

# Annex 1

## Good pharmacopoeial practices

<b>1. Background</b>	68
<b>2. Purpose and scope of good pharmacopoeial practices</b>	69
<b>3. Glossary</b>	69
<b>4. Benefits of good pharmacopoeial practices</b>	70
<b>5. Implementation</b>	70
<b>6. Monograph development</b>	70
6.1 General considerations	71
6.1.1 Adoption of pharmacopoeial standards	72
6.1.2 Open and transparent process	73
6.1.3 Harmonization	73
6.1.4 Legal recognition	73
6.1.5 Compliance with a pharmacopoeial monograph	74
6.1.6 Analytical requirements	74
6.1.7 Acceptance criteria	74
6.2 Technical guidance	74
6.2.1 Monographs for pharmaceutical substances	75
6.2.2 Monographs for finished pharmaceutical products	80
<b>7. Analytical test procedures and methods</b>	84

# 1. Background

A pharmacopoeia's core mission is to protect public health by creating and making available public standards to help ensure the quality of medicines. Pharmacopoeia standards support regulatory authorities in controlling the quality of pharmaceutical substances, their finished pharmaceutical products (FPPs) and related materials and will provide a tool with which the user or procurer can make an independent judgement regarding quality, thus safeguarding the health of the public.

Today there are 49 pharmacopoeias in the world (according to the World Health Organization (WHO) list of pharmacopoeias, 2015). There are differences between these pharmacopoeias, including the use of technology reflected in each pharmacopoeia as well as the breadth of medicines and other articles included. Pharmacopoeias are embedded in their respective national or regional regulatory environment and reflect specifications approved by the regulatory body.

Efforts towards pharmacopoeial harmonization started more than a century ago. When WHO was created in 1948, this was included in its mandate. This led to the creation of *The International Pharmacopoeia*, which was the first global pharmacopoeial activity. Many others followed.

Pharmacopoeial harmonization has been defined by the Pharmacopoeial Discussion Group (PDG) as “when a pharmaceutical substance or product tested by the document's harmonized procedure yields the same results and the same accept/reject decision is reached”.

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

The 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 led to further 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.

The main suggestion emerging from all these events was the development of good pharmacopoeial practices (GPhP) to encourage harmonization, facilitated by WHO.

It was agreed to develop the GPhP 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 consultation process, which enables the 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 and scope of good pharmacopoeial practices

The primary objective of the GPhP guidance is to define approaches and policies in establishing pharmacopoeial standards with the ultimate goal of harmonization.

These GPhP describe a set of principles that provide guidance for national pharmacopoeial authorities (NPAs) and regional pharmacopoeial authorities (RPAs) that facilitates the appropriate design, development and maintenance of pharmacopoeial standards.

Although the principles may also apply to other products, the focus of these good practices is pharmaceutical substances and FPPs.

## 3. Glossary

Terms in this document are used in accordance with WHO terminology, while recognizing that individual pharmacopoeias may apply their own nomenclature policies.

**active pharmaceutical ingredient.** Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

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

**excipient.** A substance or compound, other than the active pharmaceutical ingredient and packaging materials, that is intended or designated to be used in the manufacture of a pharmaceutical product.

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

**period of use.** Utilization period of multidose products after opening, reconstitution or dilution of a solution.

**pharmaceutical substance.** Any substance of a defined quality used in the production of a pharmaceutical product, but excluding packaging materials. This includes active pharmaceutical ingredients and pharmaceutical excipients.

**shelf life.** The period of time during which a pharmaceutical product, if stored as indicated on the label, is expected to comply with the specification as determined by stability studies on a number of batches of the product. The shelf life is used to establish the expiry date of each batch.

## 4. Benefits of good pharmacopoeial practices

GPhP are designed to facilitate collaboration among pharmacopoeias, leading to possibilities for work-sharing, harmonization of standards and the recognition of published standards between NPAs and RPAs.

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

- 1) strengthening of global pharmacopoeial cooperation;
- 2) providing stakeholders with a better understanding of how pharmacopoeial standards are developed and maintained in a transparent manner;
- 3) improving cooperation between NPAs/RPAs and stakeholders (e.g. regulators, pharmaceutical industry) with a view to facilitating the harmonization of pharmacopoeial standards and reducing duplication of work;
- 4) increasing access to and the availability of affordable, quality medicines.

By establishing common practices, GPhP can facilitate adoption or adaptation of the standards from one pharmacopoeia by another pharmacopoeia, proactively harmonizing the requirements with considerably less effort than is currently needed.

GPhP should ultimately enable harmonization of pharmacopoeial standards.

## 5. 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.

## 6. Monograph development

Development of a monograph requires consideration of information and candidate materials. This information may come from donors, literature, various

publicly available sources, from other pharmacopoeias, or may be generated within the laboratory resources of a pharmacopoeia and/or of a competent authority (such as an official medicines control laboratory). The draft text should be displayed for public comments with sufficient time allowed for review and input by stakeholders.

Pharmacopoeias are encouraged to conform, where possible, to the work of harmonization initiatives (e.g. WHO, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and the PDG)).

## 6.1 General considerations

Pharmacopoeial monographs provide an important tool for assurance of the quality of marketed pharmaceutical ingredients and products through testing of their quality. They generally cover chemical, biological and herbal FPPs and their ingredients, which have either been approved by national regulatory authorities or are otherwise legally marketed. Some pharmacopoeias also include standards for items such as natural products, nutritional products and medical devices. The principles of GPhP apply equally to substances and products used in both human and veterinary medicine. It is recognized that different requirements may be applied to human and veterinary medicines, such as those included in the ICH and the corresponding Veterinary International Conference on Harmonization (VICH) requirements.

Specifications in pharmacopoeias are one facet of the overall control of the quality of FPPs and their ingredients (active pharmaceutical ingredients (APIs) and excipients). Monographs provide publicly available standards that a product or a component of a product is expected to meet during its shelf life. Thus, a substance should be able to demonstrate compliance with a pharmacopoeial monograph up to the point at which it is used to prepare an FPP. 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 developing a monograph it is important to consider the specifications (tests and acceptance criteria) needed to assure the quality of a given pharmaceutical substance or FPP. Specifications that limit market access by, for example, favouring one manufacturer to the exclusion of others should be avoided.

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

regardless of whether the requirements are specified in the specific monograph or are incorporated in general monographs. However, there may be situations where different acceptance criteria are required depending on the national or regional regulatory authorities. Additional tests might be added by NPAs and RPAs, depending on national or regional regulations.

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 FPPs. They are closely allied with good manufacturing practice (GMP) standards.

Pharmacopoeial standards should be available for FPPs and their APIs and associated materials at an appropriate time to support and benefit patients through the availability of medicines with consistent quality. They are usually based on the shelf-life specifications approved by regulatory authorities<sup>1</sup> or on the specifications of unlicensed products (e.g. compounded and other preparations, as defined by national or regional regulations).

The monographs may employ various validated analytical procedures for the tests that are designed to be suitable for a competent analyst to perform using established technologies and facilities.

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

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 regulators (including medicines regulatory authorities, official medicines control laboratories and inspectorates), the pharmaceutical industries (including manufacturers and trade associations), academia, health-care professionals and patient advocacy groups (as appropriate), and other stakeholders in the development of public standards.

### 6.1.1 Adoption of pharmacopoeial standards

- (a) Text in a pharmacopoeial monograph or general chapter is approved by an expert body of the pharmacopoeia, following publicly available rules and procedures. This includes public consultation and the application of conflict of interest and confidentiality rules.
- (b) Reference standards cited in a pharmacopoeia are also approved by a pharmacopoeial expert body.

<sup>1</sup> In the case of *The International Pharmacopoeia* this relates to the shelf-life specifications evaluated by the WHO Prequalification Team.

### 6.1.2 Open and transparent process

Pharmacopoeial standards are based on current scientific knowledge and reflect the quality of pharmaceutical substances and FPPs available.

Pharmacopoeias ensure openness and transparency throughout the development and revision of monographs and other texts, which includes:

- i. engaging stakeholders in the routine development and revision of pharmacopoeial standards through adequate and timely public notice and comment;
- ii. engaging stakeholders in the timely development and revision of standards to address major public health concerns;
- iii. general transparency of the pharmacopoeial approaches, including making work programmes publicly available;
- iv. good communication with stakeholders through forums, workshops and other interactions;
- v. timely response to user enquiries;
- vi. opportunities for user training and education on the pharmacopoeial process and finalized standards;
- vii. rapid correction of errors published in compendial text, when necessary;
- viii. 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.)

### 6.1.3 Harmonization

Pharmacopoeias should harmonize standards wherever possible through monographs and general chapters. Harmonization may occur through several processes including, but not limited to: adoption or adaptation<sup>2</sup> of existing standards; development of a new standard through coordinated consideration (prospective harmonization); revision of a standard between two or more pharmacopoeias (bilateral or multilateral harmonization); and creation or revision of standards through a harmonization initiative (e.g. PDG).

### 6.1.4 Legal recognition

Pharmacopoeial monographs may acquire legal status and then provide a basis for enforcement depending on applicable national or regional requirements.

<sup>2</sup> The source of the text should be indicated.

### 6.1.5 Compliance with a pharmacopoeial monograph

Any pharmaceutical substance or FPP 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. Subject to regulatory approval an alternative method of analysis may be used for routine analytical purposes. In this case it is necessary to provide a rationale for its inclusion, validation data and data comparing results obtained using the pharmacopoeial method and the alternative method.

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

### 6.1.6 Analytical requirements

Pharmacopoeial procedures and acceptance criteria 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.

### 6.1.7 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 pharmaceutical substances or FPPs must comply throughout their shelf life or period of use.

## 6.2 Technical guidance

The technical guidance provided in this section shall be considered as the minimum requirements agreed between the participating pharmacopoeias. They do not preclude national or regional pharmacopoeias from supplementing such requirements in their monographs in accordance with national or regional regulations.

## 6.2.1 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:

- the origin of the substance;
- the method(s) of preparation of the substance, if needed;
- whether the substance is a mixture or a single entity;
- whether different entities (e.g. acid, base or salt) are available;
- the physicochemical characteristics of the substance that contribute to its identity and classification, for example, 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 or solvates are available.

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

### 6.2.1.1 Monograph title

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

### 6.2.1.2 General information to define the pharmaceutical substance

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

- graphic formula;
- 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;
- the possible existence of isomers, so as to be able to specify either which isomer is present or to state that the substance 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);
- state of hydration or solvation, where relevant, ascertaining the state of hydration or solvation by an appropriate technique in order to distinguish clearly between substances which are well-defined hydrates and solvates and those that contain variable quantities of water or solvent(s):
  - for well-defined hydrates or solvates, water or solvent content ranges are specified;
  - for substances containing variable amounts of water or solvents, only a maximum content is given;
  - where substances exist as both non-hydrated (or non-solvated) and hydrated (or solvated) forms, and if all these forms are used and can be clearly distinguished, they may be treated as individual substances depending on the regulatory approach prevailing in the country or region.

In therapeutics, 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.

### 6.2.1.3 Content

Assay limits are specified between which the content must fall. In certain instances the content may be given only as a lower limit. 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 limits for the API 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 extent 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 release testing);
- a sufficient number of experimental results obtained on several batches (at least three), if possible, of different origins and ages.

#### 6.2.1.4 Qualitative properties of the pharmaceutical substance

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

The principal characteristics that may be referred to are:

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

#### 6.2.1.5 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 specificity of the identification should be such that pharmaceutical substances exhibiting similar structures can be 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 known impurities should 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 impurity procedure may be introduced to differentiate the analyte from similar, common, dangerous adulterants.

In the case of monographs for similar pharmaceutical substances, identification of the type of substances may be supplemented by selective but discriminating tests to identify individual members of the group.

### 6.2.1.6 Impurities and other tests

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

#### 6.2.1.6.1 Organic impurities

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

In the interests of transparency, information may be included on the impurities controlled by a test and the approximate equivalent (e.g. percentage or parts per million) of the prescribed limit in terms of the defined impurities or class of impurities.

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 and degradation products.

Monographs on pharmaceutical substances 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 should be covered by thresholds considered appropriate for these substances. 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.

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, especially the detection system, are chosen for the test so as not to make it unnecessarily narrow in scope.

Where monographs include a chromatographic method, this should provide a reliable means of locating all specified impurities on the chromatogram.

#### 6.2.1.6.2 *Inorganic impurities*

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

Where known impurities are present, these are typically covered by specific tests.

#### 6.2.1.6.3 *Residual solvents*

When applicable, residual solvents need to be controlled, for example, as outlined in the ICH guideline Q3C (Impurities: guideline for residual solvents).

#### 6.2.1.6.4 *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 (colorimetric titration);
- sulfated ash/residue on ignition;
- residue on evaporation;
- sterility;
- microbiological quality;
- bacterial endotoxins.

#### 6.2.1.7 *Assay*

Assays are included in monographs unless, for example:

- all the foreseeable impurities can be detected and limited with sufficient precision;
- certain quantitative tests, similar to assays, are carried out with sufficient precision;
- the tests performed are sufficient to establish the quality of the substance (usually a non-active ingredient, for example, ethanol and water).

In certain cases more than one assay may be necessary, for example, 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 to determine correctly the content of the substance as a whole.

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

## 6.2.2 Monographs for finished pharmaceutical products

General tests and acceptance criteria that are applied to a specific pharmaceutical dosage form (and are not specific to a particular formulation) may be grouped together, for example, uniformity of mass/content, friability and disintegration as applied to tablet testing. These tests may be included in a general monograph for a pharmaceutical dosage form, in this example, tablets, as the test procedures are the same for all tablets.

Specific tests group together those procedures that are required to provide evidence that an FPP is of a suitable quality, and are specific to a particular pharmaceutical dosage form. As an example, tests described in tablet monographs may include identification, related substances, assay and dissolution. Specific tests are designed to control the purity, composition and release; these tests are dependent on the pharmaceutical substance.

Prior to the preparation of any monograph it is essential to gather as much information as possible on the product in question. In particular it is necessary to ascertain:

- if the FPP contains a mixture or a single pharmaceutical substance;
- if the FPP can be prepared from different entities (e.g. acid, base or salt);
- in cases where the pharmaceutical substance exhibits polymorphism, if the crystallographic form of the entity should be identified in the FPP monograph;
- if the FPP is available in different strengths, whether all strengths can be controlled under one monograph.

### 6.2.2.1 Monograph title

The titles of monographs for FPPs combine the name of the pharmaceutical substance and the pharmaceutical dosage form.

The pharmaceutical substance 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, by the INN<sup>m</sup>. The name is followed by the nationally or regionally accepted pharmaceutical dosage form taxonomy (or published standard term).

For FPPs containing more than one pharmaceutical substance (“combination products”), the individual INNs should be used where possible.

Combination Names (Co-names) may exist in national pharmacopoeias for prescribing purposes.

#### 6.2.2.2 General information to define the finished pharmaceutical product

Such information may include elements relating to the API, an expression of the content and other essential features of the dosage form. An appropriate reference to the relevant general monographs may be included.

The following should be observed:

- the pharmaceutical substance will be referred to in this section; it is not necessary to reproduce the defining information found in the pharmaceutical substance monograph within this section of the FPP monograph (e.g. the chemical name);
- any reference to producing a salt of the active moiety *in situ* during the manufacture of the FPP should be made in this section;
- the definition only refers to the name of the pharmaceutical substance; where the content is expressed in terms other than those described in the title of the monograph, the limits stated under “Content” (see 6.2.2.3) should reflect the label claim.

#### 6.2.2.3 Content

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

Limits should be justified and account should be taken of:

- the strength of the FPP;
- the stability of the pharmaceutical substance in a specific FPP.

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, for example:

“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”.

#### 6.2.2.4 Identification

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

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

#### 6.2.2.5 Impurities and other tests

This section should include all of the specific tests that are required to prove the quality of the specific FPP.

The “Tests” section is intended to:

- limit the impurities within the FPP. This includes degradation impurities throughout the shelf life of the FPP and impurities that occur due to the manufacturing process. In certain circumstances it is necessary to control FPP impurities resulting from the synthesis of the pharmaceutical substance;
- ensure the homogeneity of the API(s) from dose to dose within the FPP;
- take account of the potential for the sample matrix to restrict the release of the active moiety in the FPP (i.e. a dissolution test in a monograph for tablets);
- limit the pyrogenic content of a parenteral FPP (i.e. a test for bacterial endotoxins or a monocyte activation test).

##### 6.2.2.5.1 *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.

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

##### 6.2.2.5.2 *Related substances (or related compounds)*

Further to the section on pharmaceutical substance monographs, the following should be considered for related substances tests specified in FPP monographs:

- specific, quantitative techniques (i.e. high performance liquid chromatography (HPLC)) are preferred;
- non-specific or non-quantitative techniques should be used only if a specific method is not available or is unsuitable;
- methods should be developed with the aim of controlling degradation products and impurities. In certain circumstances it is necessary to control impurities from synthesis of the pharmaceutical substance in the FPP (for example, when they are detected in the test for related substances at a level greater than the limit for unspecified impurities);
- impurities being controlled at a level above the limit for unspecified impurities should be identified using a reference standard or other suitable techniques.

The principles outlined in, for example, ICH guideline Q3B (R2) (*Impurities in new drug products*) could be used as a starting point.

#### 6.2.2.6 Performance testing

Depending on the dosage form, adequate performance testing may need to be included in the monograph. Such tests may include, but are not limited to, dissolution or deposition of the emitted dose.

#### 6.2.2.7 Uniformity

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

Acceptance criteria will be specified regionally for a specific product or pharmaceutical form.

#### 6.2.2.8 Other tests

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

- sterility;
- bacterial endotoxins;
- microbiological quality;
- if necessary, tests for excipients such as antioxidants and antimicrobial agents.

#### 6.2.2.9 Products of natural origin

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

#### 6.2.2.10 Assay

The assay quantifies the amount of API in the FPP. It may also quantify certain excipients, such as preservatives, depending on national and regional legislation. Where possible the method used should be harmonized with that in the pharmaceutical substance monograph, but this may not be possible because of the sample matrix.

Assays are included in all FPP monographs unless certain quantitative tests, similar to assays, are carried out with sufficient precision (for example, 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, for example, where the FPP contains two or more APIs.

For products such as antibiotics, the results of the quantitative tests may not fully represent the therapeutic activity, in which case a microbiological assay and a test for composition are included.

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.

Whenever possible, a stability-indicating procedure should be used for the assay. Generally, chromatographic procedures are preferred. When a non-stability-indicating assay is proposed, a separate stability-indicating impurity procedure should be provided.

## 7. Analytical test procedures and methods

Analytical test procedures and methods are employed to establish quality aspects such as identity, purity and content of pharmaceutical substances and FPPs. An analytical method and/or technique specified in a pharmacopoeia should be robust, reliable, accurate, precise, sensitive, specific and use readily available materials and equipment.

A pharmacopoeia provides different types of methods, mainly physical, physicochemical or chemical methods and microbiological tests, for the analysis of pharmaceutical substances and FPPs. The type of method applied for analysis depends on the nature of the substance or product.

The principles of method validation apply to all types of analytical procedures in a pharmacopoeia. However, it is the responsibility of the user to verify that a particular method is valid for the particular pharmaceutical substance or FPP being tested.

The validation of analytical procedures described in monographs should comply with the requirements as laid down, for example, in the *WHO*

*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 guideline Q2 (R1) (*Validation of analytical procedures: text and methodology*).

