

INNOVATIVE MEDICINES CANADA SUBMISSION TO HEALTH CANADA

CONSULTATION ON POSSIBLE CHANGES TO THE *FOOD AND DRUG REGULATIONS* (GENERIC DRUG EQUIVALENCE AND RELATED TERMINOLOGY)

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 Health Canada's public consultation regarding proposed changes to the *Food and Drug Regulations* regarding generic drug equivalence.

IMC is deeply concerned and strongly disagrees with Health Canada's proposal to allow generics with the same therapeutic ingredient but in a different physicochemical form (e.g. salts, esters and complexes) compared to its Canadian Reference Product (CRP) to be approved via the Abbreviated New Drug Submission (ANDS) pathway. Key reasons as outlined below include:

1. Lack of clarity in defining "pharmaceutical alternatives" and the requisite safety standards for therapeutic equivalence.
2. A significant departure and lack of harmonization with major jurisdictions.
3. Serious intellectual property implications.

1. Lack of clarity in defining "pharmaceutical alternatives" and the requisite safety standards for therapeutic equivalence

Health Canada is proposing changes around establishing pharmaceutical equivalence between a proposed generic drug product and the CRP (the "Proposal"). IMC is concerned with the proposed introduction of a new concept of "pharmaceutical alternatives", which would be approvable under an ANDS. Under this Proposal generic drug products with different salts, esters or complexes of the medicinal ingredient, and/or generic 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.

The current Proposal is a marked departure from Health Canada's long-held policy that different complexes, esters, or salts of the same active moiety should be considered as *non-identical*¹. As recently as June 2012, a

¹ 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-



Health Canada consultation with stakeholders resulted in the Scientific Advisory Committee on Pharmaceutical Sciences and Clinical Pharmacology's recommendation that **"Salts, esters, complexes of the same active moiety, different isomers, or mixtures with different proportions are not considered identical medicinal ingredients"** [emphasis added].²

In this section, we discuss our concerns with the Proposal within the context of: (a) the non-identical physicochemical, pharmacodynamic and toxicity profiles of pharmaceutical alternatives; (b) the unwelcome consequences of deemed therapeutic equivalence and interchangeability; (c) the diluted impact of policies regarding the point at which sameness is determined; and (d) Health Canada's safety-related mandate.

a) Non-identical physicochemical, pharmacodynamic and toxicity profiles of pharmaceutical alternatives

Health Canada's proposed departure from its existing treatment of compounds such as salts and esters as non-identical is particularly concerning given the safety and efficacy rationale underlying the *status quo*. For example, as a result of 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 "based on the fact 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".³ The same consideration was afforded to esters, being that they were acknowledged by Health Canada as having covalent bonds that do not dissociate on dissolution in the gastrointestinal tract, resulting in the active moiety that reaches the bloodstream not being identical to the reference product⁴.

Indeed, there are numerous studies within the academic literature that point to specific examples of how alternative salt or ester 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 use⁵. 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

[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, "Different complexes, esters, or salts of the same active moiety are considered non-identical".

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

³ 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

⁴ *Ibid.*

⁵ 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.



being distinct chemical entities with distinctive chemical and biological profiles that may lead to differences in their clinical efficacy and safety⁶.

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 ⁷	besylate 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 ⁸	tosylate vs. pamoate	Variable solubility profiles.	<i>In vivo</i> absorption rate of trazodone in tosylate salt significantly lower
Perindopril ⁹	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.
Propoxyphene ¹⁰	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.
Alprenolol ¹¹	hydrochloride and fumarate vs. benzoate, maleate and sebacate	Variable solubility profiles.	Hydrochloride and fumarate have the highest water solubility and gave the most serious oesophageal lesions, where low-solubility salt forms of maleate and sebacate produced no irritant effects.

Important safety concerns also arise regarding the use of different esters, being that some of the alternative physicochemical forms of esters may contain functional groups that may cause genotoxicity – therefore

⁶ 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.

⁷ *Supra*, note 5.

⁸ *Supra*, note 5.

⁹ Patel, Aateka, et al. "Pharmaceutical salts: a formulation trick or a clinical conundrum?." *British journal of cardiology* 16.6 (2009): 281-286.

¹⁰ *Ibid.*

¹¹ *Supra*, note 9.



requiring additional safety testing. For instance, alkyl esters of phosphonates and sulfonates are considered alerting functional moieties for genotoxicity¹². The alerting structures are considered to have genotoxic (mutagenic) potential, creating a need for the enforcement of genotoxicity testing on these physicochemical forms. The use of esters requires that the mechanism of action be well understood to ensure there is no impact on safety for efficacy.

In addition, in respect of true chemical sameness and in consideration of a determination of pharmaceutical equivalence, a new drug – in comparison with the innovator's drug – should contain identical amounts of identical medicinal ingredients throughout its approved shelf-life and within each commercial lot marketed. If the active medicinal ingredient degrades within the new drug (i.e. at different rates and to different extents versus marketed drug), it does not contain identical amounts as per the marketed drug. The impurity profile of both drugs therefore should be "equivalent" prior to identifying an active ingredient as being identical. The same holds true for stability profiles.

We also wish to emphasize the growing body of medical evidence aimed at clinicians that caution 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 patients¹³. Notably, this study discusses the issue of inter-individual variability that may pose risks to patients given the unpredictable nature of their response to generic 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 certainty¹⁴. Another article, by Meredith, summarizes a number of concerns that have emerged relating to the interchangeability between innovator drugs and generic counterparts using the example of amlodipine (see also Table 1)¹⁵. In particular, the author notes that "To date, there is no reliable way of predicting exactly the effects of changing the salt form of an active substance", adding that "It 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".

Differences between pharmaceutical alternatives and their CRP are even more pronounced when dealing with dosage forms (i.e. drug-device combinations, inhaled products) where drug-device and patient-device interfaces are critical factors in determining drug performance. For this reason, we seek clarity around the Proposal that pharmaceutical alternatives could be generic drug products with different but comparable

¹² Müller, Lutz, et al. "A rationale for determining, testing, and controlling specific impurities in pharmaceuticals that possess potential for genotoxicity." *Regulatory Toxicology and Pharmacology* 44.3 (2006): 198-211.

¹³ *Supra*, note 9.

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

¹⁵ 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.



dosage forms to the CRP. In the absence of clarity, there is a risk of the unwanted misinterpretation that pharmaceutically alternative products only have to be in a comparable dosage form without any regard for different/same physicochemical form to meet the definition. The reality is that comparable dosage forms vary widely. We offer as an example the Patented Medicine Prices Review Board's wide-ranging classification of comparable dosage forms, which consists of nine different categories of dosage forms (topical, nasal/pulmonary, oral solid, oral liquid, vaginal, parenteral, otic/ophthalmic, rectal, dental/sublingual and buccal) – each being an umbrella term for anywhere from 5 to 32 possible product types¹⁶.

According to the Proposal, the submission requirements and evidence standards for pharmaceutical equivalents and alternatives would be addressed through a guidance document. The Proposal further advises that it is the first in a series of consultations on the topic. It is not clear from this statement whether additional public notice would be provided in regard to such guidance. Given the significant ramifications of this integral component of generic equivalence, Health Canada is strongly encouraged to consult with stakeholders as to any such form of guidance. In addition, a valuable source of information for any particular product that should be considered is the CRP manufacturers' input when submissions of different salts, esters, complexes or different but comparable dosage forms ANDS are received or contemplated from generics. The innovative manufacturers of CRPs will often have experience and knowledge 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. If the Proposal moves forward despite the stated observation, an official pathway similar to the FDA's "citizen petition" should be put in place, allowing manufacturers to submit their scientific evidence while mandating a response from Health Canada within a prescribed timeline¹⁷. Disclosure on the Submissions Under Review ("SUR") list of pharmaceutical alternative forms 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.

b) Unwelcome consequences of deemed therapeutic equivalence and interchangeability

The above commentary highlights the fact that establishing bioequivalence between drug products containing different salts or esters of the same active substance will not usually suffice to claim therapeutic equivalence and consequently substitutability/interchangeability. Even if a generic drug is safe in and of itself, this does not mean that the drug should automatically be interchangeable with the innovative CRP. For comparable safety and efficacy, proof that pharmacokinetics, pharmacodynamics and/or toxicity of the active substance are not modified must be provided.

And yet, Health Canada proposes to include pharmaceutical alternatives in the ANDS pathway, thereby paving the way for the issuance of a notice of compliance (NOC) that would also constitute a declaration of

¹⁶ Patented Medicine Prices Review Board, *Patentee's Guide to Reporting*, July 2015, available online: <http://www.pmprb-cepmb.gc.ca/view.asp?ccid=523#819>

¹⁷ A "citizen petition" is a process provided by the US FDA for individuals and organizations to make requests to the FDA for changes to health policy (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.



therapeutic equivalence. By virtue of section C.08.004(4) of the *Food and Drug Regulations*, a NOC issued in respect of a generic drug on the basis of information and material contained in an ANDS shall constitute a declaration of equivalence to the CRP.

The proposal to deem therapeutic equivalency upon the issuance of an NOC may be considered by provincial formularies when decisions are made for the listing of a new drug as interchangeable with the CRP. Drug interchangeability refers to the ability of a pharmacist to substitute one drug for another without contacting the physician to change the prescription. The requirements governing interchangeability vary by province and are directly affected by any changes to the regulatory approval regime. Since most provinces generally only reimburse pharmacies for the lowest cost interchangeable drug, a pharmacist would have no choice but to dispense such a pharmaceutical alternative if it were the cheapest¹⁸.

Before such a substitution by pharmacists is applied, it is of utmost importance that the generic drug being substituted is proven to be therapeutically equivalent to its innovator drug. As discussed in the previous section, there are significant safety concerns with broadening the definition of “interchangeable” and permitting/requiring pharmacists to dispense any of a multitude of drugs to patients¹⁹.

For example, if multiple drugs are interchangeable, this would mean that 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 (as illustrated by Figure 1). However, Drugs B, C and D would not have been compared to each other but would be interchangeable under provincial interchangeability rules. Given the potential interchangeable scenarios in pharmacy practice, Health Canada must be extremely mindful in creating the potential for pharmaceutical alternatives to be declared equivalents.

¹⁸ 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.

¹⁹ 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.”

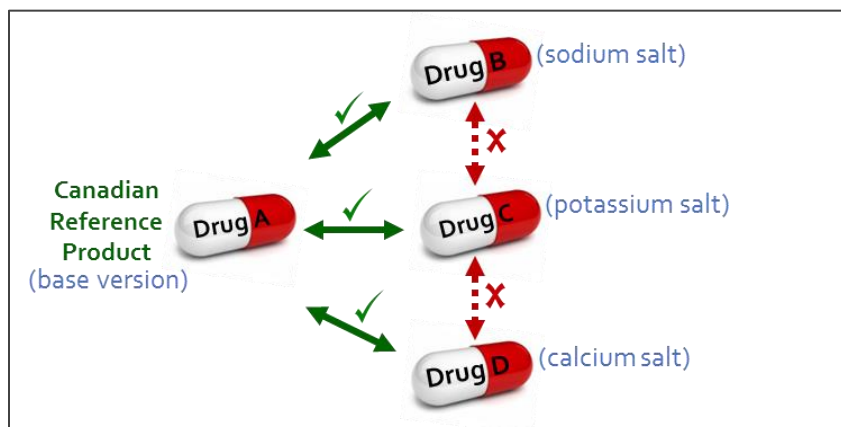


Figure 1. Where Drug A is a CRP for each of Drugs B, C and D the ANDS process will have involved a comparison of products with Drug A (green arrow). However, Drugs B, C and D would not have been compared to each other as part of the ANDS process (red arrow).

It is our understanding that even pharmaceutical “alternatives” that have been approved via the NDS pathway at the federal level are being interchanged in practice at the provincial level. As such, alignment and consideration of the Proposal is needed between federal and provincial regulatory agencies. Knowing that the provinces will automatically deem a generic product as interchangeable, Health Canada should consider the possibility of subjecting patients to undue risk and harm if it implements this proposal.

Correspondingly, there is an argument to be made that post-marketing adverse drug report (ADR) collection for the purpose of labelling safety updates will be jeopardized. For example, it will not be possible to distinguish ADRs from one form of a drug to another, since much of the time the brand name is not specified in adverse drug reporting.

c) Diluted impact of policies regarding the point at which sameness is determined

By way of its current Proposal, Health Canada is mandating against its long-held position that the determination of sameness “should occur at the stage where the drug products are ready to be administered to, or consumed by, Canadians” (i.e. at the final dosage form (FDF) stage)²⁰. In the case that led to this policy, Health Canada’s rationale behind determining sameness at the dosage stage was at issue. Specifically, Health Canada contended that ingredients must be compared in the finished product to account for the fact that *in situ* transformations and reactions take place during manufacture, which may lead to different salts (in that case)²¹. Health Canada furthermore noted that the determination of sameness at the input stage “could result in a drug being declared equivalent [...] even where the Minister is not satisfied of its safety and effectiveness”²².

²⁰ Health Canada, *Notice: Interim Policy on Health Canada's Interpretation of Medicinal Ingredient*, June 16, 2015, available online: <http://www.smart-biggar.ca/files/Health%20Canada%20Notice%20Interim%20Policy%202015.pdf>

²¹ *Apotex Inc. v. Canada (Health)* 2013 FC 1217 at 160.

²² *Apotex Inc. v. Canada (Health)* 2013 FC 1217 at 135



More recently, in October 2017, Health Canada released an *Interim Policy on Health Canada's Interpretation of Medicinal Ingredient and Assessment of Identical Medicinal Ingredient*, expanding upon the interim policy published in 2015 (the "2017 Interim Policy")²³. The 2017 Interim Policy appears to indicate that only where medicinal ingredients are the same as the CRP in their FDF will medicinal ingredients be considered "identical". However, the 2017 Interim Policy is unclear as to whether or not medicinal ingredients that remain in different physicochemical forms in the FDF stage would go through the ANDS pathway. It should be clarified that, in such instances and in view of the profound concerns expressed herein, these would need to be filed via a NDS.

The end result of the current Proposal, even when paired with the 2017 Interim Policy, would be that Health Canada would seek to mitigate certain risks associated with manufacturing-level transformations, while at the same time introducing new safety risks inherent to pharmaceutical alternatives (as demonstrated above). It is imperative that additional clinical safety, effectiveness and quality data be adequate and conclusive in such instances – which, as noted above, is extremely difficult to ascertain.

Given the above concerns, we refer to advantages of Health Canada's existing *Interim Policy on Health Canada's Interpretation of Medicinal Ingredient (2015)*²⁴, and seek rationale as to why the Proposal is diverging from this regime.

d) Health Canada's safety-related mandate

The above noted concerns 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"²⁵. 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. Furthermore, generic medicines should be subject to pharmacovigilance planning as per the International Conference on Harmonization E2E Guideline and include integrated risk

²³ Health Canada, *Updated Notice: Interim Policy on Health Canada's Interpretation of Medicinal Ingredient and Assessment of Identical Medicinal Ingredient*, October 5, 2017, available online: <https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/policies/notice-interim-policy-health-canada-interpretation-identical-medicinal-ingredient.html>

²⁴ *Ibid.*

²⁵ 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>



management strategies with risk management plans²⁶. Based upon the increase of drug shortages and quality issues with generics, pharmacovigilance activities should be enhanced for generics regulated by a mandatory regulatory review framework.

There are also labelling considerations with respect to pharmaceutical alternatives. Based upon the current Health Canada framework regarding the Notification of Safety Labelling Changes to the Product Monographs of Pharmaceutical Drug Products, manufacturers of approved generic products are expected to file submissions to update their labelling within 30 days of the posting date of the table describing the labelling change for the CRP²⁷. It is important to note that the 30-day period is a recommendation, not a mandatory requirement, to support transparency and drug safety for Canadian patients. Actions should be taken to ensure that these updates are done in a timely manner.

Through the lens of Health Canada's safety-related mandate, the importance of establishing the safety and efficacy of a new drug in this context cannot be overstated. We commend Health Canada's July 2017 draft policy on bioequivalence of multiphasic drugs, which proposes requiring more stringent comparative bioavailability requirements for generics of multiphasic innovative drugs²⁸. The basis for the Proposal was stated to be Health Canada's recognition that, for some such multiphasic products, the current comparative bioavailability standards for modified-release products may not be sufficient. If Health Canada is to proceed with their proposed amendment to the definition of therapeutic equivalency, they need to enforce accountability on generic manufacturers in a like manner, particularly if they are relaxing the required data to secure generic drug approval.

In addition, we respectfully recommend that Health Canada conduct in-depth consultations with the Therapeutic Products Directorate's (TPD's) Bureau of Pharmaceutical Science (BPS) and clinical bureaus, in order to understand their perspectives on the validity and credibility of this proposal and ensure alignment when assessing generic submission with different salts, esters, complexes, etc. It is our understanding that BPS does not currently review these types of submissions and asks that the clinical bureaus do so. In our experience, the clinical bureaus expect that different salts (for example) with different release profiles have potential effects on active ingredients and are not assumed to be inert.

²⁶ See, e.g. Health Canada, *Guidance Document - Submission of Risk Management Plans and Follow-up Commitments*, June 26, 2015, available online: <https://www.canada.ca/en/health-canada/services/drugs-health-products/reports-publications/medeffect-canada/guidance-document-submission-risk-management-plans-follow-commitments.html>.

²⁷ Health Canada, *Notice - Notification of Safety Labelling Changes to the Product Monographs of Pharmaceutical Drug Products*, February 21, 2013, available online: <https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database/label-safety-assessment-update/notification-safety-labelling-changes-product-monographs-pharmaceutical-drug-products.html>.

²⁸ Health Canada, *Notice: Proposed Modification to Bioequivalence Standards for Multiphasic Modified-Release Drug Products*, July 27, 2017, available online: <https://www.canada.ca/en/health-canada/services/drugs-health-products/public-involvement-consultations/drug-products/multiphasic-modified-release.html>



2. A significant departure and lack of harmonization with major jurisdictions

In addition to the safety and efficacy concerns discussed above, IMC does not believe that Health Canada's stated objective for the Proposal, "to create greater alignment and convergence with the practices of other major regulatory jurisdictions and to standardize their use with those applied internationally" will be achieved.

In fact, Health Canada is not harmonizing but creating a position that is different from EU and US regulatory regimes. This creates the unwanted opportunity for generics to be sold in Canada without meeting adequate safety standards and without being subject to the same stringent safety vigilance regime as implemented for innovators. The legislation for regulatory approval is different in the US and EU as compared to Canada, and therefore any suggestion to harmonize with these countries must take this into account, as further explained below. It is of note that both Australia and Japan employ the same equivalence regimes as Canada's current system – i.e., a proposed generic drug product must be a pharmaceutical equivalent of the reference product²⁹.

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"³⁰. The European Agency for the Evaluation of Medicinal Products (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"³¹.

Thus, 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 equivalent³². Health Canada on the other hand is proposing that both equivalents and alternatives be treated equally in their pursuit of a NOC through the ANDS pathway, with no clear mandate for additional safety and efficacy data – thus, a marked departure from EU regulations. Against this background, some regulatory authorities

²⁹ 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.

³⁰ European Agency for the Evaluation of Medicinal Products, *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

³¹ *Ibid.*

³² 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:

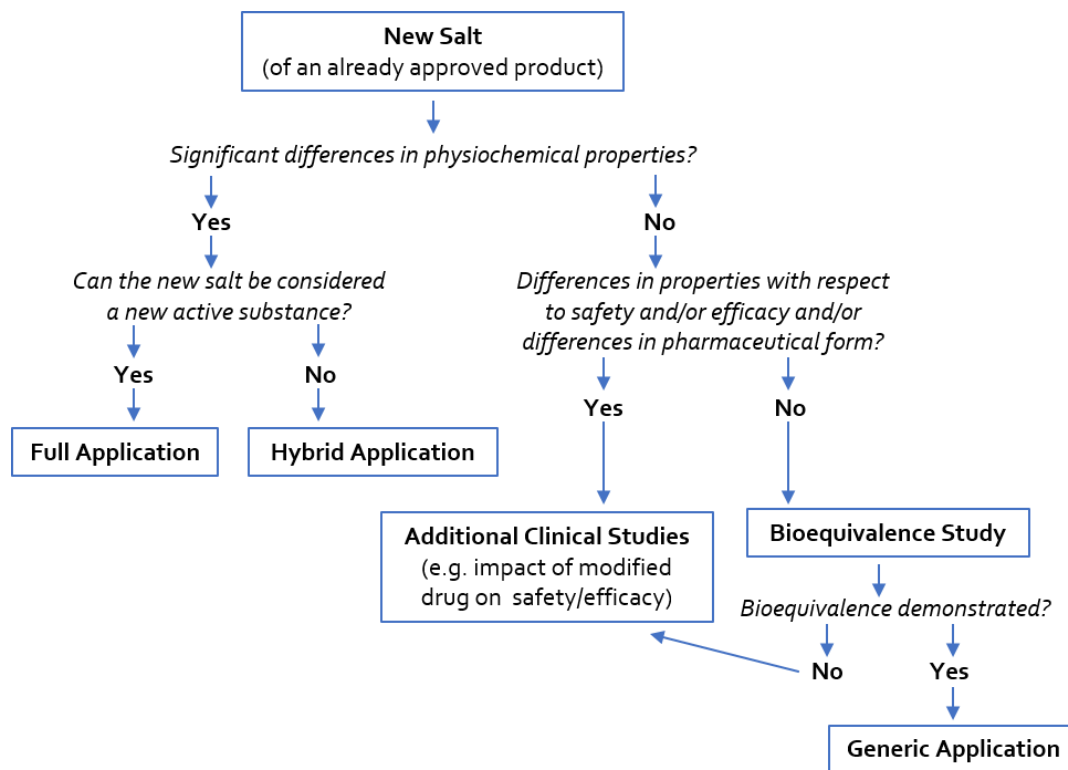
http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC50004481.pdf.



demand more extensive investigations before approval of a modified salt or ester form. For example, in 2009 the EMA issued a letter to pharmaceutical manufacturers stating that in medicinal products containing mesitates, isetionates, tosilates or besilates, alkyl or aryl sulfonic ester contaminations might be formed during the production of the active ingredient and remain as impurities in the product³³. As these have been associated with mutagenic, carcinogenic or teratogenic effects, manufacturers were mandated to provide risk assessment reports to regulatory authorities.

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 application³⁴.

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



A discussion about these various routes follows³⁵.

³³ European Medicines Agency, *Request to assess the risk of occurrence of contamination with mesilate esters and related compounds in pharmaceuticals*, January 24, 2008, available online:

http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/11/WC500015375.pdf

³⁴ As adapted from Schulze, Brita. "Different Salts of a Drug Substance—Comparison of Regulatory Pathways in the EU and USA."

³⁵ *Ibid.*



- 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 demonstrated³⁶. The definition of a generic medicinal product states explicitly that a different salt in a generic medicinal product is considered the *same active substance* as the reference medicinal product *only* if it does not differ “significantly in properties with regard to safety and/or efficacy”³⁷. It is the responsibility of the applicant to generate data to address the above cited criteria³⁸. 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.”³⁹
- 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.”⁴⁰ 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., 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 outlined⁴¹. As a consequence, a full dossier must to be submitted.

The definition of pharmaceutical alternatives under the US FDA’s Orange Book is the following: “Drug products are considered pharmaceutical alternatives if they contain the same therapeutic moiety, but are different salts, esters, or complexes of that moiety, or are different dosage forms or strengths”⁴². However, the definition of therapeutic equivalence in the Orange Book precludes the substitutability of pharmaceutical alternatives, and “drug products are considered to be therapeutic equivalents only if they are pharmaceutical equivalents for which bioequivalence has been demonstrated, and they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions

³⁶ *Supra*, note 32, at Article 10(2)(b).

³⁷ *Supra*, note 32, at Article 10(2)(b).

³⁸ 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.

³⁹ *Supra*, note 32, at Article 10(2)(b).

⁴⁰ *Supra*, note 32, at Article 10(3).

⁴¹ *Supra*, note 38.

⁴² U.S. Department of Health and Human Services, Food and Drug Administration Center for Drug Evaluation and Research, *Approved Drug Products with Therapeutic Equivalence Evaluations, 2017*, available online:

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/UCM071436.pdf>



specified in the labeling”⁴³. Based on this definition, it is not possible to register a different salt of an already approved drug substance as a generic medicinal product in the US.

As a consequence, in the US, a different salt can only be authorized as New Drug Application according to Section 505(b)(2) of the *Federal Food, Drug and Cosmetics Act*⁴⁴, which resembles the EU’s hybrid application. Under the 505(b)(2) regulatory pathway, the sponsor of a 505(b)(2) application will refer to pre-clinical and clinical data (including safety data) of an originator. In addition, the sponsor must provide data that allow bridging from the original medicinal product to the newly developed 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 additional therapeutic studies.

It is worth noting that Health Canada is already using a lower requirement for bioequivalence determination for C_{max} (point-estimate rather than 90% confidence interval) as compared to both the FDA or EMA. In fact, a study of bioequivalence of generic drugs commercialized on the Canadian market found that only 57.09% in 2012 and 65.20% in 2013 of the total eligible generics were bioequivalent and had all the required data from Health Canada’s website⁴⁵. The study’s authors concluded, “It is quite remarkable that somehow, these generics were able to find their way on the Canadian generic market, even though they were not ideal for clinical use”. This, combined with proposed loosening of criteria for therapeutic alternatives would increase the probability of lack of identity between the generic and its CRP.

3. Serious intellectual property implications

Any changes contemplated to the *Food and Drugs Regulations* must also consider the impact on other regulatory regimes applicable to pharmaceuticals in Canada. For instance, Canada deliberately established the *PM(NOC) Regulations* (patent linkage) regime so that Health Canada would be prohibited from issuing regulatory approval to a generic drug until the innovator’s patents were first addressed. More particularly, the regulation-making power in subsection 55.2(4) of Canada’s *Patent Act* that has been used to implement the *PM(NOC) Regulations* provides that the Governor in Council “may make regulations respecting the infringement of any patent that, directly or indirectly, could result or results from the making, construction, use or sale of a patented invention” by a generic manufacturer⁴⁶.

Accordingly, any change to the *Food and Drug Regulations* to permit pharmaceutical alternatives would result in a loophole for the generics under the *PM(NOC) Regulations* and would violate the principle behind the regulations – i.e. to prevent patent infringement. It would be very unfair to continue to require that the innovator NDS dovetail with the claims of a patent – meaning that claims covering pharmaceutical

⁴³ *Ibid.*

⁴⁴ *Federal Food, Drug, and Cosmetic Act*, 21 U.S.C. at 505(b)(2).

⁴⁵ Trudel E, Parent M, Côté A (2016) “Bioequivalence of Generic Drugs Commercialised on the Canadian Market”. *J Develop Drugs* 5: 150.

⁴⁶ *Patent Act*, R.S.C., 1985, c. P-4.



alternatives could not be listed on the Patent Register – but then allow another manufacturer to rely on the data in that NDS for approval without having to effectively address the PM(NOC) regime.

As indicated in Section 10 of the 2003 Questions and Answers document regarding the consultations received on the draft IMI policy of that year, TPD 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*⁴⁷. 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*⁴⁸:

*[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*⁴⁹.

To maintain consistency with the Proposal, the definition of "claim for the medicinal ingredient"⁵⁰ in the *PM(NOC) Regulations* would need to be amended to include "different chemical forms of the medicinal ingredient". Other definitions in the *PM(NOC) Regulations* that include "medicinal ingredient" as part of the definition, including "claim for the dosage form", "claim for the formulation", and "claim for the use of the medicinal ingredient", would also need to be amended. Likewise, the definition of "claim for the dosage form"⁵¹ would have to be extended to "different but comparable dosage forms".

It is important to note that, as a result of its very recent negotiations under the Canada-European Union Comprehensive Economic and Trade Agreement (CETA), Canada was required to amend its intellectual property legislation (*Patent Act* and *PM(NOC) Regulations*) to offer comparable protections to Europe. The changes proposed by Health Canada would dilute the obligations enshrined in CETA by putting Canada out of step with the EU and tilt the intellectual property landscape to favour generics over innovators.

Conclusions

Health Canada's consultation on the Proposal and the 2017 Interim Policy offers stakeholders the opportunity to contribute to the Federal Government's valuation of the laws and policies respecting generic

⁴⁷ *Supra*, note 3.

⁴⁸ *Canada Gazette, Part II*, vol. 140, No. 21, October 18, 2006 at 1510.

⁴⁹ *Ibid.* at 1516-17.

⁵⁰ *Patented Medicines (Notice of Compliance) Regulations*, SOR/93-133 at subsection 2(1).

⁵¹ *Ibid.* at subsection 2(1).



drug equivalence. Supported by a team of our industry's regulatory and intellectual property law experts, the primary objective of our submission is to impart our industry's extensive practical knowledge of the NDS and ANDS regulatory pathways and patent legislation. In so doing, we respectfully communicate and highlight evident risks and concerns with how these proposals might impact upon key enforcement activities meant to ensure that Health Canada and generics abide by their commitments to patient safety.

In particular, our association is concerned that the consultation proposals may fall short of these safety-related objectives and result in negative consequences for Canadian patients, while opening the door for a weakened intellectual property regime. Innovative Medicines Canada strongly recommends that additional consultations are required to ensure that these policy concerns and implications are adequately assessed in an open and inclusive manner, certainly well in advance of proceeding further with any draft regulatory proposals. The implications for patient safety as well as the need for additional pharmacovigilance activities must be clearly identified and assessed.

In summary, our key recommendations are as follows:

- Keep Health Canada's existing *Interim Policy on Health Canada's Interpretation of Medicinal Ingredient (2015)*.
- Maintain alignment with other regulators.
- Ensure continued and ongoing consultation with industry prior to drafting new regulations and/or guidelines.
- Meet with Innovative Medicines Canada to discuss its current submission.

Innovative Medicines Canada appreciates Health Canada's careful consideration of our comments. We recognize that the current Proposal is the first in a series, and would appreciate the opportunity to meet with Health Canada representatives to elaborate and to engage in a transparent and collaborative discussion.