



TEVA PHARMACEUTICAL INDUSTRIES Ltd.

NAVA ROTEM - API DIVISION, TEVA GROUP

P. o. Box 3190 PETAH TIQVA 49131 Israel, Tel. +972-3-9267146, Fax. +972-3-9267325

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To: Docket No. 2004D-0524  
Division of Dockets Management (HFA-305)  
Center for Drug Evaluation and Research  
Food and Drug Administration

From: Nava Rotem Ph. D.  
Global QA/RA Knowledge Management Director  
Teva API Division  
ISRAEL  
Tel. 972-3-9267146, Fax 972-3-9267325

**Re: Comments to Guidance for industry ANDAs: pharmaceutical solid polymorphism**

**Our comment concerns the paragraph:**

“Characterization of polymorphs” lines 82-88 of the guidance which state that “demonstration of a nonequivalent structure by single crystal X-ray diffraction is currently regarded as the definitive evidence of polymorphism. X-ray powder diffraction can also be used to support the existence of polymorphs”. See the paragraph below:

80 **B. Characterization of Polymorphs**

81

82 There are a number of methods that can be used to characterize polymorphs of a drug  
83 substance.<sup>12</sup> Demonstration of a nonequivalent structure by single crystal X-ray diffraction is  
84 currently regarded as the definitive evidence of polymorphism. X-ray powder diffraction can  
85 also be used to support the existence of polymorphs. Other methods, including microscopy,  
86 thermal analysis (e.g., differential scanning calorimetry, thermal gravimetric analysis, and hot-  
87 stage microscopy), and spectroscopy (e.g., infrared [IR], Raman, solid-state nuclear magnetic  
88 resonance [ssNMR]) are helpful to further characterize polymorphic forms.

**We suggest the following revision:**

**“There are a number of methods that can be used to characterize polymorphs of a drug substance, however the X-ray powder technique should be regarded as the primary technique. Although that for demonstration of a nonequivalent structure the single crystal X-ray diffraction is currently regarded as a definitive evidence of polymorphism, the X-Ray powder diffraction is equally a specific, unequivocal, sensitive technique to be routinely used for identifying the polymorphic content of drug substances. Other methods .....can be helpful to further characterize polymorphis forms, according to the specific cases.”**

**Our reasoning is as follows:**



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The guideline statement implies that the single crystal analysis is the method to be used in order to prove existence of polymorphism, and the X-ray powder diffraction **can** be used to support (but not prove) existence of polymorphism.

The current phrasing may mislead, because it may be wrongly understood that the technique to be used and the analysis to be provided to prove existence of polymorphism is the single crystal analysis.

While both techniques are capable to determine the crystal structure, the X-Ray powder diffraction has several advantages:

- It is well explained in the current literature and it is well known that the X-ray powder diffraction is the unequivocal analysis to be used to identify and distinguish among crystal forms (*Polymorphism in Molecular Crystals, by Prof. Joel Bernstein, page 112: "...the X-ray powder diffraction is probably the most definitive method for identifying polymorphs and distinguishing among them."*).
- The single-crystal analysis provides a detailed information of the symmetry of the lattice (unit cell data), symmetry of the molecular packing (space group), and exact position of the molecules in the lattice (atomic coordinates). The powder diffraction contains all the above three-dimensional information folded within a two-dimensional pattern, which is unique for each existing crystal form.
- The single crystal technique is not a routine test for monitoring powders, it is an expensive, long technique that can characterize only one crystal (rather than a powder).
- The powder diffraction technique is a quick, inexpensive test suitable for monitoring powders, it is very specific and sensitive to the presence of different crystal forms, mixtures of them etc...
- Most of drug substances can not be crystallized as single crystals (at conditions used for powder production) .
- 2. Even in the cases when the crystal structure is known (single crystal analysis) the polymorph characterization will be based on the comparison of the pattern simulated for the crystal structure with the observed powder XRD.

Taking into consideration the explanation above, the X-ray powder diffraction method should be described in the guidance as the primary technique, rather than a "supporting" technique for determination of polymorphism. The other techniques should be suggested as complementary

Comments received from:

J. Aronhime Ph. D.

Global R&D Solid State Characterization Manager

And

B. Iosefzon Ph. D.

Solid State Studies Manager

Regards,

*Nava Rotem*

Nava Rotem