December 3, 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. 2003D-0385
Draft Guidance for Industry on Comparability Protocols – Protein Drug Products and Biological Products – Chemistry, Manufacturing, and Controls Information [Federal Register Volume 68, No. 172, page 52776, September 5, 2003]

Dear Sir/Madam:

Aventis appreciates the opportunity to comment on the above-referenced draft guidance entitled "*Comparability Protocols – Protein Drug Products and Biological Products – Chemistry, Manufacturing, and Controls Information*".

The Agency states that the draft guidance provides recommendations to applicants on preparing and using comparability protocols for changes in chemistry, manufacturing and controls of products in approved marketing applications.

We offer the following comments and questions for your consideration.

GENERAL COMMENTS:

This draft guidance is practically identical to the draft guidance for small synthetic molecules that was published in July 2003 by FDA. There are several process areas such as cell banking, plasmid manipulations to increase gene expression for improving commercial yields and fermentation changes that are not covered in this guidance.

SPECIFIC COMMENTS:

Lines 52-58: *"As part of its review and approval of a comparability protocol to evaluate the effects of a change, if supported by the submission, FDA may determine that a CMC change made under the comparability protocol will fall into a less restrictive reporting category. In many cases, using a comparability protocol will facilitate the subsequent*

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implementation and reporting of CMC changes, which could result in moving a product into distribution sooner than if a protocol were submitted."

Recommendation: Since this guidance applies to both CDER and CBER for BLAs and NDAs, are there different expectations for comparability protocols for CBER-based as compared to CDER-based biotechnology/protein-based drug products? This guidance does not clearly differentiate between biotech products that are now divided between the two centers and whether CMC changes will be reviewed differently by each center.

Lines 59-89: Definition of *"Annual Report (AR)"*, definition of *"Change-Being Effected Supplement (CBE)"*, definition of *"Change–Being-Effected-in-30-Days Supplement (CBE-30)*, and definition of *"Prior Approval Supplement (PAS)."*

Recommendation: This guidance has included CBE as an additional reporting category for biotech/protein products. CBE was not formally discussed as a distinct category in prior Guidances (Guidance for Industry: Changes To An Approved Application: Biological Products – July 1997 and Guidance for Industry: Changes to An Approved Application for Specified Biotechnology and Specified Synthetic Biological Products – July 1997). PAS, CBE-30 and AR are indicated as reporting categories for biotech/protein products.

In this guidance, the same basic definition is provided for CBE Supplement and CBE-30 Supplement. Although some differences are indicated in the CBE definition, we suggest adding text to specify the differences between a CBE Supplement and a CBE-30 Supplement in more detail. Also, if there are new examples of CBEs for biotechnology/protein drug product changes, we suggest that they be described in this section for clarity.

Lines 92-101: *"This 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,*
- *manufacturing equipment,*
- *manufacturing facilities,*
- *container closure systems, and*
- *process analytical technology (PAT)"*

Recommendation: "*The manufacturing process*" category is too general. For clarity, we suggest including a reporting category for cell banking and indicate what cell bank changes are applicable for a reduced reporting category under a comparability protocol.

Lines 117-119: *"At the same time, we approve a comparability protocol, we can designate, if appropriate, a reduced reporting category for future reporting of CMC changes covered by the approved comparability protocol (See section III.A.)"*

Recommendation: In this section, it is written that FDA "can" designate a reduced reporting category for the CMC changes covered by the approved comparability protocol. The term "can" is rather vague. What happens if there is no designation? Can it be assumed that the proposed reporting category is accepted if the protocol is approved? We suggest adding text for clarification.

Lines 176-179: *"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 to AR). In some cases, a reduction of more than one reporting category may be possible (e.g., PAS to AR)."*

Recommendation: For clarity, we suggest adding examples of a reduction in reporting category from PAS to AR for a biotech/protein drug product.

Lines 183-185: *" A comparability protocol could be useful for a variety of CMC changes, but there are some exceptions (See Section III.C). In addition, a comparability protocol can describe a single CMC change or multiple related changes, and can be particularly useful for changes of a repetitive nature."*

Recommendation: We suggest adding text to clarify if a protocol covering repetitive changes must be submitted each time the same change is planned.

Lines 245-277: Entire Section: *"C. When Might A Comparability Protocol Be Inappropriate?"*

Recommendation: We suggest adding text to clarify the term "non-specific plans of CMC changes" (Line 255).

This section does not address the changing method of fermentation using the same cell line. We suggest adding examples to clarify the conditions of upstream processing changes and their reporting category. A suggested example: Changing from a batch-fed to a continuous perfusion process to improve post approval commercial yields of a drug substance/drug product, assuming this would be a PAS reporting category.

This type of upstream CMC change is important because sponsors may develop improved fermentation methods at the time of submission. Such improvements could increase yields for the commercial process when compared to yields described in the approved application. Also, this type of change often required media modifications and, depending on the process, could present improved impurity profiles. Assuming no new impurities are present, limited PK/PD studies might be justified to establish if post-translational modifications have occurred and that isoforms are comparable to the prior approved process.

Lines 263-277: *"It may be possible to design a comparability protocol for certain CMC changes, but we may be limited in our ability to designate a reporting category other*

than PAS for changes implemented under such a protocol. Moreover, in some situations, these changes could require the submission of an IND, INDAD, or new application. Examples of such changes can include:

- *A change in the drug substance or drug product specifications (for exceptions, See Sections V.A.4 and V.C),*
- *A change in the qualitative or quantitative formulation of the drug product,*
- *A change in the type of delivery system.*
- *A change in or move to a manufacturing site, facility, or area when a prior approval supplement is recommended because an inspection (e.g., current good manufacturing practice (cGMP) inspection) is warranted (e.g., see examples listed in Section II.D.), and*
- *Facility-related changes for products with facility/establishment information provided in a BLA or postapproval supplement to a BLA..."*

Recommendation: Where would a change in plasmid expression fit into the reporting category (or categories) for a CMC change? We suggest adding examples for situations like this.

Lines 281-309: Entire Section *"A. How Should a Comparability Protocol Be Submitted?"*

Recommendation: We suggest adding text to define what FDAs expectations are for an acceptable manufacturing history to support a CMC change for a biotech/protein drug product.

We suggest adding text to specify where a comparability protocol should be located within the CTD Quality module. The CTD Draft guidance: "Common Technical Document – Quality. Questions and Answers/Location Issues – September 2003)" also does not describe where a comparability protocol should be located within the CTD Quality module.

There is no mechanism in this guidance to resolve a disagreement between the FDA and sponsor on the classification of a CMC change. We suggest adding text to describe the mechanism for resolution.

We suggest adding text to clarify why a comparability protocol and results in a PAS. Does this mean that FDA might review and notify the sponsor of a different category (such as a CBE-30), after submission?

We suggest adding text to define a timeframe for determining the length of review time that FDA has to assign a reporting category for a comparability protocol.

Lines 335-346: *"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 may determine that a reporting category made in the approval of a comparability protocol that becomes obsolete is no longer applicable. We may also request additional information to support a change that is evaluated by using an obsolete protocol. If you find the comparability protocol is no longer correct or adequate, you should modify or withdraw the current protocol."

Recommendation: We suggest adding text to further clarify the discussion on "obsolete protocols". A sponsor may want a new reading on a protocol that is more than six months old; otherwise studies may be considered conducted at risk.

Lines 378-379: *"Changes related to this change in culture medium could include modification in the length of cell fermentation, increase in harvesting time, and/or changes to purification columns."*

Recommendation: Changes in cell culture medium could be interpreted that either a new cell line is used or certain changes in growth media were made for an existing cell line to optimize yield. Would this type of change also include a change in gene expression of a gene within the same cell line?

Lines: 500-502: *"Development or feasibility studies can provide insight into the relevance and adequacy of the choice of the battery of tests you have identified to assess the product and/or process."*

Recommendation: We suggest adding text to clarify how many development or feasibility lots are considered to be acceptable for a process or product change.

Lines 524-525: *"We recommend that you include a commitment in your comparability protocol to update or withdraw your protocol when it becomes obsolete (see Section IV.D)."*

Recommendation: We suggest adding text to clarify FDAs criteria for determining when a comparability protocol becomes obsolete.

Lines 535-540: *"A comparability protocol would include a plan to compare the physiochemical and biological characterization of the product produced using the old and new processes when these characteristics are potentially affected by the change and are relevant to the safety and/or efficacy of the product. For recombinant DNA-derived protein products and other products when appropriate, such characterization can include structural analysis (e.g., primary, secondary, tertiary, quaternary), glycoform analysis, and bioassay, as appropriate."*

Recommendation: If a sponsor is using the same cell line, does this apply also to cell bank changes while using the same cell line?

Lines 572-595: Entire Section "C. Does FDA Have Specific Concerns About Changes in Analytical Procedures That Should Be Addressed in a Comparability Protocol?"

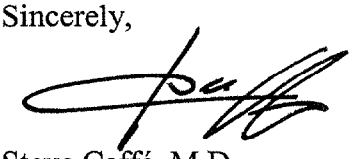
Recommendation: In this section, a complete validation protocol with acceptance criteria is requested as part of the comparability protocol in the case of changes in analytical procedures. This is reasonable for new analytical procedures. However, if the same principle is retained, it makes sense to focus on selected validation characteristics influenced by the method change.

Lines 685-692: *"A comparability protocol can be included in a master file. The protocol can be cross-referenced for CMC changes. ...Ordinarily, we neither independently review master files nor approve nor disapprove submissions to a master file."*

Recommendation: If another party cross-references a DMF, would a comparability protocol in the DMF preclude the applicant/sponsor from having to file a CBE, CBE-30 or a PAS? We suggest adding text to clarify what advantage there is for a sponsor to file a comparability protocol within a DMF (Type II) and what plans there are to harmonize this process with European DMF requirements.

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

Sincerely,



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