Control by Pharmacopoeias

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Questions

1. Who controls the development, production and use of drugs?
2. What are the fundamental principles of the state policy in the field of medicinal product circulation?
3. What is state registration of medicines? For which products state registration is not required?
4. What is the master file?
5. What drug quality standards do you know?
6. What is the pharmacovigilance system?
1. Introduction
2. Terminology of Drugs
3. Drug Design and Quality standards
4. Falsification of Medicines
5. Quality Assurance in Medicines
6. Control by Pharmacopeias
7. Trends in Pharmaceutical Industry
The principles and practices outlined in the WHO document on 'Good Practices in the Manufacture and Quality Control of Drugs' serve as technical guidelines for governmental authorities for the development of quality control systems for medicines to be sold and distributed in the country of origin or for export.

There should at all times be close relationships between the regulatory agency on the one hand and the representatives of the pharmaceutical industry, and experts in scientific research and in clinical medicine, to ensure that national and international regulations for quality control can be adapted to the changing requirements resulting from scientific advances and public attitudes.
The term 'competent authority' means the national, supranational or international body or organization vested with the authority for making decisions concerning the question. It may, for example, be a national pharmacopoeia authority, a licensing authority or an official control laboratory.
The History of Medicines

- **BC**: Remedies prepared from natural sources (plant extracts, etc).
- **1803**: Alkaloid morphine was first isolated.
- **1828**: Alkaloid caffeine was first isolated.
- **90s XIX**: Aspirin used as an analgesic, synthesis of antipyrine.
- **30s XX**: Synthesis of sulfonamides.
- **40s XX**: Industrial production of penicillin.
- **50s and later**: Obtaining of hormones, synthetic antibiotics etc.
Although older writings exist which deal with herbal medicine, the major initial works in the field are considered to be:

- **the Edwin Smith Papyrus** in **Egypt**
- **Pliny’s pharmacopoeia** (Rome)
- **De Materia Medica**, a five-volume book originally written in **Greek** by **Pedanius Dioscorides**

(is considered to be precursor to all modern pharmacopoeias, and is one of the most influential herbal books in history. In fact it remained in use until about CE 1600)

A number of early pharmacopoeia books were written by **Persian physicians**
<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1025</td>
<td>The <em>Canon of Medicine</em> of Avicenna is published.</td>
</tr>
<tr>
<td>1025</td>
<td>Works by Ibn Zuhr (Avenzoar) are published.</td>
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<tr>
<td>1561</td>
<td>The term <em>Pharmacopoeia</em> first appears (Basel, Switzerland).</td>
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<tr>
<td>1820</td>
<td>The first USP created a system of standards.</td>
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<tr>
<td>1864</td>
<td>The first British Pharmacopoeia was published.</td>
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<tr>
<td>1866</td>
<td>The first Russian Pharmacopoeia was published.</td>
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Global Harmonization

Today’s pharmacopoeias focus mainly on assurance of quality of products by various tools of analytical sciences. The aim to achieve a wide global harmonization of quality specifications for selected pharmaceutical products, excipients and dosage forms came with increased globalization and reciprocal collaboration.

History of these approaches goes back to 1902–1925 when agreements established a “Unified” Pharmacopoeia. In 1929 the "Brussels Agreement" stipulated the League of Nations to carry out related administrative functions. Eight years later, in 1937, the first meeting of the “Technical Commission of Pharmaceutical Experts” was held.
An important date in the history of quality assurance of medicines is

1948

when the First World Health Assembly (WHA) approved the Expert Committee on Unification of Pharmacopoeias to continue this work

One year later (1949)

the WHA renamed it the Expert Committee on International Pharmacopoeia
Today there are 49 pharmacopoeias in the world (according to 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.

It was agreed to develop the GPhP (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 consultation process, which enables the participation of all stakeholders and users in the development process.
Pharmacopoeial monographs can be used by manufacturers, regulators and other stakeholders for quality control of active pharmaceutical ingredients (APIs) and finished products against internationally recommended specifications.

Pharmacopoeial requirements in countries form part of national legislation, defining the specifications which pharmaceutical products circulating on their market must fulfil.
Pharmacopoeias

There are national, regional and international pharmacopoeias as you see.

Compared to national and regional pharmacopoeias, The International Pharmacopoeia (Ph. Int.) is issued by WHO as a recommendation with the aim to provide international standards – including less technically demanding alternatives where needed – for adoption by Member States and to help achieve a potentially global uniformity of quality specifications for selected pharmaceutical products, excipients and dosage forms.
The International Pharmacopoeia was created to help promote harmonized and suitable quality control testing standards among WHO Member States. It aims to provide analytical tests that can be performed with the recommended equipment for first-stage and medium-sized pharmaceutical quality control laboratories in all regions of the world, including remote areas.
What is a Pharmacopeia
Regional pharmacopoeias and compendia are now playing an increasingly important role in providing guidance on the quality control of drugs, excipients and pharmaceutical formulations, and in the reference substances in pharmacopoeial specifications for various procedures.

The pharmacopeia in the EU is prepared by a governmental organization, and has a specified role in law in the EU.
The European Pharmacopoeia (Ph. Eur.) was created by eight Member States in 1964 and today consists of 36 Member States and the European Union (EU), which are signatory to the Convention on the Elaboration of a European Pharmacopoeia.

Ph. Eur. members are: Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg etc.

In addition there are 24 observers, including 23 countries and WHO.

The 8th Edition consists of two initial volumes (8.0) and 8 non-cumulative supplements (8.1 to 8.8). Each volume contains a complete table of contents and index. Volume 1 and 2 combined contain 2224 monographs, 345 general chapters illustrated with diagrams or chromatograms and 2500 descriptions of reagents.
Pharmacopoeias

National pharmacopoeias continue to contribute to the control of quality standards of products in accepted use within the countries in which they operate.

In the U.S., the USP-NF (United States Pharmacopeia – National Formulary) has been issued by a private non-profit organization since 1820.

In the U.S. when there is an applicable USP-NF quality monograph, drugs and drug ingredients must conform to the compendial requirements (such as for strength, quality or purity) or be deemed adulterated or misbranded under the Federal food and drug laws.
Some progress has been made under the banner of the International Council on Harmonization (ICH), a tri-regional organization that represents the drug regulatory authorities of the European Union, Japan, and the United States.

Representatives from the Pharmacopoeias of these three regions have met twice yearly since 1990 in the Pharmacopoeial Discussion Group to try to work towards "compendial harmonisation".

Specific monographs are proposed, and if accepted, proceed through stages of review and consultation leading to adoption of a common monograph that provides a common set of tests and specifications for a specific material (not surprisingly, this is a slow process)
Pharmacopoeias

National/regional legislation often includes *reference to other pharmacopoeias* in case their own pharmacopoeial texts are not available.

Thus, the EU pharmaceutical legislation and hence the legislation of all EU Member States includes references both at the national/regional and international levels.

Historic and language ties also play a role:

For example the Portuguese pharmacopoeia is also accepted in the legislation from Brazil and other countries where Portuguese is an official language (Mozambique, Guinea or Sao Tomé e Princípe, for instance).
The development of GPhP

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.

The development of good pharmacopoeial practices (GPhP) to encourage harmonization, facilitated by WHO

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.
Purpose and scope of GPhP

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*.

*finished pharmaceutical products*
Pharmacopoeias

For **which products** does the pharmacopoeia provide specifications?
### Number of monographs included in pharmacopoeias

<table>
<thead>
<tr>
<th>Scope</th>
<th>APIs+ excipients</th>
<th>Finished dosage forms</th>
<th>Biologicals</th>
<th>General monographs + methods</th>
<th>Supplementary information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Organization, region or country</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>International</td>
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<td></td>
</tr>
<tr>
<td>WHO (Ph. Int.)</td>
<td>441</td>
<td>141</td>
<td>N/S**</td>
<td>82</td>
<td>14</td>
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<td>EU (Ph. Eur.)</td>
<td>1850</td>
<td>30</td>
<td>295</td>
<td>22</td>
<td>3210</td>
</tr>
</tbody>
</table>

N/S – not specified in country’s response
Pharmacopoeias

Let us remember some definitions

Active pharmaceutical ingredient (API)

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.
Pharmacopoeias

Let us remember some definitions

**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 (drug)**
Any substance of a defined quality used in the production of a pharmaceutical product, but excluding packaging materials (API + 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 (is used to establish the expiry date of each batch).
Benefits of GPhP

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.
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.

When implementing a pharmacopoeial method, the user must assess whether and to what extent the suitability of the method under the actual conditions of use needs to be demonstrated according to relevant monographs, general chapters and quality systems.
Pharmacopoeial monographs provide an important tool for assurance of the quality of marketed pharmaceutical ingredients and products through testing of their quality

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

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
Monograph development

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 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. Pharmacopoeial Discussion Group (PDG))

Legal recognition

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

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
Monograph development

Analytical requirements

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.

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.

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.
Pharmacopoeia, pharmacoepia, or pharmacopoea (literally, "drug-making“, φάρμακον and ποι), in its modern technical sense, is a book containing directions for the identification of compound medicines, and published by the authority of a government or a medical or pharmaceutical society.

A quality specification is composed of a set of appropriate tests that will confirm the identity and purity of the product, ascertain the strength (or amount) of the active substance and, when needed, its performance characteristics.

Reference substances are used in testing to help ensure the quality, such as identity, strength and purity, of medicines.

Descriptions of preparations are called monographs (in a broader sense it is a reference work for pharmaceutical drug specifications).
The State Pharmacopoeia includes **general** and **individual pharmacopoeial monographs** approved by authorized agencies and published in the form of classified compendium thereof.

**General pharmacopoeial monographs of the State Pharmacopoeia**

set general requirements to the quality of medicinal products, pharmaceutical substances, including requirements to individual stages of their commercial production, to medicinal plant raw materials, reference standards used for quality control of medicinal products, pharmaceutical substances, medicinal plant raw materials, to methods of quality control of medicinal products, to the test procedures and equivalence assessment of generic medicinal products as related to the brand-name medicinal products.
Individual pharmacopoeial monographs

set requirements to the quality of specific medicinal products, pharmaceutical substances, medicinal plant raw materials, reagents, excipients, packaging materials used in the commercial production and pharmacy manufacture of medicinal products

The manufacturer’s pharmacopoeial monograph (to be approved by authorized agencies e.g. the Ministry of Health in Belarus)

for a medicinal product of domestic manufacture is developed by the manufacturer of the state taking into consideration the requirements of general and individual pharmacopoeial monographs of the State Pharmacopeia
Which has priority, a general monograph or an individual monograph?

Basic principle is that general and individual monographs are complementary and one does not overrule the other.

Exceptions are clearly indicated either in the general monograph or in the individual one.
Types of Monographs

- Drug substances
- Excipients
- Finished dosage forms
- General methods and requirements:
  - oral sold dosage forms, e.g. tablets
  - dissolution testing…
Substances and preparations that are the subject of an individual monograph are also required to comply with relevant, applicable general monographs.

Cross-references to applicable general monographs are not normally given in individual monographs.

General monographs on dosage forms apply to all preparations of the type defined.

The requirements are not necessarily comprehensive for a given specific preparation and requirements additional to those prescribed in the general monograph may be imposed by the competent authority.
Monographs for pharmaceutical substances

Before preparing any monograph is necessary to gather as much information as possible on this matter. In particular, it is necessary to establish:

- 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 behavior 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
Monographs for pharmaceutical substances

- Monograph title (INN – International Nonproprietary Name)
- General information to define the pharmaceutical substance (graphic formula, chemical name, the possible existence of isomers etc.)
- Potential adulteration
- Content (the method of preparation, which determines the degree of purity, the evaluation of the extent of degradation during storage etc.)
- Qualitative properties of the pharmaceutical substance (solubility, stability factors, hygroscopicity etc.)
- Identification
- Impurities and other tests
- Some others
Monographs for pharmaceutical substances

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.

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
LABELLING
The label states:

- the number of units of toxin per vial with a statement that units are product specific and not applicable to other preparations containing botulinum toxin type A,
- the name and the volume of the diluent to be added for reconstitution of a dried product.

methanol R and 9 volumes of methylene chloride R and dilute to 10 ml with the same mixture of solvents.

Reference solution (b). Dissolve 10 mg of bromazepam CRS and 10 mg of temazepam CRS in a mixture of 1 volume of methanol R and 9 volumes of methylene chloride R and dilute to 10 ml with the same mixture of solvents.

Apply separately to the plate 5 μl of each solution. Develop over a path of 10 cm using a mixture of 30 volumes of diethylamine R and 70 volumes of ether R.

Dry the plate in a current of air and examine in ultraviolet light at 254 nm. The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a). The test is not valid unless the chromatogram obtained with reference solution (b) shows two clearly separated principal spots.

D. Dissolve about 20 mg in 5 ml of methanol R. Add 5 ml of water R and 1 ml of a 10 g/l solution of ferrous ammonium sulphate R. A violet colour develops.

E. To 0.15 g in a porcelain crucible add 0.5 g of anhydrous sodium carbonate R. Heat over an open flame for 10 min. Allow to cool. Take up the residue in 10 ml of dilute nitric acid R and filter. To 1 ml of the filtrate add 1 ml of water R. The solution gives reaction (a) of bromides (2.3.1).
Monographs for pharmaceutical substances

Potential adulteration

This section constitutes requirements for the whole supply chain, from manufacturers to users (e.g. manufacturers of intermediate products, bulk products and finished products, where relevant).

The absence of this section does not imply that attention to features such as those referred to above is not required.

Content (the quantitative 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
Qualitative properties of the pharmaceutical substance

The principal characteristics that may be referred to are:

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

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.
**Solubility**

*Note:* In statements of *solubility* in the Characters section, the terms used have the following significance, referred to a temperature between 15 °C and 25 °C

<table>
<thead>
<tr>
<th>Descriptive term</th>
<th>Approximate volume of solvent in millilitres per gram of solute</th>
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</thead>
<tbody>
<tr>
<td>Very soluble</td>
<td>less than 1</td>
</tr>
<tr>
<td>Freely soluble</td>
<td>from 1 to 10</td>
</tr>
<tr>
<td>Soluble</td>
<td>from 10 to 30</td>
</tr>
<tr>
<td>Sparingly soluble</td>
<td>from 30 to 100</td>
</tr>
<tr>
<td>Slightly soluble</td>
<td>from 100 to 1000</td>
</tr>
<tr>
<td>Very slightly soluble</td>
<td>from 1000 to 10000</td>
</tr>
<tr>
<td>Practically insoluble</td>
<td>more than 10000</td>
</tr>
</tbody>
</table>

The term 'partly soluble' is used to describe a mixture where only some of the components dissolve.

The term 'miscible' is used to describe a liquid that is miscible in all proportions with the stated solvent.
Impurities and other tests

- organic impurities
- inorganic impurities
- unusually potent or toxic impurities
- Indication of permitted limit of impurities
- residual solvents
- other tests:
  - 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 etc.
Monographs for pharmaceutical substances

Impurities and other tests

✓ organic impurities
✓ inorganic impurities
✓ unusually potent or toxic impurities
✓ Indication of permitted limit of impurities
✓ residual solvents
✓ other tests:
  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 etc.
Monographs for pharmaceutical substances

Storage

The articles described in the pharmacopoeia are stored in such a way as to prevent contamination and, as far as possible, deterioration.

Where special conditions of storage are recommended, including the type of container and limits of temperature, they are stated in the monograph (e.g. In an airtight container or Protected from light).

Warnings

Materials described in monographs and reagents specified for use in the pharmacopoeia may be injurious to health unless adequate precautions are taken.

The principles of good quality control laboratory practice and the provisions of any appropriate regulations are to be observed at all times.

Attention is drawn to particular hazards in certain monographs by means of a warning statement; absence of such a statement is not to be taken to mean that no hazard exists.
Monographs on excipients may have a section on functionality-related characteristics.

The characteristics, any test methods for determination and any tolerances are not mandatory requirements.

They may nevertheless be relevant for use of the excipient and are given for information (section General statements).
Reference standards


The European Pharmacopoeia Commission establishes the official reference standards, which are alone authoritative in case of arbitration. These reference standards are available from the European Directorate for the Quality of Medicines & HealthCare (EDQM)

Information on the available reference standards and a batch validity statement can be obtained via the EDQM website
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
Monographs for finished pharmaceutical products (FPP)

✓ **Monograph title** (the name of the pharmaceutical substance (INN) + the pharmaceutical dosage form)

✓ **General information to define the finished pharmaceutical product**

✓ **Content** (assay limits are specified between which the content of the pharmaceutical substance in the FPP must fall)

✓ **Identification**

✓ **Impurities and other tests**

✓ **Performance testing** (dissolution or deposition of the emitted dose)

✓ **Uniformity**

✓ **Other tests** (sterility, bacterial endotoxins, microbiological quality etc.)

✓ **Some others**
Monographs for finished pharmaceutical products (FPP)

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

✓ impurities being controlled at a level above the limit for unspecified impurities should be identified using a reference standard or other suitable techniques
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.

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.

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.
For **herbal drugs**, the sulfated ash, total ash, water-soluble matter, alcohol-soluble matter, water content, content of essential oil and content of active principle are calculated with reference to the drug that has not been specially dried, unless otherwise prescribed in the monograph.
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.
Analytical test procedures and methods (Validation)

The principles of method validation apply to all types of analytical procedures in a pharmacopoeia.

*According to US FDA: “establish documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes”*

The equipment used in pharmaceutical manufacturing has an important role in maintaining medicine quality. Thus the validation considered a prerequisite for quality starts with installation qualification (IQ) (equipment), followed by operation qualification (OQ), and then performance qualification (PQ).

The test methods given in monographs and general chapters have been validated in accordance with accepted scientific practice and current recommendations on analytical validation.
The industry should have a validation team comprising staff in engineering, production, quality assurance, and quality control.

**Systems, equipment, and machinery for different technologies in the pharmaceutical industry with necessary validation**

<table>
<thead>
<tr>
<th>Technology</th>
<th>Systems, equipment, and machineries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Utilities</td>
<td>Air (heating, ventilating, and air conditioning), compressed air, vacuum system, boiler, potable water, water for injection</td>
</tr>
<tr>
<td>Production</td>
<td>Tablet compression machine, capsule filling machine, blister machine, liquid filling machine, fluid bed dryer, blender, lyophilizer, oven, autoclave etc.</td>
</tr>
<tr>
<td>Quality control</td>
<td>pH meter, incubator, centrifuge, dissolution tester, disintegrator, friability tester, freezer, refrigerator, HPLC, UV-VIS, FTIR, NIR, GC, GC-MS</td>
</tr>
</tbody>
</table>
Bioequivalence (in vivo equivalence)

according to US FDA: “pharmaceutical equivalents whose rate and extent of absorption are not statistically different when administered to patients or subjects at the same molar dose under similar experimental conditions”

Pharmaceutical equivalence (in vitro equivalence)

Bioequivalent products can be substituted for one another, and as a whole they show therapeutic equivalence to each other
Equivalence Relationships

Original Drug

Pharmaceutical equivalency
- API
- Dosage form
- Dose
- Route of administration
- Labeling

Bioequivalency
- PK profile
- Cmax
- Tmax
- AUC

Generic

Cmax (maximum concentration in plasma)

Tmax (time for maximum concentration in plasma)

Difference
- Shape, color, flavor or excipients may be different

PK profile (the pharmacokinetic profile)

AUC (area under curve)

Documents of generic drug’s chemistry, manufacturing steps, quality control measures and drug’s stability required
Inspection of manufacturing site also required
Drug plasma concentration over time
In vitro in vivo correlations of solid dosage forms
Monograph Example

Monograph of Didanosine

- **DIDANOSINE**
- **C\textsubscript{10}H\textsubscript{12}N\textsubscript{4}O\textsubscript{3}**
- **Relative Molecular Mass.** 236.2
- **Chemical name.** 9-[(2R,5S)-5-(hydroxymethyl)tetrahydrofuran-2-yl]-1,9-dihydro-6H-purin-6-one; 9-(2,3-dideoxy-\(\beta\)-D-glycero-pentofuranosyl)-1,9-dihydro-6H-purin-6-one; 2',3'-dideoxyinosine(DDI); **CAS Reg. No.** 69655-05-6
- **Description.** A white to almost white powder
- **Solubility.** Sparingly soluble in water; slightly soluble in methanol R and ethanol (95 per cent) R
- **Category.** Antiretroviral (Nucleoside Reverse Transcriptase Inhibitor)
- **Storage.** Didanosine should be kept in a tightly closed container
Monograph of Didanosine

Requirements

- Identity test
- Specific Optical Rotation
- Heavy metals
- Sulfated ash
- Loss on drying
- Related Substances
- Assay
- Impurities
- Reagents

Assay

- Dissolve about 0.200 g, accurately weighed, in 50 ml glacial acetic acid R1 and titrate with perchloric acid (0.1 mol/l) VS as described under “Non-aqueous titration”; Method A (Vol. 1, p.131) determining the end-point potentiometrically.
- Each ml of perchloric acid (0.1 mol/l) VS is equivalent to 23.62 mg of \( \text{C}_{10}\text{H}_{12}\text{N}_{4}\text{O}_{3} \)
Monograph of Didanosine

Related Substances (extract)

Note: Prepare fresh solutions and perform the tests without delay

✔ Carry out the test as described under “High-performance liquid chromatography” (Vol. 5, p. 257), using a stainless steel column (25cm x 4.6mm), packed with octadecylsilyl base-deactivated silica gel for chromatography R (5µm)

✔ Maintain the column temperature at 20 – 25°C

✔ The mobile phases for gradient elution consist of a mixture of aqueous phase (Mobile phase A) and methanol (Mobile phase B), using the following conditions:

Mobile phase A: A 0.05 M solution of ammonium acetate R adjusted to pH 8.0 using a 20% v/v ammonia (~260 g/l) TS

Mobile phase B: Methanol

1 Hypersil BDS is suitable
Monograph of Didanosine

Impurities

A. 1,7-dihydro-6H-purin-6-one (hypoxanthine)

B. 9-β-D-ribofuranosyl-1,9-dihydro-6H-purin-6-one (inosine)

C. 9-(2-deoxy-β-D-erythro-pentofuranosyl)-1,9-dihydro-6H-purin-6-one (2'-deoxyinosine)

D. 9-(3-deoxy-β-D-erythro-pentofuranosyl)-1,9-dihydro-6H-purin-6-one (3'-deoxyinosine)

E. 9-(2,3-anhydro-β-D-ribofuranosyl)-1,9-dihydro-6H-purin-6-one (2',3'-anhydroinosine)
Thank You!

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