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

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This poster will present and discuss key elements for a drug substance/drug product related substance method verification and validation, including system suitability criteria establishment, etc. There are usually four categories of analytical methods have been identified in submissions: method adapted from the USP; in house method and equivalent to compendial procedure; interference found in USP method hence in-house method applied; and complete in-house method without a corresponding compendial method. We will present observations and considerations for each category to illustrate the scientific and regulatory issues and potential impact on decision making and ending with a summary. These examples are from Module 3 (CMC) documents in ANDA eCTD submissions.

I. Compendial procedure
   - ❖ System suitability requirement for checking standard accuracy.

II. In-house procedure and equivalent to compendial procedure
   - ❖ In house method verified based on USP <1225> Category II, and found adequate.
   - ❖ In house method is verified via determining samples by in house and compendial procedure parallel, and results are found comparable. The established system suitability of in house method complies with the USP.

III. USP method doesn't work on the submitted drug substance or drug product, so In-house method is developed.
   - ❖ Drug substance impurity method is an in-house procedure, firm sufficiently validated the method based on USP <1225> Category II recommendations, provided method equivalency study, and illustrated the rational of not being equivalent to the USP monograph procedure, although the in-house system suitability is different from the compendial method.
   - ❖ Drug product assay method is in a house procedure, firm could not provide method equivalency study. Upon review of the submission, the agency asked for additional chromatograms for justification. After two cycles of communication with firm, the agency recommended that the firm petition USP to add the in-house method in the monograph and acknowledge the method specified in the USP monograph is the regulatory method that will prevail in the event of a dispute.

IV. In-house method without a corresponding compendial method
   - ❖ Additional method validation request for drug product degradants

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

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