Drug Chemistry and Technology Basics,
Cleaner Production and Mega-Trends in Pharmaceutical Industry

Control by Pharmacopoeias

Dr. As. Prof. Anastasiya Sladkova
Dr. Sci. Prof. Natalya Loginova

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?

LECTURES

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

Introduction

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

Introduction

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.

The History of Pharmacopoeias

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***

The History of Pharmacopoeias

VII	pharmacopoeial work in Tang Dynasty (China)
1025	***The Canon of Medicine*** of Avicenna
XII	works by Ibn Zuhr (Avenzoar)
XIV	works by Ibn Bayta
XVI	***Antidotarium Florentinum*** (Florence)
1561	term **Pharmacopoeia** first appears (Basel, Switzerland)
1820	the first **USP** created a system of standards
1864	the first **British Pharmacopoeia** was published
1866	the first **Russian Pharmacopoeia** was published

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

Global Harmonization

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**

Pharmacopoeias

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

Pharmacopoeias

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

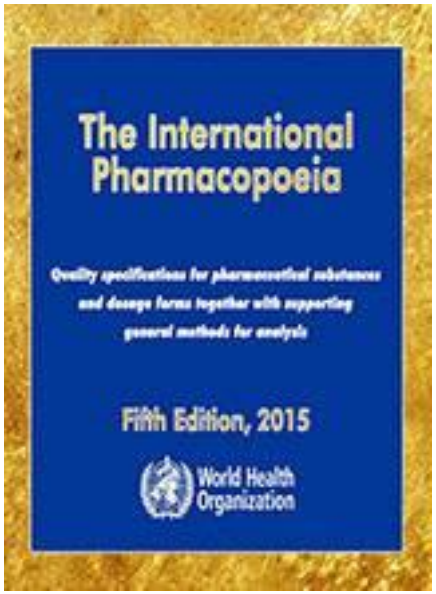
There are **national, regional** and **international** pharmacopoeias as you see

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

Pharmacopoeias

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

Pharmacopoeias

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

Ph. Eur.

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

ICH

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 r**eference 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

The development of GPhP

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*

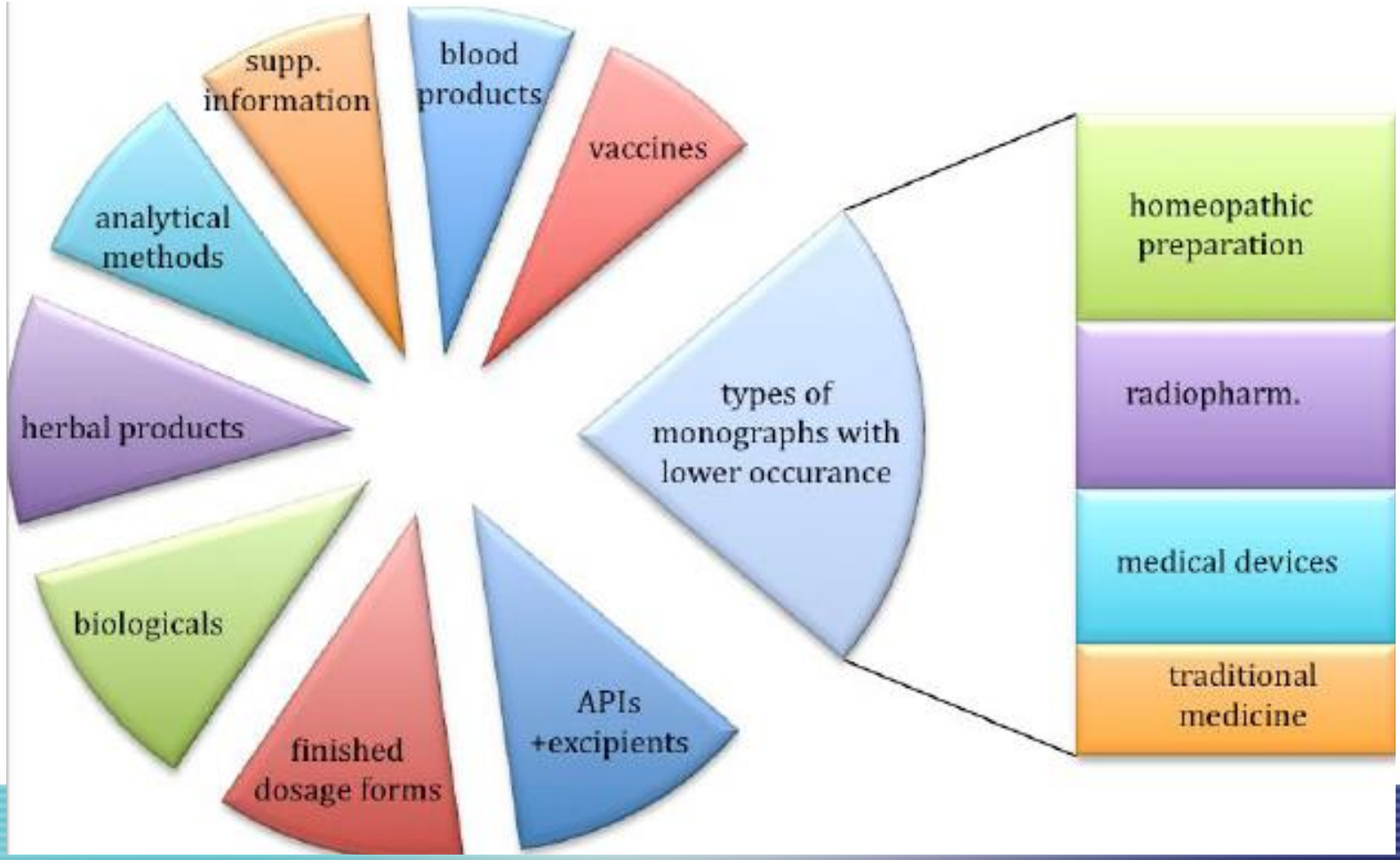
These GPhP describe a set of principles that provide guidance for **national pharmacopoeial authorities (NPAs)** and **regional pharmacopoeial authorities (RPAs)** that facilitates the appropriate design, development and maintenance of pharmacopoeial standards

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?



Pharmacopoeias

Number of monographs included in pharmacopoeias

Scope Organization, region or country	APIs+ excipients	Finished dosage forms	Biologicals	General monographs + methods	Supple-mentary information
International					
WHO (Ph. Int.)	441	141	N/S**	82	14
Regional					
EU (Ph. Eur.)	1850	30	295	22	3210

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

Implementation of GPhP

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

Monograph development

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

The State (National) Pharmacopoeia

Pharmacopoeia, pharmacopeia, 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 (National) Pharmacopoeia

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

The State (National) Pharmacopoeia

Individual pharmacopoeial monographs

set requirements to the quality of specific medicinal products, pharmaceutical substances, 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…

General Monographs

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

Example

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.

01/2005:0879

BROMAZEPAM

Bromazepamum

$C_{14}H_{10}BrN_3O$ M_r 316.2

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

Monographs for pharmaceutical substances

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

Descriptive term	Approximate volume of solvent in millilitres per gram of solute			
Very soluble	less than	1		
Freely soluble	from	1	to	10
Soluble	from	10	to	30
Sparingly soluble	from	30	to	100
Slightly soluble	from	100	to	1 000
Very slightly soluble	from	1 000	to	10 000
Practically insoluble	more than			10 000

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

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

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

Functionality-related characteristics of excipients

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

Certain monographs require the use of **reference standards** (chemical reference substances, herbal reference standards, biological reference preparations, reference spectra) (chapter *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

Monographs for finished pharmaceutical products (FPP)

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

Monographs for finished pharmaceutical products (FPP)

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

Herbal drugs

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

Analytical test procedures and methods (Validation)

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

Analytical test procedures and methods (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

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

Equivalence Relationships

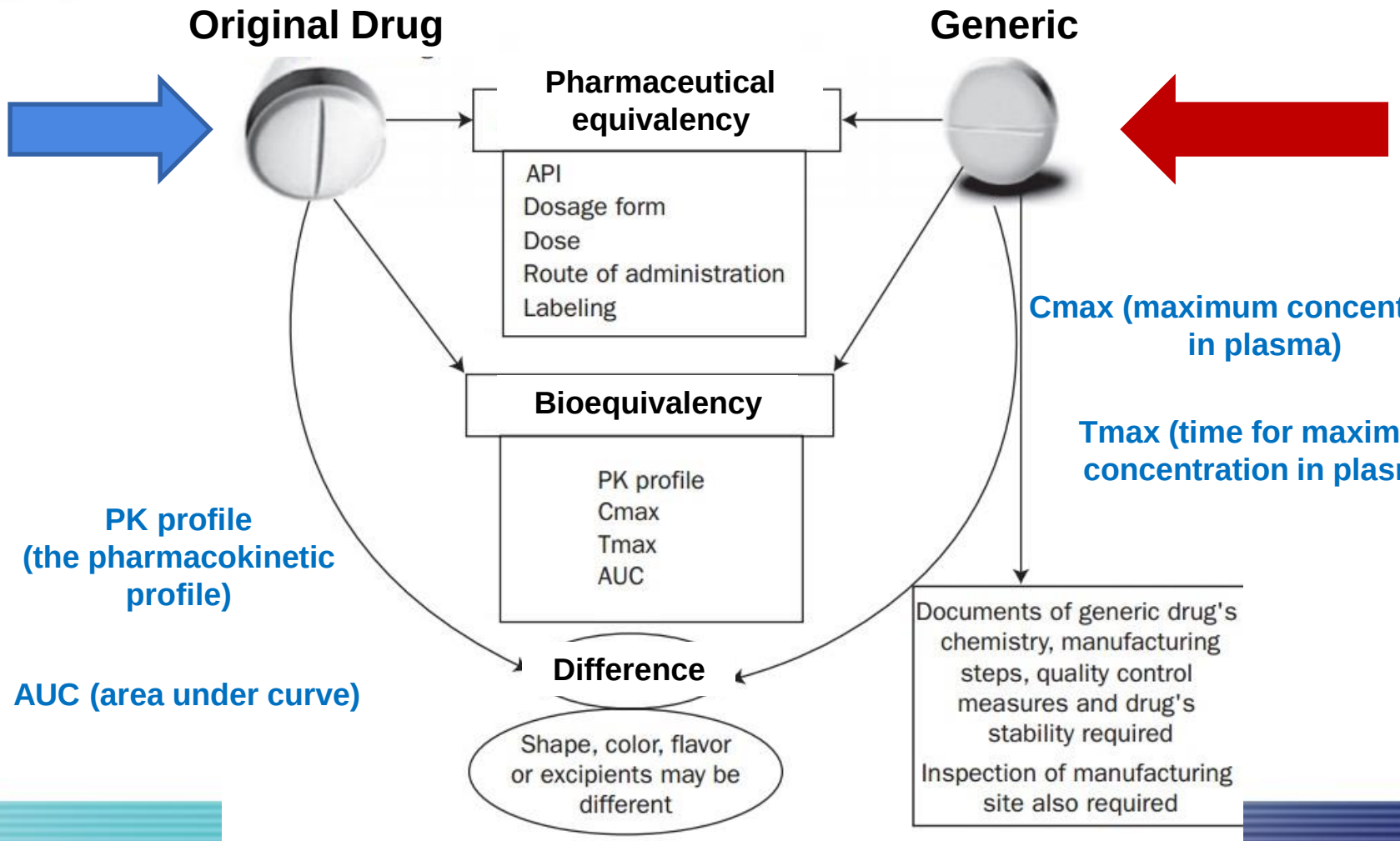
Bioequivalence (*in vivo* equivalence)

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)

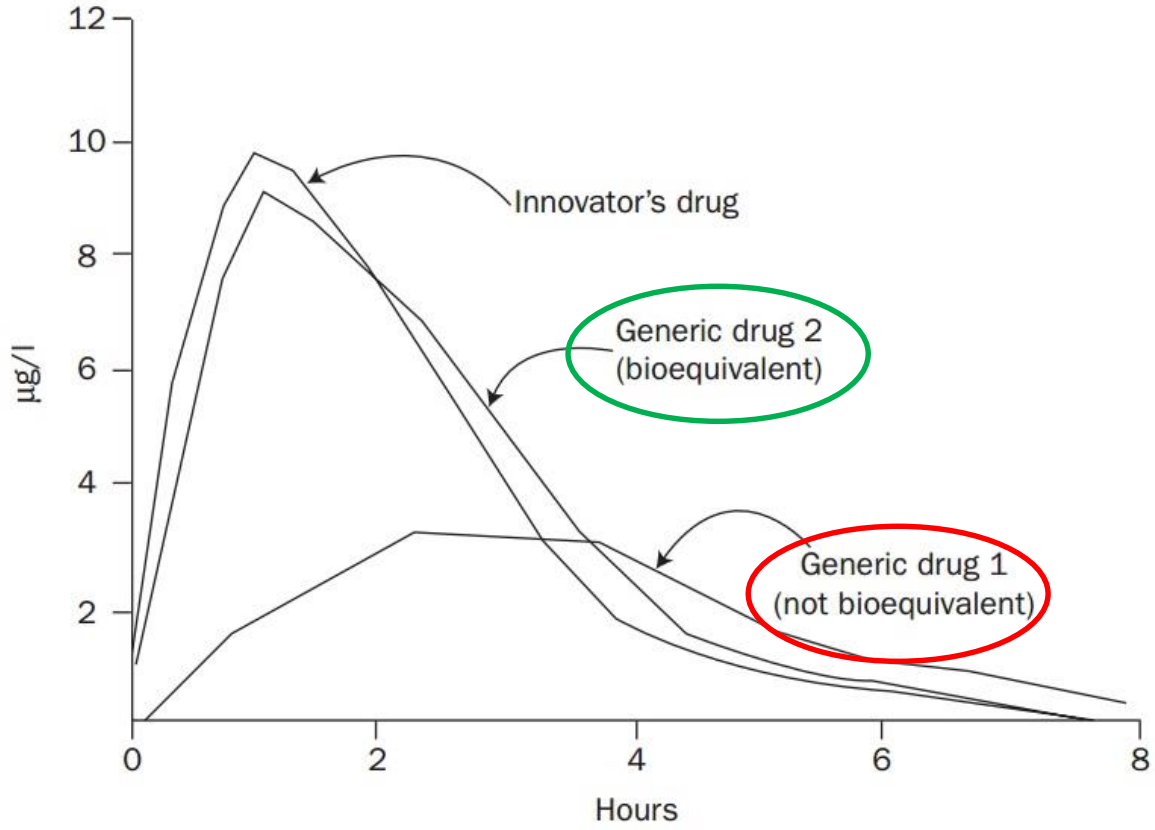
Bioequivalent products can be substituted for one another, and as a whole they show therapeutic equivalence to each other

Equivalence Relationships

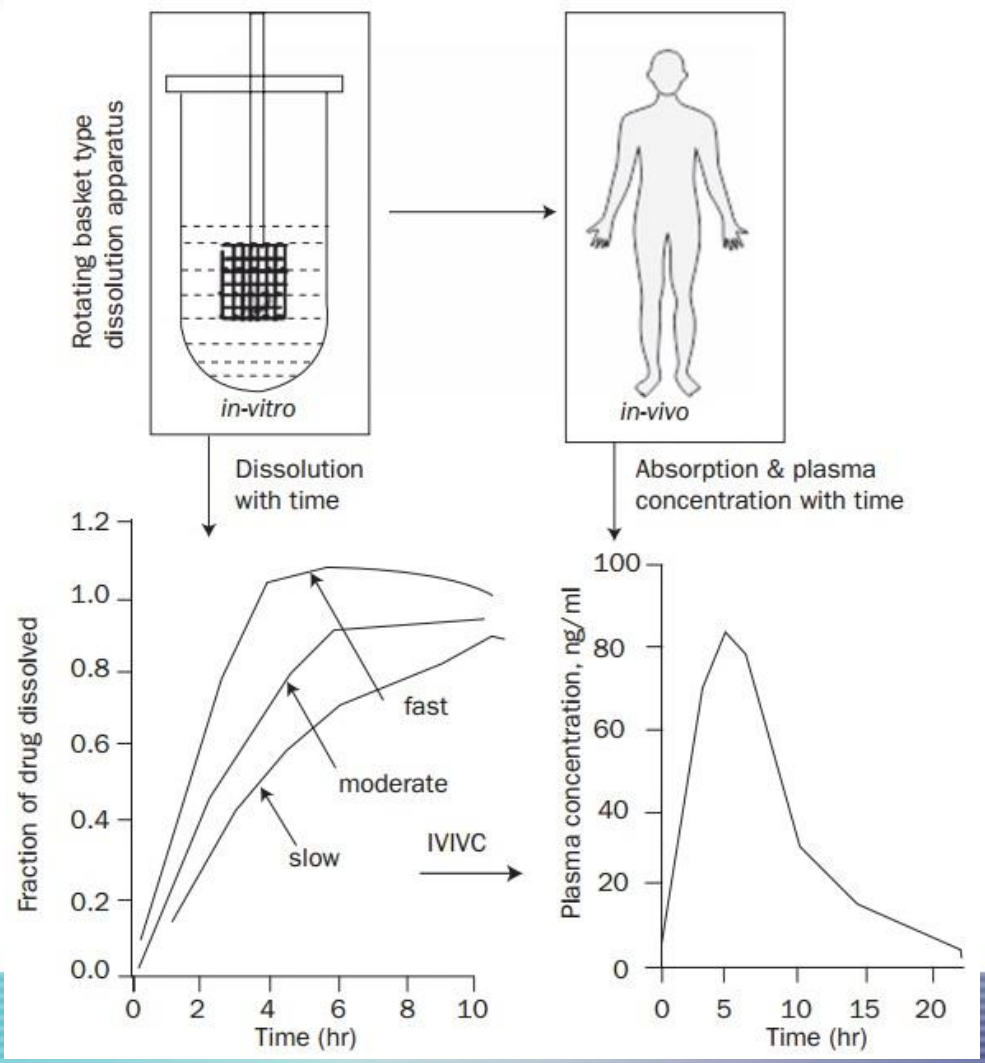


Equivalence Relationships

Drug plasma concentration over time

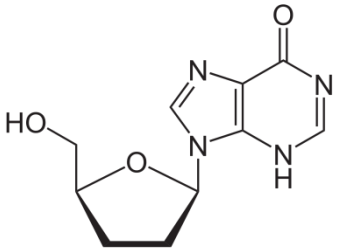


In vitro in vivo correlations of solid dosage forms



Monograph Example

Monograph of Didanosine



- ✓ **DIDANOSINE**
- ✓ **$C_{10}H_{12}N_4O_3$**
- ✓ **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-β-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; slightlysoluble in methanol R and ethanol (95 per cent) R
- ✓ **Category.** Antiretroviral (Nucleoside Reverse Transcriptase Inhibitor)
- ✓ **Storage.** Didanosine should be kept ina 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 $C_{10}H_{12}N_4O_3$

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 ofammonium 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 !

sladkova-an@yandex.ru