



sanofi aventis

Because health matters

July 13, 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. 2005D-0122

Draft Guidance for Industry on Exploratory Investigation New Drugs Studies

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Pharmaceuticals, members of the sanofi-aventis Group, appreciates the opportunity to comment on the above-referenced Draft Guidance entitled "Exploratory Investigation New Drugs Studies".

This draft guidance clarifies what preclinical and clinical approaches (including CMC) should be considered when planning exploratory IND studies in humans, including studies of closely related drugs or therapeutic biological products, under an IND application (21 CFR 312).

We have evaluated the content of the draft guidance and offer the following comments and/or clarifications for your consideration.

GENERAL COMMENTS

The term "exploratory study" is now being used in various contexts. Since "exploratory IND studies" which are the subject of this guidance, are described as "first in human studies" and "limited, early exploratory IND studies in humans" we recommend that it be clarified that this guidance does not seek to define the range of the clinical studies that may be considered "exploratory," but only to address elements needed for an IND for certain early exploratory studies.

Additionally, the intent of this guidance is unclear as it relates to CMC information since the Phase I guidance (Content and Format of Investigational New Drug Applications for Phase I Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products) already describes a graded approach to CMC information that allows reduced information in early phase studies. Although this draft guidance discusses exceptions to the Phase I guidance no specific reduction in information is apparent other than the availability of formatting CMC information in a summary report.

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Although the summary report is suggested, method of presenting the content is not well defined and should be further elaborated. For example, in the summary report what would be the order of content (CTD, bulleted sections from draft guidance, etc...) and how would information from dual drug substances be presented in the summary report. Additionally, providing some examples of what CMC information may not be needed in an exploratory IND would be useful in order to better apply the guidance to a specific submission.

An alternative to creating this new guidance document would be to modify the existing Phase I IND guidance to incorporate exploratory INDs rather than to have two separate guidance documents covering very similar topics. This would allow a clearer presentation of how the content or format for an Exploratory IND would differ from another early Phase I IND.

SPECIFIC COMMENTS:

Lines 226 - 227: *“For oral administration, sponsors can consider using suspensions or solutions in addition to pills, powders, and capsules.”*

We suggest replacing the term “pills” with the term “tablets”.

Lines 237 - 239: *“The method of preparation of the candidate product lots used in preclinical studies and intended for the proposed human study, including a brief description of the method of manufacture and packaging including a description of the container and closure system.”*

We suggest adding a clarifying statement to cover any differences between synthesis process used for preclinical drug substance and the drug substance proposed for the clinical study such as the following: *“In the case where the method of preparation for the API used in preclinical studies and that intended for human studies are different, the sponsor should only describe the latter and state any potential impact on safety or quality resulting from these differences.”*

Lines 240 - 241: *“For the active substance include a list of the starting materials, reagents, solvents, catalysts used, and purification steps employed to prepare the candidate product.”*

We suggest eliminating the need for a separate list of synthesis materials by category and to have them included at the appropriate steps of the process flow diagram. Additionally, we suggest dropping the term “starting materials” for this phase of development since it is too early to classify starting materials and instead refer to them as “materials” and to simply provide all materials on the flow diagram.

Lines 246 - 247: *“We recommend the use of a detailed flow diagram as the usual, most effective, presentation of this information.”*

We request further clarification as to whether or not a narrative is necessary for synthesis processes in addition to the flow diagram.

On behalf of Sanofi-Synthelabo Inc. and Aventis Pharmaceuticals, members of the sanofi-aventis Group, we appreciate the opportunity to comment on the *Draft Guidance for Industry on Exploratory Investigation New Drugs Studies* and are much obliged for your consideration.

Sincerely,

A handwritten signature in black ink, appearing to read 'Caffé', with a stylized flourish at the end.

Steve Caffé, M.D.
Vice President, US Deputy Head
Regulatory Development