

Common Deficiencies Related to LC and GC Methods in Type II DMFs

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Scope and Objective

- Discuss commonly observed issues related to LC and GC analytical methods in DMF submissions
 - Easily Correctable Issues
 - Common Issues Related to Analytical Procedures
 - Common Issues Related to Method Validation
- Present expectations from CMC perspective
- Assist industry to prepare DMFs with improved quality and avoid unnecessary review cycles

Easily Correctable Issues Related to Analytical Procedures

- Referencing a compendial method without providing a description of analytical procedures
- No information regarding the name of manufacturer, the brand of an analytical column
- System suitability not being demonstrated throughout a whole analytical run
- Misusing “ppm” while it actually means “ $\mu\text{g/mL}$ ”

Easily Correctable Issues

Related to Analytical Procedures (cont'd)

- No caution statement in the method when special sample handling is needed, especially for highly hygroscopic DS, unstable standard/sample solution
- No reporting or discarding threshold stated in the method of determining impurities
- Multiple sample preparations or multiple injections of the sample solution without predefined criteria of accepting results in the method

Common Issues Related to Analytical Procedures



- Inadequate system suitability acceptance criteria
 - %RSD of replicate injections of the standard solution not following USP<621> for assay
 - No demonstration of the system sensitivity when determining impurities and residual solvents
 - No or inadequate resolution criterion for closely eluted peaks
 - No peak tailing acceptance criterion especially using an isocratic method
 - System suitability acceptance criteria not justified by the validation data

Common Issues Related to Analytical Procedures (cont'd)

- Using the chromatographic purity of a DS standard as the potency of the DS standard
- Exceeding the validated range when modifying the chromatographic conditions of a compendial or a validated method
- Using a different column when adopting a compendial method without demonstrating the column equivalency

Case Study 1 – Modifying chromatographic conditions



- Scenario – Firm proposes to increase the injection volume for a compendial impurity HPLC method. The impurity content is determined by peak normalization.

$$\% \text{Impurity} = 100(r_i / r_s)$$

r_i is the peak response for each impurity

r_s is the sum of the responses of all the peaks

- Concerns
 - Whether the previously validated linearity range still applies
 - Whether the RRF of each specified impurity changes

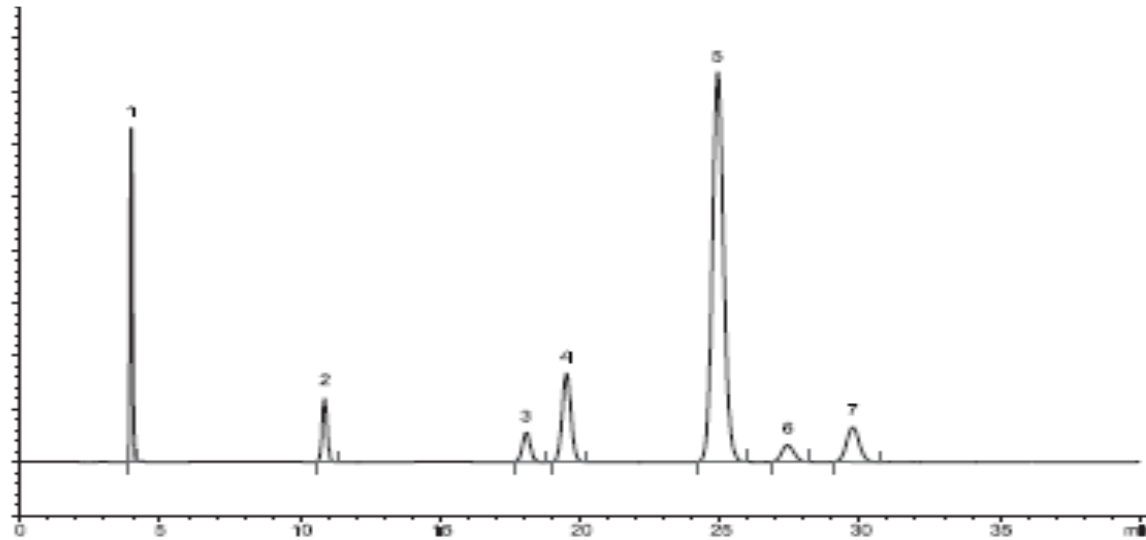
Case Study 1 (cont'd)

- Request the firm to
 - Re-validate the linearity
 - Re-calculate the RRF of each impurity per the slope ratio
 - Re-validate the accuracy
- Result

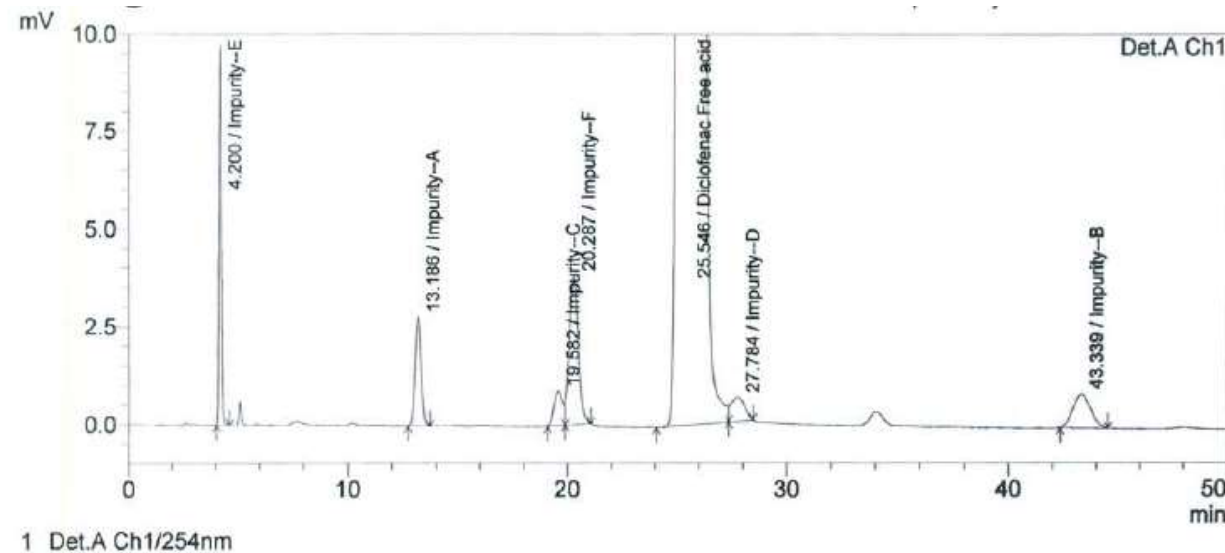
| Name of analyte | Slope | RRF | CF |
|-------------------------------|--------|------|------|
| API (80-120% of sample conc.) | 175931 | 1.00 | 1.00 |
| Impurity 1 | 226652 | 1.29 | 0.78 |
| Impurity 2 | 232180 | 1.32 | 0.76 |
| Impurity 3 | 291579 | 1.66 | 0.60 |
| Impurity 4 | 162810 | 0.93 | 1.08 |

- Except the impurity 4, the RRFs of other impurities exceed the range of 0.8-1.2

Case Study 2 – Column Equivalency



Column used by USP



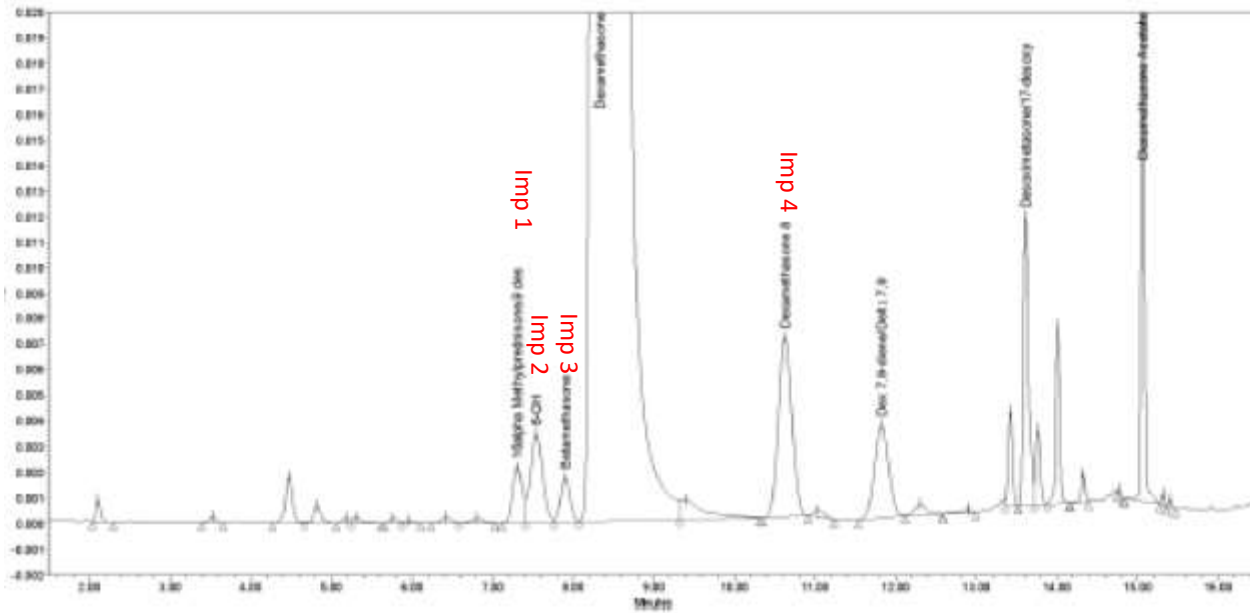
**Column used by
the DMF holder**

Common Issues Related to Method Validation

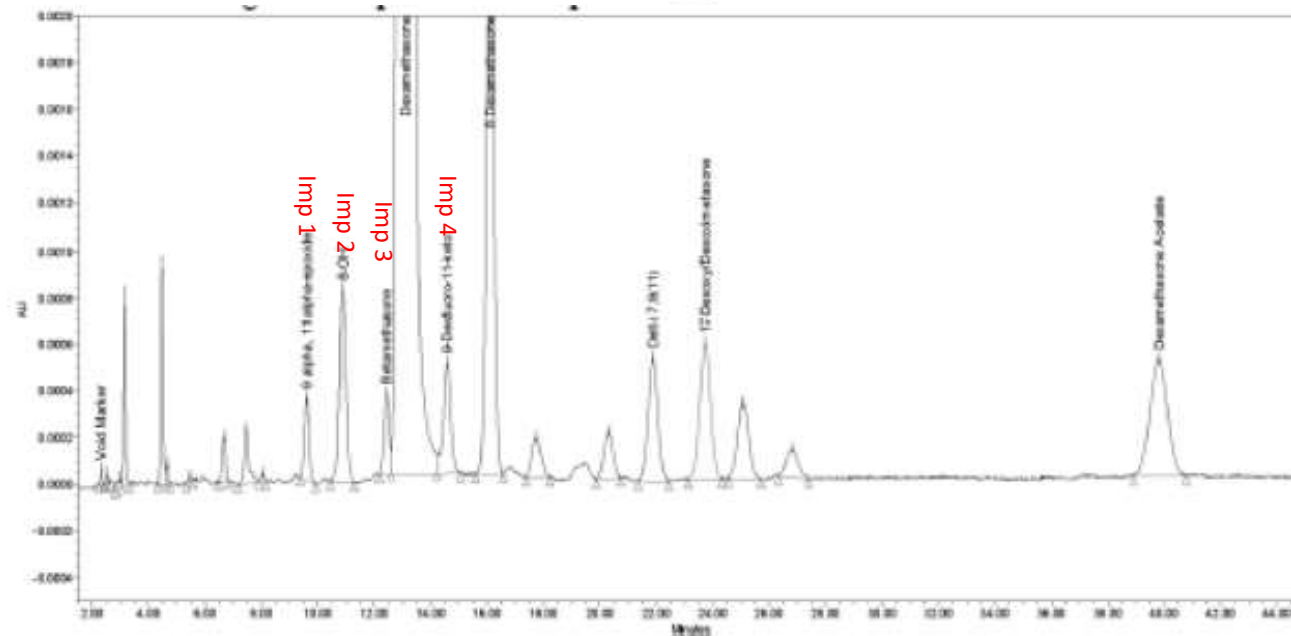


- Implementation of a USP method without verification
- Missing a method equivalency study
 - Using an in-house method instead of a USP monograph method
 - Replacing an in-house method with a USP monograph method

Case study 3 – Method Equivalency



USP method



In house method

Case study 3 – Method Equivalency



| Impurity | USP | In house |
|------------|--------|----------|
| Impurity 1 | ND | <0.05 |
| Impurity 2 | 0.0660 | 0.0625 |
| Impurity 3 | ND | 0.0993 |
| Impurity 4 | <0.05 | <0.05 |
| Impurity 5 | 0.2494 | 0.2548 |
| Impurity 6 | 0.0628 | 0.0972 |
| Impurity 7 | 0.1323 | 0.1190 |
| Impurity 8 | 0.1904 | 0.1836 |
| RRT 0.62 | 0.0982 | ND |
| RRT 1.60 | 0.0741 | ND |
| RRT 1.63 | 0.0501 | ND |
| RRT 1.65 | 0.0592 | ND |
| RRT 1.90 | ND | 0.0677 |
| Total | 0.9832 | 0.8842 |

Common Issues Related to Method Validation



- Unjustified detection wavelength (LC-UV)
- Calculated or extrapolated DL & QL without confirmation

Detection Limit (DL)

$$DL = \frac{3.3 \sigma}{S}$$

Quantitation Limit (QL)

$$QL = \frac{10 \sigma}{S}$$

where σ = the standard deviation of the response
 S = the slope of the calibration curve

Common Issues Related to Method Validation (cont'd)



- Missing linearity data of DS in the range of QL-120% of spec limit for an impurity HPLC method
- Using a very clean DS sample for validation of an impurity method
 - Method precision, intermediate precision
 - Robustness
- Providing raw data unable to be used directly for assessment
 - Peak area used for demonstration of method robustness
 - Peak area used for method precision and intermediate precision

Common Issues Related to Method Validation (cont'd)



- Missing or inadequate forced degradation study
 - Inadequately stressed or overly stressed sample
 - Not the same stressed sample analyzed by the assay and impurity methods
 - Unaddressed mass imbalance

Case Study 4 – Mass Imbalance

- Scenario – Assay result for the thermal degradation sample is 83.2%, while only 2.6% of total impurities are found by the related substance HPLC method. Significant mass imbalance is observed.
- Concern – Degradants are not detectable by the related substance method.
- Request the firm to investigate the root cause
 - A much late eluting peak at ~35 minutes was observed
 - A new HPLC was developed using the column with a different stationary phase
 - Analyzed the same stressed sample with the old method and the new method

| Stressed condition | Assay (w/w) | Total impurities | Total mass |
|--------------------|-------------|------------------|------------|
| Control | 99.6% | 0.2% | 99.8% |
| 105°C/48 h | 83.2% | 2.8% (Method 1) | 86.0% |
| 105°C/48 h | 83.2% | 14.9% (Method 2) | 98.1% |

Common Issues Related to Method Validation (cont'd)

- No demonstration of the extraction efficiency when a DS sample is not totally dissolved
 - Spiked sample suitable for a totally dissolved DS sample
 - Simulated sample suitable for a partially dissolved DS sample

Case Study 5 – Validation of the Sample Preparation



- Scenario – An LC-MS was developed to quantify GTIs at a trace level. The DS sample cannot be completely dissolved due to the limited solubility. The method accuracy was validated by spiking the DS with a GTI stock solution.
- Concern – The extraction efficiency of the sample preparation was not validated.
- Request the firm to use a simulated DS sample

Case Study 5 – Validation of the Sample Preparation (cont'd)

| Impurity | Accuracy | QL (3.75 ppm) | 50% spec. (18.75 ppm) | 100% spec (37.5 ppm) | 150% spec (56.25 ppm) |
|----------|-----------|------------------|--------------------------|-------------------------|--------------------------|
| GTI-1 | %Recovery | 76 | 90 | 107 | 105 |
| | %RSD | 1.5 | 2.4 | 2.5 | 0.4 |
| GTI-2 | %Recovery | 101 | 107 | 93 | 88 |
| | %RSD | 3.4 | 0.4 | 1.1 | 1.1 |

References



- ✓ USP <621> : Chromatography
- ✓ USP <467> : Residual Solvents
- ✓ USP-PF 39(5): Stimuli to Revision Process – System Suitability for USP Chromatographic Procedures – Small Molecules
- ✓ USP <1010>: Analytical Data – Interpretation and Treatment
- ✓ MAPP 5310.7 – Acceptability of Standards from Alternative Compendia (BP/EP/JP)
- ✓ FDA Guidance: Analytical Procedures and Methods Validation for Drugs and Biologics (2015)
- ✓ ICH Q2: Validation of Analytical Procedures: Text And Methodology
- ✓ FDA Reviewer Guidance: Validation of Chromatographic Methods (1994)
- ✓ USP <1225> : Validation of Compendial Procedures
- ✓ USP <1226> : Verification of Compendial Procedures

Thank You!

- For questions regarding the content of this presentation, please type them into the “Q&A Box” so that they can be addressed during the panel Q&A after this session.
- To submit questions on this presentation for inclusion in the Follow-on webinar on April 9th , send them by March 19th to: DMFWorkshop2021@fda.hhs.gov
- Please refer to the following presentations on March 4th for additional information:
 - *“Major and Common Deficiencies in DMFs”* by Wei Liu