World Health Organization

GOOD PHARMACOPOEIAL PRACTICES

(DRAFT 14 JANUARY 2015)

REVISED DRAFT FOR COMMENT

Please address any comments on this proposal by **10 March 2015** to Dr S. Kopp, Group Lead, Medicines Quality Assurance, World Health Organization, 1211 Geneva 27, Switzerland, fax: (+41 22) 791 4730 or email: kopps@who.int with a copy to gaspardm@who.int.

SCHEDULE FOR THE PROPOSED ADOPTION PROCESS OF DOCUMENT QAS/13.526: *GOOD PHARMACOPOEIAL PRACTICES*

Need for good pharmacopoeial practices (GPhP) stated during first international meeting of world pharmacopoeias, Geneva, and other related events with stakeholders	28 February–1 March 2012 7–8 October 2012 9–12 October 2012 21–22 October 2012
First draft of good pharmacopoeial practices (GPhP) sent out for comment (QAS/12.516)	17 October 2012
Compilation of feedback and comments received	November–December 2012
Circulation of GPhP to drafting group on good pharmacopoeial practices with comments, as well as Concept paper on scope and background (QAS/13.518)	18 January 2013
Formation of initial drafting group (IDG), including representatives from each pharmacopoeia, as per self-nomination, to review draft concept paper via teleconference call	February 2013
Preparation of new skeleton and first draft with more detailed structure	February 2013
Mailing to world pharmacopoeias for additional feedback, preparation of draft chapters by drafting group	February–March 2013
Compilation of feedback	April 2013
Discussion of draft working document on good pharmacopoeial practices at second international meeting of world pharmacopoeias, New Delhi, India	18–19 April 2013
Revised version of GPhP prepared and mailed out for comments to all pharmacopoeias, for feedback to be provided to lead pharmacopoeias for each chapter	28 May 2013
Discussion of feedback during informal consultation to discuss new medicines, quality control and laboratory standards	12–14 June 2013
Revision of each chapter by each GPhP lead pharmacopoeia	28 June 2013

Mailing of each chapter to WHO for compilation into a revised working document	July 2013–December 2013
Presentation to forty-eighth meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations	October 2013
Compilation of all various chapters received from the lead pharmacopoeias and mailing out to all world pharmacopoeias	January 2014
Compilation of all comments received	March 2014
Discussion during the 3rd international meeting of world pharmacopoeias in London, United Kingdom	10–11 April 2014
Revised version of GPhP prepared and mailed out for comments to all pharmacopoeias, for feedback to be provided to each chapter	July 2014
Compilation of all comments received	22 September 2014
Following feedback and discussions during two telephone conference calls of the subgroup working on the Technical Annex to the future GPhP the Ph.Eur. Secretariat prepared a significantly shortened draft which is circulated for comments	23 September 2014
Compilation of all comments received	30 September 2014
Discussion during the 4th international meeting of world pharmacopoeias in Strasbourg, France	8–10 October 2014
Briefing on progress to forty-ninth meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations	13–17 October 2014
Continuation of consultation process with world pharmacopoeias	October 2014–January 2015
Continuation of consultation process with world pharmacopoeias and worldwide	Mid-January–mid-March 2015
Compilation of all comments received	10–15 March 2015

Discussion of feedback during the 5th international meeting of world pharmacopoeias in Washington, USA	20–22 April 2015
Continuation of consultation process with world pharmacopoeias and worldwide	May–July 2015
Compilation of all comments received	15 August 2015
Discussion during the 6th international meeting of world pharmacopoeias	September 2015, dates tbc with host
Presentation to the fiftieth meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations	12–16 October 2015
Any follow-up action as necessary	

38

39

CONTENTS

page

1. BACKROUND ….……

2. PURPOSE AND SCOPE OF GOOD PHARMACOPOEIAL PRACTICES ……..

3. BENEFITS OF GOOD PHARMACOPOEIAL PRACTICES

4. IMPLEMENTATION

5. MONOGRAPH DEVELOPMENT …….
   5.1 General considerations … ……
   5.2 Technical guidance ……..
      5.2.1 Monographs for pharmaceutical substances
      5.2.2 Monographs for finished products ……
      [5.2.3 Monographs on biologicals *on hold, to be discussed later*]
      [5.2.4 Monographs on herbals *on hold, to be discussed later*]
      [5.2.5 Monographs on other products *on hold, to be discussed later*]

[6. REFERENCE SUBSTANCES *on hold, to be discussed later*]

7. ANALYTICAL TEST PROCEDURES AND METHODOLOGIES …….
   (ANALYTICAL METHOD)

[8. PRINCIPLES OF COLLABORATION AND EXCHANGES AMONG ……..
   PHARMACOPOEIAS
   including discussion on coordinating versus leading pharmacopoeias, etc.
   on hold, to be discussed later]

[9. COLLABORATION WITH STAKEHOLDERS
   on hold, to be discussed later]

GOOD PHARMACOPOEIAL PRACTICES

1. BACKGROUND

Harmonization efforts in the area of pharmacopoeias started more than a century ago. The World Health Organization (WHO) was mandated with its Secretariat in 1948. This led to the creation of *The International Pharmacopoeia*, which was the first global pharmacopoeial activity. Many others followed.

Pharmacopoeias are embedded in their respective national or regional regulatory environment. Retrospective harmonization has proven difficult to achieve. Prospective harmonization may be easier but presents certain challenges after the initial work has been done, as the maintenance process over time of the pharmacopoeial standards (pharmacopoeial texts and reference standards) needs to be viewed within a long-term perspective.

The term "harmonization" may be legally binding and therefore have different connotations in the national and regional context. In the context of this document "harmonization" is maintained in some parts in the view of its historical use and is understood to mean the following: "The process through collaborative effort whereby differing requirements within participating pharmacopoeias move towards becoming more similar or aligned over time." This is nowadays also referred to as "convergence" *[Note from Secretariat: cross-reference to the new Good Review Practices definition as footnote will be added]*.

Developments in science and medical practice, globalization and the presence of spurious/falsified/falsely labelled/counterfeit (SFFC) products require pharmacopoeias to constantly revise. Convergence and reinforced collaboration among pharmacopoeial committees and regulators, supported by adequate interaction with industry, will assist in facing new challenges and resource constraints.

A first initiative to reopen the discussion on international harmonization of quality control specifications on a global scale was taken in a side meeting of the 10th International Conference of Drug Regulatory Authorities (ICDRA) entitled: "Pharmacopoeial Specifications – Need for a Worldwide Approach?" in Hong Kong on 24 June 2002. This further led to discussions among regulators during the 11th ICDRA meeting held in Madrid in 2004.

Other international events during the following years enabled discussions with and among pharmacopoeias on this topic.

In 2012 a series of meetings and events focused on and reopened this debate worldwide among the pharmacopoeias and their stakeholders. These events included:

- 28 February–2 March 2012: the first international meeting of world pharmacopoeias held at WHO, Geneva, Switzerland;
- 7–8 October 2012: joint FIP-WHO Conference during the FIP Centennial Congress, Amsterdam, Netherlands;
- 9–12 October 2012: forty-seventh meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations, Amsterdam, Netherlands;
- 21–22 October 2012: pre-ICDRA meeting on *Quality of medicines in a globalized world: focus on active pharmaceutical ingredients*, Tallinn, Estonia;
- 23–26 October 2012: 15th International Conference of Drug Regulatory Authorities (ICDRA), Tallinn, Estonia.

The main emerging suggestion from all these events was the development of good pharmacopoeial practices to favour harmonization/convergence facilitated by WHO.

A number of pharmacopoeias agreed to participate in an initial drafting group.

It was agreed to develop the good pharmacopoeial practices under the auspices of the WHO Expert Committee on Specifications for Pharmaceutical Preparations, benefiting from its well-established international standard-setting processes and procedures. These processes include an international wide consultation process, which enables participation of all stakeholders and users in the development process. The final guidance would then be presented, in line with the procedure, to WHO's 194 Member States and pharmacopoeial authorities.

2. PURPOSE OF GOOD PHARMACOPOEIAL PRACTICES

The primary objective of the *WHO Good Pharmacopoeial Practices* (GPhP) guidance is to converge approaches and policies in establishing pharmacopoeial standards, which will support regulatory authorities in controlling the quality of pharmaceutical ingredients, their finished products and other materials and will provide a tool by which the user or procurer can make an independent judgement regarding quality, thus safeguarding the health of the public.

GPhP describes a set of principles that provides guidance for national pharmacopoeial authorities (NPAs) and regional pharmacopoeial authorities (RPAs) which facilitates the appropriate design, development, maintenance, publishing and distribution of pharmacopoeial standards.

3. BENEFITS OF GOOD PHARMACOPOEIAL PRACTICES

GPhP is designed to facilitate collaboration among pharmacopoeias leading to possibilities for work sharing, harmonization/convergence of standards, and the recognition of published standards between NPAs and RPAs), increasing access to and availability of affordable, quality medicines.

In addition to the above the establishment of GPhP may result in the following:

- strengthening of global pharmacopoeial cooperation;
- providing stakeholders with a better understanding of how pharmacopoeial standards are developed and maintained in a transparent manner;
- improving cooperation between NPAs/RPAs and stakeholders (e.g. regulators, industry) with a view to facilitating the global harmonization/convergence of pharmacopoeial standards, to reduce duplication of work.

Pharmacopoeial standards that are developed following GPhP can be relied upon for adequately validated analytical procedures and suitable reference standards for assessing conformity of pharmacopoeial requirements and to assure access to affordable, safe, effective and high-quality medicines. Adherence to GPhP can foster exchanges, work sharing and acceptance of monographs among pharmacopoeias.

GPhP should ultimately enable convergence and harmonization of pharmacopoeial standards.

4. IMPLEMENTATION

While the implementation of the GPhP by NPAs and RPAs is voluntary it is recommended and encouraged, as a high level of participation will result in greater benefit to the stakeholders and ultimately to patients.

5. MONOGRAPH DEVELOPMENT

Development of a monograph requires consideration of information and candidate materials. This information may come from, e.g. donors, literature, various publicly available material, from other pharmacopoeias or may be generated within the laboratory resources of a pharmacopoeia. The draft text should be displayed for public comments.

Pharmacopoeias are encouraged to conform where possible to the work of harmonization bodies and initiatives towards convergence (e.g. WHO, International Conference on Harmonisation (ICH) and Pharmacopoeial Discussion Group (PDG).

5.1 General considerations

Pharmacopoeial monographs generally cover chemical, biological and herbal medicines and their ingredients approved by national regulatory authorities and/or otherwise legally marketed within a national or regional sphere of control. Some pharmacopoeias also include standards for, e.g. medical devices, nutritional ingredients and products.

Specifications in pharmacopoeias are one facet of the overall control of the quality of finished pharmaceutical products (FPP) and their constituents (components, ingredients). Monographs provide publicly-available standards that a product or a component of a product is expected to meet at any time during its period of use. Thus, a substance should be able to demonstrate compliance with a pharmacopoeial monograph up to the point at which it is used to prepare a finished dosage form. An FPP should demonstrate compliance with a monograph, if available, throughout its shelf-life. Pharmacopoeial specifications are used within pharmaceutical product marketing authorization systems and by manufacturers, suppliers, purchasers and those acting on behalf of patients.

Before the process of writing a monograph can begin, it is important to consider the tests that are required to demonstrate the quality of a given substance or pharmaceutical product; specifications that favour one manufacturer to the exclusion of others should be avoided.

For example, the ICH guidelines Q6A (*Specifications: test procedures and acceptance criteria for new drug substances and new drug products: chemical substances*) could be used as a basis. Whenever possible, the specifications should be applied consistently in monographs across all participating pharmacopoeias. For example, certain regions

specify compliance with manufacturing-based testing (usually measures of the physical or physicochemical acceptability) in the specific monograph, while others incorporate these requirements in General monographs for a particular pharmaceutical product.

Additional tests might be added by NRAs and RPAs depending on, e.g. national/regional regulations.

Monographs set forth an article's nonproprietary name, definition, specification and may include other requirements such as packaging and storage. The specification consists of tests, procedures and acceptance criteria that define quality aspects as to the identity, strength and purity of the monographed material.. Pharmacopoeial monographs provide an important tool for assurance of the quality and safety of marketed pharmaceutical ingredients and products through testing of their quality.

Pharmacopoeial standards allow independent testing and are a critical part of the "safety net" of standards that help ensure the quality, safety and efficacy of medicines. They are closely allied with good manufacturing practice (GMP) standards, which are process standards.

Pharmacopoeial monograph procedures often call for suitable reference standards.

5.1.1 General principles

(a) Pharmacopoeial standards should be available for medicines and their ingredients and associated materials. They are usually based on the shelf-life specifications approved by regulatory authorities *[*add footnote: In the case of* The International Pharmacopoeia *specifications are developed for those medicines included in The Essential Medicines List (EML) and those that are of major public health interest, including, e.g. those that are on the Expression of interest (EOI) for prequalification by WHO]* or on the specifications provided by manufacturers of unlicensed products.

(b) The monographs may employ various validated analytical procedures for the tests that are feasible to be performed and a trained and experienced analyst could perform without any repetition or development of new procedure. The validation of analytical procedures described in monographs should comply with the requirements as laid down, for example, in the WHO *[Ref:* Supplementary guidelines on good manufacturing practices: validation**,** Appendix 4 on Analytical method validation, in WHO Technical Report Series, No. 937, 2006, Annex 4] and ICH guidelines [*Ref:* (Q2R1) "Validation of Analytical Procedures: Text and Methodology"].

(c) Pharmacopoeial standards are public standards that are science-based and data-driven and based on sound analytical measurement and accompanying validation data.

(d) A pharmacopoeia's core mission is to protect public health by creating and making available public standards to help ensure the quality of medicines.

Pharmacopoeias respect the intellectual property of donors and recognize the importance of maintaining the confidentiality of proprietary third-party information. Pharmacopoeias endeavour to work collaboratively with manufacturers and regulators and other stakeholders in the development of public standards.

5.1.2 Adoption of pharmacopoeial standards

(a) Text in a pharmacopoeial monograph and general chapter is approved by an expert body of the pharmacopoeia, following publicly available rules and procedures, including public consultation and applicable conflict of interest and confidentiality rules.

(b) Reference standards cited in a monograph and/or their compendial uses also are approved by a pharmacopoeial expert body.

5.1.3 Open and transparent process

Pharmacopoeias ensure openness and transparency throughout the development of pharmacopoeial standards, which includes:

(i) engaging stakeholders in the routine development and revision of pharmacopoeial standards through adequate and timely public notice and comment;
(ii) inviting the participation of stakeholders, especially when the discussion has impact on the access to medicines;
(iii) engaging stakeholders in the accelerated development and revision of standards to address major public health concerns;
(iv) timely inclusion of strategic monographs that address major public health demands;
(v) rapid correction of errors published in compendial text, when necessary;
(vi) timely and appropriate revision and/or withdrawal of compendial standards, when necessary. The legal status of monographs that have been withdrawn will depend on the national regulatory framework.

5.1.4 Continuous revision

Pharmacopoeial standards are in a continuous revision process to ensure that they are based on current scientific knowledge.

5.1.5 Harmonization

Pharmacopoeias should harmonize standards wherever possible, through monographs and general chapters. Harmonization may occur through several processes including, but not limited to: adoption/adaptation of existing standards; revision of a standard between two or more pharmacopoeias (bilateral or multilateral harmonization); development of a new

standard through coordinated consideration (prospective harmonization); revision or creation of standards through a coordinating body (e.g. PDG); or other approaches.

5.1.6 Legal recognition

Pharmacopoeial monographs may acquire legal status and then become subject to enforcement depending on applicable national or regional requirements.

5.1.7 Compliance with a pharmacopoeial monograph

Any substance or product subject to a monograph must comply with all of the mandatory requirements within the pharmacopoeia throughout its period of use or shelf-life.

The assays and tests described are the official methods upon which the standards of the pharmacopoeia depend. The analyst may not be precluded from employing alternative methods depending on national and regional legislation. A validation of the alternative analytical procedure should be done to show at least an equivalent performance to the analytical procedure described in the monograph. If an alternative analytical procedure is used, it is necessary to provide a rationale for its inclusion and identify its use (e.g. release, stability testing), validation data and comparative data to that of the analytical procedure described in the monograph, subject to regulatory approval.

In case of doubt or dispute the official pharmacopoeia methods prevail and are alone authoritative.

5.1.8 Analytical requirements

Pharmacopoeial methods and limits are set with the intention that they should be used as compliance requirements and not as requirements to guarantee total quality assurance. To achieve maximum benefit from the examination of a product, the recommended approach is that, wherever possible, a variety of different analytical techniques should be

employed, considering the feasibility and affordability of the methods. As analytical methods become more precise, it will become increasingly possible to combine precision with specificity which optimize analytical effort and time.

5.1.9 Acceptance criteria

Acceptance criteria are numerical limits, ranges or other suitable measures for acceptance of the results of analytical testing to allow determination of pass/fail criteria. Acceptance criteria indicated in a pharmacopoeial monograph allow for analytical error, for unavoidable variations in manufacturing processes and for deviations to an extent considered acceptable under practical storage conditions. They provide standards with which substances or products must comply throughout their shelf-life or period of use. Different acceptance criteria may be required depending on the national or regional regulatory authorities.

5.2 Technical guidance

The technical guidance provided in this section shall be considered as the minimal requirements agreed between the participating pharmacopoeias. They do not preclude national or regional pharmacopoeias to supplement such requirements in their monographs due, e.g. to national/regional regulations.

5.2.1 Monographs for pharmaceutical substances

Prior to the preparation of any monograph, it is essential to gather as much information as possible on the substance in question.

In particular it is necessary to ascertain:

- whether the substance is of natural, synthetic or semi-synthetic origin;
- whether the substance is a mixture or a single entity;

- the method(s) of preparation of the substance;
- intrinsic properties of the substance that contribute to its identity and classification such as solubility or optical rotation;
- whether there are differences in physical form, for example, crystallinity or polymorphism since these properties may affect the behaviour of the substance ;
- whether a single optical isomer (e.g. enantiomer) as well as mixtures of isomers (e.g. racemate) are available;
- whether anhydrous or different hydrates are available;
- whether different entities (acid, base, salt, etc.) are available.

Substances that are to be described in a monograph may be members of a group of very similar substances (family).
A master monograph may be drafted stating the attributes common to all members of the family and that can be used to identify single members of the family (family monograph).

5.2.1.1 Monograph title

The International Nonproprietary Name (INN) or modified INN (INNM) established by WHO should be considered for use wherever it is available, while recognizing that individual pharmacopoeias may apply their own nomenclature policies.

5.2.1.2 General information to define the pharmaceutical substance

A pharmacopoeial monograph includes information regarding the pharmaceutical substance, such as:

- graphic formula. The recommendations of WHO on the drawing of structures should be followed;

- empirical/molecular formula and relative molecular mass. The latter is calculated based on the figures of the International Table of Relative Atomic Masses considering where appropriate the degree of hydration;
- Chemical Abstracts Service (CAS) registry number, if available;
- chemical name.

This implies, but is not limited to, investigating in particular:

- the possible existence of isomers so as to be able to specify which isomer is used or, otherwise, to state that the product is a mixture of isomers;
- in the case of an optical isomer, the absolute configuration is given by the *R*/*S* system at the asymmetrical centre(s) or any other appropriate system (e.g. for carbohydrates and amino acids);
- ascertaining the state of hydration or solvation by an appropriate technique, so as to distinguish clearly between the well-defined hydrates and solvates and the products that contain variable quantities of solvent(s). As regards the former, water or solvent content ranges are specified but for the latter only a maximum content is given. When a substance exists both in a non-hydrate or solvent-free form and in the form of (a) hydrate(s) or (a) solvate(s) with different water or solvent contents, and if all these forms are used and can be clearly distinguished, they may be treated as individual substances.

5.2.1.2.1 Combinations

In therapeutics, more or less well-defined chemical combinations or even mixtures are sometimes used. In such cases, it is necessary to specify precisely each component of the combination or mixture, with its chemical structure and the proportion in which it is present.

5.2.1.3 Content

Assay limits are specified between which the content falls. The content may be also defined in a one-sided manner. The assay limits take account of the precision of the

method as well as the acceptable purity of the substance. Assay limits are normally expressed with reference to the dried, anhydrous and/or solvent-free substance.

In setting these limits for the active ingredient content, account is taken of:

- the method of preparation, which determines the degree of purity that may be reasonably required;
- the precision and accuracy of the analytical method;
- where a separation technique is employed both for the test for related substances and the assay, content limits are set taking into account the maximum permitted amount of impurities and the analytical error;
- the evaluation of the tolerable degree of degradation during storage (since the limits are intended to apply throughout the shelf-life of the substance and not just at the time of testing);
- a sufficient number of experimental results obtained on several batches (at least 3), if possible, of different origins and ages.

5.2.1.4 Qualitative properties of the pharmaceutical substance

The statements under this heading may not be interpreted in a strict sense and are not regarded as analytical requirements. Caution statements may be included here.

The principal items that may be referred to are the following:

- appearance;
- solubility;

- stability factors;
- hygroscopicity;
- solid-state properties;
- other characteristics, as necessary.

5.2.1.5 Identification

The tests given in the identification section are not designed to give a full confirmation of the chemical structure or composition of the substance. They are intended to give confirmation with an acceptable degree of assurance that the substance is the one stated on the label. The physical and/or chemical tests and reactions, when taken together, that enter into the Identification section ensure, as far as possible, specificity. The specificity of the identification should be such that active substances and excipients exhibiting similar structures are distinguished. When an identification series is being investigated, it is desirable that other similar substances, whether or not they are the subject of monographs of the pharmacopoeia, are examined at the same time to ensure that a particular combination of tests within a series will successfully distinguish one similar substance from another. False positive reactions caused by the presence of tolerated impurities are to be avoided.

Some of the purity tests in a monograph may also be suitable for identification purposes, possibly in a modified form. A system of cross-references to the section(s) can be exploited. This is particularly relevant in cases where distinction between closely related materials depends on properties that are also parameters in purity or composition control. In some cases an organic impurities procedure may be introduced to differentiate the analyte from similar, common, dangerous adulterants.

In the case of a family monograph, identification of the type of substances may be supplemented by non-specific but discriminating tests to identify individual members of the family.

5.2.1.6 Impurities and other tests

5.2.1.6.1 Organic impurities

This section is principally directed at limiting impurities in chemical substances.

In the interest of transparency, information may be included on: the impurities controlled by a test; the approximate equivalent (percentage, ppm, etc.) of the prescribed limit in terms of the defined impurities or class of impurities.

Certain tests may apply to special grades (parenteral, dialysis solutions, etc.) or a test may have a special limit for a particular use: the particular application of a test/limit is indicated within the test.

Monographs should include tests and acceptance criteria for impurities that are likely to occur in substances used in approved medicinal products, insofar as the necessary information and samples (substance and impurities) are available from the producers. Monographs on organic chemicals usually have a test entitled “Related substances” (or a test with equivalent purpose under a different title), designed to control related organic impurities. Impurities to be controlled include: intermediates and by-products of synthesis, co-extracted substances in products of natural origin, degradation products. Monographs on active pharmaceutical ingredients (APIs) should take account of the principles defined in ICH guideline Q3A (R2) “Impurities in New Drug Substances”, or comparable guidelines and follow regulatory decision-making. Products of fermentation and semi-synthetic products derived therefrom, should be limited applying the same principles but be covered by thresholds considered appropriate for these products. The same principle applies to excipients.

Unusually potent or toxic impurities. In addition to the above-mentioned requirements, impurities that are unusually potent or produce toxic or unexpected pharmacological effects, need to be specifically considered. In this context requirements for genotoxic impurities may be followed.

Monographs frequently have to be designed to cover different impurity profiles because of the use of different synthetic routes and purification procedures by producers.

For pharmacopoeial purposes the objective of a purity test using a separation method will usually be the control of impurities derived from one or more known manufacturing processes and decomposition routes. However, the experimental conditions are chosen for the test, especially the detection system, so as not to make it unnecessarily narrow in scope.

Monographs should provide a reliable means of locating all specified impurities on the chromatogram. Identification of unspecified impurities is necessary if a correction factor is to be applied.

5.2.1.6.2 Inorganic impurities

Inorganic impurities include reagents, ligands and catalysts, elemental impurities, inorganic salts and other materials such as filter aids (where relevant).

Known impurities, likely to be present, are typically covered by specific tests.

5.2.1.6.3 Residual solvents

Residual solvents need to be controlled, for example, as outlined in the ICH Guideline Q3C.

5.2.1.6.4 Other tests

The following tests should be considered, but are not limited to :

- foreign anions and/or cations;
- loss on drying;
- semi-micro determination of water (Karl Fischer);
- micro determination of water (coulometric titration);
- sulfated ash/residue on ignition;
- residue on evaporation

- sterility;
- microbiological purity;
- bacterial endotoxins.

5.2.1.7 Assay

Assays are included in monographs unless otherwise justified. In certain cases, more than one assay may be necessary when:

- the substance to be examined consists of a combination of two parts that are not necessarily present in absolutely fixed proportions, so that the assay of only one of the two constituents does not make it possible correctly to determine the substance as a whole;
- the results of the quantitative tests do not fully represent the therapeutic activity, in which case a biological assay is included.

In the case of well-defined salts, the assay of only one of the ions, preferably the pharmacologically active component, is generally considered sufficient.

5.2.2 Monographs for finished products

5.2.2.1 General monographs

Where General monographs for pharmaceutical forms are prescribed, general tests may group together those tests that are applied to a specific pharmaceutical form and are not formulation specific; examples of this include uniformity of weight, friability and disintegration as applied to a tablet or the microbial quality of any finished product (i.e. a test for total aerobic microbial testing). These tests may be included in a general monograph for a pharmaceutical form, in this example, Tablets, as the test procedures are the same for all tablets.

Where prescribed, General monographs include analytical methods and acceptance criteria for all of the general tests required for a given pharmaceutical form.

5.2.2.2 General information to define specific finished product monographs

Specific tests group together those procedures that are required to provide evidence that a finished product is of a suitable quality and are specific to a particular pharmaceutical dosage form. Examples include identification, related substances assay and dissolution (for a finished product tablet monograph). Specific tests are measures of the purity, composition and drug release; these tests are dependent on the active substance and would be included in a finished product monograph.

It is necessary to ascertain:

- if the finished product contains a mixture or a single drug substance;
- whether the synthetic routes of the drug substance(s) used in the available finished products are different (the stability profile of the finished products may vary in accordance with this parameter);
- if the finished product monograph covers different entities (acid, base, salt, etc.) or not, e.g. when this is not possible;
- in case of polymorphism, if the crystallographic form of the entity must be mentioned in the finished product monograph; if different dosage strengths are described in one finished product monograph.

Monographs for specific finished products include analytical procedures and acceptance criteria for tests required for the specific finished product.

The monograph should be split up into the subsections including, but not limited to:

5.2.2.4.1 Monograph title

The titles of monographs for finished products combine the appropriate drug substance name and pharmaceutical dosage form.

The accepted name should be based on the INN or national name wherever it is available (the common name should be used where an INN or national name is not available); it is supplemented, when required, as appropriate by the International Nonproprietary Name Modified (INNM), as agreed by the users of INNs. Where possible the INN should be used in the monograph title as this would reflect the expression of strength of a finished product as recommended by ICH Guidelines. The name is followed by the nationally or regionally accepted pharmaceutical dosage form taxonomy (or published standard term).

For finished products containing more than one drug substance ("combination products"), the individual INNs should be used where possible. Combination Names (Co-names) may exist in national pharmacopoeias for prescribing purposes.

5.2.2.4.2 Definition

This constitutes an official definition of the product that is the subject of the monograph. Such statements may include inter alia elements relating to the active pharmaceutical substance, an expression of the content and other essential features of the dosage form. Where specified, the definition in the General monographs describes the scope of the monograph.

The following should be observed:

- the drug substance will be referred to in this section; it is **not** necessary to reproduce the defining information found in the drug substance monograph within this section of the finished product monograph (i.e. chemical name, etc.);
- any reference to producing a salt of the active moiety in situ during the manufacture of the finished product should be made in this section;
- the composition of individual components in a drug substance should be described under content where necessary; the definition would refer only to the name of the drug substance.

5.2.2.4.3 Content

Assay limits are specified between which the content of the drug substance in the finished product must fall. Limits for each active substance (if more than one) or individual components are included. The assay limits must take account of the precision of the method as well as the strength of the finished product. Assay limits are normally expressed with reference to the active moiety or the label claim**,** in accordance with national or regional requirements.

Specific assays should be used where possible, for example, liquid or gas chromatography. Specific assays remove interference from excipients (formulation matrix) which could lead to significant errors when using non-specific assays. Limits should be justified and account be taken of:

- the strength of the finished product; the stability of the active substance in a specific finished product. Unstable active substances may require an increased content;
- in the case of antibiotics determined by microbiological assay, the content limit is expressed in International Units (IU); where these exist a content limit is given in terms of a range, i.e. *"The precision of the assay is such that the fiducial limits of error are not less than 95% and not more than 105% of the estimated potency. The upper fiducial limit of error is not less than 97.0% and the lower fiducial limit of error is not more than 110.0% of the stated number of IU"*;
- see also the section *Assay*.

5.2.2.4.4 Identification

The tests given in the identification section are not designed to give a full confirmation of the chemical structure or composition of the product. They are intended to give confirmation with an acceptable degree of assurance that the product is the one stated on the label. Special attention must be given to the sample preparation to ensure that the active substance is adequately extracted from the sample matrix.

The minimum number of tests is used commensurate with providing adequate assurance of identity. For example, the monograph may contain at least two procedures to identify the active substance(s) in a pharmaceutical dosage form; one test may be sufficient if the technique used is considered to be a fingerprint of the active moiety (e.g. infrared absorption spectrophotometry).

5.2.2.4.5 Impurities and other tests

This section should include all of the specific tests that are required to prove the quality of the given pharmaceutical form and in line with the format of the pharmacopoeias in the different territories.

The Tests section is intended to:

- limit the impurities within the finished product. This includes degradation impurities throughout the shelf-life of the finished product and impurities that occur due to the manufacturing process. In certain circumstances it is necessary to control impurities from synthesis in the finished product, e.g. if they are known to be toxic or when they are detected in the test for related substances at a level greater than the limit for unspecified impurities;
- to ensure the homogeneity of the active substance(s) from dose to dose within the finished product;
- to take account of the influence of the sample matrix to restrict the release of the active moiety in the finished product (i.e. a dissolution test in a monograph for tablets);
- to limit the pyrogenic content of a parenteral finished product (i.e. a test for bacterial endotoxins or a monocyte activation test).

5.2.2.4.6 Impurities: Title of test(s)

Where the test is intended to control specified and unspecified impurities the title of the test should be Related Substances or Related compounds or similar in-line with national or regional practices *[glossary]*.

Where the test is intended to control one or a limited number of specified impurities the title of the test should indicate the impurity(ies) controlled.

5.2.2.4.7 Related substances [or Related compounds]

Further to the section on drug substance monographs, the following should be considered for related substances of finished product monographs:

- specific, quantitative techniques (i.e. HPLC) are preferred;
- non-specific or non-quantitative techniques should be used only if a specific method is not available or suitable;
- methods should be developed with the aim to control degradation products and impurities. In certain circumstances it is necessary to control impurities from synthesis in the finished product, e.g. if they are known to be toxic or when they are detected in the test for related substances at a level greater than the limit for unspecified impurities;
- impurities being limited above the limit for unknown impurities in a finished product should be identified using a reference standard or other suitable techniques.

Monographs should take account of the principles as, for example, defined in ICH guideline Q3B (R2) "Impurities in New Drug Products" and follow regulatory decision-making.

5.2.2.4.8 Performance testing

Depending on the dosage form adequate performance testing may need to be included in the monograph.

5.2.2.4.9 Uniformity

Pharmaceutical preparations presented in single-dose units shall comply with the test(s) as prescribed in the relevant specific dosage form monograph.

Acceptance criteria would be specified regionally for a specific product/pharmaceutical form.

5.2.2.5 Other tests

The following tests should be considered, but are not limited to, where applicable:

- *sterility*;
- *bacterial endotoxins*;
- *microbiological quality.*

5.2.2.6 Products of natural origin

Attention needs to be paid to the requirements in the different territories for minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products.

5.2.2.7 Assay

The Assay quantifies the amount of active substance in the finished product and certain excipients such as preservatives depending on national and regional legislation. Ideally the method used should be harmonized with that in the active substance or excipient monograph but this may not be possible because of the sample matrix.

Assays are included in all finished product monographs unless certain quantitative tests, similar to assays, are carried out with sufficient precision (uniformity of content, where a mean of individual results could be considered an accurate assay). In certain cases more than one assay may be necessary when:

- the finished product to be examined contains two, or more, active substances;
- for products such as antibiotics the results of the quantitative tests do not fully represent the therapeutic activity, in which case a microbiological assay and a test for composition are included.

Specific stability-indicating assays should be included in the monograph where possible. This avoids interference from the sample matrix.

7. ANALYTICAL TEST PROCEDURES AND METHODOLOGIES (ANALYTICAL METHOD)

Analytical test procedures and methodologies are employed to establish quality aspects such as identity, purity,, strength of drug substances and drug products. An analytical method mentioned in a pharmacopoeia should be simple, reliable, accurate, sensitive and specific.

A pharmacopoeia provides, e.g. physical, physicochemical and chemical methods for analysis of quality of pharmaceutical substances and drug products (finished dosage forms). The type of method applied for analysis depends on the nature of the substance and product.

The principles of method validation as, e.g. *[Ref: to WHO and ICH texts as above]* apply to all types of analytical procedures. It is established by demonstrating documentary evidence with respect to any particular pharmaceutical substance or product.

Glossary and Thesaurus

*[**Note from Secretariat**: will need to be developed and is intended to include the various terms used in the national and regional pharmacopoeias]*

Active pharmaceutical ingredient (API)

A substance used in a finished pharmaceutical product (FPP), intended to furnish pharmacological activity or to otherwise have direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to have direct effect in restoring, correcting or modifying physiological functions in human beings.

Dosage form

The form of the completed pharmaceutical product, e.g. tablet, capsule, elixir or suppository.

Finished pharmaceutical product (FPP)

A finished dosage form of a pharmaceutical product that has undergone all stages of manufacture, including packaging in its final container and labelling.

***