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OCT 27 2000

Dockets Management Branch
Food and Drug Administration
HFA No. 305, Room No. 1061
5630 Fishers Lane
Rockville, MD 20852

Dear Sir or Madam:

Re: Docket Number 00D-1424
Response to Food and Drug Administration Call for Comments

Reference is made to the Food and Drug Administration Draft Guidance for Industry "Analytical Procedures and Methods Validation: Chemistry, Manufacturing, and Controls Documentation."

AstraZeneca Pharmaceuticals LP (AstraZeneca) has reviewed this guidance and has the following comments:

- This draft guidance is unnecessary apart from the sections describing the methods validation package, selection and shipment of samples, and the responsibilities of various parties. Current International Conference on Harmonization (ICH) Guidelines on Validation of Analytical Procedures Q2A and Q2B, coupled with revisions to ICH Guidelines on Impurities in New Drug Substances and Drug Products Q3A and Q3B are satisfactory to allow applicants to validate methods and report data for New Drug Applications (NDAs). Further, the level of detail is excessive compared with the content of current New Drug Applications and pharmacopeia. This will inevitably lead to increased pre- and post-approval regulatory burden for the sponsor, as well as the FDA.
- The draft guidance proposes redundant, additional, and contradictory requirements beyond those previously agreed by the Food and Drug Administration (FDA) at ICH regarding specific issues on robustness data, reporting criteria and limits, and specifications. These proposed requirements would also necessarily increase the regulatory burden both on the innovating company, as well as the FDA.

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Regulatory Issue	ICH Guidance	FDA Draft Guidance for Industry: <i>Analytical Procedures and Methods Validation: CMC Documentation</i>
Robustness Data	<p>ICH Q2A: "It should be noted that robustness is not included ... but should be considered at an appropriate stage in the development of the analytical procedure."</p> <p>ICH Q2B: "The evaluation of robustness should be considered during the development phase ..."</p>	Lines 366-378: "Applicants should submit information on the validation of their proposed analytical procedures ... Typical validation characteristics are ... robustness."
Reporting Criteria and Limits	<p>ICH Q3A(R): "Levels of impurities which are not more than the reporting threshold given in Attachment 1 need not be reported."</p> <p>ICH Q3B(R): "Degradation products present at a level of not more than the threshold generally would not need to be identified."</p>	Lines 323-326: "The name and location/identifier (eg, retention time (RT), relative retention time (RRT)) of impurities and the type of impurity (eg, process, degradant, excipient degradant) should be included in the analytical procedures for impurities in the drug substance and drug product."
Specifications	ICH Q6A: "A stereospecific identity test is not generally needed in the drug product release specification ..."	Lines 554-557: For other identification tests (eg, a chiral HPLC retention time as confirmation of the presence of an enantiomer) ... applicable to both the drug substance and drug product."

- Lines 36-37: The principles in this guidance do not apply to all types of analytical procedures. Some pharmacopeial procedures, for example the disintegration test, cannot be validated.
- Lines 44-47: The guidance briefly addresses the need to use validated analytical procedures for the testing of raw materials, intermediates, excipients, container closure components and other materials used in the production of drug substances and drug products. These issues are sufficiently addressed in other Agency guidelines and guidance documents.
- Lines 120-129: The wording of this paragraph should be revised to differentiate between the assay and other test procedures that may also be stability indicating. A method need not be quantitative to be stability indicating. Dissolution testing can be stability indicating but not require the selectivity discussed above.
- Lines 157-162: The quantitative and qualitative procedures used to characterize a reference standard (that is not obtained from an official source) need to be more extensive than those used to control the drug substance/drug product. As written, it is inferred that all procedures used to characterize the reference standard are *different from* those used to control drug substance/drug product. Some procedures used during characterization may be applicable as quality control tests for the drug substance/drug product. The inference that all procedures used during characterization be different than those used to control the drug substance/drug product is inappropriate.

It is stated that USP standards do not require additional characterization. Yet, this testing would require extensive characterization, even if the proposed standard gave the same response for a given test as the USP standard. The need for this requirement is unclear.

The guidance does not address requirements for reference materials in early stages of product development. It is common practice in the industry to use reference materials early on which have not been characterized to the full extent indicated in this guidance document. The guideline should address this.

- Line 192: Please drop the word “detailed” from the above sentence. A detailed description should not be needed.
- Lines 216-224: Further reference to these guidelines and guidance documents is unnecessary.
- Line 258: List only critical or relevant instrumentation.

- Lines 265-266: The exact grade of reagents should not be specified unless the grade is critical to the method. Unnecessarily restricting the grade would cause undue commercial and regulatory burden to sponsors.
- Line 302: Provision of injection sampling sequence is an excessive level of detail and has minimal impact on validation criteria.
- Lines 317-319: Results should be reported in a manner consistent with the specifications such that conformance to those specifications can be readily assessed. Specifying the exact number of significant figures should not be needed.
- Line 323: The section on reporting criteria is contrary to that agreed by ICH where reporting limits are defined. Use of quantitation limit routinely is unreasonable since it varies from day-to-day, instrument-to-instrument and laboratory-to-laboratory, and would lead to inconsistent tables of data. Quantitation limits can also be very low using current technology and would lead to imprecise, irrelevant data. Validation should ensure that quantitation limit is always lower than the reporting limit.
- Lines 327-328: These lines should be removed. The DL and QL should be reported in the method validation package.
- Line 378: "Robustness" is not a validation characteristic but a method development issue.
- Lines 384-385: Analytical solution stability does not need to be reported in an NDA. Therefore, requiring the reporting of standard solution stability in an NDA would be an excessive and unnecessary burden.
- Line 506: There is no scientific rationale for requiring that the raw drug product stability data at the latest available time point be included in the validation report. The requirement to include the raw data at the latest available stability time point in the validation report would introduce unnecessary redundancy, delay the preparation and review of the application, and thus contribute to undue regulatory burden. The validation report should contain representative instrumental output, such as chromatograms. The drug product results at the latest available stability time point should be included in the stability section of the application. If there are concerns with raw data, those data may and should be reviewed during the conduct of a pre-approval inspection (PAI) by the FDA.
- Line 535: The heading "Limit" should be changed to "Limit Test." The terms "Limit Test" and "Specific Tests" should be listed and defined in the glossary. Footnote five (5) should be changed to footnote two (2) (please refer to comment regarding Lines 541-542, 545). The robustness line should be deleted as per agreements already made in ICH Q2A.

- Lines 541-542, 545: To be consistent with ICH Q2A, lines 541-542 should be changed to “Lack of specificity for an analytical procedure may be compensated for by other supporting analytical procedure(s)” and footnote number five (5) in line 545 should be deleted. One particular concern with this re-write is that it implies that dissolution and content uniformity analyses need to be specific for impurities, which does not have to be the case.
- Lines 547-557: Much of this section is related to specifications, not method validation. Specifications are covered in ICH Q6A and this section should simply refer to ICH Q6A. In particular, the need for a chiral identity method in drug product in this draft guidance appears to be in contradiction to what is stated in ICH Q6A.
- Lines 600-603: The last two sentences should be deleted. As written, lines 600-603 seem to imply the need for pre-approved protocols for method validation, which causes concern for the potential of additional and unnecessary regulatory burden. Analytical procedures must be validated for their intended purposes according to the principles of good science and guidance provided in ICH Q2A and Q2B. Internal guidelines for achieving this are often useful, but strict acceptance criteria and requirements on the amount of data to collect would only add compliance burden and not improve the quality of the analytical methods. A method validation protocol (written prior to the start of a validation study) would be a Good Manufacturing Practice (GMP) record, but it is not required as part of the application.
- Lines 605-608: The need to include raw methods validation data seems unnecessary. Raw data for all calculations cannot feasibly be included in a submission, since the documents would be excessively long. The correctness of specific calculations based on raw data is better addressed at time of pre-approval inspection.
- Line 740: Replace the term “original packaging” for drug product with “commercial packaging.”
- Lines 807-1072: The details are excessively restrictive for inclusion in an NDA and represent an undue regulatory reporting burden.
- Lines 1091-1095: Manual procedures may not always be possible, and there could be significant differences in validation parameters (accuracy and precision) between an automated and manual method.

Please direct any questions or requests for additional information to me, or in my absence to Dr. Robert J. Timko, Associate Director, Technical Regulatory Affairs, at (302) 886-2164.

Sincerely,



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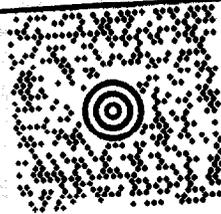
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