

Chiron Corporation
4560 Horton Street
Emeryville, California 94608-116
510.655.8730

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27 November 2000

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

RE: *Draft Guidance for Industry: Analytical Procedures and Methods Validation*

Chiron Corporation would like to make the following comments and suggestions regarding the proposed draft guidance on analytical procedures and methods validation:

General Comments:

The purpose of this guidance document, as outlined in the Introduction section, is to provide "recommendation to applicants on submitting analytical procedures, validation data, and samples..." However, certain sections and suggestions within the guidance document go beyond this purpose to discuss data that would normally not be included with analytical methods validation packages, such as the following: (1) assay robustness information that would normally be part of assay development, but is not recommended as required information for analytical validation packages as defined in the ICH Q2 guidance documents; (2) product characterization information, that would normally be an element of development; and (3) stress studies, which are included in the stability documentation. Chiron Corporation recommends, therefore, that this information should not be included in the analytical methods validation documentation.

Specific Comments:

Section II, line 64 BACKGROUND

In this section, the Agency recommends that analytical procedures should be validated regardless of their purpose, including "in-process, release, acceptance, or stability testing." The glossary for the guidance document does not define these testings, specifically the difference between release and acceptance criteria. Chiron Corporation requests clarification on the methodologies for which this guidance document applies.

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Section IV.A, lines 102-103 **REFERENCE STANDARDS, Types of Standards**

For applicability to biologic products, Chiron Corporation recommends the following revised wording:

When there is no official source for a new chemical entity, a reference standard should be of the highest possible purity and be fully characterized. Reference materials for biologic products should be representative of the manufacturing process.

For further clarity within the guidance document, *reference standard* should be defined in the GLOSSARY.

Section IV.C, lines 120-121 **REFERENCE STANDARD, Characterization of a Reference Standard**

Chiron Corporation recommends the following revised wording:

Analytical procedures used to characterize a primary reference standard (material) should not rely solely on comparison testing to a previously designated reference standard (material). Following analytical methods validation and primary reference standard (material) selection, subsequent reference standards (materials) should be subjected to complete release testing requirements.

Section VI.C, line 203 **CONTENT AND FORMAT OF ANALYTICAL PROCEDURES FOR NDAs, ANDAs, BLAs, AND PLAs, Equipment and Equipment Parameters**

As the purpose of the guidance document is to clarify the submission requirements for analytical methods validation documentation, Chiron Corporation recommends adding "gradient" to the list of equipment parameters.

Section VI.D, line 210 **CONTENT AND FORMAT OF ANALYTICAL PROCEDURES FOR NDAs, ANDAs, BLAs, AND PLAs, Reagents**

Chiron Corporation suggests the following revised wording:

used, detailed directions for their preparation should be included.

Section VI.E, lines 222-223 **CONTENT AND FORMAT OF ANALYTICAL PROCEDURES FOR NDAs, ANDAs, BLAs, AND PLAs, System Suitability Testing**

For clarification in line 222, Chiron Corporation suggests the following revised wording:

(November, 1994), and should be selected to demonstrate resolution and precision.

And for consistency with the ICH Q2b section on system suitability (Section 9):

System suitability testing is recommended as a component of many analytical procedures,

Section VI.J.2, lines 252-255 CONTENT AND FORMAT OF ANALYTICAL PROCEDURES FOR NDAs, ANDAs, BLAs, AND PLAs, Reporting of Results, Impurities Analytical Procedures

In order to further incorporate biologic products into the guidance document and to maintain consistency with the definitions of impurities as set forth in ICH-Q6B, Chiron Corporation recommends the following revised wording:

The ~~name and location~~ identifier and location (e.g., retention time (RT), relative retention time (RRT)) of impurities and the type of impurity (e.g., process-related, product-related [degradant], excipient degradant) should be included in the analytical procedures for impurities in the drug substance and drug product. For biologic products, information regarding product-related substances should be excluded from the section Impurities Analytical Procedures. Instead, this information should be included in the product characterization documentation section of the marketing application.

Section VII.A.1, line 300 METHODS VALIDATION FOR NDAs, ANDAs, BLAs, AND PLAs, Noncompendial Analytical Procedures, Validation Characteristics

Chiron Corporation recommends that "Robustness" be eliminated from the list of typical validation characteristics, as it is not included in the list of characteristics in ICH-Q2A. In fact, ICH-Q2A specifically states "It should be noted that robustness is not listed in the table but should be considered at an appropriate stage in the development of the analytical procedure." In concurrence with the ICH, Chiron Corporation believes robustness should be addressed during development and through validation of intermediate precision.

Section VII.A.2 METHODS VALIDATION FOR NDAs, ANDAs, BLAs, AND PLAs, Noncompendial Analytical Procedures, Other Methods Validation Information

As expressed in the GENERAL COMMENTS section of this letter to the Agency, many aspects addressed in this guidance document are either beyond the scope of what is required by ICH or not normally provided within analytical methods validation documentation. Specifically, Chiron Corporation recommends the following revisions:

- Deletion of lines 303-304, as they are beyond the scope of the ICH-Q2 documents

- Deletion of line 311, as this information is included within the stability documentation and is not generally considered appropriate for inclusion in the methods validation documentation.
- For consistency and clarity within the guidance document, line 312 should be revised as follows: “Impurities labeled with their ~~names and location~~ identifiers and location...”
- Deletion of “and characterization” from line 317, as characterization is not considered part of analytical methods validation.
- Deletion of lines 324-325, as this information belongs in the characterization section of the marketing application, and deletion of lines 327-328, as this information belongs in the stability section of the application.
- Lines 329-330 describe one of the elements of accuracy. If this information is to be included in the guidance document, Chiron Corporation recommends that this be discussed in a section describing how to demonstrate accuracy, rather than in a section on drug product.
- Lines 331-332 describe one of the elements of specificity. If this information is to be included in the guidance document, Chiron Corporation recommends that this be discussed in a section or definition of how to demonstrate specificity, rather than in a section on drug product.

Section VII.A.2.a & b METHODS VALIDATION FOR NDAs, ANDAs, BLAs, AND PLAs, Noncompendial Analytical Procedures, Other Methods Validation Information

Chiron Corporation suggests that the section requesting more detail on robustness and stress studies be eliminated from the guidance document, as it is beyond the scope of the ICH-Q2 documents and is addressed during method development (robustness) or in the stability documentation (stress studies).

Section VII.A.2.c.i, lines 376-377 METHODS VALIDATION FOR NDAs, ANDAs, BLAs, AND PLAs, Noncompendial Analytical Procedures, Other Methods Validation Information, Instrument Output/Raw Data, Organic Impurities

Chiron Corporation recommends that the sentence “Assumptions should be discussed and justified” be deleted from the guidance document. This information should be included in the rationale for the determination of release specifications.

Section VII.A.2.c.ii, lines 380-383, 387-388 METHODS VALIDATION FOR NDAs, ANDAs, BLAs, AND PLAs, Noncompendial Analytical Procedures, Other Methods Validation Information, Instrument Output/Raw Data, Drug Substance

Chiron Corporation recommends that the sentence "Complete impurity profiles as graphic output (e.g., chromatograms) and raw data (e.g., integrated peak areas) of representative batches should be submitted in the sections on analytical procedures and controls for the drug substance" be deleted from the guidance document, as it refers to information that is to be submitted in separate sections.

In addition, the sentence on lines 387-388 "The analytical procedure used should be capable of differentiating changes, if any, between past and present batches" should be deleted. Differentiation between past and present batches is contained within the characterization and comparability section of the application, and is not an element of analytical methods validation. Often multiple analytical procedures are required to identify and quantitate impurities. Individual analytical procedures, depending on their functionality, may not be able to differentiate changes "if any" between batches.

Section VII.A.2.c.ii, lines 393-397, 401-403, 407-408 METHODS VALIDATION FOR NDAs, ANDAs, BLAs, AND PLAs, Noncompendial Analytical Procedures, Other Methods Validation Information, Instrument Output/Raw Data, Drug Product

Chiron Corporation recommends deleting lines 393-397 and 401-403 as they refer to data that should be provided in other sections of the marketing application.

As was recommended for lines 387-388 for drug substance, lines 407-408 should be removed from the drug product section.

Section VII.A.2.c.ii, line 439 METHODS VALIDATION FOR NDAs, ANDAs, BLAs, AND PLAs, Noncompendial Analytical Procedures, Other Methods Validation Information, Instrument Output/Raw Data, Recommended Validation Characteristics for Types of Tests

As per previous comments regarding robustness, Chiron Corporation recommends that line 439 be removed from Table 1 as this is beyond the scope of the ICH Q2A guidance document and is more appropriately examined during assay development than during method validation.

Section VII.A.3, line 424 and line 425 METHODS VALIDATION FOR NDAs, ANDAs, BLAs, AND PLAs, Noncompendial Analytical Procedures, Recommended Validation Characteristics for Types of Tests

For consistency and comprehensibility in this section, Chiron recommends that the phrase "those types of tests" on line 424 be replaced with "specific tests".

In order to direct the reader to further guidance regarding developing and validating particular methodologies, Chiron recommends that the following sentence be added to line 425 as the last sentence of the paragraph (see related comments on page 7 of this response):

For further guidance regarding development of methodologies (such as HPLC, GC, CE, etc.) and suggestions for validation of these methods, consult Appendix 1.

Section VIII.A, lines 496-498 STATISTICAL ANALYSIS, General

As it is difficult to define when exactly is the "start" of a validation study, Chiron Corporation recommends the following revised wording:

The statistical procedures for the analysis of the validation data should be ~~determined~~ specified prior to the start of any validation study analysis.

Section XI.A.1.a METHODOLOGY, High-Pressure Liquid Chromatography (HPLC), Column, Column Parameters

Chiron Corporation recommends adding "System requirements: biocompatible, dwell volume" to the list of column parameters.

Section XI, line 695-698 and 788-791 METHODOLOGY, High-Pressure Liquid Chromatography (HPLC) & Capillary Electrophoresis, System Suitability

It is not always possible to achieve complete resolution between the active ingredient and the closest eluting "impurity" using a particular HPLC method. Therefore, resolution of the "impurity" may need to be defined by comparison with a different peak than the active ingredient. Therefore, Chiron Corporation recommends the addition of the following sentence at lines 698 and 791:

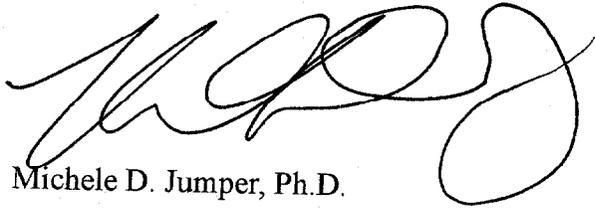
...should be given. Choice of peaks should be justified.

Section XI, lines 754-755, 811-812, 840-843 METHODOLOGY, Spectrophotometry, Spectroscopy, Spectrometry and Related Physical Methodologies

The descriptions contained within Section XI are not consistent between methodologies. In addition, characteristics of validation are described elsewhere in both the guidance document and the ICH-Q2A. Therefore, Chiron Corporation recommends deleting references to validation characteristics within Section XI (lines 754-755, 811-812, 840-843).

Enclosed, please find an electronic copy of these comments.

Thank you for your attention,

A handwritten signature in black ink, appearing to read 'M. Jumper', with a large, stylized flourish at the end.

Michele D. Jumper, Ph.D.

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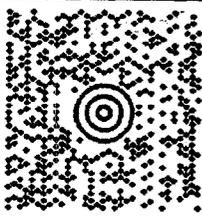
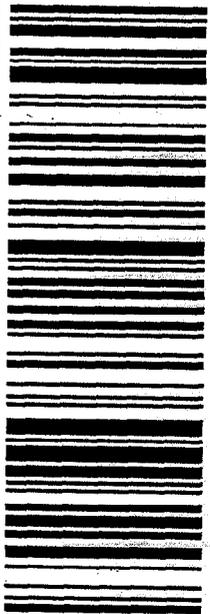
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<p style="text-align: right;">LTR 1 OF 1</p> <p>MICHELLE L REPOSE 510-923-5527 CHIRON CORPORATION 4560 HORTON STREET EMERYVILLE CA 94608</p> <p>SHIP TO: CDER 301-827-5849 FOOD AND DRUG ADMINISTRATION 5630 FISHERS LANE, ROOM 1061 DOCUMENT MANAGEMENT BRANCH HRA-305 ROCKVILLE MD 20852</p>	<p style="font-size: 2em; text-align: center;">MD 207 9-04</p>  	<p style="text-align: center; font-weight: bold; font-size: 1.5em;">UPS NEXT DAY AIR</p> <p style="text-align: center; font-size: 2em; font-weight: bold;">1</p> <p>TRACKING #: 1Z 966 667 01 9271 2961</p>		<p style="text-align: center;">BILLING: PREPAID</p>  <p style="font-size: 0.8em; text-align: right;">UPS 02.00.22c Mozilla/4.72 [en] (W60NT; U)</p>
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