Considerations and Observations when Validating and Verifying Drug Substance/Drug Product Assay or Related Substance Methods for ANDA Submissions.

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BACKGROUND

This poster focuses on some of the deficiencies observed in Abbreviated New Drug Application (ANDA) submissions and these are related to drug substance/drug product related substance method verification and validation, including system suitability criteria establishment, etc. In general, four categories of analytical methods have been identified in submissions: (I) methods adopted from the USP; (II) inhouse method that is equivalent to compendial method; (III) in-house method when a compendial method cannot be applied; and (IV) in-house method when a compendial method is not available. We will present observations and considerations for each category that illustrate the scientific and regulatory issues and potential impact on decision making. These examples are from Module 3 (CMC) documents in ANDA eCTD submissions.

I Compendial procedure

Observations: Standard accuracy not verified

In this example, impurity method is compendial, performed method veriﬁcation. During the assessment, we noted that the peak area of the same concentration impurity standard used for stability sample determination was quite different (see highlighted content in table below); only one standard was injected, firm didn’t check the standard accuracy during measurements. The impurity calculation didn’t use the mean peak area of standard, which is different from the provided equations.

Typical sample chromatogram using USP Assay method (214 nm)

Assessor’s Observations:

- API 1’s peak height is very low, AU is less than 0.02.
- Possible interference from diluent or mobile phase, especially at detection wavelength 214 nm, more variability could be observed in API 1’s quantitation. (No data was provided.)

Summary of good practices regarding method verification or validation based on category of method

Based on the provided data and firm’s justification to control degradants A and B as unknown impurities, we requested firm to provide the LOQ and accuracy at LOQ level to demonstrate that the method is suitable to monitor these degradants. In the response, firm provided data for LOQ and method accuracy at LOQ level for degradants A and B, LOQ is 0.05% which is sufficient for 0.2% spec level for the two degradants, accuracy data was also found adequate.

Summary of good practices regarding method verification or validation based on category of method

Adopting USP procedures are the most straightforward approach. In-house procedures in place of USP should be fully validated according to USP <1225> and relevant FDA guidance. Fully validated in-house methods may be needed if USP methods are not compatible with a specific drug product. In response to agency’s comments, sufficient data and justification are very helpful for product quality assessment.

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Disclaimer

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Reference


III USP method is not compatible the submitted drug substance or drug product, so in-house method is developed

Observation: This is a two APIs drug product. Large dose differences exist between the two APIs (API 1) 5 mg/(API 2) 300 mg. The assay method is an in-house procedure. Firm performed method validation and the validation results met acceptance criteria and the USP requirements. However, firm did not provide Method Comparative Study to demonstrate the equivalence of USP & In-House Assay methods; the Assay System Suitability acceptance criteria doesn’t have a resolution requirement which is required in the USP monograph; per review cycle #1, we request firm to provide method equivalence data and revise system suitability to include resolution requirement.

In the 1st cycle response, resolution was included in the system suitability criteria and met the USP monograph requirement; firm stated that the method equivalence study could not be provided due to one of the drug substances (DS) peak is too small to be integrated. Firm didn’t provide any data and chromatograms using the USP assay method in the submission; reviewer could not differentiate how small of the DS peak that is difficult to be integrated. As per review cycle #2, we request firm to:

- Provide the corresponding chromatograms
- Petition the USP for adding their in-house assay method into the USP monograph since the USP assay method could not be applied to their drug product.
- Acknowledge the method specified in the USP monograph is the regulatory method that will prevail in the event of a dispute.

In the 2nd cycle response, firm provided assay chromatogram and justified that the USP assay method is not suitable for OP based on two observations:

- DS peak elutes very close to the solvent front as seen in chromatograms
- Furthermore, due to the low concentration of API 1 in solution (5µg/mL) and at the UV wavelength of the detector (214nm), quantitation of content of API 1 in finished drug product could be problematic.

Summary of good practices regarding method verification or validation based on category of method

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