June 23, 2003

Via fax and UPS

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

Re: Docket No. 02D-0526
Draft Guidance for Industry on Drug Product: Chemistry, Manufacturing and Controls Information [Federal Register Volume 68, No. 18, page 4219, January 28, 2003]

Dear Sir/Madam:

Aventis Pharmaceuticals Inc. appreciates the opportunity to comment on the above-referenced draft guidance entitled "Drug Product: Chemistry, Manufacturing and Controls Information".

This draft guidance provides recommendations on the chemistry, manufacturing and controls (CMC) information for drug products that should be submitted in original new drug applications (NDAs) and abbreviated new drug applications (ANDAs). This draft guidance is structured to facilitate the preparation of applications submitted in Common Technical Document (CTD) format.

We offer the following comments/clarification for your consideration.

General Issues

For clarity and consistency, please consider the following comments:

- Since there is heavy emphasis on excipients, especially novel excipients in Section IV. PHARMACEUTICAL DEVELOPMENT (P.2) - Part P.2.1.2, specifications for novel excipients should also be listed in Section VI. CONTROL OF EXCIPIENTS (P.4) – Part P.4.6 and in Section XI. APPENDICIES (A) – Part A.3.
- Cross references are given either to the CTD section number, or the FDA guidance hierarchy. This makes it confusing and difficult to navigate the guidance. For clarity, we suggest that one style should be chosen.

  Example: (Lines 332-335): *For excipients (e.g., coatings, lubricants) where a*

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range has been justified (see section IV. A.2), the target amount should be listed in composition statement. However the target and range should be included in the batch formula (P.3.2).

In this case, Section IV.A.2 correlates with P.2.1.2, and alternately P.3.2 correlates to Section V.B.

Section II. BACKGROUND
Part B. Content Information Included in an Application
Page 5, Lines 161-163

If information is not provided in a P subsection at all or for a particular product presentation or manufacturing scheme, this should be stated in the application and a reason given.

We suggest adding clarification to confirm that the statement, and corresponding rationale, for not providing information for a P subsection should immediately follow the relevant section./subsection number.

Section IV. PHARMACEUTICAL DEVELOPMENT (P.2)
Part A. Components of the Drug Product (P.2.1)
No. 1. Drug Substance (P.2.1.1), a. Key Physiochemical Characteristics
Page 11, Lines 383-386

Key physiochemical characteristics (e.g., water content, solubility, particle size distribution, polymorphic form, solvation or hydration state, pH, dissociation constant (pKa)) of the drug substance identified in S.3.1 that can influence the performance or manufacturability of the drug product should be discussed.

We suggest replacing curved brackets "( )" with square brackets "[ ]" since a subset is included within the sentence.

Section V. MANUFACTURE (P.3)
Part A. Manufacturer(s) (P.3.1)
Page 18, Lines 688-689 and Footnote 19
Page 19, Lines 695-697 and Lines 710-712

Each site should be identified by the street address, city, state, and when available, the drug establishment registration number.[19]

Footnote[19] - See 21 CFR part 207 for registration requirements for producers of drugs. The registration number is the seven-digit central file number (CFN) or ten-digit FDA Establishment Identifier (FEI).

Addresses for foreign sites should be provided in comparable detail, and the name, address and phone number of the U.S. agent for each foreign drug establishment as required under 21 CFR 207.40(c), should be included.

To facilitate preapproval inspection related activities, it is recommended that the name, telephone number, fax number and e-mail addresses of a contact person be provided for each site listed in the application.

Should full establishment information be included in both the body of the application and the Form FDA 356h?

Section V. MANUFACTURE (P.3)
Part C. Batch Formula (P.3.2)
No. 1. Flow Diagram
Page 22, Lines 790-796

The flow diagram should include:

- *each manufacturing step with identification of the critical steps and any manufacturing step where, once the step is completed, the material might be held for a period of time (i.e., noncontinuous process) before the next processing step is performed*
- *the material being processed*
- *critical process controls and the points at which they are conducted*
- *the type of equipment used (equipment model number is not needed)*

We suggest that a more precise definition of "noncontinuous process" be included in this section. In-process material that is held must be validated for a time period in excess of the designated "hold time" in the appropriate container/closure system.

Section V. MANUFACTURE (P.3)
Part C. Batch Formula (P.3.2)
No. 3. Reprocessing and Reworking
Page 24-25, Lines 887-912

Reprocessing is the introduction of an in-process material or drug product, including one that does not conform to a standard or specification, back into the process and repeating steps that are part of the approved manufacturing process. Continuation of a process

step after a process test has shown that the step is incomplete is considered to be part of the normal process and is not reprocessing. For most drug products, reprocessing need not be described in the application. In general, the documentation of and data to support the reprocessing of a production batch should be retained by the manufacturer and be available for review by FDA upon request. However, if there is a significant potential for the reprocessing operation to adversely affect the identity, strength, quality, purity, or potency of the drug product, the reprocessing operations should be described and justified in this section (P.3.3) of the application. For example, reprocessing of proteins would be considered a reprocessing operation that should be described in the application. Any data to support a justification should be either referenced or submitted in P.3.3. However, validation data, when warranted to support the reprocessing operation, should be provided in P.3.5.

Reworking is subjecting an in-process material or drug product that does not conform to a standard or specification to one or more processing steps that are different from the manufacturing process described in the application to obtain acceptable quality in-process material or drug product. In general, reworking operations are developed post approval, and the application is updated through submission of a prior approval supplement. However, if reworking operations are anticipated at the time of original submission, they should be described in this section of the application (P.3.3) with justification for the reworking operation and any data (or references to data) to support the justification. Validation data, when warranted to support the reworking operation, should be provided in P.3.5.

Although narrative definitions are given for *reprocessing* and *reworking* in this section, the Glossary contains no definitions for these terms. We suggest adding these terms to the Glossary.

Section V. MANUFACTURE (P.3)
Part D. Controls of Critical Steps and Intermediates (P.3.4)
Page 25, Lines 920-930

In this section of the application, all critical process controls (see section V.C.2) and their associated numeric ranges, limits, or acceptance criteria should be identified and justified and a brief description of the test provided. Any experimental data to support the justification should be included in this section (P.3.4) as well. For critical operating parameters and environmental controls, numeric ranges, limits, or acceptance criteria typically can be based on the experience gained during the development of the manufacturing process. (See section V.E for possible exceptions when process validation information is warranted.) Critical process control values from relevant batches (i.e., those for which batch analyses have been provided in P.5.4) should be provided as part of the justification. Additional information should be provided in this section (P.3.4) under the following circumstances.

We suggest adding a provision in this section for applicants to include justification for providing interim specifications for product release. This suggestion is based on the understanding that, for most new drug products, there may limited historical data for in-process or final release specifications at the time of submission. With the addition of this provision, an applicant could commit to introduce finalized specifications in a post approval submission.

Section V. MANUFACTURE (P.3)
Part D. Controls of Critical Steps and Intermediates (P.3.4)
Page 25, Lines 932-935

- *Biological Tests*

Analytical Procedures and associated validation information should be provided for biological tests.[23]

There is no reference provided in this bullet point to refer the applicant to appropriate guidances for establishing acceptance limits for biological tests. Several guidances, points to consider and compendia have suggestions on how to establish fiducial limits, particularly for biological potency assays, which inherently have higher variability (CVs).

Section VI. CONTROL OF EXCIPIENTS (P.4)
Page 27, Lines 991-995

- *Noncompendial – Non-novel Excipients*

When warranted, the additional CMC information or a cross –reference to a DMF that provides the additional CMC information should be included in A.3. See sections IV.B.2 and XI.C for additional guidance on the information that should be submitted to support the use of this type of excipient.

- AND -

Section XI. APPENDICES (A)
Part C. Excipients (A.3)
Page 49, Lines 1765-1769

- *Other Excipients*

Depending on the functionality (e.g., complexing agent) and the route of administration of the drug product, additional information, up to and including the level of information

recommended for novel excipients, can be warranted for noncompendial – non-novel excipients. The additional CMC information or a cross-reference to a DMF that provides the additional CMC information should be included in A.3.

Advice regarding the content and location of information on non-compendial – non-novel excipients is provided in different sections of this guidance and appears to be inconsistent.

Why should "additional CMC information be included in A.3", the CTD appendix for Novel Excipients, when an excipient is by definition "non-novel" (e.g. flavor, colorant, etc.)?

Section VII. CONTROL OF DRUG PRODUCT (P.5)
Part A. Specification(s) (P.5.1)
Page 32, Lines 1153-1155

- *Tests that can be performed in-process in lieu of testing the finished product (the results of such tests performed in-process should be included in the batch analysis report (e.g., certificate of analysis))*

We suggest adding text to this section clarifying how "tests performed in-process in lieu of finished product testing" should be reported on a Certificate of Analysis - especially for extensive in-process results such as PAT generated data.

Section VII. CONTROL OF DRUG PRODUCT (P.5)
Part D. Batch Analyses (P.5.4)
Page 37, Lines 1297

- *Batch identity (i.e., batch number), strength, and size*

We suggest including "formulation number" in the list to cover formulation changes during development.

Section VII. CONTROL OF DRUG PRODUCT (P.5)
Part E. Characterization of Impurities (P.5.5)
No. 1. List of Expected Impurities
Page 38, Lines 1343-1346

All expected drug product impurities (e.g., degradation products of the active ingredient, residual solvents, entiomeric impurities, excipient degradants, leachables from the container closure system) should be listed in this section of the application whether or not the impurities are included in the drug product specification.

Since "Miscellaneous Drug Product Impurities" is defined later in this section (Lines 1393-1409), we suggest that the impurities listed initial in Lines 1343-1346 should include miscellaneous drug product impurities.

For Example: *"All expected drug product impurities (e.g., degradation products of the active ingredient, residual solvents, entiomeric impurities, and miscellaneous drug product impurities such as excipient degradants..."*

Section VII. CONTROL OF DRUG PRODUCT (P.5)
Part E. Characterization of Impurities (P.5.5)
No. 2. Identification of Impurities
Page 39, Lines 1379-1380

When identification is warranted, the recommendations in S.3.2 of the forthcoming drug substance guidance on approaches for identifying impurities are applicable.

It is difficult to comment on "recommendations from a forthcoming guidance". We suggest that all referenced text be included in the draft guidance that is being reviewed, (i.e., reference only those guidances that can be accessed).

Section VII. CONTROL OF DRUG PRODUCT (P.5)
Part E. Characterization of Impurities (P.5.5)
No. 2. Identification of Impurities
Page 39, Lines 1395-1398

For purposes of this guidance, a miscellaneous drug product impurity other than (1) a degradation product, (2) a residual solvent, or (3) an extraneous contaminant that is more appropriately addressed as a good manufacturing practices issue (e.g., metal shavings).

We suggest adding "extraneous contaminant" to the definition list.

Section IX. CONTAINER CLOSURE SYSTEM (P.7)
Page 43, Lines 1531-1537

A description of the container closure system for the drug product should be provided, including the identity of materials of construction of each primary packaging component and its specification. The same type of information should be provided for functional secondary packaging components as is provided for primary packaging components. For nonfunctional secondary packaging components (e.g., those that neither provide additional protection nor serve to deliver the product), only a brief description should be provided. Information about the suitability of a container closure system should be provided in P.2.4.

We suggest including the container closure system for the proposed marketed drug product in this section.

Section X. STABILITY (P.8)
Page 44, Line 1546

Information relating to the stability of the drug product should be provided in P.8.

We suggest including a statement in this section (P.8) indicating that stability testing of the drug product should be conducted using the final container closure systems that are proposed in the market application.

Section XI. APPENDICES (A)
Part C. Excipients (A.3)
Page 49, Line 1748-1751

The chemistry, manufacturing, and controls information for a novel excipient should be provided in the same level of detail and in the same format as the information provided for a drug substance (see the forthcoming substance guidance).

We suggest removing the reference to the "forthcoming drug substance guidance", as it does not yet exist.

ATTACHMENT 1
Drug Product Specification, Test Recommendations for Specific Dosage Forms
Page 54, Line 1964

- *Uniformity of Dosage Units*

We suggest that the bullet point for this item be properly indented to be consistent with the other bullet points in this section.

GLOSSARY
Pages 58-61

We suggest adding the following list of terms to the Glossary section:

Adventitious Agents
Batch Analysis Data
Certificate of Analysis
Comparability Testing
Compatibility Testing
Compendial Excipient
Executed Batch Record
Non-compendial Excipient
Novel Excipient
Reference Standard
Reprocessing
Reworking
Sunset Testing
Validation

On behalf of Aventis Pharmaceuticals Inc. we appreciate the opportunity to comment on the Draft Guidance for Industry on Drug Product: Chemistry, Manufacturing and Controls Information and are much obliged for your consideration.

Sincerely,

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