

Genentech

IN BUSINESS FOR LIFE

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December 2, 2004

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

Subject: **Docket No. 2004D 0431, OC 2004219**
Comments on Current Good Manufacturing Practice for Combination
Products (DRAFT GUIDANCE)

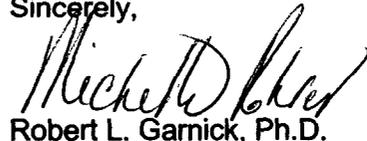
Dear Dockets Management Branch:

Enclosed are comments, provided by Genentech, for the *Draft Guidance* Current Good
Manufacturing Practice for Combination Products.

Thank you for providing us the opportunity to comment on this Draft Guidance. We hope
that you will find our comments useful and constructive.

If you have any questions regarding this submission, please contact Kelly Dodge,
Senior Associate, Regulatory Affairs at 650-225-3254.

Sincerely,



Robert L. Garnick, Ph.D.
Senior Vice President
Regulatory Affairs, Quality,
and Compliance

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2004D-0431

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This submission contains information that constitutes trade secrets and/or is confidential within the meaning of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. §331 [j]), the Freedom of Information Act (5 U.S.C. §552[b][4] and 18 U.S.C. Section 1905) and 21 CFR Sections 312.130, 314.430, 601.50, and 601.51 and may not be revealed or disclosed without the prior written authorization of Genentech, Inc.

Comments on Guidance for Industry and FDA

**Current Good Manufacturing Practice for
Combination Products (*DRAFT GUIDANCE*)
Docket No. 2004D-0431, OC 2004219**

Issued for Comment September 2004

Genentech, Inc.
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GENERAL COMMENTS ON THE DRAFT GUIDANCE

Genentech would like to thank the Agency for providing the industry with a DRAFT GUIDANCE on “Current Good Manufacturing Practice for Combination Products”. Genentech has provided some general comments below, followed by specific comments on the Guidance Document in tabular format. The following suggestions are made:

- Inclusion of specific examples in tabular format may enhance clarifying the applicability of the cGMP provisions.
- Genentech recommends a statement should be included within the Guidance Document clarifying that the submission requirements for different classes of devices (i.e., IDE/MA, 510k or no submission) remain unchanged to avoid any confusion within the industry. It would be helpful if the Guidance Document delineated the requirements for different types of combination products. For example, Class III device combination products requiring PMA or clinical trial data would have a higher level of expectation (e.g., studies on the in-vivo and in-vitro drug release rate for a drug coated stent), than a Class II device which is filled with a drug (e.g., functional secondary pen packaging which also serves a drug delivery purpose).

Furthermore, it is recommended to clarify expectations for combination products when one or more are already approved or cleared. For example, in the event that a device is approved for use, is not modified, other than printing of a name or appliqué, and is merely being provided to the patient as a convenience (e.g., sterile needle) in the final packaging, we recommend alternative requirements. Clarification of the requirements would be beneficial to avoid repetitive review and oversight of a device already under the oversight of another agency, as well as duplication of efforts for both the manufacturers and the Agency. In this labeled for or off-the-shelf approach example, the drug manufacturer would treat the needle as an incoming raw material and apply the same quality systems and oversight as defined in 21 CFR parts 210 and 211. The needle manufacturer would separately follow the requirements outlined in 21 CFR 820.

SPECIFIC COMMENTS ON THE DRAFT GUIDANCE

Table 1-1 contains specific comments on the Draft Guidance, “Current Good Manufacturing Practice for Combination Products.” Verbiage in red/underlined indicates changes to the Agency’s verbiage. Verbiage in blue/bold indicates recommended additions to the Agency’s Guidance Document

Table1-1

Genentech Comments for Draft Guidance “Current Good Manufacturing Practice for Combination Products”

| Section | Line Reference | FDA Guidance | Genentech Comment |
|---------------------------|----------------|--|---|
| Entire doc, where present | | The statement “strength, quality, identity, and purity” | Genentech recommends “strength/potency, quality, identity, and purity” because potency is an important quality attribute for protein products and other biologics. Many protein and biologic products have to be dosed based on potency (activity) not strength (weight). |
| II.A.3 | 49–55 | A drug, device, or biological product packaged separately that according to its investigation plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where, upon approval of the proposed product, the labeling of the approved product would need to be changed (e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose); or | Please see Genentech’s comment on Section III.B, lines 159–163. Clarification and examples of types of packaging would be very beneficial. |
| III.A | 112-113 | Drug products not subject to these regulations | Genentech suggests the following wording “Components (e.g., bulk drugs or active pharmaceutical ingredients) of a drug product not subject to these regulations”, because the example given (bulk drug) in the original text is not a drug product. |
| III.A. | 136–139 | Under the QS regulation for a combination product with a drug constituent part, yield and stability requirements would be incorporated more generally as part of the design validation provisions [21 CFR 820.30(g)] | Under the QS regulation for a combination product with a drug constituent part, device yield (e.g., dosage assurance) and stability requirements would be incorporated more generally as part of the design validation provisions [21 CFR 820.30(g)]. |

Table1-1 (cont'd)

Genentech Comments for Draft Guidance “Current Good Manufacturing Practice for Combination Products”

| Section | Line Reference | FDA Guidance | Genentech Comment |
|---------|----------------|---|--|
| III.A. | 134–143 | <p>Calculating the yield and stability of a drug constituent part: The CGMP regulation has specific requirements for the calculation of yield (21 CFR 211.103) and for ensuring stability of the drug product (21 CFR 211.166). Under the QS regulation for a combination product with a drug constituent part, yield and stability requirements would be incorporated more generally as part of the design validation provisions [21 CFR 820.30(g)].</p> <p>Corrective and preventive action (CAPA): The QS regulation has detailed CAPA requirements (21 CFR 820.100), while CAPA principles are more generally identified in the CGMP regulation as part of Production Record Review (21 CFR 211.192).</p> | <p>The format of the two examples (134–139 and 141–143) in this section is inconsistent. One gives advice for a combination product (134–139) the other provides a comparison/ contrast between a drug and a device (141–143). It is difficult to understand the message the Agency is trying to convey. Therefore, it is suggested to reword one or both paragraphs for harmonization and consistency of message.</p> |
| III.B | 155–157 | <p>Similarly, during the time of separate manufacture (i.e., before drug and device combination products are produced as a single entity or are co-packaged) 21 CFR Parts 210 and 211 apply only to the drug constituent, and 21 CFR 820 applies only to the device constituent.</p> | <p>Similarly, during the time of separate manufacture (i.e., before drug and device combination products are produced as a single entity or are co-packaged as a functional unit) 21 CFR Parts 210 and 211 apply only to the drug constituent, and 21 CFR Part 820 applies only to the device constituent.</p> |

Table1-1 (cont'd)

Genentech Comments for Draft Guidance "Current Good Manufacturing Practice for Combination Products"

| Section | Line Reference | FDA Guidance | Genentech Comment |
|---------|----------------|--|--|
| III.B | 159-163 | However, for combination products that are produced as a single-entity or are co-packaged, see 21 CFR 3.2(e)(1) and (2), both sets of current good manufacturing practice regulations are applicable during and after joining the constituent parts together. The rest of this section refers only to situations when combination products that are produced as a single entity or are co-packaged as defined in 21 CFR 3.2(e)(1) and (2) are joined together. | However, for combination products that are produced as a single-entity or are co-packaged (as a functional unit) , see 21 CFR 3.2(e)(1) and (2), both sets of current good manufacturing practice regulations are applicable during and after joining the constituent parts together. For example, a secondary functional packaging device, such as an auto-injector, may be provided preassembled with a drug cartridge. The primary drug packaging (container-closure system) would be subject to standard drug stability requirements (21 CFR Parts 210 and 211). During assembly, both drug and device cGMPs should be observed. After assembly, stability in accordance with drug expectations for packaging (e.g., ICH Q1C light sensitivity studies) should be observed. In addition, standard device functionality and component stability according to design validation provisions (21 CFR 820.30(g)) should be observed. The rest of this section refers only to situations when combination products that are produced as a single entity or are co-packaged as defined in 21 CFR 3.2(e)(1) and (2) are joined together. |
| III.C | 235-238 | | Genentech recommends adding a statement indicating both sets of regulations also apply during the manufacture of the combination product. |