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. 03D-0061
Draft Guidance for Industry on Comparability Protocols – Chemistry, Manufacturing, and Controls Information [Federal Register Volume 68, No. 37, page 8772, February 25, 2003]

Dear Sir/Madam:

Aventis Pharmaceuticals Inc. appreciates the opportunity to comment on the above-referenced draft guidance entitled "Comparability Protocols – Chemistry, Manufacturing, and Controls Information".

This draft guidance provides recommendations to applicants on preparing and using comparability protocols for post-approval changes in chemistry, manufacturing and controls (CMC) information.

We offer the following comments and questions for your consideration.

Section II. BACKGROUND
Page 2, Lines 39-45

As an applicant, you are responsible for assessing , prior to distribution of a product, the effect of any postapproval CMC changes on the identity, strength, quality, purity, and potency of the product as these factors relate to the safety or efficacy of the product (section 506A(b) of the Federal Food, Drug and Cosmetic Act (the act)). Such an assessment often includes demonstration that the pre- and postchange products (i.e., products manufactured prior to and subsequent to a change are equivalent. Postapproval CMC changes must be reported to FDA in one of four reporting categories (Section 506A of the Act):

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We suggest adding a Glossary to either this BACKGROUND section or the INTRODUCTION section to provide the sponsor with a clear definition of regulatory and technical terms used in preparing a comparability protocol.

Examples of terms to be included in the suggested Glossary are as follows:
Comparability protocol
Comparability report
Analytical reference standard
Related CMC changes
Unrelated CMC changes
Drug substance
Intermediate
Drug product
Isoforms
Orthogonal Testing
Product-specific
Process-specific
Current protocol
Obsolete protocol (criteria)
Qualification or validation lots
PAS
Reportable categories
FDA review period for comparability protocol
Method validation
Process validation
Criteria for non-comparability
Stability-indicating assays

Section II. BACKGROUND
Page 3, Lines 81-91

This guidance describes the general principles and procedures associated with developing and submitting a comparability protocol to the FDA. The guidance also describes the basic elements of a comparability protocol and specific issues to consider when developing comparability protocols for changes in:

- *the manufacturing process*
- *analytical procedures*[4]
- *manufacturing equipment*
- *manufacturing facilities*
- *container closure systems*
- *process analytical technology (PAT)*

We suggest adding *starting materials* and *raw materials* to the list of basic elements as these are critical CMC elements, which are subject to change during both drug development and post approval.

Section II. BACKGROUND
Part A. What is a Comparability Protocol?
Page 3, Lines 97-103

A comparability protocol is a well-defined, detailed, written plan for assessing the effect of specific CMC changes in the identity, strength, quality, purity, and potency of a specific drug product as these factors relate to the safety and effectiveness of the product. A comparability protocol describes the changes that are covered under the protocol and specifies the tests and studies that will be performed, including the analytical procedures that will be used, and acceptance criteria that will be achieved to demonstrate that specified CMC changes do not adversely affect the product. The submission of a comparability protocol is optional.

We suggest that this guidance not be restricted to just a comparison of drug products as there are examples of change controls that focus directly on drug substance. Comparability of drug products may not need justification if drug substance CMC changes have no adverse effect on the safety or efficacy of drug product attributes. The CMC distinction between drug substance and drug product changes is also consistent with the current CTD format. However, if CMC changes occur in a drug substance process that affect the drug product's attributes then drug product comparability is justified.

Section III. WHAT TO CONSIDER IN PLANNING A COMPARABILITY PROTOCOL
Part A. How Does a Comparability Protocol Affect the Reporting of CMC Changes?
Page 5, Lines 146-157

A comparability protocol prospectively specifies the tests and studies that will be performed, analytical procedures that will be used, and acceptance criteria that will be achieved to assess the effect of CMC changes. A well-planned protocol provides sufficient information for FDA to determine whether the potential for an adverse effect on the product can be adequately evaluated. With comparability protocol, the FDA can determine if a specified change can be reported in a category lower than the category for the same change, were the change to be implemented without an approved comparability protocol. Typically, categories designated for reporting changes under an approved comparability protocol are one category lower than normally would be the case (e.g.,

from PAS to CBE-30, CBE, or AR). In some cases, a reduction of more than one reporting category may be possible (e.g., PAS to AR).

It is unclear what the Agency means by the following sentence:

"With comparability protocol, the FDA can determine if a specified change can be reported in a category lower than the category for the same change, were the change to be implemented without an approved comparability protocol.

Does this mean that the Agency can set a lower reporting category for the same change(s) if the same change(s) were submitted without an approved comparability protocol? We suggest including additional text to this section for clarification.

Section III. WHAT TO CONSIDER IN PLANNING A COMPARABILITY PROTOCOL
Part B. When Might a Comparability Protocol Be Useful for a CMC Change?
Page 5, Lines 162-163

In addition, a comparability protocol can describe single CMC change or multiple related changes.

We suggest adding text to this section that clarifies the meaning of "*multiple related changes*".

Section III. WHAT TO CONSIDER IN PLANNING A COMPARABILITY PROTOCOL
Part B. When Might a Comparability Protocol Be Useful for a CMC Change?
Page 5, Lines 163-171

However, we recommend that each change be discrete and specific. A comparability protocol can be particularly useful for changes of a repetitive nature. We recommend that you have sufficient manufacturing information (e.g., developmental studies, manufacturing experience, demonstrated process capability, out-of-specification (OOS) investigations, stability data) with the particular product or process or similar products or processes so you can specify a priori the tests, studies, analytical procedures, and acceptance criteria appropriate for demonstrating that the CMC change or changes will not adversely affect the product. We recommend that comparability protocols be considered for CMC changes that applicants anticipate will be made.

It is unclear what the Agency means by "*sufficient manufacturing information*". We suggest adding text to this section for clarification.

What range of stability data would FDA recommend at the time of submitting the comparability report?

Section III. WHAT TO CONSIDER IN PLANNING A COMPARABILITY PROTOCOL
Part B. When Might a Comparability Protocol Be Useful for a CMC Change?
Page 5-6, Lines 173-188

We recommend you consider product-specific and process-specific attributes when determining whether to develop a comparability protocol. Attributes can include, but are not limited to the following:

- *Complexity of the product structure*
- *Ability to characterize the chemical, physical, microbiological, and biological properties of the product*
- *Degree to which differences in product structure and physical properties (e.g., polymorph) can be detected*
- *Degree of product heterogeneity if present*
- *The effect on safety of changes in the impurities*
- *The robustness of the product (i.e., the availability of product to remain unaffected by changes)*
- *Rigorousness of the manufacturing process controls (i.e., the availability of the manufacturing process controls to ensure that the product remains unaffected by changes)*

For clarity, we suggest including text that distinguishes between examples of product-specific and process-specific attributes.

Section IV. PROCEDURES FOR COMPARABILITY PROTOCOLS
Part A. How Should a Comparability Protocol be Submitted?
Page 7, Lines 238-252

You can submit a comparability protocol in a prior approval supplement or as part of the original application. We recommend that you indicate clearly in the cover letter that you are submitting a comparability protocol.

The submission can consist of the proposed comparability protocol in

- *A prior approval supplement that is reviewed and approved prior to generating data supporting the change*
- *A prior approval supplement that includes the proposed comparability protocol and test and study results as specified in the proposed comparability protocol and any other pertinent information to support a change covered under the protocol. The product already manufactured with the change can be distributed only after approval of the supplement.*
- *An original application that is reviewed and approved prior to generating data supporting the change*

Where are the comparability protocol and report placed within the structure of the CTD?

Would comparability protocols be placed as regional-specific templates in the specific sections under which they directly apply, (i.e., If a comparability protocol is for a drug product manufacturing change, would the template be placed under CTD Section 3.2.P.3.3 - Description of the Manufacturing Process?

If so, what would be recommended for comparability protocols that support multiple changes?

Section IV. PROCEDURES FOR COMPARABILITY PROTOCOLS
Part A. How Should a Comparability Protocol be Submitted?
Page 7, Lines 254-255

In all cases, a comparability protocol would be reviewed and approved by FDA prior to an applicant implementing a change under the protocol.

The guidance states that a comparability protocol must be approved prior to implementing the change. Since protocol review times are not defined or described in this guidance, will a comparability protocol be reviewed within the same 45 day review period that is defined by the *Guidance for Industry: Special Protocol Assessment (May 2002)*?

Will FDA designate a fee structure for the review and approval of a comparability protocol once a predetermined review period is set?

Section IV. PROCEDURES FOR COMPARABILITY PROTOCOLS
Part D. When Does a Comparability Protocol Become Obsolete?
Page 8, Lines 286-291

New regulatory requirements, identification of a safety issue (e.g., screening for new infectious agents in materials from a biological source), identification of a new scientific issue, or technological advancement after the comparability protocol has been approved can render a protocol obsolete. We recommend you review the tests, studies, analytical procedures, and acceptance criteria in your approved comparability protocol to ensure they remain current and consistent with the approved application and current FDA policy.

Currently, there are no compendial test methods available to quantitatively assess BSE/TSE risks. Screening tests for new infectious agents from biologically-sourced materials are in a dynamic state. Changes occur constantly as new proven technologies and methods are acquired.

Would the CMC information required obtaining an EU Certificate of Suitability be acceptable to FDA, or would FDA require additional/different CMC information for BSE/TSE safety assessments?

Section IV. PROCEDURES FOR COMPARABILITY PROTOCOLS
Part D. When Does a Comparability Protocol Become Obsolete?
Page 8, Lines 294-296

If you find the comparability protocol is no longer correct or adequate, the current protocol should be modified or withdrawn. FDA can request additional information to support a change that is implemented using an obsolete protocol.

The guidance states that FDA can request additional information if an "obsolete" protocol is used. We suggest that text be added to this section that clarifies the criteria for defining an "obsolete" protocol.

Section V. CONTENT OF A COMPARABILITY PROTOCOL
Part B. Does FDA Have Specific Concerns About Changes in the Manufacturing Process That Should Be Addressed in a Comparability Protocol?
Page 13, Lines 495-498

The predefined criteria would indicate when qualification studies will be warranted to evaluate an increased level of an existing impurity or a new impurity (or an applicant could reference a relevant FDA guidance that recommends qualification levels).

Does reference to a "relevant FDA guidance" exclude ICH Q7A?

When does FDA expect to harmonize US Guidances with ICH documents?

Section V. CONTENT OF A COMPARABILITY PROTOCOL
Part E. Does FDA Have Specific Concerns About Changing Manufacturing Facilities That Should Be Addressed in a Comparability Protocol?
Page 15, Lines 570-579

We recommend a statement be included in the comparability protocol for changing manufacturing facilities saying that a move to a different drug substance or drug product manufacturing site will be implemented only when the site has a satisfactory CGMP inspection for the type of operation. Furthermore, in the case of aseptically processed product, the statement would also indicate that a move to a different facility or area (e.g., room or building on a campus) will be made only when the specific facility or area has a satisfactory CGMP inspection (irrespective of the overall CGMP status for the campus). For a move to another type of site (e.g., drug substance intermediate manufacturing site, testing laboratory), a statement would be included that the move to this site would not be implemented if there were an unsatisfactory CBMP inspection for the site.

If a change in manufacturing site is proposed for an aseptically processed product, would FDA sanction the site change if the specific facility or area has successfully met a CGMP inspection within two years of when the comparability report is submitted?

If not, would successful media fills (3 lots) be satisfactory evidence if the last inspection period exceeded two years at the time the comparability report is submitted?

Section V. CONTENT OF A COMPARABILITY PROTOCOL
Part E. Does FDA Have Specific Concerns About Changing Manufacturing Facilities That Should Be Addressed in a Comparability Protocol?
Page 15, Lines 570-579

In the past, applicants have used protocols for container closure system changes, and they can continue to use them. A comparability protocol can be particularly useful for repetitive container closure system changes.

The guidance states that comparability protocols are useful for repetitive container Closure changes. Does this imply the comparability protocol must be submitted each

time for the change?

For example, if a sponsor proposes to change the same rubber stopper for closures on multiple drug products can a single comparability protocol be submitted for all affected drug products?

Section V. CONTENT OF A COMPARABILITY PROTOCOL
Part I. Can a Comparability Protocol Be Included in a DMF or VMF?
Page 16, Lines 610-617

A comparability protocol can be included in a master file. The protocol can be cross-referenced for CMC changes. An applicant's submission must include a letter authorizing the FDA to review the master file (e.g., 21 CFR 314.420(b)). Comparability protocols are product specific. Therefore, the applicant's submission would provide a comparability protocol that augments the information provided in the master file by specifying , for example, any additional studies that will be performed to demonstrate suitability of the postchange material (e.g., conformance to approved specification, compatibility studies, stability studies). The FDA ordinarily neither independently reviews master files nor disapproves submissions to a master file.

By what regulatory mechanism would a sponsor know if their comparability protocol was approved if the protocol is imbedded within a Drug Master File, which FDA neither approves nor disapproves?

Would a comparability protocol first be submitted for approval and then incorporated into the DMF?

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

Sincerely,

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