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 focusses 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) method 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 to 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, firm 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.

ID	Area	Actual Conc (mg/mL)
Standard	4352.1849	0.0005155
Release sample	4280240.8568	0.5000000
Standard	4300.7021	0.0005023
3M sample	4363787.1308	0.5000000
Standard	2680.5894	0.0005058
6M sample	2745794.7706	0.5000000
Standard	4291.2893	0.0005056
9M sample	4165112.1007	0.5000000
Standard	5209.6192	0.0005028
12M sample	5122290.4025	0.5000000
Standard	4138.3418	0.0005081
18M sample	4076486.5678	0.5000000

Calculation:

$$\%impurity = \frac{Rimp}{Rstd} \times \frac{Wstd \times P}{Vstd} \times Dstd \times \frac{Vsam}{Wsam} \times \frac{ATW}{LC} \times 100$$

Rstd = Mean area response of XXX in bracketing standard injections

Considerations: in the sample determination, standard accuracy should be checked in bracketing standard injections, at least two standard solutions should be injected.

II In-house procedure and equivalent to compendial procedure

Observations: Absent method equivalency study

Firm developed and validated In-house method for assay or impurity/degradant. The method validation can be based on USP <1225>, ICHQ2 (R1) and FDA guidance for industry July, 2015: Analytical Procedures and Methods Validation for Drugs and Biologics, etc.

Besides the full method validation, if there is a compendial procedure, method equivalency study is always required to demonstrate that the in-house procedure is equivalent to the compendial procedure.

Sometimes, we could not locate the method equivalency / comparability study in the submission and we will request it.

Considerations:

Sample preparation

For impurity or degradants method equivalency study, spiked samples are recommended when the level of individual impurities are lower than LOQ or not detected in un-spiked samples.

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 difference exists 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 resolution requirement which is required in the USP monograph; per review cycle #1a, we request firm to provide method equivalency data and revise system suitability to include resolution requirement.

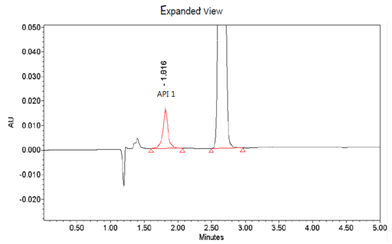
In the 1st cycle response, resolution was included in the system suitability criteria and met the USP monograph requirement; firm stated that the method equivalency study could not be provided due to one of the drug substance (DS) peak is too small to be integrated. Firm didn't provide any data and chromatograms 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 #1b, we request firm:

- 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 DP 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 (3µg/mL) and at the UV wavelength of the detector (214nm), quantitating the content of API 1 in finished drug product could be problematic.

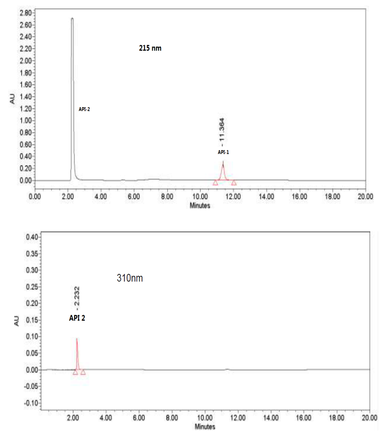
Typical sample chromatogram using USP Assay method (214 nm)



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.)

Typical sample chromatogram using In-house Assay method (215 nm & 310 nm)



Assessor's Observations:

- API 1's peak height increased, AU is about 0.3, API 1's concentration in sample is ~150 µg/ml.
- No mobile phase or diluent interference.
- Two detection wavelength were selected for assay.

Consideration:

Sufficient data is needed for agency to make efficient assessment and proper decision. Firm petitioned USP to consider adding the in-house assay method in the USP monograph, and acknowledged that the USP monograph method is the regulatory method that will prevail in the event of a dispute. Firm's justification for the in-house validated method is acceptable.

IV In-house method without a corresponding compendial method, additional method validation request for drug product degradants

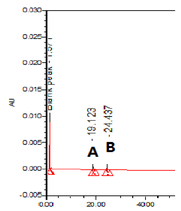
Observations:

This is a two API ANDA. During the assessment, we found firm did not control two known degradants A and B. Therefore, per review cycle #1, we recommended firm to include the two impurities in drug product release and stability specifications or provide justification. We also requested firm to demonstrate the impurity method is capable of monitoring the two degradants.

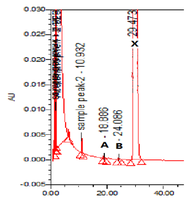
In the 1st cycle response, firm verified that the established degradants method is specific for A and B, the retention time was ~20.5 minutes and ~24.9 minutes respectively, no interference from all other peaks. Firm did not perform full method validations for the two degradants. However, all stability chromatograms from release up to 6M ACC and 12M CRT storage conditions were evaluated for presence of A and B peaks. There was no peak found in any of stability chromatograms.

Based on obtained chromatograms for three lots of each strength on stability, it can be justified that if present, A and B will be reported on stability as as unknown degradants with limit NMT 0.2%.

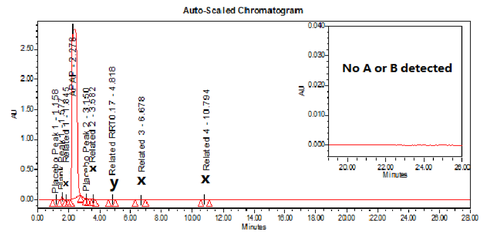
Representative Chromatogram of Std. A and B at LOQ of 0.05%



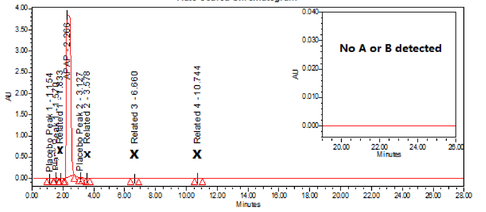
Representative Chromatogram of drug product Sample (LotRD16010) Spiked with A&B at LOQ (0.05% Level)



Representative Chromatogram (from 0 to 180 min) of drug product Sample (Lot RD16010) 6 M at Accelerated Condition



Representative Chromatogram (form 0 to 180min) of drug product Tablets Sample (Lot RD16010) 12 M at Long Term Condition



For space limit, HPLC chromatogram (28-180 min) is not shown in poster.

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

Views presented in this poster do not necessarily reflect those of the Food and Drug Administration.

Reference

USP <1225>, <1226>, <1224>, <621>. FDA Guidance for Industry: Analytical Procedures and Methods Validation for Drugs and Biologics, July 2015.