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

Re: *Docket No. 2003D-0385 Draft "Guidance for Industry: Comparability Protocols–Protein Drug Products and Biological Products–Chemistry, Manufacturing, and Controls Information;" Availability*, 68 Fed. Reg. 52776 (Sep. 5, 2003)

To whom it may concern:

Genentech, Inc. ("Genentech") offers the following comments in response to the agency's Notice of Availability and invitation to provide comments.

Genentech is a biotechnology company based in South San Francisco, California. Our mission is to be the leading biotechnology company, using human genetic information to discover, develop, manufacture and commercialize biotherapeutics that address significant unmet medical needs. Genentech commits itself to high standards of integrity in contributing to the best interests of patients, the medical profession, our employees and our communities, and to seeking significant return to our stockholders based on the continued pursuit of excellent science.

Genentech's product portfolio now includes 12 approved protein-based biotherapeutics for serious or life-threatening medical conditions. We believe that transparent direction from FDA and science-based implementation of the applicable laws and regulations are essential to our ability to continue developing and providing safe and reliable therapeutic products to the public. On the whole, we believe that the draft guidance serves these objectives well.

We commend the agency for developing the draft guidance document. We provide the following general comments concerning the way the final Guidance will be used by the agency and offer specific comments directed to particular elements of the document.

A. General Comments

The draft guidance arrives at a time of significant procedural changes – and considerable public interest – in the regulation of recombinant therapeutics. In particular, some are calling for FDA to adopt new procedures to take "shortcuts" in the approval of "follow-on" versions of approved therapeutic biologic products developed and manufactured by a party other than the

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original sponsor. Presumably, such shortcuts would employ an abbreviated "comparability" analysis to review and approve such products. Advocates of these shortcuts will want to view the present draft guidance as applying to such products.

As FDA has acknowledged, contemporary science does not support, and the current statutory scheme does not permit, the approval of "follow-on" biologics in the same manner that generic drug products are approved under FFDCA[1] § 505(j) and (b)(2). We do not question that it would be possible for a follow-on manufacturer, adhering to proper procedures, to develop a manufacturing process capable of producing a product that would be safe and effective. Nor do we question the general proposition that a follow-on product could be useful for some or all of the same indications as an innovator product with which it was designed to compete. The critical point is *not* that an follow-on biological product can *never* be "as good as" an innovator product, but that *it is a different product.*

The biological activities of protein therapeutics are closely linked to the processes used to make them. The safety, purity, and potency of a biologic therapeutic are ensured – to this day – by maintaining the constancy of the result of each step in the production process. Analytical science has made spectacular advances in recent years. Nevertheless, recombinant protein therapeutics cannot be *completely* characterized, and their behavior in human patients cannot be predicted with certainty from a comparison of chemical and biological analyses, in the same way that "small molecule" drugs can. The regulatory frameworks established by statute are based upon and reflect these fundamental scientific differences.

Clinical evaluation is not simply the "gold standard" for monitoring the safety and efficacy of biologics: it is the *sine qua non* of developing and commercializing a recombinant protein therapeutic. The human immune system is more sensitive than any available analytical method to subtle changes in protein products. Its behavior cannot be effectively modeled or predicted based on *in vitro* analytical data and bioassays. The recent adverse experience associated with process changes for EPREX™, the recombinant erythropoietin product marketed for the treatment of anemia by Johnson & Johnson ("J&J") in Europe and elsewhere, provides a case in point. [2]

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[1] Federal Food, Drug, and Cosmetic Act (codified at 21 U.S.C. § 321 *et seq.*).

[2] Responding to regulatory concerns from EMEA relating to the use of materials of human origin, J&J changed its formulation for EPREX by substituting one well-known, thoroughly characterized expander (sorbitol) for another (human serum albumin). Routine testing of the new formulation in biological and chemical assay systems revealed no cause for concern. After the reformulated product had been marketed, some 200 patients developed pure red cell aplasia (PRCA) as a result of neutralizing antibodies they generated against the erythropoietin protein in the reformulated product – meaning that their bodies cannot produce new red cells in response to the erythropoietin they produce, and they are now dependent on transfusions.

To its credit, J&J moved aggressively, in cooperation with regulatory authorities and academic scientists, to determine the cause of the adverse reactions. Yet some two years after the relationship between the reformulated EPREX and the increased incidence of PRCA was established, the reason the reformulated product led to neutralizing antibodies in some patients has not been finally established. Only clinical experience was able to reveal and characterize the enhanced risk associated with the reformulated product.

The lesson of this experience is not that every process change must be validated by controlled clinical trials, but that extensive evaluation in humans must be the foundation for regulating every recombinant therapeutic. As the agency certainly must appreciate, effective regulation focuses resources and requirements on the areas of greatest risk. Properly used, a comparability protocol serves that objective by asking whether the risks to patient safety associated with a given change in an *established manufacturing process* are lessened through careful evaluation of the result of the change on the affected elements *of the process*.

"Comparability" is not an appropriate standard for evaluating a new recombinant therapeutic. The tools that the developer of a recombinant protein therapeutic can bring to bear on a comparability assessment include not only the appropriate analytical techniques but also the "know how" garnered from experience with the manufacturing process. This knowledge – and, often, product- or process-specific reagents and assay methods – are proprietary to the developer, and thus not available to the manufacturer of another product. The important point, however, is not simply that the innovator will have access to more tools than the developer of a follow-on product. Rather, it is the critical questions of safety and efficacy for a new, different protein product cannot be answered with the tools that a comparability protocol provides.

A regulatory approach geared to assessing the risks arising from discrete modifications to an existing protocol cannot effectively probe the risks related to differences between final products made by *different* processes. The methodology of comparability protocols cannot simply be "conscripted" and "trained" to assess the relative risks associated with products made using different host cells, different materials, and different fermentation and purification protocols. The agency would not appropriately manage the safety risks, as it is required to do, if it did so. An *assumption* that the risks for a new product can be extrapolated from the risk basis acquired with a product made by a wholly different process is a fundamentally unsound proposition for recombinant therapeutics.

The Agency seems to recognize in the draft guidance that "comparability" is not an appropriate paradigm for evaluating the safety of a "follow on" therapeutic protein product that is not produced by the original sponsor of the product.[3] A careful reading of the draft guidance document reveals that FDA does not consider such "follow-on" products to be within the scope of this Guidance.[4] Recognizing the significant scientific and legal questions that exist regarding the feasibility of abbreviated procedures for approval of "follow on" protein therapeutics, we believe the agency must more affirmatively and clearly state that comparability protocols developed for a therapeutic protein product can be used only for that producer's product.

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[3] However, the term "comparability" has been employed recently in the European regulatory environment with respect to both intra- and inter-manufacturer product comparisons. *See* "[Draft] Note for Guidance on Comparability of Medicinal Products Containing Biotechnology-Derived Proteins as Drug Substance," EMEA Committee for Proprietary Medicinal Products (CPMP), Doc. no. CPMP Ad-Hoc Working Group on (Pre-)clinical comparability of Biotechnology Products/ 3097/ 02 (July 30, 2002).

[4] See, e.g., the first sentence of the guidance document, which states that "[t]his guidance provides recommendations ... on preparing and using comparability protocols for changes in [CMC] of products *in approved marketing applications*." Draft at lines 18-20 (emphasis added).

Accordingly, we urge the agency to revise the guidance to more explicitly and clearly indicate that comparability protocols are irrelevant outside the context of a single marketing authorization.

B. Specific Observations and Recommendations

1. Title

The title could be misinterpreted to refer only to biological products that are proteins. We recommend reversing the two elements of the title: "Comparability Protocols – Biological Products and Protein Drug Products," *etc.*, to make clear that the scope of the guidance applies to all biological products.

2. Section I

Lines 30-31

The draft guidance makes reference in lines 30 to 31 to abbreviated new drug applications (ANDAs) under § 505(j) of the FFDCA. As ANDAs may not be filed with respect to a biologic or a protein drug product, the reference in this section to ANDAs is inappropriate and confusing. We recommend deleting the reference to "abbreviated new drug applications (ANDAs)" and relocating footnote 3.

3. Section III.B

Lines 183-184

The draft guidance makes reference to the utility of comparability protocols for "changes of a repetitive nature." We believe it would be helpful for the Agency to clarify what it envisions as "changes of a repetitive nature" and to provide examples of such changes.

Lines 187-197

We believe that it is not only "important," but critical that the sponsor have sufficient manufacturing and analytical experience before making changes in the CMC of an approved protein product. Such experience enables a manufacturer to efficiently convey to FDA information that the Agency needs to evaluate manufacturing changes. In our view, it is not appropriate or desirable for a manufacturer to be required to submit *all* information arising from developmental and investigational studies, as implied by this section. Such a requirement would be burdensome on both the agency and the manufacturer, and would not be necessarily helpful to the agency. Instead, such information should be made available to FDA at its request when the agency believes that the information would be relevant to its review of the proposed change.

We recommend this passage be rearranged as follows:

> "It is also essential that you have sufficient manufacturing and analytical experience ... to assess the impact of the change on the product. This experience should include information from developmental and investigational studies .... You should be prepared to demonstrate to the satisfaction of the agency that a comparability protocol is appropriate for the proposed change."

We also believe that this section should focus more directly on the product- and process-specific nature of the proposed changes and their evaluation. In our experience, for example, recombinant antibodies are not all similar. A process change that has no discernible effect on the biological characteristics of one antibody may have profound effects on another. We therefore recommend revising lines 193-194 to "manufacturing information with similar products or processes (e.g., for some monoclonal antibody products) when the applicability of such information to the proposed change can be justified".

Line 203

We believe a comma should be inserted between "immunological" and "microbiological."

Line 214-216

Item (a) should be revised to reflect the recognition that a comparability protocol for an analytical method change will inherently involve a specification change. We recommend inserting cross-references to Sections V.A.3, V.A.4, and V.C for exceptions to this item.

Line 217

In our experience, not all analytical methods used for characterization are validated. We believe the phrase employed in the ICH guidelines (i.e., that "assays must be demonstrated as suitable for their intended purpose") would be more appropriate than the phrase "validated or qualified."

Line 225

We recommend that the terminology employed here be more general than the words presently employed (i.e., use the commonly used term, "change in scale" rather than "increase or decrease in batch size").

Line 232-233

We believe that this section should include analytical methods among the examples, preferably as a new bullet. Alternatively, the parenthetical discussion of mode changes could be expanded, e.g., "usually associated with equipment changes such as tangential flow filtration to centrifugation, or analytical method changes such as SDS-PAGE to CZE."

Lines 241-243

The wording suggests that some BLAs might not contain facility or establishment information. To our knowledge, BLAs must contain such information. We recommend clarifying the reference, e.g., "for products regulated under a BLA" or "where applicable." Alternatively, the reference to BLAs may simply be deleted. The cross-reference should include Section V.D as well as Section V.E.

4. Section III.C

Line 260-262

We recommend that you delete the reference to PK/PD data and truncate the line as follows: "A CMC change that requires efficacy or safety (clinical or nonclinical) data to evaluate the effect of the change.

Line 269

The cross-reference should also include Section V.A.3.

Line 272

In our experience, comparability protocols associated with new manufacturing facilities or sites have been useful only when we have maintained close direct control over the transition.

Footnote 13

We agree that a change in the species of the cellular source for any protein product will almost always require an IND. Our experience indicates that comparability protocols can be used for evaluating the effect of a cell line change involving an amplification of the original cell line.

Footnote 14

We believe that caution is warranted when "excipients" are discussed in the context of therapeutic protein products. Whereas an excipient in a small-molecule drug formulation is viewed as essentially inert, an "excipient" in a biologic can contribute to biological activities affecting the safety or efficacy of the product. For example, some reports have suggested that the sorbitol "excipient" in EPREX may have contributed directly to the immunological response observed in PRCA patients. However, we believe that comparability protocols may be appropriate for certain substitutions, such as replacing an animal-derived polysorbate with a non-animal-derived polysorbate. Further guidance or examples illustrating the agency's view of such changes would be helpful.

Line 276-277

We believe it is confusing to find essentially the same example listed in this section (comparability protocols possibly appropriate, with limitations) and in the preceding section at lines 241-243 (situations where comparability protocols have been used and may be useful in the future). The confusion should be eliminated by providing further discussion of the circumstances which would tend to preclude comparability protocols. Our comments above regarding lines 241-243 (clarity of the reference to facility or establishment information in a BLA; additional cross-reference to Section V.D at lines 241-243) also apply to this section.

5. Section V

Line 372-380

In some cases, multiple raw materials within a single stage of manufacturing are changed concurrently (e.g., in cell culture or protein purification). It would not make sense to evaluate the effect of changing each of the materials serially. We suggest revising the wording of this section to accommodate such scenarios.

Lines 396-399

In our experience, even extensive analytical characterization – by itself – is not necessarily predictive of the clinical interchangeability of the pre- and post-change material. Such data, of course, are most useful for assessing comparability when experience allows a manufacturer to correlate particular observed product features with the clinical performance or safety of the product. This passage should include "the relationship of the change to clinical experience with the product, to the extent known" among the factors used to support a rationale for the selected protocol.

Line 495

We recommend deleting the reference to "AR" in this sentence since an AR is not a pre-implementation reporting category.

Footnote 16

The following corrections should be made: "guidance" should be plural; the second "and" should be in roman rather than italic type; and "*Biologics*" should be "*Biological Products*" to match Section II.E, line 159.

Lines 514-520

We find the last sentence in this section confusing. It appears to suggest that it is possible to specify in advance the additional tests that would have to be conducted if comparability tests fail to meet the original acceptance criteria, and that satisfactory performance of these additional tests would allow reduced reporting requirements – as if the original acceptance criteria had been

met. Thus, this passage implies that if one can explain why and how a comparability protocol is inappropriate or insufficient in a given situation, a comparability protocol may nevertheless be used. If this interpretation is correct, we recommend that the Agency include examples of particular situations where more extensive testing would be indicated and give.) examples of the types of steps that the Agency would believe are appropriate to take.

This section also appears to conflict with Section IV.C, which indicates that if "unpredicted or unwanted outcome[s]" result from implementing an approved comparability protocol, further formal consultation with the agency will generally be required if the change is pursued. Similarly, Section V.B.C states that a change cannot be made under a comparability protocol if data obtained as a result of the protocol indicate that further nonclinical (or clinical) qualification studies are needed to evaluate the safety associated with an altered impurity profile. We believe the Agency should reconcile these apparently divergent provisions.

Line 540

We recommend including analysis of immunogenicity in the list of characterization tests to consider.

Lines 547-549

We do not believe that that an affirmative demonstration of the absence, clearance, or inactivation of impurities in downstream process steps is necessary in every instance. Certain kinds of process impurities are essentially irrelevant in view of the nature of the process. Moreover, if the process change involves an analytical procedure, the question of impurities does not arise in the first instance. We recommend rewording this sentence to require "that you demonstrate, if appropriate, that no new impurities or contaminants are present, or that they are removed ... ."

Line 558

Downstream effects (or their absence) should be considered as part of the comparability assessment but not necessarily included as part of a comparability protocol. Accordingly, we suggest that "examine" be replaced by "assess."

Lines 565-570

The use of the term "controls" throughout this section is confusing. The term is often used to refer specifically to in-process testing. Here, in contrast, it is being used to refer to "checks" on particular process steps or to additional process steps that perform a process-modulating function. We recommend that you use a different term to avoid confusion.

Lines 575-581

We agree that a comparability protocol may be used for evaluating a change to an analytical method. This appears to contradict the statement at Section III.C, line 268, that

specification changes are inappropriate for comparability protocols, since an analytical method may be part of a specification. Please resolve the conflict or illustrate the intended distinction through examples.

Footnote 17

The reference to VICH documents is unclear. It would be helpful to indicate more directly that guidances GL1 and GL2 apply to veterinary products.

Lines 619-620

Please clarify what is meant by an "Establishment Description section." Does this refer to products licensed under the former PLA/ELA regime? If so, the draft guidance should explicitly state this.

Lines 623-635

Please clarify statements about preapproval inspection in conjunction with comparability protocols. It would appear that if an inspection is needed, the reporting category would necessarily be PAS. It is not clear to us why comparability protocols would be useful if the reporting category for implementing the change would be PAS in any case.

Lines 644-646

As noted for lines 619-620, please clarify the reference to an "Establishment Description section." Also as noted above for lines 241-243, the reference to facility and establishment information in BLAs should be clarified.

Lines 649-650

The guidance should explain why heating, ventilation and air conditioning changes may not qualify for a reduced reporting category. If sufficient reasons cannot be provided, the guidance should be modified to specify that such changes can qualify for a reduce reporting category. A comma should follow "heating", and there is an unmatched left parenthesis.

Footnote 18

The wording should be modified to clarify that NAI and VAI are terms referring to Form 483 citations. There is an unmatched left parenthesis at "Voluntary Action Indicated."

Lines 665-669

The term "Process Analytical Technology," as we understand it to be used in Agency parlance, is a "small molecule" concept. If this is the case, this phrase should not be used in this guidance.

Line 687

We believe it would be useful to clarify the statement that "[c]omparability protocols are product specific" by adding "i.e., they apply to the product of a specified process manufactured under a particular license."

Conclusion

Genentech appreciates the opportunity to offer these comments. We would be pleased to clarify or amplify our remarks, or to assist the agency in any other way to develop a pertinent and useful guidance document.

Sincerely yours,

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for Robert L. Garnick, Ph.D.
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