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

Re: Docket No. 00D-1424-FDA Draft Guidance for Industry on Analytical Procedures and Methods Validation: Chemistry, Manufacturing, and Controls Documentation (Federal Register/ Vol. 65, No. 169/ August 30, 2000).

Dear Sir/Madam:

B. Braun is pleased to have the opportunity to offer comments on the draft Guidance for Industry Analytical Procedures and Methods Validation. The general and specific comments/suggestions are as follows:

General Comment:

Biologics should be excluded from the guidance, since ICH specifically calls out a separate document for validation of analytical methods associated with biologics.

Specific Comments:

1. Section IV. Reference Standards

A. Types of Standards

The draft guidance states, a *working standard* (i.e., in-house or secondary standard) is a standard that is qualified against and used instead of the reference standard. However, "working standard" is commonly used in a different context. Normally it means a diluted standard preparation. Therefore we suggest, line-142, 143, should read: A *secondary standard* (i.e., in-house standard) is a standard that is qualified against and used instead of the reference standard.

2. Section IV. Reference Standards

B. Certificate of Analysis

The sentence on Line 148 to 149, should be changed to read " For standards from official sources, the user should ensure the suitability of the reference standard *for its intended use*."

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3. Section IV. Reference Standards
 - C. Characterization of a Reference Standard
 - 3.1. The definition of "quality" for reference standards on line 157 is not clear. Specific criteria for the quality should be included.
 - 3.2. Lines 157-159 reads: The qualitative and quantitative analytical procedures used to characterize a reference standard are expected to be different from, and more extensive than,.....drug product. We suggest it should read: The qualitative and quantitative analytical procedures used to characterize a reference standard are expected to be different from, and more extensive than,.....drug product.
 - 3.3. The characterization information presented is appropriate for a drug substance primary standard but is excessive for drug impurity or degradant reference standards. Specifically, the method of manufacture of an impurity or degradant standard may be proprietary and the details of the manufacturing process are not available to the end user (bulk drug or dosage form manufacturer). This does not detract from the validity of the reference standard, particularly since its synthesis method is very likely different than that of the drug substance the impurity/degradant is associated with.
 - 3.4. The guidance should present the expectations for characterization of a secondary standard. A secondary standard of a drug substance should meet the bulk drug testing requirements (such as USP monograph requirements), with additional measures taken in characterization of potency.
 - 3.5. We suggest to change "empirical formula" on line 179-180 to "molecular formula".
4. Section VI. CONTENT AND FORMAT OF ANALYTICAL PROCEDURES FOR NDAs, ANDAs, BLAs, AND PLAs
 - B. Sampling

According to the draft guidance the number of samples selected, how they are used and the number of replicates analyses per sample should be described in an analytical procedure. We suggest to have a separate document for sampling information.
5. Section VI. CONTENT AND FORMAT OF ANALYTICAL PROCEDURES FOR NDAs, ANDAs, BLAs, AND PLAs
 - J. Reporting of the Results
 1. General

According to the draft guidance: "The specific number of significant figures to be reported on the results should be provided according to the draft guidance." This can not be easily done since it will depend on balance/equipment. Additionally, it will vary in each laboratory.

6. VII METHODS VALIDATION FOR NDAs, ANDAs, BLAs, AND PLAs
 - 6.1. Information of drug chemistry, including organic/inorganic impurities, degradants, isomers, and degradation pathways should be separated from analytical method validation. This important information is used in the development of the analytical testing scheme of drugs substance and drug products but is not appropriate within the method validation study. We do acknowledge that selected impurity/degradant/isomer information may be needed to substantiate the method validation acceptance criteria.
 - 6.2. The guidance does not discuss establishment of acceptance standards for the analytical method validation. B. Braun feels it is important to define acceptance criteria for key method characteristics such as precision, accuracy, and specificity in advance of the validation studies. B. Braun is not proposing that specific acceptance criteria be included in the guidance.
7. Intermediate Precision versus Ruggedness: The guidance uses the term intermediate precision in several places. We recommend use of the term ruggedness to remain consistent with USP <1225> terminology.
8. Section X.A.

HPLC column characteristics for frit size and filter type are not commonly provided by the column manufacturers. This information is generally known only when an external in-line filter is employed.
9. Section X. C.

The guidance specifies validation of specificity, linearity, repeatability, intermediate precision, and robustness for spectrophotometric, spectroscopic, and related methods. This section should instead refer to table 1 for validation challenge requirements.
10. Section X. E.

The guidance calls for a validation criterion of specificity for optical rotation. This should be clarified to call for a justification of using optical rotation in the drug product formulation, since optical rotation is inherently nonspecific between optically active compounds.
11. A Standard/sample stability challenge should be included in the validation and justified by the investigator.
12. XI. METHODOLOGY
 - A. High-Pressure Liquid Chromatography (HPLC)
 1. Column

The criteria for establishing "equivalency of columns" is not defined. System suitability alone may not be sufficient to establish equivalency. Each investigator should establish and justify chosen criteria.

Sincerely,

Pushpa Mehta

Pushpa Mehta
Senior Regulatory Affairs Analyst

PM:rz

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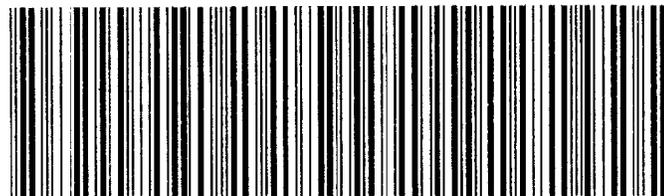
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