Consultancy:
Technical Insights Series

How to author a robust validation of an analytical method for regulatory submission

Linda Cutler, a consultant at Regulink provides a short guide on how manufacturing site validation of would typically be formatted and summarised for regulatory submissions.

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Introduction

A robust 'Validation of an Analytical Method' for regulatory submission should provide a level of detail to satisfy the health authority that the method is fit for purpose, thereby reducing requests for further information, whilst minimising superfluous information.

Key concepts

Some key concepts which are discussed within this article include:

- CTD validation sections are usually not required for compendial analytical methods in EU and UK submissions (except for microbiological methods). US submissions, however, will generally require, at minimum, a verification of the analytical method.
- A cover page listing a summary of the analytical method validations with cross-referencing to each validation section will provide a clear overview and clarity for the assessor.
- Information already provided in the analytical method need not be reiterated in the validation and can be cross-referenced.
- Each validation parameter assessed should provide a brief description of the procedure, together with calculations, results, a discussion and a conclusion. These should align chromatograms or spectrograms (where applicable), with the information held in the protocol. Trending or results not meeting the acceptance criteria should be discussed and justified.

The purpose of this article is to provide some guidance on preparing common technical documents (CTD) for 'validation of analytical methods' (32S43, 32P43 and 32P53 sections) suitable

for regulatory submissions to health authorities, in particular in the EU, UK, and US markets. Regulatory validation of analytical methods can generally be less detailed than the testing laboratory's validation report and this article provides some hints and tips on the acceptable level of detail typically required by these health authorities. This article, however, does not endeavour to be a comprehensive guide to authoring the validation of analytical methods but aims to cover some areas which may help reduce the risk of questions.

The suggestions provided within this article have been previously used in regulatory submissions without further requests for information. However, there is no guarantee that a health authority will not request further information if they consider this necessary. In addition, this article is not intended to cover information provided in health authority guidelines and regulations, and these should be referred to when preparing any submission. Useful guidelines include ICH Q2(R2), FDA Analytical Procedures and Method Validation for Drugs and Biologics, USP <1225> Validation of Compendial Methods, and USP <1226> Verification of Compendial methods.

Cover Page

A cover page listing the validations provided for the analytical methods detailed in the specifications section (32S41, 32P41 and 32P51 as applicable), with crosslinking to each validation section, provides a helpful overview for the reviewer. This could be provided in a tabular form. The table below provides an example with a few selected method validations.

Table Validation of Analytical Procedures – [*Drug Product*]

Attribute	Test Method	3.2.P.5.3 Reference
Appearance	In-house procedure	Not Applicable
ID and Assay by HPLC	In-house procedure	[3.2.P.5.3 ID and Assay HPLC]
Related substances by HPLC	In-house procedure	[3.2.P.5.3 Related Substances HPLC]
pH	Ph.Eur. (2.2.3) / USP <791>	Not applicable

Where an analytical method complies with a compendial method, it is generally acceptable to refer only to the compendia when submitting an analytical method in the EU or UK. In addition, method validation is not usually required (except for microbiological methods). Reference to validation of the analytical methods in this instance can be denoted by 'Not Applicable' in the cover page. Other simple methods such as 'Appearance' may also not warrant validation.

There is, however, an expectation for US submissions to provide a method validation according to USP <1225 Validation of Compendial Methods or, at a minimum, a method verification according to USP <1226> Verification of Compendial Procedures, unless the analytical method is a basic compendial method. Examples of basic compendial procedures include, but are not limited to, loss on drying, residue on ignition, various wet chemical procedures such as acid value, and simple instrumental methods such as pH measurements (USP <1226> Validation of Compendial Methods).

Validation of Analytical Methods Presentation

Sub-headings within the validation of the analytical method, together with a table of contents, can aid review for lengthier method validations. Sub-headings could include, as applicable:

1 Validation Summary

2 Validation Procedure

2.1 Preparation of Reagents, Standards and Samples

2.2 Validation Program

3 Validation Parameters

3.1 Accuracy

3.2 Precision

3.2.1 Repeatability

Information generally required for each of these sections is provided in the numbered sections below.

1. Validation Summary

The validation summary should include a brief description of the method being validated and state, if applicable, that the method has been validated according to ICH guidelines, e.g. 'The analytical method for the determination of related substances in [drug substance] by HPLC has been validated according to ICH guidelines.' It may also be useful to state compendial compliance of the analytical method, if applicable.

A summary table of the validation results will also aid the reviewer. An example summary table detailing a few typical validation parameters is provided below.

Table Validation Summary

Validation Parameter	Acceptance Criteria	Result	Conclusion
Specificity	There should be no interference between the residual solvent peaks and any peaks attributable to the sample.	There was no interference between the residual solvent peaks and any peaks attributable to the sample.	Acceptance criterion was met.
Linearity	The correlation coefficient for each residual solvent should be ≥0.99.	Correlation coefficients: Residual solvent *A* 1.000 Residual solvent *B* 1.000 Residual solvent *C* 1.001	Acceptance criterion was met.
Precision as repeatability	The RSD must be ≤20%.	RSD: 0.8%	Acceptance criterion was met.
Accuracy	The average accuracy of each residual solvent must be 80 – 120%.	Accuracy range: 102.9 to 105.1% Mean: 104.4%	Acceptance criterion was met.

RSD: Relative Standard Deviation

2. Validation Procedure

2.1 Preparation of Reagents, Standards and Sample

It is only necessary to include steps which are not present in the analytical method. Such steps might include the preparation of spiked solutions and such preparations can often be presented in a tabulated form. Refer to the example below.

Table Preparation of spiked samples

Level	Sample	Total Volume	Spike Solution	Concentration of Spike Solution	Theoretical Value
L_0	100 mg	10 mL	0 mL	0.02 mg/mL Related Substance A in 0.5% Acetonitrile	0.00% w/v
L_1	100 mg	10 mL	1.5 mL		0.03% w/v
L_2	100 mg	10 mL	2.5 mL		0.05% w/v
L_3	100 mg	10 mL	3.0 mL		0.06% w/v
L_4	100 mg	10 mL	4.0 mL		0.08% w/v
L_5	100 mg	10 mL	5.0 mL		0.10% w/v

Reference with cross linking can be made to any steps already presented in the method e.g. preparation of standards, reagents, and samples. These do not need to be re-iterated within the validation.

2.2 Validation program

A table of validation parameters and testing criteria may aid review. An example table is provided below.

Table Validation program

Test set	Analyst	Validation day	System (Instrument)	Concentration Levels / Parallels P_0	P_1	P_2	P_3	P_4	P_5	Validation parameters
1	1	1	1	6	6	6	3	6	3	Specificity Accuracy as Recovery Precision as Repeatability Intermediate Precision Linearity QL/DL
2	1	1	2	3	-	-	-	6	-	Intermediate precision
3	2	2	3	3	-	-	-	6	-	Intermediate precision

QL/DL Quantitation Limit/Detection Limit
P_x Sample Solutions

Note: Instruments used for intermediate precision can be referred to as Instrument 1, 2, 3 etc. without the need to detail makes, models, serial numbers. Similarly, Analysts and Days can also be provided numerically without further detail.

3. Validation Parameters

Each validation parameter can be provided under a separate sub-heading for clarity and should include the following. Details provided should align with the validation protocol.

- **Introductory paragraph**

  This should describe briefly how the validation was performed. Apparatus, reagents, standards, and samples used in the analytical methods can be cross-referenced to and do not need to be described again in the validation.

- **Acceptance criteria**

  The acceptance criteria or criterion should be provided.

- **Calculations**

  Any calculations or equations, unless simple and obvious, should be included. Units of measure should be stipulated for each parameter within the equation or equation footnote.

- **Results**

  Results are typically tabulated where feasible. An example chromatogram and/or spectrogram should be provided for each sample, blank or standard as applicable. These can be included under the 'Results' section or provided in a 'Chromatograms and spectrograms' sections at the end of the method validation.

- **Discussion and conclusion**

  A brief conclusion should be provided stating where acceptance criteria have/have not been met. Trending or out of scope data should be discussed and justified. Deviations from protocol may also need to be discussed.

  An overall discussion and conclusion may be provided to state that all results met acceptance criteria (as applicable) and that the analytical method is suitable for use.

- **Chromatograms and spectrograms**

  Example chromatograms and spectrograms can be included in each validation parameter section or in a separate section at the end of the validation report.

Conclusion

A well authored and presented validation of an analytical method containing the optimal level of information should decrease health authority review time and requests for information. Standardisation of the format and level of information presented will also allow for consistency across dossiers and reduce ongoing authoring time on method validation sections.

REGULINK

Regulink is a UK based specialist regulatory consultancy and was established in 2014 by veterans, Stuart Reed and Sunil Singh. They provide expert-led Regulatory Affairs solutions to the life sciences industry for the UK and Europe.