Working document QAS/17.716/Rev.2
December 2018
Revised document for comments

World Health Organization

POLYMORPHISM

Draft chapter for *The International Pharmacopoeia*

(December 2018)

DRAFT FOR COMMENTS

Please send any comments you may have on this draft to **Dr Herbert Schmidt**, Medicines Quality Assurance Programme, Technologies Standards and Norms, Department of Essential Medicines and Health Products, World Health Organization, 1211 Geneva 27, Switzerland; email: schmidth@who.int, with a copy to **Ms Sinéad Jones** (email: jonessi@who.int) by **28 February 2019.**

In order to speed up the process for receiving draft monographs and for sending comments, please send us your email address and we will add it to our electronic mailing list. Please specify if you wish to receive monographs.

SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/17.716:

DRAFT CHAPTER FOR *THE INTERNATIONAL PHARMACOPOEIA*

POLYMORPHISM

Drafting of the text by a WHO Expert.	March 2017
Discussion at the informal consultation on quality control laboratory tools and specifications for medicines.	2–4 May 2017
Draft text sent out for public consultation.	July–September 2017
Presentation to the Fifty-second WHO Expert Committee on Specifications for Pharmaceutical Preparations.	October 2017
First revision drafted based on the comments received during the public consultation.	March 2018
Discussion at the consultation on screening technology, sampling and specifications for medicines.	2–4 May 2018
Revision 1 sent out for public consultation.	June – July 2018
Second revision drafted based on the comments received during the public consultation.	October 2018
Presentation to the Fifty-third WHO Expert Committee on Specifications for Pharmaceutical Preparations.	October 2018
Revision 2 sent out for public consultation.	December 2018 – February 2019
Further follow-up action as required.	

*[**Note from the Secretariat.** It is proposed to publish the following chapter on Polymorphism in the* Supplementary Information *section under "Notes for guidance".*

The text was revised based on the comments received during the last public consultation in June – July 2018 (see history).]

POLYMORPHISM

1. INTRODUCTION AND TERMINOLOGY

The aim of this chapter is to provide a brief overview of:

- the terminology associated with crystal polymorphism;
- some analytical techniques commonly used to characterise polymorphs;
- the relevance of polymorphism for active pharmaceutical ingredients (APIs) and finished pharmaceutical products (FPPs); and
- the control strategies for polymorphism employed by *The International Pharmacopoeia.*

APIs and excipients, in the solid phase, can be classified as either crystalline or non-crystalline solids. A crystalline structure implies that the structural units (i.e. the unit cells) are repeated in a long range order (i.e. three dimensional crystal lattice). The arrangement of atoms and/or molecules in an amorphous solid is non-ordered (i.e. does not have a long range order), or random system, analogous to the liquid state, and does not possess a distinguishable crystal lattice. Amorphous solids are classified as non-crystalline solids.

Variation in the crystallization conditions (temperature, pressure, solvent composition, concentration, rate of crystallization, seeding of the crystallization medium, presence and concentration of impurities, etc.) may cause the formation of different crystalline forms.

When a chemical element (e.g. sulfur) exists in different crystalline forms, it is referred to as *allotropy*, not polymorphism *(1).* When a chemical compound with a given chemical structure crystallizes in more than one crystalline lattice with different unit cells, these

crystalline phases are called *polymorphs* and the phenomena is referred to as *polymorphism*. The difference in internal crystal structure could be attributed to differences in molecule packing arrangements and/or different molecular conformations. Polymorphic substances, having identical chemical composition, will on dissolution exhibit the same chemical behaviour in solution.

Crystals of a given chemical compound with the same internal structure may exhibit different external shapes or *crystal habits*. In addition, variations in crystal habit may indicate the presence of polymorphism but is not necessarily indicative of polymorphic forms (*12*).

Solvates are crystal forms containing stoichiometric or non-stoichiometric quantities of a solvent. When the solvent incorporated into the crystal structure of the compound is water, the molecular adduct formed is referred to as a *hydrate*. Hydrates can be classified as three categories based on different structural aspects: *Class I* represents hydrates where the water molecules exist at isolated sites; *Class II* hydrates are generally referred to as channel hydrates; and *Class III* hydrates are generally referred to as ion-coordinated site hydrates. In such systems, water molecules form ion-water bonds that are usually much stronger than hydrogen bonds (*13*). Solvation and hydration products are also sometimes referred to as *pseudopolymorphs (2, 3, 4)*. However, the term "pseudopolymorphism" is ambiguous because of its use in different circumstances. It is therefore preferable to use only the terms "solvates" and "hydrates".

Occasionally, a compound of a given hydration/solvation composition may crystallize into more than one crystalline form; an example of such a compound is nitrofurantoin *(5).* Nitrofurantoin can be crystallized as two monohydrate forms (Forms I and II) and two anhydrous forms (designated polymorphs α and β) *(5).*

Crystal forms are said to be *isostructural* (also referred to as *isomorphous)* when they have the same overall crystal packing. Solvates, which have the same overall crystal packing, but differ only in the solvents included in their crystal structures, are termed *isostructural or isomorphous solvates*, e.g. hydrate and isopropanolate of hexakis(2,3,6-tri-O-acetyl)-α-cyclodextrin *(6).*

The term *desolvated solvate* (or *desolvated hydrates*), also referred to as *isomorphous desolvates*, has been used to describe a solid form obtained by removing solvent from the solvate crystal structure (or water from a hydrate) without significantly changing the crystal structure *(4)*, as in the desolvated monohydrate of terazosin HCl *(7)*.

Amorphous forms of APIs and excipients are of substantial interest because they are usually more soluble (also having a faster kinetic solubility) than their crystalline counterparts but are thermodynamically less stable. Solid-state properties of amorphous forms of the same chemical compound (i.e. thermal behaviour, solubility profile, density, etc.) may differ;

Co-crystals are crystalline materials composed of two or more different molecules, typically an API and co-crystal formers ("coformers") within the same crystal lattice that are associated by nonionic and noncovalent bonds. An example of a co-crystal is the succinic acid co-crystal of fluoxetine HCl *(8)*. Co-crystals are thus more similar to solvates, in that both contain more than one component in the lattice. However, for co-crystals the coformer is non-volatile (i.e. exists as solid material at ambient conditions) *(3)*.

Pharmaceutical co-crystals have gained considerable attention as alternative forms in an attempt to enhance the bioavailability, stability and processability of the API in the manufacturing process. Another advantage of co-crystals is that they generate a diverse array of solid state forms for APIs that lack ionisable functional groups, which is a prerequisite for salt formation *(3)*. Guidance and reflection papers on the use and classification of pharmaceutical co-crystals have been published *(3, 9)*.

2. CHARACTERIZATION AND THERMODYNAMIC STABILITY OF SOLID FORMS

Crystalline and amorphous forms are characterized based on their physicochemical properties. Table 1 lists some examples of the properties that may differ among different forms *(9)*.

Table 1. Examples of physicochemical properties that may differ among different forms

1.	**Packing properties**
	a. Molar volume and density
	b. Refractive index
	c. Conductivity (electrical and thermal)
	d. Hygroscopicity
2.	**Thermodynamic properties**
	a. Melting and sublimation temperatures
	b. Internal energy (i.e. structural energy)
	c. Enthalpy (i.e. heat content)
	d. Heat capacity
	e. Entropy
	f. Free energy and chemical potential
	g. Thermodynamic activity
	h. Vapour pressure
	i. Solubility
3.	**Spectroscopic properties**
	a. Electronic state transitions
	b. Vibrational state transitions
	c. Nuclear spin state transitions
4.	**Kinetic properties**
	a. Dissolution rate
	b. Rates of solid state reactions
	c. Stability
	d. Solid state
5.	**Surface properties**
	a. Surface-free energy
	b. Interfacial tensions
	c. Habit (i.e. shape)
6.	**Mechanical properties**
	a. Hardness
	b. Tensile strength
	c. Compactibility
	d. Flow

Table 2 summarizes some of the most commonly used techniques to study and/or classify different amorphous or crystalline forms. These techniques are often complementary and it is indispensable to use several of them. Demonstration of a non-equivalent structure by single crystal X-ray diffraction is currently regarded as the definitive evidence of polymorphism. X-ray powder diffraction and/or solid state NMR can also be used, as bulk techniques, to provide unequivocal proof of polymorphism *(10)*.

Any technique(s) chosen to confirm the identity of the specific form(s) must be proven to be suitably specific for the identification of the desired form(s). Care must be taken in choosing the appropriate sample preparation technique, as heat generation, mechanical stress or exposure to elevated pressure and other environmental conditions (humidity) may trigger conversion between different forms.

Table 2. Examples of some techniques that may be used to study and/or classify different crystalline forms

1. X-ray powder diffraction* & Single crystal X-ray diffraction
2. Microcalorimetry
3. Thermal analysis (*1.2.1 Melting point,** differential scanning calorimetry, thermogravimetry, thermomicroscopy)
4. Moisture sorption analysis
5. Polarized optical microscopy and electronic microscopy with diffraction capability (ex. Transmission Electron Microscopy)
6. Solid-state nuclear magnetic resonance;
7. Solubility studies
8. *Spectrophotometry in the infrared region (1.7)** and Raman spectrophotometry
9. Intrinsic dissolution rate
10. Density measurement

* Methods currently employed by *The International Pharmacopoeia*

Using suitable analytical techniques, the thermodynamic stability of the forms should be investigated. The form with the lowest free energy is the most thermodynamically stable at a given temperature and pressure. All other forms of the given system are in a metastable state. At standard temperature and pressure, a metastable form may remain unchanged or may change to a thermodynamically more stable form. In general, the more stable the form the less soluble it is. Conversion to a thermodynamically more stable form, may cause changes

in some of the physicochemical properties (see Table 1) of the compound that may result in changes to other critical properties such as bioavailability, manufacturability (also referred to as processability), etc.

If there are several crystalline forms one form is thermodynamically more stable at a given temperature and pressure. A given crystalline form may constitute a phase that can reach equilibrium with other solid phases and with the liquid and gas phases.

If each crystalline form is stable within a given temperature range the change from one form to another is reversible and is said to be *enantiotropic*. The change from one phase to another is a univariate equilibrium so that at a given pressure this state is characterized by a transition temperature. However, if only one of the forms is stable over the entire temperature range, the change is irreversible or *monotropic (11).*

3. RELEVANCE OF POLYMORPHISM FOR APIs AND FPPs

Polymorphism (and hydrate formation) of APIs and excipients are of interest as they may affect bioavailability, toxicity and processability. Also, the thermodynamic stability of the form included in the FPP is considered important as environmental conditions may compromise the stability thereof. For formulations where the API is dissolved, attention has to be paid to supersaturation with regards to different forms. A formulation might not be supersaturated regarding a metastable polymorph but supersaturated with regards to the thermodynamically stable polymorph. Control of the form by the manufacturer may be required during the processing of APIs and excipients and during the manufacturing of a dosage form to ensure the correct physicochemical characteristics thereof. The control of a specific form is especially critical in the areas where the bioavailability, stability or processability are directly impacted *(4).*

The form of a readily soluble API that is incorporated into a solution, for example, an injection, an oral solution or eye drops, is normally non-critical (exceptions to this statement might be if the concentration of the solution is such that it is close to the limit of solubility of one of the possible polymorphs – as mentioned above - or solvate formation is observed with one of the excipients). Similarly, if an API is processed during the manufacturing process to

obtain an amorphous form (e.g. hot melt extrusion, spray-dried dispersion, etc.), the original form is considered non-critical, as long as the processability is not influenced.

The form may be critical when the material is included in a solid dosage form or as a suspension in a liquid dosage form. In such cases, the characteristics of the different polymorphs may affect the bioavailability or dissolution of the material. The polymorphic form of a biopharmaceutics classification system (BCS) class I or III API in a solid oral dosage form is normally non-critical in terms of dissolution rate or bioavailability as by definition it would be readily soluble, but confirmation thereof by the manufacturer, is recommended. The ICH Harmonised Tripartite Guideline on Specifications: Test procedures and acceptance criteria for new drug substances and new drug products: Chemical substances Q6A, provides guidance on when and how polymorphic forms should be controlled and monitored *(4)*.

The inclusion of potentially harmful solvents in the crystal lattice, which may render APIs or excipients to be toxic or harmful to patients (i.e. solvates), should also be suitably regulated and monitored by the manufacturer.

4. POLYMORPHISM IN *THE INTERNATIONAL PHARMACOPOEIA*

Where a monograph indicates that a compound shows polymorphism this may be true crystal polymorphism, occurrence of solvates/hydrates or occurrence of the amorphous form.

The International Pharmacopoeia controls the polymorphic or crystalline forms (hereafter referred to as form) of a limited number of substances by restricting it to either:

- a single form, for example, carbamazepine API (Anhydrous Form III), mebendazole API (Form C); or
- by limiting the presence of unwanted forms, for example, chloramphenicol palmitate API (should contain at least 90% of polymorph B).

The control of forms specified in *The International Pharmacopoeia* may be achieved by:

- permitting no deviation from the infrared absorption spectrum of the reference substance prescribed (or reference spectrum supplied) – when the infrared absorption spectrum has been proven to be specific to the preferred form and able to distinguish the undesired form(s), for example, indomethacin API;
- restricting the melting point range, when the melting properties of the forms are clearly distinguishable, for example, phenobarbital API;
- recommending the use of any other suitable methods such as X-ray powder diffractometry, for example, carbamazepine tablets; and
- limiting the incorporated solvent (in the case of solvates/hydrates) with a specific limit test, for example, nevirapine hemihydrate API.

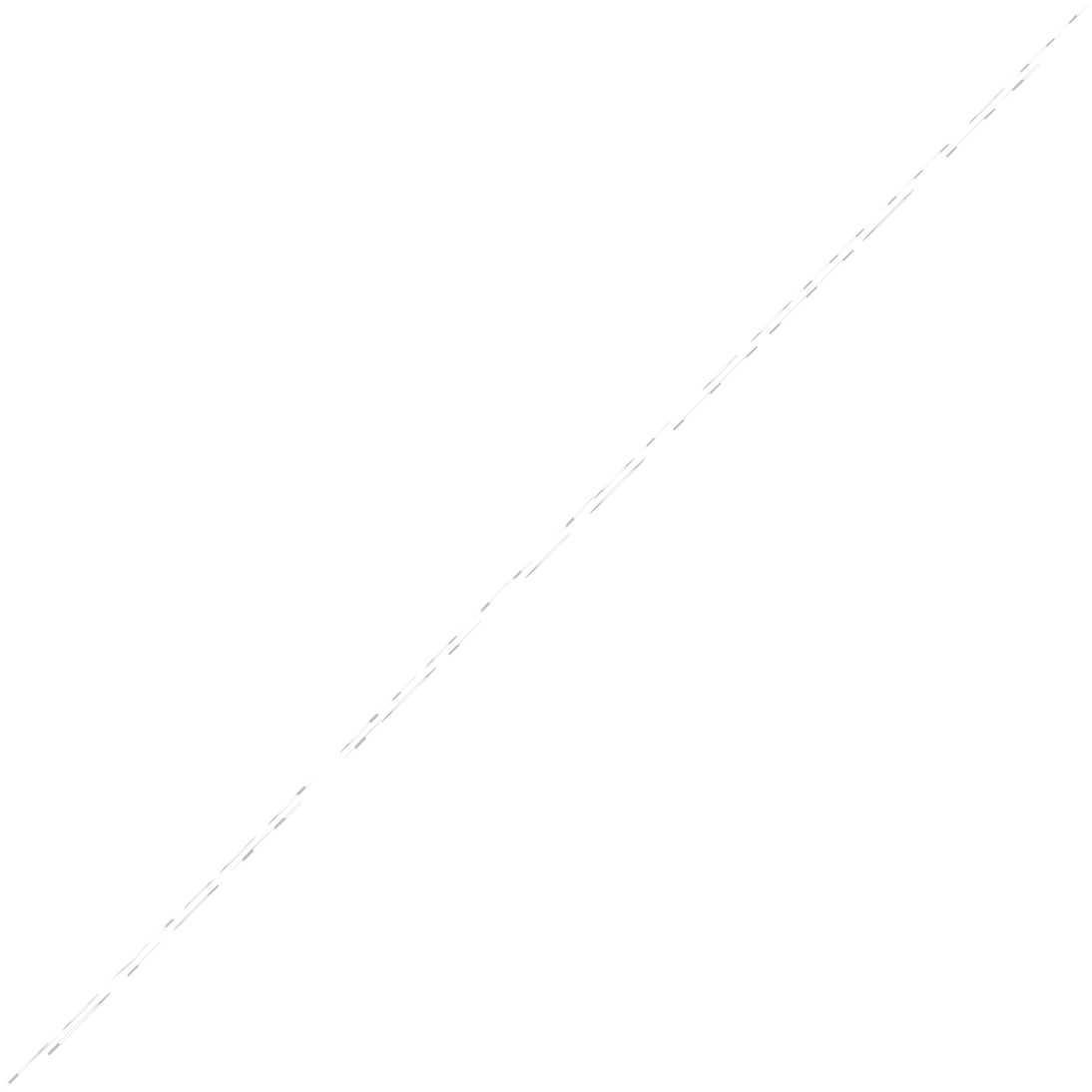
The specific control to be used will be indicated in the applicable monograph.

When the infrared identification test is able to detect differences in forms for a specific compound (i.e. polymorphism may be present for this compound), but the control of a specific form is not required by the monograph, the user may be instructed to:

- recrystallize both the test substance and the specified reference substance, in the event where the infrared spectra are found to be not concordant, for example, fluconazole API; and/or
- dry the API and/or specified reference substance to ensure that both forms are in the anhydrous or dehydrated state, for example, nevirapine hemihydrate API.

Whenever the choice of a specific form is critical with regard to bioavailability and/or stability, the method of the manufacturer of the product must be validated to consistently yield the desired polymorph in the final product at release and over its shelf life. The monograph will include a statement under the heading “Manufacturing” to draw attention to the control of a specified form during manufacturing where control is known to be critical, for example, carbamazepine oral suspension.

331 It is the intention of *The International Pharmacopoeia* to extend the inclusion of explicit
332 statements in monographs, where appropriate, as information on the occurrence of
333 polymorphism becomes available. The Secretariat thus cordially invites the users of *The*
334 *International Pharmacopoeia* and manufacturers to share any relevant information that could
335 be included in the monographs.
336
337



References

1. Gaskell, DR. 2005. Allotropy and Polymorphism. Reference Module in Materials Science and Materials Engineering. Encyclopedia of Condensed Matter Physics, 8–17.
2. Brittain, HG. 2007. Polymorphism and Solvatomorphism 2005. *Journal of Pharmaceutical Sciences,* 96(4):705–728.
3. US Department of Health and Human Services, Food and Drug Administration. Center for Drug Evaluation and Research. 2013. Guidance to Industry: Regulatory Classification of Pharmaceutical Co-crystals.
4. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. 1999. ICH Q6A – Specifications: The Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances.
5. Caira, M, Pienaar, EW, Lötter, AP. 2006. Polymorphism and Pseudopolymorphism of the Antibacterial Nitrofurantoin. Molecular Crystals and Liquid Crystals, 179(1):241-264.
6. Bettineti, G., Sorrenti, M., Catenacci, L., Ferrari, F. & Rossi, S. Bettinetti, G, et al. 2006. Polymorphism, Pseudopolymorphism, and Amorphism of Peracetylated α-, β-, and γ-cyclodextrins. *Journal of Pharmaceutical and Biomedical Analysis,* 41:1205-1211.
7. Bauer, J, et al. 2006. Identification, Preparation and Characterization of Several Polymorphs and Solvates of Terazosin Hydrochloride. *Journal of Pharmaceutical Sciences,* 95(4):917-928.
8. Peterson, ML, et al. 2006. Expanding the Scope of Crystal Form Evaluation in Pharmaceutical Science. *Journal of Pharmaceutical Sciences,* 9(3):317-326.
9. European Medicines Agency. 2015. Reflection Paper on the Use of Co-crystals of Active Substances in Medicinal Products.
10. US Department of Health and Human Services, Food and Drug Administration. Center for Drug Evaluation and Research. 2007. Guidance to Industry: ANDAs: Pharmaceutical Solid Polymorphism. Chemistry, Manufacturing and Controls Information.
11. British Pharmacopoeia Commission. 2017. SC I B. Polymorphism. *In: British Pharmacopoeia Commission. British Pharmacopoeia 2017. Supplementary chapter*. London: TSO.
12. J. Bernstein. 2002. Polymorphism in Molecular Crystals, Clarendon Press, Oxford, United Kingdom volume.
13. Byrn, R.S, Zografi, G. & Chen, X. 2017. Solid state properties of pharmaceutical materials, John Wiley & Sons. Inc.

***