

Baxter

November 22, 2000

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

**Re: Federal Register Notice August 30, 2000 (FR Vol. 65, No. 16)
Pages 52776-52777)**

Docket No. 00D-1424

Dear Colleague:

Baxter Healthcare Corporation is submitting comments on the draft FDA Guidance for Industry on "*Analytical Procedures and Methods Validation: Chemistry, Manufacturing and Controls Documentation*" released for comment on August 30, 2000. General comments are presented first, followed by specific comments with reference to the page number and applicable line numbers.

General Comments:

Baxter appreciates and supports the Agency's initiative to provide industry with revised guidances that communicate FDA's current thinking and expectations.

With regard to the subject draft FDA guidance, it appears that the draft guidance incorporates the philosophies and requirements of various existing ICH guidelines and USP General Chapter <1225>, Validation of Compendial Methods. We found the draft guidance to be very prescriptive, too detailed, and redundant with the requirements of existing ICH guidelines. Due to the redundancy of information between this draft and ICH guidelines, confusion of the requirements will exist in industry as these documents are revised over time. We, therefore, propose the Agency streamline the draft guidance by referencing the various ICH guidelines and sections of USP as appropriate. Streamlining the draft guidance in this manner will help the Agency and

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industry avoid inconsistencies between the various documents and requirements.

We believe the requirement to include raw methods validation data in the submission could be very burdensome (see specific comment for line 605) considering the amount of data normally generated during the validation process. We, therefore, recommend that submission of validation information include an example of the data since all raw data are available to FDA during preapproval and general GMP inspections.

Specific Comments:

Page 3, lines 116-118

We believe that two independently validated methods meeting the same requirements for accuracy, precision, etc. is sufficient to demonstrate equivalency. Section III.B., lines 116-118 should be changed to: "If an alternative analytical procedure is submitted, the applicant should provide a rationale for its inclusion and identify its use (e.g., release, stability testing), validation data and/or comparative data to the regulatory analytical procedure."

Page 5, Section starting at line 164

We would like to propose that non-USP reference standards be divided into three categories:

1. New chemical entities, where all requirements in the guideline would apply;
2. Reference standards used as alternates to existing USP RS – it would require the establishment of standard stability, including critical parameters, i.e., potency, impurities, moisture;
3. Well known substances but with no USP RS available – similar requirements as for (1) above, but no physical characterization, etc.

Page 10-11, Lines 402-403 and 419-420

We acknowledge the relevance of understanding possible degradants and impurities; however, degradant and impurity information is provided to the Agency elsewhere in the submission. As a result, we feel that the inclusion of this information in methods validation is redundant. We recommend that lines 402-403 and 419-420 be deleted from the guidance.

Page 12, lines 490-491

We found the first sentence (lines 490-491) to be confusing since “capable of differentiating changes” is too broad a requirement. We propose the sentence be changed to read as follows: “The analytical procedure should be capable of differentiating changes in the chromatographic impurity profile, if any.”

Page 12, lines 492-494

The purpose of this section of the guidance is to show the method is capable of differentiating changes. The inclusion of the analytical procedure number is an unnecessary requirement. Please delete “analytical procedure number” from line 493.

Page 14, Table 1 starting at line 534

- Column title “Specific Tests” should be changed to “Other Tests” to avoid confusion with the specificity of analytical tests. The same change would be required in line 571.
- The Quantitation Limit may be required for limit tests (column 4). We recommend including footnote 3 for Quantitation Limit in column 4.
- Footnote 2 regarding specificity should be expanded to include: “The identification test should be selected based on its application.” The substance should be able to be clearly distinguished from other materials that can be present at a given facility. Absolute specificity may not be achievable in all cases (e.g. semi-quantitative, identification, and physical methods).

Page 15, lines 571 and 573

We recommend “specific tests” be changed to “other tests” to avoid confusion with the specificity of analytical tests.

Page 15, lines 581-591

The requirement to provide information on the specificity of a compendial method may be inappropriate since absolute specificity may not be achievable in all cases (e.g. semi-quantitative, identification, and physical methods). We recommend that this section of the guidance be limited to assays used for potency and chromatographic purity only.

Page 15, lines 590-591

Methods that determine a physical property, like osmolality or optical rotation, can not be validated in the usual way. The instrument can be

standardized/calibrated, and the reading precision and linearity can only be verified.

Page 16, line 605

The document specifies, e.g. line 605, that the raw method validation data should be provided. We believe this could be a very burdensome requirement when considering the amount of raw chromatographic data normally generated during the validation process. Since all raw data are available to FDA during preapproval and general GMP inspections, we suggest that perhaps the submission of an example of the chromatography be submitted.

Page 16, line 619

Alternate methods that meet the same validation requirements as the regulatory method (e.g. requirements for accuracy, precision, etc) should be considered valid for use without a direct comparison study to the regulatory method. We recommend the following be added to Section VIII.B., Line 619: "Alternately, two independently validated methods meeting the same requirements for accuracy, precision, etc. is sufficient to demonstrate equivalency." By allowing this change, the same level of validation (burden of proof) would be required for the alternate method as is required in the case where the regulatory method is the only method identified (e.g. to meet the validation criteria).

Page 20, line 796

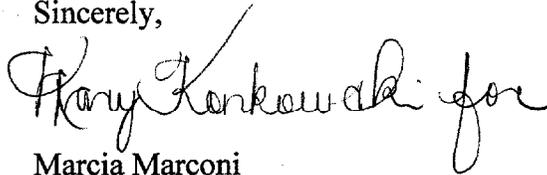
It is our understanding that CGMP is the standard for test laboratories. Please delete "GLP" from line 796.

Page 31, line 1228-1229

Please delete the reference to the unofficial (draft) "Interpretation and Treatment of Analytical Data". It is our opinion that only official references should be included in the guidance document.

Baxter appreciates the opportunity to comment on this important draft guidance. If you have any questions regarding our comments, please contact Mary Konkowski at (847) 270-5619.

Sincerely,

A handwritten signature in cursive script that reads "Marcia Marconi for". The signature is written in black ink and is positioned above the typed name and title.

Marcia Marconi
Vice President
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