



# OTSUKA AMERICA PHARMACEUTICAL, INC.

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June 5, 2000

Dockets Management Branch (HFA-305)  
Food and drug Administration  
5630 Fishers lane, Room 1061  
Rockville, Maryland 20852

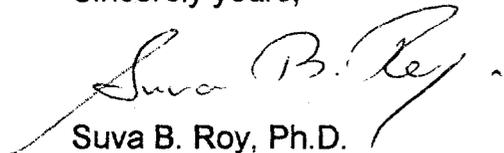
**Re: Docket No. 93D-0139**

Dear Sirs:

Please find enclosed comments from Otsuka America Pharmaceutical Inc. (OAPI) on the International Conference on Harmonisation: Draft Revised Guidance on Q1A9(R) Stability Testing of New Drug Substances and Drug Products.

Please feel free to contact me at (301) 527-4701 should you need additional information or clarification.

Sincerely yours,

  
Suva B. Roy, Ph.D.  
Senior Director, Regulatory Affairs CMC

enclosure

93D-0139

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# **OAPI's Comments on Draft Revised Guidance on ICH Q1A(R) Stability Testing of New Drug Substances and Drug Products**

## **General Comments**

We commend the ICH Stability expert working group (EWG) for this draft guidance, it is a significant improvement over the 1994 ICH Q1A Stability Guidance. We specially appreciate the efforts of the EWG for the 1) inclusion of the refrigerated and freezer storage conditions, 2) the semi-permeable containers for the drug products, 3) clarification on the stability commitments and 4) cross referencing the ICH Q1B and ICH Q6A and ICH Q6B guidances in this draft.

## **Specific Comments**

### ***Drug Substance***

**Stress testing** - The draft guidance is silent on the study of the effects of stress testing on the intrinsic physical stability of the drug substance, such as crystal forms, crystal growth, hydration etc. Such changes can affect the drug product quality. Considerations of the physical stability of the drug substance in addition to the chemical stability should be included in the final guidance.

**Storage condition** - The draft guidance uses the phrase "proposed label storage condition" for the drug substance intended for storage in a Refrigerator or in a Freezer. The term label storage is generally associated with the drug product labeling that requires FDA's prior-approval, drug substance storage condition on the other hand does not require FDA approval. Perhaps a more generic terminology that does not suggest the need for FDA approval can be used instead.

### ***Drug Product***

**Packaging/Containers** - The draft guidance states "Additional testing of unprotected drug product can form a useful part of stress testing and packaging evaluation as can studies carried out on other related packaging materials in supporting the definitive package(s)." The sentence sets out an expectation that such studies should be carried out routinely as a part of the definitive or formal stability study program. We strongly advise that the sentence be rephrased to make such studies optional.

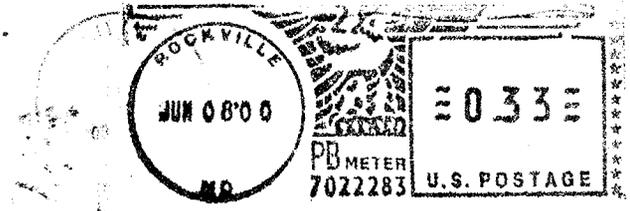
**Statements/Labeling** - The draft guidance appears to have side stepped the issue of harmonized label storage statements. Applying various storage temperature statements in accordance with national/regional requirements defeats the very purpose of harmonization. If stability studies are conducted according to this harmonized ICH guidance one should logically be able to apply harmonized label storage statements. We strongly urge the EWG to develop and include harmonized label storage statements in this guidance before it is finalized. The proposed label storage statements in the FDA's Draft Stability Guidance, June 1998 may be the basis for such statements.

We also recommend that in addition to harmonized textual label storage statements the EWG also consider intuitive icons that are universally recognized to depict storage statements. For example, a thermometer with markings for the target and upper and lower range for storage temperature, or dark glasses for protect from light, a snowflake with an X over it to denote prevent from freezing and similar icons can be adopted. The icons may be used with the label storage statements or used alone.



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