

# Interpretation of "Identical Medicinal Ingredient"

## Questions and Answers

(dated 2003/07/09)

The draft policy *Interpretation of "Identical Medicinal Ingredient"* was posted on the TPD Website for Stakeholder consultation on January 13, 2003. Following is a compilation of the comments received from the respondents, together with a discussion and recommendation for revisions (where necessary). The comments are excerpts from the original responses.

	Comment Received	Discussion and Recommendations
<b>1. General</b>		
1.1	Does this policy apply to Biological products? Specifically, would it apply to the interchangeability of Albumin, i.e. between Human Serum Albumin and recombinant Human Albumin.	The draft policy is intended for chemical entity-type drug submissions. This would exclude biological and radiopharmaceutical products. The scope has been amended to clarify this.
1.2	The "Guiding Principals" of this policy state that the listed considerations are not intended to be exhaustive and could be amended to include other classes of medicinal ingredients. It is not clear from this statement whether additional public notice would be provided in regards to such amendments. Given the significant ramifications of this policy to the pharmaceutical industry, Health Canada is strongly encouraged to consult with stakeholders in regards to any changes to this policy or its implementation.	It is understood that revisions will go through the consultative process.
1.3	Issues related to a new drug's "pharmaceutical equivalence" to a CRP could extend beyond the context of the medicinal ingredient. Specifically, the policy excludes considerations related to the CRP's drug formulation (e.g., excipients, coatings) and/or physical characteristics (e.g. shape and/or size) that may be important to establishing "pharmaceutical equivalence". If Health Canada has established any internal positions in these regards, it is expected that these would be addressed in a separate policy.	This is not within the scope of this policy.
1.4	In Canada, when TPD has expressed concern about the appropriateness of an ANDS, TPD has reviewed such submissions on a case-by-case basis, and typically has required generic applicants to file a full NDS. This has led to some uncertainty within the industry as to which route an applicant should take. For example in Reddy-Cheminor Incv. Minister of Health, 2001 FCT 1065, the applicant Reddy-Cheminor Inc. ("Reddy-Cheminor") has commenced a judicial review application of the Minister's refusal to treat Reddy-Cheminor's product as pharmaceutically equivalent to the brand product and required Reddy to do an NDS rather than an ANDS.	Health Canada is aware of this case ( <i>Reddy -Cheminor Inc. v. The Attorney General of Canada (Minister of Health)</i> 2003 FCT 542). This policy clarifies the requirements and assists the Directorate in defining the submission type.
1.5	Are there really clear distinctions between the terms solvate, clathrate, complex? If solvent molecules are tightly bound in the solid state or have a high affinity for the active moiety in solution, then a conclusion of "chemical identity" has to be questioned for different 'solvates'.	Definitions have now been included in the glossary.
1.6	As a starting point in respect of true chemical identity and in consideration of a determination of pharmaceutical equivalence, a new drug, in comparison with the innovator's drug, should	The generic sponsor is required to meet acceptable limits for individual impurities.

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	contain identical amounts of identical medicinal ingredients throughout its approved shelf-life and within each commercial lot marketed. ... The impurity profile of both drugs should also be 'equivalent' prior to identifying an active ingredient as being identical. The same holds true for stability profiles.	Where relevant, stability studies are required to show the form of the drug substance is acceptable throughout the shelf life. Any change in polymorphic form is of concern and is addressed on a case by case basis.
<b>2. Polymorphic and Pseudopolymorphic Forms (e.g. Hydrates, Solvates) of the Drug Substance</b>		
2.1	FDA scientists have reviewed the available literature respecting different polymorphs of a drug substance and have found that "it is scientifically concluded that differences in polymorphic compositions of drug substances in generic drug products and reference listed drugs are not directly relevant in the determination of drug substance sameness in ANDAs." (L.X. Yu et al. Scientific Considerations of Pharmaceutical Solid Polymorphism in ANDAs, April 2003, Pharmaceutical Research). ... Different polymorphic forms in crystalline or anhydrous state and different solvates may have different solubility and dissolution rates that can impact on bioavailability and stability. However, the tests required to obtain approval of an ANDS will demonstrate any unacceptable differences.	This further supports Health Canada's position. The reference noted by the respondent includes a detailed discussion on the relevance of polymorphism, including solvates, hydrates and anhydrous forms, on determining the "sameness" of the drug substances in ANDAs.
2.2	These differences in [solid state] properties may affect the ability of the medicinal ingredient to be formulated into an effective dosage form. These differences in properties typically do not result in significant differences in respect of bioavailability of the solid state forms. ... However, the literature has recognized that the differences in physical properties in comparing one solid state form to another may be more significant. The leading text entitled Pharmaceutical Dosage Forms (2nd Ed., Marcel Dekker, New York and Basel) ... In some cases, these differences in properties between different solid state forms can lead to differences in bioavailability. ... In light of the potential differences in the safety and effectiveness profiles of different solid state forms, it is important that Health Canada maintain its requirements for appropriate in vivo and/or in vitro testing to confirm the safety and effectiveness of a subsequent entry drug product.	Health Canada draws attention to the guiding principles of the policy.  As stated in the policy, Health Canada will continue to require supporting <i>in-vivo</i> and/or <i>in-vitro</i> studies to demonstrate the equivalence of the drug products. This would provide evidence that differences in pseudopolymorphic form would not be expected to effect safety or efficacy.
2.3	In such cases where the active moiety is not physically and chemically identical, bioequivalence studies alone may not reflect the full impact changes to chemical constituents may have on the living organism. ....Accordingly, it is recommended that wording be added to the Draft Policy under Guiding Principles that takes this into account. It should simply state: "Where the formulation within which the 'identical medicinal ingredient' is to be produced is not chemically and physically identical to the first entry product, the consequences of such differences shall be addressed by appropriate in vivo and/or in vitro studies."	
2.4	It is important to keep in mind that bioavailability can vary with solid state form. As a result, it will remain important that the TPD continue to require appropriate in vivo and in vitro testing to ensure that there are no significant differences in the safety and efficacy profiles of drug products containing different solid state forms of a medicinal ingredient.	

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2.5	<p>Different physical forms may have different properties inducing different hygroscopicity, drying characteristics, density, flowability, filterability, ease of handling, mechanical properties, stability (chemical and physical), solubility, crystallinity, ease of preparation, purity, greater yields, and unique spectra and diffraction patterns. These different properties are due to the different arrangements of molecules in the solid state and are discussed in the document attached. Accordingly, in its interpretation of the expression "identical medicinal ingredient" the Directorate should not apply it for different physical forms of the same drug. Stated differently, it is incorrect to classify different physical forms as pharmaceutically equivalent or identical medicinal ingredients. ... Based on the arguments presented in the attached document and the published literature, different physical forms are not pharmaceutically equivalent, and to define them as identical medicinal ingredients is incorrect.</p>	
2.6	<p>"(a) Anhydrous and the various hydrated forms of the same medicinal ingredient would generally be considered identical." &lt;Respondent name&gt; agrees that it is correct to state that the principle is 'general'. It makes the most sense to take a case-by-case approach in respect of different hydrates, i.e., this principle cannot be applied universally. In order to fully reflect this, it is suggested that the following statement be added, i.e. <i>Results of appropriate studies of the product should be available.</i></p>	
2.7	<p>In the draft policy, Health Canada is suggesting that hydrates and solvates be considered identical medicinal ingredients and therefore pharmaceutically equivalents. If the new policy is to be implemented, it will be very important for Health Canada to ensure that the requirements of in vitro and in vivo testing remain to address concerns of differences in physical properties of medicinal ingredients.</p>	
2.8	<p>... However, where the medicinal ingredient is not exactly the same in every respect [physically and chemically identical], careful consideration needs to be made with respect to non-medicinal ingredients and the impact they have on the medicinal ingredient form which is being sought to replace the medicinal ingredient in the original product. This consideration appears to be addressed by the Directorate when it provides that "any concern arising from these differences in physical properties is generally addressed by appropriate in vivo and / or in vitro studies", however, this comment is directed to the physical properties of the active moiety and, with respect, does not appear to take into consideration the physical environment in which the active moiety is situated.</p>	<p><i>In-vivo</i> and <i>in-vitro</i> studies are on the formulated product, and would take into account the effect of the proposed formulation.</p>

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2.9	<p>The ICH Q6A Guideline defines polymorphisms including “solvation or hydration products (also known as pseudopolymorphs)”. Health Canada’s Draft Guidance also emphasizes this statement: “Polymorphism can also include solvation or hydration products (also known as pseudopolymorphs).”</p> <p>Therefore, solvates of medicinal ingredients are considered polymorphs, the same pure substance with a different physical property. Polymorphs, in the strictest sense, “are different crystalline forms of the <u>same pure substance</u>” (Ref: David J.W. Grant. Theory and Origin of Polymorphism. In H.G. Brittain (eds.). Polymorphism in Pharmaceutical Solids. Marcel Dekker, 1999.) and are therefore identical. It follows that since the <i>draft policy</i> addresses the term ‘identical’ in the context of <u>chemical properties</u> then the reference to solvated forms of medicinal ingredients in guiding principle (b) may not be considered relevant.</p>	<p>The respondent appears to be in agreement with the policy.</p> <p>This policy provides clarification of the term "identical medicinal ingredient".</p> <p>Also the guiding principles in the policy have been amended to describe "forms of the same active moieties" rather than "forms of the same medicinal ingredient."</p>
2.10	<p>On the basis of the draft policy, TPD is suggesting to change its interpretation of "identical medicinal ingredients" such that anhydrous and various hydrated forms of a compound, as well as unsolvated and various solvated forms of a compound, which previously were held to be different medicinal ingredients, would be considered the same medicinal ingredient.</p>	<p>In the past, Health Canada has considered different hydrated forms to be identical. This policy clarifies our position on pseudopolymorphs.</p>
2.11	<p>We are in agreement with point (a) of the Guiding Principles (lines 54 &amp; 55) which states that “Anhydrous and the varied hydrated forms of the same medicinal ingredient would generally be considered identical.”</p>	<p>This is in agreement with the policy.</p>
2.12	<p>We are in agreement in principle with point (b) of the Guiding Principles (lines 57 - 59) which states that “Unsolvated and the various solvated forms of the same medicinal ingredient would generally be considered identical, provided the solvate content is within acceptable levels”.</p>	
2.13	<p>&lt;Respondent name&gt; agrees with the draft policy that unsolvated and various solvated forms of the same medicinal ingredient would generally be considered identical provided the solvate concentration is within acceptable levels.</p>	
2.14	<p>In addition, if a compendial standard (e.g. USP) recognizes a particular hydrated or solvated form of medicinal ingredient, other forms should not be considered identical.</p>	<p>The drug substance must comply with compendial standards for purity and potency according to Section C.01.011(4) of the <i>Regulations</i>. However, there is no requirement to claim a compendial standard if it exists. The sponsor would not be able to claim a compendial standard if that compendia recognized a particular form.</p>
2.15	<p>&lt;Respondent name&gt; agrees with the draft policy that anhydrous and the various hydrated forms of the same medicinal ingredient should be considered identical. ... We trust that where the draft policy refers to anhydrous forms, that anhydrate forms are also included. Anhydrous means no significant amounts of water in the compound (neither loosely bound nor bound within the crystal lattice) whereas anhydrate means no water bound within the crystal lattice but there could be significant levels (e.g. in the order of 0.1% to 2%) of water loosely associated with the solid compound.</p>	<p>Definitions have now been included in the glossary. The policy has been revised to specify anhydrates and anhydrous forms.</p>
2.16	<p>&lt;Respondent name&gt; proposes that hydrates and solvates not be treated separately, and instead proposes the following wording for the policy: unsolvated forms (including anhydrous forms)</p>	<p>These sections have been treated separately to provide further clarity on our position for hydrates and solvates.</p>

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	and various solvated forms (including hydrates) of the same medicinal ingredient would generally be considered identical, provided the solvate content is within acceptable levels. ... "Acceptable levels" of solvate concentration would be either within levels of that solvent already allowed in an approved drug product, or within the ICH guidelines for allowable daily intake of that solvent.	
2.17	... The A/NDS was rejected and not evaluated, based on the decision that Q1 (qualitative identity) was not met. ... Under the current draft policy, would not the new solvate be acceptable?	The new solvate would be considered identical, however as the toxicity of the solvate was not known, safety data would have to be provided under this policy to demonstrate an acceptable level.
2.18	Similar to differences in physical properties, if the manufacturer can meaningfully demonstrated that a particular hydrated/solvated form of medicinal ingredient would impact the safety and/or efficacy profile of a CRP, the policy should indicate that other forms would not be considered identical.	A published, scientifically demonstrated difference in safety and/or efficacy for a pseudopolymorphic form of a drug substance would be taken into consideration at time of review.
<b>3. Acceptable Levels of Solvate</b>		
3.1	Further clarification is required pertaining to what would be considered acceptable levels of the solvate content. The ICH Q3C guideline states that it does not apply to solvates. In addition the solvate levels are usually at levels exceeding those in the Q3C guideline. ... It is evident that the ICH Q3C guideline is not suitable for solvates. ... A specific guideline for specifications of solvate content should be developed.	The policy has been revised to include reference to ICH Q3C and further guidance as to qualification.
3.2	With respect to solvates, it is important to note that organic solvents bound in the crystal structure of the solvates may be toxic even in relatively low concentrations. As such, it is critical that the levels of bound solvent comply with the F&DRs in respect of impurities and solvent levels, ...	
3.3	... The key element here is what is meant by "acceptable levels".	
3.4	Under point (b), Section 4: It is not clear what criteria will be used to determine whether the solvate content is acceptable.	
3.5	Taking into account our comments above, <Respondent name> also agrees with the second element suggested in the Draft Policy as a guiding principle, namely: “(b) Unsolvated and the various solvated forms of the same medicinal ingredient would generally be considered identical, provided the solvate content is within acceptable levels.” However, as noted above, for clarity the expression “acceptable levels” should be defined.	
3.6	Subject to the discussion in 1), the term “within acceptable levels” requires further elaboration. ... We propose that further clarification of the term “within acceptable levels” be provided by TPD in order for the sponsor to meet the requirements of this <i>draft policy</i> and submit that limits as low as those permitted by ICH Q3C guideline would be unreasonable.	

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<b>4. Different Salts, Complexes or Esters of the Drug Substance:</b>		
4.1	It is agreed that different complexes, esters, or salts of the same active moiety should be considered as non-identical.	This is in agreement with the policy.
4.2	<Respondent name> is also in agreement that the third category represents an area of non-identical medicinal ingredient, namely: “(c) Different complexes, esters, or salts of the same active moiety are considered non-identical.”	
4.3	We do not agree with point (c) of the Guiding Principle (lines 61 & 62) which states that “Different complexes, esters, or salts of the same active moiety are considered non-identical”. It would appear that the issue should revolve around whether they are the same active moiety. Species such as salts, where there is no covalent bond, and which dissociate into the active moiety should be considered identical. Esters on the other hand, require a breaking of a bond and would not be considered identical. Complexes, if dissociable into the active moiety, like salts should also be classed as identical. ... It is noted that the European Community is in agreement that salts of a medicinal ingredient are considered the same. The following is an excerpt from the Official Journal of the European Communities - Commission Regulation (EC) No. 847/2000 – Article 3.	The European policy mentioned refers to the requirement for therapeutic alternatives. However, the Food and Drug Regulations only includes provision for declaring pharmaceutical equivalence.
4.4	We disagree with guiding principle (c) of the <i>draft policy</i> : “Different complexes, esters, or salts of the same active moiety are considered non-identical”..... We propose that the determination of identity of different complexes, esters or salts of medicinal ingredients be considered on a case-by-case basis. The results of the <i>in vivo</i> study will determine if the two drug products are bioequivalent and mute the discussion of identity between the two medicinal ingredients.	Health Canada's position is discussed individually for complexes, esters and salts in the following sections.
<b>5. Salts</b>		
5.1	HPFB's proposal to treat salts as non-identical medicinal ingredients is inconsistent with the science that justifies treating hydrates, solvates, and formulations with different excipients as identical medicinal ingredients. ... If a generic is able to show bioequivalence with the active moiety and appropriate product stability, there is no reason, scientifically or in law, why it cannot be shown to be equivalent for the purposes of an ANDS. The study conducted by FDA researchers also found: If the applicant demonstrates that the proposed drug product meets the standards for identity, is bioequivalent to the RLD, and exhibits sufficient stability, the drug substance in a proposed generic drug product need not have the same physical form (particle size, shape, or polymorph form) as the drug substance in the RLD.	Health Canada has justified the exclusion of salts 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. This is consistent with the regulatory practices of different regions for determining equivalence. The possibility for synergism or differences in toxicity is noted in “Biological Effects of the Drug Salt Form” in Handbook of Pharmaceutical Salts (2002) Eds P.H. Stahl, C.G. Wermuth.

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5.2	The agency [Health Canada] allows for the formulations of a proposed product to have different excipients compared to an approved product, since the excipients become dissociated from the active ingredient in the gastrointestinal tract. The Regulations require in vivo studies to demonstrate that the concentrations of excipients do not influence bioavailability (i.e. within the 80 percent to 125 percent). Accordingly, Health Canada should have no difficulty in applying this logic to salts.	
5.3	Health Canada has already accepted in its definition of new active substance, above, that an isomer, derivative or salt that is different from that which was approved, is not necessarily considered to be a "new active substance" where it does not differ in properties with regard to safety and efficacy. [HC policy "New Active Substance", 1991]	The "Identical Medicinal Ingredient" policy reflects Health Canada's current thinking.
5.4	This rationale underlies the European Commission proposal on this issue: Where the active substance of an essentially similar medicinal product contains the same therapeutic moiety as the original authorized product associated with a different salt/ester, complex/derivative evidence that there is no change in the pharmacokinetics of the moiety, pharmacodynamics and/or toxicity which could the safety/efficacy profile shall be demonstrated. Should this not be the case, this association shall be considered as a new active substance [Modifications of Directive 2001/83/EC Annex 1 Section 2.3]	The European policy mentioned refers to the requirement for therapeutic alternatives. However, the <i>Food and Drug Regulations</i> only includes provision for declaring pharmaceutical equivalence.
5.5	We would greatly appreciate having clarification on the draft of interpretation of "identical medicinal ingredient" Does the following statement (from the draft) apply to injectable products? <i>(c) Different complexes, esters, or salts of the same active moiety are considered non-identical.</i> For example can we use Ciprofloxacin HCL as an active ingredient for a generic drug for Cipro IV (ciprofloxacin injection) or is the ciprofloxacin salt considered not identical in this case?	For solutions, the <i>in-situ</i> salt form or base would be considered in the assessment of the medicinal ingredient.
<b>6. Complexes</b>		
6.1	<Respondent name> submits that HPFB's blanket refusal to treat all complexes as non-identical is inconsistent with its position on identity of polymorphs. Following the scientific reasoning set out above for hydrates, solvates and salts, if the complex dissociates in the gastrointestinal tract, then certain acceptable complexes could be considered identical medicinal ingredients. This would be acceptable where the part of the complex that is not the active moiety has been used in a previously approved drug product and meets impurity guidelines.	As complexes can persist in solution, the effect of the complex on the safety and efficacy cannot be guaranteed to be the same as for the dissociated components. To treat different complexes as identical medicinal ingredients is therefore not warranted. Options are available to the submission sponsor to discuss with Health Canada, in advance, when the "identity" of two medicinal ingredients is in doubt.
<b>7. Esters</b>		
7.1	<Respondent name> agrees that HPFB should treat esters as non-identical medicinal ingredients. Unlike hydrates, solvates, salts and complexes, esters have covalent bonds that do not dissociate on dissolution in the gastrointestinal tract. Accordingly, the active moiety that reaches the bloodstream is not identical to the reference product.	This is in agreement with the policy.

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<b>8. Drug substances that do not Possess a Unique Chemical Structure</b>		
8.1	The current draft policy fails to address one of the most difficult and contentious areas of 'identity'; i.e., for those drugs that do not possess a unique chemical structure but instead are a mixture of molecules, usually spanning a range of molecular weights; dextrans and starches are examples of this type of drug. The current (unwritten) TPD policy for this category appears to be that drugs of this type must be sole-sourced. The practical implication of this requirement is that generic competition is effectively locked out, since the approved source will almost always be a proprietary source and if a generic company has to repeat all the S&E studies, then it is not really a generic product. ... It is recommended that you put forward your current position for those drugs that do not possess a unique chemical structure and engage the interested parties in scientific/regulatory debate on the issues.	<p>The policy is not intended to include an exhaustive list. Other situations may arise that would take into consideration the safety and efficacy of the products.</p> <p>The policy has been amended to indicate that ingredients which do not possess a unique chemical structure are excluded from the scope of the policy.</p>
<b>9. Isomers</b>		
9.1	Finally, <Respondent name> recommends the addition of a fourth category which recognized the non-identity of different chemical stereoisomers. The non-identity of such chemically equivalent "in formula only" medicinal ingredients has been recognized in the Policy Guideline published by Health Canada which is titled: Stereochemical Issues in Chiral Drug Development."	The policy has been revised to clarify the position on isomers. (i.e. Different isomers or mixtures of different proportions of isomers are considered non-identical.). This is consistent with the Health Canada guidance document entitled "Stereochemical Issues in Chiral Drug Development."
9.2	....In addition, chiral molecules are physically different forms of the same chemical entity that often have different pharmacological effects ... . Racemates may differ from single enantiomers in regards to pharmacokinetic, pharmacodynamic and toxicity characteristics. In such instances, it would not be possible to conclude that such medicinal ingredients are identical. ...	
<b>10. Linkages with PM(NOC) Regulations</b>		
10.1	Finally, another significant concern with this draft policy is the far-reaching implications that it could have on patents. Under the PM (NOC) Regulations, a scheme promulgated under the Patent Act and designed to prevent patent infringement, a patent covering the specific structure and formulation of a CRP could potentially be avoided by the sponsor of an ANDS: a sponsor could capitalize on a broad definition of "pharmaceutical equivalence" to permit an abbreviated filing while arguing that its product is not the same medicine for the purposes of infringement. ... The creation and application of a policy to direct the "pharmaceutical equivalence" should therefore not only be aligned with but further the objects of the Patent Act, and in particular the PM (NOC) regulations.	<p>Comments received from respondents regarding the potential impact of updating the Identical Medicinal Ingredient policy on the administration of the <i>Patented Medicines (Notice of Compliance) Regulations</i> have been forwarded to the Office of Patented Medicines and Liaison. The TPD recognizes the importance of maintaining a consistent approach to the concept of identical medicinal between the <i>Food and Drug Regulations</i> and the <i>PM(NOC) Regulations</i>.</p> <p>The Office of Patented Medicines and Liaison should be contacted in regard to linkages with the <i>PM (NOC) Regulations</i>.</p>
10.2	Health Canada also must keep in mind the linkage between the regulatory approval of subsequent entry manufacturers and the protection for patents provided by the PM (NOC) Regulations (also known as the Linkage Regulations). ... In this regard, it is critical that Health Canada's interpretation of "identical medicinal ingredient" in the F&DRs be consistent with its interpretation of "medicine" and "same medicine" in the Linkage Regulations.	

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10.3	<p>In considering the term “identical medicinal ingredients” in the context of the approval of subsequent entry drug products, Health Canada cannot ignore the linkage to patent protection required by the Linkage Regulations. ... In light of the foregoing, it is critical that “medicine” in section 4 and subsection 5(1) and “same medicine” in subsection 5(1.1) of the Linkage Regulations be interpreted in a manner consistent with “identical medicinal ingredient” in the F&amp;DRs.</p>	
10.4	<p>Additionally, this policy should state that the F&amp;DRs must be read consistently with the PM (NOC) Regulations. This means that the term “medicinal ingredient” should continue to be understood to mean the same as the term “medicine” in sections 5(1) and (1.1) of the PM (NOC) Regulations. ... This is consistent with the purpose of the PM (NOC) Regulations and the recent jurisprudence such as the Eli Lilly Canada Inc. v. Minister of Health decision dated January 22, 2003. ... Finally, we would also recommend that the policy states that this same definition of medicine be consistent with the use of this word in section 4 of the PM (NOC) Regulations, the section permitting patent lists to be filed.</p>	
10.5	<p>A significant effect of the proposed interpretation of different hydrates and solvates as being identical medicinal ingredients is that it would permit generic manufacturers to attempt to avoid patent infringement by virtue of coming with a different hydrate potentially at the expense of safety and efficacy.</p>	