



Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

Finished product (medicine) analytical procedure validations for Complementary Medicines

March 2006

TGA Health Safety
Regulation



About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. The TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

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Finished Product (Medicine) Analytical Procedure Validation for Complementary Medicines

March 2006

Scope

Testing of complementary medicines, either at initial release or during a stability study must use analytical methods which are appropriately validated for that purpose. Only starting materials which are approved by the testing facility (for example, the manufacturer of the medicine or contracted testing laboratory) using suitably validated tests can be used as ingredients in medicines. In determining the minimum validation activities to be applied to a test procedure, a risk-based assessment should be undertaken.

Validation is defined as the process of demonstrating that the analytical procedure is suitable for its intended purpose, for example, identification, determination of impurities, assay of active or other ingredients.

This guideline document describes the minimum approach acceptable to achieve validation of the test procedure used for complementary medicines (products). Additional validation activities may also be undertaken. Additional validation activities are at the discretion of the Sponsor. Different approaches to the validation of test procedures may be acceptable. Such approaches must be documented and justified.

Various terms are used to describe validation requirements. Definitions of the terms specificity, accuracy, precision, detection limit, quantitation limit, linearity, range and robustness are described in '[Note for Guidance on Validation of Analytical Procedures: Text and Methodology \(CPMP/ICH/381/95\) Rev 1](#)' and in other references included at the end of this guideline document. Some additional definitions (method transfer, system suitability testing and authenticated primary standard) are provided in the Glossary at the end of this guideline document.



Note: The *British Pharmacopoeia* (BP) and Therapeutic Goods Orders (TGOs) are the official standards for regulatory purposes in Australia. Where a product is covered by a monograph in the BP, then this is the minimum standard that must be applied in its entirety, otherwise a justification* is required. Note that the BP specifications for formulated products are expiry specifications. The requirements of applicable general monographs of the BP must also be met except where a justification for not doing so is authorised by the TGA*. The TGA will consider the suitability of other national or international pharmacopoeial monographs or standards on a case-by-case basis. Note that the most recent edition of any cited

pharmacopoeial monograph or standard should be used, or a justification* for not doing so is authorised by the TGA.

* Sponsors seeking to justify deviations from the use of official standards should apply to TGA in writing, seeking an exemption under Section 14 of the *Therapeutic Goods Act 1989*. Section 14 Exemption requests should explain why the standard(s) cannot be met and detail what alternative(s) are proposed and why. The delegate of the Secretary will review the request and sponsors will be advised in writing of the delegate's decision.

If the analytical procedure for product testing is included in the current edition of the BP or other peer reviewed pharmacopoeia or reference text, then validation of that procedure is not required. Examples of peer reviewed pharmacopoeias or reference texts include, but are not limited to, the European Pharmacopoeia (Ph Eur.), United States Pharmacopoeia (USP), Japanese Pharmacopoeia (JP), French Pharmacopoeia (FP), German Pharmacopoeia (DAB), Chinese Pharmacopoeia (CP) or Official Methods of Analysis of the Association of Analytical Chemists (AOAC International).

Note: While pharmacopoeial methods do not require re-validation, certain procedures should be undertaken to ensure that methods are applicable at the point of use. See the *Method Transfer* section below.

Method Transfer

System suitability tests and requirements are often included in validated methods. The ability to achieve these system suitability requirements is a key step in ensuring method transfer, but it is not the only step.

There may be several factors that are not explicitly described in a validated analytical method which can influence the performance of the method. The effectiveness of transferring a validated method from the original laboratory (or from a pharmacopoeia) to another laboratory needs to be verified. Differences in instrumentation and other equipment, for example, chromatography columns of different brands, age etc, capability of detectors, different filter materials, quality of reagents used, etc. It may also be necessary to confirm the precision of the method or the ability to achieve the detection levels of the validated method.

There may be no assurance that the composition of the product to be tested is the same as those for which the method has been validated. Furthermore, many products undergo reformulation as market experience is gained. To allow for this, pharmacopoeial methods must be revalidated to demonstrate that excipients do not interfere in the tests. For identification, further revalidation is not usually required. Validation of impurity testing usually needs to demonstrate that excipients do not interfere and that quantitation limits can be achieved to ensure effective transfer. The assay of the product usually needs to demonstrate that specificity, accuracy (mainly recovery), precision (repeatability) – around the target test concentration (minimum of 2 independent determinations), and linearity at 3 points around the target value needs to verify effective transfer.

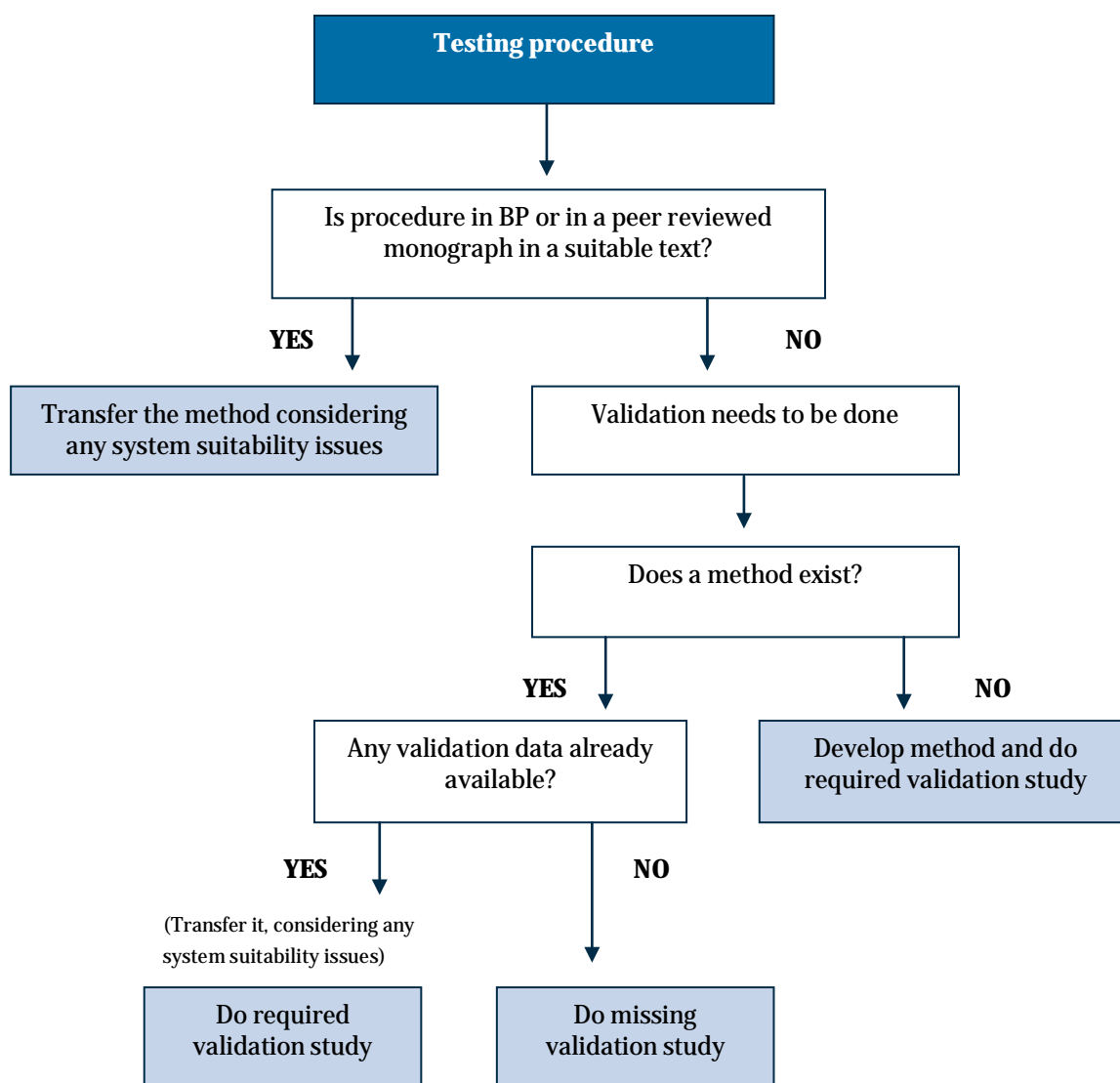
It is essential to establish and document that the validated analytical method functions properly in the test laboratory.

It should be noted that certain changes to method parameters can be made without having the effect of creating a 'new' method. Guidance on this is contained in the BP and Ph. Eur. <see for example, Appendix III of the British Pharmacopoeia 2005 - Chromatographic Separation Techniques (Ph. Eur. Method 2.2.46): guidance beginning at the heading *Adjustment of chromatographic conditions*, until the end of the Appendix, but not including Appendix III A>.

Determining the need for validation (refer to Flow Chart)

Once that initial decision within the flow chart below has been made and if no method is suitable for transfer, then the decisions about what actions are required are summarised in the flow chart below. Formal validation studies are required for newly developed analytical methods. The requirements described in '*Note for Guidance on Validation of Analytical Procedures: Text and Methodology (CPMP/ICH/381/95) Rev 1*' should apply in this situation.

Flow Chart: Determining the need for validation



It is possible that the analytical test procedure being transferred has been partially or fully validated by someone else. If this is the case, it should be possible to obtain a 'Summary statement of validation' from whoever certified the validation. This statement must include the following:

- which aspects of validation have been addressed (such as specificity, accuracy, precision [repeatability, intermediate precision], detection limit, quantitation limit, linearity, range and robustness).
- the extent of compliance with '*Note for Guidance on Validation of Analytical Procedures: Text and Methodology (CPMP/ICH/381/95) Rev 1*' or with other accepted guidance documents (including this guidance document) for each aspect of validation required.
- documented details of the equipment used in the validation activities.
- the details of the equipment that was used in the validation activities.

The five types of analytical testing procedures that require validation when testing complementary medicines are:

- Quantitative tests for:
 - the active substance,
 - the accepted therapeutically active component(s) or marker(s) ¹ in a quantified herbal substance; or
- Semi-quantitative Limit tests for the control of impurities in the medicine.
- Quantitative Limit tests for the control of impurities in the medicine.
- Identification tests for the active ingredient substance(s) in the medicine.
- Profiling of the herb based active ingredient substance(s) in the medicine.

Laboratories that undertake any or all of these tests are to conduct the appropriate validation activities using protocols consistent with the principles outlined in this document. Each of the activities specified in the protocol for each of these procedures should define the details of the activity and the acceptance criteria for that activity. The requirements of this guideline are the minimum necessary to achieve validation of the test procedure for starting materials for use in complementary medicines. Additional validation activities may also be undertaken at the discretion of the Sponsor.

Validation of similar products

Once validation studies have been undertaken for a product (in accordance with the principles outlined in this guidance), a reduced level of validation may be considered acceptable for other products which the sponsor can demonstrate and / or justify as 'essentially similar'. This means that the composition of the 'essentially similar' product is such that validation studies undertaken on the initial product are not compromised.

Note that the onus is on the sponsor to document the basis for any decision to perform limited validation studies, and to make this documentation available to the TGA for review, upon request.

¹ For complementary medicines, if, according to the state of scientific knowledge, the constituent(s) responsible for the therapeutic activity is (are) not known, the substance itself is considered to be the active ingredient. Markers are chemically defined constituents of a herbal substance that are of interest for control purposes, independent of whether or not they have any therapeutic activities. Markers may serve to quantify the amount of a herbal substance in a herbal medicinal product if they have been quantitatively determined in the herbal substance or herbal preparation.

Table 1 - Validation requirements for each type of test procedure

Test procedure	Mandatory Validation activities	Other validation activities* (depending on the circumstances)	Not required to be done**
Quantitation <ul style="list-style-type: none"> Content Dissolution (measurement only) 	Specificity Accuracy (if not inferred) Repeatability Linearity Range	Intermediate Precision (unless reproducibility is done) Robustness	Detection limit Quantitation limit
Impurities (Quantitative)	Specificity Accuracy (if not inferred) Repeatability Quantitation limit Range	Intermediate precision (unless reproducibility is done) Linearity Robustness	Detection limit
Impurities (Limit tests eg. semi – quantitative determination of impurities)	Specificity Detection limit	None	Accuracy Precision Quantitation limit Linearity Range Robustness
Identification tests (Non Profiling)	Specificity	None	Accuracy Precision Detection limit Quantitation limit Linearity Range Robustness
Profiling	Specificity Robustness	None	Accuracy Precision Detection limit Quantitation limit Linearity Range

* A reason should be documented for not performing 'other validation activities'.

** No justification is required for either doing or not doing any of the non-mandatory validation activities.

Additional comments on validation requirements

Validation of quantitative tests of content

Any standards used in validation or subsequent testing must be able to be traced back to an authenticated primary standard. If no pharmacopoeial standard is available, or secondary standard derived thereof, the suitability of the authentication process must be confirmed.

When a complementary medicine is subject to reformulation, such quantitative tests of content only need to be revalidated to the extent that the reformulation compromises the validation previously undertaken.

Validation of limit tests

Limit tests are used to control either the amounts of general impurities (e.g. moisture etc) in a product or the amounts of a specific substance (e.g. residual starting materials in a substance or degradation products from a substance) in a product. The general impurities commonly use pharmacopoeial methods whilst the specific impurities can use pharmacopoeial or proprietary methods. Pharmacopoeial methods can be used without any validation subject to method transfer being confirmed. Proprietary limit test methods will require appropriate validation at the testing laboratory.

Any standard substances or components used in the validation or subsequent testing must be able to be traced back to an authenticated primary standard.

Validation of identification tests (other than profiling tests)

Any standard substances or components used in the validation or subsequent identity testing must be able to be traced back to an authenticated primary standard.

Validation of chromatographic profiling (fingerprinting) tests

Validation of chromatographic profiling tests of products containing complex complementary substances used either at batch release or during a stability program needs to provide assurance that the correct material is being adequately profiled. The chromatographic profiling method can be sourced from a pharmacopoeia, a peer reviewed monograph or publication or it can be available as a proprietary method. Any standards used in validation or subsequent testing must be able to be traced back to an authenticated primary standard.

Australian Regulatory Guidelines for Complementary Medicines ([ARGCM Part III](#)) Section 4.7 has more details about profile chromatograms. The TGA's [Questions & Answers for the Identification of Herbal Materials and Extracts](#) which has been incorporated as an adjunct Guideline to the ARGCM should also be consulted.

Glossary of Terms

The definitions specifically involved in the validation of analytical methods are available in the ICH Harmonised Tripartite Guidelines published as '*Note for Guidance on Validation of Analytical Procedures: Text and Methodology (CPMP/ICH/381/95) Rev 1*'.

This guideline on validation provides additional assistance to Sponsors and testing laboratories involved with Starting Materials for use in complementary medicines. Other definitions provided below are based on definitions in pharmacopoeia or provided by international analytical societies or by government agencies.

Authenticated primary standard:

This is a reference standard that is required to validate standards used in tests and assays. Features of the authenticated primary standard such as the identity, purity, method of synthesis, fabrication or derivation and the general chemical characteristics have to be defined and approved by a competent authority such as a national pharmacopoeia authority, a licensing authority, official control laboratory, or where appropriate, other authoritative source.

Examples of authenticated primary standards include some British Pharmacopoeia Chemical Reference Substances (BPCRS) and United States Pharmacopoeia Reference Standards. Herbal materials and extracts whose identity, purity, method of derivation and general chemical characteristics have been defined and approved by an internationally recognised authority, agency or scientist, can be regarded as an authenticated primary standard.

Sponsors should also make reference to the TGA guidance document: [Questions & Answers for the Identification of Herbal Materials and Extracts](#).

Method Transfer:

The validated method could be available in the BP or some other suitable text. It may also be available from another laboratory. If so, it can be transferred to the testing laboratory under a suitable method transfer procedure. Such a procedure should consider and document conclusions relating to the suitability and similarity of the equipment to be used. Technique issues such as the ability of the recipient laboratory to undertake a recovery step with the same efficiency as the providing laboratory, including any need to re-optimize extraction times, need to be considered.

Robustness:

The robustness of an analytical procedure is a measure of its capacity to remain unaffected by small, but deliberate variations in method parameters and provides a indication of its reliability during normal usage.

If measurements are susceptible to variations in analytical conditions, the analytical conditions should be suitably controlled or a precautionary statement should be included in the procedure. One consequence of the evaluation of robustness should be that a series of system suitability parameters (e.g. resolution test) is established to ensure that the validity of the analytical procedure is maintained whenever used.

System suitability testing:

- Different equipment may have different limitations. When transferring a test procedure developed on a particular instrument to another instrument, consideration has to be given to relevant differences between the instruments. In particular, testing laboratories should confirm Detection Limit and Quantitation Limit where applicable.
- Dependent upon what differences exist between equipment, protocols have to be written to validate the test procedure on the new equipment that examine the effect of these differences.
- System suitability is useful for confirming a method transfer activity.

References

Document/s	Internet Address
Australian Regulatory Guidelines for Complementary Medicines (ARGCM)	http://www.tga.gov.au/industry/cm-argcm.htm
Questions & Answers for the Identification of Herbal Materials and Extracts	http://www.tga.gov.au/industry/cm-identification-herbal-extracts.htm
Note for Guidance on Validation of Analytical Procedures: Text and Methodology (CPMP/ICH/381/95) Rev 1	http://www.tga.gov.au/industry/pm-euguidelines-adopted-quality.htm#analytical
British Pharmacopoeia 2004 (BP)	http://www.pharmacopoeia.org.uk
European Pharmacopoeia (Ph Eur.)	http://www.edqm.eu/en/Homepage-628.html
Therapeutic Goods Orders (TGO's)	http://www.tga.gov.au/industry/legislation-tgo.htm
<i>Therapeutic Goods Act 1989</i>	http://www.comlaw.gov.au/Series/C2004A03952
Guidance for Industry: Analytical Procedures and Methods Validation – Chemistry, Manufacturing, and Controls Documentation (Draft) U.S. FDA - Center for Drug Evaluation and Research (CDER)	http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064979.htm

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Reference/Publication #