October 15, 2003

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. 2003D-0367
Draft Guidance for Industry on Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions [Federal Register/ Volume 68, No. 168, page 52044, August 29, 2003]

Dear Sir/Madam:

Aventis appreciates the opportunity to comment on the above-referenced draft guidance entitled "*Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions.*"

This guidance provides recommendations regarding the use of eCTD document information backbone files to facilitate efficient submission handling. It also provides more specificity than in previous guidances with regard to the organization of individual submissions and harmonizes the organization and formatting of multiple submission types.

We offer the following comments and questions for your consideration.

GENERAL COMMENTS:

Aventis recommends that additional identifiers for any guidances be included (e.g., date of guidance, guidance status, etc.) for more specificity on guidance version being referenced.

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SPECIFIC COMMENTS:

Lines 21-26: "*This is one in a series of guidance documents intended to assist applicants making regulatory submissions to the FDA in electronic format. This guidance discusses issues related to the electronic submission of applications for human pharmaceutical products and related submissions, including abbreviated new drug applications (ANDAs), biologics licensing application (BLAs), investigational new drug applications (INDs), new drug application (NDAs), master files, advertising material, and promotional labeling.2*"

and

Lines 64-67: "*This guidance applies to marketing applications (ANDAs, BLAs, NDAs), investigational applications (INDs), and related submissions (master files, advertising material, and promotional labeling). The guidance applies equally to original submissions, supplements, and amendments to these applications and related submissions.*"

Recommendation: Aventis suggests adding "Annual Reports" to the list of submissions covered by this guidance. Additionally, Aventis requests clarification on whether Agency's Questions and Answers, Briefing Documents, and General Correspondence with Regulatory Agencies fall within the scope of this guidance.

Lines 90-91: "*Submissions are a collection of documents that include forms, reports, and datasets. When making an electronic submission,* ***each document should be provided as a separate file***."

Recommendation: Aventis suggests defining the term "document" and providing examples for clarity.

Lines 100-101: "*You should contact our electronic submission coordinator prior to using any other headings.*"

Recommendation: With regard to "other headings," Aventis requests clarification on where information, which is commonly included in an "Introduction" or as regulatory or technical summary text that often precedes CMC information, should be included.

Lines 223-226: "*Documents required by regulations to be submitted with an original signature (e.g., FDA form 356h, FDA form 1571) can be submitted with electronic signatures provided that you follow the controls described under 21 CFR part 11 and that our system can automatically validate the signature.*"

Recommendation: Aventis suggests including a more comprehensive list of documents that would be required for submission with an original signature. Additionally, we suggest inclusion of more details regarding the validation of signatures.

Lines 241-242: "*You should use only letters (lower case), numbers, or hyphens in the name.*"

Recommendation: Aventis suggests clarification on whether "spaces" would be permitted when naming electronic files.

Lines 252-253: "*You should not include empty folders in the submission.*"

Recommendation: With regards to "empty folders", it is not clear how an amendment or a post-approval change, when only specific sections of Module 3 are changed, will be submitted electronically according to the eCTD. Aventis suggests providing an example on how such submission would be handled.

Line 345: "*Module 1 contains administrative and labeling documents.*"

Recommendation: Per the *FDA Draft Guidance for Industry "Submitting Marketing Applications According to the ICH-CTD Format – General Considerations"* (August 2001), Environmental Assessments are defined as administrative documents to be included in Module 1. Aventis suggests that the Comprehensive Table of Contents Headings and Hierarchy document include a reference to "Environmental Assessments" as administrative documents.

Lines 362-370: "*If you decide to include a cover letter, we recommend you include the following information:*

- *Description of the submission including appropriate regulatory information 364*
- *Description of the submission including the approximate size of the submission (e.g., 2 gigabytes), the format used for DLT tapes, and the type and number of electronic media used (e.g., three CDROMs), if applicable*
- *Statement that the submission is virus free with a description of the software (name, 368 version, and company) used to check the files for viruses*
- *Regulatory and technical point of contact for the submission"*

Recommendation: Aventis requests clarification on the possibility of having hyperlinks from the cover letter to the document within the submission.

Lines 491-497: "*You should include documents that are provided in information amendments in the appropriate module using the appropriate headings to describe the subject matter. In the unusual case when information amendments do not fit appropriately under any heading in the CTD, you should place the documents in module 1 under the heading "information amendment: Information not covered under modules 2 to 5." Provide a separate PDF file for each subject covered. Documents that apply to more than one module should be placed under the heading "Multiple module information amendments."*

Recommendation: Aventis suggests the final guidance include an example on how "placebo" and "comparator" information should be presented in eCTD format of an IND

or IND Annual Report. Additionally, we request an example of "Multiple module information amendments" for clarity.

Lines 514-515: "*The only exception is for pharmaceutical development information, which can be provided as a single document.*"

Recommendation: For clarity, Aventis suggests including an example of how "pharmaceutical development information" can be provided as a single document in eCTD.

On behalf of Aventis we appreciate the opportunity to comment on the *Draft Guidance for Industry on Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions* and are much obliged for your consideration.

Sincerely,

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