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Ed Morgan
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Dear Mr. Morgan,

On behalf of Innovative Medicines Canada (IMC) and its membership, I am writing with respect to the *Regulations Amending Certain Regulations Made Under the Food and Drugs Act (Agile Licensing*) released for comments on December 17, 2022.

IMC is the national association representing the voice of Canada's innovative pharmaceutical industry. The association advocates for policies that enable the discovery, development, and delivery of innovative medicines and vaccines to improve the lives of all Canadians and supports the members' commitment to being a valued partner in the Canadian healthcare system. The association represents companies which support 107,000 high-quality, well-paying jobs in Canada and invest $2.4 billion in R&D every year. Collectively, our members contribute $15.9 billion per year to Canada's knowledge-based economy.

IMC supports Health Canada's efforts to increase regulatory agility to keep pace with innovation and facilitate more efficient and predictable access to advanced treatments for Canadian patients. We welcome the changes to the *Food and Drug Regulations* (Regulations) that permanently embed important and beneficial regulatory flexibilities introduced during the pandemic through interim orders.

While the current amendments to the regulations are necessary and welcomed, we encourage Health Canada to further consider how science and research is shifting in the next decade and to continue to evolve the regulatory system to allow for the fast and efficient review and approval of new innovative treatments, such as precision medicines, that do not fit within the current regulatory framework.

Health Canada also needs to think beyond the current framework and be prepared for innovations that will be developed following, among others, the use of Artificial Intelligence (AI) in research, the development of digital health solutions, and the advancement in

diagnostic testing. While we acknowledge that Health Canada has developed guidance to address some innovative advancements (e.g., for the review of advanced therapeutic products), more should be done to ensure an efficient and fast review and approval of such therapies. Canada needs to keep pace with other jurisdictions by being progressive and forward thinking.

Canada needs to continue to be a welcoming and supporting environment for innovative medicines, vaccines and medical devices that enhance the health of Canadians. As a crucial part of the Canadian regulatory system, Health Canada must continue to be at the forefront of regulatory innovation and agility. IMC remains committed to supporting these efforts. With evolving international Health Authority collaborations and convergence, IMC supports efforts to incorporate reliance frameworks, where appropriate, enabling Health Canada to rely upon other Health Authorities' review and approval to ensure that innovative medicines are available to Canadians in a similar timeframe as they are in peer jurisdictions such as the United States, United Kingdom, the European Union, or Japan. Given that products are generally approved earlier in the US and Europe, and the convergence of regulatory requirements (i.e., ICH), the use of foreign decisions which is equivalent to a "near automatic sign-off" model recently announced by the Medicines & Healthcare products Regulatory Agency would further allow for more predictable and potentially faster availability of products in Canada.

Building on Health Canada's leadership at the regulatory level, other steps in Canada's HTA, negotiation and listing processes should be streamlined to ensure that the full societal benefits of faster access to new medicines are realized equitably for all Canadians. IMC believes that much more must be done to ensure faster and more predictable access to innovative medicines for Canadians. Of the new medicines that are already available internationally, Canadian patients wait twice as long (732 days) as patients in most peer countries for public access to those medicines following Health Canada approval. Canada ranks last in the G7 and 19th out of 20 peer OECD countries in respect of the time it takes for patients to get access to new medicines following regulatory approval[1].

IMC has reviewed the proposed amendments set out in the Canada Gazette Part I in addition to the related guidance documents and is providing the following comments for consideration. Additional and more detailed comments are provided separately in the "submission of comments" template form for each guidance document.

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[1] *Source: PhRMA analysis of IQVIA MIDAS and U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA), and Japan Pharmaceutical and Medical Devices Agency (PMDA) data, August 2022.*

A- Terms and conditions

IMC is pleased with Health Canada's consideration of its comments provided on October 28, 2021, and in particular that the use of Terms and Conditions (T&Cs) should be limited to those circumstances where the initial authorization or continued authorization would not be possible without the use of T&Cs. We maintain that the use of T&Cs must be limited to cases where there is a need to manage defined risks and to address important uncertainties within a given benefit/risk decision that could not be resolved otherwise. T&Cs should be used exceptionally and only when other legislative and regulatory mechanisms could not be used to mitigate risks and manage uncertainties. That said, the "uncertainty" threshold which could warrant the use of the T&C mechanism remains unclear in the language of the draft Guidance document. It is also unclear how T&Cs and post-approval commitments will be differentiated. Definitions of T&Cs and post-approval commitments should be added using terminology that clearly distinguishes them as often these two concepts are used interchangeably. Clarity is also required for the transition of drugs approved with post-approval commitments (i.e., prior to the full T&Cs coming into effect).

In addition, IMC continues to advocate for an approach whereby there is sufficient time during the review process to discuss potential T&Cs with the sponsor and that there is a clear mechanism for sponsors to make representations on the feasibility or the appropriateness of proposed T&Cs, in advance of any final written response. In addition, in the event that conditions evolve (e.g., slower than anticipated enrollment in a confirmatory clinical trial) there is a need for a clear process that allows sponsors to engage with Health Canada at the earliest possible juncture to discuss potential revisions to the T&Cs.

As noted in our comments on the previous Notice of Intent (NOI), in order to remain competitive globally, T&Cs that require the generation of data uniquely for Canada (such as Canadian specific studies) must be discouraged, and in the exceptional case where they are required and agreed to by the sponsor, they should be justified by an obvious difference between the Canadian medical system/environment and other global environments. Any imposition of country-specific requirements increases the cost and complexity of bringing medicines to Canada, thereby introducing a disincentive for manufacturers. Health Canada should continually seek to harmonize its regulatory system with international peers to ensure that it remains globally competitive, improves efficiencies, and reduces unnecessary regulatory burden and potential delays caused by unique Canadian requirements. Therefore, we strongly suggest that T&Cs should be harmonized with other peer jurisdictions and that the provision of resources required to implement and manage T&Cs should not reduce Health Canada's resources available to review and approve innovative drugs.

In addition, the future status and role of the Notice of Compliance with Conditions (NOC/C) submission pathway remains unclear. While in the Regulatory Impact Analysis Statement (RIAS), it is noted that the "amendments would codify in law existing practices under the NOC/C policy and allow the imposition of T&Cs at issuance of market authorization and post-authorization", we are unsure if the NOC/C policy will be revised, changed or completely replaced by a T&C approach for other submission types. If the NOC/C pathway will cease to exist following the implementation of T&Cs, it is critical that products that would currently qualify for NOC/C continue to have access to review via an accelerated pathway.

Furthermore, according to the current proposal, in the first year after registration of the Agile Licensing Regulations, T&Cs will be limited to public health emergency drugs (i.e., COVID-19 drugs or drugs with a condition on the *List of Conditions that Threaten Public Health in Canada*). After one year, these limiting provisions will be repealed and T&Cs will apply to all drugs, which makes the need to clarify the future of the NOC/C pathway even greater.

IMC also notes that the cost analysis in the RIAS appears to be based on the accumulated Canadian experience with NOC/C drugs. It does not however appear to account for the possibility that the imposition of T&Cs post-NOC could result in greater costs to industry beyond those set out in the RIAS, especially in cases where there is no harmonization between the T&Cs and what is required in other jurisdictions. IMC believes that the costing is very much dependent on the nature of the terms and conditions imposed and whether they are unique to Canada. Given the industry's past experience, in particular with respect to the Public Release of Clinical Information and the Plain Language Labelling, the cost to industry is likely to be significantly higher than Health Canada's estimate in the RIAS.

Finally, we encourage Health Canada to engage in discussions with Canadian HTAs and payers to ensure that invoking T&Cs for a particular product does not negatively impact reimbursement decisions or time to reimbursement for a product. It remains unclear whether and how T&Cs imposed post-NOC will impact market access after listings are in effect.

B- <u>Risk management plans</u>

IMC and its members are concerned by the stipulation in the draft regulations that if manufacturers do not submit updates to an RMP following a significant change, they shall not sell the product in Canada. An RMP is an important document that identifies and characterizes risks and uncertainties of a drug product and describes risk minimization measures. However, the document itself is a tool and not a direct indicator of the acceptability for market of a drug product. The current Regulations include sufficient authorities and penalties for Health Canada to take action to stop sale of a drug product that is deemed to have a significant change in the benefit/risk profile. We believe the proposal to have a "stop sale" of a medicine or vaccine due to the status of a RMP document is excessive and counterproductive, since it

could potentially harm Canadian patients by delaying or interfering with their access to impacted treatments.

IMC welcomes the continued practice of accepting RMPs prepared for the United States Food and Drug Administration (FDA) or the European Medicines Agency (EMA) along with the submission of a Canadian addendum. The implementation of global RMPs and minimizing Canada-specific requirements will have significant value for the Canadian healthcare system by limiting additional costs and delays for manufacturers hence helping to keep Canada competitive with other global markets. Harmonization of RMPs with other major Health Authorities is also expected to enable more and better communications and collaborations with these Health Authorities.

IMC notes that Health Canada is imposing a new obligation on manufacturers to submit a summary of new and updated RMPs in both official languages at the time of filing, with the intent of publishing these summaries online. Making summaries of RMPs available at the time of filing will create another Canada-specific and burdensome requirement, and the need to create and translate these summaries will inevitably cause delays in filing in Canada. This added burden adds no value to the review process since Health Canada does not review the translated version of the document. Requests for changes to RMPs are made frequently during the course of the review, resulting in the need to update and translate the summaries again at the conclusion of the review. It is also important to note that currently, review timelines for RMPs are often not aligned with the reviews of other parts of regulatory packages, and revisions to RMPs are frequently provided to sponsors after issuance of an NOC. It will be important for Health Canada to ensure completion of the RMP review within the submission performance target to allow for expeditious posting of the RMP summary post approval. Respecting the policy intent and to ensure that the requirement is both feasible and efficient, IMC recommends that RMP summaries be provided only at the end of the review in a single official language, with a translation to the other official language to follow within 30 days.

C- Rolling reviews

IMC welcomes a clear regulatory mechanism that provides sponsors with the discretion to file for rolling reviews that will accelerate the review and approval of new innovative vaccines and medicines in Canada. However, it is important to clarify that this is an optional mechanism available to manufacturers on a voluntary basis, and Health Canada should not be able to compel sponsors to file in this manner. IMC also wishes to clarify that the regulations should allow for rolling reviews to be layered over a priority review if the eligible criteria are met for each pathway (i.e., that a priority review product submission could benefit from the rolling review pathway).

The proposed amendments will introduce rolling reviews into regulation for new drug submissions and supplemental new drug submissions where the new drug meets certain conditions. While there is a reference to drugs for rare diseases in the RIAS under the "Benefit to Canadians" for rolling reviews, it is unclear under which "condition" drugs for rare disease will be considered. IMC believes that drugs for rare diseases should benefit from rolling reviews and a definition of rare diseases should be formally established in alignment with the definition adopted by EMA.

In addition, the proposed amendments will introduce rolling reviews for drugs related to a condition that threatens public health as set out on the *List of Conditions that Threaten Public Health (List)*, which will be incorporated by reference. It is currently unclear how conditions will be identified and considered for inclusion on the List. According to the proposed regulations, the condition would only require the general concept of "immediate action" to respond to the risk. It is unclear if major specific public health issues, such as seasonal influenza, would be captured under this definition. Further clarification and transparency regarding how and when drugs will be included on the List would be helpful.

Although Health Canada states that the rolling review process does not apply to the abbreviated new drug submission (ANDS) pathway, there are references in the guidance document as to how it may apply to other comparison-based submissions, raising the need for greater clarity and specificity as to both the intent and application. For instance, the guidance document references that sponsors of generic and biosimilar drugs "may seek", or "are not intended to seek" or "are not expected to seek" to establish eligibility for those submissions on the basis of the different conditions that should be met for a rolling review. We recommend that greater clarity be provided regarding whether the eligibility conditions set out in the proposed regulations may also apply to drugs for which approval is sought on the basis of direct or indirect comparison with another drug, (i.e., to generics or to biosimilars).

The filing timelines with respect to drug submissions have significant impacts on the rights of patentees. The proposed rolling review process places the onus on sponsors to ensure their submission plan allows for the drug submission to be deemed "administratively complete" as early as possible. Given the significance of having an "administratively complete" filing date in order to trigger valuable clinical data protection rights, we recommend that this issue be expressly addressed by Health Canada with a transparent policy that provides clear communication on filing date status and expectations for all parties under a rolling review submission.

Health Canada has also noted that based on "the priority reviews timelines and the types of drugs expected to qualify for a rolling review, it is estimated that these drugs would be approved on average two months earlier than under current processes". Based on the performance target for the review of drugs under the rolling review pathway, it is unclear how

this estimate was derived. That said, assuming this could be the case, in order to realize the full benefits of any policy change, rolling submissions must also be aligned with HTAs and pricing negotiations (i.e., pCPA and provincial drug plans) to ensure that Canadian patients can have faster access to treatments. The entire Canadian public access continuum – starting with Health Canada, followed by HTA review, pCPA negotiation, and public plan listing processes - needs to be better aligned to ensure that where Health Canada has implemented policies to expedite reviews, that those bodies responsible for ensuring access for patients are also set up to prioritize and improve their own performance targets.

IMC members' collective experience indicates that open dialogue with Health Canada is of real benefit for rolling submissions. Open dialogue must be maintained and encouraged in all aspects of Health Canada's drug review framework. A documented process and defined timeframes should exist to assist with sustaining the current benefits of rolling submissions into the future. As such, Health Canada's resources dedicated to reviewing rolling submissions must be sufficient to ensure continued uptake and the overall success and sustainability of this initiative.

D- Assuring drug quality during manufacturing

IMC welcomes the updates related to Good Manufacturing Practices (GMPs) and encourages continued alignment with other peer jurisdictions. IMC recommends harmonization with the EMA guidance document with respect to when specific nitrosamine tests must be included in the Drug Specifications.

E- Modernizing requirements for biologics drugs

IMC supports Health Canada's proposal to remove outdated product- or class-specific provisions in Part C, Division 4 of the Regulations. These provisions in the Regulations should be deferred to Good Manufacturing Practices (GMPs), since controls over manufacturing are detailed in GMPs, Division 2, including materials of biological origin.

With regards to C.04.008, it is noted that the Minister may require information regarding the quality of drug. IMC interprets this provision to relate to the current practice of Health Canada to require, under certain circumstances, a Yearly Biologic Product Report (YBPR). YBPR documents are in a Canadian-specific format and create a significant burden to sponsors in Canada and also delay Health Canada from receiving the most up-to-date information. IMC recommends that Health Canada eliminate the need for a Canadian-specific format and consider the acceptance of documents with similar content that are already produced for other peer regulators. Health Canada should continue to extend its risk-based approach, moving ultimately to the elimination of YBPRs and instead relying on the internationally accepted GMP Annual Product Quality Reports during inspections when this level of detail is necessary.

As a first step, we propose that Health Canada start with products having a low risk and where there is an established history of good quality management practices. Taking this approach would ensure information is provided to Health Canada in a timely manner with limited additional burden or cost to Canadian sponsors.

The Lot Release program can also be harmonized with other health authority testing. Specifically, if testing for a particular drug product has already been conducted by EMA or FDA, it should not require Health Canada re-testing.

Requests for samples may include not only the final drug product, but also reference standards and reagents, which may come from various facilities around the world. IMC proposes that a longer time period (i.e., 30 days) than the current 15-day clarifax deadline be implemented in order to provide all requested materials. IMC does not believe that requesting samples of the active ingredient is necessary since quality can be controlled through the testing of the finished drug product.

IMC also notes that the definition of biological source materials is very broad and further guidance is needed in order to understand what would be "in scope" materials. Further, prescribing a 5-year minimum retention period is unnecessary and the decision should be left with the manufacturer to determine the appropriate retention period on a case-by-case basis, or to align with other peer jurisdictions like the EMA. Additionally, the requirement to conduct an assessment on the retention period for tracing information should not be applied retrospectively to currently approved products.

Based upon the learnings from the pandemic, IMC requests that Health Canada enable in regulation and guidance, the ability to accept universal labels in limited situations, which could include leveraging tools such as QR or 2D barcodes that link to a website that provides current Canadian specific labelling (Product Monograph and Patient Medication Information) in both official languages and Health Product Risk Communications (HPRCs). This would be particularly important in the case of small volume products, such as some pediatric formulations, where the requirement for a Canadian specific label may prevent the product from being made available in Canada.

The pandemic highlighted the benefits of a modernized approach in the publishing of specific product labeling, where eLeaflets/digital labelling allowed for quicker to market communications of important information about the medicinal products used to address the pandemic. Steps should therefore be undertaken to modernize the approach to eLeaflets/digital labeling including the development of progressive guidance on the use of eLeaflets/digital labeling in Canada.

IMC has noted that the proposed amendments to Division 4 contain requirements for inner/outer labels that are duplicative of information existing in C.01.004 and could be replaced with a cross-reference to this section in order to further streamline Division 4 content. Only requirements that are specific to this category of product should be detailed in Division 4. IMC also believes that a labelling guidance document is needed for these products and suggests that the current labelling guidance document titled *Labelling of Pharmaceutical Drugs for Human Use* be expanded to include Division 4 products. With regard to the requirement to include biological source material used in the fabrication of the drug on the labels, this would be quite challenging since these products may have multiple biologic source materials used in the fabrication of the drug and therefore this requirement should be removed or made subject to space constraints. The inclusion of these proposed requirements onto the drug labels would be extremely challenging given the limited space available, the need to include all the other required elements on the label, in addition to ensuring that manufacturers meet plain language labelling requirements. These provisions and the limitations of physical labels are another important consideration to enable the introduction of eLeaflets/digital labels.

With regard to C.08.003.1, IMC believes that there are many opportunities to improve the transparency and process of On-Site Evaluations (OSE) by Health Canada. We recommend that additional information, such as a Q&A document, should be developed that outlines Health Canada's decision-making process including criteria to determine when an OSE would be conducted by Health Canada and reasonable expectations of sponsors. Specifically, IMC requests that Health Canada host a workshop with industry partners to enhance the OSE process and develop a Q & A document. The goal would be to enhance the clarity and transparency of the decision-making process for:

1- Establishing the need for an OSE; and
2- Information requirements and timing to support the execution of an OSE.

Having transparency with respect to the above OSE practices would help sponsors better plan for these activities and would result in valuable process improvements that would benefit both Health Canada and industry.

F- <u>Information considered to support the examination of drug submissions</u>

The proposed regulations indicate that the Minister can consider any information provided by any person under the Act, information or material obtained from sites and information and material obtained, directly or indirectly, from a foreign regulatory authority. The RIAS further notes that this is already "in line with current practice" and that the Minister's authority will only be used on a risk-based, case-by-case analysis during Health Canada's assessment of drug submission.

It is unclear why this expanded authority is being considered given industry's historically strong cooperation with these requirements. In addition, there is no guidance as to how the Minister will determine that a risk-based justification exists for considering these categories of information. Finally, it is unclear if the Minister will notify or seek authorization from the manufacturer when exercising this new authority, which we would strongly recommend. IMC therefore seeks further clarity from Health Canada with respect to these issues, including any process surrounding submission, receipt and notice related to information received outside of the drug submission.

G- Disaggregated clinical trial data for new human drug submissions and supplemental human drug submissions

IMC welcomes and encourages diversity in clinical trials and appreciates Health Canada's request to manufacturers to submit human clinical trial data broken down by population subgroups (disaggregated data) for new and supplemental human drug submissions to enhance its ability to assess the safety and effectiveness of new drugs for human use in certain patient subgroups. We also welcome and encourage continued harmonization of requirements and expectations for the content and format of disaggregated data in global clinical trial report documentation. IMC member companies are dedicated to improving representation of diverse populations in clinical trials conducted globally and nationally. However, increasing diversity in clinical trials, and collecting real-world data on underrepresented populations has proven to be challenging and will require long-term and concentrated efforts from a variety of stakeholders. IMC would welcome further dialogue and partnership with Health Canada, other government agencies, and the wider stakeholder community to make further progress, while ensuring full alignment and harmonization with requirements and expectations of other major Health Authorities for regulatory submission documentation. Specifically, IMC encourages Health Canada to partner with the industry to incentivize more diversity in clinical trials with a focus on the prioritized recruitment of women, children, the elderly, racialized individuals and Indigenous Peoples.

It must be noted that disaggregated data necessarily results in small patient populations, which are not statistically powered, rendering the data inappropriate for informing conclusions related to the use of a drug in a sub population. In addition, small patient populations increase the risk of inadvertently identifying individual patients as these submissions might also be subject to PRCI.

The RIAS states that the disaggregated data expected to be submitted by manufacturers will be the same data submitted to the FDA or EMA. However, in the associated guidance document there are some suggestions that the data requests could go beyond what is provided to FDA and EMA. IMC recommends that the intent and practical implementation should align requests for disaggregated data to those being submitted to the FDA and EMA,

and there should be no other specific requirements imposed on sponsors. The corresponding references in the regulations and guidance document related to encouraging companies to submit beyond that which is submitted elsewhere, or to segregate the data according to Canadian specific criteria/definitions should be removed to avoid any misunderstandings or misdirection of resources by both sponsors and Health Canada. As a practical consideration, it will not be feasible for companies to provide Health Canada with any clinical trial data beyond that which will be disaggregated and submitted to the US and Europe.

IMC understands that Health Canada's intention in amending the FDR to require the submission of disaggregated data in alignment with FDA and EMA is the first phase of a 3-phase proposal. Phase 2 (2023-2025) would involve working with international regulators and industry partners to explore greater consideration of diversity in drug development (e.g., gender considerations and intersectionality) and phase 3 (2025-2026) would require disaggregated data for more sub-populations (e.g., gender diverse individuals and First Nations, Inuit and Metis, where applicable). IMC encourages Health Canada to reflect on the feasibility of the objectives for each phase with reference to the aforementioned time periods. To reduce regulatory burden on Canadian companies, it is critical to achieve regulatory alignment with other jurisdictions as the overall policy landscape evolves.

Lastly, because sub-populations may respond differently to biosimilars, IMC recommends that the requirements related to disaggregated data should also be extended to biosimilar applications (i.e., biosimilar NDS and SNDS).

H- <u>Standards and Labelling</u>

IMC supports the proposed revisions to remove the requirements to declare a compendial standard in the labels and to loosen the requirements when declaring a manufacturers' standard. Since the proposed changes are intended to provide regulatory flexibility and reflect modernized approaches, IMC suggests that the language in the labelling guidance document should be broad enough to allow for universal labels and use of digital technology such as QR codes/2D barcodes to link to the current Canadian specific labelling electronically and that would enable consideration of eLeaflets/digital labelling in the future.

We also believe that the scope of the labelling guidance document should be expanded to include biologic products since many of the considerations are similar and applied to these products already. Furthermore, there is currently no guidance document for the labelling of biologic products and therefore any specific guidance to sponsors on considerations for the labelling of these products is missing.

I – Conclusion and Next Steps

In conclusion, IMC believes that agile regulations will provide a meaningful opportunity for Health Canada to enhance all components of the drug review process and to improve the department's overall review efficiency. However, IMC expects that the costs of implementation may be more significant than the limited impact projected in the RIAS, particularly if there is scope creep with respect to some of the authorities being enabled.

Given the importance of these changes, IMC would recommend that Health Canada implement a multi-stakeholder review process specific to regulatory agility to measure the costs, benefits and results against the policy intent of these proposals. This process will also allow for an inclusive and considered approach to any necessary amendments at a later date on the basis of collective experience.

IMC also encourages Health Canada to promote the policy intent of the changes with other agencies and organizations in the Canadian access continuum (e.g., HTA, pCPA, and P/T governments). The drug review process is an important step to ensuring better availability and access to innovative treatments, but it is only the first step of many before Canadian patients benefit from the new medicines. The improvements and efficiencies anticipated from agile regulations must not be reduced or undermined by inertia and inefficiencies in other parts of the system.

IMC thanks Health Canada for the opportunity to respond to this important consultation and looks forward to continued dialogue to ensure the development and implementation of such important regulatory changes are successful in achieving Health Canada's priorities.

Please do not hesitate to contact IMC should you have any questions or comments.

With Kind Regards,

Declan Hamill
Vice President, Policy, Regulatory and Legal Affairs

Enclosed: submission of comments template forms for each guidance document (10).