted (i.e. for ethical purposes, limitations on study design);
    o Patient populations refractory to current treatment or more likely to benefit from a certain therapy;
    o Patient populations associated with specific biomarkers or genetic profiles undergoing various sequences of treatments;
    o Patient populations experiencing different QOL experiences either due to disease or treatment impact;
    o Products that receive accelerated and conditional regulatory approval on the basis of limited data packages;
    o Diseases/conditions for which there remains uncertainty about the most appropriate treatment or course of therapy, despite a substantial body of evidence from conventional RCTs;
    o Chronic conditions for which long-term follow-up – beyond the typical duration of conventional RCTs – could significantly contribute to more informed assessment of the clinical and economic outcomes of treatment alternatives; and

- o Diseases where patient adherence is a known/suspected factor impacting treatment effectiveness and health outcomes (e.g., asthma/COPD, diabetes).
  - Conventional RCTs with high degrees of control and procedural rigor typically do not capture the true impact of poor adherence or incorrect use of therapy.

d. **How do we best define our core outcome sets/minimal data sets across the product life cycle?**

- It would be difficult to define a common core outcome or data sets as these should be specific to the therapy area, specific indication, and patient population in question.
- Harmonized data across different sources are desirable, but multiple datasets could be used if data are mapped and standard queries are applied.
- Additionally, factors affecting data quality and relevance should be discussed, including common definitions, coding terminology, reporting process and audit system allowing verification of the accuracy and completeness of the registry data.
- The October 2018 multi-stakeholder workshop will be a useful opportunity to start a discussion to identify a list of core common data elements necessary for efficacy and safety evaluation at the time of treatment and in later follow-up. Partnerships will be critical to ensuring optimal relevance of study designs and endpoints for all parties.

3. **WHAT GUIDANCE DOES INDUSTRY REQUIRE: What information does industry need from Health Canada and CADTH to help guide collection of RWD and the generation and submission of RWE across the pharmaceutical product life cycle?**

Industry requires guidance on a range of issues, including but not limited to:
- Clarity that agencies have an appetite and a willingness to engage in RWE discussions with industry including an authentic commitment to incorporate RWE in decision-making in appropriate situations;
- Alignment among CADTH, HTA bodies, provincial payers and industry that RWD will be collected and RWE generated in a transparent, methodologically sound, and coherent fashion;
- The process for sponsor-regulator interactions on RWE generation planning and study design should be better explained - for example, how would future dialogue on RWE with agencies fit into the existing structure for interactions (pre-NDS, scientific advice, etc.);
- Alignment on how to define timepoints for finalization of data collection (for example start and stop rules) is also important;
- Clear process for how, when and by whom RWE will be reviewed in the context of existing evidence, industry needs to be able to confidently and accurately communicate to clinicians and patients how the evidence will be evaluated at a later date to secure commitment from these stakeholders to participate in the data generation process;
- A legal framework will be required that connects RWE to the applicable regulatory standard and provides appropriate guidance on design, conduct and acceptability suitable for regulatory decision-making;
- Considerations for reconciling and accepting various forms of evidence, including from various Canadian and international sources;
- Considerations for bridging endpoints in conventional RCTs to outcomes that can be measured in real world data;

- Ongoing dialogue is critical when there are data gaps - a plan for managing these gaps should be evaluated at specific timepoints along the data collection timeline;
- Expectations for transparency in RWE generation approaches (e.g., registering and reporting results from observational studies conducted with regulatory intent); and
- Industry is not limited to biopharmaceutical companies - guidance should extend to EMR and registry developers, data vendors, and others that collect (or design tools used to collect), aggregate, or out-license the RWD that research sponsors use to generate RWE (e.g. the data quality and transparency standards that data collectors/custodians should meet to help research sponsors meet our obligations to decision-makers must be clarified).

4. **HOW DO WE ENSURE ACCESS TO NECESSARY, HIGH QUALITY DATA: What should be done in Canada to optimize the collection, use and quality of data sources (both existing and new) to meet our collective RWD needs?**

- Multiple databases exist across Canada in academic, clinical practice and payer settings. These are not well integrated by stakeholder group or geography. There needs to be a commitment to finding a way to connect these multiple databases across geographies and disease states.
- We would therefore identify two broad areas of focus in order to optimize data collection, use and quality:
  - **Streamline systems and technologies**
    - Seek common infrastructure and platforms.
    - Leverage efficiencies and increase consistency of data collection, system inter-operability, and data reliability.
  - **Optimize the access to and use of data**
    - Awareness and availability: many industry partners are unaware of what datasets are in existence as these are not always publicly shared. It would be beneficial if there were transparency about the existence of datasets to fully understand implications and reasonableness of engaging in study. Establishing a common, regularly updated directory or registry of available datasets would be a significant step forward in this respect. This will also help reduce the time consumed as industry tries to uncover data sources and capabilities.
    - Develop data standards which include standards for data quality, as well as, format, ontology, definitions, etc.
    - Access policies will be required that incorporate relevant policy objectives, legal requirements, and technical realities (e.g. anonymization and/or encryption techniques, privacy implications, etc.).
    - The purpose for data collection and ongoing analysis needs to be clearly outlined, including decision-making purpose, intent to publish, engagement and consent of clinicians and patients.
    - Cross-jurisdictional issues must be identified and addressed to account for different rules, regulations, governing bodies, etc.
    - Ongoing education for healthcare providers, health systems, patients, and the public is required to address the need for data collection and potential use in researching, developing, and making available new medicines and for public health purposes. This will assist with gaining stakeholder commitment to participate in data collection initiatives.

5. **WHAT ARE THE MAIN CHALLENGES FOR INDUSTRY? What are the main challenges industry is anticipated to face in using RWE in submissions across the product lifecycle (e.g., access to quality data, capacity to undertake analyses)? How might challenges be best addressed?**

Industry faces a wide range of challenges in the use of RWE. These include:
- Access to data by different stakeholders is a challenge and the development and governance of public data infrastructures, including but not limited to the following is needed:
  - Purpose of collection.
  - Data ownership and source transparency.
  - Procedures for protocol development, disclosure and implementation of findings.
- Practical/technical challenges in integrating databases and the acceptance of data across jurisdictions, geographies and disease states.
- Uncertainty of regulator and HTA/payer views on the acceptability of RWE.
  - There is a growing need for frameworks and guidance on when decision-makers would find RWE most useful and how they will evaluate it. Without this, industry will be reluctant to invest in RWE approaches and RWE will not fulfill its potential.
  - There is a strong need to ensure that agencies develop consensus on frameworks to ensure more aligned and predictable approaches to RWE (e.g. the ability to draw meaningful conclusions between different reviewers or agencies).

IMC and BIOTECanada are willing and prepared to work together with government, government-funded agencies and other stakeholders to develop necessary guidance, and this should be a continuous process.