



Date: MAR 14 2005

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

Re: Docket Number 2004D-0524  
Response to FDA Call for Comments  
Draft Guidance for Industry on ANDAs: Pharmaceutical Solid Polymorphism;  
Chemistry, Manufacturing, and Controls Information

Dear Sir or Madam:

Reference is made to the December 20, 2004 Federal Register notice announcing the request for comments on the draft "Guidance for Industry on ANDAs: Pharmaceutical Solid Polymorphism; Chemistry, Manufacturing, and Controls Information."

AstraZeneca has reviewed this draft guidance and our comments are attached.

Please direct any questions or requests for additional information to me, or in my absence, to Robert Timko, Director, at (302) 886-2164.

Sincerely,

Lan-Chi Nguyen, Manager  
Regulatory Affairs CMC  
Telephone: (302) 886-3533  
Fax: (302) 886-3533

LCN

Enclosure

2004D-0524

**US Regulatory Affairs**  
**AstraZeneca LP**  
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

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**AstraZeneca Comments**  
**Draft Guidance for Industry on ANDAs: Pharmaceutical Solid Polymorphism;**  
**Chemistry, Manufacturing, and Controls Information**  
**Federal Register Docket No. 2004D-0524**

**General Comments**

- Comment 1

Page 2, lines 63 - 65

The text on hydrates should be more specific, for example, 'As the drug substance will inevitably be exposed to water, the possibility of hydrate(s) formation should be checked'.

Concerning solvents, it is suggested that the search for solvates is restricted to those solvents with which the drug substance has contact, for example, the solvent(s) in the final crystallization. It is not necessary to include all solvents.

- Comment 2

Page 3, lines 95-96

“The solid-state properties of a drug substance can have a significant influence on the solubility of a drug substance”.

This is rather vague. First of all, the solubility is a solid-state property in itself and secondly, most of what normally is referred to as the solid-state properties (density, particle size distribution, crystal habit, melting point etc.) do not affect solubility (although some of them e.g. specific surface area can affect rate of dissolution). However, different crystal modifications have different solubilities, which is probably the aim of this sentence.

- Comment 3

Page 4, lines 129-130

“...we recommend that you pay close attention to polymorphism and crystalline habit as they relate to pharmaceutical processing.”

This guidance is about “polymorphism”, why is crystalline habit involved? If the aim is to relate to properties, which affect pharmaceutical processing, there are many more properties that should be addressed such as particle size distribution, melting point, and etc.

- Comment 4

Page 5, lines 155-157 and Page 7, line 248

“The most stable polymorphic form...”

It is suggested the Agency to change this to “The more stable polymorphic form ...” since it is not possible to scientifically prove which crystal modification is the definitely most stable one.

- Comment 5

Page 6, lines 184 – 185

“Polymorphic forms of a drug substance differ in internal solid-state structure, but not in chemical structure.”

It is suggested that the Agency keeps a consistent definition of polymorphism as on page 3.