



November 18, 1998

Dockets Management Branch (HFA-305)  
Food and Drug Administration  
12420 Parklawn Dr., Rm. 1-23  
Rockville, MD 20857

**Re: Docket No. 98D-0514  
Guidance for Industry  
ANDAs: Impurities in Drug Substances**

To Whom It May Concern:

Apotex Corp. has reviewed the above-listed draft guidance and is hereby providing comments as follow:

### **III. RATIONALE FOR THE REPORTING AND CONTROL OF IMPURITIES**

#### **A. Organic Impurities Lines 80-105**

These lines reference an impurity with an "apparent" level of 0.1%. We suggest elimination of the use of the word apparent. It is not clear what is meant by this term. The use of the word apparent could imply that rounding is acceptable. However, as found in lines 102-105, rounding is not acceptable. In addition, one could have an impurity that is around 0.1%; sometimes .09% and sometimes 1.1%. Apparent in this type of scenario could be construed as an average. By better defining what is meant by the word apparent, ambiguity and incorrect interpretation of acceptance criteria could be eliminated.

#### **C. Residual Solvents, Line 114**

It is unclear what is meant by the use of "appropriate level of sensitivity" in relation to analytical procedures. We suggest further clarification. This could be accomplished by listing factors that should be considered in determining the appropriate level of sensitivity for a method.

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#### **IV. ANALYTICAL PROCEDURES**

##### **Lines 126-136**

This section discusses the use of response factors in measuring organic impurity levels. In some instances, it is difficult to determine the response factor due to the inability in obtaining a standard for the impurity. This is particularly applicable in the case where the ANDA holder is determining impurity levels.

#### **VI. ACCEPTANCE CRITERIA FOR IMPURITIES**

This section discusses acceptance criteria. Both unidentified impurities as well as unspecified impurities are referenced. It is unclear as to the difference (if any) between these. The acceptance criteria for an unidentified impurity (at or above .1%) is stated differently from that for the unspecified impurity (not more than 0.1%). This criteria allows for a test result of 0.1% to be acceptable for an unspecified impurity where it would be rejected for the unidentified impurity. Why are the criteria different? We suggest an explanation of this difference or a unification of the criteria.

#### **VI. ACCEPTANCE CRITERIA FOR IMPURITIES**

##### **Lines 184-192**

The setting of acceptance criteria is discussed. It states that as long as there is no safety concern, the criteria should be set on data generated from manufactured batches and on the methodologies used to perform the analysis. This is a process that works well for a noncompedial item. However, if the drug substance is compedial with stated impurity specifications, an organization that produces a material that has lower levels of the impurity based on their procedures would be required to tighten their specifications based on their generated data versus another organization whose process produces higher levels of the impurity. This process favors the manufacturer with a less pure material and appears to be inequitable.



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**Line 203**

This sentence discusses mass balance and the fact that it need not add exactly to 100 percent because of the analytical error associated with a method. We suggest further clarification as to the meaning behind "not exactly to 100 %".  
Would 95% be acceptable? 90%?

Thank you for your consideration in these matters.

Sincerely,

Marcy Macdonald  
Associate Director,  
Regulatory Affairs