

## INNOVATIVE MEDICINES CANADA SUBMISSION

### CONSULTATION ON THE PROPOSED REGULATIONS AMENDING THE FOOD AND DRUG REGULATIONS (IMPROVING ACCESS TO GENERICS)

#### INTRODUCTION

Innovative Medicines Canada (IMC) is the national voice of Canada's innovative pharmaceutical industry. We advocate for policies that enable the discovery, development and commercialization of innovative medicines and vaccines that improve the lives of all Canadians. We support our members' commitment to being valued partners in the Canadian health and regulatory system. IMC appreciates the opportunity to engage as part of the public consultation on the prepublication in Canada Gazette, Part I of *Regulations Amending the Food and Drug Regulations (Improving Access to Generics)* (the "Proposed Regulations").

Health Canada is proposing changes relating to establishing pharmaceutical equivalence between a proposed second entrant (or generic) drug product and the Canadian Reference Product ("CRP"). The Proposed Regulations would change the test to require that the second entrant and the CRP share an identical "therapeutically active component", which is defined as the medicinal ingredient, excluding those appended portions, if any, that cause the medicinal ingredient to be a salt, hydrate or solvate.

Pursuant to the Proposed Regulations, any drug that contains the same "therapeutically active component" as a CRP could proceed via the Abbreviated New Drug Submission ("ANDS") pathway and, upon approval, would be declared therapeutically equivalent to the CRP. This is the case even if the "medicinal ingredient" in the subsequent entry drug is a different hydrated or solvated form, polymorph or salt form from the CRP. This is a marked change in the regulation of subsequent entry drugs in Canada.

The IMC membership has serious concerns about the safety and therapeutic efficacy of subsequent entry drugs approved via the ANDS pathway where the subsequent entry drug contains the same therapeutically active component, but not the identical medicinal ingredient as the CRP. As set out more fully below:

- There is no guarantee that alternative hydrates, solvates, polymorphs or salts will have the same therapeutic efficacy or safety profile as the CRP;
- The Proposed Regulations lack the necessary mechanisms to account for these potential differences, resulting in increased risk to the health of Canadians;
- The Proposed Changes are not aligned with regulation in other jurisdictions, and provide fewer safeguards to the health and safety of Canadians than the approval pathways in these other jurisdictions; and
- The Proposed Regulations fail to account for intellectual property rights, particularly in the context of the *Patented Medicines (Notice of Compliance) Regulations* and associated framework.



## 1. SAFETY AND THERAPEUTIC EFFICACY OF DIFFERENT SALTS, POLYMORPHS, SOLVATES AND HYDRATES

The Proposed Regulations represent a marked departure from Health Canada's long-held policy that different salts of the same active moiety are *non-identical* for the purpose of determining the appropriate CRP<sup>1</sup>. As recently as June 2012, a Health Canada consultation with stakeholders resulted in the Scientific Advisory Committee on Pharmaceutical Sciences and Clinical Pharmacology's recommendation that "[s]alts, esters, complexes of the same active moiety, different isomers, or mixtures with different proportions are not considered identical medicinal ingredients".<sup>2</sup>

The proposed departure from Health Canada's longstanding treatment of different salts as non-identical is particularly concerning given the safety and efficacy rationale underlying the *status quo*. Following Health Canada's 2003 stakeholder consultation on the finalization of the policy *Interpretation of 'Identical Medicinal Ingredient'*, Health Canada justified the exclusion of salts as pharmaceutical equivalents on the basis that "salts are not chemically the same as unionized forms of the active moiety, and the possibility that the nature of the counter ion could have an effect on the safety or efficacy of the product", noting further that "this is consistent with the regulatory practices of different regions for determining equivalence"<sup>3</sup>.

We note that Health Canada's informal consultation on this subject in October 2017 proposed that subsequent entry drugs with different salts, esters or complexes of the medicinal ingredient in the CRP, and/or drug products with different but comparable dosage forms to the CRP, would be considered "pharmaceutical alternatives" and declared therapeutically equivalent to the CRP upon approval<sup>4</sup>. However, Health Canada has abandoned the proposal to include esters and complexes within the scope of the Proposed Regulations – thereby distinguishing between the safety profiles of different salts, solvates and hydrates versus different complexes, clathrates, esters, and isomers or mixtures with different proportions of isomers.

The underlying rationale for this distinction, according to the Regulatory Impact Analysis Statement (RIAS) accompanying the Proposed Regulations, is that "[d]ifferent salts, similar to different solvates and hydrates,

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<sup>1</sup> Health Canada, *Interpretation of "Identical Medicinal Ingredient"*, July 23, 2003, available online: [https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt\\_formats/hpfb-dgpsa/pdf/prodpharma/medingred\\_pol-eng.pdf](https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/medingred_pol-eng.pdf), at Section 4, (stating that "[d]ifferent complexes, esters, or salts of the same active moiety are considered non-identical").

<sup>2</sup> Health Canada, Scientific Advisory Committee on Pharmaceutical Sciences and Clinical Pharmacology (SAC-PSCP), *Record of Proceedings*, June 26 and 27, 2012.

<sup>3</sup> Health Canada, *Interpretation of "Identical Medicinal Ingredient" Questions and Answers*, July 9, 2003, available online: [https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt\\_formats/hpfb-dgpsa/pdf/prodpharma/medingred\\_pol\\_qa\\_qr-eng.pdf](https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/medingred_pol_qa_qr-eng.pdf).

<sup>4</sup> Health Canada, *Possible Changes to the Food and Drug Regulations: Generic Drug Equivalence and Related Terminology*, last modified October 6, 2017, available online: <https://www.canada.ca/en/health-canada/services/drugs-health-products/public-involvement-consultations/drug-products/generic-drug-equivalence-notice.html>.



will dissociate upon dissolution of the dosage form to yield the identical therapeutically active component or, in the case of liquid dosage forms, will already be dissociated in the dosage form to yield the identical therapeutically active component”<sup>5</sup>. However, IMC maintains and reiterates that there are significant concerns about the safety and therapeutic efficacy of non-identical products such as different hydrates, solvates, polymorphs or salts approved via the ANDS pathway given that many, as outlined further below, have non-identical physicochemical, pharmacodynamic and toxicity profiles when compared to the CRP.

There are numerous studies within the academic literature that point to specific examples of how alternative salt forms of a particular active pharmaceutical ingredient (API) can differ markedly in physicochemical properties, and can impart toxicity and/or undesirable biological activity that differ from the drug’s intended clinical use<sup>6</sup>. Table 1, below, summarizes several well-cited examples of different salts of an active substance that result in a change in the substance’s pharmacokinetic and/or pharmacodynamic behaviour. Although the APIs in these different salts are the same, each of these salts may be considered as being distinct chemical entities with distinctive chemical and biological profiles that may lead to differences in their clinical efficacy and safety<sup>7</sup>.

**Table 1.** Examples of active substances with different salts that impact upon physicochemical, pharmacodynamic and toxicity profiles

| Active Moiety           | Alternative Salt Forms | Causality                     | Implications for patients  |
|-------------------------|------------------------|-------------------------------|--|
| Amlodipine <sup>8</sup> | bessylate vs. maleate  | Variable stability profiles.  | Amlodipine maleate’s chemical instability results in the formation of a degradation product (particularly following the manufacture of dosage forms and on prolonged storage). Significant implications for safety and toxicity. |
| Trazodone <sup>9</sup>  | tosylate vs. pamoate   | Variable solubility profiles. | <i>In vivo</i> absorption rate of trazodone in tosylate salt significantly lower   |

<sup>5</sup> RIAS, Canada Gazette, Part I, Vol. 153, No. 13 at p. 1298.

<sup>6</sup> See, e.g. Verbeeck, R. Kanfer, I. Kanfer, and R. B. Walker. “Generic substitution: the use of medicinal products containing different salts and implications for safety and efficacy.” *European journal of pharmaceutical sciences* 28.1 (2006): 1-6.

<sup>7</sup> Berge, S.M., Bigly, L.D., Monkhouse, D.C., 1977. “Pharmaceutical salts”. *J. Pharm. Sci.* 66, 1–19; Gould, P.L., 1986. “Salt selection for basic drugs”. *Int. J. Pharm.* 33, 201–217; Davies, G., 2001. “Changing the salt, changing the drug”. *Pharm. J.* 266, 322–323; Stahl, P.H., Wermuth, C.G., 2002. “Monographs on acids and bases”. In: Stahl, P.H., Wermuth, C.G. (Eds.), *Handbook of Pharmaceutical Salts: Properties, Selection and Use*. Wiley-VCH, Weinheim, pp. 265–327.

<sup>8</sup> *Supra*, note 6.

<sup>9</sup> *Ibid.*



|                                   |   |   |  |
|-----------------------------------|---|---|--|
| <b>Perindopril</b> <sup>10</sup>  | arginine vs. erbumine   | Variable stability profiles.  | Arginine salt is more stable, leads to a 50% increase in shelf-life, and resulted in half as many reports of adverse events as compared to the erbumine alternative.                                     |
| <b>Propoxyphene</b> <sup>11</sup> | hydrochloride vs. napsylate                                   | Hydrochloride salt becomes unstable when administered with aspirin (as it is intended to be). | Acute oral toxicity of propoxyphene was halved when prepared as napsylate salt rather than hydrochloride salt.   |
| <b>Alprenolol</b> <sup>12</sup>   | hydrochloride and fumarate vs. benzoate, maleate and sebacate | Variable solubility profiles.   | Hydrochloride and fumarate have the highest water solubility and resulted in the most serious oesophageal lesions, where low-solubility salt forms of maleate and sebacate produced no irritant effects. |

IMC also notes the growing body of medical evidence that cautions clinicians about chemical differences that may translate into differences in therapeutic effectiveness. For example, Patel *et al.* explore, with examples, what the clinical cardiologist should consider when prescribing pharmaceutical salts for their patients<sup>13</sup>. Notably, this study discusses the issue of inter-individual variability that may pose risks to patients given the unpredictable nature of their response to substitutions. Darius *et al.* likewise present the clinical aspects associated with the use of various clopidogrel salts, and advise that additional investigations into patients' medical and prescription-taking histories are required before therapeutic equivalence of a new salt formulation to the clopidogrel hydrogen sulfate parent can be presumed with sufficient certainty<sup>14</sup>. Another article by Meredith summarizes several concerns that have emerged relating to the interchangeability between innovator drugs and generic counterparts using the example of amlodipine (see also Table 1)<sup>15</sup>. In particular, the author notes that "[t]o date, there is no reliable way of predicting exactly the effects of changing the salt form of an active substance", adding that "[i]t would logically follow that therapeutic equivalence for those generic drugs cannot be established on bioequivalence data alone and additional pre-clinical and/or clinical data may be required before they can be routinely applied in clinical practice".

Given this evidence, IMC is very concerned about the proposed expansion of products that can proceed by way of the ANDS pathway, and the ability to do so without the requirement to provide evidence of the safety and therapeutic efficacy of a subsequent entry drug that does not contain the identical medicinal

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<sup>10</sup> Patel, Aateka, et al. "Pharmaceutical salts: a formulation trick or a clinical conundrum?" *British journal of cardiology* 16.6 (2009): 281-286.

<sup>11</sup> *Ibid.*

<sup>12</sup> *Ibid.*

<sup>13</sup> *Ibid.*

<sup>14</sup> Darius, H., et al. "Clopidogrel Salts-Pharmacokinetic, Pharmacodynamic and Clinical Aspects." *Journal für Kardiologie-Austrian Journal of Cardiology* 16.11 (2009): 412-416.

<sup>15</sup> Meredith, Peter A. "Potential concerns about generic substitution: bioequivalence versus therapeutic equivalence of different amlodipine salt forms." *Current medical research and opinion* 25.9 (2009): 2179-2189.



ingredient as the CRP. This is significantly compounded by the rules around interchangeability, as discussed below.

## Synthetic biologic drugs

IMC also questions why the Proposed Regulations prohibit submissions being made via the ANDS pathway for Schedule D (i.e. biologic) drugs, but allow drugs not referred to in Schedule D (e.g. a chemically synthesized drug) to proceed by way of this abbreviated mechanism with a biologic CRP. Specifically, on the synthetic biologic issue, the RIAS makes the following statement:

“Due to the size, complexity and natural variability of Schedule D (i.e. biologic) drugs, and because biologic drugs are made in living cells rather than with chemicals, a biosimilar and its reference biologic drug can be shown to be highly similar, but not identical. Therefore, the ANDS pathway is not considered appropriate for approval of biologic drugs. However, the proposed amendments would not prevent a manufacturer from filing an ANDS for a drug that is not referred to in Schedule D (e.g. a chemically synthesized drug), where the CRP is a drug referred to in Schedule D.”<sup>16</sup>

It stands to reason that if biologic drugs cannot be sufficiently compared due to size, complexity and natural variability, one cannot compare a chemically synthesized peptide to a biologic (in the sense that it could be identical) or for the same reasons. The biologic comparator would have the size, complexity and natural variability that would preclude such a comparison.

Further, no provision in the Proposed Regulations or current regulations actually addresses the regulatory filing of a chemically synthesized product by way of ANDS with a biologic CRP, nor does Health Canada maintain any guidelines to address such a process. Health Canada has never conducted consultations on this particular issue. For all of the above reasons, any reference to this particular issue lies outside of the scope of the Proposed Amendments. As such, the following sentence should be removed from the RIAS: *‘However, the proposed amendments would not prevent a manufacturer from filing an ANDS for a drug that is not referred to in the Schedule D (e.g. a chemically synthesized drug), where the CRP is a drug referred to in Schedule D.’*

IMC also submits that the rationale from the RIAS (i.e. that while they may be shown to be highly similar but not identical) applies equally to hydrates, solvates, polymorphs or salts. These variations can, and as outlined above often do, affect therapeutic efficacy and safety.

## Safety and Therapeutic Efficacy Concerns Magnified by Deemed Therapeutic Equivalence and Interchangeability

When drugs are approved, they are deemed by section C.08.004(4) of the *Food and Drug Regulations* to be therapeutically equivalent to the CRP. The Proposed Regulations therefore permit alternative forms of medicinal ingredients to be declared therapeutically equivalent to innovative drugs. As noted in the RIAS, the regulatory proposal “would facilitate processes for generic drug products with different medicinal ingredients (e.g. different salts) as being interchangeable.”<sup>17</sup>

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<sup>16</sup> *Supra*, note 5 at p. 1299.

<sup>17</sup> *Supra*, note 5 at p. 1296.



The deeming of subsequent entry products as “therapeutically equivalent” is often considered by provincial formularies when decisions are made regarding drug interchangeability. Drug interchangeability refers to the ability of a pharmacist to substitute one drug for another (i.e. the CRP or another subsequent entry drug) without contacting the physician to change the prescription. Since most provinces only reimburse pharmacies for the lowest cost interchangeable drug, pharmacists often have no choice but to dispense the least expensive therapeutically equivalent drug<sup>18</sup>. Therefore, the dispensing of drugs to patients is directly affected by any changes to the regulatory approval regime, and specifically by the Proposed Regulations.

The above-noted concerns about the safety and therapeutic efficacy of the expanded scope of subsequent entry drugs that will be permitted to use the ANDS pathway is an important consideration and highlights that establishing bioequivalence of drug products containing different salts of the same active substance will not usually suffice to claim therapeutic equivalence, with consequent issues for substitutability and interchangeability.

Even if a subsequent entry drug is safe in and of itself and can be shown to be equivalent to the CRP (which, as discussed above, is not necessarily a conclusive finding), this does not mean that it should be automatically interchangeable with the innovative CRP. For example, if multiple drugs are interchangeable, a pharmacist could dispense to a patient Drug A (base version) the first time, Drug B (sodium salt version) the second time, Drug C (potassium salt version) the third time, Drug D (calcium salt version) the fourth time etc. Patients may go to different pharmacies to obtain their prescriptions so they may not consistently receive the same brand of interchangeable drug. Further, even for patients who always obtain their prescriptions at the same pharmacy, there is no requirement imposed on pharmacies to dispense the same brand of interchangeable drug each time to the patient. This is important because if Drug A were the CRP, then in the above example, each of Drugs B, C and D would only have been compared to Drug A as part of the ANDS process. However, Drugs B, C and D would not have been compared to each other but would be interchangeable under provincial interchangeability rules.

Given the significant safety and efficacy concerns with subsequent entry products that do not contain the identical medicinal ingredient as the CRP, which are compounded by provincial interchangeability rules, alternate forms such as hydrates, solvates, polymorphs and salts cannot be considered equivalent without additional supporting data.

## **2. CLEAR IMPLEMENTATION PROPOSAL REQUIRED TO ADDRESS SAFETY AND THERAPEUTIC EFFICACY AND INTERCHANGEABILITY**

As discussed in the previous section, there are significant safety concerns with relying on data generated for the approval of a CRP when approving an alternate form such as a hydrate, solvate, polymorph, or salt.

These concerns are amplified if the expanded regulatory pathway broadens the scope of products that will be deemed “interchangeable”, thereby permitting/requiring pharmacists to dispense any of a multitude of

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<sup>18</sup> Subject to a patient either choosing to pay the portion of the drug cost exceeding the lowest cost, or receiving special authority from the province for coverage of the higher priced drug.



non-identical drugs to patients<sup>19</sup>. Given the potential interchangeable scenarios in pharmacy practice, and before such a substitution by pharmacists is applied, it is of the utmost importance that the generic drug being substituted is proven to be therapeutically equivalent and as safe as the innovative drug and any other interchangeable drug already on the market.

In particular, for two products to achieve comparable safety and therapeutic efficacy, proof that the pharmacokinetics, pharmacodynamics and/or toxicity of the active substance are not modified must be provided. In addition, labelling requirements must be sufficient to achieve the objectives of greater consistency and transparency as set out in the RIAS<sup>20</sup>. These requirements should be regulatory in nature – as opposed to being provided by way of non-binding guidance – and must align with other jurisdictions such as the EU and US (as discussed more fully below).

As currently structured under the Proposed Regulations, guidance on the implementation of this regulatory proposal would be outlined in Health Canada's guidance documents *Generic Drug Equivalence: Medicinal Ingredients and Identifying and Labelling Medicinal Ingredients in New Drug Products*.

Concerns regarding safety remain pertinent notwithstanding the guidance documents, given that both documents contain requirements leaving considerable room for interpretation with respect to submission requirements and the interpretation thereof. IMC submits that the regulations should clearly state that, where a difference in safety/efficacy requires additional safety data to be submitted as per the guidance documents, the drug should not be eligible to proceed per the ANDS pathway and as a result should not be deemed interchangeable with the CRP.

While the guidance documents acknowledge that the Minister can request information from a manufacturer to ensure the safety and therapeutic efficacy of the subsequent entry drug, given the concerns outlined above, IMC submits that amendments are needed to the Proposed Regulations that require such information be provided. A proposed amendment to draft section C.08.002.1 follows:

*(3.1) Where there is a difference between the medicinal ingredient in a new drug and the medicinal ingredient in the Canadian reference product, or the Minister has reasonable grounds to believe there is a difference, the manufacturer of the new drug shall proceed per C.08.002(1).*

Further, given the potential that a subsequent entry drug could be interchanged with other generic drugs containing different hydrates, solvates, polymorphs, or salts, IMC submits that, at a minimum, any new medicinal ingredient being approved based on its “therapeutically active component” (e.g. a new salt) must demonstrate not only that it is bioequivalent to a CRP, but also that it is bioequivalent to all marketed forms with which it may be considered interchangeable.

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<sup>19</sup> See, e.g. Amrita Singh, Nicole M. Maisch and Maha Saad, “A Closer Look at Generic Interchangeability in Narrow Therapeutic Index Drugs, US Pharm. 2014;39(6)(Generic suppl):8-12: “[W]ith NTI drugs, generic interchange further adds to variability among patients in blood concentrations and required special consideration.”

<sup>20</sup> *Supra*, note 5 at p. 1299.





Alternatively, a new drug that does not contain the identical medicinal ingredient and is not approved per the ANDS pathway (i.e. in comparison to a CRP) should not be declared therapeutically equivalent.

### Expertise of Canadian Reference Product Manufacturers

In addition, the input of the CRP manufacturer should be considered a valuable source of information when regulatory submissions for different salts, polymorphs, hydrates or solvates are received or contemplated. The innovative manufacturers of CRPs will often have experience and knowledge (potentially including study results) regarding the impact of different physicochemical properties of alternative forms of the CRP on the performance of their products in terms of physicochemical and pharmacodynamic efficacy and safety.

IMC submits that an official pathway similar to the FDA's "citizen petition" should be put in place, allowing manufacturers to submit scientific evidence relating to the safety and therapeutic efficacy of any alternate hydrate, solvate, polymorph or salt and mandating a response from Health Canada within a prescribed timeline<sup>21</sup>. Disclosure on the Generic Submissions Under Review ("SUR") list of alternative forms of medicinal ingredients under review by Health Canada is also proposed, and would allow parties to submit additional information to Health Canada to ensure the safety of Canadians. Additional mechanisms would have to be put in place to limit the liability of innovators with respect to their submission on safety and efficacy.

### 3. THE REQUISITE SAFETY STANDARDS FOR THERAPEUTIC EQUIVALENCE AND INTERNATIONAL ALIGNMENT

IMC does not believe that the stated goal of the regulatory proposal to "reduce regulatory differences with other jurisdictions such as the United States Food and Drug Administration (U.S. FDA) and the European Union (EU) European Medicines Agency (EMA)"<sup>22</sup> will be achieved by the Proposed Regulations.

Rather than harmonizing with other regulators, the Proposed Regulations are different from other regulatory regimes. The Proposed Regulations would create an opportunity for subsequent entry drugs to be sold in Canada without meeting adequate safety standards, and without being subject to the same stringent safety vigilance regime as is required for innovative drugs. The legislation for regulatory approval is different in the US and EU as compared to Canada, and any suggestion to harmonize with these countries must take this into account, as further explained below. It is also noteworthy that both Australia and Japan employ

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<sup>21</sup> A "citizen petition" is a process provided by the US FDA for individuals and organizations to make requests to the FDA (see Code of Federal Regulations, Title 21, Section 10.30). Innovator pharmaceutical companies routinely file citizen petitions to present arguments to the FDA that the ANDA should not be accepted. The Regulations mandates a response from the FDA to a citizen petition within 150 days. It is notable that citizen petitions are also published, which is helpful with respect to transparency.

<sup>22</sup> *Supra*, note 5 at p. 1296.





similar regimes to Canada's current system – i.e. a proposed generic drug product must be a pharmaceutical equivalent of the reference product<sup>23</sup>.

According to the EU guidelines, "medicinal products are pharmaceutical alternatives if they contain the same active moiety but differ in chemical form (salt, ester, etc.) of that moiety or in the dosage form or strength"<sup>24</sup>. The European Medicines Agency (EMA) makes provision for medicinal products which are either pharmaceutically equivalent or pharmaceutical alternatives to be declared as therapeutic equivalents, as follows: "In practice, demonstration of bioequivalence is generally the most appropriate method of substantiating therapeutic equivalence between medicinal products which are pharmaceutically equivalent or pharmaceutical alternatives, provided they contain excipients generally recognized as not having an influence on safety and efficacy and comply with labelling requirements with respect to excipients"<sup>25</sup>.

Under the EU's regulatory pathway, pharmaceutically equivalent products can clearly be considered therapeutically equivalent based on a bioequivalence study, but additional pre-clinical and/or clinical data may be required for a pharmaceutical alternative to be considered therapeutically equivalent<sup>26</sup>. In this context, some regulatory authorities demand more extensive investigations before approval of a modified salt or ester form.

Figure 2 demonstrates the three different approval pathways that exist in the EU for pharmaceutical alternatives in the context of new salts: a generic application, a hybrid application or a full application<sup>27</sup>.

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<sup>23</sup> Davit, Barbara, et al. "International guidelines for bioequivalence of systemically available orally administered generic drug products: a survey of similarities and differences." *The AAPS journal* 15.4 (2013): 974-990.

<sup>24</sup> European Medicines Agency, Note for Guidance on the Investigation of Bioavailability and Bioequivalence, December 14, 2000, available online:

[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/09/WC500003519.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003519.pdf)

<sup>25</sup> *Ibid.*

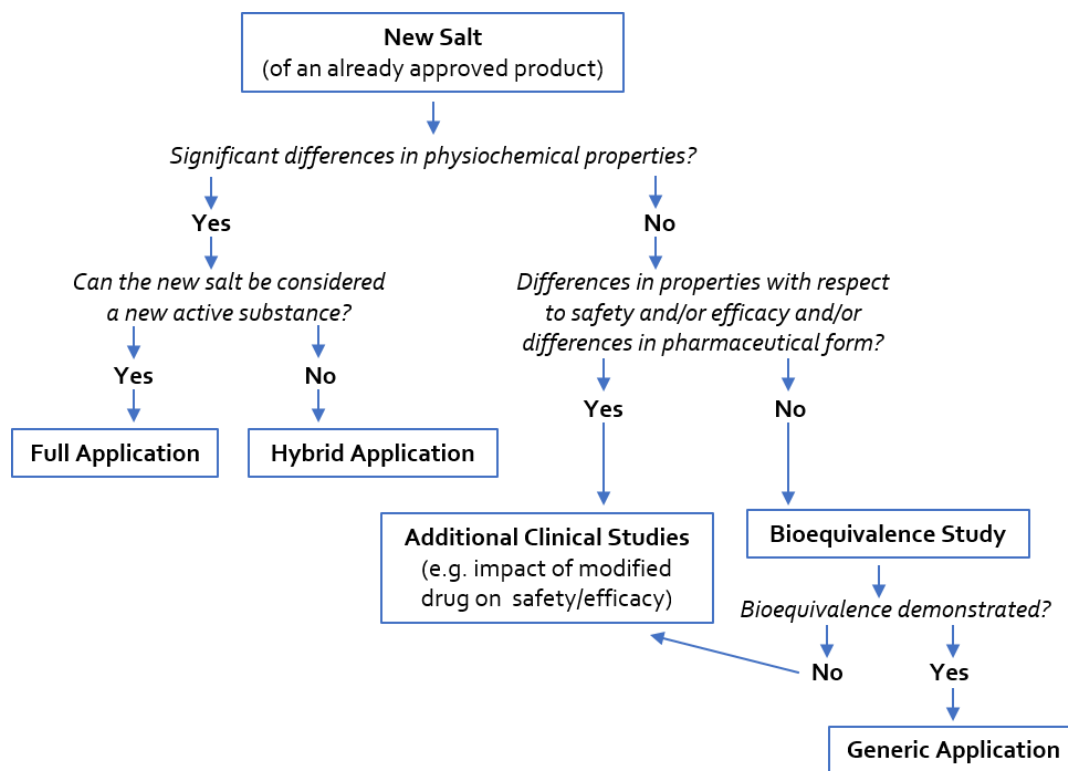
<sup>26</sup> The European Parliament and the Council of the European Union, Directive 2001/83/EC on the Community Code Relating to Medicinal Products for Human Use, November 28, 2004, available online:

[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Regulatory\\_and\\_procedural\\_guideline/2009/10/WC50004481.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC50004481.pdf).

<sup>27</sup> As adapted from Schulze, Brita. "Different Salts of a Drug Substance—Comparison of Regulatory Pathways in the EU and USA."



Figure 2. Regulatory Pathways in the EU for a New Salt



A discussion about these various routes follows<sup>28</sup>:

- 1) **Generic application:** A pharmaceutical alternative of an active substance which is already marketed in a medicinal product can be approved in a generic medicinal product, provided that the new medicinal product has: (i) the same qualitative and quantitative composition in active substance(s) as the reference; (ii) the same pharmaceutical form; and (iii) bioequivalence has been demonstrated<sup>29</sup>. It is the responsibility of the applicant to generate data to address the above cited criteria<sup>30</sup>. If the applicant comes to the conclusion that there are significant differences between the new salt and the original salt, “additional information providing proof of the safety and/or efficacy of the various salts, esters, or derivatives of an authorized active substance must be supplied by the applicant.”<sup>31</sup>

<sup>28</sup> *Ibid.*

<sup>29</sup> *Supra*, note 26, at Article 10(2)(b).

<sup>30</sup> European Commission Health and Food Safety Directorate-General, Notice to Applicants, Volume 2A: Procedures for marketing authorisation, December, 2016, available online: [https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-2/vol2a\\_chap1\\_rev6\\_201612.pdf](https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-2/vol2a_chap1_rev6_201612.pdf).

<sup>31</sup> *Supra*, note 26, at Article 10(2)(b).



- 2) **Hybrid Application:** There are instances where “the medicinal product does not fall within the definition of a generic medicinal product ... or where bioequivalence cannot be demonstrated.”<sup>32</sup> In these situations, additional pre-clinical and clinical data are to be provided with the objective to allow bridging from data of the original medicinal product to the new product (e.g. a new salt).
- 3) **Full Dossier:** In the event that an alternative salt of an already existing medicinal product differs significantly with respect to safety and/or efficacy data, this new substance might be considered a new active substance as outlined<sup>33</sup>. As a consequence, a full dossier must be submitted.

Similarly, in the US, a different salt can only be authorized by way of a New Drug Application according to Section 505(b)(1) or 505(b)(2) of the *Federal Food, Drug and Cosmetics Act*<sup>34</sup>. Under the 505(b)(2) regulatory pathway, which resembles the EU’s hybrid application, the sponsor of a 505(b)(2) application may refer to pre-clinical and clinical data (including safety data) of an originator. The applicant must scientifically justify the studies it seeks to use by bridging from each medicinal product upon which it has relied to the proposed medicinal product, e.g. from an immediate release formulation to a new prolonged release formulation, or from the originator’s medicinal product to a new combination product. This bridging data will most likely include data from bioequivalence studies alone, and *in vitro* studies.

Further, unlike the EMA and FDA, which proactively identify products with complex formulations (e.g. multi-phasic, long-acting, esters and salts relevant to safety or effectiveness) and produce product-specific guidance for generic products, Health Canada does not produce such guidance and generic companies may at times produce a lower quality product for Canada due to the lack of specific requirements. It is important for Health Canada to align with the EMA and FDA in terms of creating guidelines on additional bioequivalence/clinical requirements for these products and be transparent regarding such alignment.

#### 4. SERIOUS INTELLECTUAL PROPERTY IMPLICATIONS

IMC is very concerned that the RIAS makes no mention of the considerable overlap of the Proposed Regulations with the patent regime, nor the serious concerns raised during Health Canada’s informal consultation on the subject in 2017 by IMC and others.

In particular, Canada deliberately established the *PM(NOC) Regulations* regime so that Health Canada would be prohibited from issuing regulatory approval to a generic drug until the innovator’s patents listed on the Patent Register were first addressed. However, the *PM(NOC) Regulations* do not allow a first person to list a patent on the Patent Register unless the patent contains a claim to the approved medicinal ingredient, the approved formulation, the approved dosage form or the approved use of the medicinal ingredient. A first person would not be permitted to list a patent that claimed a different salt, hydrate or solvate to its approved medicinal ingredient. As such, the Proposed Regulations would create a loophole for generics under the *PM(NOC) Regulations*, allowing a generic manufacturer to file an ANDS for an alternative form of the medicinal ingredient, yet patents which claim that different form would have been ineligible for listing

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<sup>32</sup> *Supra*, note 26, at Article 10(3).

<sup>33</sup> *Supra*, note 30.

<sup>34</sup> Federal Food, Drug, and Cosmetic Act, 21 U.S.C. at 505(b)(2).



on the Patent Register. This would violate the principle behind the regulations – i.e. to prevent patent infringement.

As indicated in Section 10 of the 2003 Questions and Answers document regarding the consultations received on the draft IMI policy of that year, Health Canada’s Therapeutic Products Directorate clearly recognized the importance of maintaining a consistent approach to the concept of identical medicinal ingredients between the *Food and Drug Regulations* and the *PM(NOC) Regulations*<sup>35</sup>. Likewise, the 2017 Interim Policy states that the established meaning of “claim for the medicinal ingredient” continues to apply to the listing of patents on the Patent Register in accordance with section 4 of the *Patented Medicines (Notice of Compliance) Regulations*.

Indeed, the nexus between the definition of “claim for the medicinal ingredient” in the *PM(NOC) Regulations* and Health Canada policy is evident in the Regulatory Impact Analysis Statement accompanying the 2006 amendments to the *PM(NOC) Regulations*<sup>36</sup>:

*[The definition for “claim for the medicinal ingredient”] also serves to clarify, in so far as small molecule drugs are concerned, that patents claiming different crystalline, amorphous, hydrated and solvated forms of the approved medicinal ingredient (i.e. “polymorphs”) are eligible for listing when submitted in relation to the NDS, but that different chemical forms, such as salts and esters, are not. This accords with Health Canada policy on what constitutes an “identical medicinal ingredient” for the purposes of establishing pharmaceutical equivalence under section Co8.001.1 of the Food and Drug Regulations*<sup>37</sup>.

Any changes proposed by Health Canada to the *Food and Drug Regulations* must therefore also account for associated changes that will be necessary to the *PM(NOC) Regulations* to ensure the alternative forms of medicinal ingredients are eligible for listing on the Patent Register – including the definition of “claim for the medicinal ingredient” and the accompanying product specificity requirements.

The amendments also change the data protection provisions in the Regulations. These seem necessary to account for the changes to the term “medicinal ingredient”, which is also contained within the data protection section. It appears that the language has only been amended for the purpose of consistency, and are not otherwise intended to change or expand the 2006 list of variations that prevent a drug from being considered an “innovative drug”. IMC requests that clearer language be used in the RIAS to emphasize this point, including to confirm that the current list of variations will not be expanded to include a mixture of enantiomers or a drug that is a combination of the enumerated variants (for example of different ester and salt form of a previously approved drug)<sup>38</sup>.

Finally, the fact that the data protection regime was amended for the purpose of consistency is further evidence that the PM(NOC) regime must also be amended for consistency.

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<sup>35</sup> *Supra*, note 3.

<sup>36</sup> Canada Gazette, Part II, vol. 140, No. 21, October 18, 2006 at 1510.

<sup>37</sup> *Ibid.* at 1516-17.

<sup>38</sup> See draft subsection C.o8.004.1(1).



## CONCLUSIONS

The serious concerns set out above call into question Health Canada’s ability to pursue its regulatory mandate under the *Food and Drug Regulations* through the *Health Products and Food Branch* – that being to “take an integrated approach to managing the health-related risks and benefits of health products and food by minimizing health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products”<sup>39</sup>. Indeed, Health Canada’s current mandate stems from the multiple changes that were brought to the regulation of therapeutic products to protect patients and the public from unsafe products through Bill C-17, *Protecting Canadians from Unsafe Drugs Act*. In particular, Bill C-17 sought to enable Health Canada to regulate drugs more efficiently and effectively, and expanded the Minister of Health’s ability to collect additional product information from the sponsor, require new tests/studies, and monitor patient experience for product assessment. IMC is concerned that the Proposed Regulations fall short of these safety-related objectives and will result in negative consequences for Canadian patients, while opening the door for a weakened Canadian intellectual property regime.

In summary, our key recommendations are as follows:

- Manufacturers wishing to obtain approval for a new drug that does not contain the identical medicinal ingredient should not be eligible to proceed per the ANDS pathway and as a result should not be deemed interchangeable with the CRP;
- Alternate hydrates, solvates, polymorphs, and salts should not be declared therapeutically equivalent unless they have been compared with all other products for which they could be interchanged; and
- Changes must be made to the *PM(NOC) Regulations* to account for the increased variability in potentially infringing products.

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<sup>39</sup> Health Canada, Health Products and Food Branch, October 5, 2017, available online: <https://www.canada.ca/en/health-canada/corporate/about-health-canada/branches-agencies/health-products-food-branch.html?wbdisable=true#do>.