3.2.2.2 Analytical requirements

The tests can be placed in one of two categories, general (or physical) testing and specific (chemical) testing. Where possible, analytical techniques used in pharmacopoeias should reflect those used in the pharmaceutical industry and encompass widely-used modern techniques. The analyst is not precluded from employing alternative methods, including methods of micro-analysis, in any assay or test if it is known that the method used will give a result of equivalent accuracy. Local reference materials may be used for routine analysis, provided that these are calibrated against the official reference materials. In the event of doubt or dispute, the methods of analysis, the reference materials and the reference spectra of the pharmacopoeia are alone authoritative.

Where possible, monographs for finished products should contain procedures that an experienced analyst could perform without the need for secondary analysis or method development.

Procedures used in new monographs should be suitably validated and, where possible, the validation should conform to the published expectations of the pharmacopoeia, for example, ICH guidance.

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. Pharmacopoeial monographs apply throughout the shelf-life of a finished product. Compliance of a product with pharmacopoeial requirements demands that the product meets all mandatory aspects of the appropriate monograph and that those requirements shall be interpreted in the light of any relevant General Notices prescribed within the pharmacopoeia.

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. As chromatographic methods become more precise, it will become

increasingly possible to combine precision with specificity and economise on analytical effort and time.

3.2.2.3 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.

3.2.2.4 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 form. Examples include identification, dissolution, related substances and assay (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.

Monographs are based on the specifications for finished products approved by licensing authorities or internal specifications of licensed "specials" manufacturers. Interested parties should be invited to participate in the elaboration of the monograph before publication.

Prior to the preparation of any monograph, it is essential to gather as much information as possible on the available finished products from all stakeholders.

In particular it is necessary to ascertain:

- whether 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);
- whether different entities (acid, base, salt, etc.) are used in different finished products;
- if a finished product made with one entity is interchangeable with another made with a different entity;
- the release and shelf-life specifications of available finished products.

Monographs for specific finished products include analytical procedures and acceptance criteria for all of the tests required for the specific finished product. The monograph should be split up into the subsections:

3.2.2.4.1 Monograph title

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

The regionally accepted name, e.g. within the EU, the INN should be used wherever it is available (the common name should be used where an INN is not available); it is supplemented as appropriate by The International Nonproprietary Name Modified (INM), 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 INN or INNM is followed by the regionally accepted pharmaceutical form, e.g. in the EU this is described in the Standard Terms publication,

published by the European Directorate for the Quality of Medicines and HealthCare (EDQM).

For finished products containing more than one drug substance ("combination products"), the individual INNs should be used where possible (i.e. "Amoxicillin and Potassium Clavulanate Tablets x/y mg Tablets"). Combination Names (Co-names) may exist in national pharmacopoeias for historical prescribing; where these exist, the national pharmacopoeia would select the monograph title as necessary.

3.2.2.4.2 Action and use

Where included (not all pharmacopoeias include this information), the statement reflects the main pharmacological action and/or the main use of the finished product. It is provided for information and it is not intended to restrict the clinical use of the finished product.

3.2.2.4.3 Production

Where included (not all pharmacopoeias include this information), the production statements draw attention to particular aspects of the manufacturing process and constitute mandatory instructions to manufacturers. A production statement is only required when there is a specific test that needs to be performed but a method capable of analysing all available marketed products is not available. For finished products, the inclusion of production statements is the exception rather than the rule.

3.2.2.4.4 Definition

This constitutes an official definition of the substance 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 prescribed, 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 (e.g. Neomycin Tablets contain Neomycin Sulfate).

3.2.2.4.5 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 component 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.

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. In Europe, the generally accepted content limit is 95.0% to 105.0% of label claim. Alternate limits may be applied where justified and account should be taken of:

- the strength of the finished product. Very low strength finished products are difficult to manufacture and it may be permitted to increase the acceptable content limit. Further testing to show content uniformity would be required for these products;
- the stability of the active substance in a specific finished product. Unstable active substances may degrade over the shelf life of the finished product and require an increased content limit to make the product economically viable. Toxicological

data would be required to ensure the impurities (degradants) would not pose a risk to the patient;

- in the case of antibiotics determined by microbiological assay, the content limit is expressed in International Units; 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"*;
- biological products whose content may be defined by potency;
- see also the section *Assay*.

3.2.2.4.6 Characteristics

A description may be included if particular characteristics provide additional information on the expected appearance of the finished product. This section may not be relevant to a specific finished product monograph as the information may be included in a general monograph. Careful consideration to the inclusion of colour, size and shape of a finished product should be made as these can vary depending on the manufacturer of the finished product and regional requirements. References to odour and taste should not be included. Solubility, hygroscopicity and solid-state properties are not required in this section of a finished product monograph. Stability factors would be considered under a separate storage statement where the finished product cannot be stored under ambient conditions.

3.2.2.4.7 Identification

The purpose of the Identification section of a monograph is to provide confirmation of the identity of the active substance(s) in the finished product. The physical and/or chemical tests and reactions are the same as those included in sections 3.2.1.5.1 to 3.2.1.5.10, however, 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 form; one test may be sufficient if the technique used is considered to be a fingerprint of the active moiety (e.g. infrared).

3.2.2.4.8 Specific tests

While it is an essential function of the monograph to ensure adequate purity in the interests of public health, it is not the aim of the pharmacopoeia to impose excessive requirements that restrict unnecessarily the ability of manufacturers to produce compliant products.

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 specific tests in sections 3.2.1.6.3 to 3.2.1.6.16.1, where applicable, also apply to finished product monographs.

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 synthetic impurities in the finished product, e.g. when they are detected in the test for related substances at a level greater than the limit for unspecified impurities;
- the homogeneity of the active substance(s) within the finished product;
- 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);
- the pyrogen content of a parenteral finished product (i.e. a test for bacterial endotoxins/monocyte activation).

3.2.2.4.9 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.

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

Where two techniques/systems are required to control all of the impurities and both limit specified and unspecified impurities the titles of the test should be Related Substances A and Related Substances B, etc.

3.2.2.4.10 Related substances

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

- Non-specific or non-quantitative techniques should not be used (i.e. TLC);
- Methods should be validated using ICH Guidelines;
- Methods should be developed with the aim to control degradents and impurities;
- Impurities being limited above the limit for unknown impurities in a finished product should be identified using a reference material;

3.2.2.4.11 Dissolution

This requirement is used for solid oral dose finished products.

Regionally accepted dissolution apparatus should be used wherever possible. For example:

- Round-bottom dissolution vessel;
- paddle agitation at 50 rpm;
- dissolution medium maintained at 37 ± 0.5 °C;

- where feasible use 0.1 M hydrochloric acid as the dissolution medium;
- 45 minute run time;
- filter the dissolution medium immediately; removing the possibility of undissolved particles of active material causing errors (centrifuge should not be used);
- where possible use ultraviolet (UV) to quantify the active released. Where UV cannot be employed, use the LC conditions from the Assay (adapted as necessary). A reference material with a declared content should be used;
- regionally approved acceptance criteria should be included.

3.2.2.4.12 Uniformity of content

Products with a content of active substance less than 2 mg and/or less than 2% by mass comply with the uniformity of content requirements of single-dose preparations. If the preparation has more than one active substance, the requirement applies only to those active substances which correspond to the above conditions.

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

Sample preparation should be based on a single unit in a given solvent. The quantification should follow the requirements for a specific assay; LC is preferred (the requirements under 3.2.1.7 would apply).

3.2.2.5 Sterile finished products

Where it is essential for a finished product to be sterile, the following requirements are included in the monograph:

- *Sterility*. Include a requirement where this is not invoked as a General monograph requirement or where a modification to the requirement is necessary.

- ***Bacterial endotoxins***. Include a requirement where this is not invoked as a General monograph requirement or where a modification to the requirement is necessary.

3.2.2.6 Microbiological quality

In the manufacture, packaging, storage and distribution of certain finished products, suitable means are taken to ensure their microbial quality; acceptance criteria are provided where control is necessary; recommendations on microbiological aspects are provided by the pharmacopoeia.

3.2.2.7 Abnormal toxicity

Included where necessary, in particular, for finished products where the active ingredient or excipients are known to be of natural origin. The use of experimental animals should be reduced wherever possible. Where necessary, consider the inclusion of this requirement under Production to allow manufacturers to replace the use of experimental animals with a validated in vitro alternative.

3.2.2.8 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.

3.2.2.9 Assay

The Assay quantifies the amount of active substance in the finished product. Ideally the method used should be harmonized with that in the active substance 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;
- the results of the quantitative tests do not fully represent the therapeutic activity, in which case a biological assay and a test for composition are included.

Specific assays should be included in the monograph where possible. This removes interference from the sample matrix. Every assay method proposed must be validated.

3.2.2.9.1 *Non-specific assays*

- *Ultraviolet and visible spectrophotometry*
- *Volumetric analysis*

Non-specific assay procedures should only be used if LC cannot be used. Where these techniques are suitable for use the methods must be in line with the requirements specified under 3.2.1.7.1 to 3.2.1.7.2.

3.2.2.9.2 *Specific assays*

Where possible LC and a reference material with a declared content should be used, in line with the requirements specified in sections 3.2.1.7.3.

3.2.2.10 Storage

Although the statements given under this heading in a monograph of the Pharmacopoeia do not constitute pharmacopoeial requirements, the appropriate information to safeguard the quality of a pharmacopoeial material during storage is to be given where the finished product cannot be stored under ambient conditions.

Manufacturers should be requested to provide stability data. In considering the guidance to be given in the monograph, the behaviour of the material towards exposure to

atmospheric air, various degrees of humidity, different temperatures and daylight will be taken into account.

3.2.2.11 Labelling

As the labelling of medicines is subject to international agreements and supranational and national regulations, the indications given under LABELLING are not exhaustive: they consist of mandatory statements (necessary for the application of the monograph) and other statements that are included only as recommendations. When the term "label" is used in the pharmacopoeia, the statements may appear on the container, the package, a leaflet accompanying the package, or a certificate of analysis accompanying the product, in accordance with the provisions of regulations issued in the territory in which the medicinal product is to be used.

3.2.2.12 Impurities

Information on impurities that are known to be detected by the prescribed tests and that have been considered in defining the acceptance criteria should be included in the monograph in a transparency statement, wherever possible. The transparency statement should list all specified impurities covered by the monograph. Impurities that are additional to those published in the drug substance monograph should include a molecular structure and chemical nomenclature.

3.2.2.2 Tests for pharmaceutical preparations (by compounding)

Or

3.2.3. Monographs for compounded/extemporaneous preparations [BP, Russian Pharmacopoeia, text as received from USP]

I. Introduction

Compounded/extemporaneous preparations involve the preparation, mixing, assembling, altering, packaging and labeling of a drug, drug-delivery device or device in accordance with a licensed practitioner's prescription, medication order or initiative based on the practitioner/patient/pharmacist/compounder relationship in the course of professional practice. Compounding can include the following special consideration to be given to the

fact that medical devices and drugs for animals may not be included in all pharmacopoeias:

- preparation of compounded/extemporaneous preparations for human use following a licensed practitioner's prescription;
- preparation of compounded/extemporaneous preparations for hospital patients following a licensed practitioner's medication order;
- preparation of compounded/extemporaneous preparations or medical devices for regularly needed drugs;
- preparation of compounded/extemporaneous drugs for animals;
- preparation of drugs or devices for the purposes of, or as an incident to, research (clinical or academic), teaching or chemical analysis;
- preparation of drugs and devices for prescriber's office use where permitted;
- preparation of compounded/extemporaneous preparations for both human and animal patients based on a licensed practitioner's outpatient prescription or inpatient medical order;
- preparation of drugs or devices in anticipation of prescription drug orders based on routine, regularly observed prescribing patterns;
- reconstitution or manipulation of commercial products that may required the addition of one or more ingredients;
- preparation of drugs or devices for the purposes of, or as an incident to, research (clinical or academic), teaching, or chemical analysis;
- preparation of drugs and devices for prescriber's office use where permitted by federal and state law.

This section of GPhP helps define good practices for developing pharmacopoeial monographs for compounded/extemporaneous preparations. Pharmacopoeial monographs for compounded/extemporaneous preparations help ensure the quality of compounded/ extemporaneous preparations used for patient care. They also help ensure uniform, high quality preparations that are consistent from institution-to-institution.

II. Approach

Pharmacopoeial monographs for compounded/extemporaneous preparations can include formulas (ingredients and quantities), specific directions to correctly compound the particular preparation, packaging and storage information, labeling information, pH (when appropriate), beyond-use dates (BUDs) based on stability-indicating studies and detailed validated assays and tests for degradation impurities.

III. Monograph development

1. Pharmacopoeial monographs for compounded/extemporaneous preparations generally are developed by a pharmacopoeia and its expert committees rather than being donated by a manufacturer, like traditional pharmacopoeial monographs. Typical sources of pharmacopoeial monographs for compounded/extemporaneous preparations include:
    (a) laboratory studies;
    (b) peer-reviewed literature;
    (c) donated scientific data (including method development, validation data, and stability studies).

2. Pharmacopoeial monographs for compounded/extemporaneous preparations may be developed using laboratory conducted method development, validation and stability studies.

3. Pharmacopoeial monographs for compounded/extemporaneous preparations may be developed using peer-reviewed literature that has been evaluated on stringent criteria.

4. It is preferable to have a reference active pharmaceutical ingredient (API) monograph available for pharmacopoeial monographs for

compounded/extemporaneous preparations.

5. BUDs should be assigned conservatively. When assigning a BUD, compounders shall consult and apply drug-specific and general stability documentation and literature when available and should consider:
    - the nature of the drug and its degradation mechanism ;
    - the dosage form and its components;
    - the potential for microbial proliferation in the preparation;
    - the container in which it is packaged;
    - the expected storage conditions;
    - the intended duration of therapy.

- When a manufactured product is used as the source of the API for a non-sterile compounded preparation, the compounder shall refer to the manufacturer for stability information and to the literature for applicable information on stability, compatibility, and degradation of ingredients; and shall use his or her compounding education and experience.

IV. Stability information/beyond-use dating for non-sterile compounded/ extemporaneous preparations

Compounded/extemporaneous preparations should be stored under conditions that prevent contamination and minimize degradation.

While it is preferable to assign a BUD based on laboratory-derived stability data in the pharmacopoeial monographs for non-sterile compounded/extemporaneous preparations, the following default parameters may be used in the absence of stability data: These maximum BUDs are recommended for non-sterile compounded/extemporaneous preparations in the absence of stability information that is applicable to a specific drug or preparation:

(a) **For non-aqueous formulations.** The BUD is not later than the time remaining until the earliest expiration date of any API or six months, whichever is earlier.

(b) **For water-containing oral formulations.** The BUD is not later than 14 days when stored at controlled cold temperatures.

(c) **For water-containing topical/dermal and mucosal liquid and semi-solid formulations.** The BUD is not later than 30 days.

1. The BUD shall not be later than the expiration date/shelf-life on the container of any component. Susceptible preparations should contain suitable antimicrobial agents to protect against bacteria, yeast and mould contamination inadvertently introduced during or after the compounding process. When antimicrobial preservatives are contraindicated in such compounded preparations, storage of the preparation at controlled cold temperature is necessary; to ensure proper storage and handling of such compounded/extemporaneous preparations by the patient or caregiver, appropriate patient instruction and consultation is essential.

V. Stability information/beyond-use dating for sterile compounded/extemporaneous preparations

1. In addition to chemical stability information, microbiological purity and safety is important to sterile compounded/extemporaneous preparations (CSPs). It is preferable to include laboratory-derived stability and sterility information into pharmacopoeial monographs for CSPs. In the absence of sterility and bacterial endotoxin testing (when appropriate), the following default storage times may be used based on the microbial contamination risk level of the preparation. The risk level is assigned primarily according to the potential for microbial contamination during the compounding of low-risk level CSPs and medium-risk level CSPs or the potential for not sterilizing high-risk level CSPs, any of which would subject patients to risk of harm, including death. These maximum storage times are

recommended for CSPs in the absence of sterility testing the specific preparation:

(a) For a low-risk level preparation, in the absence of passing a sterility test, the storage periods cannot exceed the following time periods: before administration, the CSPs are properly stored and are exposed for not more than 48 hours at controlled room temperature, for not more than 14 days at a cold temperature, and for 45 days in solid frozen state between –25 °C and –10 °C.

(b) For a medium-risk level preparation, in the absence of passing a sterility test, the storage periods cannot exceed the following time periods: before administration, the CSPs are properly stored and are exposed for not more than 30 hours at controlled room temperature, for not more than 9 days at a cold temperature, and for 45 days in solid frozen state between –25 °C and –10 °C.

(c) For a sterilized high-risk level preparation, in the absence of passing a sterility test, the storage periods cannot exceed the following time periods: before administration, the CSPs are properly stored and are exposed for not more than 24 hours at controlled room temperature, for not more than 3 days at a cold temperature, and for 45 days in solid frozen state between –25 °C and –10 °C.

2. The laboratory-derived sterility information evaluates the suitability of the sterilization method (filtration, steam or dry heat) and container-closure system and validates the sterility and bacterial endotoxin testing. However, stability testing, sterility testing and bacterial endotoxin testing are required for BUDs longer than the default storage times described above.

VI. Nomenclature

1. Pharmacopoeial monographs for compounded/extemporaneous preparations can be named using the following convention: **[medicine name] dosage form**

2. Some pharmacopoeias may use the following convention for compounded/ extemporaneous preparations that are used for both humans and animals: **[medicine name] compounded [route] [dosage form]**

3. Some pharmacopoeias may use the following convention for compounded/ extemporaneous pharmaceutical preparations that are used for animals only: **[medicine name] compounded [route] [dosage form], veterinary**

VII. Components of the compounded preparation monograph

1. Title
2. Definition (lists the acceptable range of labelled amount of main ingredient(s))
3. Formula (lists all ingredients and quantities)
4. Specific directions to correctly compound the particular preparation
5. Assay:
   - procedures for a validated stability-indicating assay
6. Specific tests:
   - pH (for appropriate preparations)
   - sterility tests (for CSPs)
   - bacterial endotoxin tests (for CSPs except for inhalation and ophthalmic administration)
   - other tests, as appropriate (e.g. for degradation impurities)

7. Additional requirements:
   - Packaging and storage information
   - Labelling information. Pharmacopoeial labelling requirements are not comprehensive and only those statements that are necessary to demonstrate compliance with the monograph are mandatory. National and

international requirements may not apply to compounded/extemporaneous preparations and national guidance should be available.

- BUD (based on stability studies or parameters provided above)

[*3.2.3 Monographs on biologicals*] *Action:* on hold, to be discussed later]

3.2.4 Monographs on herbals [received from IPC]

3.2.4.1 Introduction

Herbal medicines have been used by humanity since time immemorial for various health-care needs. In some communities they still comprise the core element of their health-care systems. Medicinal plants are widely distributed throughout the world but most abundantly in tropical countries. It is estimated that about 25% of all modern medicines are directly or indirectly derived from higher plants.

Herbal medicines/traditional medicines are usually the mixtures of several chemical components. Their complex nature poses the challenge for analysis and quality control. Multiple factors affect the quality of herbal medicines. A few of them are climatic conditions for growth of plants, sampling procedures, nature of processing, conditions of storage, time of harvesting, protection from pests/rodents, lack of adequate regulations, etc.

While herbal medicines are well integrated into the health-care systems of many nations, there is a need to promote their use. Thus, pharmacopoeial herbal monographs specifying the quality standards for such medicines help ensure that the herbal medicines are of required quality and this generates public confidence. Also they serve as a reference for stakeholders such as manufacturers, academicians, health-care providers, regulators, etc.

Pharmacopoeial herbal monographs may contain information including the definition of the herbal ingredient relative to the monograph title followed by specifications. The specifications may cover the various tests for critical quality attributes of the herbal

ingredients, procedures and acceptance criteria. 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.

Inclusion of a herbal monograph in pharmacopoeias may consist of the following criteria, but is not restricted to:

- the herbs should have a therapeutic activity;
- it should have a specific name and a definitive botanical identity;
- availability and usage in trade and commerce;
- public health interest;
- knowledge and availability of a specific chemical compound of well-characterized structure (either responsible for the biological activity of the herb (bio-marker) or a chemical compound known to be present in the herb even if not responsible for biological activity (chemical/ analytical marker);
- availability of a quantitative method for estimation of chief ingredients/biomarkers for such a compound;
- knowledge of safety of the herb and its sustainability (monographs may also be prepared and included in the pharmacopoeia if there is knowledge that there are good efforts to improve sustainability, even if the plant material is at present in any red lists);
- in case of some herbs if more than one "cultivar" or variety exists that differ in size, shape or contents of compounds but is of the same botanical identity as per the genera and species, two different and distinguishable monographs may be prepared and included.