Health Canada Santé Canada

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To: Associations, Registrars of Medicine, Registrars of Pharmacy

I am pleased to inform you of the release of the *International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use*(ICH)/ Therapeutic Products Programme guideline, “Text on Validation of Analytical Procedures”. This guideline has been developed by an ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. The ICH Steering Committee has endorsed the final draft and recommended its adoption by the regulatory bodies of the European Union, Japan and the United States.

Aux : Associations, Ordre des pharmaciens, Corporation professionnelle des médecns du Québec

J’ai le plaisir de vous annoncer la publication de la ligne directrice de la *Conférence internationale sur l’harmonisation des exigences techniques pour l’enregistrement des médicaments à usage humain* (CIH)/ Programme des produits thérapeutiques, intitulée “Texte concernant la validation des méthodes d’analyse”. La directive présentée ici a été élaborée par un groupe d’experts de la CIH et a fait l’objet de consultations, menées par les organismes de réglementation, conformément au processus convenu à la CIH. Le Comité directeur de la CIH a approuvé la version finale et en a recommandé l’adoption aux organismes de réglementation de l’Union européenne, du Japon et des États-Unis.

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The Therapeutic Products Programme has adopted this international guideline. In accordance with ICH rules, the document was adopted verbatim. This guideline represents an approach that will be considered acceptable for the review of new drug substances and products. This document should be read in conjunction with the relevant sections of other applicable Programme guidelines.

Le Programme des produits thérapeutiques a adopté cette ligne directrice internationale, textuellement comme l'exige la CIH. L'approche qu'on y recommande est considérée comme acceptable pour l'examen des nouvelles substances médicamenteuses et des nouveaux produits. Il convient de prendre connaissance du document présenté ci-après en se reportant, lorsqu'il y lieu, aux autres sections pertinentes d'autres directives du Programme.

A separate annex will be developed to accompany the guidelines entitled "Text on Validation of Analytical Procedures" and "Validation of Analytical Procedures: Methodology" which will provide further guidance on the Programme's requirements regarding analytical methodology. This annex will apply to both new and "existing" drugs. In the context of the guidance document, an "existing" drug substance is one for which a Notice of Compliance has previously been issued pursuant to Division 8 of the *Food and Drug Regulations* (e.g., generics).

Nous ajouterons aux directives intitulées "Texte concernant la validation des méthodes d'analyse" et "Validation des méthodes d'analyse : méthodologie" un annexe séparé, présentement en préparation, contenant d'autres renseignements sur les exigences du Programme concernant la méthodologie analytique. Cette annexe s'appliquera autant aux nouveaux produits qu'aux médicaments « existants ». Dans le contexte de la directive, une substance médicamenteuse « existante » en est une pour laquelle un Avis de conformité a déjà été émis en vertu du Titre 8 du *Règlement sur les aliments et drogues* (p. ex. médicaments génériques).

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The guideline is available through Internet at **www.hc-sc.gc.ca/hpb-dgps/therapeut**. For those clients who do not have access to Internet, printed copies will be available through Health Canada Publications, telephone (613) 954-5995 or fax (613) 941-5366.

La ligne directrice est disponible sur l'Internet à **www.hc-sc.gc.ca/hpb-dgps/therapeut**. Les clients qui n'ont pas accès à l'Internet peuvent obtenir le document en s'adressant au service des publications de Santé Canada, par téléphone au (613) 954-5995 ou par télécopieur au (613) 941-5366.

Should you have any questions regarding the content of the guideline, please contact:

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Health Canada Santé Canada

THERAPEUTIC PRODUCTS PROGRAMME GUIDELINE

ICH HARMONISED TRIPARTITE GUIDELINE

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR THE REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

TEXT ON VALIDATION OF ANALYTICAL PROCEDURES

Published by authority of the
Minister of Health

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Disclaimer

The material herein was prepared under the direction of the Therapeutic Products Programme, Health Canada. No changes are permitted.

Avertissement

Le document ci-joint a été préparé sous la direction de la Programme des produits thérapeutiques, Santé Canada. Aucune modification n'est permise.

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Également disponible en français sous le titre :
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FOREWORD

This guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. The ICH Steering Committee has endorsed the final draft and recommended its adoption by the regulatory bodies of the European Union, Japan and USA.

The Therapeutic Products Programme (TPP) has adopted this guideline and reproduced it in this document. This guideline represents an approach that will be considered acceptable for the review of new drug substances and products. This document should be read in conjunction with the relevant sections of other applicable Directorate guidelines.

Alternate approaches to the principles and practices described in this document may be acceptable provided they are supported by adequate scientific justification. Submission sponsors may discuss, in advance, alternate approaches with the Directorate to avoid the withdrawal/ rejection of a submission. For example, the Directorate's guideline *Acceptable Methods* would be considered an acceptable alternate approach.

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1. INTRODUCTION

This document presents a discussion of the characteristics for consideration during the validation of the analytical procedures included as part of registration applications submitted within the EC, Japan and the USA. This document does not necessarily seek to cover the testing that may be required for registration in, or export to, other areas of the world. Furthermore, this text presentation serves as a collection of terms, and their definitions, and is not intended to provide direction on how to accomplish validation. These terms and definitions are meant to bridge the differences that often exist between various compendia and regulators of the EC, Japan and the USA.

The objective of validation of an analytical procedure is to demonstrate that it is suitable for its intended purpose. A tabular summation of the characteristics applicable to identification, control of impurities and assay procedures is included. Other analytical procedures may be considered in future additions to this document.

2. TYPES OF ANALYTICAL PROCEDURES TO BE VALIDATED

The discussion of the validation of analytical procedures is directed to the four most common types of analytical procedures:

- Identification tests.
- Quantitative tests for impurities' content.
- Limit tests for the control of impurities.
- Quantitative tests of the active moiety in samples of drug substance or drug product or other selected component(s) in the drug product.

Although there are many other analytical procedures, such as dissolution testing for drug products or particle size determination for drug substance, these have not been addressed in the initial text on validation of analytical procedures. Validation of these additional analytical procedures is equally important to those listed herein and may be addressed in subsequent documents.

A brief description of the types of tests considered in this document is provided below.

- Identification tests are intended to ensure the identity of an analyte in a sample. This is normally achieved by comparison of a property of the sample (e.g., spectrum, chromatographic behavior, chemical reactivity, etc.) to that of a reference standard.

- Testing for impurities can be either a quantitative test or a limit test for the impurity in a sample. Either test is intended to accurately reflect the purity characteristics of the sample. Different validation characteristics are required for a quantitative test than for a limit test.

- Assay procedures are intended to measure the analyte present in a given sample. In the context of this document, the assay represents a quantitative measurement of the major component(s) in the drug substance. For the drug product, similar validation characteristics also apply when assaying for the active or other selected component(s). The same validation characteristics may also apply to assays associated with other analytical procedures (e.g., dissolution).

The objective of the analytical procedure should be clearly understood since this will govern the validation characteristics which need to be evaluated. Typical validation characteristics which should be considered are listed below:

Accuracy
Precision
    Repeatability
    Intermediate Precision
Specificity
Detection Limit
Quantitation Limit
Linearity
Range

Each of these validation characteristics is defined in the attached Glossary. The table lists those validation characteristics regarded as the most important for the validation of different types of analytical procedures. This list should be considered typical for the analytical procedures cited but occasional exceptions should be dealt with on a case-by-case basis. It should be noted that robustness is not listed in the table but should be considered at an appropriate stage in the development of the analytical procedure.

Furthermore revalidation may be necessary in the following circumstances:

- changes in the synthesis of the drug substance;
- changes in the composition of the finished product;
- changes in the analytical procedure;

The degree of revalidation required depends on the nature of the changes. Certain other changes may require validation as well.

TABLE

Type of analytical procedure characteristics	Identification	Testing for impurities quantitat.	 limit	Assay - dissolution (measurement only) - content/potency
Accuracy	-	+	-	+
Precision				
Repeatability	-	+	-	+
Interm. Precision	-	+ (1)	-	+ (1)
Specificity (2)	+	+	+	+
Detection Limit	-	- (3)	+	-
Quantitation Limit	-	+	-	-
Linearity	-	+	-	+
Range	-	+	-	+

- signifies that this characteristic is not normally evaluated
+ signifies that this characteristic is normally evaluated.

(1) in cases where reproducibility (see Glossary) has been performed, intermediate precision is not needed

(2) lack of specificity of one analytical procedure could be compensated by other supporting analytical procedure(s)

(3) may be needed in some cases

GLOSSARY

1. Analytical Procedure

The analytical procedure refers to the way of performing the analysis. It should describe in detail the steps necessary to perform each analytical test. This may include but is not limited to: the sample, the reference standard and the reagents preparations, use of the apparatus, generation of the calibration curve, use of the formulae for the calculation, etc.

2. Specificity

Specificity is the ability to assess unequivocally the analyte in the presence of components which may be expected to be present. Typically these might include impurities, degradants, matrix, etc.

Lack of specificity of an individual analytical procedure may be compensated by other supporting analytical procedure(s).

This definition has the following implications:

Identification:	To ensure the identity of an analyte.
Purity Tests:	To ensure that all the analytical procedures performed allow an accurate statement of the content of impurities of an analyte, i.e., related substances test, heavy metals, residual solvents content, etc.
Assay (content or potency):	To provide an exact result which allows an accurate statement on the content or potency of the analyte in a sample.

3. Accuracy

The accuracy of an analytical procedure 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.

This is sometimes termed trueness.

4. Precision

The precision of an analytical procedure 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. Precision may be considered at three levels: repeatability, intermediate precision and reproducibility.

Precision should be investigated using homogeneous, authentic samples. However, if it is not possible to obtain a homogeneous sample it may be investigated using artificially prepared samples or a sample solution.

The precision of an analytical procedure is usually expressed as the variance, standard deviation or coefficient of variation of a series of measurements.

4.1. Repeatability

Repeatability expresses the precision under the same operating conditions over a short interval of time. Repeatability is also termed intra-assay precision

4.2. Intermediate precision

Intermediate precision expresses within laboratories variations: different days different analysts, different equipment, etc.

4.3. Reproducibility

Reproducibility expresses the precision between laboratories (collaborative studies usually applied to standardization of methodology).

5. Detection Limit

The detection limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be detected but not necessarily quantitated as an exact value.

6. Quantitation Limit

The quantitation limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be quantitatively determined with suitable precision and accuracy. The quantitation limit 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.

7. Linearity

The linearity of an analytical procedure is its ability (within a given range) to obtain test results which are directly proportional to the concentration (amount) of analyte in the sample.

8. Range

The range of an analytical procedure 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 procedure has a suitable level of precision, accuracy and linearity.

9. 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 an indication of its reliability during normal usage.