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November 27, 2000

PHARMACIA

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

Subject: Docket No. 00D-1424

Dear Sir or Madam:

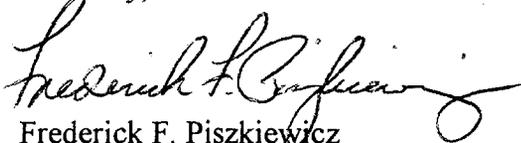
Pharmacia hereby provides its comments on FDA's Draft Guidance for Industry on Analytical Procedures and Methods Validation: Chemistry, Manufacturing, and Controls Documentation.

As a general comment, we believe that this draft guidance requires more information and documentation supporting analytical procedures and methods validation than what ICH requires. We would like to see FDA and ICH requirements in closer harmony with each other.

The appendix to this letter contains consolidated comments from Pharmacia. For your convenience, we have provided the line numbers to which our comments refer.

If you have any questions or need additional information regarding Pharmacia's comments, please feel free to contact me directly at 1-847-982-7310.

Sincerely,



Frederick F. Piskiewicz
Regulatory Affairs
CMC Manager

00D-1424

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Appendix

Line 69. We suggest the noncompendial reference standards be addressed in a separate guidance for industry.

Line 91. The meaning of the word “acceptance” is unclear in the sentence beginning on line 89 “In general, validated analytical procedures should be used, irrespective of whether they are for in-process, release, acceptance, or stability testing.” We do not understand the difference between release testing and acceptance testing. Please clarify.

Line 104. We suggest adding the word “registered” for clarification. The sentence would then read, “A regulatory analytical procedure is the registered analytical procedure used...” This will clarify the meaning and intent of this sentence.

Lines 120-130. We think that this section entitled “Stability-Indicating Assay” should replace the definition of “stability indicating assay” in the glossary. This section provides a clearer description of “stability-indicating assay” than the definition on the glossary. If this section is moved to the glossary, this section could then be deleted.

Line 142. We found the word “in-house” confusing and suggest that it be deleted. The sentence would then read, “A working standard (i.e., secondary standard) is ...” Alternatively, the definition of “in-house standard” could be added to the glossary.

Line 192. Regarding the bullet “A detailed description of the analytical procedures...” we suggest that this should be provided for information purposes only, like a snapshot in time, and that this does not constitute a commitment.

Line 246. We believe that this section “Principle” is unnecessary as it is already included in methods validation reports or rationale reports. We suggest deleting this section.

Lines 251-254. We believe that specifying the number of samples and replicates is a GMP issue. Specifying the number of samples and replicates should not be required in the registered analytical procedures.

Lines 260-261. We suggest an editorial change for clarification purposed, moving the phrase “when appropriate” to the beginning of the sentence. We suggest this sentence to read: “When appropriate, a drawing representing the experimental configuration...”

Line 265. We recommend that grade of solvent be specified only when it is critical to the analysis. At manufacturing sites outside the U.S., USP/NF or ACS grade may not be available.

Line 268. We believe that specific directions for safe use of solvent, reagents, etc. should come from the solvent or reagent manufacturer rather than from the drug product manufacturer. If the drug product manufacturer believes that special

precautions are needed, then the drug product manufacturer can provide these special precautions.

Lines 283-287. For clarification purposes, we suggest that this paragraph be move in front of the paragraph beginning on line 273. Placing the paragraph "System suitability testing is recommended as a component..." at the beginning of this section ("E. System Suitability Testing") clarifies the purpose to this section.

Line 302. Injection sampling sequence seems to be more of a GMP issue and need not be specified in the analytical procedure. We believe that injection sample sequencing may be specified, however, if it is critical to obtaining accurate measurements.

Lines 307-311. Under the section entitled "Calculations", we recommend deleting the word "representative" from the sentence "Representative calculations, with a tabulation..." We believe that the resulting sentence "Calculations, with tabulation..." is clearer. We also suggest, for clarification purposes, that the second sentence "Any mathematical transformations..." be changed to read: "Mathematical transformations... should be described."

Lines 318-319. We believe that the number of significant figures is a GMP issue and need not be addressed in this guidance. The sentence beginning on line 317 would then read: "The format used to report results (e.g., percent label claim, weight/weight, weight/volume, parts per million (ppm)) should be reported."

Lines 326-328 and 332-335. We suggest that ICH terminology be adopted for this guidance. We recommend that "QL" (i.e., quantitation limit) be change to ICH limits or "reporting threshold."

We suggest deleting the sentence "The detection limit (DL)..., as appropriate." The Quantitation Limits of modern analytical procedures are often lower (sometimes much lower) than the ICH reporting thresholds for organic impurities in a drug product or drug substance. The proposed FDA requirement to report at levels equal to or greater than the Quantitation Limit(s) of an analytical procedure is inconsistent with the ICH reporting threshold practices.

Lines 335. For clarification purposes, we suggest that the sentence beginning "Inorganic impurities..." be moved to the end of the next paragraph following the sentence ending "... labeling should be addressed."

Lines 363-579. We suggest deleting these lines as they repeat ICH guidance. Perhaps the reader of the guidance should be directed to the appropriate ICH guidance documents instead.

Line 586: We suggest adding the word "accuracy" to this sentence. The resulting sentence becomes: "Information on the specificity, accuracy, intermediate precision..."

Lines 594-625. We suggest that section "VIII. Statistical Analysis" be deleted as statistical analyses are already included in ICH guidance documents.

Lines 628-643. We feel that section "IX. Revalidation" should be deleted from the methods validation guidance, as this is a GMP issue.

Lines 683-685. We feel that the sentence "Representative instrument output and raw data..." should be deleted from methods validation package. Representative instrument output is normally included in the test method and/or the report on forced degradation. We also feel that requests for raw data in this document are unnecessary. Raw data should be available at the time of pre-approval inspections and need not be included in the methods validation package.

Line 690. We also feel that dates of analysis are a GMP issue and need not be included in the methods validation package.

Lines 710-713. We suggest adding "(if necessary)" to this sentence. The revised sentence becomes "On request from CDER, and blanks (if necessary), so that..." In the majority of cases, we think the blanks will not be needed, but should be provided if needed.

Lines 729-730. We feel that the phrase "preferably samples from an aged batch" is unnecessary, if the FDA requests samples "from any batch."

Line 740. For clarification purposes, we suggest that the first sentence of this paragraph be revised to read: "The drug product should be supplied in the primary package representative of the commercial product." This will clarify which packaging is required.

Lines 823-824. We suggest deleting "frit size" and "filter type" as these are not column parameters.

Line 829. We suggest revising this bullet to read "Particle size: size, shape (as appropriate), pore diameter (as appropriate)"

Line 832. We suggest deleting this bullet, as it is already included in the test method.

Lines 836-837. We feel that the first sentence under "system suitability testing" should read: "Each analytical procedure submitted should include the appropriate system suitability tests." The number of tests is more of a GMP issue and need not be addressed in this document.

Line 838. We feel that this sentence can be revised to read: "Several system suitability tests are defined in CDER's reviewer guidance on *Validation of Chromatographic Methods* (November 1994)."

Lines 842-847. We feel that this list of tests is confusing. The reader may interpret that all these items must be performed when some of them need not be performed. In most cases, "capacity factor" and "number of theoretical plates" are unnecessary parameters and need not be included as system suitability parameters.

Lines 849-858. We believe that these lines can be deleted, as they are redundant with lines 837-838.

Lines 862-863. Under subsection "3. Operating Parameters" we believe that the first sentence may be deleted, as these are not typical compendial requirements.

Lines 866-867. We feel that this sentence should be clarified to indicate that the preparation of the mobile phase for HPLC should be provided only when critical to method performance. Under the majority of circumstances, preparation of the mobile phase is not critical to the analysis.

Line 883. We suggest deleting "external diameter" for the GC column as this does not affect column performance.

Line 890. We suggest deleting "purity" and revising the bullet to read "Gases: flow rate(s) and/or pressure(s)." Purity of the gas(es) depends on what is available from the supplier. Also, more than one gas may be used in a GC.

Line 899. Under the section discussing system suitability testing for GC, we suggest revising the first sentence to read, "Appropriate system suitability tests and criteria should be..." We feel that adding "tests and" will clarify the meaning of this section.

Lines 901-911. We feel that these paragraphs are redundant and could be deleted.

Lines 920-922. The sentence beginning "The bias of the analytical procedure..." can be deleted, as this appears to be redundant with the validation section.

Line 924. We feel that another sentence may be needed for clarification purposes. We suggest revised line 924 to read, "... between sampling and reading. The time period should be supported by method validation data for solution stability. As appropriate, system suitability and/or calibration testing is recommended."

Line 977-978. We feel that the sentence beginning "If measurements are to be made..." should be deleted, as this information would appear in the method rationale document.

Lines 1030-1031. "To ensure proper instrument operation, the system should be calibrated..." We suggest that this sentence be deleted as this a GMP issue.

Line 1033. We feel that the sentence beginning "The methods validation..." can be deleted, as this is included in ICH guidance documents.

Line 1044. We feel that this sentence ("A brief discussion of the reasons for selecting the medium.") should be deleted from the test method and methods validation. The reasons for selecting dissolution medium are included in the method rationale.
Line 1061. We suggest that this line be deleted and replace with line 961-963. These lines provide a better description of what is expected.

Line 1062. We suggest adding “(as appropriate)” to this sentence for clarification purposes. The revised sentence then reads, “Blank (as appropriate) and standard solution spectra...”

Line 1068. We suggest deleting the sentence “The time needed for completion of the sample analysis...” Analysis time can vary between analysts and cannot be predicted.

Lines 1269-1272. We recommend replacing “quantitation limit” in the glossary with the ICH terminology “reporting threshold” and its definition as described in ICH guidance.

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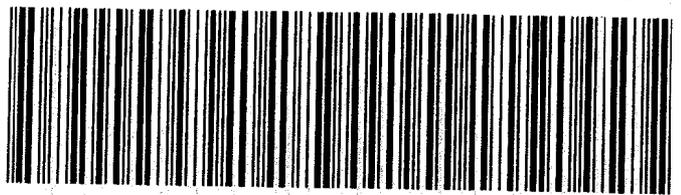
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