Biotechnology Industry Organization
1225 Eye Street NW, Suite 400
Washington, DC 20006

December 4, 2003

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, Maryland 20852

Re: Docket No. 2003D-0385, Federal Register: September 5, 2003 (Volume 68, Number 172, Pages 52776-52777)

Dear Sir/Madam:

The following comments are provided by the Biotechnology Industry Organization (BIO). BIO represents more than 1,000 biotechnology companies, academic institutions, state biotechnology centers and related organizations in all 50 U.S. states and 33 other nations. BIO members are involved in the research and development of health-care, agricultural, industrial and environmental biotechnology products. We appreciate the opportunity to comment on the Food and Drug Administration's (FDA's) draft Guidance for Industry: *Comparability Protocols – Protein Drug Products and Biological Products – Chemistry, Manufacturing, and Controls Information*.

This important guidance has the potential to clarify the FDA's expectations concerning comparability protocols and to assist industry preparing and using these protocols for manufacturing changes in approved marketing applications.

General Comments

1. Scope of the guidance: BIO suggests that the statement made beginning at line 30 of the draft guidance is misleading: "This guidance also applies to new drug applications

(NDAs), abbreviated new drug applications (ANDAs), new animal drug applications (NADAs), abbreviated new animal drug applications (ANADAs), or supplements to these applications for protein drug products, and not sufficiently characterizable peptide products (e.g., complex mixture of small peptides)." Because of the inherent complexity of biologically derived products, and the susceptibility of such products to change, BIO believes that there is no abbreviated approval process appropriate for protein drug products and complex mixtures of small peptides. Furthermore, the term "comparability" should not be applied to a comparison of an innovator's biologic product to another manufacturer's follow-on biologic product because the second manufacturer will not have access to the innovator's historical data nor to in-process and bulk product materials from the innovator, so a comparison of before and after is not relevant. Therefore, we ask that lines 30 ff. be revised accordingly, and that the scope of the guidance be clarified to reflect that it does not apply to generic or follow-on products.

2. Submission of *in vivo* data under a comparability protocol: Depending on the molecule, type of CMC change, and knowledge of the manufacturing process, the sponsor may specify additional testing in a comparability protocol, including *in vivo* studies, to complement analytical testing and confirm that the CMC change does not affect PK, PD, immunogenicity, efficacy, and safety. BIO believes that a sponsor who proposes clinical and nonclinical *in vivo* testing to assess the impact of a CMC change should retain the option of submitting a comparability protocol (please also see our comments on lines 260-262 of the draft guidance, below).

3. Reductions in reporting category: FDA's review of the comparability protocol will include a determination of whether changes made in accordance with that protocol may be submitted under a reduced reporting category because the use of the protocol will sufficiently assess the product pre and post change. BIO recognizes that the use of a comparability protocol does not lessen the requirements for assessment of comparability, and we support FDA's intent to reduce reporting requirements, where such reduction in reporting is science-based.

Detailed Comments

Our detailed comments and proposed changes to the draft guidance are given below. Italicized wording under the Comments/Proposed Change(s) heading is the suggested additional or alternative language.

Line	Comments/ Proposed Changes	Justification
21	Tests *or* validation studies and acceptable limits to be achieved to demonstrate the lack of adverse….	BIO suggests the use of the word "*or*" to allow more flexibility to the requirement for validation studies associated with a comparability protocol.

Line	Comments/ Proposed Changes	Justification
27	This guidance applies to comparability protocols that *an innovator company may submit with an original* biologics license application (BLA),	We believe that incorporating the sponsor as the "*innovator company*" to correspond with an original biologics application provides further clarification as to the applicability of the guidance document.
48	Remove end parenthesis to read, "the safety or efficacy of the product."	Grammatical Change
52	Add end parenthesis to read, "Cosmetic Act (the act) (21 USC 356a))."	Grammatical Change
67	Add word "*that*" to read, "This submission to an approved application reports changes *that* have moderate potential to adversely..."	Grammatical Change
97	...*specified* analytical procedures,[7]	We believe use of the word *specified* will clarify that comparability protocols may be useful for analytical procedures used for specification testing that when significantly changed, may require notification to FDA.
125	Eliminate entire section titled "**C. When and Why Were Comparability Protocols Created?"**	BIO believes that this section does not provide useful guidance and can be eliminated.
142	CMC changes for biologics, including specified *biologicals* and protein drug products, has been …	We believe use of "specified products" is vague. Reference to "specified biologicals" refers to those products that would be categorized as "well characterized biotechnology products."
170	A comparability protocol ~~prospectively~~ specifies the planned CMC change and the studies that …	For clarification, "prospectively" may be eliminated with reference to the CMC change.

Line	Comments/ Proposed Changes	Justification
178	BIO agrees with the utility of a comparability protocol to allow regulatory flexibility and to reduce the reporting category once the protocol is approved. Examples regarding a reduction in more than one reporting category would be useful (e.g., as shown in lines 225 to 243). Additionally, BIO suggests the inclusion of a section that allows the sponsor to provide justification for the reporting category based on an assessment of the change and the probability that the change will adversely impact product quality based on the historical knowledge of the product and process.	General Comment
179	Please provide an example of when a reduction of more than one category is possible (e.g., PAS to AR).	General Comment
183	A comparability protocol could be useful for a variety of CMC changes, *with* some exceptions.	Word change for clarification
184-185	BIO suggests that the agency provide clarity regarding multiple CMC changes, including when related changes would not be appropriate for a comparability protocol. Additionally, we request clarification of the definition of "repetitive" change.	General Comment. Clarification requested.
196-197	BIO suggests that line item 196 and 197 be eliminated.	General Comment
199	*...whether a comparability protocol is appropriate*. Attributes can include, but are not limited to, the …	Word change for clarification
203	Delete "biochemical" from this line.	We believe use of the word biochemical is not necessary as physiochemical properties encompass biochemical properties.

Line	Comments/ Proposed Changes	Justification
216	BIO believes that the use of "non-routine characterization studies" may not be applicable in all cases and more general guidance regarding specific data requirements for specific changes would be more useful.	General Comment
218	…characterization studies) to assess the effect of the change on the approved product; and (c) the *currently* approved manufacturing process…	Addition of the word "*currently*" clarifies that the change refers to the impact to approved process (pre-change). Process validation studies related to the change would typically comprise part of the comparability protocol.
218	BIO requests that the agency provide examples of when a comparability protocol would be useful to justify changes in analytical procedures.	General Comment
227-228	Modification of production operating parameters in fermentation *and/or cell culture conditions*, such as pH, dO2, *and/or downstream processing parameters, such as column flow rates and buffer compositions).*	For clarification, this statement can be expanded to include changes in fermentation and purification.
260-262	Delete lines 260-262	BIO does not believe that a general recommendation against use of comparability protocols involving efficacy, safety (clinical or nonclinical) or PK/PD data is appropriate.
263-264	*For certain types of changes, a comparability protocol will not be able to reduce the reporting category below PAS.*	Change in sentence for word clarification
268	A change in the drug substance or drug product *acceptance criteria on a specification* (for exceptions, See Sections…	We believe changes to acceptance criteria on a drug substance or drug product specification that includes broadening of limits should be the basis for reporting to the agency.

Line	Comments/ Proposed Changes	Justification
270	• *In certain cases,* a change in the qualitative or quantitative formulation of the drug product	This change would be consistent with Footnote 14, which allows for flexibility based on the data.
272-273	Please clarify the restriction on use of a Comparability Protocol for move to a manufacturing site, facility, or area when a prior-approval supplement is recommended because an inspection (e.g. CGMP) is warranted. Following PreApproval Inspection (PAI) and Comparability Protocol approval, the site change could be reported at the reduced reporting category without the need for the increased regulatory time constraints for implementation. Distribution of product would not be permitted prior to the receipt of acceptable GMP status.	Clarification requested.
275	Change to read, "II.E.), and"	Correction
279	Section IV.A details the procedures for submitting a comparability protocol. BIO recommends allowing more flexibility regarding whether or not a comparability protocol needs to include prospectively defined acceptance criteria in all cases.	General Comment
317	Section IV.B includes details regarding information that may be included in the data package that supports a comparability protocol. BIO feels that the reporting of deviations, investigations, etc. should be included only for those items that are related to the comparability protocol and not every event that may be out of the scope of the protocol or manufacturing change yet related to the batch manufactured with the change.	General Comment

Line	Comments/ Proposed Changes	Justification
323	Section IV.C – BIO feels that provisions should be made for changes to comparability protocols that do not necessarily require extensive regulatory review and require a Prior Approval Supplement (PAS). It would be useful to have a mechanism to make changes to approved comparability protocols without submission of a PAS.	General Comment
328-331	Recommend addition of statement to the end: *"Where the acceptance criteria for the change are not met, the change should be evaluated for impact on expected product. The results should be reported to FDA prior to formal submission of the data and reporting category determined following consultation with the FDA".*	Additional sentence recommended.
372	Change to read, *"**...** or multiple related changes*" since this is the agency's recommendation.	Recommended wording change.
374-380	Eliminate lines 374-380. BIO requests that Section V be eliminated or revised to provide clarity regarding use of a comparability protocol for multiple related and unrelated changes. We suggest that it may be possible to implement a comparability protocol for nominally unrelated changes at the same time using the same panel of analytical tests to assess product quality.	This would allow manufacturers more flexibility for changes that may be associated with single or multiple unit operations. Additionally, BIO requests that the agency consider a mechanism for filing a comparability protocol that would apply for any change to a specific unit operation.

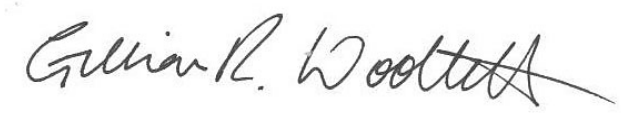
Line	Comments/ Proposed Changes	Justification
454-460	BIO is unclear about the comment that analytical method qualification data for methods that are used for characterization testing would need to be submitted when a post-approval change is implemented. Details regarding method qualification may not always be appropriate to provide in a CMC submission. Additionally, clarity is requested regarding changes to analytical methods and the applicability of a comparability protocol for changes that are for existing methods and/or new methods.	General Comment and clarification requested.
520	Change to read, "(see Section IV.C.)"	Correction
554	Change to read "IV.C and V.A.7)."	Correction
572-595	BIO proposes the following paragraph re-wording for Section V, Part C entitled**, "Does FDA Have Specific Concerns About Changes in Analytical Procedures That Should Be Addressed in a Comparability Protocol?"** "A comparability protocol for changing an analytical procedure should describe the nature of the change (revision of an existing procedure, or new procedure based on a different principle). We recommend that your design of the comparability protocol include an assessment of the suitability of the analytical procedure. Additionally, the protocol should provide the plan for validation of the changed analytical procedure. The plan should include prespecified acceptance criteria for relevant validation parameters such as precision, range, accuracy, specificity, detection limit, and quantitation limit for the revised analytical method.[17] The proposed acceptance criteria for these parameters should ensure that the analytical procedure is appropriate for its intended use. In the	Clarification is provided by including suggested paragraph edits to distinguish between comparability protocols and methods validation.

Line	Comments/ Proposed Changes	Justification
	validation plan you would assess whether a revised procedure is more susceptible than the original procedure to matrix effects by process buffers/media, product-related contaminants, or other components present in the dosage form. The comparability protocol should identify any statistical analyses that you will perform and whether you intend to perform product testing to compare the two procedures. Testing to compare two procedures may vary depending on the extent of the proposed change, type of product, and type of test. In some cases a change in acceptance criteria may be required as a result of a new analytical method utilizing new technology. The comparability protocol should contain appropriate rationale and justification as to the strategy for implementing a change in criteria. When you use the new revised analytical procedure for release or process control, you should not delete the old test or relax acceptance criteria that we approved in your application, unless and until FDA informs you that the approved acceptance criteria are no longer required."	
610-611	We recommend the Guidance state clearly whether FDA will permit changing manufacturing facilities using a comparability protocol.	General Comment
626	Correct prepproval to "preapproval".	Correction
658	BIO requests that examples regarding changes in container/closure be included in this guidance document so readers can fully understand the applicability of a comparability document for changes of this nature.	General Comment

Line	Comments/ Proposed Changes	Justification
662	Please clarify the use of the word "repetitive" – does this mean a single change applied to numerous applications or a series of changes that have predefined acceptance criteria but which may extend beyond any single change?	Clarification requested.

In closing, BIO appreciates this opportunity to comment on the draft guidance on *Comparability Protocols – Protein Drug Products and Biological Products – Chemistry, Manufacturing, and Controls Information*. We look forward to seeing the final guidance, and would be glad to work with the agency to provide further input or clarification of our comments, as needed.

Sincerely,



Gillian R. Woollett, MA, DPhil
Vice President
Science and Regulatory Affairs