



May 2, 2005

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

Re: **Docket No. 1998D-0514**
Draft Guidance for Industry on Abbreviated New Drug Applications;
Impurities in Drug Substances; Chemistry, Manufacturing and Controls
Information

Dear Sir/Madam:

The following comments are submitted by Apotex Inc. further to the publication of Docket No. 1998D-0514 on January 31, 2005 regarding the revision to the guidance on Impurities in ANDAs.

This most recent revision of the guidance (January 2005 Draft, Revision 1) includes the following text:

Lines 201 - 215:

Comparative Analytical Studies:

An impurity present in a drug substance covered by an ANDA can be qualified by comparing the analytical profiles of the drug substance with those in an approved human drug product using the same validated, stability-indicating analytical procedure (e.g. comparative HPLC studies). This approved human drug product is generally the reference listed drug (RLD)...

*An impurity present in the ANDA drug substance is considered qualified if the amount of identified impurity in the ANDA drug substance **reflects the levels observed** (emphasis added) in the corresponding approved human drug product.*

Lines 139 - 142:

*If the acceptance criterion for a drug substance impurity does not exist in the USP and this impurity can be qualified by comparison with an FDA-approved human drug product, it is important that the acceptance criterion **be consistent with the level observed** (emphasis added) in the approved human drug product.*

The approved version of the guidance currently in effect contains the following text:

*Third Level (L3b): A comparison of the impurity profile of the generic drug substance with the process impurities profile on an average of three or more different lots of the innovator's drug product is recommended. This comparative study should be performed using appropriate discriminating analytical tests such as HPLC or Capillary Electrophoresis. **The impurity is qualified if it is found at similar levels (no more than twofold higher,** (emphasis added) *but not to exceed 1.0% for most drug substances*). Twofold higher criteria are justified for several reasons. For example, the innovators' impurity acceptance criteria are set higher than levels observed in drug substances, and the safety studies that qualified the innovators' drug substances are carried out at significantly higher levels than the specifications agreed to under FDA's pharmacology and toxicology evaluations.*

The text in the draft document indicates that an impurity may be considered qualified if the amount of identified impurity in the ANDA drug substance “reflects the levels observed” in the corresponding approved human drug product and that acceptance criterion be “consistent with the level observed” in the approved human drug product. The currently approved version states that an impurity is qualified if it is found at “similar levels (to the RLD) (no more than twofold higher)”.

The current version of the guidance includes the justification for the twofold higher criteria which, to our knowledge, has not changed. Therefore, Apotex Inc. recommends that this same criteria be maintained and explicitly stated in the new revision of the guidance document with respect to qualification and acceptance criterion for impurities that are qualified against the RLD.

In addition, Apotex Inc. recommends that more specific guidance be provided with respect to how the qualification and acceptance limits are to be established based on the RLD data (i.e., is the “level observed” considered to be the mean of the observed values from three lots of the RLD?). This definition should be included for greater clarity on the process.

Should you have any questions or concerns regarding the above, please do not hesitate to contact me at (416) 401-7690 or by e-mail at jdochert@apotex.com

Sincerely,

Jennifer Docherty
Manager, Regulatory Affairs Strategy & Intelligence