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April 19, 2005

Via fax and UPS

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

**Re: Docket No. 1998D-0514**

*Draft Guidance for Industry on ANDAs: Impurities in Drug Substances*

Dear Sir/Madam:

Sanofi-Synthelabo Inc. and Aventis Pharmaceuticals, members of the sanofi-aventis Group, appreciates the opportunity to comment on the above-referenced Draft Guidance entitled "*ANDAs: Impurities in Drug Substances*".

This draft guidance provides revised recommendations on what chemistry, manufacturing and controls (CMC) information to include regarding the reporting, identification, and qualification of impurities in drug substances produced by chemical synthesis when submitting documentation for an abbreviated new drug applications (ANDAs), drug master files (DMFs) including type II DMFs, or supplement to support changes in drug substance synthesis or process. It also provides recommendations for establishing acceptance criteria for impurities in drug substances.

We have evaluated the content of the draft guidance and offer the following comments and/or clarifications for your consideration.

**SPECIFIC COMMENTS:**

**Lines 135-137:** "*However, if the level of the impurity is above the level specified in the USP, we recommend qualification. Then, if appropriate qualification has been achieved, an applicant may wish to petition the USP for revision of the impurity's acceptance criterion.*"

It is highly unlikely that generic companies will petition a revision to the USP monograph of the reference product before filing an ANDA. Therefore, the guidance should include additional statement to clarify whether or not a generic product with higher qualified levels of impurities can still be labeled as "USP".

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**Lines 161-164:** *“An impurity is considered qualified when it meets one or more of the following conditions:*

- *When the observed level and proposed acceptance criterion for the impurity do not exceed the level observed in an FDA-approved human drug product.”*

**Lines 246-249, footnote d:** *“An impurity is considered qualified for ANDAs when one or more of the following conditions are met:*

- *When the observed level and proposed acceptance criterion for the impurity do not exceed the level justified by an FDA-approved human drug product.*

This statement is too general in that it implies that an impurity can be considered qualified if the observed level and proposed acceptance criterion does not exceed the level observed in *any* FDA-approved drug product containing the particular drug substance. This statement should be clarified to state that the impurity level and criterion must not exceed the level observed in the **Reference Listed Drug (RLD)**.

**Lines 203-205:** *“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).”*

Additional clarification is requested on the definition of “**the same** validated, stability indicating etc...” since it is difficult to ascertain the actual method used for the reference product. This type of information is either not available through FOI or if the drug substance is a monograph item, some of the USP methods are outdated.

On behalf of the sanofi-aventis Group, we appreciate the opportunity to comment on the *Draft Guidance for Industry on ANDA: Impurities in Drug Substances* and are much obliged for your consideration.

Sincerely,



Steve Caffé, M.D.  
Vice President, Head US Regulatory Affairs