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August 16, 2004

Via fax and UPS

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2004-0018

Proposed Rule – Human Subject Protection; Foreign Clinical Studies Not Conducted Under an Investigational New Drug Application [Federal Register/ Volume 69, No. 112, pages 32467-32475]

Dear Sir/Madam:

Aventis Pharmaceuticals appreciates the opportunity to comment on the above-referenced docket with regards to the Proposed Rule entitled "*Human Subject Protection; Foreign Clinical Studies Not Conducted Under an Investigational New Drug Application.*"

The proposed rule is intended to update the standards for the acceptance of non-IND foreign studies and to help insure the quality and integrity of data obtained from such studies.

We offer the following comments and questions for your consideration.

GENERAL COMMENTS:

The supporting information described in section (b) 1,2,3,5,7,8,10 appears to be largely consistent with content requirements already specified in relevant ICH documents. However, it is noted that some of the requirements listed in section (b) of the proposed revisions are not entirely consistent with guidance provided in relevant ICH documents. If a non-IND study is conducted under GCP, then assurance of GCP compliance and presenting the conditions of its conduct and the results with content and format agreed upon in the ICH documents should be sufficient for its acceptance.

Preferably all of the requirements outlined in this proposed rule would describe content compatible with the agreed upon and FDA endorsed ICH standards for the Clinical Study Report (CSR, ICH E-3) and the Common Technical Document (CTD). In particular, we note the following differences in section (b) "*Supporting information*" of the proposed revisions and would ask FDA for consideration of the following changes.

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SPECIFIC COMMENTS:

(b)(6) The names and qualifications for the members of the IEC that reviewed the study;

This section is inconsistent with the ICH CSR format and with other FDA guidance on the submission of study results. For instance, FDA's Guidance for Industry on "Providing Regulatory Submissions in Electronic Format — NDAs" requires in section H.3 to provide "all appendices as defined in the ICH E3 Structure and Content of Clinical Study Reports (July 1996)." The ICH E3 document requires that the ethics committee information be provided in appendix 16.1.3 in the form of a "List of EIC's or IRB's (plus the name of the committee Chair, if required by the regulatory authority)." In requiring "the names and qualifications for the members of the IEC that reviewed the study," Section (b)(6) deviates from the ICH format and would thus require industry to utilize different formats for the CSRs from IND and non-IND studies as well as different formats for the submission of non-IND studies to FDA and to other countries' authorities.

(b)(9) A description of what incentives, if any, were provided to subjects to participate in the study;

The requirement to provide a description of what incentives, if any, are provided to subjects to participate in the study is unclear. It would seem adequate and even more descriptive to provide a model consent form. This is already a requirement that is described in ICH E3 (Appendix 16.1.3). The consent is required to include the anticipated prorated payment, if any, to the subject for participating in the trial. If this is not deemed to be adequate, more detail should be provided to define "incentive" as used in the context of the proposed revision.

(b)(11): A description of how investigators were trained to comply with GCP (as described in paragraph (a)(1)(i) of this section) and to conduct the study in accordance with the study protocol, and copies of written commitments, if any, by investigators to comply with GCP and the protocol.

The written investigator commitments required in this section are usually included in the investigator signature page of the study protocol. A blank copy of this page is provided with the protocol in ICH CSR appendix 16.1.1. ICH-GCP 8.2.2 requires archival of the individual investigators' signature pages in the sponsor's TMF. It should suffice to only require a description of how the investigator commitment was obtained to comply with GCP and the protocol and eliminate the proposed requirement to submit an individual form for each participating investigator.

In summary, we would ask FDA to confirm that conducting a study according to GCP and reporting and submitting the study according to the ICH CSR and CTD standards and FDA's corresponding guidance documents satisfies all the requirements of the proposed

revised 21 CFR 312.120. In the cases listed above where the individual requirements of section (b) deviate from the ICH standards the agency should consider modifying the requirements to conform with the ICH CSR and CTD standards thus allowing sponsors to prepare and submit IND and non-IND studies according to a single unified standard.

On behalf of Aventis Pharmaceuticals, we appreciate the opportunity to comment on the *Proposed Rule on Human Subject Protection; Foreign Clinical Studies Not Conducted Under an Investigational New Drug Application* and are much obliged for your consideration.

Sincerely,

A handwritten signature in black ink, appearing to read 'Caffé', written in a cursive style.

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