

March 17, 2005



Via fax and UPS

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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2004D-0524

Draft Guidance for Industry on ANDAs: Pharmaceutical Solid Polymorphism; Chemistry, Manufacturing, and Controls Information

Dear Sir/Madam:

Sanofi-Synthelabo Inc. and Aventis Pharmaceuticals, members of the sanofi-aventis Group, appreciates the opportunity to comment on the above-referenced Draft Guidance entitled "ANDAs: Pharmaceutical Solid Polymorphism; Chemistry, Manufacturing, and Controls Information".

This draft guidance provides a framework for making regulatory decisions on drug substance sameness in terms of polymorphic form, and decision trees which provide a recommended course to monitor and control polymorphs in the drug substance and/or drug product when the drug substance exists in relevant polymorphic forms.

GENERAL COMMENTS

The guideline seems to be a bit vague about what is required to demonstrate bioequivalence (or does not provide sufficient reference to other documentation which may provide guidance), particularly if the drug substance is known to be of a different form from that in the reference listed drug (RLD). There is an assumption made that an in vivo-in vitro (IVIV) correlation has been made for the RLD, which may not always be the case. However, at some stage, it will be necessary to demonstrate that the chosen method of dissolution will adequately discriminate between any factors which may affect bioavailability for the generic drug product if it is known that a different form (or a mixture of forms that are different from the original) is being used. If the IVIV correlation has already been made for the RLD, this will be easier. However, in the absence of any IVIV correlation for the RLD, it may be necessary to make an IVIV correlation for the generic. (It may seem unlikely that different polymorphic forms would be used in this way. However, different amorphous content or different solvate content may readily occur, subsequently not be detected using established dissolution methods but bioavailability may differ). This may depend on the Biopharmaceutics Classification System (BCS) classification of the drug, since, if it is class 1 then dissolution is not an issue. For class 2, it will be problematic.

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Additionally, the Titles for Decision Trees 1, 2 and 3 should be differentiated and more in line with the specific Section V. Parts A. B. and C. on page 7. As they are currently, one cannot easily distinguish from the titles what aspects the decision trees address.

We also recommend that the FDA include a glossary of terms (e.g. “metastable”).

SPECIFIC COMMENTS:

Lines 73-74: Polymorphic forms of a drug substance can have different chemical and physical properties, including melting point, chemical reactivity, apparent solubility, etc...

Reference 11: Apparent solubility refers to the concentration of material at apparent equilibrium (supersaturation). Apparent solubility is distinct from true thermodynamic solubility, which is reached at infinite equilibrium time.

The guideline differentiates between the term “apparent solubility” and “true thermodynamic solubility”; however, throughout the document the term solubility is used. We recommend clarification of which “solubility” term is used throughout the document.

Lines 155-157: The most stable polymorphic form of a drug substance is often chosen during development based on the minimal potential for conversion to another polymorphic form and on its greater chemical stability.

We recommend that the term “stable” be further clarified and suggest using the term “thermodynamically stable” when appropriate as opposed to just “stable.”

Lines 181-182: However, FDA may prescribe additional standards that are material to the sameness of a drug substance.

We suggest that FDA provide examples of the additional standards that will be used to assess “sameness” other than compendial standards of identity.

Lines 194-207: In addition to meeting the standards for identity, each ANDA applicant is required to demonstrate that, among other things, the drug product exhibits sufficient stability and is bioequivalent to the RLD. While the polymorphic form can affect drug product stability and bioequivalence, these performance characteristics are also dependent on the formulation, the manufacturing process, and other physicochemical properties (e.g., particle size, moisture) of both the drug substance and formulation excipients. Thus, using a drug substance polymorphic form that is different from that of the RLD may not preclude an ANDA applicant from formulating a generic drug product that exhibits bioequivalence and stability. Therefore,

the drug substance in the generic drug product need not have the same polymorphic form as the drug substance in the RLD.

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).

It should not be assumed that a stable and bioequivalent generic product can be approved even if it is of a different polymorphic form than the reference product. We recommend that the FDA include language in the guidance that addresses the potential need for additional proof of efficacy especially for narrow therapeutic index drugs. Warfarin, one of the examples cited in line 207, has a narrow therapeutic index and it has been shown that efficacy of brand versus generic for this product is not predictable and could be catastrophic for patients if one product is switched for another in the middle of treatment.

Lines 252-254: 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.

If the FDA accepts using dissolution as a control test for polymorphic ratio changes for poorly water soluble drugs, then we recommend that ANDA sponsors be required to demonstrate that the dissolution method, if not compendial, is stability-indicating. The applicant should also perform multiple media tests.

Lines 255-256: Only in rare cases would we recommend setting specifications for polymorphic forms in drug products.

For clarity, we recommended that the agency provide an example of a "rare" case.

On behalf of the sanofi-aventis Group, we appreciate the opportunity to comment on the *Draft Guidance for Industry on ANDAs: Pharmaceutical Solid Polymorphism; Chemistry, Manufacturing, and Controls Information* and are much obliged for your consideration.

Sincerely,


Steve Caffé, M.D.
Vice President, Head US Regulatory Affairs