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November 28, 2000

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

**Re: Docket No. 00D-1424
Comments on the Draft Guidance for Industry on Analytical
Procedures and Methods Validation: Chemistry, Manufacturing,
and Controls Documentation**

Dear Sir or Madam:

On behalf of 3M Pharmaceuticals, I am writing to register comments to Docket Number 00D-1424 on the *Draft Guidance for Industry on Analytical Procedures and Methods Validation: Chemistry, Manufacturing, and Controls Documentation*, dated August 29, 2000. This document was published in the Federal Register on August 30, 2000 as a Notice. The comments begin on the next page.

An electronic file (MS Word 6.0) of this document has been sent to cunninghamp@cder.fda.gov. Additional electronic files are available upon request.

Should you have any questions regarding the comments, please don't hesitate to call me (651 736-1590).

Sincerely,

Amy E. Fowler
Senior Regulatory Associate

00D-1424

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3M Pharmaceuticals' Comments to FDA's *Draft Guidance for Industry on Analytical Procedures and Methods Validation: Chemistry, Manufacturing, and Controls Documentation, August, 2000*

Introduction: Line numbers are identified, followed by the guidance text in italics. The 3M comment/justification follows. Where suggestions are made for change, the proposed changes to the text in quotation marks follow the justification. Suggested deletions are marked with a strike-through font and suggested additions are underlined.

Lines 24 - 26: *This guidance provides recommendations to applicants on submitting analytical procedures, validation data, and samples to support the documentation of the identity, strength, quality, purity, and potency of drug substances and drug products.*

We suggest definitions of “potency” and “strength” be added to clarify the difference between these two concepts.

Lines 44 – 48: *Although this guidance does not specifically address the submission of analytical procedures and validation data for raw materials, intermediates, excipients, container closure components, and other materials used in the production of drug substances and drug products, validated analytical procedures should be used to analyze these materials.*

This is a very broad comment. “...other materials used in the production of drug substances and drug products...” can mean cleaning agents and other materials that do not end up as a part of the drug substances and products. These materials may not require methods validated to the same standards as those used for the characterization of drug substances or drug products.

Lines 89-91: *All analytical procedures are of equal importance from a validation perspective. In general, validated analytical procedures should be used, irrespective of whether they are for in-process, release, acceptance, or stability testing.*

Although all methods listed may be of equal importance from a validation perspective, not all methods require the same level of validation. This is an important point that is not obvious in the text as written and we recommend it be clarified within this section.

Lines 91-92: *Each quantitative analytical procedure should be designed to minimize assay variation.*

Minimizing assay variation (i.e., precision) is not the only goal of method development. In some cases, such as on-line analysis techniques, accuracy may be more important than the precision of a measurement. A trade-off must often be made between precision, accuracy, sensitivity, and other parameters in the development and validation of methods. It is *always* possible to further reduce assay variation by a variety of techniques such as increasing sample size or increasing the number of replicates, but there are practical limitations to these approaches. In many cases minimizing assay variation is not appropriate. We suggest this line should be deleted or modified.

“Each quantitative analytical procedure should be designed to ~~minimize~~ with appropriate assay variation matched to its intended use.”

or

“Each quantitative analytical procedure should be ~~designed to minimize assay variation~~ suitable for its intended use.”

Line 152: “C. Characterization of a Reference Standard”

Based on the text it appears FDA uses the term “reference standard” for quantitative standards and not retention time markers. An explicit definition of the meaning and use of the term “reference standard” should be made within this section. It is not necessary to use the “highest purity that can be obtained” for retention time markers.

Lines 157-160: *The qualitative and quantitative analytical procedures used to characterize a reference standard are expected to be different from, and more extensive than, those used to control the identity, strength, quality, purity, and potency of the drug substance or the drug product.*

Methods for a reference standard do not necessarily need to be arbitrarily “different” from the methods used to characterize the drug substance. More extensive testing overall should be employed to characterize reference standards as compared to the overall testing used for drug substances and drug products. The individual methods (e.g., content assay), however, do not necessarily have to be made “more extensive”, as long as their specificity, sensitivity, precision, accuracy, etc. are suitable for their intended purpose.

“...more extensive testing should be procedures used to characterize a quantitative reference standard~~are expected to be different from, and more extensive than, those the testing that is~~ used to control the identity, strength, quality, purity and potency of the drug substance or the drug product.”

Lines 253-254: *The number of samples (e.g. vials, tablets) selected, how they are used (i.e., as individual or composite samples), and the number of replicate analyses per sample should be described.*

We agree with FDA that sampling information and number of replicate analyses is important information that should be provided in submissions, but there are drawbacks to requiring this information to be included in the method itself. Sampling schemes often differ depending on the purpose of the testing. For example, the sampling scheme and number of replicates required for batch release testing are usually quite different than the requirements for testing large numbers of process validation samples. The guidance should provide flexibility to include sampling information in specifications, stability protocols, process validation protocols, SOPs, etc. instead of requiring this information to always be included in the method.

“The number of samples (e.g. vials, tablets) selected, how they are used (i.e., as individual or composite samples), and the number of replicate analyses per sample should be described within the regulatory submission, either within the method document, specifications or stability protocols.”

Lines 267-269: *Unstable or potentially hazardous reagents should be identified, and storage conditions, directions for safe use and usable shelf life for these reagents should be specified.*

All reagents are *potentially* hazardous if mishandled. We recommend the term *unusually* since we believe this is the intent of FDA. Although we normally indicate unusual safety hazards in the method, laboratory personnel always have access to the MSDS for each reagent, which gives very specific information that is too extensive and updated too frequently to be included in the method itself.

“Unstable or ~~potentially~~ unusually hazardous reagents should be identified, and storage conditions, directions for safe use, and usable shelf life for these reagents should be specified.”

Lines 283-287: *System suitability testing is recommended as a component of any analytical procedure, not just those that involve chromatographic techniques. Regardless of the type of analytical procedure, testing should be used to confirm that the system will function correctly independent of the environmental conditions. For example, titration analytical procedures should always include the evaluation of a blank (commonly referred to as a blank titration).*

We agree with the concept that system suitability has broader applicability than for just chromatographic methods. We further agree that many analytical procedures could benefit from a system suitability evaluation. However, all analytical procedures do not necessarily need a system suitability evaluation. The USP/NF does not require system suitability for non-quantitative and quantitative tests such as a flame test, loss on ignition, gravimetric tests and many wet chemical tests. We suggest the deletion of the example cited of running a blank to assess the suitability of a titration method. It is good practice to run a blank for titration methods, but this is not a system suitability test. The analyst has no way of knowing whether the blank value generated is correct. Titration of a positive control sample, such as a reference standard, would be more useful in terms of providing meaningful information about the suitability of a titration system than titration of a blank.

~~“System suitability testing is recommended as a component of any most quantitative analytical procedures..., ...For example, titration analytical procedures should always include the evaluation of a blank (commonly referred to as the blank titration).”~~

Line 307: *Representative calculations, with a tabulation defining...*

We agree that the equations for calculations should be provided in method documents, including definitions and units for each variable. Example calculations (presumably with example data) are less useful, however.

~~“Representative eCalculations,…”~~

Lines 326-327: *The detection limit (DL) or quantitation limit (QL) should be stated, as appropriate.*

We disagree that the DL or QL should be stated in any method since DL and QL are instrument specific, and may vary from one analysis to the next. We have adopted the concept of a “quantitation limit level” (QLL), which is the minimum concentration that a chromatographic system must be capable of quantifying at the time of use, rather than the minimum level that was quantifiable during method validation. The QLL concentration is selected to meet the needs of the particular method/specification and must be greater than or equal to the QL obtained during method validation. A QLL standard is prepared and injected as a part of system suitability and its response is checked against the specified criteria to assure that an appropriate level of sensitivity and precision is obtained each time the method is run. We propose this QLL concept be used in place of the text in lines 326-327.

~~“The detection limit (DL) or quantitation limit (QL) should be stated, as appropriate.”~~

Lines 337-338: *For the drug product, drug substance process impurities may be excluded from reporting if an acceptable rationale is provided in the sections on analytical procedures and controls.*

The guidance should be consistent with the ICH Q3B document.

“For the drug product, drug substance process impurities ~~may~~ should be excluded from reporting if and an acceptable rationale is provided in the sections on analytical procedures...”

Lines 392-393: *Representative calculations using submitted raw data, to show how the impurities in drug substance are calculated.*

Rather than raw raw data and representative calculations, the analytical method with calculation equations along with results in the corresponding method validation document should be sufficient.

Lines 428-453: *ICH Q2A and Q2B address almost all of the validation parameters. Areas that should be provided in more detail are described below. ...*

This line may be acceptable if the following concerns are addressed.

Lines 431-437: *a. Robustness*

No additional detail is provided. Robustness is included in the ICH guidances as noted in this guidance’s text. The guidance also states that in cases where an effect is observed,

representative instrument output should be submitted. In light of section “c. Instrument Output/Raw Data” section, “a. Robustness” is redundant.

Lines 451-452: *The design of the stress studies and the results should be submitted to the stability section of the application.*

If studies are used to support the stability evaluation of the drug substance or drug product, we agree that the experiments and results should also be included within the stability section of the application. It is important to note that stress studies are often used for the evaluation and validation of methods not referenced in the stability section (e.g. residual solvents methods for product release).

“The design and result of stress studies, or a description of samples and their source *used for the purpose of selectivity evaluation within method validation* should be provided in the method validation section.”

Lines 455-520: *c. Instrument Output/Raw Data*

The focus appears to be on the raw data requirements for the *stability section* of the application (for example, lines 493-494, 503-504, 507-508 and 512-513, 515) with very little description of what is required for analytical procedures and method validations. It is unclear how method validation relates to the stability section. Perhaps there is a need to clarify that information in the stability section is a duplicate, as are the methods and validation information in the CMC section.

Lines 605-606: *The raw methods validation data and statistical procedures used to analyze the raw data should be provided and discussed in the sections on analytical procedures and controls.*

Please see our comment for lines 392-393. We see greater merit in the use of *method results* rather than raw data.

“The ~~raw methods validation data~~ analytical results and statistical procedures used ~~to analyze for the analysis of~~ the raw data should be provided and discussed in the sections on analytical procedures and controls.”

Lines 702-703: *The applicant should include material safety data sheets (MSDSs) for all samples, standards, and reagents (29 CFR 1910.1200(g))*

This section should be moved to the section on selection and shipment of samples (~line 714). We suggest adding the text “in the shipment” as noted below to differentiate from those materials obtained by the FDA laboratory. MSDSs are provided for all materials *shipped*. It is expected that the vendors used by the FDA in acquiring solvents and other common reagents would provide the MSDSs for those materials.

“The applicant should include material safety data sheets (MSDSs) for all samples, standards, and reagents (29 CFR 1910.1200(g)) as required for shipment.”

Line 748: *If a sample is toxic or potentially hazardous,...*

All chemical materials are “potentially” hazardous. We recommend the use of “unusually”.

“If a sample is toxic or ~~potentially~~ unusually hazardous...”

Lines 922-924: *When manually operated equipment is used, the description of the analytical procedure should include an acceptance criterion for the amount of time that may elapse between sampling and reading.*

Please clarify the scope and intent of this sentence. Is sampling when the sample is prepared, when the sample is removed from its container, or when it is collected from the bulk material? Are manually operated pieces of equipment such as pH meters, balances, and manually read spectrometers included in the scope of this line of the guidance? Is this comment only relevant to manually operated equipment?

Thank you for your consideration of our comments to the guidance.