Procedure: Analytical Method Validation

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# Purpose

This procedure describes a system, provides instructions and assigns responsibilities for validating analytical test methods at [Company].

# Scope

The scope of this procedure includes validation of analytical methods for use in the testing of raw materials, in-process samples and finished bulk product manufactured to good manufacturing practice (GMP).

# Responsibilities

Amend as appropriate

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| --- | --- |
| Role | Responsibility |
| Quality Manager | Ensures that all laboratories, including contract laboratories, comply with this procedure. |
| Quality Control (QC) and Research and Development (R&D) chemists/staff | Complete required activities described in this procedure. |

# Occupational health, safety and environment

Chemicals, materials, reagents and solvents used in the manufacturing process are hazardous and potentially harmful to the environment. Material Safety Data Sheets (MSDS) must be supplied with the samples sent to contract laboratories and samples received from external sources. Furthermore, the analysts testing the materials must be trained in the safe use of the material and have ready access to MSDSs at all times.

# Procedure

## General validation requirements

Validation of methods is performed to demonstrate that the methods used are suitable for their intended use and that the analysts and equipment are suitable and qualified. Validation demonstrates that the methods used are qualified to confirm the identity, strength, quality, purity and potency of the product under test.

Analytical methods are fully validated unless the method is from a recognised pharmacopoeia or other international or national standard. Recognised standards include the USP/NF and the BP. These methods (compendial methods) will not require full validation when used as detailed in the pharmacopoeias but will require qualification to demonstrate that they are suitable for the application under actual working conditions (verification).

Analytical methods from pharmacopoeias must be used in their entirety. Tests cannot be left out or substituted for tests from other pharmacopoeias. If this does occur the justification must be documented and reported to the TGA.

Where there is no current standard analytical method then a method will need to be fully developed and validated. Validation is to be performed as described in the ICH Q2(R1) Validation of Analytical Procedures: Text and Methodology. The FDA draft guidance document, Analytical Procedures and Methods Validation may also be a useful reference.

Complete documentation of all method validation and any subsequent changes to validated methods is required.

Appropriate qualification of analytical equipment is to be considered prior to the validation of any analytical methods.

## Compendial analytical procedures

Qualification of compendial procedures will include:

* a robustness test to confirm the method is suitable for the application in this laboratory
* specificity (where appropriate)
* intermediate precision (where appropriate)
* sample solution stability testing (where appropriate).

There are no other specific requirements for compendial analytical procedures. Linearity and accuracy are recommended to be evaluated where appropriate.

A validation protocol (qualification) is to be developed and will contain the appropriate tests to demonstrate the qualification of the procedure. These tests will be justified and will be performed by two separate analysts to demonstrate the robustness and the suitability of the method.

The method validation will demonstrate the suitability of the equipment and procedures and will qualify the analysts in the procedure.

## Non-compendial analytical procedures

Non-compendial analytical procedures require full validation; recommendations for each type of test are described in the following table.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Type of Tests / Characteristics | Identification | Testing for Impurities | | Specific Tests |
| Quantitative | Limit |
| Accuracy | - | + | - | +4 |
| Precision – Repeatability | - | + | - | +4 |
| Precision – Intermediate Precision | - | +1 | - | +4 |
| Specificity | +2 | + | + | +4 |
| Detection limit | - | -3 | + | - |
| Quantitation limit | - | + | - | - |
| Linearity | - | + | - | - |
| Range | - | + | - | - |
| Robustness | - | + | -3 | +4 |

- not normally evaluated

+ normally evaluated

1 – Where reproducibility has been performed, intermediate precision is not required.

2 – Lack of specificity can be compensated by a second procedure.

3 – May be needed in some cases.

4 – Not needed in all cases

(Extract from the FDA Guideline, based on the ICH guide)

## Revalidation requirements

If any changes are made to an established validated analytical method then revalidation will be required to verify that the method still performs satisfactorily.

The degree of revalidation of the method will be dependent on the change. Changes in pharmacopoeial monographs may only require minor qualifications such as system suitability or major changes could require a full validation. In general, verification of specificity is required for most changes.

The level of validation or revalidation will be determined by the Quality Manager and be based on the following guidelines:

* For a change to an operating parameter – revalidation is only required if the parameter is not within the validated operating range.
* For a change to the equipment required for the test method – revalidation is only required if a different brand with significantly different characteristics is to be used.
* For a change to the raw material supplier or to the route of synthesis - revalidation is required to ensure that the test method is still reliable and specific. Revalidation should assess specificity as a minimum.

## Review of monographs

When a new pharmacopoeia is issued, the relevant methods are reviewed to determine any changes to the methods in use within the laboratory. Where changes have occurred they will be incorporated into the methods and validated, if necessary, within 12 months of the issue of the pharmacopoeia.

Where changes to the monographs are recommended then a change control form is to be completed detailing the reason for the change.

Irrespective of the need to update the analytical methods in the monographs, the methods will be reviewed and issued with another version/revision number to demonstrate that they have been reviewed against the current pharmacopoeia and the section detailing the version of the pharmacopoeia will be updated.

The same review process applies to the approval of the updated monographs as was used in the original issue of the monograph. That is the monograph is reviewed and approved by the Quality and Production Managers.

**Note:** Where significant changes have occurred, the Managing Director will be notified.

Where methods that are used by contract laboratories are updated then the updated methods are to be issued to the relevant laboratory and the effective date of the changes recorded.

Appendices

Amend as required or delete.

Definitions

| Terms & abbreviations | Definition |
| --- | --- |
| Accuracy | The accuracy of an analytical test method expresses the closeness of agreement between the value which is accepted either as a conventional true value or an accepted reference value and the value found (ICH Q2). |
| API | Active pharmaceutical ingredient |
| DL | The detection limit (DL) of an individual analytical test method is the lowest amount of analyte in a sample which can be detected but not necessarily quantitated as an exact value (ICH Q2). |
| FDA | Food and Drug Administration (USA) |
| GxP | Good aseptic practice (GAP)  Good laboratory practice (GLP)  Good manufacturing practice (GMP) |
| HPLC | High performance liquid chromatography (also known as high pressure liquid chromatography) |
| ICH | International Conference on Harmonisation |
| Intermediate precision | Intermediate precision expresses within-laboratory variations: different days, different analyst, different equipment etc. (ICH Q2). |
| Linearity | The linearity of an analytical test method is its ability (within a given range) to obtain test results which are directly proportional to the concentration (amount) of analyte in the sample (ICH Q2). |
| Precision | The precision of an analytical test method expresses the closeness of agreement (degree of scatter) between a series of measurements obtained from multiple sampling of the same homogeneous sample under the prescribed conditions (ICH Q2). |
| QL | The quantitation limit (QL) of an analytical test method is the lowest amount of analyte in a sample which can be quantitatively determined with suitable precision and accuracy. The QL is a parameter of quantitative assays for low levels of compounds in sample matrices, and is used particularly for the determination of impurities and/or degradation products (ICH Q2). |
| Range | The range of an analytical test method is the interval between the upper and lower concentration (amounts) of analyte in the sample (including these concentrations) for which it has been demonstrated that the analytical test method has a suitable level of precision, accuracy and linearity (ICH Q2). |
| Repeatability | Repeatability expresses the precision under the same operating conditions over a short interval of time (ICH Q2). |
| Reproducibility | Reproducibility expresses the precision between laboratories (collaborative studies, usually applied to standardisation of methodology) (ICH Q2). |
| Robustness | The robustness of an analytical test method is a measure of its capacity to remain unaffected by small, but deliberate variations in method parameters and provides an indication of its reliability during normal usage (ICH Q2). |
| Specificity | Specificity is the ability to assess unequivocally the analyte in the presence of components which may be expected to be present (including impurities, degradants, matrix etc) (ICH Q2). |
| TGA | Therapeutic Goods Administration (Aust.) |
| UV | Ultra violet |

Document Information

| Revision History | | | |
| --- | --- | --- | --- |
| Revision | Modified by | Change Control No. | Description of Change |
| 01 |  |  |  |
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