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Pharmaceutical Solid Polymorphism in Abbreviated New Drug Application (ANDA) – A Regulatory Perspective

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ABSTRACT:

Sponsor of Abbreviated New Drug Application (ANDA) is responsible for submitting the sufficient information which demonstrates that their proposed generic version is equivalent to Reference Listed Drug (RLD) in quality, safety & efficacy with enhanced awareness in pharmaceutical industry and regulatory agencies after Ritonavir history in 1998, Polymorphism evolved out as a major point of attention for industry as well as regulatory agencies. Many pharmaceutical compounds exist in different crystalline forms and thus exhibit polymorphism. Polymorphism may affect Chemical and Physical Stability, Apparent Solubility, Dissolution, Bioavailability and Bioequivalence and Manufacturability of drug product, which require special attention during product development as it affects the quality, safety and efficacy of drug product. In addition to this, impact of polymorphism, monitoring and control of polymorphism and reporting scheme of polymorphic information in Abbreviated New Drug Application (ANDA) are also covered in this review. Careful attention is given to the issue of irrelevance of polymorphism for establishing drug substance "sameness". For better understanding, case studies are also provided for scientific and regulatory assessment of polymorphism in Abbreviated New Drug Application (ANDA).

Keywords: Polymorphism, Generics, Abbreviated New Drug Application (ANDA), Regulatory assessment.

INTRODUCTION

From enlightenment of Polymorphic forms existence in Ritonavir, the case of ritonavir changed the view of Pharmaceutical Scientists towards Polymorphism and a new viewpoint has been emerged in light of Polymorphism in Drug Substance. After Ritonavir history in 1998, FDA recommends to researchers to pay more attention at the time of development of new drug substance or drug product. With this improved understanding, there has come regulatory recommendations with regard to the polymorphism appearing in both new drug applications

(NDAs) and abbreviated new drug applications (ANDAs); particularly those for solid-oral dosage forms **[1–3].** But in the case of ANDA, polymorphism may or may not be the hurdles during regulatory approval.

When the drug substance is known to exhibit polymorphism, it can present special analytical concerns for the product. This review will be discussed from two points of view: the type of information that should be acquired during drug development and how this information relates to issues of drug quality, safety and efficacy concerns. Polymorphism may influence every stage of product development starting from pre-clinical stages to post marketing phase of the drug product. In the earliest pre-clinical stages (in case of NDA), there is little concern beyond identity. In the early investigational stages, there is more attention on the examination of consequences of scale-up in the bulk drug manufacture. In the late investigational stages, Sponsor has to pay careful attention on polymorphs and its impact on bioavailability of the drug product. At the same time emphasis is given to assess impact of polymorphism on chemical degradation during stability. At post marketing stage, holder of ANDA considers whether polymorphism can have impact upon the quality of the finished product during storage, transportation and distribution. At last, cumulatively all these concerns, imparts in to the generic product development program for setting high scientific standard.

So, from Regulatory perspectives, clear understanding of the polymorphism and its impact on drug product is essential in demonstrating consideration of polymorphism in the determination of drug substance ‘‘sameness’’. With the objective of simplification for polymorphism and its impact on Abbreviated New Drug Application (ANDA), this review article is cited.

Overview of an ANDA:

An Abbreviated New Drug Application (ANDA) contains data submitted to FDA's Center for Drug Evaluation and Research, Office of Generic Drugs for the review and ultimate approval of a generic product. Once approved, an applicant may market the generic product to provide a safe, effective, low cost alternative to the american public. A generic product is the one that is comparable to a Reference Listed Drug (RLD) in dosage form, strength, route of administration, quality, performance characteristics and intended use. All approved products, both innovator and generic, are listed in FDA's “Approved Drug Products with Therapeutic Equivalence Evaluations (*Orange Book*)”.

Generic product applications are termed "abbreviated" because they are generally not required to include preclinical (animal) and clinical (human) data to establish safety and effectiveness of these drugs. Instead, generic applicants must scientifically demonstrate that their product is bioequivalent (i.e., performs in the same manner as the innovator).

Overview of polymorphism:

Polymorphism in Pharmaceuticals:

Polymorphism means existence of substance in more than one form. Many pharmaceutical solids can exist in different physical forms. Polymorphism is often characterized as the ability of a drug substance to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice. However, they share one common form once they are in solution form.

According to W.C.Mc Crone, “Every compound has different polymorphic forms and that, in general, the number of forms known for a given compound is proportional to the time & energy spent in research on that compound”.

Solvates are crystal forms containing either stoichiometric or non-stoichiometric amounts of a solvent. If the incorporated solvent is water, the solvates are also commonly known as hydrates. Amorphous solids consist of disordered arrangements of molecules and do not possess a distinguishable crystal lattice.

Polymorphs seem to be more common for compounds with:

- Low solubility in water
- Organic salts
- Formation of hydrates -for larger molecules
- Organic solvates –neutral compounds with larger molecular weights.
- Compounds with molecular weight below 350

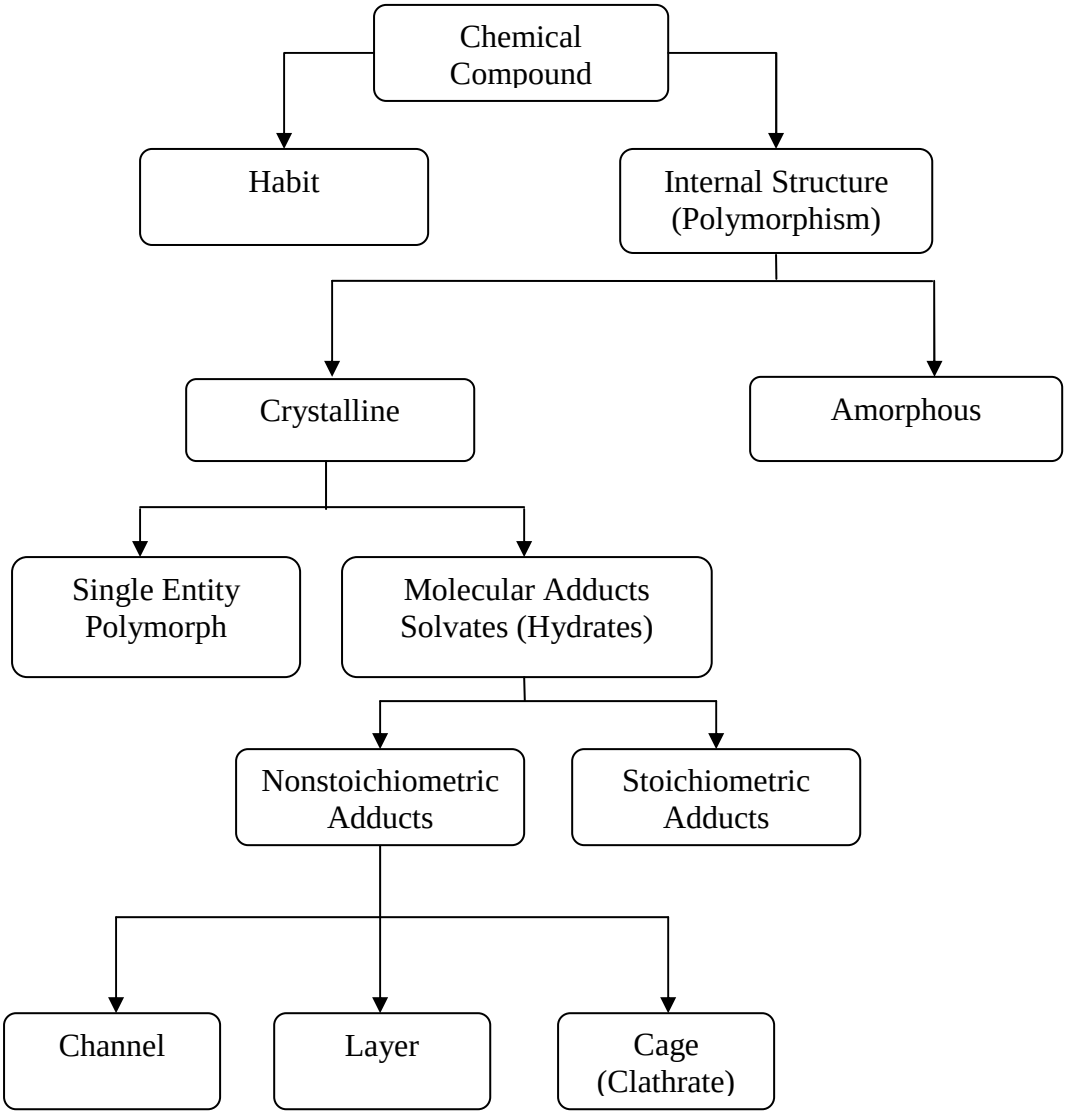


Figure 1 - Types of different polymorphic forms

Pharmaceutical Properties exhibited by Different Polymorphs:

- Density
- Melting Point,
- Hygroscopicity,
- Chemical and Physical Stability,

- Apparent Solubility and Dissolution,
- Bioavailability and Bioequivalence,
- Manufacturability.

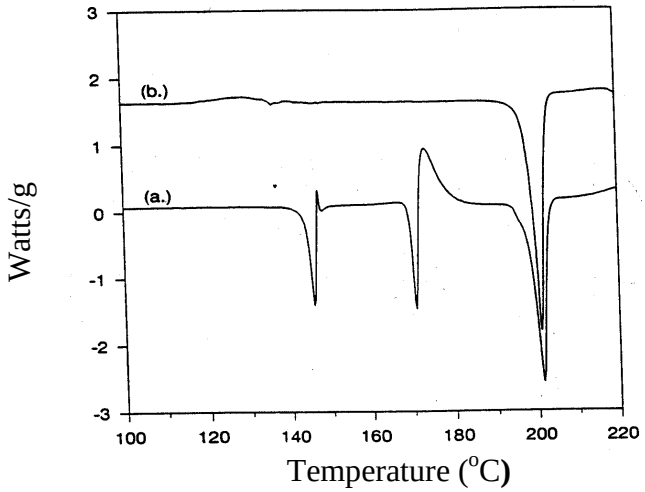
Characterization of Polymorphs by;

- X-ray powder diffraction (XRPD)
- Microscopy,
- Thermal analysis (e.g. differential scanning calorimetry (DSC),
- Thermal gravimetric analysis (TGA),
- Hot-stage microscopy,
- Spectroscopy (e.g. IR, Raman, solid-state NMR)

The sponsor of an ANDA may adopt these test methods or other applicable tests (e.g. Karl Fischer, melting point) for the routine testing and control of a drug substance polymorphic form, provided that they are validated against the X-ray method.

Influence of polymorphism on pharmaceutical properties of drugs:

- **Influence on Melting Point**



(a.) : Form I

(b.) : Form III

Figure 2 - DSC profiles of the fluoroquinolone (US Patent 5,985,893)

Influence on Hygroscopicity

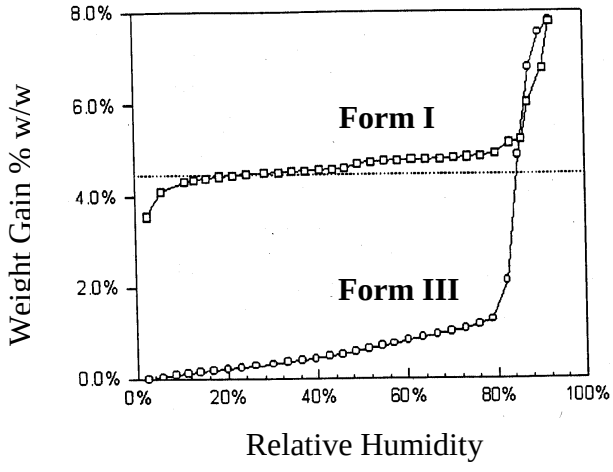


Figure 3 - Hygroscopicity of fluoroquinolone (US Patent 5,985,893)

- **Influence on Apparent Solubility**

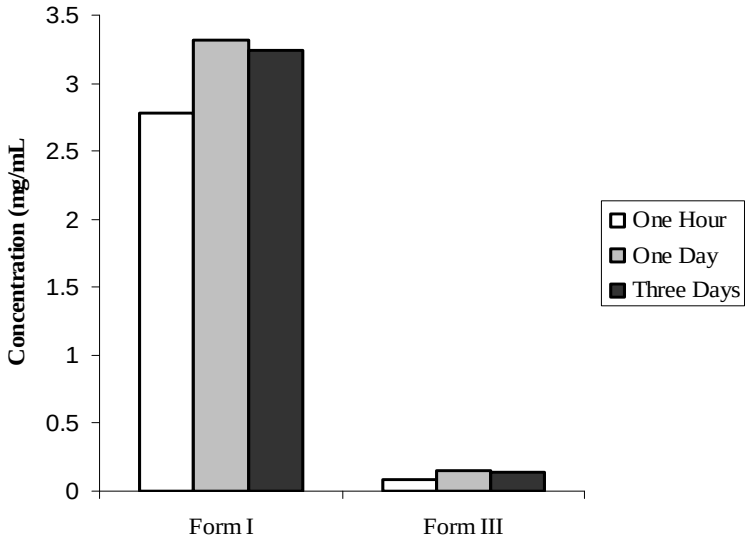


Figure 4 - Solubility of fluoroquinolone (US Patent 5,985,893)

- **Influence on Intrinsic Dissolution**

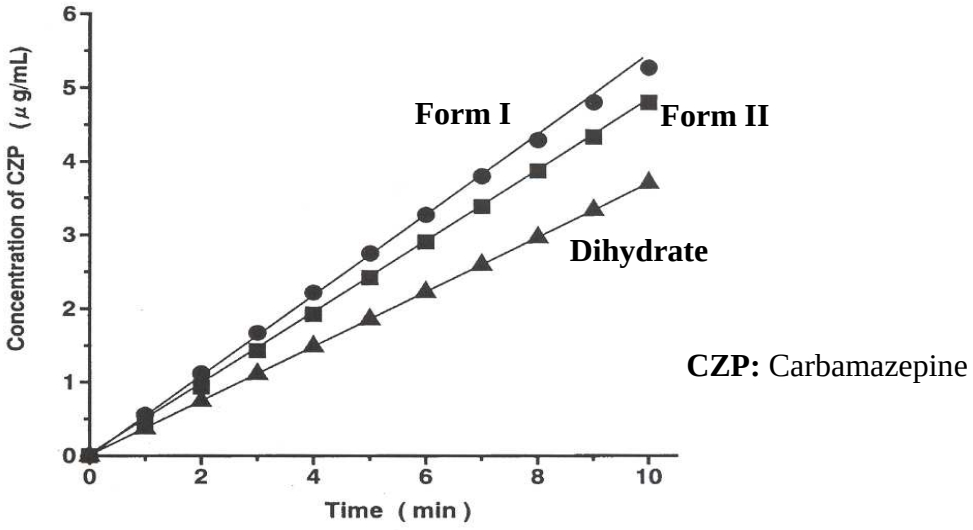
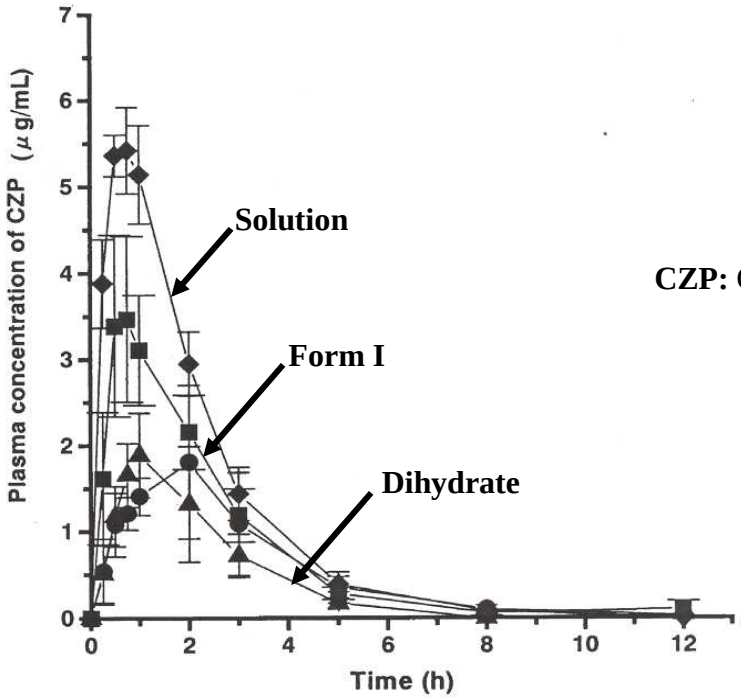


Figure 5 - Intrinsic dissolution of Carbamazepine

- **Influence on Stability**

Polymorphs of a pharmaceutical solid may have different physical and solid-state chemical reactivity) properties. These differences arise based upon differences in thermodynamic ability and also upon differences in molecular mobility, particularly in the case of an amorphous form. For this reason, the most stable form of the drug substance is often chosen during development, based upon its minimal potential for conversion to another form and upon its greater chemical stability.

- **Influence on Bioavailability: Low Solubility Drug**



CZP: Carbamazepine

Figure 6 - Bioavailability of Carbamazepine

Polymorphism in ANDA – From regulatory viewpoint:

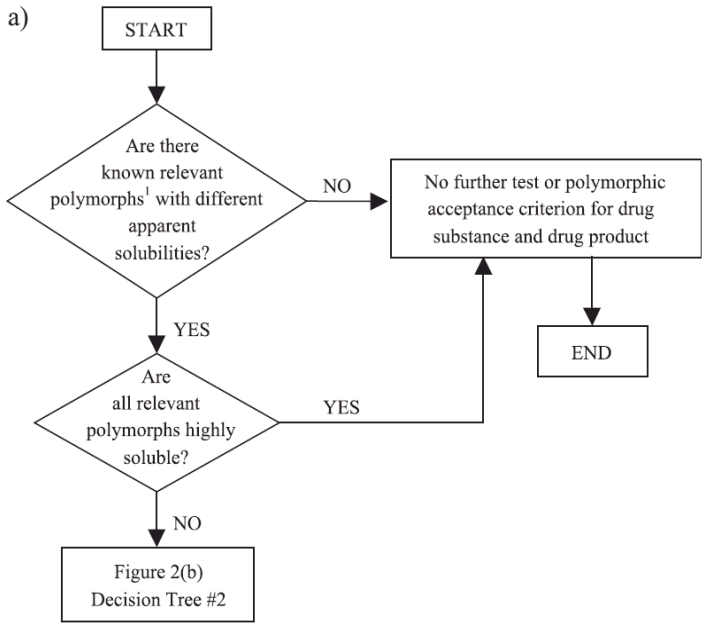
The sponsor of an ANDA must demonstrate that the proposed generic drug product contains the ‘‘same’’ active ingredient as the Reference Listed Drug (RLD). Although the active ingredient may be shown to be the ‘‘same’’ in both generic and innovator drug products, it may also exist in several crystalline forms and hence, exhibit polymorphism. Polymorphism may result in differences in the physico-chemical properties of the active ingredient and variations in these properties may result in a drug product not exhibiting bioequivalence, and hence in a product that is not therapeutically equivalent to the innovator brand. This may carry serious concerns over patient safety.

Therefore, in the context of the ANDA review, careful attention is paid to the effect that polymorphism may have on generic drug product equivalency to the innovator product.

The following discussion provides some of the principles and concepts in the ANDAs that are relevant to pharmaceutical solid polymorphism and which have been adopted to assure the therapeutic equivalence of marketed generic drug products.

Control and monitoring of Polymorphism in ANDA:

Process for evaluating when and how polymorphs of drug substances in ANDAs should be monitored and controlled is based on the **ICH Guidance Q6A** decision trees on polymorphism. According to **ICH Guidance Q6A**, Various decision trees can give following acceptance criteria for polymorphism.



[1] Relevant polymorphs are those that could form during manufacture of drug substance, manufacture of drug product, and/or during storage

Figure 7 - Decision Tree # 1

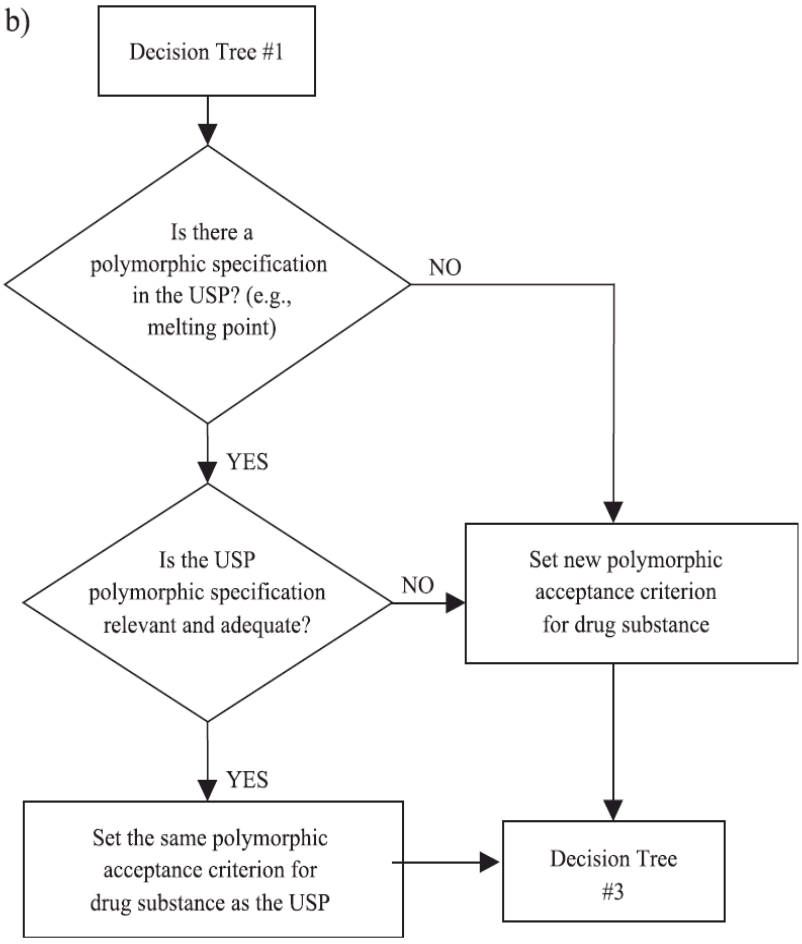
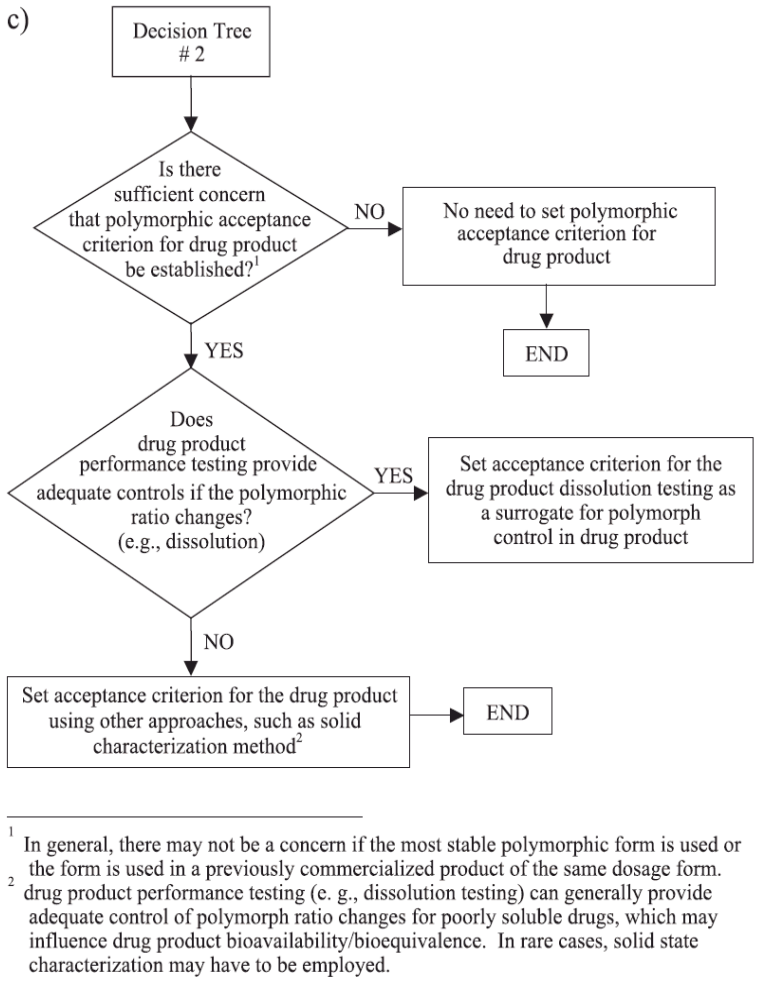


Figure 8 - Decision Tree # 2



[1] In general, there may not be a concern if the most stable polymorphic form is used or the form is used in a previously commercialized product of the same dosage form.
[2] drug product performance testing (e. g., dissolution testing) can generally provide adequate control of polymorph ratio changes for poorly soluble drugs, which may influence drug product bioavailability/bioequivalence. In rare cases, solid state characterization may have to be employed.

Figure 9 - Decision Tree # 3

Decision Tree #1: Investigating the need to set acceptance criteria for polymorphs in drug substances and drug products for solid dosage forms or liquids containing undissolved drug substances.
Decision Tree #2: What might be considered when setting acceptance criteria for polymorphs in drug substances for solid dosage forms or liquids containing undissolved drug substance.

Decision Tree #3: Investigating the need to set acceptance criteria for polymorphs in drug products for solid dosage forms or liquids containing undissolved drug substance.

Reporting tactics of polymorphism information in ANDA:
As on date, a new highly comprehensive review methodology is implemented by USFDA for NDA/ANDA submission, known as Question based Review (QbR) system. QbR is a general framework for a science and risk-based assessment of product quality.

It contains the important scientific and regulatory review questions to;

- Comprehensively assess critical formulation and manufacturing variables.
- Set quality specifications relevant to adequate quality control.
- Determine the level of risk associated with the manufacturing and design of the product.

ANDA submission contains following modules,
Module 1: Administrative information
Module 2: Quality Overall Summary (QOS)
Module 3: Body of Data (Quality)
Module 4: Preclinical Study Data
Module 5: Clinical Study Data
Polymorphic information should be included in Module 3 in brief, while summarized in Module 2 QOS. QOS is developed as per QbR process by FDA.

Pharmaceutical solid polymorphism and the issue of ‘‘SAMENESS’’
An Abbreviated New Drug Application (ANDA) contains data that demonstrates that the proposed generic product is comparable to a Reference Listed Drug (RLD) in dosage form, strength, route of administration, quality, performance characteristics and intended use through documented evidence which proves that the generic product meets performance characteristics benchmarked by compendial or other applicable standards for quality, purity, and identity. From this Context, one question has arisen that is whether the various drug substance polymorphic forms are considered the ‘‘same’’ or “different”.

From the perspective of a material scientist who focuses on solid-state properties, the various polymorphic forms will generally be considered different. However, from the perspective of a regulatory professionals who focuses on end quality, overall safety and efficacy of the drug product, the various polymorphs may be considered the ‘‘same’’.

In the context of regulatory requirements, the provisions do not require the sponsor of an ANDA to demonstrate that the active ingredient in its proposed generic drug product and the active ingredient in the RLD ‘‘exhibit the same physical characteristics and solid state forms of the drug have not been altered.”. Therefore, there is no regulatory requirement that require the generic drug product and the RLD to have the same drug substance in terms of its polymorphic forms.

Over the years, FDA has approved a number of ANDAs in which the drug substance in the generic drug product had a different polymorphic form from the drug substance in the respective RLD (e.g., warfarin sodium, famotidine, and ranitidine). FDA also has approved some ANDAs in which the drug substance in the generic drug product differed in solvate or hydrate forms from the drug substance in the corresponding RLD (e.g., terazosin hydrochloride, ampicillin, and cefadroxil).

Therefore, based upon scientific principles of analytical Science and regulatory considerations as per published guidance & enforced policies & acts, it is concluded that pharmaceutical solid polymorphism has no relevance to the determination of drug substance ‘‘sameness’’ in ANDAs provided physical and chemical attributes remains the same. ‘‘Sameness’’ between the drug substance in the generic drug product and the RLD is established by demonstrating the same chemical structure, as appropriate.

Followings are the case studies that illustrate the conceptual framework adopted from the decision trees and in the ANDA review process. These examples also demonstrate that polymorphism is not directly relevant to the determination of ‘‘sameness’’ in ANDAs.

Case One: Ritonavir

The first time that the pharmaceutical industry took serious note of polymorphism was in 1998, when Abbott Laboratories had to stop sales of Novir, its novel protease inhibitor for human immunodeficiency virus (HIV).

Ritonavir is the active pharmaceutical ingredient (API) of Abbott's HIV drug Novir.
Ritonavir Story:
In 1992 : Discovered at Abbott Laboratories.
Dec 1995 : Filed New Drug Application (NDA).
Jan. 1996 : Commercial Start-up.
March 1996 : FDA approval of Novir as a semisolid capsule formulation and also as liquid formulation.
Early 1998 : Final product lots failing the dissolution test, and a large portion of the drug substance precipitating out of the final (semisolid) formulated product.

Precipitate was identified as a new polymorph of ritonavir (Form II).
Form II was thermodynamically more stable and much less soluble than Form I.

After about two years hard work & hundreds of millions of dollar being spent, Abbott scientists finally found ways to control the formation of either Form I or Form II polymorphs and received FDA approval on reformulated Novir soft gelatin capsules in June 1999.

Case Two: Aspirin

In 2005, researchers reported that they had isolated and characterized a second form (Form II) of Aspirin. This second form (Form II) was obtained during co crystallization experiments with aspirin and other compounds. Form II is kinetically stable at 100 K, but it converts back to Form I at ambient conditions. Both forms contain a hydrogen-bonded carboxylic acid dimer. But they differ in the arrangement of the dimers with each others through their acetyl groups. The Form I containing dimers of dimers, whereas form II containing chains of dimers.

Case Three: Enalapril maleate

Enalapril maleate is an ACE inhibitor, which has two polymorphic forms. Form II is more stable but it is more degradable than form I. simple addition of sodium bicarbonate or some other stabilizer to the tablet formulation can minimize that. By applying this approach various ANDAs for enalapril maleate tablet without inclusion of polymorphic form were approved.

Case Four: Ranitidine hydrochloride

Ranitidine is a histamine H2-receptor antagonist; exist in two polymorphic modifications. As it is highly water soluble drug, different polymorphic forms have no effect on bioavailability. Innovator brand of Ranitidine HCl (Zentac®) contains Form II established by FT-Raman. Many ANDAs containing Form I were approved, which contains sufficient supporting data to demonstrate bioequivalency with innovator. So, they have not to include specification for control of polymorphic forms like other approved ANDAs, which includes XRPD/FT-IR for controlling polymorphic form II for generic ranitidine hydrochloride tablets. This case illustrates that drug substance polymorphism has no relevance to the determination of ''sameness'' in ANDAs.

Case Five: Warfarin sodium

Warfarin sodium is an anticoagulant that exists as an amorphous solid or as a crystalline clathrate (nonstoichiometric solvate). The clathrate consists of warfarin sodium: isopropanol: water in a ratio that may vary from 8:4:0 to 8:2:2. Coumadin tablets were evaluated by FT-Raman which

showed presence of crystalline clathrate in RLD. Generic version of Coumadin tablets (contain both the amorphous form and the crystalline clathrate in the dosage form) have been approved. In view of monitoring polymorphic form in the drug product, two possibilities are there. In the first possibility where warfarin sodium exists as amorphous form and there is no need to monitor the solid-state form, as the amorphous form is stable and does not spontaneously crystallize. In the second possibility where warfarin sodium exists as a crystalline clathrate which require to monitoring for polymorphic form in the drug product as loss of isopropyl alcohol would result in ‘‘collapse’’ of the clathrate into the corresponding amorphous form. From second possibility, it was concluded that loss of crystallinity of warfarin sodium directly proportional to the loss of isopropyl alcohol content. Hence, by controlling the content of isopropyl alcohol in the drug product, we can easily control and monitor the integrity of the clathrate in the dosage form.

Case Six: Cefuroxime axetil

It is a broad spectrum cephalosporin antibiotic, exist in two polymorphic forms, amorphous and crystalline. RLD contains amorphous form while ANDAs for Cefuroxime axetil containing amorphous dispersion and an amorphous/crystalline mixture were approved. In case of ANDAs containing amorphous dispersion of Cefuroxime axetil, no need to control because of sufficient availability of data with regard to innovator. In second case of ANDAs containing amorphous/crystalline mixture of Cefuroxime axetil, using USP monograph for Cefuroxime axetil tablet which incorporates two-tiered acceptance criteria for dissolution. Drug product performance testing (e.g., dissolution testing) can also generally provide adequate control of polymorph ratio changes that can influence drug product BA/BE for poorly soluble drugs. In such instances, setting specifications for polymorphs in the drug product would generally not be considered essential for ensuring adequate product performance. Only in rare cases would we recommend setting specifications for polymorphic forms in the drug products. Dissolution test can ensure product quality and performance throughout the shelf life of the product.

CONCLUSION

With the view to improve the understanding of scientific & regulatory consideration of Solid Pharmaceutical Polymorphism in ANDA, this review is cited. With respect to the same, this review provides comprehensive aspect of solid pharmaceutical polymorphism & its impact in the perspective of generic product equivalency to the innovator product. In addition to this, criteria for controlling & monitoring of Polymorphism in Pharmaceuticals (**Decision Tree # 1, 2 & 3 from Q.6A**) are also discussed. From regulatory perspective, the case studies in this review illustrates that drug substance polymorphism may or may not have significant relevance to the determination of ‘‘sameness’’ in ANDAs and hence shall be critically evaluated. To summarize, overall review gives clear understanding of solid pharmaceutical polymorphism in ANDA based on scientific principles and regulatory considerations.

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