Medication Delivery
Regulatory Affairs

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June 25, 2003

Dockets Management Branch (HFA-305)
Food and Drug Administration
5230 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Federal Register Notice January 28, 2003 (FR Vol 68, No. 18, Pages 4219-4220)

Docket No. 02D-0526

Dear Colleague:

Baxter Healthcare Corporation is submitting comments on the Draft Guidance for Industry entitled "*Drug Product: Chemistry, Manufacturing and Controls Information,* " released for comment on January 28, 2003. General comments are presented first, followed by specific comments with reference to the applicable section numbers.

General Comments:

1. Baxter appreciates and supports the Agency's recommendations on the CMC information for drug products that should be submitted in original NDAs and ANDAs in CTD format. The draft guidance is applicable to generic products, but does not contain specific information relative to ANDAs. Some examples include: line 149 states that the application should include information in every P subsection, but some sections may not apply to a generic product such as P.2.2.1 Formulation Development; lines 667-673 discuss the compatibility of drug products with diluents and the necessity of performing compatibility studies, but such studies may not apply to a generic product. Specific notations where the guidance does not apply to generic drug products or where requirements for generic drug products may be different would help to clarify the recommendations.

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2. In general, this draft guidance document should be consistent with the ICH guidance documents. In some areas, such as the Characterization of Impurities section V.II.E. below, this new guidance attempts to broaden the scope of the ICH guidances.

Specific Comments:

Section III.C. Composition Statement

Please clarify what is meant by "per unit basis" in lines 327-329?

Section IV.B. Drug Product, 2. Overages

Lines 537 – 539 state that use of an overage of drug substance to compensate for degradation during manufacture or shelf-life is not appropriate. The drug GMPs allow for the formulation of a drug product to meet label claims. Please clarify what is meant by degradation vs. manufacturing loss. Manufacturing losses may occur due to filtration or other means besides degradation.

Section IV.F. Compatibility

Lines 661 and 662 are very broad, covering many possible device categories. Please clarify that compatibility studies should assess devices and administration sets only if they are specifically indicated in the drug product labeling.

Section V.A. Manufacturer

Please clarify that lines 693-695, sterile processing area (room and filling line), apply to aseptic processing only and not terminally sterilized drug products.

Line 711 requests the e-mail address of the contact person at the manufacturing site. Please clarify the purpose of the email address. In many cases, we do not believe, that e-mail is an appropriate medium for notification of a pre-approval inspection.

Section V.B. Batch Formula

Please clarify line 720, "intended validation batch size" vs. the maximum batch size, especially for solution drug products. Specific batch sizes are validated for manufacturing efficiency and market demand and may not be known at the time of submission.

Section V.C. Description of Manufacturing Process and Process Controls

Please clarify if the recommendations regarding the BSE statement specified in lines 824-826 are new requirements for NDAs and ANDAs. Are these recommendations applicable to the Drug Substance and Drug Product?

The Process Controls section (lines 832-916) is very detailed and requires more information than previous guidances or GMP's require. Line 850 should be revised from "All" process controls to "Appropriate" process controls per the ICH CTD guidance document.

Section V.II. Control of Drug Product, A. Specifications

In Table 3, please identify and define the footnoted terms elsewhere in the document so that the footnotes do not need to be repeated.

Section V.II.B. Analytical Procedures

Please clarify that "Official Compendium" includes other compendia besides the USP.

Section V.II.C. Validation of Analytical Procedures

Please clarify in lines 1276 and 1277 that validation information is not required to be submitted for compendial procedures.

Line 1278 should be revised to state that stability data, including data from stress studies, "may" be used to support the validation of the analytical procedures.

Section V.II.D. Batch Analyses

Please clarify lines 1289 – 1291 to state that batch analyses data "may" also be provided for other batches. Batch analyses data should not be required for supportive batches including feasibility, process evaluation, formulation studies and batches prepared for registration in other regions.

Section V.II.E. Characterization of Impurities

The list of expected impurities is inconsistent with the ICH guidance on Impurities in New Drug Products. Leachables from the container closure system are not included as impurities per this ICH guidance.

Section X.C. Stability Data

Please clarify lines 1570-1571 by defining "stability study report" because this may not be common terminology across the industry.

Section X.C.3 Stress Studies

Please clarify lines 1617-1618, to state that results from drug product stress testing and thermal cycling should be provided if used to support the *product's labeled storage statement.*

Section XII.A. Executed Product Records (EPR)

Lines 1799-1800 require only one representative EPR to be submitted for an NDA. Please clarify lines 1803-1804 whether one representative EPR would be acceptable for submission of an ANDA also. One batch record clearly represents the product manufacture, multiple batch records in a submission contain very redundant information.

Baxter appreciates the opportunity to comment on this important draft guidance. If you have any questions regarding our comments, please contact Judy Kannenberg or myself at (847) 270-2577.

Sincerely,

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