**Issue Number: 015**

Managing “Waters of Hydration” in Substance Information in the Canadian Clinical Drug Data Set

### The Issue

How should substances that include waters of hydration information be described in the CCDD, and particularly should there be separate NTPs for products where the substance is expressed with waters of hydration from those where it is not?

1. Background Information

Water of hydration (also called “water of crystallization” and sometimes “lattice water”) describes the water molecules that exist within the molecules of (usually) complex substances.

Water of hydration is described chemically using a dot or period after the main formula (e.g. CuSO4.5H2O – copper sulfate with 5 molecules of water hydrating it).  In text, which is where we find it in substance names in medicinal products, the term is “hydrate” with the Greek numeric descriptions – monohydrate, dihydrate, trihydrate, quadrahydrate, pentahydrate, hexahydrate etc.

Water of hydration information is present for precise ingredient substance in approximately 10% of the moieties currently in scope for the CCDD, and approximately 5% of the eventual total scope of the CCDD.

#### Waters of hydration in IDMP 11238

Within IDMP, specifically ISO 11238 and its implementation guidance in TS 19844, waters of hydration are dealt with as “solvates and hydrates”, which are a subgroup of co-crystals (where a hydrate is specifically a water molecule, whereas a solvate could be any substance, e.g. ethanol). The standard notes that the *“terms “hydrates” and “solvates” are descriptive and widely used and should be therefore retained while keeping in mind that they are part of, rather than separate from, the general concept of co-crystals”* and so to distinguish hydrates and solvates from (other) co-crystals it has been stated that components of a co-crystal should exist as individual solids at ambient conditions.

Co-crystals are widely used in the pharmaceutical industry, either specifically designed to achieve crystals with certain properties, but also occur as the result of a selection of the final solvent for a substance, based on other criteria. They can explicitly alter the solid state properties of a moiety, such as solubility, hygroscopicity and stability may be improved as well as manufacturing behavior (e.g. compaction, followability, filterability, etc.). This is why hydration information is important in pharmacy and pharmaceutics, but has limited if any importance in therapeutics.

In IDMP, (11238) solvates and hydrates are considered as separate substances from their parent substance, and so will have a separate Substance ID from the active moiety and moiety plus base, acid or counter-ion combination. For example, each of the following have separate substance IDs and its own molecular weight, which will also have an effect on description of product strength

* Edoxaban
* Edoxaban tosilate
* Edoxaban tosilate monohydrate

#### Waters of hydration in describing the Medicinal Product (11615) and Pharmaceutical Product (11616)

There is no specific example or mention of this issue in either standard. The 11615 standard states that, for the Medicinal Product, **all** ingredient substances should be described, with their role (active, adjuvant, excipient etc.), using a Substance ID or a Specified Substance Group 1 ID, and their strength (presentation and concentration). The 11616 standard takes just the active and adjuvant substances with their strength(s) into consideration for generation of the PhPIDs.

Since 11238 assigns separate Substance IDs to the each of a) the active moiety, b) the active moiety plus any base/acid/counter-ion and c) the active moiety plus any base/acid/counter-ion plus any hydrate/solvate, it is assumed that there will be different PhPIDs for products with active ingredient substances with waters of hydration as opposed to those without.

#### Medicinal product terminology

Medicinal product terminology needs to accurately describe products both in their pharmaceutical description (and pharmaceutical equivalence) – which IDMP does – and in their clinical description. For most situations, these two descriptions are the same; in the case of substances with waters of hydration, they may not be. Medicinal product terminology needs to accommodate the situation when there is difference because prescribers need the clinical description (for which waters of hydration information is irrelevant) and dispensers (usually pharmacists) must deal with the pharmaceutical description of the licensed products, where waters of hydration information may have relevance.

### *Proposed actions and Options for resolution*

The options below examine how waters of hydration information should be considered as part of the description of the precise active ingredient substance, of an MP and an NTP, in their formal name and therefore in participation in the “substance-strength set” which is one of the definitional attributes of an NTP.

#### Option 1: No waters of hydration information in any description of substance in the CCDD

This leans heavily towards the clinical description of medicinal products.

Any information in the DPD for Manufactured Products where waters of hydration is currently included would need to be stripped out. This would produce a smaller set of NTPs than if waters of hydration are taken into account, but they would (probably) be clinically acceptable.

This does not “fit” with the IDMP pattern, and it may be confusing, because what pharmacists would see for the MP formal name would not match the DPD, nor would it match the information in/on the product itself.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| For example:**NTP\_code** | **NTP formal name** | **MP\_code** | **MP formal name** | **DPD precise active ingredient** |
| 9002921 | esomeprazole (esomeprazole magnesium) 20 mg gastro-resistant tablet | 02339099 | APO-ESOMEPRAZOLE [esomeprazole (esomeprazole magnesium) 20 mg gastro-resistant tablet] APOTEX INC | esomeprazole magnesium |
| 02423855 | ACT ESOMEPRAZOLE [esomeprazole (esomeprazole magnesium) 20 mg gastro-resistant tablet] ACTAVIS PHARMA COMPANY | esomeprazole magnesium **dihydrate** |

#### Option 2: Include waters of hydration information for MP and for the NTP

For Manufactured Products where waters of hydration is currently included in the description of the substance, this would be included in the MP formal name. This information would be used to generate the NTPs directly, so some NTPs would contain waters of hydration information and some would not. This fits with the likely IDMP pattern, including for Pharmaceutical Product Identifiers (PhPID4), although until the actual algorithms and sample data are released, this cannot be confirmed.

However, it creates NTPs that clinicians are likely to find confusing and irrelevant.

For example:

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **NTP\_code** | **NTP formal name** | **MP\_code** | **MP formal name** | **DPD precise active ingredient** |
| 9002921 | esomeprazole (esomeprazole magnesium) 20 mg gastro-resistant tablet | 02339099 | APO-ESOMEPRAZOLE [esomeprazole (esomeprazole magnesium) 20 mg gastro-resistant tablet] APOTEX INC | esomeprazole magnesium |
| 9002910 | esomeprazole (esomeprazole magnesium **dihydrate**) 20 mg prolonged release oral tablet | 02423855 | ACT ESOMEPRAZOLE [esomeprazole (esomeprazole magnesium **dihydrate**) 20 mg gastro-resistant tablet] ACTAVIS PHARMA COMPANY | esomeprazole magnesium **dihydrate** |

#### Option 3: Include waters of hydration information in the precise ingredient substance information for MP but not include precise ingredient substance information for the NTP

This walks the “middle ground”, reflecting both what clinicians wish to see in the NTP and what pharmacists actually see on the MP and its attendant information.

For Manufactured Products, where waters of hydration is currently provided for the precise active ingredient substance, this should be included in the MP formal name following the standard pattern.

But, when generating the NTP, the waters of hydration information would be disregarded in the precise ingredient substance. This provides a smaller, more clinically acceptable set of NTPs for prescribing (as in Option 1) but continues to maintain the granular detail of actual manufactured products in the MP.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **NTP\_code** | **NTP formal name** | **MP\_code** | **MP formal name** | **DPD precise active ingredient** |
| 9002921 | esomeprazole (esomeprazole magnesium) 20 mg gastro-resistant tablet | 02339099 | APO-ESOMEPRAZOLE [esomeprazole (esomeprazole magnesium) 20 mg gastro-resistant tablet] APOTEX INC | esomeprazole magnesium |
| 02423855 | ACT ESOMEPRAZOLE [esomeprazole (esomeprazole magnesium **dihydrate**) 20 mg gastro-resistant tablet] ACTAVIS PHARMA COMPANY | esomeprazole magnesium **dihydrate** |

This allows a prescription written as the NTP to be fulfilled using any of the associated MPs; the dispense is not inappropriately constrained by waters of hydration information (or lack of it) in the description of the precise ingredient substance.

For those products where the precise ingredient substance is the hydrated form of the basis of strength substance with no other modification, by disregarding the waters of hydration in the NTP, the precise ingredient substance will not be stated as it is redundant information without the hydrate. However, this gives a clinically correct and recognizable NTP.

For example:

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **NTP\_code** | **NTP formal name** | **MP\_code** | **MP formal name** | **DPD precise active ingredient** |
| 9001227 | azithromycin 250 mg oral tablet | 02255340 | ACT AZITHROMYCIN [azithromycin (azithromycin monohydrate) 250 mg oral tablet] ACTAVIS PHARMA COMPANY | azithromycin monohydrate |
| 02265826 | SANDOZ AZITHROMYCIN [azithromycin (azithromycin dihydrate) 250 mg oral tablet] SANDOZ CANADA INCORPORATED | azithromycin dihydrate |

There are one or two very rare cases where the basis of strength substance is the same as the precise ingredient substance and includes the water of hydration information that is required for correct expression of strength; for example, the dopamine agonist used in Parkinson’s disease: pramipexole dihydrochloride monohydrate. In some healthcare cultures (particularly in Europe), the clinically used description of strength of pramipexole products (and dosage quantity for administration) refers to the base substance; but in Canada the description of strength refers to the full hydrated precise ingredient substance. In the US, the strength also refers to the full hydrated precise ingredient substance, but it is clinically described using only the salt (pramipexole dihydrochloride). It is proposed that the CCDD will follow that pattern, acknowledging that it is not, for this product, a strictly correct basis of strength substance.

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| --- | --- | --- | --- | --- |
| **NTP\_code** | **NTP formal name** | **MP\_code** | **MP formal name** | **DPD precise active ingredient** |
| 9005174 | pramipexole dihydrochloride 0.25 mg oral tablet | 02237145 | MIRAPEX [pramipexole dihydrochloride monohydrate 0.25 mg oral tablet] BOEHRINGER INGELHEIM (CANADA) LTD LTEE | pramipexole dihydrochloride monohydrate |
| 02269309 | TEVA-PRAMIPEXOLE [pramipexole dihydrochloride monohydrate 0.25 mg oral tablet] TEVA CANADA LIMITED | pramipexole dihydrochloride monohydrate |

This option will require an update to the naming pattern for the NTP and MP formal names in the overall Editorial Guidelines. Since several of the issues currently being resolved will also affect formal name patterns slightly, this is deemed acceptable.

#### Note on DPD Information

It is likely, particularly for older products, that the granularity of description of ingredient substances in the DPD may not be as complete as for more recently authorized products. For example, recent investigation has confirmed that all solid dose oral presentations of amoxicillin contain amoxicillin trihydrate, although the DPD information does not reflect this at present.

In the current situation, where regulatory agencies and pharmaceuticals manufacturers are moving towards implementation of IDMP with its increased level of precision and consistency in description of CMC data and active ingredient substances in particular, option 3 above is likely to be the most pragmatic for all concerned, particularly as data is made more consistent over time, and will minimise change in the NTP description, which is important for clinical use

### *Recommendation*

*That Option 3 be adopted for the CCDD.*

### *Discussion and Comments*

Examples requested

### *Decision*

Recommendation approved. The CCDD Editorial Guidelines will be updated

### *Document History*

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| --- | --- | --- |
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