

SB
SmithKline Beecham
Pharmaceuticals

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November 22, 2000

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

Re: Docket No. **00D-1424**; Draft Guidance for Industry on
Analytical Procedures and Method Validations:
Chemistry, Manufacturing and Controls
Documentation
Federal Register, August 30, 2000 (65FR169)

Dear Sir/Madam:

The draft guidance, according to the Notice issued at the time of the publication is intended to provide recommendations to applicants on submitting analytical procedures, validation data and samples to support the identity, strength, quality, purity and potency of drug substances and drug products.

Reference is made to our initial comments submitted to Docket No. 00D-1424 on November 14, 2000.

Provided herein, are additional detailed specific comments from SmithKline Beecham Biologicals on the aforementioned draft guidance.

SmithKline Beecham welcomes the opportunity to work with FDA and industry in crafting improved versions of this draft guidance.

Sincerely



Thomas M. Hogan
Director
North America Regulatory Affairs

Attachment

00D-1424

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SUP1
see C3

**FDA Guidance for Industry for public comment:
Analytical Procedures and Methods Validation - Chemistry, Manufacturing, and Controls
Documentation**

Posted: 8/30/2000, Publish Date: 8/30/2000

SB Biologicals Comments

Section	Guidance Line (or page #)	Comment	Rationale
II	71	Replace "demonstrates" by "confirms"	The suitability should be determined by the applicant and confirmed by the FDA.
II	72-73	Define "regulatory purposes" or change wording.	An analytical procedure should be suitable for its intended use (which can be release, characterization, stability testing, ...). It is unclear what regulatory purposes means.
II	91	What is the difference between in process and acceptance testing? Please add to glossary.	
III	104-105	Clarify definition	The definition of a regulatory analytical procedure is very unclear, as alternative analytical procedures would also evaluate a defined characteristic of the drug substance or product. Does a regulatory analytical procedure mean compendial method ?

Section	Guidance Line (or page #)	Comment	Rationale
III	113-114	Clarify definition	We suppose that alternative analytical procedures would also include methods developed by the applicant in the absence of a compendial method ?
III	118	Remove	It may not be possible, or relevant, to compare an alternative method and a compendial method.
III	122-125	Please add that this may not be applicable to biologicals	The definition of “ <u>quantitative</u> analytical procedure” only applies to chemicals, not to biologicals. E.g. a stability-indicating assay for a vaccine is often a potency test that measures the induction of antibodies in an animal model. This is not a quantitative assay.
VI	248-249	Change example	The example is unclear. It seems to us that the principle would be: “For example, quantification of the substance by UV spectrometry after separation of ... by isocratic HPLC.
VI	279	Add “quantitative” before “chromatographic”	We suppose that “all <u>quantitative</u> chromatographic methods” are meant. For e.g. qualitative TLC it will be difficult to establish system suitability parameters.

*SB Biologicals comments on FDA Guidance for Industry:
Analytical Procedures and Methods Validation - Chemistry, Manufacturing, and Controls Documentation*

Section	Guidance Line (or page #)	Comment	Rationale
VII	378	Remove robustness	It is our opinion that evaluation of robustness should be performed during the development of the analytical procedure. The result of the robustness evaluation would be the inclusion of specific parameters or warnings in the SOP, rather than a complete description of assay development in the validation package.
VII	384-385	Remove	This should be part of robustness analysis. See previous remark.
VII	400-415	Remove	This information should be discussed in the product characterization section, not under method validation. Inclusion of all this information in the validation report will make the latter unreadable.
VII	419-420	Remove	This information should be in the stability section, not under method validation.
VII	425-426	Remove	This is part of robustness analysis. See remarks on line 378.

*SB Biologicals comments on FDA Guidance for Industry:
Analytical Procedures and Methods Validation - Chemistry, Manufacturing, and Controls Documentation*

Section	Guidance Line (or page #)	Comment	Rationale
VII	435-436	Remove "... and the data discussed and/or submitted. In cases where an effect is observed, representative instrument output should be submitted ..." and replace by "... and the data used to set appropriate parameters in the standard operating procedure".	See rationale to line 378.
VII	450-453	Replace "should be submitted in the sections on analytical procedures and controls" by "should be submitted in the most appropriate section".	For a lot of stress testing results, the instrument output (SDS-PAGE photo's, Western blots, etc.) should be included in the stability section, which would otherwise become incomplete and unreadable. Inclusion in the methods description or validation will, on the other hand, make those documents too complex.
VII	455-520	Please summarize.	The section on instrument output/raw data contains a lot of overlapping and repetitions statements between i, ii and iii. It is unclear why "organic impurities" is a separate section, next to "drug substance" and "drug product".
VII	578	Delete robustness	See remark on line 378.
VIII	603	Delete "and the criteria used in determining the acceptability of the analytical procedure"	If criteria need to be set a priori, this means that standard acceptability criteria exist. If so, then those should be part of the guidance document.

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*SB Biologicals comments on FDA Guidance for Industry:
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Section	Guidance Line (or page #)	Comment	Rationale
X	668	Add "if known at submission"	Commercial lots may not yet be produced at BLA submission, in which "case batch numbers etc. cannot yet be given.
X	740	Add "primary" before packaging	Clarifies.
XI	926	Delete "robustness"	See comment to line 378.
XI	1034	Delete "robustness"	See comment to line 378.
Attachment A	1115	Change "XI" to "X"	Wrong section is referenced
References		Add reference to "Guidance for industry: content and format of chemistry, manufacturing and controls information and establishment description information for a vaccine or related product	This would be appropriate if the current guideline is to be applied to vaccines.



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