# Appendix F: Hydration and Solvation

## Appendix C, Hydration and Solvation

### Introduction

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.  "Solvate" is the term used to describe small molecules other than water (such as acetone) that similarly exist within large molecules.

Water of hydration is described chemically using a dot or period after the main formula (e.g. $CuSO_4.5H_2O$ – 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 or solvate 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.

### Hydrates and Solvates for 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 and clinical equivalence.  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 hydration/solvation information is irrelevant) and dispensers (usually pharmacists) must deal with the pharmaceutical description of the licensed products, where hydration/solvation information may have relevance.

### Hydrates and Solvates for the CCDD

The requirement is to reflect 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 hydration/solvation information is currently provided for the precise active ingredient substance, this should be included in the MP formal name and French Description following the standard pattern.

But, when generating the NTP, the hydration/solvation information should be disregarded in the precise ingredient substance.  This provides a smaller, more clinically acceptable set of NTPs for prescribing but continues to maintain the granular detail of actual manufactured products in the MP.  It also allows a prescription written as the NTP to be fulfilled using any of the associated MPs; the dispenser is not inappropriately constrained by hydration /solvation information (or lack of it) in the description of the NTP precise ingredient substance.

Example:

| NTP_code | NTP formal name | MP_code | MP formal name | PM description française | 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 | APO-ESOMEPRAZOLE (ésoméprazole (ésoméprazole magnésien) 20 mg comprimé gastrorésistant) APOTEX INC | EN: esomeprazole magnesium<br><br>FR : ésoméprazole magnésien |
| | | 02423855 | ACT ESOMEPRAZOLE (esomeprazole (esomeprazole magnesium dihydrate) 20 mg gastro-resistant tablet) ACTAVIS PHARMA COMPANY | APO-ESOMEPRAZOLE (ésoméprazole (ésoméprazole magnésien dihydraté) 20 mg comprimé gastrorésistant) APOTEX INC | EN: esomeprazole magnesium dihydrate<br><br>FR : ésoméprazole magnésien dihydraté |

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

Example:

| NTP_code | NTP formal name | MP_code | MP formal name | PM description française | DPD precise active ingredient<br><br>(BDPP substance active précise) |
|---|---|---|---|---|---|
| 9001227 | azithromycin 250 mg oral tablet | 02310600 | PRO-AZITHROMYCINE (azithromycin (azithromycin monohydrate hemiethanolate) 250 mg oral tablet) PRO DOC LIMITEE | PRO-AZITHROMYCINE (azithromycine (hémiéthanolate monohydraté d'azithromycine) 250 mg comprimé oral) PRO DOC LIMITEE<br><br>Azithromycine (HÉMIÉTHANOLATE MONOHYDRATE D'AZITHROMYCINE) | EN: azithromycin monohydrate hemiethanolate<br><br>FR : azithromycine (hémiéthanolate monohydraté d' azithromycine |
| | | 02265826 | SANDOZ AZITHROMYCIN (azithromycin (azithromycin dihydrate) 250 mg oral tablet) SANDOZ CANADA INCORPORATED | SANDOZ AZITHROMYCIN (azithromycine (dihydrate d'azithromycine) 250 mg comprimé oral) SANDOZ CANADA INCORPORATED | EN: azithromycin dihydrate<br><br>FR : dihydrate d' azithromycine |

It is important that when hydration/solvation information is removed from the ingredient substance as described in the NTP, a recognizable substance is still described. Each substance that is manipulated in this way should be checked to ensure that the resulting information is reasonable both chemically and clinically.

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). The CCDD will follow that pattern, acknowledging that it is not, for this product, a strictly correct basis of strength

Example:

| NTP_code | NTP formal name | MP_code | MP formal name | PM description française | 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 | MIRAPEX (dichlorhydrate de pramipexole monohydraté<br><br>0,25 mg comprimé oral) BOEHRINGER INGELHEIM (CANADA) LTD LTEE | pramipexole dihydrochloride monohydrate |

**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.

Regulatory agencies and medicinal product manufacturers are now moving towards implementation of IDMP with its increased level of precision and consistency. This is also being seen in more regular and updated descriptions of CMC (Chemistry and Manufacturing Controls) data with a particular focus on active ingredient substances. Therefore, this pattern of including hydration/solvation information in the MP but not in the NTP is likely to be the most pragmatic for all concerned, particularly as data are made more consistent over time, and will minimize change in the NTP description, which is important for clinical use.