Course notes:

I. Legislation and quality assurance

POSTGRADUATE EUROPEAN RADIOPHARMACY COURSE

Module I: Pharmacy

UNIVERSITY OF LJUBLJANA | FFA Faculty of Pharmacy

ETH
Eidgenössische Technische Hochschule Zürich
Swiss Federal Institute of Technology Zurich

univerzitetni klinični center ljubljana
University Medical Centre Ljubljana
Department for Nuclear Medicine

EANM EUROPEAN ASSOCIATION OF NUCLEAR MEDICINE

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Welcome to Ljubljana and the Postgraduate European Radiopharmacy Course, Module 1

The University of Ljubljana, Faculty of Pharmacy, and the Divison of Nuclear Medicine, University Medical Centre Ljubljana, are pleased to welcome participants to Module 1 of the Postgraduate European Radiopharmacy Course (PERC), which has been regularly held in Ljubljana since 2003. In 2008, the University of Ljubljana, Faculty of Pharmacy, entered into a formal cooperation agreement with ETH Zürich and the University of Leipzig. Together, these three universities pool their expertise and resources to provide advanced postgraduate education in Radiopharmaceutical Chemistry and Radiopharmacy. The complete programme, consisting of three theoretical modules, is recognised by the European Association of Nuclear Medicine (EANM).

In 2023, we celebrated the 20th anniversary of postgraduate radiopharmacy courses in Ljubljana. Over the past two decades, the programme has earned a reputation for academic excellence, high organisational standards, and a collaborative spirit. We are proud of the consistently positive feedback from participants and remain committed to ensuring the course continues to evolve in line with the EANM syllabus for the European Postgraduate Specialisation Certificate in Radiopharmacy, while integrating valuable suggestions from attendees.

The printed Notes for this module are organised into four sections, each containing expert contributions covering the full scope of the respective topics:

I. Legislation and quality assurance

II. Pharmaceutical technology

III. Physico-chemical and Biopharmaceutical evaluation

IV. Drug design, Advanced therapy medicinal pProducts, and Microbiology

We trust that the programme will be both valuable for your professional development and enriching for your practical work. We also hope that the welcoming atmosphere of Ljubljana will enhance your experience, fostering new professional connections, scientific collaborations, and lasting friendships. Alongside the scientific and practical challenges presented in the lectures and sessions, we encourage you to take time to enjoy the cultural, historical, and culinary offerings of Ljubljana and Slovenia. We would also like to express our sincere appreciation to **Biomedis, Lablogic, Kemomed and Polatom** for their valuable support in making this course possible.

»Dobrodošli v Ljubljani!«

Marko Krošelj

Course Director, PERC 2025

Organizing committee PERC 2025:

Assist. dr. Marko Krošelj

Course director

University of Ljubljana, Faculty of Pharmacy, Aškerčeva 7, Ljubljana;
University of Ljubljana, Faculty of Medicine, Vrazov trg 2, Ljubljana
e-mail: marko.kroselj@ffa.uni-lj.si

Assoc. prof. dr. Martina Gobec
University of Ljubljana, Faculty of Pharmacy, Aškerčeva 7, Ljubljana
Tel.: + 386 1 47 69 636, Fax: +386 1 42 58 031, e-mail: martina.gobec@ffa.uni-lj.si

Assist. prof. dr. Petra Kolenc
University Medical Centre Ljubljana, Department for Nuclear Medicine, Zaloška 7, Ljubljana; University of Ljubljana, Faculty of Pharmacy, Aškerčeva 7, Ljubljana
University of Ljubljana, Faculty of Medicine, Vrazov trg 2, Ljubljana
Tel.: +386 1 522 47 69, Fax: +386 1 522 22 37, e-mail: petra.kolenc@kclj.si

Assist. dr. Doroteja Novak
University Medical Centre Ljubljana, Department for Nuclear Medicine, Zaloška 7, Ljubljana, e-mail: doroteja.novak@kclj.si

Prof. dr. Rok Dreu
University of Ljubljana, Faculty of Pharmacy, Aškerčeva 7, Ljubljana
Tel.: + 386 1 47 69 622, Fax: +386 1 42 58 031, e-mail: rok.dreu@ffa.uni-lj.si

Prof. dr. Igor Locatelli
University of Ljubljana, Faculty of Pharmacy, Aškerčeva 7, Ljubljana
Tel.: + 386 1 47 69 541, Fax: +386 1 42 58 031, e-mail: igor.locatelli@ffa.uni-lj.si

Dr. Aljaž Sočan
University Medical Centre Ljubljana, Department for Nuclear Medicine, Zaloška 7, Ljubljana Tel.: +386 1 522 87 21, Fax: +386 1 522 22 37, e-mail: aljaz.socan@kclj.si

CONTENTS

Pharmacopoeia

Thijs Kroon is a pharmacist who has been working in the radiopharmaceutical industry since 1987 and has a long standing experience with the QC and QA of radiopharmaceuticals, covering both SPECT and PET radiopharmaceuticals. Since this year he is partly retired.

Since 1993 he represents the Netherlands in Group 14 (radiopharmaceuticals) of the European Pharmacopoeia, which he was chairing between 2011 and 2020.

He is also a member of the (dormant) CRP working, which drafted the monograph on Extemporaneous preparation of radiopharmaceuticals (5.19.).

He was also member)20213-2020) of the USP radiopharmaceutical expert group involved in the updating of the USP radiopharmaceutical monographs.

The lecture has the following learning objectives:

1. Students are able to get an understanding of the status of pharmacopoeia's in the current pharmaceutical regulatory environment.
2. Students are able to learn what relevant European Pharmacopoeia monographs are for radiopharmaceuticals.
3. Students are able to understand how to read a radiopharmaceutical monograph.

Summary of the lecture:

The Pharmacopoeia in Radiopharmacy

Pharmacopoeia's have a long history. They date back from the old Egyptian times and were used to describe the preparation of medicines and their quality. Over the ages pharmacopoeia's were used in the various cultures and were used by the Greeks, in medieval times straight through to modern times. As time progressed the importance of the quality of the active ingredients and excipients became more important and these were also taken up in the pharmacopoeia's. Nowadays the main pharmacopoeia's dedicate most of the space to the quality of active ingredients and excipients. Other important topics are the requirements for the various analytical techniques described and the overall requirements to which medicines needs to comply with.

What is a Pharmacopoeia?

A pharmacopoeia is comparable to a book of law in which is described with what quality standards pharmaceuticals, API and excipients need to comply and how these need to be tested. The methods as described in the Pharmacopoeia can be considered to be validated. Alternative methods are allowed to be used only if these are shown to be at least equivalent or better as the method described in the pharmacopoeia.

However, in case it comes to a law case, the method of the pharmacopoeia is the official method to test the quality and must be used.

What are the important pharmacopoeia's

Generally four pharmacopoeia's that are used internationally:

- the European Pharmacopoeia
- the USP
- the Japanese Pharmacopoeia
- International Pharmacopoeia.

For radiopharmaceuticals the European Pharmacopoeia, the USP and the International Pharmacopoeia are relevant ad they contain a fair number of monographs on radiopharmaceutical preparations.

This training will focus on the European Pharmacopoeia. The international harmonization of pharmacopoeial methods is progressing for the specific methods and monographs. It is indicated in methods and monographs whether they are harmonized. There is also a specific chapter in the pharmacopoeia, describing what the limitations of the harmonization is.

No monographs on radiopharmaceuticals are harmonized.

The European Pharmacopoeia

The European Pharmacopeia is published by the EDQM, under responsibility of the Council of Europe. This not to be confused with the EU or it's related bodies; the EU is one of the members of the Europa Pharmacopoeial Convention.

The European Pharmacopoeia contains legally binding requirements for pharmaceuticals that are valid in each of it's member states.

It is essential to know that the pharmacopoeia is applicable to ALL pharmaceuticals made, irrespective whether they are made in a pharmacy, industry environment, licensed or unlicensed, all pharmaceuticals need to comply to the requirements of the pharmacopoeia.

Before using the European Pharmacopoeia (or any other) it is essential that all introductory information and applicable parts of the pharmacopeia are read. These sections contain essential information, not only on how do the tests, but also on the limitations of the tests in the monograph, what exceptions are possible, etc. They also describe to what other aspects the preparations needs to comply with.

Methods that are mentioned in the European Pharmacopoeia are validated against ICH requirements, yet the user must verify/validate that a specific preparation (with it's own formulation) can be tested according the pharmacopoeia. and complies with it's specifications.

For more detail on the monograph's, the ***Knowledge Database*** of the European Pharmacopoeia should be consulted. It contains detail on the sort and type of columns, reference chromatograms etc.

Radiopharmaceuticals.

The radiopharmaceutical monograph's are one of the very few monographs in the pharmacopoeia that describe the quality of the final products as administrated directly to the patients (note: the European Pharmacopeia will in future carry more final product monographs for other products).

As radiopharmaceuticals are special in some aspects, the European Pharmacopoeia carries a special monograph detailing specific requirements or exceptions for radiopharmaceuticals, the General Monograph on Radiopharmaceuticals 0125. However other (general) monographs need to be consulted as they may also provide information on the applicability of these for radiopharmaceuticals.

Two more documents are important for radiopharmaceuticals:

- Detection and measurement of radioactivity

This method of analysis gives some background to the measurement of radioactivity in it's various forms as well as in combination with chromatographic techniques.

- Extemporaneous preparation of radiopharmaceuticals

This general text describes requirements which the overall Quality Management System should comply when extemporaneously preparing radiopharmaceuticals. The scope of the document is for the extemporaneously preparation of radiopharmaceuticals in a hospital/radiopharmacy environment.

This document is not binding and has only the status of a guidance document.

Take home messages:

- In development of new radiopharmaceutical tracers, the pharmacopoeia needs to be used for the analytical method development and product development
- Routinely produced radiopharmaceuticals need to comply to all relevant monographs in the European Pharmacopoeia
- If you want to know in detail what is required for compliance, the actual text must be read!

References (further reading):

- The European Pharmacopoeia
- The USP
- International Pharmacopoeia (http://apps.who.int/phint/en/p/about/)

The Pharmacopoeia in Radiopharmacy

The importance and use of the pharmacopoeia in radiopharmaceutical practice

August 2025
Thijs Kroon

Disclaimer:
- The content of the presentation represents my personal view

Financial Interest:
- Self Employed

Learning objectives

The lecture has the following learning objectives:

- *To get an understanding of the status of pharmacopoeia's in the current pharmaceutical regulatory environment*
- *To learn what relevant European Pharmacopoeia monographs are applicable to radiopharmaceuticals*
- *To understand how to read a radiopharmaceutical monograph*

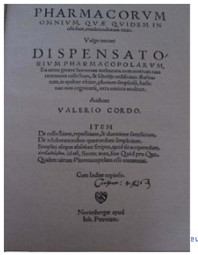
Agenda

- A short history
- Which Pharmacopoeia's
- General content of Pharmacopoeia's
- Background
- Specific chapters/monograph's of relevance for radiopharmaceuticals (Ph. Eur.)
- Example monograph

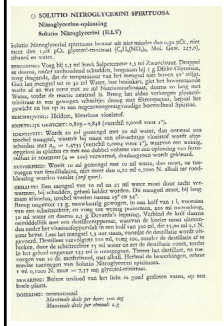
A Brief History

Pharmacopoeias have a long history; they date back from Egyptian times. A description of the preparation of medicines was found, which was made about 1600BC.

The idea further developed through the ancient Greek and in Medieval times it got wider spread into Europe where cities developed their own pharmacopoeia's to ensure that the quality of medicines was standardized within the city



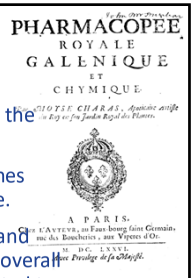
A Brief History continued

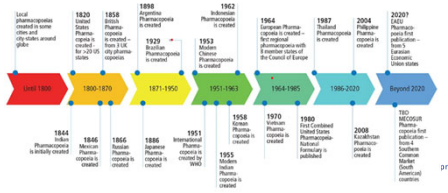

SOLUTIO NITROGLYCERINI SPIRITUOSA
Nitroglycerine-oplossing
Solution Nitroglycerinée (SLV)

As national states evolved, these states took more ownership on the quality of medicines and centralized the pharmacopoeia's to a national level.

Initially the pharmacopoeia's covered how the medicines were being prepared and what accepted dosages were.

Over time, the quality standards of active ingredients and excipients also became more important to ensure the overall quality of the medicines and the pharmacopoeia's started to cover these as well.





Current content of Pharmacopoeia's

Nowadays the focus of Pharmacopoeias is less on actual medicinal preparations but more on the overall framework on the quality of components of which a medicinal preparation is made.

NOT TO BE CONFUSED WITH GMP)*

With the quality of components is meant:

- Chemical components (API and Excipients)
- Containers
- Quality aspects of the methods used to determine the chemical/microbiological quality of medicines
- Microbiological aspects of the medicines

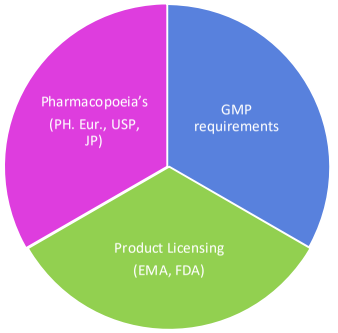
*) *See later section on Extemporaneous preparation of radiopharmaceuticals (5.19.)*

Where do Pharmapoeia's fit in the overall Quality of Medicines

GMP: how to make medicinal products of consistent Quality

Product licensing: to ensure efficacy and safety of products

Pharmacopoeia's: Set specification & test methods for medicinal products to ensure that they comply with specifications



What Pharmacopoeia's are we talking about?

The topics that are covered in the training will mainly apply to the European situation. As such most of the presentation will be on the ***European Pharmacopoeia (Ph. Eur.)***

Radiopharmaceuticals are also covered in the:

- United States Pharmacopoeia
- Japanese Pharmacopoeia
- International Pharmacopoeia
- Chinese Pharmacopoeia

What Pharmacopoeia's are we talking about

USP:

- Has a well-developed section on radiopharmaceuticals
- Refers only to licensed products, update process has started to modernize the monographs
- Of special value are chapters
  - o <825> on dispensing radiopharmaceuticals
  - o <821> and <1821> on radioactivity measurement,
  - o <823> and <1823> on compounding of PET radiopharmaceuticals.
- <825> and <823> are recommended literature.

What Pharmacopoeia's are we talking about?

The International Pharmacopoeia:

- made by the WHO
- The radiopharmaceutical monograph's are made in co-operation with the IAEA.

- The International Pharmacopoeia is
a collection of analytical procedures intended as source material for countries wishing to establish pharmaceutical requirements
(https://digicollections.net/phint/2025/index.html#p/home)

- It contains about 27 monographs on radiopharmaceuticals and additional support texts

What Pharmacopoeia's are we talking about?

The Japanese Pharmacopoeia

- Available in English
- Covers only a very few radiopharmaceuticals (6-8)

Quality standards for radiopharmaceuticals are listed in the "Radiopharmaceutical Standard" which describes approximately 46 radiopharmaceuticals approved by the MLHW and has the same standing as the JP

- Not available in English…….

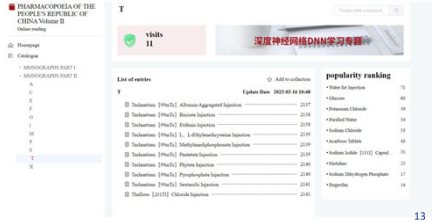
What Pharmacopoeia's are we talking about?

Chinese Pharmacopoeia

- Available in Chines and English (at a cost, book and web based)
- Radiopharmaceuticals covered in book 2 of the 4 books in total
- General monographs and monographs on kits, radiopharmaceuticals and brachytherapy sources

In total about 30 preparations covered,

all SPECT and FDG



What is the Pharmacopoeia

A Pharmacopoeia is a Book of Law which describes to what quality standards the medicines and the components of which they are made, must comply with as a minimum.

Regulatory bodies may require stricter specifications as written in the monograph's, but cannot be less strict as the pharmacopoeia.

Does this mean that you **MUST** follow a monograph?

Does this mean that you MUST follow a monograph?

Ph. Eur.:

Alternative methods. The tests and assays described are the official methods upon which the standards of the Pharmacopoeia are based. With the agreement of the competent authority, alternative methods of analysis may be used for control purposes, provided that the methods used enable an unequivocal decision to be made as to whether compliance with the standards of the monographs would be achieved if the official methods were used. In the event of doubt or dispute, the methods of analysis of the Pharmacopoeia are alone authoritative.

Process Analytical Technology (PAT) and/or real-time release testing (including parametric release) can also considered to be alternatives

USP states:

6.30. Alternative and Harmonized Methods and Procedures

Alternative methods and/or procedures may be used if they provide advantages in terms of accuracy, sensitivity, precision, selectivity, or adaptability to automation or computerized data reduction, or in other special circumstances. Such alternative procedures and methods shall be validated as described in the general chapter *Validation of Compendial Procedures* 1225 and must be shown to give equivalent or better results. Only those results obtained by the methods and procedures given in the compendium are conclusive.

You do not need to follow a monograph, but your alternative method must be validated against the specifications and, in case of a dispute the pharmacopoeial method is the method that is legally binding.

Example:

+ You may replace an existing HPLC method (impurities or assay) by an alternative one, provided the alternative method is cross-validated against the official one and leads to the same pass/fail decision.

- Not possible to replace a selective HPLC assay by a volumetric titration [since the same pass/fail cannot be obtained].

Does this mean that you MUST follow a monograph? Cont'd

Tests prescribed in a monograph can be omitted if

1) The impurity is not used in the process (e.g. TBA in FDG when Kryptofix is used)
2) Validation studies of the process have shown that an impurity is not formed/always very much below the limit

But again: in case of a dispute the pharmacopoeial method is the method that is legally binding

Can you follow a monograph?

For example the USP Technetium ^{99m}Tc Exametazime Injection monograph

of the stabilized Injection.]

Biological distribution—Inject between 18.5 MBq and 37 MBq (between 0.5 mCi and 1 mCi) of Injection in a volume not exceeding 0.1 mL into the caudal vein of each of three 130- to 190-g Sprague-Dawley rats. Five to ten minutes after the injection, sacrifice the animals and carefully remove the brain, liver, and intestines (including gall bladder). Place each organ and the remaining carcass in separate, suitable counting containers, and determine the radioactivity, in counts per minute, in each container with an appropriate detector, using the same counting geometry. Determine the percentage of radioactivity in the brain, liver, intestines, and remaining carcass by the formula:

$$100(A / B)$$

in which A is the net radioactivity, in counts per minute, in the organ, and B is the total radioactivity, in counts per minute in the brain, liver, intestines, and carcass. Not less than 1.5% of the radioactivity is found in the brain. Not more than 20% of the radioactivity is found in the intestines, and not more than 15% of the radioactivity is found in the liver, in not less than two of the animals.

Other requirements—It meets the requirements of the tests for *Radionuclidic identification* and *Radionuclide purity* and *Bacterial endotoxins* under *Sodium Pertechnetate Tc 99m*

within 6 hc
USP Refer
USP Endotc
Bacterial
Unit per µc
pH ⟨791⟩: I
Particulat
particulate
Radiocher
SYSTEM 1
Adsorber
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Coffeebreak

The European Pharmacopoeia

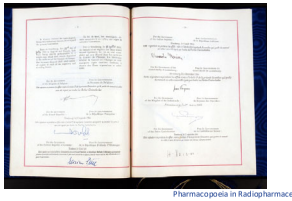
- The European Pharmacopoeia is made by the EDQM*, which is part of the *Council of Europe.*

- The goal of the Council of Europe is:

To create a common democratic and legal area throughout the whole of the continent, ensuring respect for its fundamental values: human rights, democracy and the rule of law.

NOT to be confused with the EU, European Parlement, etc.

The European Pharmacopoeia was founded in 1964 by:
BE, NL, LUX, DE, FR, IT, CH and the UK



*European Directorate for the Quality of Medicines & Healthcare

M2K2 Radiopharma Consultancy

The European Pharmacopoeia

- The *European Pharmacopoeia* is the official pharmacopoeia in Europe. It is complemented by national pharmacopoeias for texts of interest to only one Member State.
- Mandatory at the same date in 38 Member States of the Council of Europe and the EU as per decision of Ph. Eur. Commission. The Ed 12.1 is valid as from January 1st 2026 (corrected texts August 31st 2025).
- Legally binding quality standards for ALL medicinal products in its member states, i.e. raw material, preparations, dosage forms, containers must comply with the Ph. Eur. requirements when they exist.

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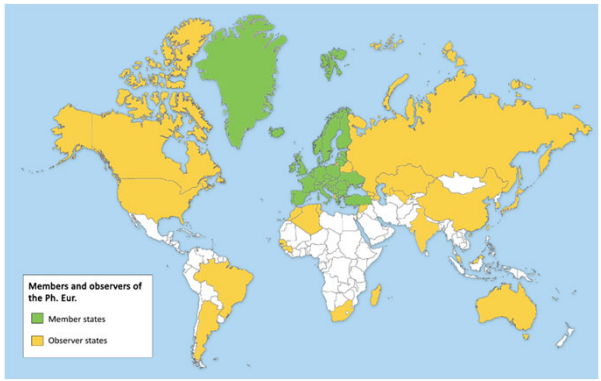
Members and Observers



The Pharmacopoeia in the EU Legislation (EU 2001/83)

"The monographs of the European Pharmacopoeia shall be applicable to all substances, preparations and pharmaceutical forms appearing in it. In respect of other substances, each Member State may require observance of its own national pharmacopoeia

However, where a material in the European Pharmacopoeia or in the pharmacopoeia of a Member State ***has been prepared by a method liable to leave impurities not controlled in the pharmacopoeia monograph,*** these impurities and their maximum tolerance limits must be declared and a suitable test procedure must be described.

If you follow a monograph, do you need to do more for licensing?

Yes, you may need to have to!!

In cases where a specification contained in a monograph of the European Pharmacopoeia or in the national pharmacopoeia of a Member State *might be insufficient to ensure the quality of the substance*, the competent authorities may request ***more*** appropriate specifications from the marketing authorisation holder…

Validation of the methods

All methods in the pharmacopoeia can be considered to be validated.

This is a requirement from the EDQM.

This implies that:

1) You cannot make changes to the method without the need to validate the method

Note: there are in the various descriptions of general methods ranges given when a revalidation may not be necessary

2) You cannot claim a higher sensitivity as described in the pharmacopoeia as the method is not suited to support the higher sensitivity

Validation of the methods

As stated in the General Notices the methods described in the monographs have been validated. However, the user of a monograph should be aware of the following:

> **Implementation of pharmacopoeial methods.** 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.

This implies that, although the method is validated, the user still needs to ensure that his/her specific preparation (with used excipients, stabilizers etc.) can be analysed with the described method.

See later Implementation of Pharmacopoeial Procedures 5.26

Validation of the methods

Contrary to what is being mentioned in the General Notices, not **ALL** methods have been validated or can be considered validated.

This is indicated with the wording: *"The following methods has been found suitable. Other validated methods, approved by the competent authority, may be used."* as is written in the *Sodium Molybdate (^{99}Mo)* monograph

A. iodine-133,
B. iodine-135,
C. 2-[^{131}I]iodobenzoic acid,
D. [^{131}I]iodide.

01/2008:1923

SODIUM MOLYBDATE (^{99}Mo) SOLUTION (FISSION)

Natrii molybdatis (^{99}Mo) fissione formati solutio

DEFINITION

radioactivity:
The following method has been found to be suitable; other validated methods, approved by the competent authority, may be used.
Gamma-ray spectrometry.
Condition a column with an internal volume of approximately 1.5 mL of *strongly basic anion exchange resin R* with a mixture of equal volumes of *glacial acetic acid R* and *water R*. All elutions of the column are made at a flow rate not exceeding 1 mL/min.
Test solution. In a test-tube, successively add, with mixing, 1 mL of a 24.2 g/L solution of *sodium molybdate R*, 0.5 mL of *strong hydrogen peroxide solution R*, 2.5 mL of *glacial acetic acid R*, 1.0 mL of *iodine-123 and ruthenium-106 spiking solution R* and 1.0 mL of solution S. Allow to stand for 30 min at room temperature.
Reference solution. Mix 1.0 mL of *iodine-123 and ruthenium-106 spiking solution R* and 4.0 mL of *water R*.

International Harmonisation (ICH)

Efforts are underway to harmonize relevant monograph's that are globally used. This is especially relevant for companies who market products globally.

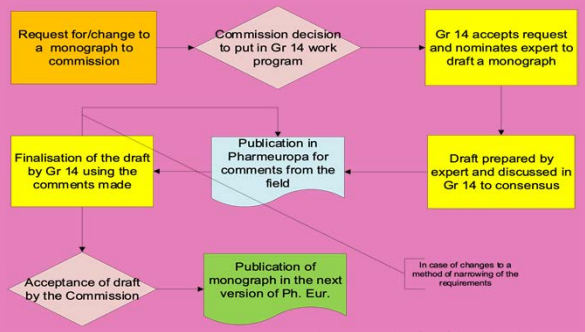
The process moves (*in my opinion*) relatively slowly and is of limited value for radiopharmaceuticals as there are only a few companies who market their products globally.

In section *5.8. Pharmacopoeial harmonisation* the status of the various monographs is mentioned. Yet be aware of the disclaimer:

The chapter does not affect in any way the status of the monographs and general chapters as the authoritative reference in any case of doubt or dispute where compliance with the European Pharmacopoeia is required.

Note that no monographs on radiopharmaceuticals have been harmonized. Contacts between USP and Ph. Eur. are relatively few and on a personal level

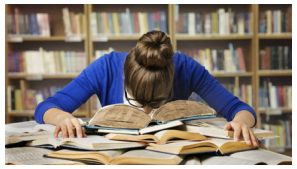
How is a monograph made for the European Pharmacopoeia



Access to Pharmeuropa website free of charge through the EDQM website

The Pharmacopoeia: How to use it?

Here is the boring bit:



BY READING IT!

Which means:

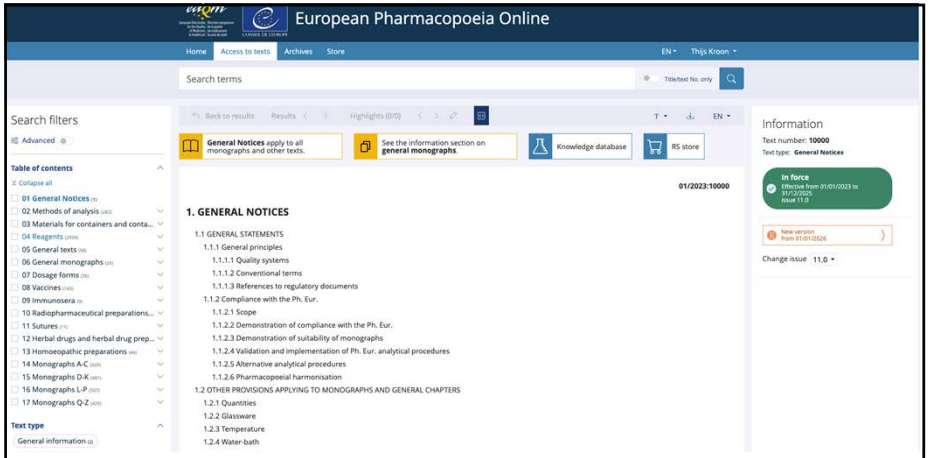
- Not going directly to the monograph but reading also the chapters at the beginning of the Pharmacopoeia. Not many people do it, but it provides good insight on what is needed when and how things need to be done/interpreted.

What is of importance for Radiopharmaceutical production/QC

In the next slides the relevant sections of the European Pharmacopoeia will be discussed for both:

- Production: what are the quality requirements of the ingredients (excipients, reagents, packaging and precursors) that are used in the production
- Quality Control of the preparation

As much as possible the order will be followed as these items are presented in the European Pharmacopoeia



General Notices

At the very beginning of the Ph. Eur.

➢ address general topics

➢ aim at providing basic information to the user

➢ apply to *all* texts incl. general chapters and texts

➢ include rules to understand texts, conventional expressions …

Essential reading before starting to use monographs

General chapters and general texts

GENERAL CHAPTERS

General chapters become mandatory when referred to in a monograph, unless the wording clearly indicates that it is not the intention to make the text referred to mandatory but rather to cite it for information.

Requirements included in general chapters are not repeated in the individual monographs, unless specific to the article in question

Provide standard analytical procedures, that may be used when no monograph (with validation) exists

As guidance

General requirements for equipment, equipment qualification or calibration

.

GENERAL TEXTS

often published for information and guidance

become mandatory when referred to in a monograph

aspects that cannot be treated in each individual monograph

specific to certain topics (e.g.Microbiology, Chemometrics)

reproduce principles of regulatory guidelines (e.g. 5.20. Elemental impurities → introduction and scope of ICH Q3D guideline and refer to it)

General monographs & Dosage form monographs

GENERAL MONOGRAPHS

Classes of substances/medicinal products

Mandatory for all substances/products within scope of their definition

Aspects that cannot be included in each individual monograph

Not cross-referenced in individual monographs (exceptions)

Overrides other monographs

Example: Radiopharmaceuticals (0125)

DOSAGE FORM MONOGRAPHS

Mandatory for all medicinal products within scope of their definition

Referred to in monographs on medicinal products containing chemical APIs

Example: Capsules (0016), Tablets (0478), Parenteral preparations (0520), …

Demonstration of compliance with the Ph. Eur.

1) *Unless otherwise indicated* in the General Notices or in the monographs, statements in monographs constitute mandatory requirements
2) What are the mandatory requirements in a monograph?

Mandatory	Informative
Definition	Characters
Production	Storage
Identification	Functionality-related characteristics
Tests	
Assay	

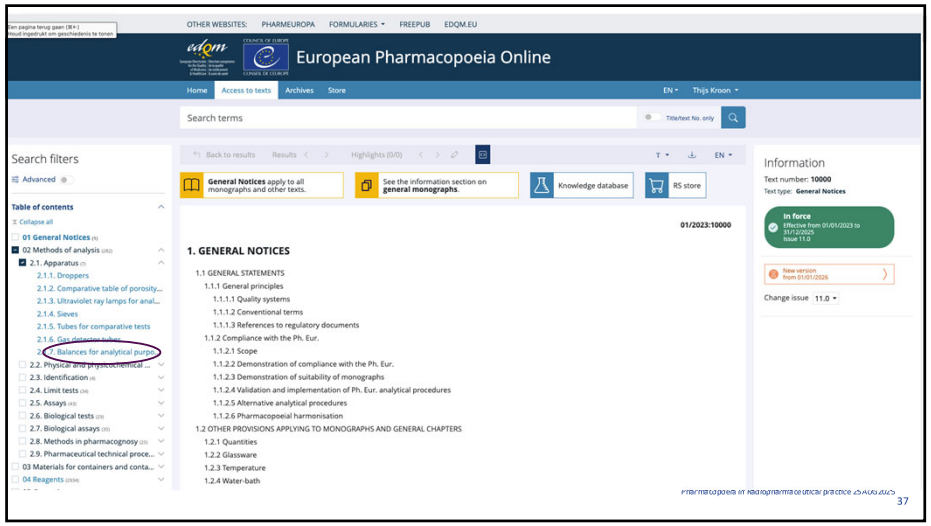
Other issues in the General Notices

1) *Identification:*
   - To give confirmation of the identity, not a full identity test itself
   - All test must be carried out, unless
     - A first and second identification given → 2nd Id test just for pharmacies
     - In case is stated "*tests A, B or tests C,D*". In this case the ID tests are equivalent

2) *Tests and assays:*

- Does not take all possible impurities into account. If an impurity is present but not mentioned/detected, it does not mean that it is accepted.
- Limits take into account analytical error etc. Results must be rounded and then compared with the limit

3) Stability: mentions that for preparations the release specifications can be more strict as the licensed specifications



2.1. Apparatus

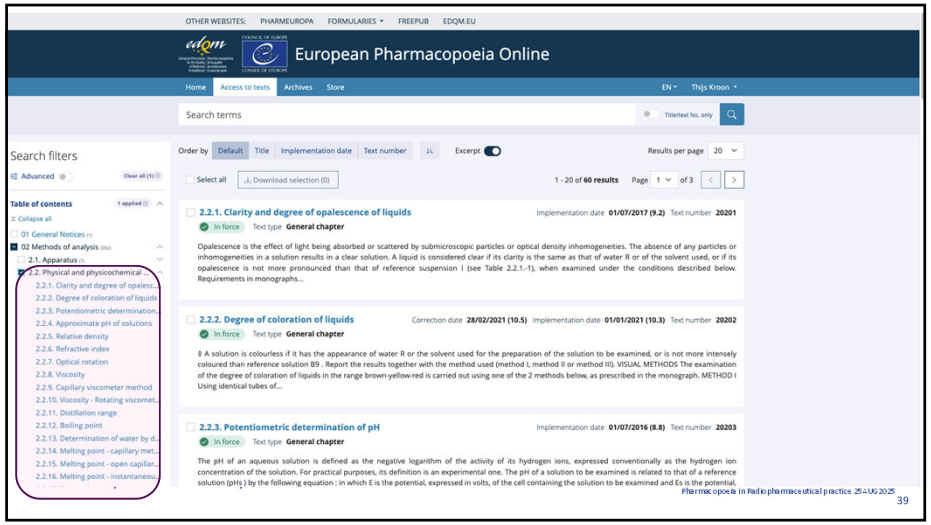
This section covers some apparatus used in the Ph. Eur.

Lamps for UV and gases are normally commercially supplied complying with these requirements.

The only chapter that is relevant for radiopharmaceutical QC is 2.1.7 Balances for analytical purposes.

- provides information on:
  - Installation
  - Calibration/Performance checks
  - Weighing procedure

M2K2 Radiopharma Consultancy



2.2. Physical and physicochemical methods

This section is highly important as it describes various methods that are used in QC of the various preparations. In these sections the requirements are mentioned to which the used physicochemical methods used, need to comply with.

Of importance are:

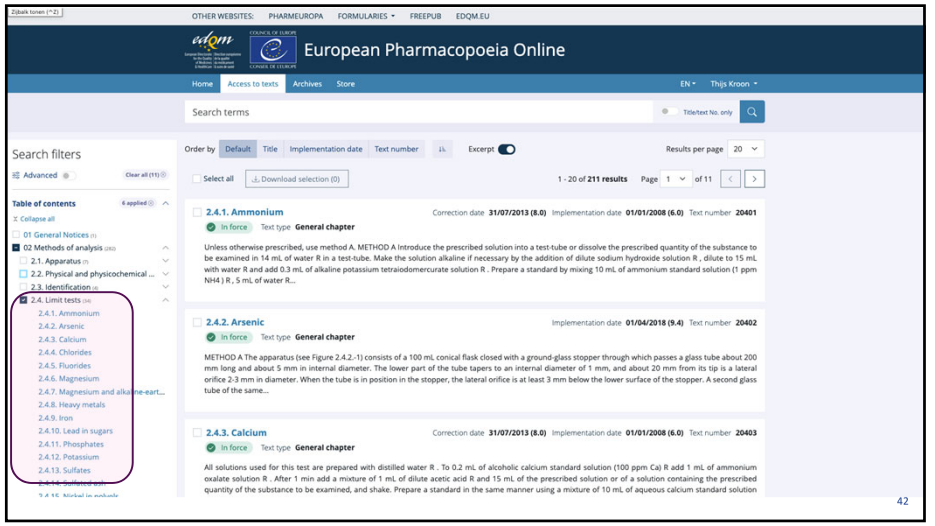
- 2.2.3. Potentiometric determination of pH
- 2.2.4. Approximate pH of solutions
  - The use of pH indicator strips is mentioned

Note: in recent monographs there has been a preference for using indicator strips above pH meters due to radiation safety issues. If indicator strips are being mentioned, a pH meter can be used as well

M2K2 Radiopharma Consultancy

2.2. Physical and physicochemical methods

- 2.2.26. Paper chromatography Still only used on a very limited scale
- 2.2.27. Thin-layer chromatography Widely used for Radiochemical Purity (RCP) testing. The chapter contains not only a description on how to perform the chromatography, but also on how to do quantitative measurements on the radiation
- 2.2.28. Gas chromatography used mainly for residual solvents
- 2.2.29. Liquid chromatography Used widely for RCP testing. Care should be taken that all radioactive species are eluted from the column to prevent false high result of the RCP
- 2.2.46. Chromatographic separation techniques This chapter (rewritten in 2023) further sets requirements to the methods used in chromatography. It also provides explanation, calculation and examples of system suitability, resolution and what adjustments, to the in the monographs described chromatographic conditions, are allowed without additional validation
- 2.2.66. Detection and measurement of radioactivity
  - Will be discussed later



Limit Tests

Most of these sections are of limited value , but they can be referred to in the various monographs for ingredients/ excipients used in the preparation.

These are considered important:

2.4.20. Determination Of Elemental Impurities

Although radiopharmaceuticals are not in the scope of this requirement*) chemical precursors are in scope, see 5.20.

*) *Note: in Canada, radiopharmaceutical kits are in scope*

2.4.24. Identification And Control Of Residual Solvents

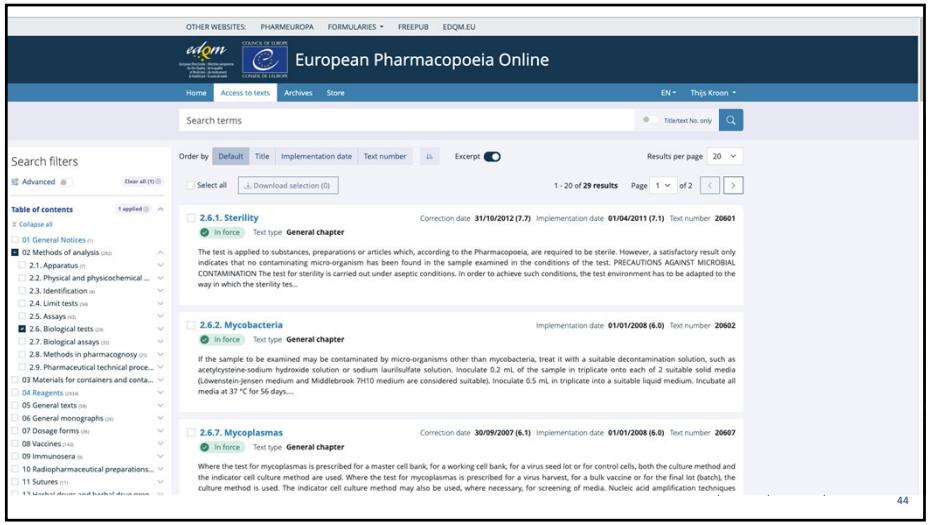
Provides the method to test for residual solvents

2.4.33. Tetrabutylammonium in Radiopharmaceutical Preparations

General method for limit test on tetrabutylammonium. Can be used in theory for all radiopharmaceuticals, but for those not covered by a monograph, should be validated. More details, see the link in the knowledge database: https://vimeo.com/272535630

2.4.35 Extractable Elements in Plastic Materials for Pharmaceutical Use

This general chapter defines the analytical procedure for determination of extractable elements in plastic materials used for the manufacture of containers for pharmaceutical use.



2.6. Biological tests

2.6.1. Sterility This chapter sets out the requirements for the sterility test. It is applicable to radiopharmaceuticals even if the test results are only available after the use of the product. Tables 2.6.1.2 (minimum quantity to be used) and 2.6.1.3 (number of containers to be used) are not applicable as the general monograph *Radiopharmaceutical Preparations 0125* overrules these tables. Chapter 2.6.1 also provides guidelines to invalidate a positive sterility test.

2.6.8. Pyrogens Hardly used anymore as the pyrogens testing is being almost completely replaced by the endotoxin testing. It is still present, but the pyrogen test ids being replaced by the monograph on Pyrogenicity 5.1.13.

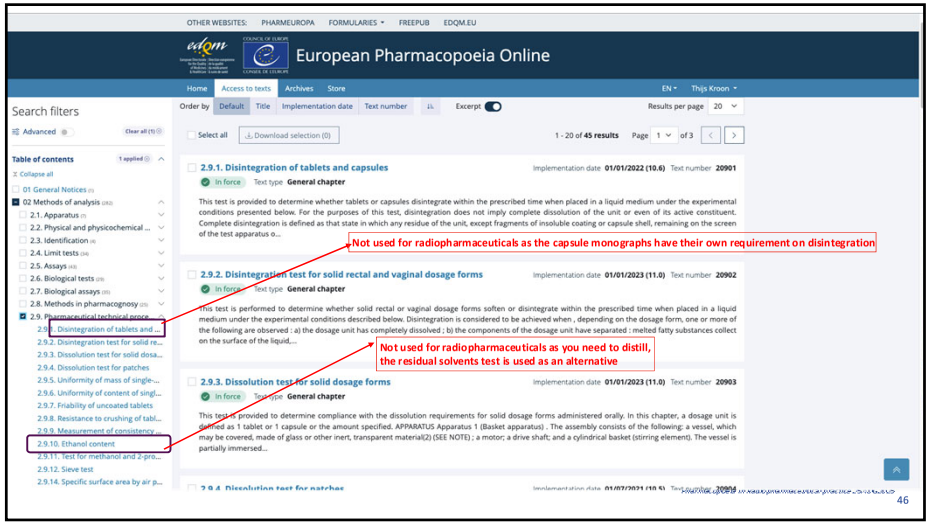
The monograph is suppressed in Ed 12.1

2.6.14. Bacterial endotoxins In almost all of the radiopharmaceutical monograph's the endotoxin test has replaced the pyrogen test, even in those preparations that contain HSA. As the HSA is tested for pyrogens as per monograph on HSA, it was considered that the monographs of preparations that contain HSA do not need to be tested for pyrogens, but only for endotoxins.

The chapter provides good procedures on how to perform the endotoxin test

Note: even if a monograph does not mention that a particular preparation needs to comply with these tests, the preparations **do need to comply with them**

Both the chapter on Sterility and Bacterial endotoxins refer also to **5.0 General Texts** for further elaboration on these topics



2.9. Pharmaceutical technical procedures

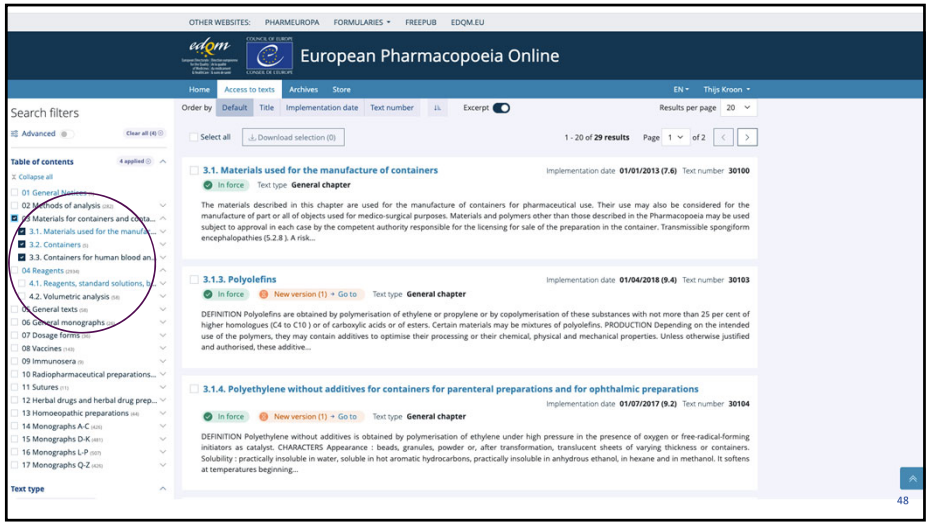
Within the sections "Biological Assays" and "Methods in Pharmacognosy" no relevant chapters for radiopharmaceuticals can be found

In the chapter "2.9. Pharmaceutical technical procedures" the only two are:

2.9.19. Particulate contamination- sub-visible particles as this chapter is **not** applicable to radiopharmaceuticals (see also Parenteral Preparations)

2.9.20. Particulate contamination- visible particles: This chapter **is** applicable to radiopharmaceuticals! The monograph allows for alternative methods, provided they are validated. Yet in testing for visible particles, care should be taken that the radiation dose received by the technician doing the test is not becoming too high!

See also 5.17.2 Recommendations on Testing of Particulate Contamination: visible particles *(Non-Mandatory)*



3 Materials and Containers

In this section the materials are discussed that are used as containers for pharmaceuticals. Important to note is that for radiopharmaceuticals always Type I glass is being used. These do not need to be pre-treated and have a low absorption.

For stoppers that are used in trans-septal vial filling, it is important to check that, after penPetration with a needle, the stopper reseals (resealing test/container closure integrity test).

Extractable/leachable requirements are vaguely mentioned in Plastic Containers and Closures for Pharmaceutical use 3.2.2.

4 Reagents

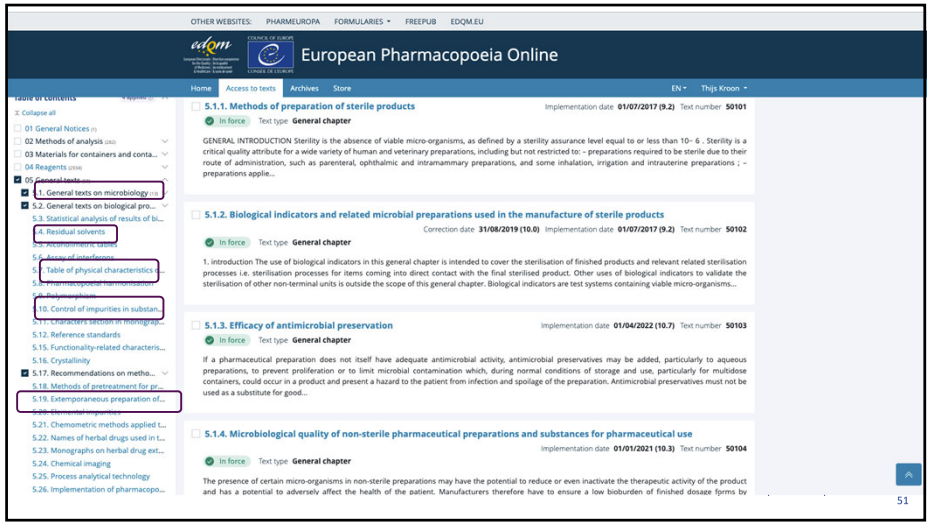
This section describes the reagents used to do the testing as described in the monographs. Many reagents are toxic substances and the designation R does not guarantee their quality and safety for use as medicines. Exceptions are those substances where the reagent description refers to a monograph in Ph. Eur.

Detailed instructions on preparing, assaying and handling reagents and reagent solutions are given. The Knowledge Database on the EDQM website may be helpful to identify some reagents stated as trademarks.

The Knowledge Database

What is it and where do I find it

This database gives background to the monograph's but more importantly it provides brands and types of material that are shown to work with the methods prescribed a monograph. As the Ph. Eur. is not allowed to mention any commercial brand names, these cannot be mentioned in a monograph. For instance a description may be too generic for a specific type of HPLC column, this information is available through the Knowledge Database.

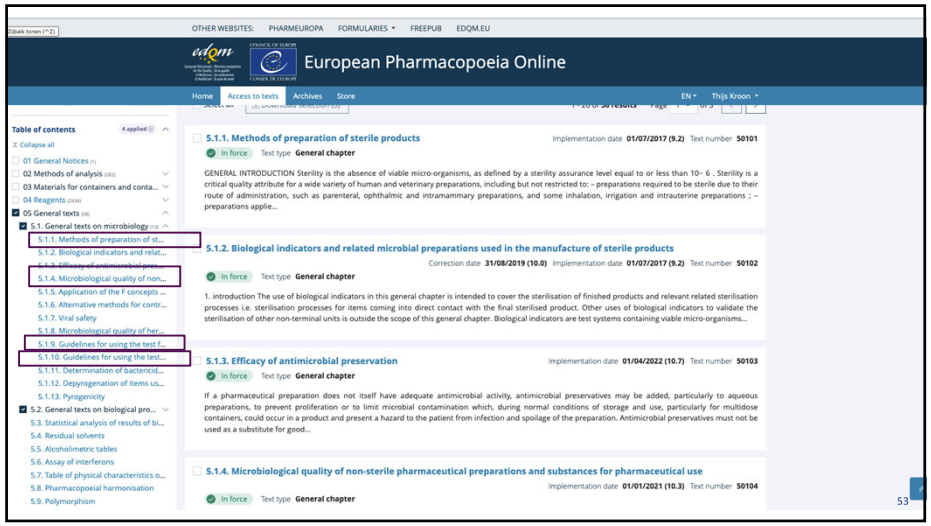


General Texts

These general texts are requirements to which all pharmaceuticals (including unlicensed ones, like those developed a hospital environment) need to comply with, irrespective of whether they are covered by a monograph or not, unless explicitly stated.

Of importance are:

- General texts on Microbiology
- Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (in General texts on biological products)
- Residual Solvents
- Table of physical characteristics of radionuclides mentioned in the European Pharmacopoeia
- Control of impurities in substances for pharmaceutical use
- Elemental Impurities
- Extemporaneous preparation of radiopharmaceuticals *for information only, to be discussed later*
- Chemometric methods applied to analytical data *for information only*
- Process Analytical Technology *for information only*
- Multivariate Statistical Process Control *for information only*
- Implementation of Pharmacopoeial Procedures *for information only*
- Comparability of Alternative Analytical Methods *for information only*
- Design of Experiments *for information only*



General texts on Microbiology

5.1.1. Methods of preparation of sterile products

This section covers the various ways to prepare sterile products. The most relevant section is on aseptic manufacture as the majority of radiopharmaceuticals are aseptically produced. The text requires sterilising filters to be integrity tested before use. This is generally not required for radiopharmaceuticals, but it is a ***must*** after the sterile filtration.

Be aware that the "*Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container*" is applicable to radiopharmaceuticals which means terminal sterilisation is required if the shelf life is >1 week.

5.1.6. Alternative methods for control of microbiological quality

Describes alternative methods to test for sterility/growth of microorganisms

5.1.9. Guidelines for using the test for sterility

This is a relevant chapter on how to perform a sterility test. It also describes the limitations towards the statistical probability to detect an infected sample in a full batch as well as the fact that not all bacteria will grow in the chosen medium. It emphasizes the need for sterility assurance (parametric release, media fills, etc.)

5.1.10. Guidelines for using the test for bacterial endotoxins

Provides additional information on how to do the endotoxin test and provides further background to validate the endotoxin test

General Text on Microbiology

5.1.13 Pyrogenicity

New text that replaces the pyrogen test.

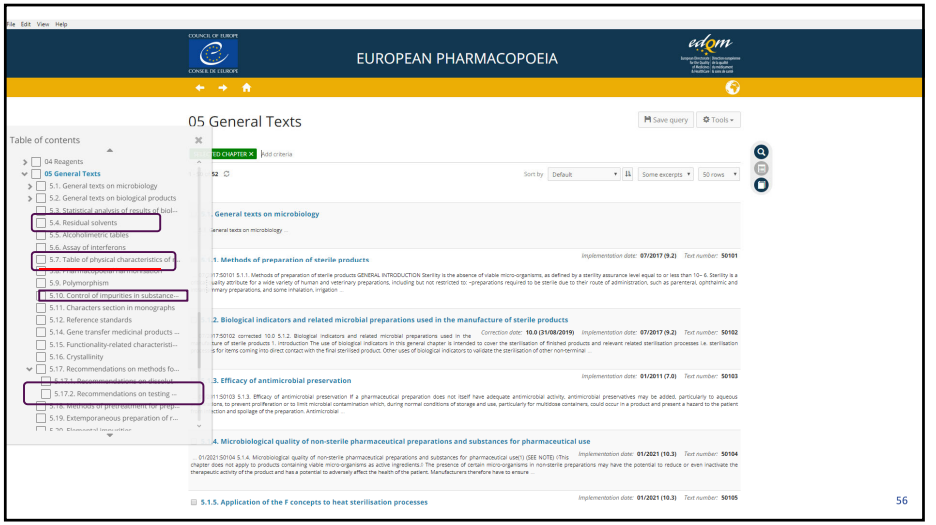
The test is meant to verify that parenteral products do not cause and side effect due to pyrogenic substances causing fever or worse.

Bacterial endotoxins from gram-negative bacteria are the most common and most active exogenous pyrogens. The tests for bacterial endotoxins are described in general chapters 2.6.14 and 2.6.32. Testing for endotoxins is only appropriate if the presence of non-endotoxin pyrogenic substances can be ruled out.

To rule out the presence of non-endotoxin pyrogens in substances or products, it is recommended to perform the monocyte-activation test (2.6.30) during development of the production process to verify whether pyrogens are present that are not detected with the endotoxin test.

Based on they outcome of this test, a risk assessment needs to be made whether testing for endotoxins is sufficient to guarantee the quality of the preparation.

If any changes are made to the production process that could influence the quality of the product with regard to pyrogenicity, it is recommended to repeat the monocyte-activation test. Examples of such changes include the use of different raw materials, a different production site and different process parameters.



General Texts

5.2.8. Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products

This text is identical to the *Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products – Rev 3.*

It deals with the iatrogenic transmission of spongiform encephalopathies and lays down requirements on the prevention of transmission of prion causing these diseases. For radiopharmaceutical practice it is important to ensure that ingredients comply to this regulation (usually through CoA from the supplier)

5.4. Residual solvents

This chapter is very relevant for those that are synthesizing their own radiopharmaceuticals as this section describes what levels of residual solvents are allowed to be present in the preparation. Although in not all monographs on radiopharmaceuticals a reference is made to this chapter, the chapter is applicable to all radiopharmaceuticals (licensed or unlicensed; with or without a monograph in the Ph. Eur.)

Note: ethanol as an excipient is not a residual solvent

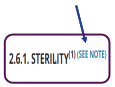
General Texts

5.7 Table of physical characteristics of radionuclides etc.

This is a listing of all radionuclides mentioned in the Ph. Eur. It kept up to date, but reference is made to the main source database:
http://www.nndc.bnl.gov/nndc/nudat/radform.html

5.8 Pharmacopoeial Harmonisation

General text on harmonised monographs between Ph. Eur., USP and JP , only relevant if your product is sold in these area's. When a monograph is harmonized, this can be seen by the reference to a note as well as in the knowledge database



5.10. Control of impurities in substances for pharmaceutical use

This chapter describes to what level and how impurities in preparations need to be controlled. This section is not applicable to radiopharmaceuticals. Also chemical precursors for radiopharmaceutical preparations are out of scope as these are no longer covered by *Substances for pharmaceutical use (2034).*

5.20 Elemental Impurities

Refers to ICH 3QD for the guideline

General Texts

5.26 Implementation of Pharmacopoeial Procedures

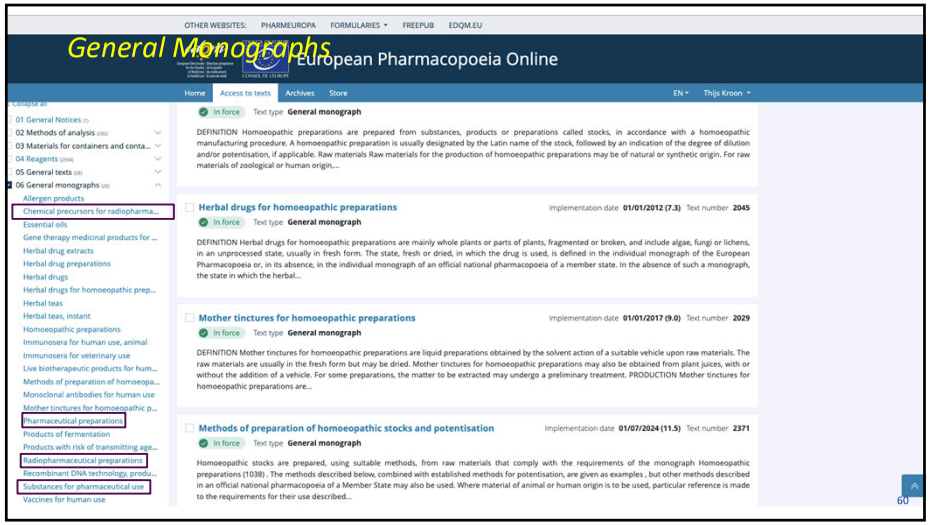
- Although pharmacopoeial methods have been validated, the composition of the preparation may vary from the composition of the preparation that was used for the validation.
- Hence an assessment needs to be made that the composition and the actual conditions at the laboratory do not interfere with the described method.
- The purpose of the verification is to demonstrate that the implementation is feasible, i.e. that the procedure is suitable for examination of the article under test, under the actual conditions of use.
- Examples are given what parameters may need to be retested to verify that the described method is indeed valid

Note: These should be read in conjunction with the guidance on validation of radiopharmaceutical test methods ***(see later)***

5.27 Comparability of alternative analytical procedures

The text describes how the comparability of an alternative analytical procedure to a pharmacopoeial analytical procedure may be demonstrated.

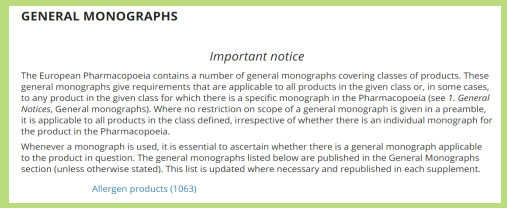
Note: Other approaches to demonstrating comparability may also be appropriate but the competent authority needs accept/approve the other approach.



General Monographs

General monographs are covering classes of pharmaceutical substances and preparations.

General monographs apply to all substances and preparations defined in the European Pharmacopoeia.



GENERAL MONOGRAPHS

Important notice

The European Pharmacopoeia contains a number of general monographs covering classes of products. These general monographs give requirements that are applicable to all products in the given class or, in some cases, to any product in the given class for which there is a specific monograph in the Pharmacopoeia (see *1. General Notices*, General monographs). Where no restriction on scope of a general monograph is given in a preamble, it is applicable to all products in the class defined, irrespective of whether there is an individual monograph for the product in the Pharmacopoeia.

Whenever a monograph is used, it is essential to ascertain whether there is a general monograph applicable to the product in question. The general monographs listed below are published in the General Monographs section (unless otherwise stated). This list is updated where necessary and republished in each supplement.

Allergen products (1063)

In other words: the General Monographs apply also too all pharmaceutical preparations

General Monographs

Important General chapters are:

Pharmaceutical Preparations,

Substances for pharmaceutical use,

Products with risk of transmitting agents of animal spongiform encephalopathies

Monoclonal antibodies for human use

and of course :

- ***Radiopharmaceutical preparations***
- ***Chemical precursors for radiopharmaceutical preparations***

These will be covered later

Pharmaceutical preparations

It is intended to be a reference source of standards in the European Pharmacopoeia on active substances, excipients and dosage forms, which are to be applied in the manufacture/preparation of pharmaceuticals, but not a guide on how to manufacture as there is specific guidance available covering methods of manufacture and associated controls (GMP)

It requires that all pharmaceutical preparations require a marketing authorisation, yet it also accepts in certain conditions the supply of an unlicensed product is necessary.

The supply of an unlicensed product requires a Risk Assessment covering:

- a review of parameters Critical to Quality
- risk to certain patient groups

The monograp sets requirements for the production of the preparation (suitable quality management system/GMP,, use of excitants, microbial quality, containers, stability, nitrosamines and what tests to perform on the preparation).

Substances for pharmaceutical use

This monograph is important for all who are involved in the development of pharmaceutical preparations, it covers the requirements to which excipients and active substances that can be used in the manufacture of a (radio)pharmaceutical preparation need to comply.

"Where a substance for pharmaceutical use not described in an individual monograph of the Pharmacopoeia is used in a medicinal product prepared for the special needs of individual patients, the need for compliance with the present general monograph is decided in the light of a risk assessment that takes account of the available quality of the substance and its intended use"

This sentence however is a possibility to exclude some of the requirements, based upon a risk assessment

Notes:

- Chemical precursors for radiopharmaceutical preparations are not covered by this monograph

- It describes requirements for pyrogenicity, that are not mentioned on the chemical precursor monograph

Substances for pharmaceutical use Cont'd

Related substances: The requirements for related substances with respect to the Reporting, identification and Quantification do not apply to radiopharmaceuticals as the chemical amount of the radioactive impurities is very low.

Note: if you have a carrier added radiopharmaceutical the requirements could still apply to the carrier amount of the active substance

The requirements for DNA reactive impurities (Mutagenic) do not apply to radiopharmaceuticals.

Authorities may expect an assessment, but the limit is relatively high as radiopharmaceuticals as they are only given to patients very infrequently

Products with risk of transmitting agents of animal spongiform encephalopathies

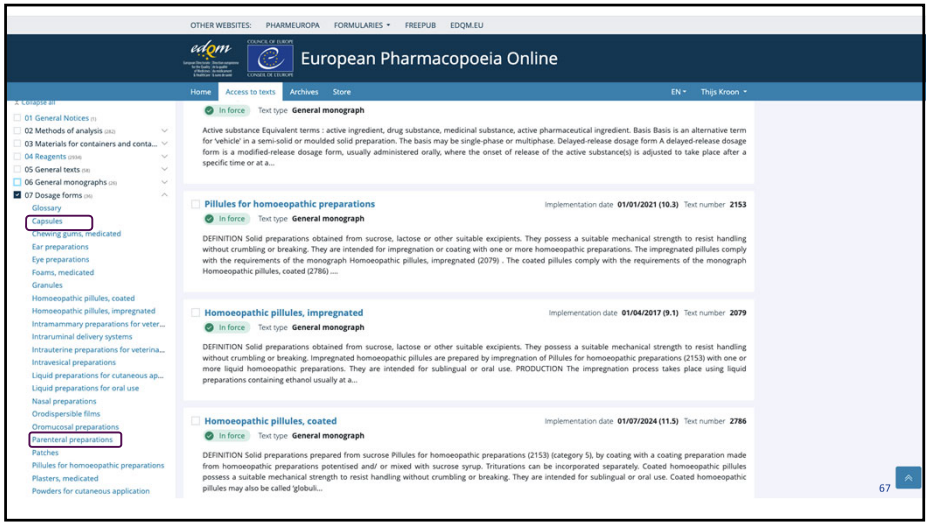
- Short text to make the general text mandatory

Monoclonal antibodies for human use

With the advance of new radiopharmaceutical based upon antibodies or antibody fragments this chapter is of importance.

- Describes requirements for production and testing of antibodies
- Must be produced by a single clone of cells.

Note: these are not covered in monograph on Chemical Precursors for Radiopharmaceuticals



Dosage Forms

This section provides an overview to all dosage forms to which the European Pharmacopoeia sets additional requirements. Dosage forms used in the Radiopharmacy are:

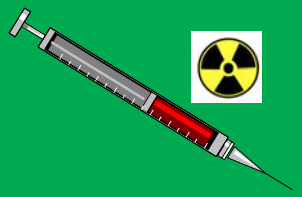
- *Capsules*

  Not so relevant at the in the monographs for the ^{131}I-Iodine capsules (therapeutic and diagnostic) more stringent requirements are mentioned. Please be aware that, when developing radiopharmaceutical capsules that the disintegration speed is an important parameter (dose to the stomach)

- *Parenteral preparations*

  The monograph starts by stating that the monograph "*does not necessarily apply to radiopharmaceuticals*". This means that, when justified, one can deviate (e.g. uniformity of content). Explicitly an exemption is given for subvisible particles (sample size, dose to operator)

Radiopharmaceuticals



General Monograph on Radiopharmaceutical Preparations 0125

- Was republished in 2023 as it needed updating.
- Parallel to redrafting the monograph it was decided to have a separate monograph on how to measure radioactivity, *2.2.66. Detection and measurement of radioactivity* .
- The "Detection and Measurement" was published in the 8.0 Version of the Ph. Eur. when at the same time the relevant section on this topic were removed from the General Monograph
- Both the General Monograph and the 'Detection and Measurement' are "MUST READ" monographs, some highlights are given on the following slides
- An update was made to cover the requirements for Pyrogenicity

General Monograph on Radiopharmaceutical Preparations 0125

04/2023:0125

RADIOPHARMACEUTICAL PREPARATIONS

Radiopharmaceutica

- Definitions on what a radiopharmaceutical preparation is are given.
- Brief explanation on production and terminology
- Identification: the concept for measurement of 'approximate half-life' is described.
- Physiological distribution : in the interest of animal welfare it is clearly stated that tests involving animals should be avoided wherever possible.
- The monograph does not cover Chemical Precursors as these have a separate monograph

Radiopharmaceutical Aspects : Microbiology

Sterility:

- Special information is given on the sterility testing of radiopharmaceuticals (see later)

Bacterial endotoxins:

- It is clarified that all radiopharmaceuticals for parenteral administration as well as eluates of radionuclide generators, solutions for radiolabelling, kits for radiopharmaceutical preparations, radionuclide precursors and chemical precursors intended for the preparation of radiopharmaceuticals for parenteral administration without further purification also comply with the test for Pyrogenicity/Bacterial endotoxins.

Radiopharmaceutical Aspects

The general monograph radiopharmaceutical preparations covers:

- Preparations, ready for administration, containing one or more radionuclides to be used for a medicinal purpose
- Radionuclide generators : any system incorporating a fixed parent radionuclide from that is produced a daughter radionuclide that is to be obtained by elution or by any other method and used in a radiopharmaceutical preparation
- Kits for radiopharmaceutical preparation : any preparation to be reconstituted or combined with radionuclides in the final radiopharmaceutical preparation, usually prior to its administration
- Radionuclide precursors : any radionuclide produced for radiolabelling of another substance prior to administration

Radiopharmaceutical Aspects

Approximate half-life: This concept allows a half-life measurement *before* release of a product. (a true half-life measurement would take a few half-lives to determine)

At the section "Tests" is stated that, if mentioned, it is allowed to do some tests after release of the preparation (*It is sometimes difficult to carry out some tests before releasing the batch for use when the half-life of the radionuclide in the preparation is short. The individual monograph indicates the tests that need **not** be completed before release for use. These tests then constitute a control of the quality of production)*

Note: if a test is mentioned in the general monograph, but not in the individual monograph, the test is obligatory and needs to be preformed before release.

Radionuclidic Purity: For short lived radioisotopes it is of importance to 'validate' the irradiation process *(As the preparation is used and injected, it may not have been possible to fully characterize the total long lived impurities. It is in these condition important to note the under the chosen conditions, the long-lived impurities are not present)*

Radiopharmaceutical Aspects

Radionuclidic Purity:

Due to differences in the half-lives of the different radionuclides present in a radiopharmaceutical preparation, the radionuclidic purity changes with time

- **Specific** relevant **radionuclides** are mentioned and **specified**
- If monograph on radionuclide precursor exists, radionuclide section in the monograph may be skipped (e.g. new Ga^{68}-monographs)
- A test for both short lived and long lived impurities may be required.
- Limits based on dosimetric (ICRP) and technical considerations
- Must be met **throughout the shelf life** of the product!]
- In specific cases waiting time needed to comp

Specific Activity: An aspect giving rise to discussion. Essential to measure in case of substances which have a pharmacological action or have a potential high level of "cold" material in the preparation

Radiopharmaceutical Aspects

Radiochemical purity: The radiochemical purity is the percentage of radioactivity in the desired chemical form. In order to do the determination correctly, all impurities should be combined as a percentage and subtracted from 100%.

- Liquid chromatography (HPLC) preferred
- Often in combination with TLC, if risk of impurities being retained on HPLC column (18F-Fluoride, radiometal colloids)
- For HPLC isocratic conditions prefered (best resolution)
- System suitability test: typically resolution of two reference substances with closely related structural features (FDM vs FDG)
- Most monographs: Overall limit (e.g. 95%), newer monographs (e.g. Ga-68): Only limit for a specific test, no overall limit, takes into account that impurities could be measured twice
- Column type and specific reference chromatograms not described (knowledge database)
- Must be met throughout the shelf life of the product!

Radiopharmaceutical Aspects
Biodistribution

A much debated topic!!

Many older monograph's have a biodistribution requirement as at the time no acceptable analytical techniques were available to test the product

New monographs cannot contain a biodistribution test anymore (EDQM requirement)

Why not replace the biodistribution test?

- No support from industry (too little money made on old products)
- Validation of a new test would require many animals

Radiopharmaceutical Aspects
Sterility

Radiopharmaceutical preparations for parenteral administration must comply with the test for sterility.

Issues arise with:

- short half-life of most radionuclides used
  - (preparation can be released before completion of the test)
- the small size of batches
  - (sample size can be smaller as described in the monograph on Sterility Testing)
- the radiation hazards
  - (product can decay before tested for sterility, under conditions that prevent false negatives)

Radiopharmaceutical Aspects
Endotoxins & Pyrogens

Radiopharmaceuticals need to comply with the monographs on pyrogens and endotoxins.

Pyrogenicty

If in radiopharmaceutical preparation starting materials are used that can cause a pyrogenic reaction (but no endotoxins) the pyrogenicity test needs to be used. For human plasma containing products, the starting materials that are used in the described preparations are already tested.

Endotoxins

All radiopharmaceutical preparations must comply with the test for endotoxins. Note that the limit is half that of normal pharmaceuticals (175 IU/V compared to 350 IU/V)

Note: the USP mentions EU as standard unit for endotoxins. 1IU = 1EU

Radiopharmaceutical Aspects
Storage & Labeling

Storage

in an airtight container, ensuring shielding for staff, complying with the local and international regulations.

Labeling

Local regulations needs to be followed. As shipped outside of the site of manufacture also European regulations need to be followed.

When isotopes with a half life of < 70 days apart from the day also the time must be mentioned as part of the activity reference time

For chemical precursors it is recommended that a new batch of precursor is tested in a trial labeling, to verify it's fitness for use.

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Radiopharmaceutical preparations (0125) 2023 update

Two changed versions published:

1) Change from 'period of validity' to 'shelf life'. (Ed. 10.7)
   - Note: the start of the shelf life is not automatically at the end of production

2) Overall review of the monograph (Ed 11.1)

- Educational texts have been removed
- Included a statement on how the deal with radionuclide precursors in a continuous process
- Clarification that a radionuclide is identified by its half-life or nature and energy of its radiation or both.
- pH: although the monograph limits may be wide to accommodate different production ways, it is expected that the pH range of a developed process is set according the validation outcomes
- Elemental impurities: although the 5.20. Elemental impurities is not applicable, control through e.g. a risk assessment is expected
- Physiological distribution: animal testing should be avoided unless there are no other ways to assess the quality of the preparation
- Sterility: pre filtration testing (PUPSIT) may be omitted (in line with Annex 1)
- Endotoxins: Test may only be done post release in case of a half-life of <90 minutes
- Clarification that preparations made from radionuclide precursors **must** comply with the precursor's radionuclidic purity requirements throughout the shelf life of the final preparation.

Detection and measurement of radioactivity

Detection and measurement of radioactivity (2.2.66.)

Purpose of the text was to allow a better description of the methods and issues around the qualitative and quantitative measurement of radioactivity.

The section is removed from the General Monograph on Radiopharmaceutical Preparations .

Detection and measurement of radioactivity

The chapter deals with the theoretical and practical aspects of detection and measurement of radioactivity in the context of Ph. Eur. monographs on radiopharmaceutical preparations.

- Introduction describing general background
- A general section describing the theoretical principles of the measurement of radioactivity, explaining dead time losses, correction of decay during measurement, statistics, linearity, limit of detection, limit of quantification.

Description of the measurement techniques

- *Measurement of radioactivity using ionisation chambers* describing the principle of ionisation chamber and how to use them
- *Measurement of radioactivity using solid-state detectors* explaining the use of scintillation crystals used for spectrometry and quantification of radioactivity
- *Liquid scintillation methods in* alpha and beta spectrometry and quantitative measurements

Detection and measurement of radioactivity

Description of methods

- *Half-life and approximate half-life:* A half-life determination takes minimum 3 half-lives to get to a right level of accuracy. Used if the radioisotope is not known. Approximate half-life is used to confirm the identity and only takes ¼ of the estimated half life. This method is developed to be able to confirm the identity before release. Please be aware that the amount of activity used, determines the precision of the method
- *Spectrometry:* Description of the methods that can be used for the spectrometry (α, β and γ) and how to do identification of a radioisotopes. Calibration of equipment and identification of radioisotopes are described.

Note on identification: a true identification requires a spectrum in combination with a half-life determination. However, for PET radioisotopes only a half-life determination is sufficient.

Detection & measurement of radioactivity *in combination with a separation technique*

Separation of the impurities from the radiopharmaceutical is necessary to determine the radiochemical purity.

The different methods are mentioned and referred to their main chapters (*e.g. thin-layer chromatography (2.2.27)*)

A section describing the detection of the radioactivity *in line* for use in liquid chromatography.

A warning is given to verify whether there are any impurities that are not eluted from the column (a separate TLC method needs to be used)

Disregard limit and peak recognition: it is important to choose an appropriate threshold setting and appropriate conditions for integration of the peak areas.

Offline measurement: taking fractions of the eluate of a column and measuring them and determining the elution profile.

Detection & measurement of radioactivity *in combination with a separation technique*

TLC measurement methods:

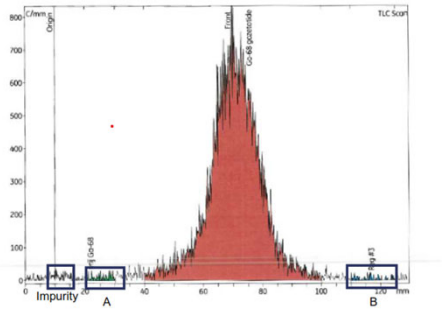
Scanning: a measuring device is moved over a TLC plate and the activity is measured. Care should be taken with respect to the resolution

Cutting: A TLC plate is cut into small strips and measured. From each measurement a TLC profile can be constructed (max 3 well separated spots)

Autoradiography: can be used with a photographic film or a phosphor imager

In all cases: LOD, LOQ and linearity are important system parameters to know

Background detection



NEW

For the determination of the impurity, what is the best place to determined the background?

- Location A
- Location B

CHEMICAL PRECURSORS FOR RADIOPHARMACEUTICAL PREPARATIONS

A monograph that covers chemical precursors for as far as they are not yet covered in individual monographs.

It provides details on:

- The production (within the framework of a suitable quality system)
- Different limits (compared to substances for pharmaceutical use) for:
  - Related substances
  - Residual solvents
  - Metal catalysts or metal reagent residues
  - Microbial contamination
  - Bacterial endotoxins

The different limits are justified as the amount of chemical precursor used per patient dose is small and not given frequently to a patient during their lifetime

Extemporaneous preparation of radiopharmaceuticals (5.19.)

- The monograph details quality requirements for the preparation of radiopharmaceuticals in hospitals, radiopharmacies etc.
- It is not the aim of the document to replace existing national legislation.
- It covers kit-based preparations (from licensed and unlicensed kits) and unlicensed preparations containing radionuclides for positron emission tomography (PET), single photon emission computed tomography (SPECT) or therapeutic applications.
- the preparation of radiopharmaceuticals is considered as a process involving all or some of the following steps: purchase of materials and products; production of radionuclides for radiolabelling; radiolabelling; chemical modification and/or purification; formulation; dispensing of the pharmaceutical form; sterilisation; analytical control; packaging; labelling; and release.
- Drawing patient doses for immediate application is not considered as part of the preparation of radiopharmaceuticals, but of clinical practice.

The monograph is not legally binding

Validation of test methods for radioactivity determinations

Validation

As part of the "Technical Guide for the elaboration of monographs on radiopharmaceutical preparations" the validation requirements of test methods for radioactivity are being mentioned

Work was done in co-operation with the EANM Radiopharmacy Committee

The text is not binding as it is not part of the European Pharmacopoeia, but it provides guidance, available from the EDQM website

https://www.edqm.eu/en/technical-guides

EANM made an explanatory article: EANM guideline on the validation of analytical methods for radiopharmaceuticals (Gillings et al. EJNMMI Radiopharmacy and Chemistry (2020) 5:7 https://doi.org/10.1186/s41181-019-0086-z)

In this slide an example of a monograph is reviewed

FDG taken as an example as it covers many aspects

..\1325E FDG.pdf

European Pharmacopoeia

Ed 11.6-11.8

Radiopharmaceuticals

New:

- *In Ed 11.6:*

- Ioflupane (^{123}I) injection (3144)

- *In Ed 11.7:*

- Lutetium (^{177}Lu) Zadavotide guraxetan (177Lu PSMA I&T injection: 1st therapeutic PSMA monograph.

No new monographs in Ed 11.8

Radiopharmaceuticals

Revisions

Ed 11.7

Gallium (^{68}Ga) chloride (accelerator produced)
Id test on Ga^{3+} is removed
Technetium (^{99m}Tc) oxidronate injection:
RCP test changed due to potential oxidation with the current mobile phase. Definition updated, inclusion of accelerator produced ^{99m}Tc

Ed 11.8

Gallium (^{68}Ga) chloride (generator produced)
Id test on Ga^{3+} is removed
Technetium (^{99m}Tc) human albumin iunjection
Definition updated, inclusion of accelerator produced ^{99m}Tc
Tetra-O-Acetyl-mannose Triflate for radiopharmaceutical preparations
Removal of hygroscopicity in the character section
General monograph on Radiopharmaceuticals
Endotoxin section replaced by Pyrogenicity section

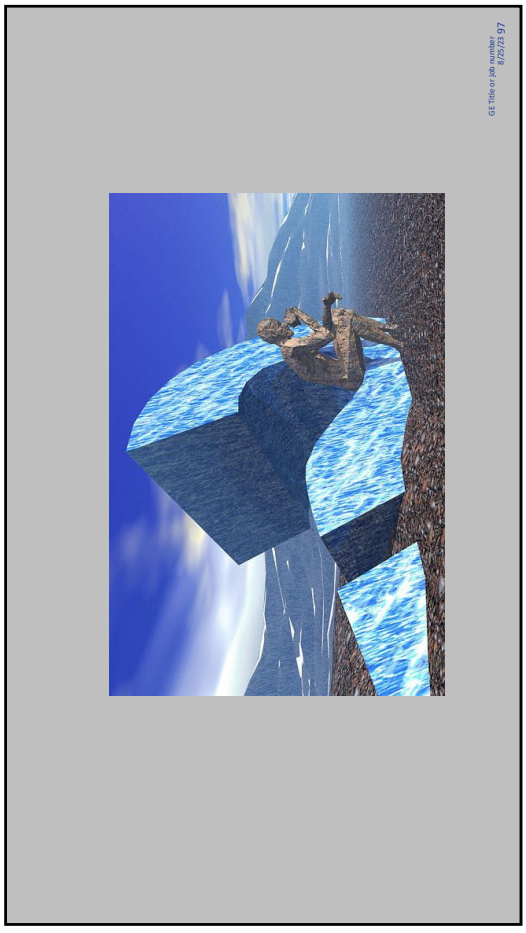
Work in Progress

Published in Pharmeuropa
- 89Zr-Zirconium oxalate (comments deadline dosed)
- Gallium (68Ga) chloride (accelerator-produced) solution for radiolabelling: AMA test for the cyclotron produced material introduced
- Multiple technetium (^{99m}Tc) monographs: inclusion of accelerator produced technetium (^{99m}Tc)

Other Work in progress:
- Ammonia (^{13}N) injection: new column still needs to be tested (old column is not available anymore)
- Gallium (68Ga) chloride (generator-produced) solution for radiolabelling: update to the title. To go to the Commission June 2024 (RNP issue 68Ge still an issue)
- Water (15O) injection: new radiochemical purity test
- Test A for the RNP for 18F-fluoride monographs (text is not 100% clear)
- Actinium (225Ac) nitrate (generator-produced) solution for radiolabelling: request for monograph considered to be too early at too little in known.
- Fluoride (18F) solution for radiolabelling: pH issue (request for revision sent in)
- Fluoride (18F) Fluoroestradiol monograph in preparation
- Revision of the Lutetium (^{177}Lu) chloride for radiolabelling monograph
- New monograph fro Copper (^{64}Cu) for radiolabeling

Take home messages

- In development of new radiopharmaceutical tracers, the pharmacopoeia needs to be used for the analytical method development and product development
- Routinely produced radiopharmaceuticals need to comply to all relevant monographs in the European Pharmacopoeia
- If you want to know in detail what is required for compliance, the actual text must be read!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9/5/23 97

GMP in the Pharmaceutical industry and for classical radiopharmaceuticals

Désirée Vendrig graduated in 1985 as a pharmacist at the State University of Utrecht, The Netherlands. After a Ph.D. study on the bioanalysis, electrochemistry and stability of Vinca Alkaloids, she joined Solvay Pharmaceuticals (now Abbott) in Weesp, The Netherlands in 1988 as Head of the R&D Pharmaceutical Analysis Department.

From 1995 to 2004 she worked as Senior GMP inspector at the Dutch Healthcare Inspectorate in Haarlem and The Hague. She joined Teva Pharmaceuticals Europe in Haarlem in October 2004 and had various regional and global quality positions. Since 2018, she is working as an independent GxP consultant.

Désirée Vendrig is active in teaching pharmacy students since the second year of her Pharmacy Study and is a lecturer of the Radiopharmacy course of the European Association of Nuclear Medicine for more than 20 years. Additionally, she regularly gives presentations during national and international seminars and post-graduate courses on both GMP and GDP related topics.

<u>The lecture has the following learning objectives:</u>

GMP in the Pharmaceutical industry

1. Students are able to define which elements of industrial GMP are relevant and/or can be applied for their own 'location'.
2. Students are able to design key elements of a Quality Management System using ICH Q10 and/or EU GMP guidelines.
3. Students are able to design a template of 'product dossier' using key elements from the EU regulatory guidance for a Marketing Authorization Application.
4. Students are able to implement Quality Risk Management principles using ICH Q9.

GMP for the Classical Radiopharmaceuticals

1. Students are able to understand the basic principles of Good Manufacturing Practices for the preparation of classical radiopharmaceuticals in a radiopharmacy.
2. Students are able to define key procedures for a Quality Management System and metrics/KPIs for monitoring the compliance status.
3. Students are able to understand the importance of training of personnel.
4. Students are able to understand how the design and the size of the premises are related to the type of activities and scale of operation.

5. Students are able to identify equipment that require qualification, regular maintenance and calibration, and IT programs that require validation.

Summary of the lecture:

The presentation provides general information on EU Directives and guidelines for the manufacturing of medicinal products in the pharmaceutical industry. Detailed information on industrial EU GMP guidelines as well as international guidelines is presented. Special attention is paid to exceptions for Radiopharmaceuticals. The information that needs to be submitted to regulatory authorities to apply for a marketing authorization is described. Examples of obligations for industrial manufacturers are discussed and where applicable a comparison with the standard practices in hospitals and PET centres is made.

The second presentation gives an overview of Good Manufacturing Practices for classical radiopharmaceuticals. Key elements are a Quality System, qualification of personnel, validation and/qualification of premises and equipment, a controlled documentation management system, worksheets for preparation and testing, validated preparation processes and test methods, and procedures for the qualification of suppliers, complaint handling and recalls as well as for self-inspection. Practical examples are discussed during the lecture.

Take home messages:

GMP in the Pharmaceutical industry

1. Pharmaceutical Industry must implement new and amended EU Directives and Regulations as well as revisions of EU GMP. The manufacturer's Qualified Person certifies every batch for compliance with EU GMP and the Marketing Authorisation.
2. Basic GMP principles for hospital pharmacies, PET Centers and industry are similar.
3. International guidelines can be used by any organization producing pharmaceutical products.
4. Facility design, staff and the Quality System should be risk based taking into consideration e.g.
    -Type of products.
    -Scale of operation.
    -Batch size.
    -Complexity of technology.
    -Product shelf life.

GMP for the Classical Radiopharmaceuticals

1. Key conditions for the preparation of high quality products meeting patients' and doctors' needs as well as regulators' expectations:
   -Qualified premises, suitable for use.
   -Approved procedures, records and specifications.
   -Calibrated equipment.
   -Validated processes.
   -Qualified staff.
2. GMP serves as a roadmap to assure products are consistently of high quality and safe for patients.
3. Quality Risk management principles should be implemented in all relevant processes and procedures.
4. Effective monitoring and control systems for process performance and product quality provide assurance of continued suitability and capability of processes.
5. A system for continuous improvements and PQS enhancements enables preparing products meeting the designed quality standards.

References:

1. EudraLex - Volume 4 Good manufacturing practice (GMP) Guidelines
   EudraLex - Volume 4 (europa.eu)
2. PIC/S guide to good practices for the preparation of medicinal products in healthcare establishments, (PE 010-4), version 4, 2021
   Publications (picscheme.org)
3. European Pharmacopoeia
   European Pharmacopoeia (Ph. Eur.) - European Directorate for the Quality of Medicines & HealthCare (edqm.eu)
4. EANM Guidelines on cGRPP in the production of radiopharmaceuticals for the small-scale preparations of radiopharmaceuticals (2021)
   eanm.org/publications/guidelines/radiopharmacy/
5. The International Pharmacopoeia (WHO)
   Health products policy and standards (who.int)
   The International Pharmacopoeia (digicollections.net)
6. (National) Guidelines on hospital pharmacy
7. Guidelines on aseptic manufacturing
   Parenteral Drug Association (Technical Reports)
   Parenteral Drug Association | Pharmaceutical Regulatory News (pda.org)
8. International Conference on Harmonisation
   ICH Official web site : ICH
   ICH Quality Guidelines
   https://www.ich.org/page/quality-guidelines
9. Guidance on good manufacturing practice and good distribution practice: Questions and answers
   https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-manufacturing-practice/guidance-good-manufacturing-practice-good-distribution-practice-questions-answers

GMP in the Pharmaceutical Industry

Désirée Vendrig, PhD

Postgraduate European Radiopharmacy Course
Module I: Pharmacy

Ljubljana, 25 August 2025

Contents

Glossary

API	Active Pharmaceutical Ingredient
BP	British Pharmacopoeia
CAPA	Corrective Actions and Preventive Actions
CEP	Certificate of Suitability
CMC	Chemistry, Manufacturing and Controls
CPMP	Committee for Proprietary Medicinal Products
CQA	Critical Quality Attributes
eCTD	electronic Common Technical Document
EP	European Pharmacopeia
FDA	United States Food and Drug Administration
GDP	Good Distribution Practices

Glossary

(c)GMP	(current) Good Manufacturing Practice
IAEA	International Atomic Energy Agency
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IPC	In Process Controls
ISPE	International Society for Pharmaceutical Engineering
JP	Japanese Pharmacopeia
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MHRA	Medicines and Healthcare Products Regulatory Agency
OOS	Out of Specification
PDA	Parenteral Drug Association

Glossary

- Ph.Eur. European Pharmacopeia
- PhV Pharmacovigilance
- PIC/S Pharmaceutical Inspection Co-operation Scheme
- PIL Patient Information Leaflet
- PQS Pharmaceutical Quality System
- PSUR Periodic Safety Update Report
- SMF Site Master File
- QA Quality Assurance
- QC Quality Control
- QP Qualified Person
- QRM Quality Risk Management
- USP United States Pharmacopeia
- WHO World Health Organisation

Learning Objectives

Participants will be able to

- define which elements of industrial GMP are relevant and/or can be applied at their own location
- implement key elements of a Quality System using ICH Q10 and/or EU GMP guidelines
- design a template of 'product dossier' using key elements from the EU regulatory guidance for a Marketing Authorization Application
- Define Metrics and KPIs

Guidelines in Industry

- EU GMP (Eudralex Vol. 4)
  - Part I: GMP for Medicinal Products: 9 Chapters
  - Part II: GMP for APIs
  - Part III: GMP related documents: SMF, QRM, PQS, templates for batch certification and written confirmation, GMP for excipients, Reflection paper on GMP and MAHs, etc
  - Part IV - GMP requirements for Advanced Therapy Medicinal Products
  - 19 Annexes
  - Other documents: GDP guidelines, Guidance on GMP and GDP: Questions and answers
- FDA cGMP 21 CFR part 210 & part 211, Japanese GMP, Brazilian GMP, Korean GMP, etc.

Guidelines in Industry

- PIC/S Guidelines (recommendations, Aide Memoires)
- Pharmacopeias (EP, USP, JP, BP)
- ICH Guidelines
- WHO Guidelines
- Professional standards: ISPE, PDA, EANM

- *Note: transportation of radiopharmaceuticals is regulated by the IAEA and radiation protection requirements*

EU GMP

- Annex 1 – Manufacture of Sterile Medicinal Products
- Annex 3 – Manufacture of Radiopharmaceuticals
- Applicable to
  - Manufacturers of registered medinical products
  - Manufacturers of IMPs
  - Nuclear Centers/Institutes
  - PET Centers

ICH Guidelines and Initiatives - overview

- Pharmacopoeial Harmonisation

- ICH Q7: GMP Guidance for Active Pharmaceutical Ingredients
- ICH Q8: Pharmaceutical Development
- ICH Q9: Quality Risk Management, also in Part III EU GMP
- ICH Q10: Pharmaceutical Quality System, also in Part III EU GMP
- ICH Q11: Development and manufacture of drug substances

- ICH Q12: Product Lifecycle Management: adopted by CHMP Jan 2020
- ICH Q13: Continuous Manufacturing for Drug Substances and Drug Products – implemented in EU: July 2023
- ICH Q14: Analytical Procedure Development – implemented in EU: June 2024

ICH Q10 Pharmaceutical Quality System

Objectives:

- delivery of products with the quality attributes appropriate to meet the needs of patients, health care professionals, regulatory authorities
- develop and use effective monitoring and control systems for process performance and product quality, thereby providing assurance of continued suitability and capability of processes
- to identify and implement appropriate product quality improvements, process improvements, variability reduction, innovations and PQS enhancements, thereby increasing the ability to fulfill quality needs consistently

QRM for identifying and prioritizing areas for continual improvement

Requirements in the Pharmaceutical Industry

- EU Regulations, Directives and Notes for Guidance, Pharmacopeias
- Marketing Authorisation (MA)
  - per product strength and pack size
  - submission and approval per region/country
  - changes may require a variation
- Manufacturing and Importation Authorisation
  - Site specific
  - Product type specific
- Wholesale Distribution License
- Adherence to regulations on radiation protection

EU Regulations and Directives

- Regulations

A "regulation" is a binding legislative act. It must be applied in its entirety across the EU.

→ delegated acts, specifying (technical) detailed rules

- Directives

A "directive" is a legislative act that sets out a goal that all EU countries must achieve. However, it is up to the individual countries to decide how.

- Decisions

A "decision" is binding on those to whom it is addressed (e.g. an EU country or an individual company) and is directly applicable.

EU Directives and Regulations

- 2001/83/EC All aspects related medicinal products amended by e.g.:
  - 2003/63/EC: MA dossier requirements
  - 2004/27/EC: free movement of products
  - 2010/84/EC: PhV revision
  - 2011/62/EC: Falsified Medicines Directive
- Directive 2017/1572 - supplementing Directive 2001/83/EC: principles and guidelines of GMP for medicinal products for human use (replaced 2003/94 EC)
- Clinical Trial Regulation No. 536/2014
- Delegated Regulation 2017/1569 - supplementing Regulation No 536/2014: principles of and guidelines for GMP for IMPs for human use and arrangements for inspections

EU Guidelines and Regulations

GDP Guidelines:

- Guidelines of 7 March 2013 on Good Distribution Practice of Medicinal Products for Human Use (2013/C 343/01)
- Guidelines of 19 March 2015 on principles of Good Distribution Practice of active substances for medicinal products for human use (2015/C 95/01)

Registration aspects

- Variations: Commission Regulations, e.g.(EC) No 1234/2008
- Notes for Guidance (CPMP), e.g.
  'note for guidance on in-use stability testing of human medicinal products CPMP/QWP/2934/99'

Marketing Authorisation Application

Common Technical Document (eCDT)

Module 1:	Administrative Information
Module 2:	Overviews and Summaries
Module 3:	Quality (Chemistry, Manufacturing and Control Documents (CMC section))
Module 4:	Non-clinical study reports
Module 5:	Clinical studies (Innovator) / Bioequivalence study (Generics) reports

Life-cycle Management of Registration Dossier

- Marketing Authorisation should be renewed after 5 years on the basis of a re-evaluation of the risk/benefit balance
- Once renewed, the marketing authorisation shall be valid for an unlimited period unless the competent authority decides, on justified grounds relating to pharmacovigilance, to proceed with one additional five-year renewal
- Risk/benefit balance is evaluated on basis of Periodic Safety Update Report (PSUR) to be submitted within the first 2 years of marketing every 6 months and than every 3 years
- For the most generic products no PSURs are required any more (e.g. well established use)

Registration Dossier

- CMC section: API and finished product
  - Development
  - Composition
  - Process description, validation, IPCs
  - Analytical methods, validation
  - Specifications
    - Excipients, API, drug product, packaging materials etc.
  - Stability data and long-term testing protocol
    - Claim storage conditions and shelf life
  - Container closure integrity

Registration Dossier

- Details of packaging configuration
  - -Vial volume, glass type, stopper type, cap type
    -Number of tablets/syringes (e.g. 4 x 7, 3 x 10 tabs)
  - Label
  - Carton
  - Patient information leaflet

Variations

- Classification of variations based on Commission Regulation (EC) No 1234/2008 of 24 of November 2008
  - Amended by Regulation (EU) No 712/2012
- Minor variations of Type IA, minor variations of Type IB and major variations of Type II
- A) Administrative changes
- B) Quality changes
- C) Safety, Efficacy and Pharmacovigilance changes
- D) Specific changes to Plasma Master Files and Vaccine Antigen Master Files

Requirements in Industry - manufacturer

- Pharmaceutical Quality System
  e.g. Deviations, CAPAs, Complaint Handling, Audits, Supplier Mngt, Management Review, Data Integrity, Risk Management Principles, etc.
- Personnel
  - Production, QC and QA manager
  - Qualified Person registered on license
- Facilities and equipment
  - shared facilities with research institutes

Requirements in Industry - manufacturer

- Batch manufacturing protocols, Packaging protocols, Testing protocols, etc.
- Approved artwork
  - Blister, bottle/syringe label, box, Patient Information Leaflet
- Testing of API, finished products, excipients, primary containers, incl. sterility test, etc.
- Release process – conditional release for radiopharmaceuticals
- Parametric release
  - Release procedure and continuous review of QA system is essential
- Quality Overview of Outsourced Activities

GMP versus Radiation Protection

- Protection of products against contamination and cross-contamination
- Protection of environment and operators against radiation
  - Effective Quality System in place
    - Environmental and Personnel monitoring
    - Media fills
    - Approved procedures and production/quality control documentation, and evaluated as part of the release process

Exception for Radiopharmaceuticals

- Allowed to label vial with partial information prior to manufacturing, provided
  - sterility not compromised
  - visual control possible after filling

Manufacturers' Obligations

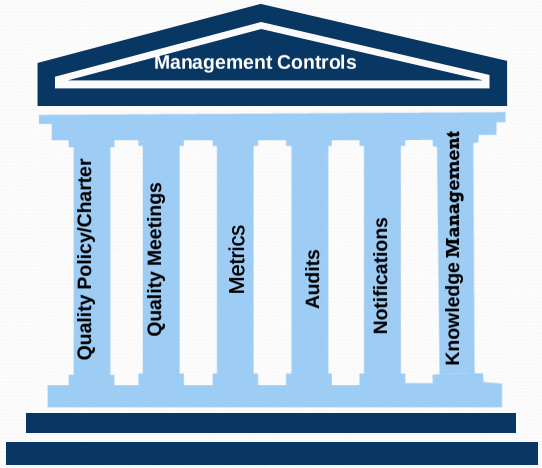
some elements of a Pharmaceutical Quality System

- Detailed Batch Records, Testing Records etc.
- Batch Certification by a Qualified Person
- System for handling Deviations, CAPAs, OOS, etc.
- Change Control
- Supplier Management (including audits)
- Complaint Handling and Recalls
- Self Inspections
- Quality Risk Management

Manufacturers' Obligations

- Maintenance and Calibration
- Validation Master Plan
- ICH Stability and on going Stability Program
- Storage of Reference and Retention samples
- (annual) Product Quality Reviews
- Management Reviews
- Risk Assessment after Competent Authorities Notifications (CEP suspensions, FDA Warning letters, Referral procedures)
- Implementation revised and new guidelines, Ph.Eur. Methods etc.
- Product Lifecycle Management

Management Controls Framework



What Metrics do you know?

What is the best metric?

A: number of complaints closed on time

B: percentage of complaints closed on time

Quality Metrics

- Clear definitions
- Requirements based on GMP compliance level

Compliance related metrics:

- closed on time: complaints, deviations, CAPA's, Change Controls, Lab investigations (OOS), etc.
- Product Quality Reviews completed by original due date
- Stability samples tested vs. plan
- Percentage of Field Alerts/ Regulatory Body notifications filed on time

Quality Metrics

Audits related

- Percentage of internal/external audits performed on time
- Number of audits without critical observations
- Regulatory Agency Audits without critical observations

Manufacturing/release related

- Number of batches released without deviations
- Number of batches released within 2 days after receipt

Training related

- Percentage of SOPs training overdue
- GMP training completed by original due date

(Quality) Management Reviews

- Who should participate in the Management Review?
- What would you discuss in your Management Review?

Topics:

- Follow up actions previous QMR
- Metrics and KPIs
- Quality Defects
- Customer feedback/complaints
- Personnel issues
- Training status/needs
- Key Changes (organisational developments impacting quality mangement, new/revised regulations)

Batch Certification and Release

- Relevant acceptance criteria are met before release
- Certification by a Qualified Person (authorized person)
  - Review of manufacturing and packaging records
  - Test results (incl. sterility) meet specifications
  - Deviations, OOS, CAPAs, Changes
  - Trend analysis results of environmental monitoring data
  - Visual inspection of sample

'Manufactured in compliance with GMP and complies with specifications in MA'

Batch Certification and Release

Exceptions for Radiopharmaceuticals (Annex 3)

- Approval for transportation
  (knowledge of QMS customer and Quality Agreement needed)
- Conditional Release
  (not all test results are available, e.g. sterility, impurities)
- Final Release
- Parametric Release requires pre-approval by Inspectorate!

Supplier Management

Full supply chain traceability should be established

- Audits and re-audits
- Quality/Technical agreement
- GMP and GDP for APIs
- Risk assessment for excipients
- Testing incoming materials
  - Identity testing of all batches
  - Full / Reduced testing of approved suppliers materials
  - Written confirmation for non-EU APIs

Storage Requirements

- Bulk finished product:
  - 6 months after expiry
  - shorter period: justified through risk management
- Starting materials
  - Two years after release of product
- Batch documentation:
  - One year after expiry or 5 years after certification of the batch (whichever is the longest)
- Other conditions may be defined by local Competent Authorities

Distribution

- Controlled conditions
- Shipment ´under quarantine´
  - Quality agreement with receiving institute that product will not be administered until satisfactory test results have been received and assessed by designated person
- Supply Chain
  - License/authorization of supplier
  - License/authorization of customer
  - Full traceability of every batch

Take Home Messages

- Pharmaceutical Industry must implement new and amended EU Directives and Regulations as well as revisions of EU GMP.
- The Qualified Person certifies **every** batch for compliance with EU GMP and the Marketing Authorisation (registration dossier)
- International guidelines can be used by any organization producing or preparing pharmaceutical products
- Facility design, staff and the Quality System should be risk based taking into consideration, e.g.,
  - -type of products
  - -scale of operation
  - -batch size
  - -complexity of technology
  - -product shelf life

Production of Radiopharmaceuticals

Acknowledgement: Curium Netherlands B.V.

GMP in the Pharmaceutical Industry

Désirée Vendrig, PhD

Postgraduate European Radiopharmacy Course
Module I: Pharmacy

Ljubljana, 25 August 2025

Contents

Glossary

API	Active Pharmaceutical Ingredient
BP	British Pharmacopoeia
BSC	Biohazard Safety Cabinet
CAPA	Corrective Actions and Preventive Actions
CEP	Certificate of Suitability
CMC	Chemistry, Manufacturing and Controls
CPMP	Committee for Proprietary Medicinal Products
CQA	Critical Quality Attributes
eCTD	electronic Common Technical Document
EP	European Pharmacopeia
FDA	United States Food and Drug Administration

Glossary

GDP	Good Distribution Practices
(c)GMP	(current) Good Manufacturing Practice
IAEA	International Atomic Energy Agency
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Products
IPC	In Process Controls
ISPE	International Society for Pharmaceutical Engineering
JP	Japanese Pharmacopeia
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MHRA	Medicines and Healthcare Products Regulatory Agency
OOS	Out of Specification
PDA	Parenteral Drug Association

Glossary

Ph. Eur.	European Pharmacopeia
PhV	Pharmacovigilance
PIC/S	Pharmaceutical Inspection Co-operation Scheme
PIL	Patient Information Leaflet
PQS	Pharmaceutical Quality System
PSUR	Periodic Safety Update Report
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person
QTA	Quality Technical Agreement
QMR	Quality Management Review
QRM	Quality Risk Management
USP	United States Pharmacopeia
WHO	World Health Organisation

Learning Objectives

Participants will be able to

- understand the basic principles of Good Manufacturing Practices for the preparation of classical radiopharmaceuticals in a radiopharmacy
- define key procedures for a Quality Management System and metrics/KPIs for monitoring the compliance status
- understand the importance of continuous training of personnel
- understand how the design and the size of the premises are related to the type of activities and scale of operation

Legislation

- National legislation for preparation of pharmaceuticals
- Directives on radiation protection
- National legislation for medical care
- Directives and guidelines on Good Clinical Practices (GCP)
- European Pharmacopeia monographs:
  - -product specific monographs
  - -compounding of radiopharmaceuticals (5.19)
- USP monographs:
  - -product specific monographs
  - -general chapters related to non-PET radiopharmaceuticals

Professional Guidelines

- EANM Guidelines on cGRPP
  - for the small-scale preparation of radiopharmaceuticals using automated modules: a European perspective (2014)
  - on validation and qualification of processes and operations involving radiopharmaceuticals (2017)
  - for the small-scale preparations of radiopharmaceuticals (2021)
  - on quality risk management for radiopharmaceuticals (2022)
- PIC/S guide to good practices for the preparation of medicinal products in healthcare establishments (2014)
- The International Pharmacopoeia (WHO)
- Guidelines on Hospital Pharmacy, Aseptic Preparations
- National: e.g. The Netherlands: GMP-Z for Hospital Pharmacies

Why GMP?

Pharmaceutical Quality System (PQS)

Quality Mngt ⟷ GMP ⟷ QC

- Quality Management covers all matters which individually or collectively influence the quality of the product
- GMP ensures products are consistently produced and controlled as required by Marketing Authorisation or product dossier

- Consider size and complexity of activities
- Incorporate Risk Management principles
- Data Integrity: attributable, legible, , contemporenous, original and accurate

Pharmaceutical Quality System

- Product and process knowledge is managed throughout all lifecycle stages
- prospective evaluation of **planned changes** and their approval prior to implementation, e.g. revalidation of analytical methods
- investigation of **deviations**, **OOS/OOT** results, suspected **product defects** and other problems
- corrective actions and/or preventative actions (**CAPAs**) should be identified
- periodic management review to identify opportunities for continual improvement of products, processes and the system itself

PQS: Senior Management

- Senior management's leadership and active support on the PQS is essential!

- Definition of mutual responsibilities
  - nuclear physician (medical care)
  - nuclear physicist (dosimetry, equipment)
  - pharmacist (radiopharmaceuticals)
  - technicians involved in preparation
  - quality manager (hospital)

GMP for Radiopharmaceuticals

- Pharmaceutical Quality System
- Trained and Qualified Personnel
- Premises and Equipment suitable for intended use
- Documentation System
  - worksheets for preparation and testing
  - Data Integrity
- Preparation and Process Controls
  - Environmental monitoring, mediafills
- Quality Control (validated analytical methods)
- Release Procedures
- Supplier Qualification
- Complaints and Recalls
- Self Inspection
- Management Review

QUALITY RISK MANAGEMENT

Personnel

- Job description for every position
- Documented training program
  - SOP's
  - ionising radiation regulations
  - GMP, pharm. microbiology, hygiene, EM
  - competence in aseptic skills
- Document training and re-qualification

Premises – Design

- Minimize risk of
  - particular and microbiological contamination
  - cross contamination
  - mix-ups
- Points to consider
  - number of people
  - classification of area
  - pressure differentials

Quality Risk Management
(Part III EU GMP, ICH Q9)

Premises – Design

Minimal risk for contamination of the product

positive pressure

and

Measures to protect the environment and operator from the materials being handled

negative pressure

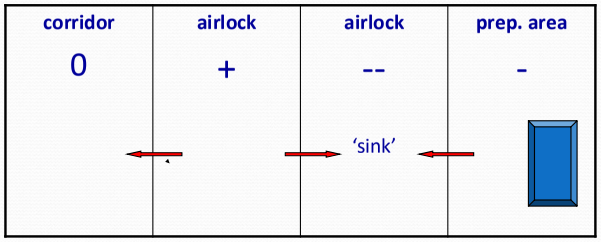
Premises – External Requirements

GMP → positive pressure
air changes dependent on size
of room, equipment and personnel

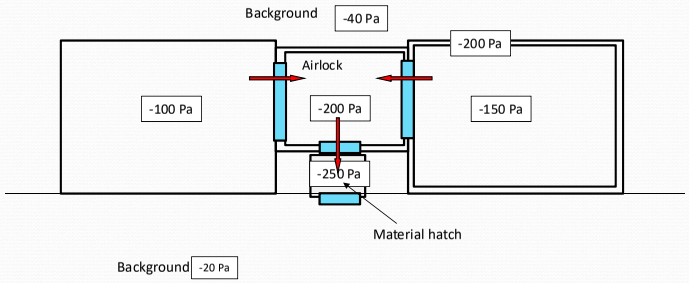
Radiation → negative pressure
legislation air changes: > 8 / hour

TWO AIRLOCKS

Pressure Differentials (1)



Pressure Differentials (2)



Pressure Measurement

Premises

- Dedicated and restricted area
- Elution Tc generator in Class A, class D background
- Entry through airlocks for personnel and materials
- Smooth and unbroken surfaces
  - floor, walls, ceiling, baseboards
- Hidden pipes and radiators
- Closed windows and outside doors
- Cupboard/drawers for cleaned materials, disposables

- No sink, no drains

Premises

Premises

Premises - preparation

- Class A area:
  - biohazard cabinet with a vertical down flow
  - negative pressure isolator

- Background environment
  - simple operations: class D
  - complex operations (e.g. open vials): class C

- Pressure differentials: ideally 10 –15 Pa

- Separate area for storage and Quality Control

Premises and Equipment
Validation and Qualification

- Storage and preparation area:
  - temperature and RH mapping
  - continuous monitoring
- Qualification of preparation area:
  - Preparation room – Class C or D
  - Biohazard Safety Cabinet
- Environmental Monitoring Program
- Equipment: DQ, IQ, OQ and PQ
- Computer validation (URS)

Environmental Monitoring

- Grade A zone and background environment
  - Particulates
  - Microbial contamination
- Frequency of monitoring:
  - Level of cleanliness
- Location of monitoring:
  - Detailed map

Air Particulate Classification

Table 5: Maximum permitted total particle concentration for monitoring.

Grade	Maximum limits for total particle ≥ 0.5 µm/m³		Maximum limits for total particle ≥ 5 µm/m³	
	at rest	in operation	at rest	in operation
A	3 520	3 520	29	29
B	3 520	352 000	29	2 930
C	352 000	3 520 000	2 930	29 300
D	3 520 000	Not predetermined [a]	29 300	Not predetermined [a]

[a] For grade D, in operation limits are not predetermined. The manufacturer should establish in operation limits based on a risk assessment and on routine data, where applicable.

Source: EU GMP, Annex 1, August 2022

Environmental Monitoring

Table 6: Maximum action limits for viable particle contamination

Grade	Air sample CFU /m³	Settle plates (diam. 90 mm) CFU /4 hours[a]	Contact plates (diam. 55mm), CFU / plate[b]	Glove print, Including 5 fingers on both hands CFU / glove
A	No growth[c]			
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

Trend analysis!

Source: EU GMP, Annex 1, August 2022

Equipment for Microbial Monitoring

Equipment

- Easy to clean
- No hazard to the products
- No redundant equipment in preparation area
- Operating instruction for each apparatus

Maintenance and Calibration

- Approved program
  - defined intervals per apparatus
  - check on performance in time

- Contract with external companies
- Contract with the hospital's Technical Services: define mutual responsibilities
- Approval by QP/ RP (pharmacist) prior to use

Cleaning (Class A and D)

- Written validated procedures
- Trained staff
- Dedicated equipment
- Mop heads disposable or re-sterilised
- Cleaning and disinfecting agents free from viable micro-organisms
  - class A and B areas sterile and spore free
- Effectiveness routinely demonstrated
  - contact plates or swabs

Documentation

- Procedures
  - SOPs, Work Instructions, Forms
- Logbooks for equipment
- Records
  - Master Preparation Protocols
  - Quality Control protocols
- Specifications
  - excipients, reagents, cleaning agents etc.
  - finished products

Documentation

- Contents section
- Uniform lay-out
- Authorized by Responsible Person
- Review Period
- Clear title and unique number
- Distinction copy and original document

Key Standard Operating Procedures (1)

- Receipt of Goods
- Check of Prescription and Calculations
- Gowning and Hygiene
- Aseptic processing in Biosafety Cabinet
- Cleaning and Disinfection of the Biosafety Cabinet
- Environmental Monitoring
- Generator Elution
- Out-of-Specification/Out-of-Trend situation (OOS/OOT)
- Product Release

Key Standard Operating Procedures (2)

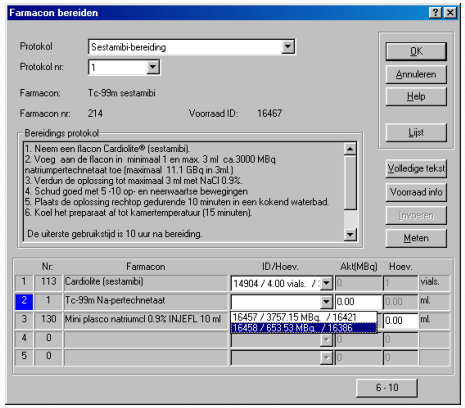
- Deviations, CAPAs, Change Control
- Calibration and Maintenance
- Validation Master Plan
- Complaints and Recalls
- Supplier Management/External Audits/QTA
- Self Inspection
- Management Reviews
- Radioactive Contamination Monitoring
- Radioactive Waste Disposal
- Calamities

Preparation Protocol

Template and Product Master Protocol approved by QP/RP/Pharmacist

- patient's name and/or ID number
- name and concentration of product
- (unique) batch number to identify the product
- name, batch and article numbers of components used to prepare the product
- method of preparation, date and time
- critical steps checked by 2nd person!!

Electronic Batch Record



Label

- Patient's name/ID and date of birth
- Radio-isotope and ligand
- Total radioactivity in container (at ART/CRT)
  - or conc./ml at reference date and time, and volume
- Volume
- Type of investigation
- Expiration date and time
- International symbol of Radioactivity

Label Outer Package

- Name and address of the radiopharmacy
- Route of administration
- Name and concentration of added antimicrobial preservative
- Where applicable, storage conditions

Aseptic Process

Aseptic Process

- Aseptic Process validation: mediafills
  - registration per employee
  - repeated at regular, predefined intervals
- Qualified and Competent staff
  - watching / video at regular intervals

Supplier Qualification

- Audit
  - Questionnaire
  - Desk audit / on site audit
  - Full monograph testing of pre-defined number of batches
    ⟹ reduced testing (risk based)
- Quality / Technical agreement
- Approved Supplier List
  - Approved / qualified status
  - Approved by QP/RP

Quality Control of Incoming Materials

- Incoming materials
  - Check against order
  - Check visual appearance
  - Internal ID code
  - Indicate quarantine status
  - Sampling for Quality control (if specified)
  - Quality control
    - Approved supplier
    - Analytical testing
    - Review CofA
  - Release for use by authorized person

Quality Control

- The level of testing required depends on:
  - scale of the operation
  - the risk to the patient
- Analytical methods
  - (European) Pharmacopeia – qualified
  - In-house development: validated
- Preferably test data on a separate record

Quality Control

- **Tc-99m generators**
- Mo-99 breakthrough first eluate
- Elution activity each 'batch' (eluate)
- Aluminum breakthrough
- Sterility

Quality Control of Kits

- Integrity upon receipt
- Specification provided by manufacturer providing instruction are followed

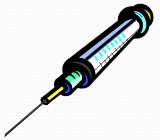
  ⇒ validation in case of deviations!

Verification of effectiveness of labelling

- final activity (at a stated time)
- labelling yield and/or radiochemical purity
- particulate contamination
- particle size (lung perfusion imaging)
- particle sizing of colloidal radiopharmaceuticals

Testing: Every - Syringe

- Appearance
- Gross particulate contamination
- Total radioactivity (concentration)
- pH
- Identity radionuclide



- Sterility
  - immediately (14 days) or after decay
  - process validation using broth
    - media fills
    - continuous monitoring

Release of Products

- Formal decision by QP/RP (responsible pharmacist)
- Releasing QP independent of preparation activities!

Batch/Product Release:

- Release Certificate Manufacturer
- Prepared in compliance with
  - Instructions in preparation protocol
  - Good Radiopharmacy Practices
- Complies with specifications / written approval physician
- Trend results of environmental monitoring
- Trend results of sterility testing/media fills

Out-of-Specification (OOS)

- Written procedure
  - re-testing
  - investigation
  - consultation physician
- Justification recorded on testing record
- Signed by Authorized Person
- Trend analysis
  - → corrective actions, e.g. adjustment of specification

Product Quality Complaints

- Written procedure for complaint handling
  - Complaints are examined, the causes of quality defects investigated and CAPAs implemented to prevent reoccurrence
- General system of complaints of the hospital
  - Returned radiopharmaceuticals (syringes)
- Product Quality issues should be reported to the manufacturer, the regulatory agency and the EANM Radiopharmacy Committee Reporting Scheme

Recalls

- a written procedure for the recall of defective products
- NB: include procedure for products intercepted or recalled by the manufacturer

Self Inspection

- Annual inspection program
- Trained and Qualified auditors
- Inspection reports to Management
- Plan for corrective actions incl. time limits
- Define responsibility for follow up

Metrics and KPIs

- Related to compliance and manufacturing
- Adequate definitions!

Examples

- % on time
  Deviations, CAPA, Changes, Documentation, Audits, Training, Stability samples, PQRs, etc.
- % batches released without deviations

Take Home Messages (1)

- The PQS and GMP serve as a roadmap to assure products are consistently of high quality and safe for patients
- Quality Risk Management principles should be implemented in all relevant processes and procedures
- Effective monitoring and control systems for process performance and product quality provide assurance of continued suitability and capability of processes
- A system for continuous improvement and PQS enhancement enables daily preparing of products meeting the designed quality standards and ensures continuous supply

Take Home Messages (2)

Key conditions for the preparation of high quality products meeting patients' and doctors' needs as well as regulators' expectations:

- Qualified premises, suitable for use
- PQS with approved procedures, records and specifications
- Validated processes
- Calibrated equipment
- QUALIFIED STAFF

- Basic GMP principles for hospital pharmacies and PET Centers are similar to the industrial GMPs


Thank you for your attention
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Legislation in Radiopharmacy

Prof. dr. Clemens Decristoforo is Radiopharmacist at the Department of Nuclear Medicine of the Medical University Innsbruck, Austria. He studied Pharmacy and did his PhD at the Leopold Franzens University Innsbruck. In 1997-1998 he was a Post-Doc Marie Curie Research Fellow at the Nuclear Medicine Research Lab at St.Bartholomews Hosp., London and 2009-2010 he worked as radiopharmaceutical Scientist at the International Atomic Energy Agency in Vienna. In 2014 he was awarded honorary Professorship of the Medical University Innsbruck. He chaired for many years the Radiopharmacy Committee of the European Association of Nuclear Medicine, is current member of its Policy and Regulatory Affairs Committee, is member of Expert Group 14 of the European Pharmacopeia (EDQM, Strasbourg) and member of several Editorial Boards. Since 2022 he is in the steering committee of a Master course on Drug Development & Regulatory Affairs at the University of Innsbruck. His research interests are focused on radiometals and peptides for molecular imaging and therapy, in this field he has published more than 200 scientific papers.

Sergio Todde, PhD has a degree in Biology (1988). Currently he is Senior Researcher at the University of Milan-Bicocca, and Director of Tecnomed, Foundation of the University of Milano-Bicocca.
Main research areas are in the field of Radiochemistry and Radiopharmacy, with special emphasis for the radiosynthesis and characterization of novel PET radiopharmaceuticals labelled with F-18 and C-11. Other research interests are in the field of target development for the cyclotron production of radionuclides and the development of automated radiosynthetic processes.
He is also Responsible of Quality Assurance and Radiopharmaceutical Preparations at the laboratories of Tecnomed, Foundation of the University of Milano-Bicocca. He has been the Head of Italian Interdisciplinary Group of Radiopharmaceutical Chemistry (GICR) in the years 2010-2011. He has been a member of the Radiopharmacy Committee of the European Association of Nuclear Medicine (EANM) in the years 2009-2017. Since 2010, he is also member of the Radiopharmacy Working Group of the Italian Agency of Medicine (AIFA).
Author or co-author of more than 50 publications on peer reviewed journals and book chapters. He is investigator in national and international research projects.

<u>The lecture has the following learning objectives:</u>

General Pharmaceutical legislation background

1. Students are able to understand the legal structure in Europe and the European Union.
2. Students are able to explain the difference between a regulation, directive and other legal texts.

3. Student are able to know different players in the pharmaceutical regulatory environment.

Specific radiopharmaceutical legislation background

1. Students are able to know where important aspects of radiopharmacy are legally defined.
2. Students are able to know how to find important documents related to radiopharmacy.
3. Students are able to understand why also legally not binding texts are essential in radiopharmacy.

Small Scale Preparation of Radiopharmaceuticals

1. Students know legal background that leads to great national differences in Radiopharmacy Practices.
2. Students know major documents dealing with the small scale radiopharmaceutical preparation and their potential impact.
3. Students are able to understand how their own working environment is regulated.

Preclinical Requirements

1. Students are able to know important aspects and documents related to the preclinical requirements for new drugs in general and radiopharmaceuticals in particular.
2. Students are able to understand the challenges resulting from the regulatory framework for translating new radiopharmaceuticals into the clinic.

Legislation background of GMP

1. Students are able to describe the legislation framework of GMP

GMP annexes relevant for radiopharmaceutical preparation

1. Students are able to summarize general principles of GMP
2. Students are able to identify which GMP annexes are relevant for radiopharmaceutical preparation, and why
3. Students are able to describe and take advantage of other useful documentation sources for GMP

Editing main GMP document: practical examples

1. Students are able to apply for adapting main GMP documentation to the specific need of radiopharmaceutical preparation

Legislation background of clinical trials

1. Students are able to describe the clinical trials legislation framework, with special emphasis for the new Regulation n. 536/2014, and focusing on specific aspects of the Regulation dedicated to radiopharmaceuticals

Guidelines for the preparation of Investigational Medicinal Product Dossier (IMPD)

1. Students are able to describe the general principles stated by EU guidelines on IMPD
2. Students are able to identify specific adaptations of IMPD to the case of radiopharmaceuticals

Summary of the lecture:

Introduction on legislation in (Radio)Pharmacy and (Radio) Pharmaceuticals

It's a common perception that in Europe the legal background for pharmaceuticals is uniform and the same rules apply in all the EU countries, but this is only partially correct. Radiopharmacists cannot be lawyers, but a good understanding of the legal basis of radiopharmaceuticals is important to cope with daily practice and to provide safe and efficacious drugs, working in one of the most highly regulated fields. Indeed, regulations concern both the ionizing radiations involved and the pharmaceutical component. Radiation safety regulation will not be addressed in detail in this course, as the focus is laid on the pharmaceutical regulatory framework, even though overlaps are unavoidable. Legislation covers the radiopharmaceutical itself and its use, the preparation step (including e.g. facilities, personnel and documentation), quality control aspects, transportation, clinical trials and its clinical use. Regulations can be international, European-wide, for European Union (EU) or only national. In the European Union (being in the focus of this course) the main legal documents are directives and regulations. Regulations apply as such (e.g. Clinical Trial Regulation 536/14), whereas directive (e.g. Directive 2001/83) are implemented into National law with some freedom of interpretation. As currently many major pharmaceutical issues are regulated via directives, differences among EU member states exist. An important organization with respect to pharmaceuticals in Europe is the European Medicines agency (EMA), important for marketing authorization, pharmacovigilance and scientific advice, working in close exchange and cooperation with National Medicines Agencies (BPharm, ASFAPS, MHRA, AIFA,….), which coordinate their work in a forum called Heads of Medicines Agency (HMA). Countries outside the EU have their own regulatory system, however usually strongly adhere to standards and developments within the EU and international harmonization strategies are prominent in particular in the pharmaceutical sector. Another important player in the pharmaceutical regulatory field is the Council of Europe, situated in

Strasbourg. It is responsible for the European Directorate for the Quality of Medicines (EDQM), which issues the European Pharmacopoeia, that is recognized as a legal text by practically all European (and partly also non-European) countries. As an important player also the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) should be mentioned, an organization of Pharmaceutical Inspecting Agencies, without strict legal power, but releasing documents that are an important basis for Good Manufacturing Practices (GMP) and are used by legally inspecting bodies, thereby becoming often mandatory.

The Pharmaceutical Legislation of the EU, including non-mandatory guidance documents, can be found in the so called EUDRALEX platform (http://ec.europa.eu/health/documents/eudralex_en) with a total of 10 Volumes of documents dealing with the legal texts but also guidance for marketing authorization, GMP, Clinical Trials, Pharmacovigilance and more. Aspects of radiopharmaceuticals can be found in a variety of texts and in the scope of this course examples are given where specific regulations can be found. The regulatorty definition of a radiopharmaceutical can be found in Directive 2001/83EC, which is the main basic directive related to Medicinal Products in the EU, e.g. providing the rules for marketing authorization and exemptions thereof. It also states the requirement of authorization of the pharmaceutical manufacturing and defines the responsibility of the Qualified Person for Release. Directive 2001/83/EC is currently under revision, and it is expected that the new Directive will be issued in the year 2024, automatically repealing Directive 2001/83/EC. GMP is defined in a separate directive (Directive 2017/1572), as well as many other aspects of pharmaceutical concern. Regulations exists e.g. for Advanced Therapy Medicinal Products and also for clinical trials, after finally entry into force of the Regulation n. 536/2014 (Clinical Trials Regulation). Related to the quality of radiopharmaceuticals, the European Pharmacopoeia provides quality standards, whereas other aspects such as responsibilities and general aspects fall into the GMP environment. Partly Internationally harmonized documents exist, such as ICH documents, an example of which is the ICH Q2(R2) describing the validation of analytical methods. However, quality control aspects are also included in texts related to marketing authorisation, such as Directive 2001/83/EC C, specifying the need for quality control description of a radiopharmaceutical kit preparation within the marketing authorization process. More examples will be given to show the structure of the legal framework, how different documents interact and where they can be found.

Legislation and GMP

Good Manufacturing Practice (GMP) may be considered as that part of a general Quality System

Management aimed to ensures that a medicinal product is prepared and controlled consistently and meeting the appropriate standard. One of the major issues in the field of radiopharmaceutical preparation, is that GMP have been designed for large scale, industrial preparation of "classic" pharmaceuticals, and they also apply not only to the industrial preparation of radiopharmaceuticals, but also, depending on the Country and on the intended use, to the small scale preparation of RPs in nuclear medicine departments or in academic institutions. GMP are made of three parts, the first of which set the basic requirements for medicinal product and is, in turn, split in 9 chapters and 19 annexes, that may be found in the "Eudralex" portal (see above). The same web page also includes legal basis for GMP, which are currently regulated by Commission Directive 2017/1572/EC. Directive 2017/1572/EC indeed states that "*All medicinal products for human use manufactured or imported into the Union, including medicinal products intended for export, should be manufactured in accordance with the principles and guidelines of good manufacturing practice*". This has to be read in connection with Directive 2001/83/EC, where the following definition of medicinal product is given in art. 1: "*(a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or (b) Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis*". Moreover, in the same article definitions of radiopharmaceutical, radionuclide generator, kit and radionuclide precursor are given, thus including radiopharmaceuticals among the drugs which have to be manufactured in accordance with GMP. Does it mean that any radiopharmaceuticals have to be prepared under GMP umbrella? No, because art. 3 of Directive 2001/83/EC also states that "*This Directive shall not apply to: 1. Any medicinal product prepared in a pharmacy in accordance with a medical prescription for an individual patient (commonly known as the magistral formula). 2. Any medicinal product which is prepared in a pharmacy in accordance with the prescriptions of a pharmacopoeia and is intended to be supplied directly to the patients served by the pharmacy in question (commonly known as the officinal formula)… Manufacturing of these products shall be authorized by the competent authority of the Member State…. "*, thus leaving room for national competent Authorities to overview and regulate radiopharmaceuticals prepared in hospital pharmacies and, in general, in "small scale radiopharmacies", which has been defined as "*…a facility where the small-scale preparation of radiopharmaceuticals is carried out in accordance with national regulations. The term small scale radiopharmacy is not related to the physical size of the facility, that may vary in a broad range, but only to the kind of radiopharmaceutical*

preparation performed." (EJNMMI, 2010, 37:1049-1062).

Directive 2017/1572/EC is a relatively brief document, laying down general principles of GMP and its structure clearly resembles that of the above-mentioned guidelines, as most of the articles include GMP main chapters, such as documentation, production, quality control, premises and equipment, etc., in a concise form. The need for inspections, as a mean to ensure that manufacturers are respecting GMP principles and a reference to the need for a Qualified Person, as defined by the art. 49, p. 2 of the Directive 2001/83/EC are also covered by the so called "GMP Directive". So, which is in the end the field of application of GMP in case of radiopharmaceutical preparations? GMP apply to Marketing Authorization (MA) applicants and MA holder in all the EU countries; this is the case of industrial manufacturers involved in the production and distribution of e.g. [^{18}F]FDG, or licensed kit and radionuclide generators. Current EU legislation, with Regulation 536/2014, also states that investigational medicinal product, including investigational radiopharmaceuticals specific for therapeutic applications, should be manufactured following GMP principles.

Official definition of GMP, as set out in art. 2, p. 6 of Dir. 2017/1572/EC, is "*the part of quality assurance which ensures that products are consistently produced and controlled in accordance with the quality standards appropriate to their intended use*". So GMP is a part, although very important, of a quality assurance system, aimed to ensure quality, safety and efficacy of (radio)pharmaceuticals. Being a very general and broad concept, it is not surprising to find many similarities among GMP and other document/guidelines, such as the guidelines released by the US Food and Drug Administration (FDA), the Radiopharmacy Committee of the European Association of Nuclear Medicine (EANM) or the World Health Organization (WHO). Further, Pharmaceutical Inspection Convention (PIC/Scheme), which is an organization that include pharmaceutical inspectors from 49 different countries worldwide, have drafted their own guidelines, which are, in part, more practical compared with official EU GMP. Looking more in-depth into GMP, it may be useful to find what is "radiopharmaceutical specific" and, looking from a reversed perspective, what it may be considered "GMP specific" in the preparation of radiopharmaceuticals. As for the first question, EU GMP have dedicated a specific Annex (Annex 3) to the manufacture of radiopharmaceuticals, whose latest 2009 version clarified that their application related to the mean of radionuclide production (cyclotron / nuclear reactor), begins with the target and radionuclide transfer system, but not include complex reactor / cyclotron machinery. In general, Annex 3 – GMP looks like a short GMP summary, where GMP have been "revisited" keeping in mind peculiarity of radiopharmaceuticals, such as the decrease with time (and sometimes this process occurs very quickly, depending on the half-life of the radionuclide)

of the radiopharmaceutical "strength" or the potential hazard due to ionizing radiations, which requires compliance to radiation protection legislation, in addition to pharmaceutical legislation. The answer to the second question (what is GMP specific in the preparation of radiopharmaceuticals?) is of course complicated and its extent may vary from country to country, depending on how "GMP like" is the local regulation. However, there are a few general "peculiarities" that may be here summarized. As said above, from regulatory point of view a production site authorization, which is usually issued after passing suitable inspections, and a Qualified Person are mandatory. Site authorization and GMP "certification" are not necessarily linked with marketing authorization; indeed, as mentioned previously, GMP is also mandatory in case of preparation of investigational medicinal products, including therapeutic radiopharmaceuticals (but not investigational diagnostic radiopharmaceuticals); furthermore, there are "centralized radiopharmacies" that are GMP authorized without holding any MA. From technical point of view GMP, compared with other guidelines, require more strict handling of the documentation, and compliance with a general and well established "testing and traceability" framework designed for the preparation of classic drugs and which is somehow overwhelming for a hospital radiopharmacy.

Issues related to the GMP part II, which is dedicated to active substances used as starting materials are also briefly discussed, while practical exampled aimed to help in evaluating and editing the main GMP related documents described in part III are provided, with special emphasis for Site Master File and Risk Assessment.

<u>Legislation/ Clinical Trials</u>

As said above, GMP also apply to the preparation of radiopharmaceuticals used for clinical trials (Investigational Radiopharmaceuticals), under the specific circumstances defined by the currently in force European Regulation 536/2014. The Regulation was approved by the EU parliament in 2014 but, due to a very long transition, it entered into force several years later, on January 31st, 2022. The need to replace the former EU Directive 2001/20/EC arose due to a significant reduction in the number of clinical trials in Europe, with a decline in competitiveness particularly significant in the field of spontaneous, non-profit clinical trials, including studies with radiopharmaceuticals. Main reasons were the significant increase of costs, due to both insurance and the need for GMP compliance, and also to the increase in administrative burden, which is sometime difficult to manage in case of small facilities. Main objectives of the new EU Regulation 536/2014 are: i) harmonize and hopefully simplify regulatory requirement in the EU; Regulations are indeed more tightly binding than Directives, as they just have to be translated in the various

languages, without room for interpretation; this was indeed one of the major drawbacks of the still enforcing Dir. 2001/20/EC; ii) simplify authorization procedures; iii) promote CT on orphan drugs, iv) promote multi-country CT. One of the key points of the new Regulation has been the implementation of an EU database (EU portal) which, as set out in art. 80 of the EU Regulation, act as a single-entry point for the submission of data and information related to clinical trials; this should hopefully lead to reduce time required for submission, increased harmonization, reduced the risk of overlapping among different CT, etc. What does it change for radiopharmaceutical preparations with the new EU Regulation? Art. 61, par. 1 still prompt for the need for manufacturing authorization, GMP, QP, etc. but art. 61, p. 5 states that "*Paragraph 1 shall not apply to any of the following processes: ……(b) preparation of radiopharmaceuticals used as diagnostic investigational medicinal products where this process is carried out in hospitals, health centres or clinics, by pharmacists or other persons legally authorised in the Member State concerned to carry out such process, and if the investigational medicinal products are intended to be used exclusively in hospitals, health centres or clinics taking part in the same clinical trial in the same Member State….*". Thus, the above article explicitly excludes the need for manufacturing license, QP, etc. for the preparation of diagnostic RPs; this means that therapeutic RPs are still subject to the previous legislation framework. Moreover, art. 61, p. 5, bullet "b" does not rule out the possibility to distribute the investigational RPs to other hospitals "*taking part in the same clinical trial in the same member state*". A question arises: which kind of quality assurance standard will then be applicable in case of investigational RPs prepared for diagnostic purposes? Art. 61, p. 6 states: "*Member States shall make the processes set out in paragraph 5 subject to appropriate and proportionate requirements to ensure subject safety and reliability and robustness of the data generated in the clinical trial. They shall subject the processes to regular inspections*". In other words, QA standards will be defined by member states, and this is of course a point that still need to be clarified.

Finally, applications for the use of investigational RPs requires the preparation of the so called "investigational medicinal product dossier" or IMPD, which include a detailed description of the pharmaceutical-chemistry characteristics of the intended product, together with information on its preparation, quality control, stability, etc. Requirements set by EU guidelines are described, as well as adaptations specific for radiopharmaceuticals proposed by the EANM guidelines.

Clinical Translation: Non-clinical regulatory aspects

The development of radiopharmaceuticals requires extensive evaluation before they can be applied in a diagnostic or therapeutic setting in Nuclear Medicine. Chemical, radiochemical, and

pharmaceutical parameters must be established and verified to ensure the quality of these novel products. Additionally, to provide supportive evidence for the expected human in vivo behaviour, particularly related to safety and efficacy, additional tests, often referred to as "non-clinical" or "preclinical" are mandatory. This lecture summarises the considerations necessary for non-clinical studies to accommodate the regulatory requirements for clinical translation of radiopharmaceuticals. These considerations include radiation exposure and effects, non-clinical pharmacology including imaging studies and toxicity testing. In particular toxicity study requirements for radiopharmaceuticals have been in discussion and resulted in an EMA draft guideline, very much focusing on a risk-based approach. References and guidelines for navigating the regulatory landscape of non-clinical studies for clinical translation of radiopharmaceuticals will be provided.

Small Scale, non-commercial preparation of radiopharmaceuticals

The small scale, typically local, preparation is a major sector providing radiopharmaceuticals extemporaneously for clinical routine, but also within clinical trials. As already described, there seems to be a clear and widely uniform regulatory framework in Europe, defining radiopharmaceuticals (including kits generators and radionuclide precursors and clinical trial products) as medicinal products, the way they have to be prepared and authorized. However, already both Directive 2001/83/EC for “normal” drugs as well as the new regulation on clinical trial products describe potential exceptions from the requirement of a manufacturing authorization and (at least) partly from the requirement of GMP, as pointed out above. From a practical point of view this is reality in many European countries for the small-scale preparation of radiopharmaceuticals, being typically prepared in hospitals or research institutions. However, differences in Europe in this particular practice are still extreme, both related to the availability of radiopharmaceuticals prepared and the standards that have to be followed. The reason is that the EU gives the responsibility of regulation back into the responsibility of individual member states, simply by not regulating it, describing it as an exemption in terms of GMP and/ or manufacturing authorization. Different concepts have therefore evolved on a National level. Some countries have put this small scale preparation into the framework of pharmacy practice, in many countries restricted to the preparation of radiopharmaceuticals from licensed kits and generators (e.g. France), in other countries also applicable to e.g. PET radiopharmaceutical preparation. Some countries have released specific national exemptions based on the radioactive nature of the drug (Austria, Germany) allowing the preparation under the final responsibility of the responsible physician. Italy has releases a specific annex to the Italian pharmacopoeia,

regulating the small-scale preparation in conjunction with a specific legal decree. National frameworks have on the one hand set the rules when a radiopharmaceutical can be prepared outside marketing authorization and clinical trial application. Partly a preparation based on the clinical need, ascertained by a physician, in a similar way as the magistral preparation as described above is possible, in UK a so called Special`s license allows such a practice and is additionally based on an explicit authorization of the site. On the other hand different interpretations exist in the standards that have to be followed, whether GMP applies or not. Again, very strict practices exist in some countries applying GMP irrespective of the entity and practice of radiopharmaceutical preparation, e.g. in the UK, whereas other countries have released dedicated national code of practices distinguishing from GMP , e.g. as in a National Pharmacopoeia in Italy. But also national examples exist, where not any indication in the legal framework is given and the practice is also not under any inspection from pharmaceutical authorities.

In recent years several bodies have reacted on this and provided guideline for the small scale preparation practice of radiopharmaceuticals. As stated above, EANM has released specific guidelines, PIC/S has added a dedicated Annex on radiopharmaceuticals to their Guidance on Good practices for Healthcare establishments and EDQM has released a chapter in the European Pharmacopoeia on the Extemporaneous preparation of radiopharmaceuticals. All these texts have no legally binding character as such, but are either used by some Inspectors as their basis of a legally required inspections or have been specifically referred to in a National regulation on radiopharmaceuticals (e.g. EANM guidelines in Switzerland and Slovenia).

Overall radiopharmaceutical regulations are manifold and embedded in the complex pharmaceutical framework with strictly binding regulation, directives or other texts, but also a multitude on non-strictly legally binding guidelines or other guidance documents. Practical examples will complement this course and attempts to find a way through the web of regulations.

<u>Take home messages:</u>

- Many players involve in regulatory issues in Europe especially in pharmaceutical legislation
- Even though the European Union seems to be a legally harmonized entity, radiopharmacy practice is very different resulting partly from subtle legal differences
- Not only the European Union, but also other players are involved in pharmaceutical regulations, including the Council of Europe with the pharmacopoeia, European (EMA) or National drug agencies
- Important regulatory documents for radiopharmacy can be found in various sources, EU directives and regulations but also guidelines from agencies, international committees or professional organisations

- Radiopharmacy Practice for the small-scale preparation of radiopharmaceuticals is often dominated by a national interpretation of European and national laws
- More and more dedicated guidelines for the small-scale production of radiopharmaceuticals have been released by professional organisations (EANM, PIC/S) and also European bodies (EDQM)
- Toxicity studies for radiopharmaceuticals are an important step introducing new radiopharmaceuticals and international guidance exists.
- Application of GMP in the preparation of small-scale radiopharmaceuticals poses severe issues
- There is a lack of harmonization in the EU about when and how to apply GMP in the small-scale preparation of RPs
- Thus, a logical and reasonable approach is required, and may be pursued through useful interactions between radiopharmacy/radiochemistry community and regulators
- Application of GMP in the preparation of RPs for clinical trials may change in the near future: entry into force and practical application of the new Regulation will have to be carefully monitored by the professionals
- IMPD preparation is, and will be, an important part in the preparation of the dossier for the application for clinical trials; practical hints may help in collecting data and editing documents
- It is important to know the relevant legislation and literature sources, including EANM guidelines, to have the broader possible view of the problems related to the compliance with GMP and clinical trials legislation in the preparation of RPs
- Due to the above cited lack of harmonization, it is important to have a deep knowledge of the situation in the respective Countries.

References (further reading):

Most of the information related to EU legislation in the field of (radio)pharmacy, including Directives, Regulations, and GMP guidelines, may be found at the following website:

- http://ec.europa.eu/health/documents/eudralex

Link related to the new regulation on clinical trials may be found at the following website:

- http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L_.2014.158.01.0001.01.ENG

Another useful source is the website of the EU pharmaceutical inspectors:

- http://www.picscheme.org/; an example is the “Guide to good practices for the preparation of medicinal products in healthcare establishments” (http://www.picscheme.org/publication.php?id=8)

General texts regarding Radiopharmacy and Legislation

- Clemens Decristoforo: Regulation of radiopharmacy practice in Europe. Sampson's Textbook of Radiopharmacy, 4th edited by Theobald T, 01/2011: chapter Regulation of radiopharmacy practice in Europe; Theobald T.
- Decristoforo Clemens, and Lyashchenko Serge K. (2022) Radiopharmaceutical legislation. In: Alberto Signore, Encyclopedia of - Nuclear Medicine and Molecular Imaging. vol. 1, pp. 274-279. Oxford: Elsevier. ISBN 9780128229804
- Clemens Decristoforo (2023). The regulatory Review of Radiotherapeutics: A European Perspective. In: Jason Lewis, Lisa Bodei & Brian Zeglis, Radiopharmaceutical Therapy. Springer, New York

Articles related to GMP and Radiopharmacy

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- Gillings N, Hjelstuen O, Behe M, Decristoforo C, Elsinga PH, Ferrari V, Kiss OC, Kolenc P, Koziorowski J, Laverman P, Mindt TL, Ocak M, Patt M, Todde S, Walte A. EANM guideline on risk management for radiopharmaceuticals. EJNMMI. 2022; https://doi.org/10.1007/s00259-022-05738-4
- Aerts J, Ballinger JR, Behe M, Decristoforo C, Elsinga PH, Faivre-Chauvet A, Mindt TL, Kolenc Peitl P, Todde SC, Koziorowski J. Guidance on current good radiopharmacypractice for the small-scale preparation of radiopharmaceuticals using automated modules: a European perspective. J. Label Compd. Radiopharm. 2014. 57: 615-620

Although FDA is not of concern in the EU, nonetheless it may be interesting and useful to compare their different regulatory approach. For instance, have a look to the following document:

- http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070306.pdf

Finally, also world health organization (WHO) deals with GMP:

- *http://www.who.int/medicines/areas/quality_safety/quality_assurance/production/en/*
- International Atomic Energy Agency and World Health Organization: guideline on good manufacturing practices for radiopharmaceutical products. WHO technical report series, n. 1025, 2020
- International Atomic Energy Agency and World Health Organization: guideline on good manufacturing practices for investigational radiopharmaceutical products. WHO technical report series, n. 1044, 2022. ISBN 978-92-4-006382-2

Small scale preparation of radiopharmaceuticals

- Hendrikse H, Kiss O, Kunikowska J, Wadsak W, Decristoforo C, Patt M. EANM position on the in-house preparation of radiopharmaceuticals. Eur J Nucl Med Mol Imaging. 2022 Mar;49(4):1095-1098. doi: 10.1007/s00259-022-05694-z. PMID: 35050391
- EDQM. Extemporaneous preparation of radiopharmaceuticals, General Chapter 5.19. European Pharmacopoeia 9.0.
- Clemens Decristoforo, Marianne Patt: Are we “preparing” radiopharmaceuticals?. 01/2017; 1(1)., DOI:10.1186/s41181-016-0011-7
- Scheepers HP, Langedijk J, Neerup Handlos V, Walser S, Schutjens MH, Neef C. Legislation on the preparation of medicinal products in European pharmacies and the Council of Europe Resolution. Eur J Hosp Pharm. 2017 Jul;24(4):224–9.
- Rogier Lange, Rob ter Heine, Clemens Decristoforo, Iván Peñuelas, Philip H. Elsinga, Monique M L van der Westerlaken, N. Harry Hendrikse: Untangling the web of European regulations for the preparation of unlicensed radiopharmaceuticals. Nuclear Medicine Communications 02/2015; 36(5):1.,

Articles related to Clinical Trials / IMPD

- Todde S, Windhorst AD, Behe M, Bormans G, Decristoforo C, Faivre-Chauvet A, Ferrari V, Gee AD, Gulyas B, Halldin C, Kolenc Peitl P, Koziorowski J, Mindt TL, Sollini M, Vercouillie J, Ballinger JR, Elsinga PH. EANM guideline for the preparation of an Investigational Medicinal Product Dossier (IMPD). Eur. J. Nuc. Med. Mol. Imaging. 2014; 41: 2175-2185
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- Peñuelas I, Vugts DJ, Decristoforo C, Elsinga PH. The new Regulation on clinical trials in relation to radiopharmaceuticals: when and how will it be implemented? EJNMMI Radiopharm Chem. 2019 Jan 11;4(1):2. doi: 10.1186/s41181-019-0055-6.
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Preclinical studies:

- J. Koziorowski, M. Behe, C. Decristoforo, J. Ballinger, P. Elsinga, V. Ferrari, P. Kolenc Peitl, S. Todde, T. L. Mindt: Position paper on requirements for toxicological studies in the specific case of radiopharmaceuticals. 01/2017; 1(1)., DOI:10.1186/s41181-016-0004-6
- Korde A, Mikolajczak R, Kolenc P, Bouziotis P, Westin H, Lauritzen M, Koole M, Herth MM, Bardies M, Martins AF, Paulo A, Lyashchenko SK, Todde S, Nag S, Lamprou E, Abrunhosa A, Giammarile F, Decristoforo C. Practical considerations for navigating the regulatory landscape of non-clinical studies for clinical translation of radiopharmaceuticals. EJMMI Radiopharmacy and Chemistry. 2022; 7:18, https://doi.org/10.1186/s41181-022-00168-x

Some of the above articles may be found at the EANM website:

- http://www.eanm.org/publications/guidelines/index.php?navId=37

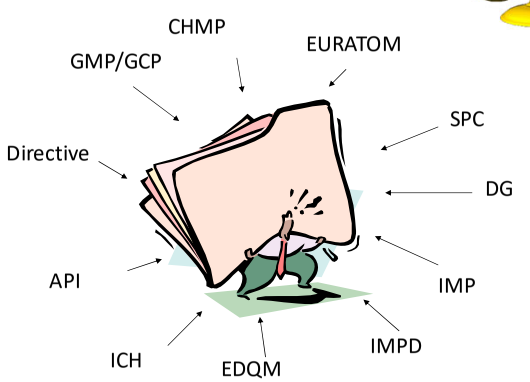
Pharmaceutical Legislation in Radiopharmacy

Introduction and overview

Clemens Decristoforo
Innsbruck, Austria

1

Radiopharmacists are no lawyers



2

Radiopharmaceuticals =

= radioactive Drugs

Legislation concerning Radiation safety

European Commission DG ENER

Physicists

Legislation concerning Drugs / medicines

Medical specialists

European Commission DG SANTE

Radiopharmacy practice

3

What is regulated in Radiopharmacy?

The **(Radio)Pharmaceutical**
- Distribution, Selling
- Use
- Regulatory Assessment

Marketing authorization

(Radio)pharmaceutical preparation
- Facility
- Personel
- Documentation

Manufacturing authorization GMP, Inspection

Quality control
- Radiopharmaceutical
- Equipment

Pharmacopeia

Evaluation
- Safety
- Efficacy

Clinical trials regulations

(*Transportation, Radiation safety, Waste management*)

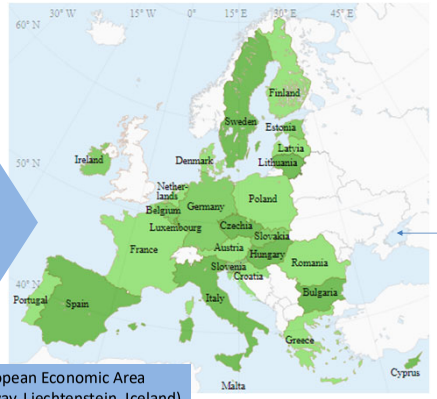
4

The European Union

Political Union of 27 States

446 million inhabitants

24 official languages



+ EURATOM (independent Treaty)

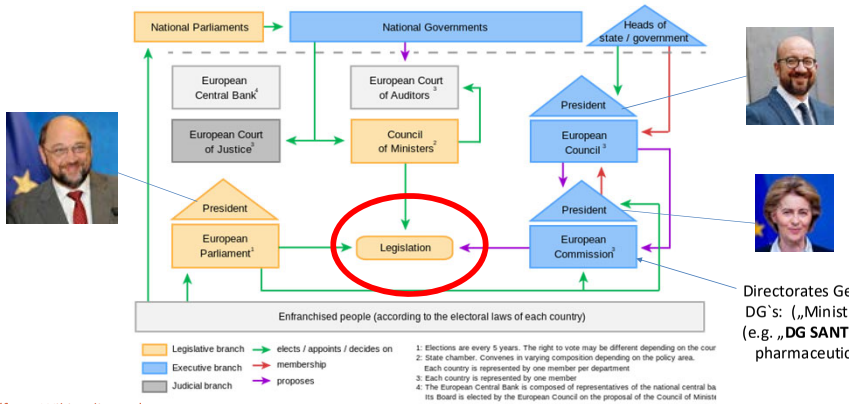
(Radiation Safety)

+ European Economic Area (Norway, Liechtenstein, Iceland)

(from Wikipedia.org)

5

Political system of the European Union



Directorates General DG`s: („Ministries") (e.g. „**DG SANTE**" for pharmaceuticals)

(from Wikipedia.org)

6

DIRECTORATE-GENERAL - SANTE

COMMISSIONER
Olivér Várhelyi

DIRECTOR-GENERAL
Sandra Gallina

- **Health and Food Safety**
- This Commission department is responsible for EU policy on food safety and health and for monitoring the implementation of related laws.
- **The goals**
- To make Europe a healthier and safer place. The mission is to protect the citizens' **health** and monitor their **food** making sure it is safe.
  - Build a strong European Health Union to protect and improve public health
  - ensure Europe's food is sustainable and safe
  - protect the health and welfare of farm animals
  - protect the health of crops and forests

7

Legislation – Different levels

European Union → **Regulations**
Directives
And…

National authorities →
Local authorities →
National Regulations

Professional organisations
National Institutes/commitees →
Guidelines
e.g. EANM, PIC/S, ICRP
Technical specifications/standards
e.g. DIN, ISO

8

European Union - laws and rules

Directives

Must be transposed/integrated into National Law to be effective

e.g. Directive 2001/83/EC → "Pharmaceutical Directive"

Regulations

Are directly applied

e.g. Regulation EU No 536/2014 → "Clinical trials"

Other rules

- Decisions (Council, Commission, Court of Justice)
- Resolutions, conclusions, recommendations (Council, Parl.)
- Communications (EU Commission); Notifications (Council)
- Guidelines (EU Commission, EMA, CPMP, ICH, OECD, WHO)

"Soft law"

9

Some Important Directives and Regulations

Directive 2013/59/Euratom	→ "Basic Safety Standards"- BSSD (Radiation)
Directive 2001/83/EC	→ „Pharmaceutical Directive"
Directive 2004/27/EC	→ Add. to 2001/83, API according to GMP
Regulation (EC) No 726/2004	→ Marketing Authorization & EMA
Regulation (EC) No 1394/2007	→ Advanced therapy regulation
Regulation EU No 536/2014	→ "Clinical Trials Regulation"
Commission Delegated Regulation (EU) 2017/1569	→ GMP for IMPs in Clinical Trials

10

How are European Union laws made?

- Pre-Phase: Public query, consultation
- Draft from the Commission
- Council Working Group (representing Nat. governments)
- Parliament Committee (representing parliament)
- Common text voted in Parliament

11

European legislation

„Soft law"

Guidelines:
Released by the Commission (**e.g. GMP guidelines**) or related organizations (EMA)

Other statements: Reflection paper, Question and answer document

Intention:
recommendations for the effective implementation of Directives and Regulations by the individual Member States
advice for involved parties (e.g. applicants for marketing authorisation). Scientific guidelines are often issued to reflect the current up to date scientific knowledge on a certain topic.

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How are Guidelines made?

Commission documents-drafting process is transparent

EUROPEAN COMMISSION
ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL
Consumer goods
Pharmaceuticals

Brussels, 10 October 2006

EudraLex
The Rules Governing Medicinal Products in the European Union

Volume 4
EU Guidelines to
Good Manufacturing Practice
Medicinal Products for Human and Veterinary Use

Draft Annex 3
Manufacture of Radiopharmaceuticals

Document History	
Concept Paper published	May 2005
Draft agreed by Ad Hoc GMP Inspection Services to release for public consultation.	September 2006
Deadline for comments	30 March 2007

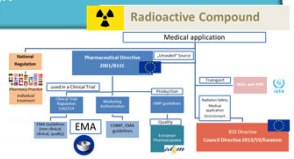
13

European Union of no importance in non-member states?

- European Union sets legal standards in Europe
- These are the basis for laws in EU countries, but also outside the EU (in Europe and, partly, out of Europe)
- Implementation of European Standards helps candidates for EU membership to gain acceptance by the EU
- Marketing of radiopharmaceuticals requires companies outside the EU to comply with EU regulations
- Not only EU but also other European bodies (e.g. European Council) are of importance in pharmaceutical legislation (e.g.Pharmacopeia)

14

The European Medicine`s Regulatory Network "United in Diversity"



Not working in isolation - working within a Network!!

- Unique system (~ 450 Mio inhabitants, 24 official languages) www.ec.europa.eu
  - 27 MSs + 3 EEA (~ 50 national agencies) HMA
- HMA (Heads of Medicines Agencies) www.hma.eu
  - EMA (European Medicines Agency) www.ema.europa.eu

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Eudralex

https://health.ec.europa.eu/medicinal-products/eudralex_en

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Guidelines
Latest updates
Documents

Body of European Union legislation

The body of European Union legislation in the pharmaceutical sector is compiled in Volume 1 and Volume 5 of the publication "The rules governing medicinal products in the European Union":

- Volume 1 - EU pharmaceutical legislation for medicinal products for human use
- Volume 5 - EU pharmaceutical legislation for medicinal products for veterinary use

Guidelines

The basic legislation is supported by a series of guidelines that are also published in the following volumes of "The rules governing medicinal products in the European Union":

- Volume 2 - Notice to applicants and regulatory guidelines for medicinal products for human use
- Volume 3 - Scientific guidelines for medicinal products for human use
- Volume 4 - Guidelines for good manufacturing practices for medicinal products for human and veterinary use
- Volume 6 - Notice to applicants and regulatory guidelines for medicinal products for veterinary use
- Volume 7 - Scientific guidelines for medicinal products for veterinary use
- Volume 8 - Maximum residue limits
- Volume 9 - Guidelines for pharmacovigilance for medicinal products for human and veterinary use
- Volume 10 - Guidelines for clinical trial

Medicinal products for paediatric use, orphans, herbal medicinal products

The Rules Governing Medicinal Products in the European Union

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

http://www.ema.europa.eu/ema/

European Medicines Agency

Executive director
Emer Cooke
Since 16 Nov 2020

- **Status:** decentralized body of the European Union with headquarters in Amsterdam
- **Responsibility:** protection and promotion of public and animal health, through the evaluation and supervision of medicines for human and veterinary use .
- **Mission statement**: to foster scientific excellence in the evaluation and supervision of medicines, for the benefit of public and animal health
- **Legal power** lies with Commission (DG-SANTE) and Eur. Parliament

EMA in Amsterdam

Laid down in **Regulation (EC) No 726/2004**

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA Competences

www.emea.europe.eu

- Scientific evaluation of applications for European marketing authorisation for medicinal products (centralised procedure).
- The safety of medicines is monitored constantly by the Agency through a pharmacovigilance network .
- Review the applications for designation of orphan medicinal products
- Stimulate innovation and research in the pharmaceutical sector.
- To give scientific advice and protocol assistance to companies for the development of new medicinal products.
- ("committees": preparing scientific guidelines and regulatory guidance and contributing to the harmonisation of regulatory requirements in the EU and internationally)

Ema DOES NOT: -develop laws, issue marketing authorisation, evaluate clinical trials

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EMA Structure

1 Management Board

28 Member States' representatives

4 Civil society representatives

2 European Commission representatives

2 European Parliament representatives

- **Scientific Committees** (in total 7)

Committee for Medicinal Products for Human Use (CHMP)

e.g. issuing „European Public Assessment Report" (EPAR)

- **Working Parties** and related groups:

Safety Working Party (SWP)

Quality Working Party (QWP)

"EMA's committees, working parties and related groups are composed of **European experts** made available by national competent authorities of the EU and EEA **Member States**."

https://www.ema.europa.eu

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Some Important EMA Guidelines and documents

- EMEA/CHMP/QWP/306970/2007 -> Guideline on Radiopharmaceuticals (under revision)
- EMA/CPMP/ICH/286/1995 -> ICH guideline M3(R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals
- CHMP/SWP/28367/2007 → First in human clinical trial guideline (EMA)
- EMEA/CHMP/SWP/28367/07 Rev. 1: Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products
- CPMP/ICH/381/95 -> Note for guidance on validation of analytical procedures
- EMA/CHMP/448228/2012 -> Guideline on core SmPC and package leaflet for fludeoxyglucose (18F)
- EMA/CHMP/SWP/686140/2018 -> Guideline on the non-clinical requirements for radiopharmaceuticals (draft)
- EMA/CHMP/451705/2024 -> Clinical evaluation of therapeutic radiopharmaceuticals in oncology (concept paper)

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How are Guidelines made at EMA?

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

10 November 2016
EMEA/CHMP/SWP/28367/07 Rev. 1
Committee for Medicinal Products for Human Use (CHMP)

Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products

Draft

Adopted by CHMP for release for consultation	10 November 2016
Start of public consultation	15 November 2016
End of consultation (deadline for comments)	28 February 2017
Adopted by CHMP	<DD Month YYYY>
Date of coming into effect	<DD Month YYYY>

Comments should be provided using this template. The completed comments form should be sent to FIH-rev@ema.europa.eu

From experts nominated by the national agencies

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National Agencies & HMA

HMA Heads of Medicines Agencies

- BPHARM
- ANSM
- AIFA
- AGES

Non-EU

- MHRA
- SWISSMEDIC

Etc.

National Marketing authorisation evaluation, Inspections, Clinical Trials

No legal Power → Bodies of National Ministry of Health

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Heads of Medicines Agencies (HMA) National Competent Authorities (NCA)

HMA Heads of Medicines Agencies

- The national competent authorities (NCAs), responsible for the regulation of human and veterinary medicines in the EU,
  - coordinate their work in a forum called Heads of Medicines Agencies (HMA).
  - The heads of the NCAs work closely with EMA and the European Commission to maximise cooperation and ensure the European medicines regulatory network functions efficiently.
  - The HMA meets four times per year to address key strategic issues for the network, such as the
    - exchange of information,
    - IT developments
    - sharing of best practices,
    - streamline mutual recognition and decentralised procedures

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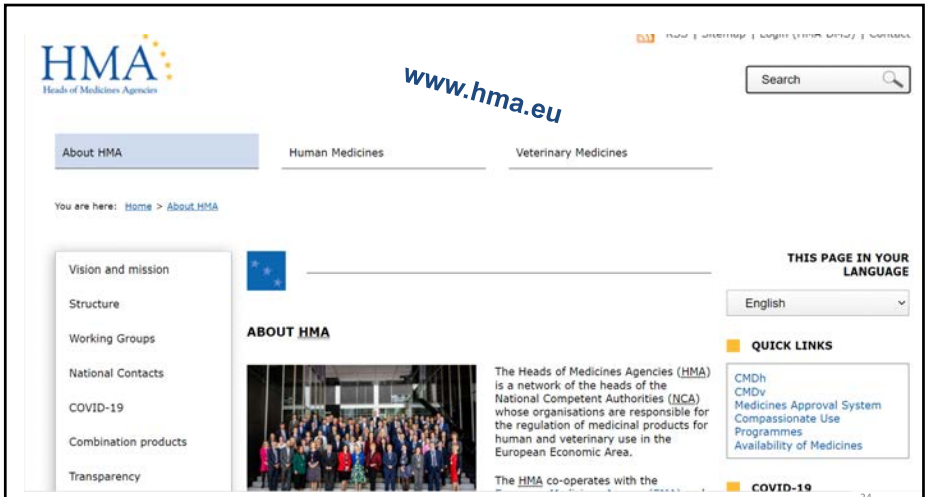

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NATIONAL CONTACTS

This page offers an overview of all National Competent Authorities , who are responsible for the regulation of Medicinal Products for human and veterinary use in the European Economic Area.

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Responsibilities and duties of National Authorities in general

Medicinal Products

- **Assessment** of applications for drug approval
- **Issuing of drug licenses**
- Maintenance of drug approvals: renewal, product variations/changes
- Risk/ benefit monitoring of authorised medicinal products –**pharmacovigilance**
- **Inspection GMP**, GCP, Pharmacovigilance
- Monitoring of the market – shortages, drug availability
- Information ot the Public

Development / Improvement of Guidelines / Recommendations

- Cooperation on evolving guidelines
- Representation of national viewpoints in international health associations and groups e.g. WHO, ICH, CHMP, CVMP

(Scientific) Advice for Applicants
Health Professionals / Consumer / Public

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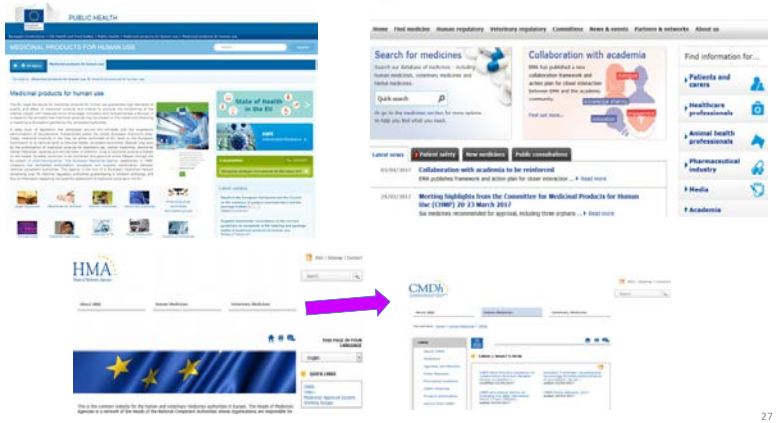
Where to find what



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Other „Players“ in (Radio)Pharmaceutical legislation

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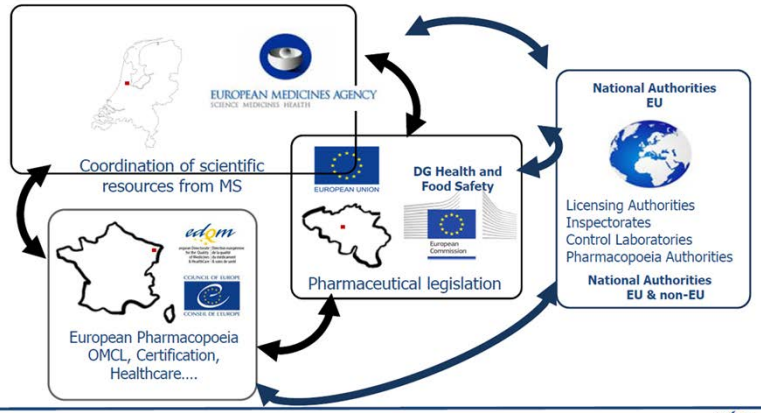
Key players for the quality of medicines



The Council of Europe

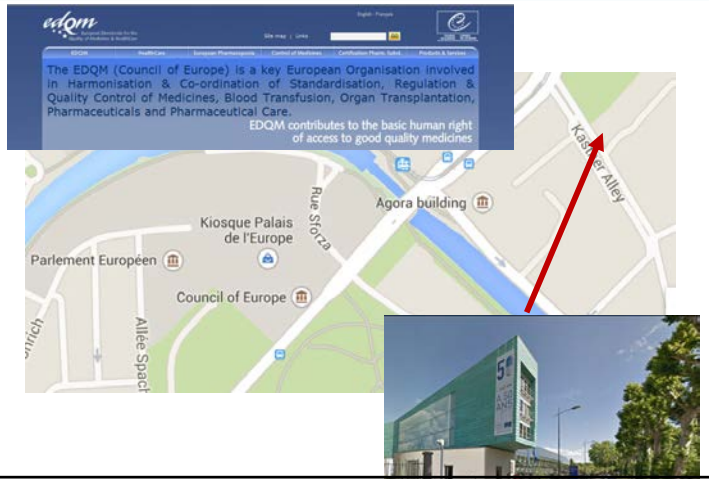
COUNCIL OF EUROPE
CONSEIL DE L'EUROPE

- Founded in 1949
- Headquarters in Strasbourg, France
- 46 member states
  680 Million Citizens
- The oldest pan-European organisation dedicated to fostering co-operation in Europe
  - Promotes democracy
  - Protects human rights
  - Protects the rule of law

NOT: EU, NOT: European Council

Member states

EDQM - European Directorate for the Quality of Medicines & Healthcare



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The European Directorate for the Quality of Medicines
EDQM and its mission

- **Publication of the Ph. Eur.** (French+English)
- Producing and distributing Pharmaceutical, Herbal and Biological Reference Standards (described in the standards)
- Certification of suitability of Ph. Eur Monographs
  Participating in the European Regulatory System by a centralised evaluation of the quality of drug substances and excipients
- European Biological Standardisation programme
- European Network of the Official Medicines Control Laboratories (OMCL)
- Grant ethics/safety/quality of blood transfusion and organ/tissue/cell transplantation
- combat falsifications of medical products (e.g. counterfeit)
- develop pharmaceutical care approaches and policies
- establishment of standards cosmetics and food contact materials, coordination of control

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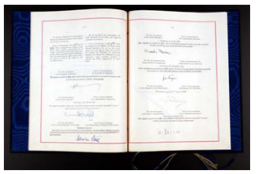
The European Pharmacopoeia Convention

Details of Treaty No.050

Title	Convention on the Elaboration of a European Pharmacopoeia (ETS No. 050)
Reference	ETS No. 050
Opening of the treaty	Strasbourg 22/07/1964 - Treaty open for signature by the member States which take part in the activities in the field of public health referred to in Resolution (59)23 and for accession by other member States and by non-member States
Entry in force	08/05/1974 (8 Ratifications.)
Summary	The Convention aims to harmonise specifications for medicinal substances in their original state or in the form of pharmaceutical preparations. The Parties undertake progressively to elaborate a European pharmacopoeia. The European Pharmacopoeia becomes the official standard applicable within the respective Parties. It is drawn up by the European Pharmacopoeia Commission which



Article 1:
The Contracting Parties undertake
a) Progressively to elaborate a Pharmacopoeia which shall be common to the countries concerned and which shall be entitled "European Pharmacopoeia";
b) To take the necessary measures to ensure that the monographs which will be adopted... and which will constitute the European Pharmacopoeia **shall become the official standards applicable within their respective countries**.

→ Legally binding in member states (e.g. defined in drug legislation)

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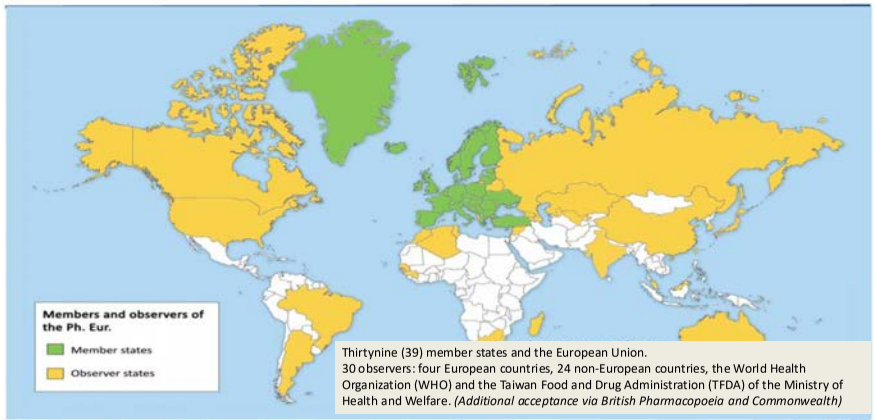
Global Impact of the EDQM and the Ph. Eur.



Thirtynine (39) member states and the European Union.
30 observers: four European countries, 24 non-European countries, the World Health Organization (WHO) and the Taiwan Food and Drug Administration (TFDA) of the Ministry of Health and Welfare. *(Additional acceptance via British Pharmacopoeia and Commonwealth)*

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Ph. Eur. Commission

Ph. Eur. Commission
Composed of :
- 38 Member States
- European Commission
- 30 Observers:
  - 6 European countries
  - 22 non European countries
  - Taiwan Food and Drug Administration (TFDA)
  - World Health Organization (WHO)

Presidium
- Chair
- 2 vice-chairs
- Ph. Eur. Secretariat

Presidium Meetings + Meeting Presidents of the Groups of Experts

Contributors:
- National Pharmacopoeia Authorities
- Competent Authorities
- Industry
- OMCL Network

Groups of Experts | Working Parties

- One delegation per Member State / Observer
- Three sessions a year
- Texts are adopted by **unanimous** vote
- Composition of groups of experts decided by Ph. Eur. Commission
- Since 2016: open to experts throughout the world

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European Pharmacopoeia General Organisation

- The European Pharmacopoeia Commission
- The Groups of experts
- The Scientific Secretariat
- The National Pharmacopoeial authorities

Group 14: Radiopharmaceuticals

Prepares RP`s
Preliminary Published in „Pharmeuropa“
→Officially adopted by Commission

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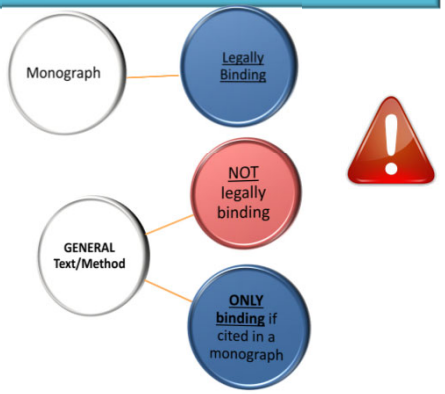
Is the Pharmacopeia „hard“ or soft law?

Legal status



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PIC/s www.picscheme.org

The Pharmaceutical Inspection Convention
and Pharmaceutical Inspection Co-operation Scheme

Status

- International instruments between countries and pharmaceutical inspection authorities, which provide together an active and constructive co-operation in the field of GMP

Mission

- To lead the international development, implementation and maintenance of harmonised GMP standards and quality systems of inspectorates in the field of medicinal products

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PIC/s www.picscheme.org

- **PIC/S GUIDE TO GOOD PRACTICES FOR THE PREPARATION OF MEDICINAL PRODUCTS IN HEALTHCARE ESTABLISHMENTS (March 2014)**

Apply to the preparation of medicinal products normally performed by healthcare establishments
“....for direct supply to patients”

pe-010-4-guide-to-good-practices-for-the-preparation-of-medicinal-products-in-healthcare-establishments-copy1

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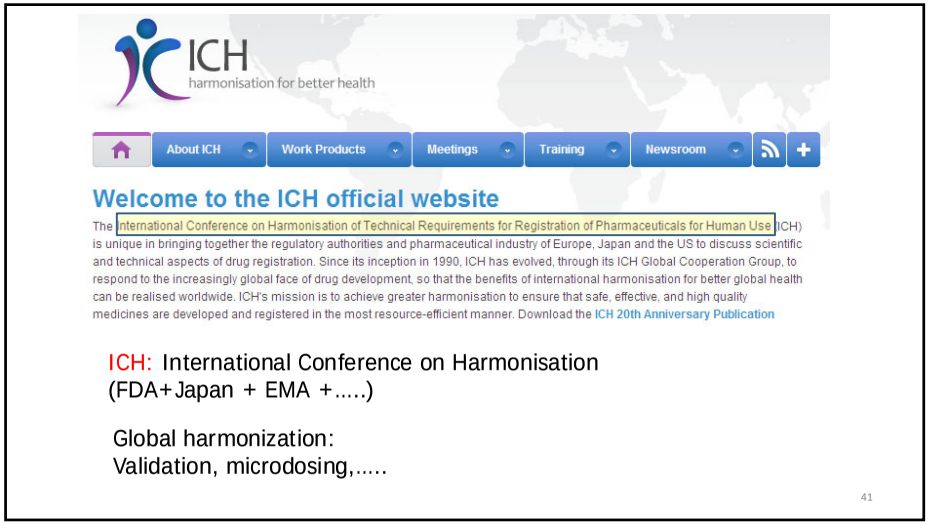
ICH
harmonisation for better health
About ICH
Work Products
Meetings
Training
Newsroom
Welcome to the ICH official website
The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is unique in bringing together the regulatory authorities and pharmaceutical industry of Europe, Japan and the US to discuss scientific and technical aspects of drug registration. Since its inception in 1990, ICH has evolved, through its ICH Global Cooperation Group, to respond to the increasingly global face of drug development, so that the benefits of international harmonisation for better global health can be realised worldwide. ICH's mission is to achieve greater harmonisation to ensure that safe, effective, and high quality medicines are developed and registered in the most resource-efficient manner. Download the ICH 20th Anniversary Publication
ICH: International Conference on Harmonisation
(FDA+Japan + EMA +.....)
Global harmonization:
Validation, microdosing,.....
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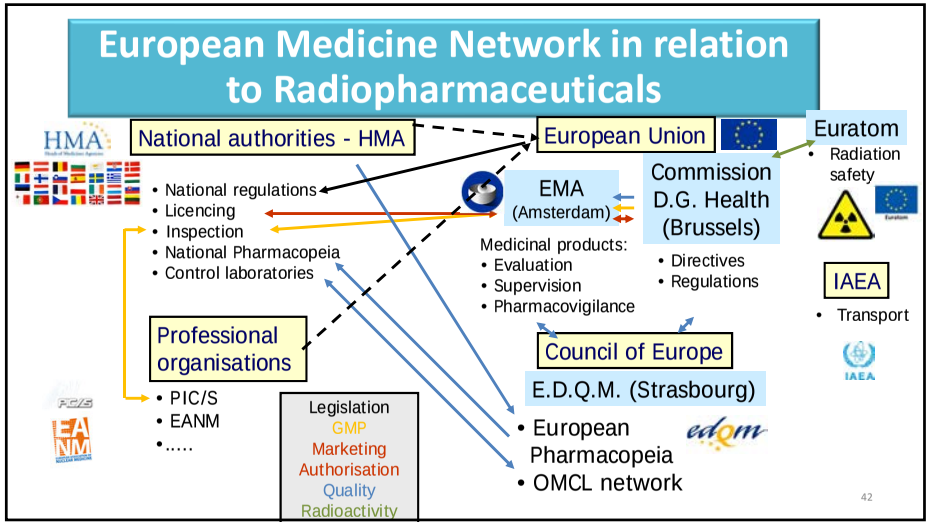
European Medicine Network in relation to Radiopharmaceuticals
HMA
National authorities - HMA
European Union
Euratom
• Radiation safety
• National regulations
• Licencing
• Inspection
• National Pharmacopeia
• Control laboratories
EMA
(Amsterdam)
Commission
D.G. Health
(Brussels)
Medicinal products:
• Evaluation
• Supervision
• Pharmacovigilance
• Directives
• Regulations
IAEA
• Transport
Professional organisations
Council of Europe
E.D.Q.M. (Strasbourg)
• PIC/S
• EANM
•.....
Legislation
GMP
Marketing Authorisation
Quality
Radioactivity
• European Pharmacopeia
• OMCL network
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Thank you for your attention
Austrian Winter
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Postgraduate Radiopharmacy Courses
Ljubljana, 26th August, 2025

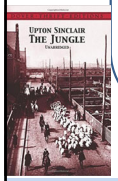
Legislation in Radiopharmacy
«European GMP legislation»

Sergio Todde

University of Milano-Bicocca
Tecnomed Foundation
Head of Radiopharmacy

WHY GMP, or simply….. WHY RULES?

- Early regulations initiated in the USA with the «pure food and drug act» in 1906 (that's why FDA, Food and Drug Administration)….
- ….initially pushed by the lack of control in the meat packing industry (**food**)……
- …..and by the lack of information about ingredients in «potions» or syrups that indeed contained morphine, opium, and other dangerous substances (**drug**)



https://biomanufacturing.org/uploads/files/305429596362804820-brief-history-of-gmps.pdf

WHY GMP, or simply….. WHY RULES?

Then, other disasters pushed for more regulations; among them…..

- In 1941, ca 300 people died due to a sulfamidic tainted with phenobarbital
- In 1955 a company failed to appropriately inactivate polio virus, causing infections in > 100 children treated with the above vaccine
- In the early '60s thalidomide caused fetus deformity in > 10.000 children in Europe (but not in the USA), due a lack of information about side effects

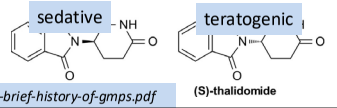
https://biomanufacturing.org/uploads/files/305429596362804820-brief-history-of-gmps.pdf

WHY GMP, or simply….. WHY RULES?

Talidomide drama: why in Europe and not in the USA?

Application for approval of Thalidomide in the US was rejected by the new FDA inspector, Frances Kelsey, in 1956. Her reasons: *"The application reflected a major dearth of safety data and no mechanism of action, as required by 1938 FD&C Act"*

Despite political pressure and 6 more application attempts by the manufacturer, Kelsey refused to approve the drug for sale. In 1962 President Kennedy awarded her the President's Distinguished Federal Civilian Service Award.



https://biomanufacturing.org/uploads/files/305429596362804820-brief-history-of-gmps.pdf

...WHAT ABOUT RADIOPHARMACEUTICALS?

Radiopharmaceuticals are usually very safe, but.....

In 2004 a critical event occurred: hepatitis C contamination of a radiopharmaceutical kit formulation compounded at a centralized nuclear pharmacy (*8*). This contamination was the result of reusing syringes and 0.9% sodium chloride vials, both of which are single-use products. It also involved the simultaneous preparation of a kit formulation by the same individual who was radiolabeling white blood cells. Two people died, and 16 people tested positive for hepatitis C RNA; all had received doses from the contaminated radiopharmaceutical vial. Though this was not a toxicity issue per se, an event that causes death will lead to increased scrutiny of a field and to increased FDA oversight in general.

THE JOURNAL OF NUCLEAR MEDICINE • Vol. 59 • No. 6 • June 2018

DIRECTIVE 65/65/EEC: A MILESTONE

Pushed by the thalidomide tragedy....

- *The first definition of Medicinal product was given*
- *Definition of Magistral and Officinal formulae*
- *It defined the need for a Marketing Authorization (MA)*
- *First version of the Summary of Product Characteristics (SPC) was included*
- *It stated the need for scientific documentation for authorization purposes*

DIRECTIVE 75/319/EEC

- Dir. 65/65 and 75/319 were not adequate for «special» medicinal products (vaccines, blood derivatives, radiopharmaceuticals)
- The Committee for Proprietary Medicinal Product (CPMP) was established
- It defined and regulated inspections
- It defined Qualified Person

Article 34

This Directive shall apply only to proprietary medicinal products for human use.

Chapters II to V of Directive 65/65/EEC and this Directive shall not apply to proprietary medicinal products consisting of vaccines, toxins or serums, to proprietary medicinal products based on human blood or blood constituents or radioactive isotopes, or to homeopathic proprietary medicinal products. A list, for information purposes, of these vaccines, toxins and serums is given in the Annex.

DIRECTIVE 75/318/EEC: A COMMON FORMAT FOR EXPERIMENTAL DOCUMENTATION

ANNEX

PART 1

PHYSICO-CHEMICAL, BIOLOGICAL OR MICROBIOLOGICAL TESTS OF PROPRIETARY MEDICINAL PRODUCTS

COUNCIL DIRECTIVE

of 20 May 1975

on the approximation of the laws of Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of proprietary medicinal products

(75/318/EEC)

PART 2

TOXICOLOGICAL AND PHARMACOLOGICAL TESTS

DIRECTIVE 89/343/EU: DEDICATED TO RADIOPHARMACEUTICALS

Peculiarity of radiopharmaceuticals needed to be considered by the legislation…..

- Definitions (kit, generators, etc.) were given
- The need for MA for industrially prepared RPs, kit, etc. was stated
- Stressed the need to take account of the special nature of RPs in defining requirement for testing, etc.
- ….and to take account of the need of radiation protection for patients and workers
- Defined the specific format of the SPC for RPs (with paragraphs for dosimetry and preparation + QC)
- …and specific indications for labelling

GMP: BASIC PRINCIPLES

- Good Manufacturing Practice (GMP): a system of principles and rules created with the aim to protect the patient
- GMP ensures that medicinal products are prepared with appropriate quality, safety and efficacy (…and traceability)
- GMP are part of more general Quality Assurance system (or Quality Management System)

EU GMP: A BRIEF HISTORY

Document History	
The *first edition* of the Guide was published, including an annex on the manufacture of sterile medicinal products.	1989
The *second edition* was published; implementing Commission Directives 91/356 of 13 June 1991 and 91/412 of 23 July 1991 laying down the principles and guidelines on good manufacturing practice for medicinal products for human use as well as for veterinary medicinal products. The second edition also included 12 additional annexes.	January 1992
An update of legal references was made. In the meantime, the guide is updated as needed on the website of the European Commission, several additional annexes added.	August 2004
Re-structuring of GMP guide, consisting of Part I for medicinal products for human and veterinary use and Part II for active substances used as starting materials, implementing Directives 2004/27/EC and 2004/28/EC. The current guide includes 17 Annexes, the former Annex 18 being replaced.	October 2005
Update of the text and introduction of a new Part III	December 2010

https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-4/2011_intro_en.pdf

DIRECTIVE 91/356/EEC: THE FIRST GMP DIRECTIVE

- It referred to first edition of GMP (1989)
- Art. 1 stated the need of GMP for MA
- General principles of GMP were described: QP, personnel, premises and equipment, documentation, independence of QC, batch records, starting material, etc.
- The importance of traceability was underlined

HOW RPs WERE PREPARED BEFORE «REGULATIONS»?

Early clinical use of RPs since the '40s, with I-131 treatments.....

*Hertz, S.; Roberts, A. (1940). "Radioactive Iodine as an Indicator in Thyroid Physiology". The American Journal of Physiology **128** (3): 565–576.*

..and then with the Mo-99/Tc-99m generator....

The original Brookhaven ^{99m}Tc generator (shown without shielding), ca. 1958.

HOW RPs WERE PREPARED BEFORE «REGULATIONS»?

..and then with PET RPs (in this picture, the first «synthesis module» for [^{18}F]FDG)

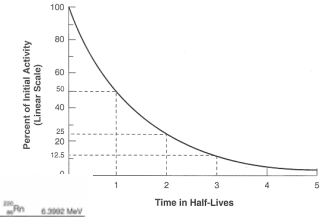
*Ido T, Wan CN, Casella V, Fowler JS, Wolf AP, Reivich M, and Kuhl DE (1978). "Labeled 2-deoxy-D-glucose analogs: ^{18}F-labeled 2-deoxy-2-fluoro-D-glucose, 2-deoxy-2-fluoro-D-mannose and ^{14}C-2-deoxy-2-fluoro-D-glucose". J Labeled Compounds Radiopharm **24**: 174–183.*

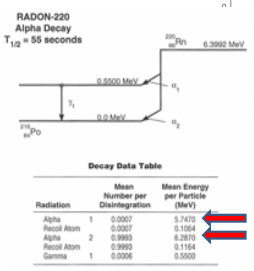
DO RPs REQUIRES SPECIFIC GMP?

«radioactive concentration» (or strenght) decreases with time

Emitted energy may be very high

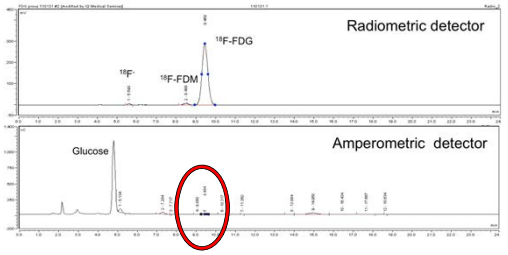
It may affect:
- (radio)chemical stability (radiolysis)
- excipients
- Container
- radiotoxicity





PECULIARITY OF RADIOPHARMACEUTICALS

Radiopharmaceuticals may contain very low mass amounts of Active Substance...although not always!



37 GBq ^{18}F$^-$

105.8 ng ^{18}F-FDG*

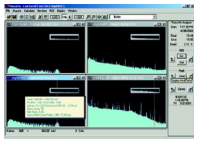
**100% theoretical yield*

FDG mass signal undetectable

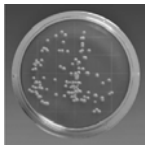
PECULIARITY OF RADIOPHARMACEUTICALS

Many QC tests may be performed pre-release.....

...but there are tests that need to be performed after the release (that's after the product administration to the patient), for instance



Radionuclidic purity test requires full decay of the main radioisotope (e.g. for F-18 at least 24-36 h)



Sterility test takes no less than 14 days before obtaining the results

PECULIARITY OF RADIOPHARMACEUTICALS

Batch size is often represented by a single vial in case of «in-house» preparations...

RPs are always handled by professionals (and never managed directly by patients)

...and often prepared at the time of use (no complicated logistic, wholesaler, street pharmacies, etc.)

PECULIARITY OF RADIOPHARMACEUTICALS

...BUT MOST OF ALL

...time constraints are very important! They affects the whole process!!

...in a normal pharma industry, a commercial batch size for solid oral dosage form should be at least 100.000 units (1 batch/month?)

...in a FDG production workshop, multiple batches / day may be prepared

DIRECTIVE 2001/83/EC

- It included the RPs in the definition of medicinal product
- It updated and merged all the previous relevant Directives (65/65/EEC, etc.)
- Foreword: «*….it is necessary to adopt specific provisions for….radiopharmaceuticals…*"
- Foreword: "*….to keep into account of relevant Euratom Directives (e.g. 80/386/euratom)*"
- Art. 1 (3a): definition of active substance
- **A MA shall not be required for a RP prepared at the time of use by a person or by an establishment authorized, according to national legislation, to use such medicinal products in an approved health care establishment exclusively from authorized radionuclide generators, kits or radionuclide precursors in accordance with the manufacturer's instructions.**

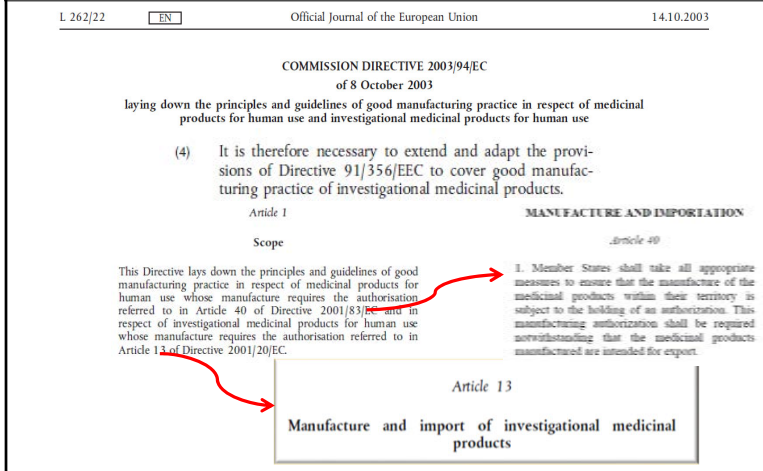
DIRECTIVE 2001/83/EC

- Art. 46 (f): it was stated the need to comply with GMP for RPs, which include:
  - Radiopharmaceuticals
  - Radionuclide generators
  - Kit
  - Radionuclide precursor
- …and for the preparation of active substances
- …art. 47: it refers to the need for a specific «GMP» Directive (…….then the Dir. 2003/63/EC)

FROM DIRECTIVE 91/356/EC TO 2003/94/EC

- Dir. 2003/94/EC repealed Dir. 91/356/EEC
- Main reason for change was the need to include investigational medicinal product after releasing Directive 2001/20/EC
- Another reason was the need to update rules for inspections

DIRECTIVE 2003/94/EC: A GMP SUMMARY



L 262/22 EN Official Journal of the European Union 14.10.2003

COMMISSION DIRECTIVE 2003/94/EC
of 8 October 2003
laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use

(4) It is therefore necessary to extend and adapt the provisions of Directive 91/356/EEC to cover good manufacturing practice of investigational medicinal products.

Article 1

Scope

This Directive lays down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use whose manufacture requires the authorisation referred to in Article 40 of Directive 2001/83/EC and in respect of investigational medicinal products for human use whose manufacture requires the authorisation referred to in Article 13 of Directive 2001/20/EC.

MANUFACTURE AND IMPORTATION

Article 40

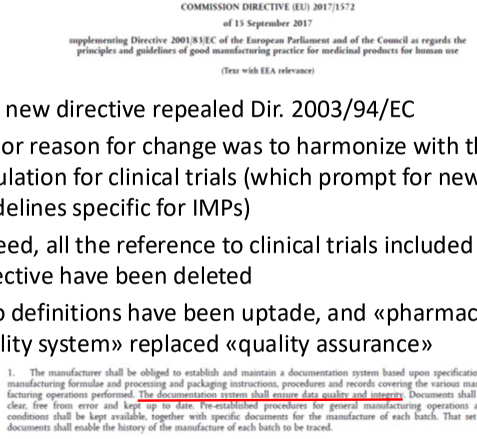
1. Member States shall take all appropriate measures to ensure that the manufacture of the medicinal products within their territory is subject to the holding of an authorization. This manufacturing authorization shall be required notwithstanding that the medicinal products manufactured are intended for export.

Article 13

Manufacture and import of investigational medicinal products

https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2003:262:0022:0026:en:PDF

FROM DIR 2003/94/EC TO DIR 2017/1572/EC



COMMISSION DIRECTIVE (EU) 2017/1572
of 15 September 2017
supplementing Directive 2001/83/EC of the European Parliament and of the Council as regards the principles and guidelines of good manufacturing practice for medicinal products for human use
(Text with EEA relevance)

- The new directive repealed Dir. 2003/94/EC
- Major reason for change was to harmonize with the new EU regulation for clinical trials (which prompt for new GMP guidelines specific for IMPs)
- Indeed, all the reference to clinical trials included in the old Directive have been deleted
- Also definitions have been uptade, and «pharmaceutical quality system» replaced «quality assurance»

1. The manufacturer shall be obliged to establish and maintain a documentation system based upon specifications, manufacturing formulae and processing and packaging instructions, procedures and records covering the various manufacturing operations performed. The documentation system shall ensure data quality and integrity. Documents shall be clear, free from error and kept up to date. Pre-established procedures for general manufacturing operations and conditions shall be kept available, together with specific documents for the manufacture of each batch. That set of documents shall enable the history of the manufacture of each batch to be traced.

SUMMARY OF GMP LEGISLATION

- Directive 2003/94/EC, replaced by Directive 2017/1572/EC: included principles of GMP
- Directive 2001/83, amended by Directive 2003/63/EC and Directive 2004/27/EC: it is also known as «Community code for medicinal products for human use»
- EU Regulation n. 536/2014 on clinical trials
- Directive 2004/27/EC: production of APIs according to GMP
- Directive 2005/28/EC: includes rules for manufacturing authorization for IMPs
- Directive 2017/1569/EC: GMP for investigational RPs

https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-4_en

DIR 2001/83/EC IS CURRENTLY UNDER REVISION

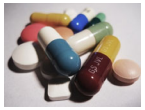
- No significant changes are to be expected as for GMP rules and applicability
- Exemptions will be granted to ATMP prepared under «hospital exemption» (but…are there RPs that fall into the definition of ATMP?), but their preparation have to comply with requirements equivalent to GMP

https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12963-Revision-of-the-EU-general-pharmaceuticals-legislation_en

https://eanm.org/wp-content/uploads/2024/05/The-revision-of-the-pharmaceutical-legislation-%E2%80%94-it-is-time-to-act-for-nuclear-medicine-in-Europe-1.pdf

GMP: FIELD OF APPLICATION FOR RPs

- Marketing Authorization Applicants (All EU countries)
- Marketing Authorization Holders (all EU countries)
- Preparation of Investigational Radiopharmaceuticals (IMP) for therapeutic purposes (all EU countries)
- Preparation of Investigational Radiopharmaceuticals (IMP) for diagnostic purposes (not required by Regulation 536/2014, but requested anyhow in some EU countries)
- Preparation of «in-house» radiopharmaceuticals (in some EU countries)



PHARMACEUTICAL LEGISLATION IN THE EU: THE EUDRALEX PORTAL

EudraLex - EU Legislation

EudraBook V1 - May 2015 / EudraLex V30 - January 2015

Overview

The body of European Union legislation in the pharmaceutical sector is compiled in Volume 1 and Volume 5 of the publication "The rules governing medicinal products in the European Union":

- Volume 1 - EU pharmaceutical legislation for medicinal products for human use
- Volume 5 - EU pharmaceutical legislation for medicinal products for veterinary use

The basic legislation is supported by a series of guidelines that are also published in the following volumes of "The rules governing medicinal products in the European Union":

- Volume 2 - Notice to applicants and regulatory guidelines for medicinal products for human use
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- Volume 4 - Guidelines for good manufacturing practices for medicinal products for human and veterinary use
- Volume 6 - Notice to applicants and regulatory guidelines for medicinal products for veterinary use
- Volume 7 - Scientific guidelines for medicinal products for veterinary use
- Volume 8 - Maximum residue limits
- Volume 9 - Guidelines for pharmacovigilance for medicinal products for human and veterinary use
- Volume 10 - Guidelines for clinical trial

https://ec.europa.eu/health/documents/eudralex_en

GMP RULES: PART I

Part I – Basic Requirements for medicinal products	
Chapter 1	Pharmaceutical Quality System
Chapter 2	Personnel
Chapter 3	Premise and equipment
Chapter 4	Documentation
Chapter 5	Production
Chapter 6	Quality control
Chapter 7	Outsourced activities
Chapter 8	Complaints and product recall
Chapter 9	Self inspection

https://ec.europa.eu/health/documents/eudralex/vol-4_en

GMP RULES: PART II AND III

Part II – Basic requirements for active substances used as starting materials
Part III – GMP related documents
Site Master File
Q9 Quality Risk Management
Q10 Note for guidance on pharmaceutical quality system
MRA Batch certificate
Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal product in shared facilities
Template for IMP batch release (applicable as from the date of entry into application of Regulation (EU) No 536/2014 on Clinical Trials)
Reflection paper on Good Manufacturing Practice and Marketing Authorisation Holders

Now there is also part 4, specific for ATMP

https://ec.europa.eu/health/documents/eudralex/vol-4_en

GMP RULES: ANNEXES RELEVANT FOR RPs

Annexes	
Annex 1	Manufacture of sterile medicinal products
Annex 3	Manufacture of radiopharmaceuticals (very important and very old and outdated, as it was released in 2008)
Annex 8	Sampling of starting and packaging materials
Annex 11	Computerised systems
Annex 13	Manufacture of investigational medicinal products And «Detailed GMP guidelines for IMPs (following art. 61.3, sub-par. 2 of regulation 536/2014)
Annex 15	Qualification and validation
Annex 16	Cetification by a Qualified Person and Batch Release
Annex 19	Reference and retention samples

https://ec.europa.eu/health/documents/eudralex/vol-4_en

GMP AND RPs: ANNEX 3 - RADIOPHARMACEUTICALS

The manufacture of radiopharmaceuticals shall be undertaken in accordance with the principles of Good Manufacturing Practice for Medicinal Products Part I and II. This annex specifically addresses some of the practices, which may be specific for radiopharmaceuticals.

Note i. Preparation of radiopharmaceuticals in radiopharmacies (hospitals or certain pharmacies), using Generators and Kits with a marketing authorisation or a national licence, is not covered by this guideline, unless covered by national requirement.

Note ii. According to radiation protection regulations it should be ensured that any medical exposure is under the clinical responsibility of a practitioner. In diagnostic and therapeutic nuclear medicine practices a medical physics expert shall be available.

Note iii. This annex is also applicable to radiopharmaceuticals used in clinical trials.

Note iv. Transport of radiopharmaceuticals is regulated by the International Atomic Energy Association (IAEA) and radiation protection requirements.

Note v. It is recognised that there are acceptable methods, other than those described in this annex, which are capable of achieving the principles of Quality Assurance. Other methods should be validated and provide a level of Quality Assurance at least equivalent to those set out in this annex.

https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-4/2008_09_annex3_en.pdf

GMP AND RPs: ANNEX 3 - RADIOPHARMACEUTICALS

Type of manufacture	Non-GMP*	GMP Part I & II (increasing) including relevant annexes			
RPs, PET RPs, radioactive precursors	Reactor/cyclotron production	Chemical synthesis	Purification steps	Processing, formulation and dispensing	Aseptic or final sterilization
Radionuclide generators	Reactor/cyclotron production	Processing			

**target and transfer systems from cyclotron to synthesis rig may be considered as the first step of active substance manufacture*

https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-4/2008_09_annex3_en.pdf

GMP AND RPs: ANNEX 3 - RADIOPHARMACEUTICALS

- Quality assurance: QA is of greater importance, due the early release of RPs (which is, in turn, due to fast decay of radionuclides)
- Quality assurance: risk assessment should be applied to determine the extent of validation
- Personnel: Annex 3 regulates production facilities shared with research institutions
- Personnel: trained also on radiation protection issues

https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-4/2008_09_annex3_en.pdf

GMP AND RPs: ANNEX 3 - RADIOPHARMACEUTICALS

- Premises: a compromise has to be found between pharmaceutical and radiation protection needs
- Equipment: in case of closed and automated process, a grade «C» is adequate (hot cell)
- Labelling: it is accepted that most of the labelling information are entered before the process start
- QC: release before completion of the tests in case of short half-life radionuclides

https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-4/2008_09_annex3_en.pdf

WHAT IS GMP SPECIFIC?

- GMP requires, for every production Site, a dedicated Authorization
- Authorization is released following an inspection
- Inspections are focused on general Compliance with GMP

Nuclear medicine / Academic Institutions usually don't require Site Authorization

WHAT IS GMP SPECIFIC?

- Marketing Authorization for a radiopharmaceutical requires GMP
- MA is product specific, and is released after dossier assessment and inspections

Nuclear medicine / Academic Institutions may require a MA as well (e.g. in France and The Netherlands)

WHAT IS GMP SPECIFIC?

- GMP production of (radio)pharmaceuticals requires a Qualified Person, following art. 7 of the Directive 2017/1752/EC
- Requisites for QP are defined in art. 49 of the Directive 2001/83/EC
- QP is responsible, among other, for the release of the batch of finished product

Also Nuclear medicine / Academic Institutions may require QP as defined by the Directive

WHAT IS GMP SPECIFIC?

- Inspections are defined by art. 3 of, Directive 2017/1752/EC
- Inspections may be managed on a local (National) basis or may be Coordinated directly by EMA (e.g. in case of Centralized procedures and for specific products)
- Although Pharmaceutical Cooperation Scheme (PIC/S) is promoting harmonization of inspections, the situation may vary from country to country, so GMP are often «country dependent»

Nuclear medicine / Academic Institutions may be subject to inspections as well

WHAT IS GMP SPECIFIC? MORE PAPERWORK....

- Site Master File (general information about the Site, the prepared product, personnel, organization, etc.)
- Validation Master file (equipment, analytical methods, ancillary systems to be validated, protocols, policy, etc.)
- Quality product review (trends of the critical parameters, review and discussion of OOS, OOT, deviations)
- All critical parameters should be checked (e.g. yield and radiochemical purity, but also environmental microbiological contamination, etc.)
- A lot of SOPs!

https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-4/2011_site_master_file_en.pdf

WHAT IS GMP SPECIFIC? IN-PROCESS CONTROLS

- For instance, monitoring of airborne and microbiological contaminatin should be performed for every batch (in class «A» environment)

	Maximum permitted number of particles per m^3 equal to or greater than the tabulated size			
	At rest		In operation	
Grade	**0.5 µm**	**5.0µm**	**0.5 µm**	**5.0µm**
A	3 520	20	3 520	20
B	3 520	29	352 000	2 900
C	352 000	2 900	3 520 000	29 000
D	3 520 000	29 000	Not defined	Not defined

	Recommended limits for microbial contamination (a)			
Grade	air sample cfu/m^3	settle plates (diameter 90 mm) cfu/4 hours (b)	contact plates (diameter 55 mm) cfu/plate	glove print 5 fingers cfu/glove
A	< 1	< 1	< 1	< 1
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

WHAT IS GMP SPECIFIC? MORE STRICT ON STARTING MATERIALS

- Detailed information about precursors / APIs need to be provided (often authorities require a dedicated 2.S section for precursor only)
- QC on starting materials are more restrictive
- Specifications for each of the starting materials should be defined
- Starting materials should be purchased by approved suppliers only
- Approved suppliers should be audited

https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-4/2014-08_gmp_part1.pdf

WHAT IS GMP SPECIFIC? COSTS

- All of the previously described differences means that complying with GMP requires:
  - More instrumentation resources
  - More personnel resources
  - More space for the facilities
- Costs are higher

CRITICAL POINTS: RADIONUCLIDES

- There are many emerging radionuclides, especially for therapeutic purposes, such as the α-emitters At-211, Ac-225, Tb-149
- Their production modes are quite variables (e.g. cyclotron, reactor, mass separation techniques, etc.), and still in progress
- ..and it's not always clear how to consider them (finished product? Active substance? Starting materials?)

Type of manufacture	Non-GMP*	GMP Part I & II (increasing) including relevant annexes			
RPs, PET RPs, radioactive precursors	Reactor/cyclotron production	Chemical synthesis	Purification steps	Processing, formulation and dispensing	Aseptic or final sterilization
Radionuclide generators	Reactor/cyclotron production	Processing			

**target and transfer systems from cyclotron to synthesis rig may be considered as the first step of active substance manufacture*

CRITICAL POINTS: ACTIVE SUBSTANCE

- What is the active substance (or API, or drug substance?)
- Strictly speaking, it should be the radiolabelled product itself (e.g. [^{18}F]FDG, [^{68}Ga]Ga-PSMA, etc.), which is often non isolated during the preparation process….
- …but also the cold kit and radionuclide precursors may be considered as APIs…
- …and also precursors for radiolabeling

FINAL REMARKS

- Did the EU Authorities succeed in keeping into account of the RPs peculiarities? Only in part…and requirements are continuously increasing (e.g. the new Annex 1 – GMP)
- More work still has to be done, also with the help of the stakeholders (e.g. EANM)
- The shorter is the radionuclide half-life, the more difficult is to be GMP compliant (e.g. in a PET RP facility may be released up to 5-6 batches / day vs e.g. 1 batch / month in normal pharmaceutical company)

OTHER USEFUL GUIDELINES

PIC/S
PHARMACEUTICAL INSPECTION CONVENTION
PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME

GUIDE TO GOOD MANUFACTURING PRACTICE FOR MEDICINAL PRODUCTS PART I

GUIDE TO GOOD MANUFACTURING PRACTICE FOR MEDICINAL PRODUCTS PART II

Developed by the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use

https://picscheme.org/en/publications


EJNMMI Radiopharmacy and Chemistry

GUIDELINE ARTICLE Open Access

Guideline on current good radiopharmacy practice (cGRPP) for the small-scale preparation of radiopharmaceuticals

https://ejnmmipharmchem.springeropen.com/track/pdf/10.1186/s41181-021-00123-2.pdf

Annex 2

International Atomic Energy Agency and World Health Organization guideline on good manufacturing practices for radiopharmaceutical products

https://cdn.who.int/media/docs/default-source/medicines/who-technical-report-series-who-expert-committee-on-specifications-for-pharmaceutical-preparations/trs1025-annex2.pdf?sfvrsn=7aceb0c1_6

Annex 3
IAEA/WHO guideline on good manufacturing practices for investigational radiopharmaceutical products

https://www.who.int/publications/m/item/trs1044-annex3

OTHER USEFUL GUIDELINES

Guidance

PET Drugs — Current Good Manufacturing Practice (CGMP)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2009
Compliance

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070306.pdf

Specific radiopharmaceutical legislation

Where are specific topics defined and/or regulated?

Clemens Decristoforo
Innsbruck, Austria

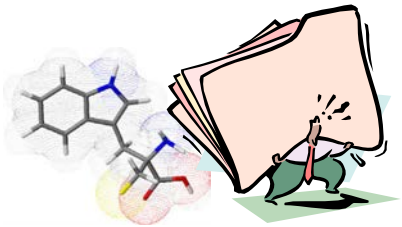
1

Specific Radiopharmaceutical legislation With respect to :

- What is a radiopharmaceutical (RP)?
- Who is allowed to prepare/ produce RPs?
- Who can be responsible for RP preparation?
- Where and how is the quality defined?
- Are QC methods defined and where?
- How can a product be released?
- (Marketing Authorization, non-clinical testing)

2

What is a Radiopharmaceutical? (legally…)



3

„Pharmaceutical“ Directive for Medicinal Products

►B ↓ **DIRECTIVE 2001/83/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL**

of 6 November 2001

on the Community code relating to medicinal products for human use

(OJ L 311 28.11.2001, p. 67)

Amended by:

Amended by (currently) 12 different directives and regulations

		No	page	date
►M1 ↓	DIRECTIVE 2002/98/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 27 January 2003	L 33	30	8.2.2003
►M2 ↓	COMMISSION DIRECTIVE 2003/63/EC of 25 June 2003	L 159	46	27.6.2003
►M3 ↓	DIRECTIVE 2004/24/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 31 March 2004	L 136	85	30.4.2004
►M4 ↓	DIRECTIVE 2004/27/EC OF THE EUROPEAN PARLIAMENT AND	L 136	34	30.4.2004

Lets have a look at Eudralex

Revision in Progress (New Proposal voted in 2026?)

4

Eudralex

https://health.ec.europa.eu/medicinal-products/eudralex_en

Public Health

Home > Medicinal products > Eudralex

EudraLex - EU Legislation

PAGE CONTENTS

Body of European Union legislation

Guidelines

Latest updates

Body of European Union legislation

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- Volume 7 - Scientific guidelines for medicinal products for veterinary use
- Volume 8 - Maximum residue limits
- Volume 9 - Guidelines for pharmacovigilance for medicinal products for human and veterinary use
- Volume 10 - Guidelines for clinical trial

Medicinal products for paediatric use, orphans, herbal medicinal products and advanced therapies are governed by specific rules.

The Rules Governing Medicinal Products in the European Union

A radiopharmaceutical is?

Directive 2001/83/EC, Article 1

6. *Radiopharmaceutical:*

Any medicinal product which, when ready for use, contains one or more radionuclides (radioactive isotopes) included for a medicinal purpose.

7. *Radionuclide generator:*

Any system incorporating a fixed parent radionuclide from which is produced a daughter radionuclide which is to be obtained by elution or by any other method and used in a radiopharmaceutical.

8. *Kit (for radiopharmaceutical preparation*)*

Any preparation to be reconstituted or combined with radionuclides in the final radiopharmaceutical, usually prior to its administration.

9. *Radionuclide precursor:*

Any other radionuclide produced for the radiolabelling of another substance prior to administration.

Legal Implications: Directive applies to all these products including requirement for **manufacturing authorisation** of the institution, licensing (**marketing authorization**), responsibilities, distribution, labelling……..

* *Proposal in new directive*

6

Marketing Authorization requirement

SmPC: 4.1 Therapeutic indications: EndolucinBeta is a radiopharmaceutical precursor, and it is not intended for direct use in patients. It is to be used only **for the radiolabelling of carrier molecules** that have been specifically developed and **authorised** for radiolabelling with Lutetium (177Lu) chloride

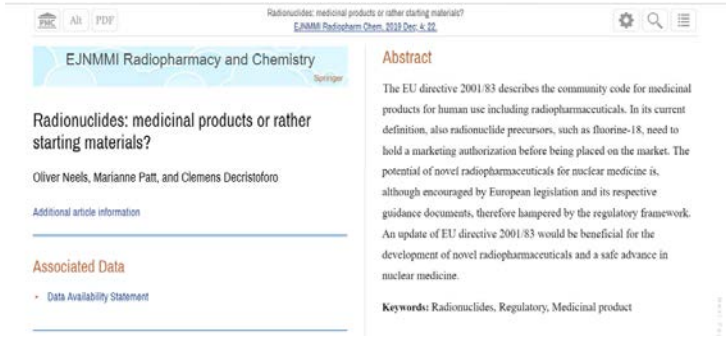
→ ***So far no authorized „carrier molecule" within the EU***

→ ***Producers with Marketing Authorisation can sell the product***

7

Do the requirements of Directive 2001/83 for radionuclides, radionuclide generators and kits always apply?

Only if they are considered as Medicinal products (Drug Products), not used in a Clinical Trial and not being exempted in general



Alt | PDF

Radionuclides: medicinal products or rather starting materials?
EJNMMI Radiopharm Chem. 2019 Dec 4; 22.

EJNMMI Radiopharmacy and Chemistry

Radionuclides: medicinal products or rather starting materials?

Oliver Neels, Marianne Patt, and Clemens Decristoforo

Additional article information

Associated Data

- Data Availability Statement

Abstract

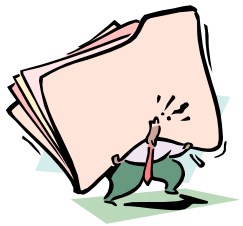
The EU directive 2001/83 describes the community code for medicinal products for human use including radiopharmaceuticals. In its current definition, also radionuclide precursors, such as fluorine-18, need to hold a marketing authorization before being placed on the market. The potential of novel radiopharmaceuticals for nuclear medicine is, although encouraged by European legislation and its respective guidance documents, therefore hampered by the regulatory framework. An update of EU directive 2001/83 would be beneficial for the development of novel radiopharmaceuticals and a safe advance in nuclear medicine.

Keywords: Radionuclides, Regulatory, Medicinal product

8

Who is allowed to prepare a Radiopharmaceutical?

- Do I need an authorisation for the Product?
- Do I need an authorisation for the Facility?



9

Regulatory basis for the use of (Radio)Pharmaceuticals within the EU

Marketing Authorization	Clinical Trial	„Extemporaneous Preparation“ , Compounding
• Directive 2001/83 EC (“Pharmaceutical Directive”)	• Regulation EU No 536/2014 („Clinical Trials Regulation“)	• National legislation

PUBLIC HEALTH

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

10

(Marketing) Authorization (Product)

Directive 2001/83/EC

Article 6

1. No medicinal product may be placed on the market of a Member State unless a **marketing authorisation** has been issued by the competent authorities of that Member State **in accordance with this Directive** or an **authorisation has been granted in accordance with Regulation (EC) No 726/2004** ……..

2. The authorisation referred to in paragraph 1 shall also be required for radionuclide generators, kits, radionuclide precursor radiopharmaceuticals and **industrially** prepared radiopharmaceuticals.

The revision of the Pharma-Directive proposes to eliminate the scope on „industrially manufacturing“

11

(Marketing) Authorization Radiopharmaceuticals

A marketing authorisation shall be required for **radionuclide generators, kits for radiopharmaceutical preparation, and radionuclide precursors, unless they are used as starting material, active substance or intermediate** of radiopharmaceuticals covered by a marketing authorisation under Article 5(1). Member States may, in justified cases, regulate **substance-related exemptions** from the authorisation requirement for radionuclide precursors for diagnostic radioactive medicinal products, if this is necessary to secure an adequate supply of radionuclides throughout the facilities for nuclear medicine and if the safety and quality profile for the radionuclide precursor is established and assure

Current Proposal

12

EU Authorisation/Registration Procedures

A medicinal product may only be placed on the market in the EU when a **Marketing Authorisation** has been issued by:

- the competent authority of the Member State(s) (MS)
- or by the European Commission (EC)

Same legal requirements irrespective of the route/procedure for the authorisations - granted **on the basis of quality, safety and efficacy.**

- Centralised Procedure (CP)
- Mutual Recognition Procedure (MRP)
- Decentralised Procedure (DCP)
- National Procedure (NP)

New directive: Hospital Exemption for ATMPs

13

Which Pathway is used for radiopharmaceuticals

Predominant Pathway

- „Old“ radiopharmaceuticals: *Technetium kits, generators, 131I-capsules*
- „standard“ PET radiopharmaceuticals *FDG and other F-18 RPs*

National procedure
Mutual recognition procedure

- Novel generators, 68Ge/68Ga-generator; Ga-68-kits

Decentralized procedure

- Novel therapeutic radiopharmaceuticals: Ra-223, Lu-177 based, some F-18 RPs, Ga-68-kits

Centralized procedure (mandatory)

14

European Medicines Agency
Inspections

London, 26 November 2008
Doc. Ref. EMEA/CHMP/QWP/306970/2007

COMMITTEE FOR HUMAN MEDICINAL PRODUCTS (CHMP)

GUIDELINE ON RADIOPHARMACEUTICALS

- Provides Guidance for Marketing Authorization Applicants
- Clarifies what is to be considered a **Drug Substance** (Active Pharmaceutical Ingredient) and **Drug Product** (Medicinal Product)
- Explicitly applicable to PET-RPs, „non radioactive components“, radionuclide precursors, generators..
- Only dedicated guideline, applied also for other purposes (e.g. clinical trial applications)

→ ***under revision***

Development; Manufacture; Quality control; Stability.

15

Exceptions from Directive 2001/83/EC relevant for in-house preparation

Non-industrial practices

This Directive shall apply to medicinal products for human use intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process.

Practice of Pharmacy

Article 3

This Directive shall not apply to:

1. Any medicinal product prepared in a pharmacy in accordance with a medical prescription for an individual patient (commonly known as the magistral formula).

2. Any medicinal product which is prepared in a pharmacy in accordance with the prescriptions of a pharmacopoeia and is intended to be supplied directly to the patients served by the pharmacy in question (commonly known as the officinal formula).

Licensed Kits/Gen/RN

Article 7

A marketing authorization shall not be required for a radiopharmaceutical prepared at the time of use by a person or by an establishment authorized, according to national legislation, to use such medicinal products in an approved health care establishment exclusively from authorized radionuclide generators, kits or radionuclide precursors in accordance with the manufacturer's in

Physician's individual treatment

Article 5

1. A Member State may, in accordance with legislation in force and to fulfil special needs, exclude from the provisions of this Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised health-care professional and for use by an individual patient under his direct personal responsibility.

16

Authorization for Manufacturing / Preparation (Facility)

Pharmaceutical Authorization

- As a Pharmaceutical Manufacturer for „routine products“
- As a Pharmaceutical Manufacturer for Investigational Medicinal Products

Directive 2001/83/EC
Regulation 536/2014

- As a pharmacy
- As „Healthcare Establishment (Hospital, Nuclear Medicine Department)

National Regulations

Authorization from Radiations Safety Authorities

Directive 2013/59/Euratom

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Manufacturing Authorization (Facility)

Directive 2001/83/EC

TITLE IV

MANUFACTURE AND IMPORTATION

Article 40

1. Member States shall take all appropriate measures to ensure that the manufacture of the medicinal products within their territory is subject to the holding of an authorization. This manufacturing authorization shall be required notwithstanding that the medicinal products manufactured are intended for export.

2. The authorization referred to in paragraph 1 shall be required for both total and partial manufacture, and for the various processes of dividing up, packaging or presentation.

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Clinical Trials Regulation 536/2014

Article 61
Manufacturing and import authorisation
1. The manufacturing and import of investigational medicinal products in the Union shall be subject to the holding of an authorisation.

Article 63
Manufacturing and import
1. Investigational medicinal products shall be manufactured in applying manufacturing practice which ensures the quality of such medicinal products in order to safeguard subject safety and the reliability and robustness of clinical data generated in the clinical trial (hereinafter 'good manufacturing practice').

Paragraph 1 **shall not apply to** any of the following processes:

preparation of radiopharmaceuticals used as diagnostic investigational medicinal products where this process is carried out in hospitals, health centres or clinics, by pharmacists or other persons legally authorised in the Member State concerned to carry out such process, and if the investigational medicinal products are intended to be used exclusively in hospitals, health centres or clinics taking part in the same clinical trial in the same Member State

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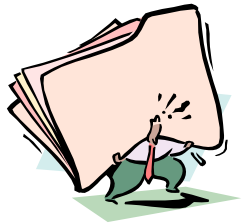
Who is responsible?



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Responsibilities depend on the legal status of facility

- **As a Pharmaceutical Manufacturer** — Qualified Person
- As a pharmacy — Pharmacist
- As other „Healthcare Establishment“ (Hospital, Nuclear Medicine Department) — NM physician? Radiopharmacist?

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Who can be responsible for RP preparation? → Responsibility for release

Directive 2001/83/EC

Article 41

In order to obtain the manufacturing authorization, the applicant shall meet at least the following requirements:

(c) have at his disposal the services of at least one qualified person within the meaning of Article 48.

Article 48

1. Member States shall take all appropriate measures to ensure that the holder of the manufacturing authorization has permanently and continuously at his disposal the services of at least one qualified person, in accordance with the conditions laid down in Article 49, responsible in particular for carrying out the duties specified in Article 51.

Article 49-53:
Education, responsibilities,……..

→Differences due to translation of directive in national legislation

- QP must be a pharmacist in some countries, in others not
- QP for RP`s: required in some countries in others not

Exeptions Nationally!!

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Who can be responsible for RP preparation? → Responsibility for production and QC

Recommended in GMP chapter 2

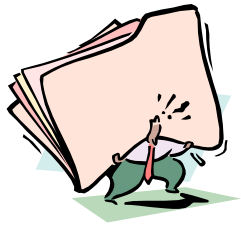
Key Personnel

2.3 Key Personnel include the head of Production, the head of Quality Control, and if at least one of these persons is not responsible for the duties described in Article 51 of Directive 2001/83/EC[1], the Qualified Person(s) designated for the purpose. Normally key posts should be occupied by full-time personnel. The heads of Production and Quality Control must be independent from each other. In large organisations, it may be necessary to delegate some of the functions listed in 2.5, 2.6 and 2.7.

Only applicable if GMP legally applies and is enforced, e.g. not in Pharmacies

23

What is Quality of a RP? How to determine it?



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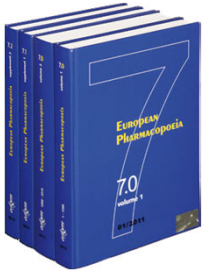
European Pharmacopoeia



Council of Europe

EDQM
(European Directorate of Quality of Medicines)

1. General Chapter on Radiopharmaceutical Preparation
2. Monographs for specific radiopharmaceuticals
3. General Chapters for pharmaceutical tests

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What is Quality?

Quality criteria for radiopharmaceuticals
(Pharm Eur: General Monograph on Radiopharmaceutical Preparations)

- Identity: Approximate half life and nature/energy of radiation
- Radiochemical Purity
- Radionuclidic Purity
- Specific Radioactivity
- Chemical Purity
- Sterility
- Bacterial Endotoxins-Pyrogens

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How to determine the quality - instrumentation

edqm European Directorate for the Quality of Medicines & HealthCare

2. Methods of analysis

01/2014:20266

2.2.66. DETECTION AND MEASUREMENT OF RADIOACTIVITY

INTRODUCTION

Within the context of the European Pharmacopoeia, the term 'radioactivity' is used both to describe the phenomenon of radioactive decay and to express the physical quantity of this phenomenon. In the monographs on radiopharmaceutical preparations, the detection and measurement of radioactivity are performed for different purposes: verification of the characters, identification, determination of radionuclidic and radiochemical purity, as well as determination of the radioactivity in a substance (assay).

Under these assumptions, the measurement can be qualitative, quantitative or both, depending whether it is directed to the identification of the radionuclide or the determination of its activity (rate of decay) or both of them.

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Quality Control methods described by a manufacturer

(e.g. Radiochemical Purity, ^{99m}Tc-radiopharmaceuticals)

Described in: For the „end user"

Summary of product Characteristics (SPC)
(and Package leaflet)

European directive 2001/83 (Article 11)

SPC has to contain
„for radiopharmaceuticals, additional detailed instructions for extemporaneous preparation and **quality control** of such preparation and, where appropriate, maximum storage time during which any intermediate preparation such as an eluate or the ready to use pharmaceutical will conform with its specifications"

→ Part of marketing authorization
→ Legal character
→ Only applicable and sufficient in the exact context of the marketing authorisation

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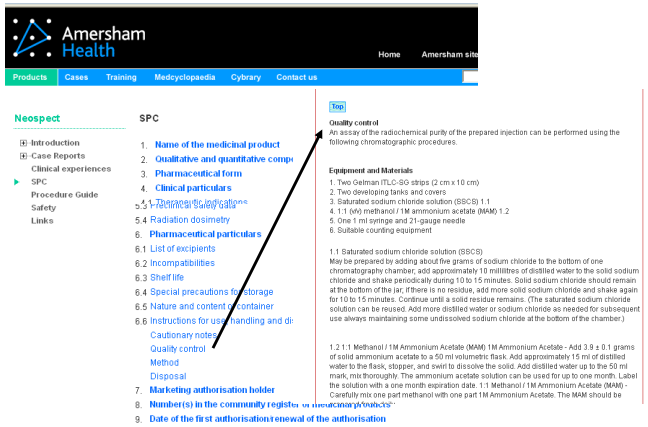
Quality Control as described in an SPC



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Analytical Validation

European Medicines Agency

June 1995
CPMP/ICH/381/95

ICH Topic Q 2 (R1)
Validation of Analytical Procedures:
Text and Methodology

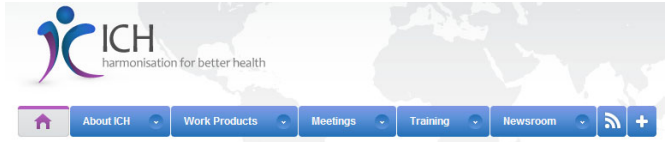
Step 5

NOTE FOR GUIDANCE ON VALIDATION
OF ANALYTICAL PROCEDURES:
TEXT AND METHODOLOGY
(CPMP/ICH/381/95)

CPMP : Committee for Proprietary Medicinal Products, (now CHMP: Committee for Medicinal Products for Human Use) issues EMA`s opinion as guidelines

Drafted by QWP and harmonized with FDA and Japan

30



ICH: International Conference on Harmonisation
(FDA+Japan+EMA + …….)

Global harmonization:
Validation, microdosing,…..

→ In Europe adopted as EMA guieline

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Extent of Validation

Measured Quality Attribute / Analytical Procedure Performance Characteristics to be Demonstrated (2)	Identity	Impurity (Purity)		Assay
		Other quantitative measurements (1)		Content or potency
		Quantitative Test	Limit Test	Other quantitative measurements (1)
Specificity (3)				
Specificity Test	+	+	+	+
Range				
Response (Calibration Model)	-	+	-	+
Lower Range Limit	-	QL†	DL	-
Accuracy (4)				
Accuracy Test	-	+	-	+
Precision (4)				
Repeatability Test	-	+	-	+
Intermediate Precision Test	-	+ (5)	-	+ (5)

ICH harmonisation for better health

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

14 December 2023
EMA/CHMP/ICH/82072/2006
Committee for Medicinal Products for Human Use

ICH Q2(R2) Guideline on validation of analytical procedures

- signifies that this test is not normally conducted

+ signifies that this test is normally conducted

† in some complex cases DL may also be evaluated

QL, DL: quantitation limit, detection limit

(1) other quantitative measurements can follow the scheme for impurity, if the range limit is close to the DL/QL; other quantitative measurements can follow the scheme for assay (content or potency), if the range limit is not close to the DL/QL

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Analytical Methods should be validated – Validation requirements for radiopharmaceutical methods

Type of analytical procedure	Radioactivity Content (assay)	Radionuclide identity (approx. T½)	Radionuclide identity (spectrometry)	Radiochemical identity (HPLC/TLC/PC)	Radionuclidic purity (limit test)	Radionuclidic purity (spectrometry after decay)	Radiochemical purity* (HPLC/TLC/PC)
Characteristics							
Accuracy	+		-	-	-	+	+
Precision (Repeatability)	+	+				(+)	(+)
Intermediary Precision						(+)	(+)
Specificity	+	+	+	+	+	+	+
Detection Limit	-				+	-	-
Quantification Limit	-					+	+
Linearity	+	+			+	-	+
Range	+	+			+	-	+

* radioenantiomeric purity measurements should be validated analogously
(+) - not always possible (e.g. short half life)

EJNMMI Radiopharmacy and Chemistry

GUIDELINE ARTICLE Open Access

EANM guideline on the validation of analytical methods for radiopharmaceuticals

Nic Gillings[1*], Sergio Todde[2], Martin Behe[3], Clemens Decristoforo[4], Philip Elsinga[5], Valentina Ferrari[6], Olaug Hjelstuen[7], Petra Kolenc Peitl[8], Jacek Kozlowski[9], Peter Laverman[10], Thomas L. Mindt[11], Mehtem Ocak[12] and Marianne Patt[13]

Release of a Product

Directive 2001/83 – QP release

Article 51

1. Member States shall take all appropriate measures to ensure that the qualified person referred to in Article 48, without prejudice to his relationship with the holder of the manufacturing authorization, is responsible, in the context of the procedures referred to in Article 52, for securing:

(a) in the case of medicinal products manufactured within the Member States concerned, that each batch of medicinal products has been manufactured and checked in compliance with the laws in force in that Member State and in accordance with the requirements of the marketing authorization;

Do I have to do all the tests described in a Pharmacopeia Monograph

1. General Notices

1.1. General Statements

"…An article is not of Pharmacopeia quality unless it complies with all the requirements stated in the monograph. This does not imply that performance of all the tests in a monograph is necessarily a prerequisite for a manufacturer in assessing compliance with the Pharmacopeia before release of a product. The manufacturer may obtain assurance that a product is of Pharmacopeia quality from data derived, for example, from validation studies of the manufacturing process and from in-process controls. Parametric release in circumstances deemed appropriate by the competent authority is thus not precluded by the need to comply with the Pharmacopeia…"

Do I have to complete all tests before release? EU-GMP Annex 3 - Quality Control

- Radiopharmaceutical product **release may be carried out in two or more stages, before and after full analytical testing**:

a) Assessment by a designated person of batch processing records, which should cover production conditions and analytical testing performed thus far, before allowing transportation of the radiopharmaceutical under quarantine status to the clinical department.

b) Assessment of the final analytical data, ensuring all deviations from normal procedures are documented, justified and appropriately released prior to documented certification by the Qualified Person. Where certain test results are not available before use of the product, the Qualified Person should conditionally certify the product before it is used and should finally certify the product after all the test results are obtained.

→ *under revision*

Preliminary Release

GUIDELINE ON RADIOPHARMACEUTICALS EMEA/CHMP/QWP/306970/2007

Specifications for radiopharmaceuticals should also include radiochemical identity and purity, chemical purity and, where relevant specific radioactivity, radionuclidic identity and purity. Special attention should be paid to impurities that influence the radiochemical purity or biodistribution of the product. Acceptance limits for the radioactive concentration for diagnostic radiopharmaceuticals should be within 90 to 110% of the label claim. For therapeutic radiopharmaceuticals, acceptance limits should be within 95 to 105% of the label claim. Wider limits must be conclusively justified (e.g. inferior accuracy of radioactivity measurement).

For some radiopharmaceuticals **it may not be possible to obtain the results of certain tests**, e.g. sterility test, before the product is released. However, these tests are important in the validation of the manufacturing process. **It should be stated which tests are normally undertaken before the release of the product for use and which are undertaken after release. The latter should be justified.**

→ *under revision*

Justification from Pharm Eur monograph:

"Sterility. It complies with the test for sterility prescribed in the monograph Radiopharmaceutical preparations (0125). **The preparation may be released for use before completion of the test.**"

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Thank you for your attention

Traces of radiopharmaceuticals in the mountains of pharmaceutical regulations

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Postgraduate Radiopharmacy Courses
Ljubljana, 26th August 2025

CLINICAL TRIAL REGULATION AND IMPD

Sergio Todde

University of Milano-Bicocca
Tecnomed Foundation
Head of Radiopharmaceutical Unit

CLINICAL TRIAL LEGISLATION

EU Legislation - Eudralex

The body of European Union legislation in the pharmaceutical sector is compiled in Volume 1 and Volume 5 of the publication "The rules governing medicinal products in the European Union".

- Volume 1 - EU pharmaceutical legislation for medicinal products for human use
- Volume 5 - EU pharmaceutical legislation for medicinal products for veterinary use

The basic legislation is supported by a series of guidelines that are also published in the following volumes of "The rules governing medicinal products in the European Union":

- Volume 2 - Notice to applicants and regulatory guidelines for medicinal products for human use
- Volume 3 - Scientific guidelines for medicinal products for human use
- Volume 4 - Guidelines for good manufacturing practices for medicinal products for human and veterinary use
- Volume 6 - Notice to applicants and regulatory guidelines for medicinal products for veterinary use
- Volume 7 - Scientific guidelines for medicinal products for veterinary use
- Volume 8 - Maximum residue limits
- Volume 9 - Guidelines for pharmacovigilance for medicinal products for human and veterinary use
- Volume 10 - Guidelines for clinical trial

Medicinal products for paediatric use, orphan, herbal medicinal products and advanced therapies are governed by specific rules.

https://ec.europa.eu/health/documents/eudralex/vol-10_en

DIRECTIVE 2001/20/EC: GENERAL PRINCIPLES

Principles are based on Helsinki declaration of 1996, related to the protection of human rights and dignity of humans

Evaluation of:

- Risks related to clinical trials
- Toxicology
- In case of radiopharmaceuticals, also toxicity due to radiation burden (dosimetry)
- Clinical trials proposal have to be evaluated by Ethic Committee

DIRECTIVE 2001/20/EC: GENERAL PRINCIPLES

- Clinical trials proposals have to be evaluated by the National Competent Authority
- Patients have to release their informed consent before to be included in clinical trials
- Cost/benefit ratio has to clearly prompt for (at least) potential benefit for the patient population

CLINICAL TRIALS WITH RPs: RISK ASSESSMENT

Limits valid for population < 50 years, excluding paediatrics
For paediatrics, limits have to be decreased by a factor 2-3
For population > 50 yrs, limits may be increased of a factor 5-10

Benefit	Risk	Risk category	Probability	Effective dose (mSv)
Low	Not significant	Cat. I	≈ 10^{-6} or less	< 0.1
Moderate/ medium	Intermediate	Cat II		
		IIa	≈ 10^{-5}	0.1-1
		IIb	≈ 10^{-4}	1-10
Significant	moderate	Cat. III	≈ 10^{-3} or more	> 10

European Commission – Directorate General Environment, Nuclear Safety and Civil Protection (1998) Guidance on medical exposure in medical and biomedical research

https://op.europa.eu/en/publication-detail/-/publication/0be8f9c1-e923-4817-845f-29d0dc87183d

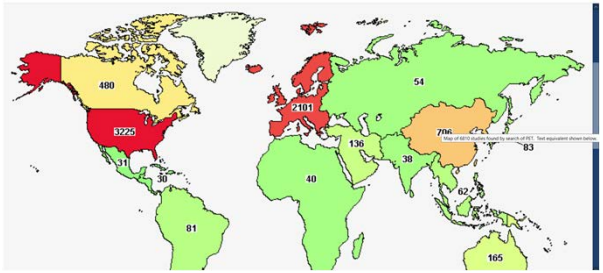
DIR. 2001/20/EC: CRITICAL POINTS (GENERAL)

- Different transposition of the Directive in EU Countries
- Different regulatory requirements from country to country
- More difficult to perform multi-centre, multi-country clinical trials (e.g. need for multiple assessments, different decisions by ethic committees)
- Increased costs: bureaucracy, documentation, toxicity studies, insurance (patients have to be covered for 5-10 years, which makes no sense for diagnostic RPs!!)
- Overregulation for RPs, with multiple reference guidelines (GMP, clinical trials directives, Euratom directives).....

DIR. 2001/20/EC: CRITICAL POINTS (RPs)

- Extent of information required are virtually the same, notwithstanding the clinical trial is conducted by Big Pharma companies or by a hospital or academic based small scale radiopharmacy
- High administrative and economic burden
- The need to comply with GMP
- The need for a QP
- The need for GMP produced APIs
- This led to a general decrease in the number of CT in EU.....
- In particular for Healthcare/Academia driven CT

LIMITATIONS OF DIR. 2001/20/EC: A PRACTICAL EXAMPLE



http://clinicaltrials.gov/ct2/results/map?term=PET

FROM DIR. 2001/20 TO REGULATION 536/2014

EUROPEAN COMMISSION

Brussels, 17.7.2012
COM(2012) 369 final
2012/0192 (COD)

Proposal for a

REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC

The data available support these criticisms:

- The number of applications for clinical trials fell by 25% from 2007 to 2011.[3]
- The costs for conducting clinical trials have increased. Compared to the situation prior to the application of the Directive 2001/20/EC, the staff needs for industry sponsors to handle the clinical trial authorisation process have doubled (107%); with small companies facing an even sharper increase. For non-commercial sponsors, the increase in administrative requirements due to the Directive 2001/20/EC has led to a 98% increase in administrative costs. In addition, since implementation of the Directive 2001/20/EC, insurance fees have increased by 800% for industry sponsors.
- The average delay for launching a clinical trial has increased by 90% (+ 82 days.

...not only for Big Pharma!

Frewer LJ. Has the European Clinical Trials Directive been a success? BMJ. 2010 340:c1862

Neaton JD. Regulatory impediments jeopardizing the conduct of clinical trials in Europe funded by the National Institutes of Health. Clin Trials; 2010 7:705-18.

Bosch, X. Europe's restrictive rules strangling clinical research. Nature Medicine 2005;11: 1260

REGULATION 536/2014: AIMS

Effectively harmonize and simplify regulatory requirement in the EU

Promote multi-country CT, targeted on more specific sub-populations

Create a single submission portal, thus reducing time and divergences

REGULATION 536/2014: AIMS

Encourage CT focused on orphan medicinal products

Simplify authorization procedures for low interventional CT (IMP with MA or "well established")

Promote CT conducted by non-commercial sponsors

REGULATION 536/2014: WHAT'S NEW?

- A Reporting Member State (RMS) is committed for the assessment of the Dossier
- A timeline for authorization is stated, which is in the range 60-106 days (+ 50 days in case of ATMP), similarly to procedures for MA applications
- A single entry point for data submission and information related to CT
- No need to submit data in different countries
- More transparency: the EU portal shall be publicly accessible (except for confidential information), and a summary of the CT contents understandable by a layperson has to be provided

REGULATION 536/2014: ENTRY INTO FORCE

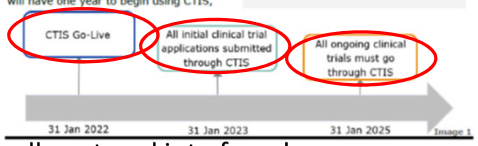
CTIS go-live date confirmed as 31 January 2022

On 31st July 2021, the European Commission confirmed the entry into application of the Clinical Trial Regulation (EU) No 536/2014 by the publication of a notice in the Official Journal of the European Union. As set out in the Regulation, this publication starts the six-month countdown to CTIS go-live and confirms the go-live date for CTIS as **31st January 2022**.

The Clinical Trial Regulation foresees a 3-year transition period to CTIS. Member States will have to work in CTIS immediately from go-live, once applications are submitted. Sponsors will have one year to begin using CTIS, and can decide whether to submit a new clinical trial application under the Clinical Trial Directive 2001/20/EC or Regulation (EU) No 536/2014 until 31 January 2023.

All new applications for clinical trials must be submitted through CTIS as of 31 January 2023, while all clinical trials must be transferred to CTIS by 31 January 2025, if still ongoing by the end of the transition period.

With 6 months until the system goes live, all future users of CTIS are encouraged to review the available CTIS training materials and ensure their organisations are prepared for the transition to CTIS.



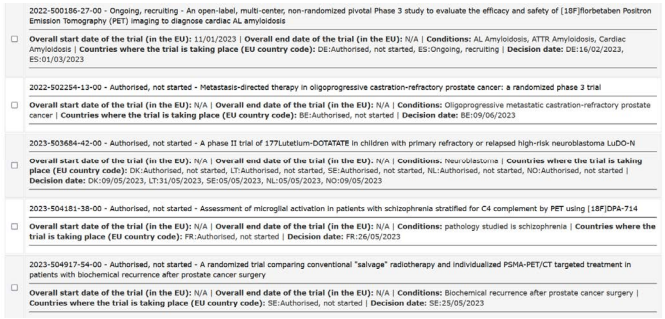
~~Directive 2001/20/EC~~

.....it finally entered into force!

https://www.ema.europa.eu/en/documents/newsletter/clinical-trials-information-system-ctis-highlights-august-2021_en.pdf

CLINICAL TRIAL INFORMATION SYSTEM (CTIS)

- It is the software platorm (portal) used to upload and handle the CT documentation
- Database is accessible via the following link: https://euclinicaltrials.eu/search-for-clinical-trials
- Registration is free (just need to create an EMA account)



REGULATION 536/2014: THERAPEUTIC RPs

Art. 61, 62, 63 of Regulation 536/2014 states that:

- Manufacturing authorization is needed
- QP is mandatory
- QP has to verify that the IMP is manufactured following GMP
- References: EU Directive 2017/1569/EC, Annex 13 – GMP
- Manufacturing Site may be inspected

So, nothing is changed?

REGULATION 536/2014: WHAT'S NEW FOR RPs?

- The need for an authorization to the manufacturing (and QP, GMP, etc.) is still of concern (art. 61, par. 1).....but:
- Art. 61, par. 5: par. 1 (b) shall not apply for....preparation of RPs used as diagnostic IMPs, where this process is carried out in hospitals...by pharmacists or other persons legally authorized in the Member State...and if the IMPs are intended to be used only in hospitals, etc.

REGULATION 536/2014: WHAT'S NEW FOR RPs?

GMP «exemption» only apply to diagnostic RPs

Person responsible for preparation will be determined on a National basis

Don't need for GMP?

Art. 61 (6): *Member States shall make the processes set out in paragraph 5 subject to appropriate and proportionate requirements to ensure subject safety and reliability and robustness of the data generated in the clinical trial. They shall subject the processes to regular inspections.*

REGULATION 536/2014: THERAPEUTIC RPs

Therapeutic RPs require GMP

"A **new Delegated Regulation will be adopted to set the GMP rules for Investigational Medicinal Products** and will apply to all clinical trials authorised on the basis of the CT Regulation"

COMMISSION DELEGATED REGULATION (EU) 2017/1569

of 23 May 2017

supplementing Regulation (EU) No 536/2014 of the European Parliament and of the Council by specifying principles of and guidelines for good manufacturing practice for investigational medicinal products for human use and arrangements for inspections

https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guideline_adopted_1_en_act_part1_v3.pdf

REGULATION 536/2014: WHAT'S NEW FOR RPs?

(b) preparation of radiopharmaceuticals used as diagnostic investigational medicinal products where this process is carried out in hospitals, health centres or clinics, by pharmacists or other persons legally authorised in the Member State concerned to carry out such process, and if the investigational medicinal products are intended to be used exclusively in hospitals, health centres or clinics taking part in the same clinical trial in the same Member State;

Art. 61 (5), b does not rule out explicitly the possibility that an IMP is prepared in one Centre and then used in a different Centre

REGULATION 536/2014: WHAT'S NEW FOR RPs?

Labelling

Art. 68: Articles 66 and 67 shall not apply to radiopharmaceuticals used as diagnostic investigational medicinal products or as diagnostic auxiliary medicinal products.
The products referred to in the first paragraph shall be labelled appropriately in order to ensure the safety of the subject and the reliability and robustness of data generated in the clinical trial.

https://ejnmmipharmchem.springeropen.com/articles/10.1186/s41181-019-0055-6

DOCUMENTATION: CLINICAL TRIAL MASTER FILE

- Clinical trial master file had to be archived for at least 5 years with EU directive 2001/20/EC, now for 25 years!

Most relevant information to be included in CTMF are:

- completed forms, checklists and reports etc. related to the trial;
- qualified person certification of the IMP (if applicable);
- assay method validation report for analysis of IMP or metabolite(s) in clinical samples;
- case report form (eCRF) and interactive response technologies (IRT) and electronic patient-reported outcomes);
- data management documentation;
- meeting minutes;
- statistics documentation

06 December 2018
EMA/INS/GCP/856758/2018
Good Clinical Practice Inspectors Working Group (GCP IWG)

Guideline on the content, management and archiving of the clinical trial master file (paper and/or electronic)

CLINICAL TRIALS DIRECTIVES: DIR. 2005/28/EC

COMMISSION DIRECTIVE 2005/28/EC

of 8 April 2005

laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products

- It establishes Good Clinical Practice (GCP) guidelines
- It better defines requisites for authorization, based on art. 13 of directive 2001/20/EC
- It includes explicitly RPs among the «medicinal products» to which the present directive apply
- Qualification of inspectors
- Inspection procedures

https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e6-r3-guideline-good-clinical-practice-gcp-step-5_en.pdf

THE DOCUMENTATION

Dossier

Part I (EU)

Cover letter
EU Application form
Protocol
Investigator's Brochure
IMPD
GMP compliance (if applicable)
Label
Scientific advice (if applicable)

Part II (MS)

Recruitment procedure
Informed consent
Suitability of Principal Investigator
Suitability of the facility/ies
Insurance
Financial aspects
Fee
Data Protection

EU portal CTIS

DIR. 2005/28/EC: INVESTIGATOR'S BROCHURE

TABLE OF CONTENTS OF INVESTIGATOR'S BROCHURE *(Example)*

https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-clinical-practice-e6r2-4-step-2b_en.pdf

IMPD: EU GUIDELINES

27 January 2022
EMA/CHMP/QWP/545525/2017 Rev. 2
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials

Draft agreed by Quality Working Party	December 2015
Adopted by CHMP for release for consultation	December 2015
Consultation of European Commission ad hoc group on clinical trials	February 2016
Start of public consultation	12 April 2016
End of consultation (deadline for comments)	12 October 2016
Agreed by Quality Working Party	May 2017
Consultation of European Commission ad hoc group on clinical trials	June 2017
Adopted by CHMP	14 September 2017
Date for coming into effect	6 months after publication

This guideline replaces the "Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials" (CHMP/QWP/185401/2004 final)

https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-requirements-chemical-pharmaceutical-quality-documentation-concerning-investigational_en.pdf

EU IMPD GUIDELINES: WHAT'S SPECIFIC FOR RPs

- Source of irradiated starting materials (e.g. to be irradiated by cyclotrons) should be stated
- Need to discuss the radionuclide manufacturing process
- Discuss about the structure of the radiolabelled kits
- It is stressed the need to provide information on chemical precursors (even if they are removed during the preparation process)
- Batch analysis is to be included
- Level of detail of requested info also depends on the CT phase (e.g. more detailed info on precursor for phase II/III studies)

IMPD EU GUIDELINES: DRUG SUBSTANCE

https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-requirements-chemical-pharmaceutical-quality-documentation-concerning-investigational_en.pdf

IMPD EU GUIDELINES: DRUG PRODUCT

https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-requirements-chemical-pharmaceutical-quality-documentation-concerning-investigational_en.pdf

DRUG SUBSTANCE: DEFINITION

- Generators: both parent and daughter radionuclides (e.g. Mo-99 and Tc-99m) are considered as active substances
- Kits: the part that carry or bind the radionuclides (e.g. betiatide, medronic acid)
- PET RPs: often the drug substance is not isolated (e.g. FDG, F-PSMA, etc.), as they are continuous processes….
- In general: drug substance is the «active principle» (es. [^{68}Ga]Ga-Dotatoc, [^{177}Lu]Dotatoc, [^{18}F]FDG, etc.)

DRUG SUBSTANCE: DEFINITION

- …and for labelled kits (e.g. [^{99m}Tc]MDP?
- They are obtained using 2 active substances: [^{99m}Tc]TcO_4^- and the «cold» kit: two different 2.S sections have to be prepared
- This is true also for Ga-68 RPs

A quality issue? The active substance is entirely administered to the patient, and IMPD guidelines now stress on this

DRUG SUBSTANCE: DESCRIPTION

- In case DS is not isolated, description is provided for the «cold» counterpart (e.g. [^{19}F]FDG for [^{18}F]FDG), but this is not considered sufficient in several countries, and also detailed information about precursor need to be provided, in a separate 2.S section (which may further increase the costs……..)
- In case of Kit or RPs where the DS is entirely administered, a full description (including information on the preparation process of the precursor) have to be provided

CHARACTERIZATION

Parent Nuclide	$T_{1/2}$	Decay mode	$\beta^+ E_{max}$	Relative intensity	γKeV	Daughter nuclide
C-11	20.38 min	β^+	960.2 KeV	99.759 %	511	B-11

Information on radionuclide

Information on physico-chemical properties (determined on non radioactive analogous… e.g. [^{19}F]F-PSMA for [^{18}F]F-PSMA)

- Solubility
- pKa
- Stereochemistry
- Log P
- Appearance
- Melting point
- Structure
- toxicity

DESCRIPTION OF THE PREPARATION PROCESS

For radionuclides:

Describe (both desired and undesired) nuclear reaction

$^{18}O(p,n)^{18}F$

....

- beam energy (and particle) and current (or flux in case of neutrons)
- target characteristics (material, volume, foils material, etc.)
- irradiated stable isotope, with a suitable CoA

RADIONUCLIDIC IMPURITIES

In case of cyclotron produced radionuclides

- Consider the isotopic enrichment of irradiated stable isotopes
- Check for impurities in irradiated stable isotopes, and their possible nuclear reactions
- Check for other materials that may be hit by the particle beam and their possible nuclear reactions (e.g. target chamber, window foil)
- The latter is especially important in case of liquid targets (> solid target > gas targets)

RADIONUCLIDIC IMPURITIES

Impurities may be estimated using the following equation:

$$D = I\ N\ \sigma\ (1 - e^{-\lambda t})$$

where

D = activity in dps
I = particle flux (number of particles/cm^2 x sec)
N = n° di irradiated atoms
σ = cross section, in barns (1 barn = 10^{-24} cm^2)
λ = decay constant
t = irradiation time

....but then they have to be experimentally determined

RADIONUCLIDIC IMPURITIES

In case of purchased radionuclides

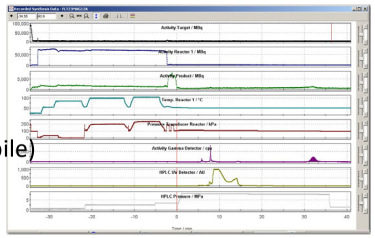
- Usually they are provided in a purified form
- ..but impurities may be present (e.g. Ge-68 or Mo-99 breakthrough)
- If a Ph. Eur. monograph exist, they have to comply with (e.g. $[^{99m}Tc]NaTcO_4$, $[^{68}Ga]GaCl_3$)
- Radionuclidic impurity content is known and described in CoA
- Possible impurities have to be considered in the light of the characteristics of the preparation process

DESCRIPTION OF THE PREPARATION PROCESS

In all cases

Describe preparation process

....
- Automated system (if applicable)
- Reagents, starting materials
- Kit/cassettes (if applicable)
- Preparation procedure
- Purification procedure (if applicabile)
- Container and closure
- Specifications
- etc……



Description is required also for Drug product, but it is often overlapping with DS…

CONTROL OF MATERIALS

- Materials should be preferably of pharmaceutical grade
- CoA is always required, but often not sufficient (see above)
- In case the starting material has a MA, Summary of Product Characteristics (SPC) may be included
- Impurities should be considered and discussed (a monograph «Chemical precursor for RP preparation», has been released by Ph. Eur.), and detailed information need to be obtained from the Supplier
- Purchased radionuclides (e.g. generators) should be fully characterized by the manufaturer (CoA) and radionuclidic impurities considered and discussed

RADIOCHEMICAL IMPURITIES

- Radiochemical impurities usually arise from preparation process
- Specification is often RCP > 95%
- Impurities may range from different isomers of the desired product, to degradation product (e.g. due to harsh reaction conditions or to radiolysis), to different ionic form or to different oxidation state, etc.
- Effect of radiolisys should be discussed

CHEMICAL IMPURITIES

- Chemical (organic, inorganic) impurities may arise from….
  - degradation of the precursor/product
  - side reactions
  - solvents used in the process
  - other reagents used in the process
  - catalysts (including phase transfer catalysts)
  - ions due to salts
- Chemical impurities may pose toxicity issues

REFERENCE STANDARD: RADIOACTIVE SOURCES

Calibrated radioactive sources for:
- Dose calibrators
- Gamma spectrometers

- Long lived radionuclides (e.g. Cs-137)
- Gamma emitting sources
- Positron emitting sources

- Multinuclide sources
- Single nuclide, multigamma sources (e.g. Eu-152)

REFERENCE STANDARD: CHEMICALS

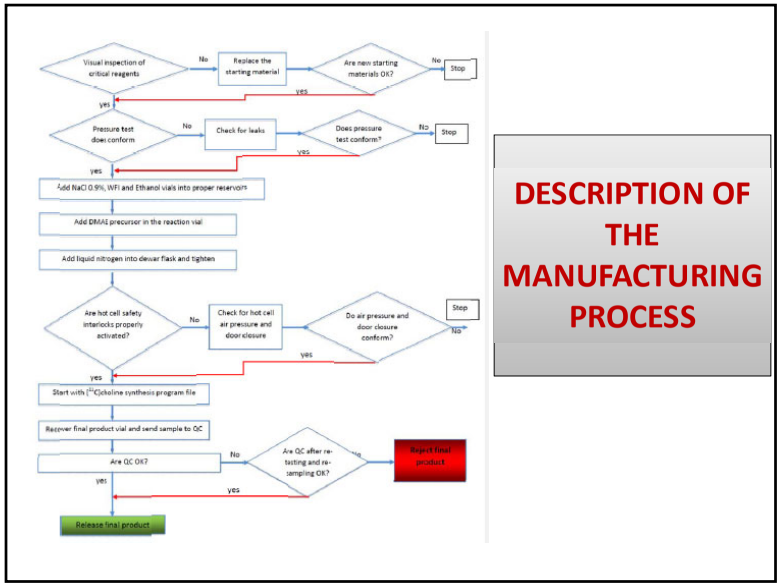
- «Chemical» standards may be the «cold» counterpart of the desired RPs (e.g. [^{19}F]FLT for [^{18}F]FLT)
- …or reference for known impurities (e.g. stavudine, as a possibile impurity in [^{18}F]FLT preparations)
- Sometimes it's not possible to have «cold» standard (e.g. there are no stable isotopes for technetium): use the cold ligand + macromolecule

DRUG PRODUCT: DEFINITION

- Drug product means a finished medicinal product which has undergone all stages of production, including packaging and excipients, purification and formulation, in its final container
- Thus, drug product is what we normally call «final (or finished) product»

DESCRIPTION AND COMPOSITION OF THE IMP

- Radioactive concentration, to be preferred to activity itself (e.g. [^{18}F]FDG, 50 MBq/ml, dissolved in saline physiological solution)
- EU guidelines require that radioactivity is defined at ART (activity reference time)
- Volume
- Container (e.g. glass vial) and closure (e.g. typical rubber stoppers)
- List of excipients (e.g. physiological solution, buffers, free radical scavengers, surfactants, bacteriostatic agents, etc.)



DESCRIPTION OF THE MANUFACTURING PROCESS

CONTROL OF THE DRUG PRODUCT: SPECIFICATIONS

- Specifications for the drug substance and drug product may be the same (in case of continuous processes) or different (when drug substance is isolated)
- Specifications should be given to define the quality of the radiopharmaceutical product
- They have to specify limits and acceptance criteria for identity, RNP, RCP, chemical and microbiological purity
- Method for radioactivity determination should be described
- Bioburden should be defined and media fill performed

DRUG PRODUCT: ANALYTICAL METHODS

- Specifications should be scientifically justified
- A description of the analytical methods should be given
- Unless they are pharmacopoeial methods, they have to be validated
- Pre- and post-release tests should be specified
- Validation criteria set by reference ICH guidelines are not always applicable in case of radioanalytical procedures and they should be adapted: check EDQM guidelines

https://www.edqm.eu/en/d/66901

DRUG PRODUCT: CONTAINER/CLOSURE

- A description of the container / closure system should be given (e.g. 10 ml vial, made of glass Ph. Eur. Type I, with bromobutyl rupper stopper, crimped with aluminum, flip-off caps)
- Test for container / closure leakage should be performed (e.g. rotating vial upside down)
- Interactions between radiopharmaceutical and container / closure should be evaluated

DRUG PRODUCT: STABILITY

- EU Stability guidelines* are fully applicable in case of the «cold» kits
- On the contrary, they are not fully applicable for the radiolabelled compounds
- Moreover, they are not a real issue in case of short or very short radionuclide half-life (e.g. $T_{1/2}$ < 60 min)
- Stability studies are aimed to verify that the RPs meet quality acceptance criteria until the expected shelf-life
- In-use stability should also be determined

** https://www.ema.europa.eu/en/ich-q1a-r2-stability-testing-new-drug-substances-drug-products-scientific-guideline*

USEFUL CT RELATED GUIDELINES: EANM

Eur J Nucl Med Mol Imaging (2014) 41:2175–2185
DOI 10.1007/s00259-014-2866-8

GUIDELINES

EANM guideline for the preparation of an Investigational Medicinal Product Dossier (IMPD)

Sergio Todde · Albert D. Windhorst · Martin Behe · Guy Bormans · Clemens Decristoforo · Alain Faivre-Chauvet · Valentina Ferrari · Antony D. Gee · Balazs Gulyas · Christer Halldin · Petra Kolenc Peitl · Jacek Koziorowski · Thomas L. Mindt · Martina Sollini · Johnny Vercouillie · James R. Ballinger · Philip H. Elsinga

https://link.springer.com/article/10.1007/s00259-014-2866-8

Peñuelas et al. EJNMMI Radiopharmacy and Chemistry (2019) 4:2
https://doi.org/10.1186/s41181-019-0055-6

EJNMMI Radiopharmacy and Chemistry

EDITORIAL Open Access

The new Regulation on clinical trials in relation to radiopharmaceuticals: when and how will it be implemented?

Iván Peñuelas[1*], Daniëlle J. Vugts[2], Clemens Decristoforo[3] and Philip H. Elsinga[4]

https://ejnmmipharmchem.springeropen.com/articles/10.1186/s41181-019-0055-6

Thank you for your attention!

Clinical Translation: Non-clinical regulatory aspects

Clemens Decristoforo

1

Application Process in Europe New Clinical Trial Regulation EU No 536/2014

Clinical Trials Information System -CTIS

EU Clinical Trial Portal and Database*
CTIS

Validation
10 days

Assessment
Notification
50 days

Radiopharmaceutical CTA

Competent Authority
Member State concerned

approval — Ethic`s + Pharmaceutical evaluation

Clinical Trial

- Streamlined application procedure
- Harmonized assessment procedure
- Single set of documents
- Single application for multinational trials

→ *Valid since January 31st 2022*
→ *Mandatory since Feb 2023*

2

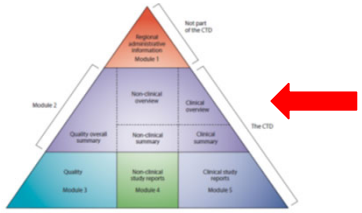
Evaluation by a Competent Authority (Europe)

- By experts in National Drug Agencies (not by EMA)
- Experts with specific qualifications
- Evaluation based on legislation (interpreted by guidelines)
- Guidelines rarely very specific, individual assessment
- **Case by case basis**

Investigational Medicinal Product Dossier IMPD

3

LEGISLATION FRAMEWORK IN THE EU



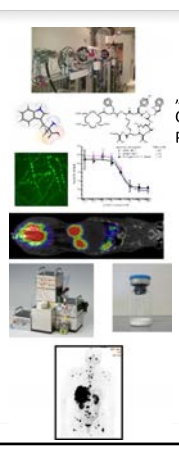
Module 2 of CTD is related to «non clinical» information, including preclinical data

- Main «operative» guideline is «**ICH guideline M3(R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals**"
- It is aimed to MA applicant, but it applies to clinical trials as well
- Being an ICH document, it is applicable in ICH regions and it is aimed to harmonize non clinical safety studies

https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-m3r2-non-clinical-safety-studies-conduct-human-clinical-trials-marketing-authorisation_en.pdf

4

Path of a new Radiopharmaceutical to the patient



„Cold" Chemistry Precursor

Radionuclide Production

Radiochemistry

Biological characterization in vitro

Biological characterization in vivo including imaging

Pharmaceutical formulation

Clinical Trial

Medicinal Product

Data generation

Quality Data

Quality Data

Safety and Efficacy Data Non-clinical studies

Quality data
Safety and efficacy

Safety and Efficacy Clinical

Non-clinical

- ***Pharmacology***
  Pharmacokinetics
  Pharmacodynamics
- ***Radiation effects***
  Preclinical Dosimetry
  Therapeutics
- ***Toxicology***

5

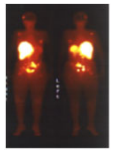
THE WHOLE EU LEGISLATION REFERENCES

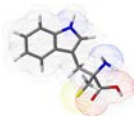
- Euratom directives (in particular, Directive 2013/59/Euratom)
- Directive 2001/83 (especially part III, on toxicological requirements)
- Directive 2010/63/Eu (protection of animal for scientific purposes)
- Directive 2004/2010/EC (GLP)
- CHMP/SWP/28367/07 (mitigation of risk for first in human CT)
- EMEA/CHMP/QWP/306970 (guideline on radiopharmaceuticals)
- ICH S6(R1) (preclinical evaluation of biotechnology derived pharmceuticals)
- ICH S9 (non clinical evaluation for anticancer pharmaceuticals)
- ICH M3(R2) (non clinical safety studies, with microdosing approach)
- ICH S7A (note for guidance on safety pharmacology studies for human pharmaceuticals)
- EMA/CHMP/SWP/686140/2018 (guidance on non-clinical requirements for radiopharmaceuticals – draft)
- (EMA/CHMP/451705/2024-Concept paper on clinical evaluation of therapeutic radiopharmaceuticals in oncology)

6

„Non-Clinical Data" Requirements

Radio - Pharmaceutical





Dosimetry
Radiation effects

7

Radiation risk – diagnostic RPs

Limits valid for population < 50 years, excluding paediatrics
For paediatrics, limits have to be decresed by a factor 2-3
For population > 50 yrs, limits may be increased of a factor 5-10

Benefit	Risk	Risk category	Probability	Effective dose (mSv)
Low	Not significant	Cat. I	≈ 10^{-6} or less	< 0.1
Moderate/medium	Intermediate	Cat II		
		IIa	≈ 10^{-5}	0.1-1
		IIb	≈ 10^{-4}	1-10
Significant	moderate	Cat. III	≈ 10^{-3} or more	> 10

European Commission – Directorate General Environment, Nuclear Safety and Civil Protection (1998) Guidance on medical exposure in medical and biomedical research

(courtesy: S.Todde)

8

Preclinical Dosimetry – Safety Data (Radiation related)

Organs	%ID/g tissue ± SD (n = 4)					
	^{111}In]CP04					
	30 min	1 h	4 h	24 h	48 h	72 h
Blood	1.74±0.22	0.51±0.14	0.02±0.01	0.00±0.00	0.01±0.01	0.01±0.01
Liver	0.77±0.11	0.32±0.15	0.12±0.02	0.06±0.01	0.06±0.00	0.05±0.01
Heart	0.70±0.10	0.21±0.04	0.03±0.01	0.02±0.01	0.02±0.01	
Kidneys	9.80±2.07	8.84±2.05	7.90±1.98	3.61±0.31	2.81±0.63	
Stomach	4.88±0.85	2.99±0.55	2.61±0.82	1.48±0.55	1.26±0.26	
Intestines	0.82±0.14	0.39±0.12	1.05±0.35	0.18±0.14	0.49±0.49	
Spleen	0.36±0.04	0.14±0.04	0.05±0.01	0.04±0.01	0.03±0.01	
Muscle	0.59±0.10	0.18±0.04	0.04±0.02	0.02±0.01	0.03±0.02	
Lung	1.05±0.10	0.40±0.10	0.06±0.01	0.03±0.01	0.02±0.01	
Femur	4.62±1.24	2.62±0.42	0.96±0.18	0.53±0.04	0.55±0.11	
Pancreas	0.67±0.08	0.26±0.08	0.10±0.01	0.05±0.01	0.04±0.01	

Maina T et al Eur J Pharm Sci. 2016

	Absorbed dose per injected activity (mGy/MBq)	
Organs	option 1	option 2
LLI Wall	0.078	0.075
Small Intestine	0.026	0.024
Stomach Wall	0.012	0.011
ULI Wall	0.037	0.035
Heart Wall	0.005	0.003
Kidneys	0.039	0.124
Liver	0.005	0.009
Lungs	0.004	0.003
Muscle	0.010	0.009
Pancreas	0.008	0.017
Red Marrow	0.010	0.012
Osteogenic Cells	0.015	0.034
Spleen	0.007	0.011
Urinary Bladder Wall	0.459	0.456
Total Body	0.011	0.010
Effective dose (mSv/MBq)	**0.045**	**0.044**

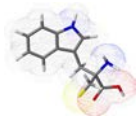
Expected whole body dose
110MBq activity:
9.9mSv

- For Therapeutics complemented by non-clinical studies on radiation induced damage/ therapeutic effect *in vivo* and *in vitro* → ***guidance missing***
- Requirement to be discussed for very short lived diagnostic radionuclides (C-11, Ga-68)

Dakanali M, Zigler SS, Schwarz SW, et al. ***FDA reconsiders rules around radiation dosimetry*** *for first-in-human studies of investigational PET radiopharmaceuticals. J Nucl Med. 2025;66:986–988.*

„Non-Clinical Data“ Requirements

Radio - Pharmaceutical



Toxicity

Pharmacology
Pharmacokinetics

10

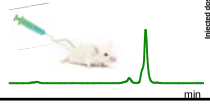
„Non-Clinical Data“ Pharmacology & Pharmacokinetics e.g. radiolabelled peptides

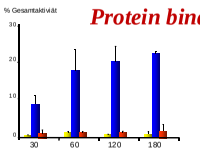
In vitro data:

- Metabolic stability (human serum, tissue homogenates)
- Protein binding, log P
- Receptor binding characterisation
- Internalisation

In vivo data:

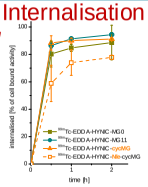
- Normal biodistribution including in vivo stability
- Biodistribution in animal models (mouse)
- Imaging

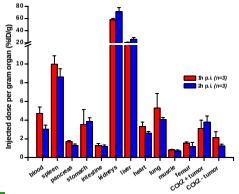


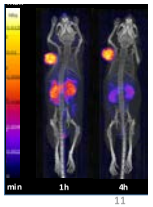


Protein binding

Internalisation







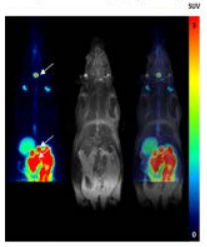
11

„Non-Clinical Data“ Increasing Role of Imaging

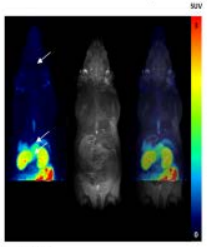
Simultaneous PET-MRI imaging

MIRaCLe MOLECULAR IMAGING RESEARCH AND CLINIC LEUVEN

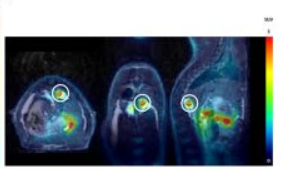
- Allows multiparameter longitudinal assessment in preclinical models
- Applications in Oncology, NeuroPET and Cardiology
- Superior mapping of organs for longitudinal biodistribution/blocking studies



Pre-block
High uptake in SSTR2-expressing regions



Post-block
Reduced uptake in SSTR2-expressing regions



Delineation of adrenal gland enabled by MRI sequence despite kidney clearance of PET tracer

Brukar PET insert/BioSpec 70/30 USR

Tshibangu *et al.*, EJNMMI Radpharm Chem 2020

12

Non-Clinical Data - Toxicity of „cold molecule“

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

December 2009
EMA/CPMP/ICH/286/1995

ICH guideline M3(R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals
Step 5

Transmission to CHMP	July 2008
Adoption by CHMP for release for consultation	July 2008
End of consultation (deadline for comments)	October 2008
Final adoption by CHMP	June 2009
Date for coming into effect	December 2009

❖ Some type of studies are typically not performed for radiopharmaceuticals:

- Subacute and chronic toxicological studies
- Teratogenicity (reproduction) studies
- Genotoxic (mutagenic) studies
- Carcinogenic studies

→ RPs given once
→ Certain risks dominated by radiation

❖ Microdosing approach (<100µg)
❖ **GLP requirement**

13

Clinical Trial with Radiopharmaceuticals = Exploratory Clinical Trials??

Table 3: Recommended Non-Clinical Studies to Support Exploratory Clinical Trials:

Clinical:		Non clinical:		
Dose to be Administered	**Start and Maximum Doses**	**Pharmacology**	**General Toxicity Studies[a]**	**Genotoxicity[b] / Other**
Approach 1: Total dose ≤ 100 µg (no inter-dose interval limitations) AND Total dose ≤ 1/100th NOAEL and ≤1/100th pharmacologically active dose (scaled on mg/kg for *i.v.* and	Maximal and starting doses can be the same but not exceed a total accumulated dose of 100 µg	*In vitro* target/ receptor profiling should be conducted Appropriate characterization of primary pharmacology (mode of action and/or effects) in a pharmacodynamically relevant model should be available to support human dose selection.	Extended single dose toxicity study (see footnotes c and d) in one species, usually rodent, by intended route of administration with toxicokinetic data, or via the *i.v.* route. A maximum dose of 1000-fold the clinical dose on a mg/kg basis for *i.v.* and mg/m² for oral administration can be used.	Genotoxicity studies are not recommended, but any studies or SAR assessments conducted should be included in the clinical trial application. For highly radioactive agents (e.g. PET imaging agents), appropriate PK and dosimetry estimates should be submitted.
Approach 2: Total cumulative dose ≤ 500 µg, maximum of 5 administrations with a washout between doses (6 or more actual or predicted half-lives) AND each dose ≤ 100 µg AND each dose ≤ 1/100th of the NOAEL and ≤ 1/100th of the pharmacologically active dose	Maximal daily and starting doses can be the same, but not exceed 100 µg.	*In vitro* target/receptor profiling should be conducted Appropriate characterization of primary pharmacology (mode of action and/or effects) in a pharmacodynamically relevant model should be available to support human dose selection.	7-day repeated-dose toxicity study in one species, usually rodent, by intended route of administration with toxicokinetic data, or via the *i.v.* route. Hematology, clinical chemistry, necropsy, and histopathology data should be included. A maximum dose of 1000-fold the clinical dose on a mg/kg basis for *i.v.* and mg/m² for oral administration can be used.	Genotoxicity studies are not recommended, but any studies or SAR assessments conducted should be included in the clinical trial application. For highly radioactive agents (e.g. PET imaging agents), appropriate PK and dosimetry estimates should be submitted.

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ICH guideline M3(R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals

Footnotes Table

- General toxicity studies should be conducted **according to GLP regulations**.
- Generally, extended single dose toxicity studies should be designed to **evaluate hematology, clinical chemistry, necropsy, and histopathology data** (control and high dose only if no treatment-related pathology is seen at the high dose) after a single administration, with further evaluations conducted 2 weeks later to assess delayed toxicity and/or recovery. The usual design for rodents consists of 10 animals/sex/group to be assessed on the day following dosing, and 5 animals/sex at the dose level(s) selected to be assessed on day 14 post-dose. The usual design for non-rodents consists of 3/sex/group for all groups on day 2 and 2/sex for the dose level(s) assessed on day 14.
- A single dose level to assess reversibility/delayed toxicity on day 14 can support the microdose approach. The dose level used need not be the high dose but should be a dose that is at least 100 times the clinical dose.

→ High costs involved > 50.000 Euro

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Toxicity studies with RP`s – a risk based approach

Kozlorowski et al. EJNMMI Radiopharmacy and Chemistry (2016) 1:1
DOI 10.1186/s41181-016-0004-6

EJNMMI Radiopharmacy and Chemistry
a SpringerOpen Journal

POSITION PAPER Open Access

Position paper on requirements for toxicological studies in the specific case of radiopharmaceuticals

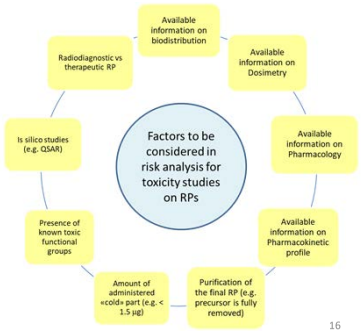
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 15 November 2018
2 EMA/CHMP/SWP/686140/2018
3 Committee for Medicinal Products for Human Use (CHMP)

4 Guideline on the non-clinical requirements for
5 radiopharmaceuticals
6 Draft

Draft agreed by Safety Working Party	October 2018

New EMA Guideline for non-clinical evaluation of radiopharmaceuticals



16

Reduced non-clinical testing of the non-radioactive part of the RP can be considered

- Radionuclide is changed in a radiopharmaceutical with known clinical evidence (trials or MA) e.g. [^{68}Ga]Ga-DOTATOC Ga-68 replaced by copper-61)
- Radionuclide added to a known non-radioactive pharmaceutical (e.g. [^{18}F]fluoroestradiol to estradiol)
- Minimal change of the non-radioactive part: small change in amino acid sequence….

→A flexible targeted approach to identify gaps in the safety information, reduced programme (no animal testing, focussed testing on organs of interest….)

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Scenarios described

- known or minimally changed non-radioactive part of a new radiopharmaceutical
- new radiopharmaceutical using microdose (<100µg with flexibility when MW is high)
- new radiopharmaceutical using single sub-pharmacological or pharmacologically active doses
- radiopharmaceuticals using multiple dosing

→Recommendations for Pharmacology, Pharmacokinetics, Toxicology and genetoxicity „non-clinical study requirements“

18

GLP

- It is recognized that GLP are not of concern for the RPs themselves
- However, GLP apply to the non radioactive part of the RP
- Non conformity to GLP may be acceptable, but it has to be justified
- Compliance with GLP is not strictly necessary in the US, where other approaches (e.g. within university or hospital labs) are allowed

19

A PRACTICAL EXAMPLE

Clinical translation of theranostic radiopharmaceuticals: Current regulatory status and recent examples

Petra Kolenc Peitl[1] | Christine Rangger[2] | Piotr Garnuszek[3] | Renata Mikolajczak[3] | Alicja Hubalewska-Dydejczyk[4] | Theodosia Maina[5] | Paola Erba[6] | Clemens Decristoforo[7]

Data	Purpose	Example of CP04
Pharmacology	In vitro binding affinity	Binding affinities were evaluated in surgically resected human tumor tissues. IC_{50}: CP04 = 1.8 ± 1.2, [^{nat}In]-CP04 = 2.5 ± 1.4 nM
	Internalization rate	AR42J cell lines; after 4-h incubation, 37°C, 5% CO_2; expressed in percentage of injected activity per million cells: 8.9 ± 1.3
Pharmacokinetics	In vitro stability, protein binding, lipophilicity	Stability in human serum: (175 ± 71) h Ca. 10% logD = −3.9
	In vivo biodistribution/ imaging	1. Lewis male rats implanted subcutaneously AR42J tumor cells: (1.24 ± 0.43) % IA/g, tumor/kidney = 1.12, (4 h p.i.) 2. SCID mice bearing A431-CCK2R(+/−) xenografts: (9.24 ± 1.35)) % IA/g, 1.66 (4 h p.i.)
Toxicity	Dosimetry study (biodistribution)	Expected equivalent human absorbed doses of ^{111}In-CP04 based on two models for translating mouse to human data would be 0.045 mSv/MBq (9.9 mSv at planned dose of 220 MBq of ^{111}In-CP04).
	Acute toxicity	Mice; LD^{50} (mouse): Greater than 178.5 µg/kg body weight
	Extended single dose toxicity	Rats; 89 µg/kg can be considered the NOAEL

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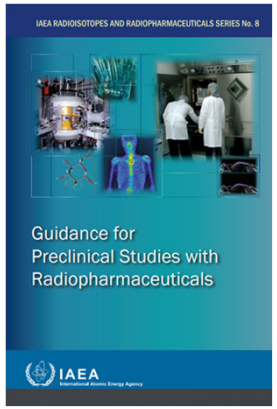
Technical basis for non-clinical studies



Content

- General Considerations
- In vitro testing
- In vivo, ex vivo testing
- Toxicology
- Dosimetry
- Data reporting & management
- Facility requirement
- QA&QC
- Protocols

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Professional Guidelines in relation to non-clinical testing of RPs - examples

- EANM guideline for harmonisation on molar activity or specific activity of radiopharmaceuticals: impact on safety and imaging quality (2021)
- EANM Position paper on requirements for toxicological studies in the specific case of radiopharmaceuticals (2017)
- EANM Guidelines to PET measurements of the target occupancy in the brain for drug development (2016)
- EANM Guideline to Regulations for Radiopharmaceuticals in Early Phase Clinical Trials in the EU (2008)
- EANM position paper on the role of radiobiology in nuclear medicine (2021)
- IAEA Guidance for preclinical studies with radiopharmaceuticals

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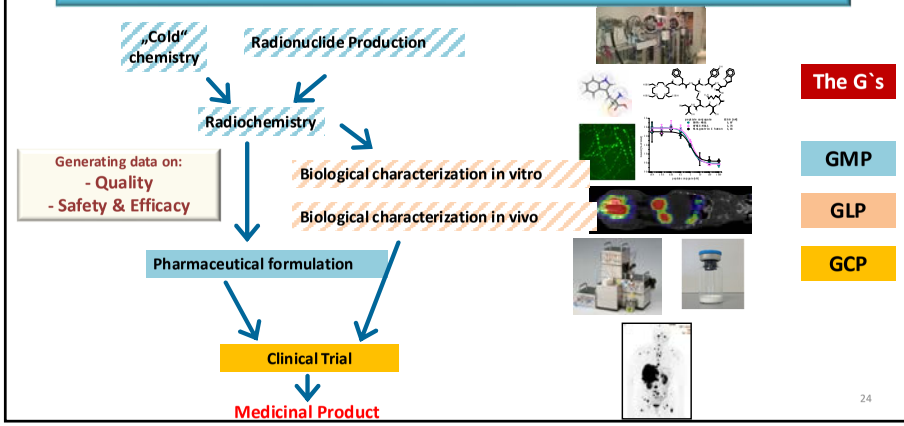
Many other guidelines – not specific for RPs, but relevant - example

CHMP/SWP/28367/07: **"Guideline on strategies to identify and mitigate risks for first in human and early clinical trials with investigational medicinal products"**

- **Quality aspects**: Strength and potency, qualification of materials, reliability of small doses
- **Non clinical aspects**: Relevance of the animal model, nature of Target, Pharmacodynamic, Pharmko- and toxicikinetics, safety pharmacology, toxicology
- **Dosing selection** for FIH

23

Regulatory Traps in RP development on their way to the patient



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Guidance in the regulatory requirements

Springer Open

EJNMMI Radiopharmacy and Chemistry

About | Articles | Submission Guidelines

Review | Open Access | Published: 19 July 2022

Practical considerations for navigating the regulatory landscape of non-clinical studies for clinical translation of radiopharmaceuticals

Aruna Korde, Renata Mikolajczak, Petra Kolenc, Penelope Bouziotis, Hadis Westin, Mette Lauritzen, Michel Koole, Matthias Manfred Herth, Manuel Bardiès, Andre F. Martins, Antonio Paulo, Serge K. Lyashchenko, Sergio Todde, Sangram Nag, Efthimis Lamprou, Antero Abrunhosa, Francesco Giammarile & Clemens Decristoforo

EJNMMI Radiopharmacy and Chemistry 7, Article number: 18 (2022) | Cite this article

1847 Accesses | Metrics

IAEA

Outcome of an IAEA TM in Coimbra, Portugal November 2021

25

Thank you for your attention

26

The small scale preparation of radiopharmaceuticals

Clemens Decristoforo

Innsbruck, Austria

1

A common legal framework for radiopharmaceuticals in Europe

European Union

Council of Europe

PUBLIC HEALTH

EUDRALEX

Directive 2001/20/EC → "Clinical Trial Directive"
Directive 2001/83/EG → Qualified Person, ...
Directive 2003/94/EG → GMP Annex 13 (IMP`s)
Directive 2004/27/EC → API according to GMP
Directive 2005/28/EC → GCP / Authorization for IMP
CHMP/SWP/28367/2007 → First in human clinical trial guideline (EMEA)
Regulation (EC) No 1394/2007 → Advanced therapy regulation

PhEur edqm

EUROPEAN MEDICINES AGENCY

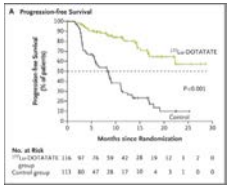
Reality in Europe:
Extreme Diversity

2

Major breakthrough in NM based on initial use of in-house preparations

Somatostatin analogs

- Based on pioneering work in **NL, I**, DACH
- Data on safety and efficacy from clinical data generated based on in-house prepared radiopharmaceuticals
- Not possible in E, F, UK and....
- Major restriction been implemented esp. in I



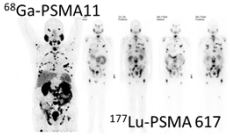
- Directly into Phase III trial to reach MA for Lutathera
- Rapid approval of ^{68}Ga-analogs

Clinically available in DACH since 20 years
In F, E since 5 years

Strosberg et al., N Engl J Med 2017; 376:125-135

Regulatory environment essential for development and access for patients

PSMA ligands



- First clinical efficacy data based on in-house preparations in many centres
- Accelerating marketing authorization for both diagnosis and therapy

3

Common European standards for the preparation of radiopharmaceuticals?

Country A

Full GMP preparation of ^{99m}Tc-adiopharmaceuticals

Country B
„ On the bench“ preparation

→Same Quality/Safety?
→ Same Costs?

4

Common Responsibilities…?

- Responsible for preparation and release
  - Qualified Person (as defined in Dir 2001/83/EC)
  - Pharmacist
  - Hospital Pharmacist
  - Radiopharmacist
  - Chemist/Radiochemist
  - Physician
  - Don`t know

5

Regulatory basis for the use of (Radio)Pharmaceuticals within the EU

Marketing Authorization	Clinical Trial	„Extemporaneous Preparation", Compounding
• Directive 2001/83 EC ("Pharmaceutical Directive")	• Regulation EU No 536/2014 („Clinical Trials Regulation")	• National legislation

Lutathera®
SOMAKIT TOC ®
LOCAMETZ®, Pluvitco ®

PUBLIC HEALTH

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Harmonization from 2022

6

Exceptions from Directive 2001/83/EC relevant for in-house preparation

Non-industrial practices

This Directive shall apply to medicinal products for human use intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process.

Practice of Pharmacy

Article 3

This Directive shall not apply to:

1. Any medicinal product prepared in a pharmacy in accordance with a medical prescription for an individual patient (commonly known as the magistral formula).

2. Any medicinal product which is prepared in a pharmacy in accordance with the prescriptions of a pharmacopoeia and is intended to be supplied directly to the patients served by the pharmacy in question (commonly known as the officinal formula).

Licensed Kits/Gen/RN

Article 7

A marketing authorization shall not be required for a radiopharmaceutical prepared at the time of use by a person or by an establishment authorized, according to national legislation, to use such medicinal products in an approved health care establishment exclusively from authorized radionuclide generators, kits or radionuclide precursors in accordance with the manufacturer's in

Physician's individual treatment

Article 5

1. A Member State may, in accordance with legislation in force and to fulfil special needs, exclude from the provisions of this Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised health-care professional and for use by an individual patient under his direct personal responsibility.

7

Exceptions from Clinical Trial regulation 536/2014 relevant for in-house preparation

Article 61
Manufacturing and import authorisation
1. The manufacturing and import of investigational medicinal products in the Union shall be subject to the holding of an **authorisation**.

Article 63
Manufacturing and import
1. Investigational medicinal products shall be manufactured in applying manufacturing practice which ensures the quality of such medicinal products in order to safeguard subject safety and the reliability and robustness of clinical data generated in the clinical trial (hereinafter '**good manufacturing practice**').

No GMP and manufacturing authorization for diagnostic RPs

Paragraph 1 **shall not apply to** any of the following processes:

preparation of radiopharmaceuticals used as diagnostic investigational medicinal products where this process is carried out in **hospitals, health centres or clinics**, by pharmacists or other persons legally authorised in the Member State concerned to carry out such process, and if the investigational medicinal products are intended to be used exclusively in hospitals, health centres or clinics taking part in the same clinical trial in the same Member State

8

What is Preparation?

Pharmaceutical preparations

04/2013:2619

PHARMACEUTICAL PREPARATIONS

Pharmaceutica

INTRODUCTION

This monograph is intended to be a reference source of standards in the European Pharmacopoeia on active substances, excipients and dosage forms, which are to be applied in the manufacture/preparation of pharmaceuticals, but not a guide on how to manufacture as there is specific guidance available covering methods of manufacture and associated controls.

Definition:

Preparation (of an unlicensed pharmaceutical preparation):
the „manufacture" of unlicenced pharmaceutical preparations by or at the request of pharmacies or other healthcare establishments (the term „preparation" is used instead of „manufacture" in order to clearly distinguish it from the industrial manufacture of licensed pharmaceutical preparations).

- Extemporaneous preparations, individually prepared for a specific patient or patient group.
- Stock preparations, prepared in advance and stored until a request for supply is received.
- **Production must take place within the framework of a suitable quality system and based on ethical considerations and risk assessment**
- Licensed prep's comply with requirements of their license.

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What is Preparation?

GMP Annex 3

"Preparation: handling and radiolabelling of kits with radionuclide eluted from generators or radioactive precursors within a hospital. Kits, generators and precursors should have a marketing authorisation or a national licence".

"Manufacturing: production, quality control and release and delivery of radiopharmaceuticals from the active substance and starting materials".

„Preparation of radiopharmaceuticals in radiopharmacies (hospitals or certain pharmacies), using Generators and Kits with a marketing authorisation or a national licence, is not covered by this guideline, unless covered by national requirement."

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When should in-house preparation be allowed?

Rulings of the **European Court of Justice**:

- Joint cases C-544/13 and C-545/13 Abcur v Apoteket
- C-535/11 Novartis v Apozyt [2013].
- 10 C-185/10 Commission v Poland [2012]

Specifying when "Magistral Preparation" applies
What means „Placing on the market"?
When is a manufacturing authorisation needed?
When do exemptions for MA apply?

Council of Europe:

- Adoption of Resolution CM/Res AP(2011)13 by the Committee of Ministers of the Council of Europe in 2011
- Signed by 36 member states
- Supports "Centralized Pharmacy Practice"
- Risk assessment to define Standards of Quality ("full GMP" (manufacturing) or PIC/S Guide for healthcare establishment)
- Risk matrix based on frequency, distribution, batch size,

Original article

Legislation on the preparation of medicinal products in European pharmacies and the Council of Europe Resolution

H PA Scheepers,[1] J Langedijk,[2] V Neerup Handlos,[3] S Walser,[4] M H Schutjens,[5] C Neef[6,7]

Eur J Hosp Pharm 2017;24:224–229.

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PIC/s www.picscheme.org

- **PIC/S GUIDE TO GOOD PRACTICES FOR THE PREPARATION OF MEDICINAL PRODUCTS IN HEALTHCARE ESTABLISHMENTS (March 2014)**

Apply to the preparation of medicinal products normally performed by healthcare establishments
"....for direct supply to patients"

Annex 1: GUIDELINES ON THE STANDARDS REQUIRED FOR THE STERILE PREPARATION OF MEDICINAL PRODUCTS

Annex 3: GOOD PRACTICES FOR THE PREPARATION OF RADIOPHARMACEUTICALS IN HEALTHCARE ESTABLISHMENTS

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edqm European Directorate for the Quality of Medicines & HealthCare

General Chapter „Exptemporaneous preparation of Radiopharmaceuticals“


EUROPEAN PHARMACOPOEIA 8.7 — 5.19. Extemporaneous preparation of radiopharmaceuticals

04/2016:51900

5.19. EXTEMPORANEOUS PREPARATION OF RADIOPHARMACEUTICALS

This general chapter is published for information.

1. SCOPE AND DEFINITION

Many radiopharmaceuticals are prepared on-site on a regular basis, typically as doses for a few patients based on specific clinical needs (extemporaneously prepared radiopharmaceuticals, EPRs). Whereas the manufacture of radiopharmaceuticals and investigational medicinal products is well covered by existing regulations, this general chapter only covers EPRs, which are also to be considered in the light of any national competent authority requirements. Radiopharmaceuticals are pharmaceutical preparations, and the provisions and terminology of the general monograph *Pharmaceutical preparations (2616)* apply.

EPRs are either prepared in accordance with a medical prescription for an individual patient, or in accordance with a pharmacopoeial monograph, and intended to be supplied directly to patients. The radiopharmaceuticals concerned are used within their specified expiration time, and include both kit-based preparations (from licensed and unlicensed kits) and unlicensed preparations containing radionuclides for positron emission tomography (PET), single photon

– environmental monitoring;
– appropriate documentation;
– procurement of materials and services used in the preparation;
– analytical methods / quality control.

All steps in the preparation of radiopharmaceuticals are designed to meet the radiation safety requirements for the personnel involved and the environment, thereby complying with national or international regulations. This includes appropriate shielding, and measures to avoid and monitor radioactive contamination.

2. PREMISES AND EQUIPMENT

The relevant premises and equipment are designed, built, maintained, cleaned and sanitised so that they protect product quality, ensure a low level of particulates and microbial contamination and protect staff and the environment from the effects of radiation.

Radiopharmacies may characteristically prepare a wide variety of radiopharmaceuticals, often in the same session and place. The premises, equipment and workflow are arranged in order to minimise the risk of cross-contamination and mix-up. Facilities and equipment are designed and controlled to reflect the specific risk of all preparations concerned, taking into account the potential for microbial contamination of the preparation. Additional considerations are taken into account when handling biological material.

Pharm Eur Supplement 8.7

Ph.Eur. 5.19

Legal status

Is the Pharmacopeia „hard“ or soft law?

MONO-GRAPH → Legally Binding

GENERAL CHAPTER → NOT legally binding

GENERAL CHAPTER → ONLY binding if cited in a monograph

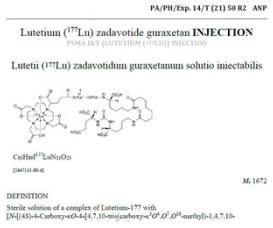
Extemporaneous preparation of radiopharmaceuticals (5.19.)

..extemporaneously prepared radiopharmaceuticals are either **prepared in accordance with a medical prescription for an individual patient**, or prepared **in accordance with a monograph** of a pharmacopoeia and **intended to be supplied directly to the patients**.

.....and include **kit-based preparations** (from licensed and unlicensed kits) and **unlicensed preparation**s containing radionuclides for positron emission tomography (**PET**), single photon emission computed tomography **SPECT**) or **therapeutic** applications.

„...in accordance with a monograph“

Specific Monograph ^{177}Lu-PSMA I&T (2024)


PA/PH/Exp. 14/T (21) 50 R2 ANP

Lutetium (^{177}Lu) zadavotide guraxetan INJECTION

Lutetii (^{177}Lu) zadavotidum guraxetanum solutio iniectabilis

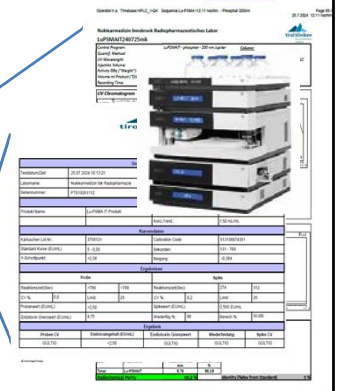
$C_{68}H_{87}{}^{177}LuN_{12}O_{23}$

M_r 1672

DEFINITION

Sterile solution of a complex of Lutetium-177 with [N-[(4S)-4-Carboxy-w-O-4-[4,7,10-tris[carboxy-w^{2}O^{4},O^{7},O^{10}-methyl]-1,4,7,10-

Batch Protocol (Auszug)


Universitätsklinik für Nuklearmedizin

Ausgeführte QC

QC Beschreibung	QC Ausführung	QC-Ergebnis
Volumen (10-25 ml)	25.07.2024 10:07	17,00
pH (5-7)	25.07.2024 10:10	6,00
ITLC: Natriumcitrat: freies Lu-177 (<1%)	25.07.2024 10:22	0,07
ITLC: NH4 Acetat/MeOH: Radiokolloid (<2%)	25.07.2024 10:22	0,12
HPLC: Probenvolumen (pbichenweise 5 µl)	25.07.2024 10:10	5,00
HPLC: Radiochemische Reinheit (>95%)	25.07.2024 10:32	98,29
HPLC: Identität Peak (+15% Abw. Standard)	25.07.2024 10:32	Ok
HPLC: Precursor-Menge µg/GBq (<20 µg/GBq)	25.07.2024 10:32	11,09
Endotoxingehalt (<8,75 EU/ml)	25.07.2024 10:32	<2,5
Medaffil ansetzen und inkubieren	25.07.2024 10:10	Ok
Syntheseparameter (Aktivität Rx/SP, Temp.) im Trend	25.07.2024 10:10	Ok
Filtertest durchgef. (identische Kurven, Plateau > 1 bar)	25.07.2024 10:10	Ok
Berichte (Kassettentest, Synthese, Filtertest) abgelegt	25.07.2024 10:10	Ok
Abwechung/OOS	25.07.2024 10:33	nein
Präliminäre Freigabe	25.07.2024 10:33	Ok
Gaschromatographie: Ethanol-Gehalt (<10%)		

General Guidelines for in-house preparation

Gillings et al. EJNMMI Radiopharmacy and Chemistry (2021) 6:8
https://doi.org/10.1186/s41181-021-00123-2
EJNMMI Radiopharmacy and Chemistry

GUIDELINE ARTICLE Open Access

Guideline on current good radiopharmacy practice (cGRPP) for the small-scale preparation of radiopharmaceuticals

Nic Gillings[1*], Olaug Hjelstuen[2], Jim Ballinger[3], Martin Behe[4], Clemens Decristoforo[5], Philip Elsinga[6], Valentina Ferrari[7], Petra Kolenc Peitl[8], Jacek Koziorowski[9], Peter Laverman[10], Thomas L. Mindt[11], Oliver Neels[12], Meltem Ocak[13], Marianne Patt[14] and Sergio Todde[15]

- Limited number of staff, responsible person definition
- Limited size: Same room may be used for multiple purposes
- Patient individual, high variety: Control of starting materials,..
- Quality assurance in controlled areas (high radioactivity): sterile filtration, in-process controls, labels,…. *Risk assessment*

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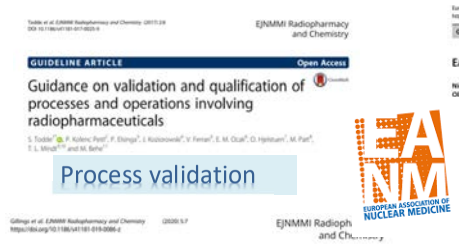
More detailed guidelines for in-house preparation



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Personel

Directive 2001/83/EC → Qualified Person → Pharmaceutical Industry

EANM Initiative
"Responsible Person for Preparation of RP"

- Need for specific training and knowledge to be qualified for the preparation of Radiopharmaceuticals
- Different from „Conventional" Pharmaceuticals
- Very small number of professionals

The EANM- Radiopharmacy and Radiopharmaceutical Chemistry Certificate

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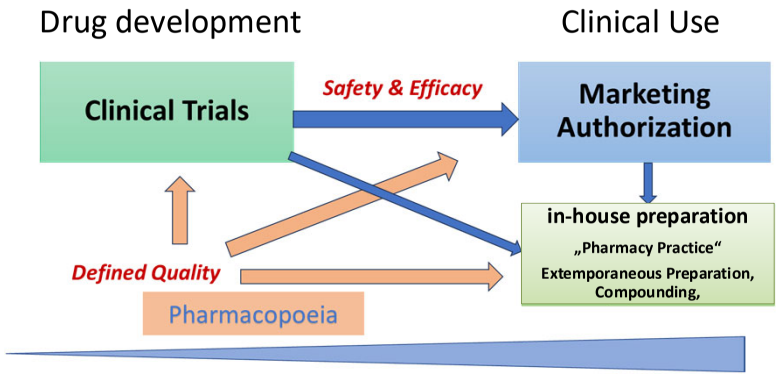
Regulatory basis for the development and use of (Radio)Pharmaceuticals

Pharmaceutical Legislation



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Thank you for your attention
tirol kliniken

Discussion

The small scale, non commercial preparation of radiopharmaceuticals

What are your regulations?

Clemens Decristoforo

Old concept

The „Isotope Pharmacy“ Concept

Denmark: small country, few specialists

- Distribution of radiopharmaceuticals through a central, authorized unit with qualified radiopharmacists (Pharmacy) responsible for the quality of the RP

Limited use for short lived radiopharmaceuticals (PET)

Specific regulations in the UK

- In the UK, RP without MA can be prepared for clinical use either:
  - Under the direct supervision of a registered pharmacist (in a **pharmacy**, if used locally), or
  - Under a **„Specials“ Manufacturing Licence** issued by the Medicines and Healthcare Products Regulatory Agency (MHRA, equivalent of FDA)

- „Named patient“ basis requiring prescription of physician
- No upper limit on number of administrations
- No official monograph required but manufacture must comply with GMP

Extending Magistral Preparations outside the Pharmacy

Specific regulations on the in-house preparation - Germany

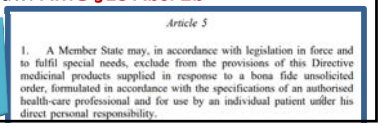
AmRadV: *RP without MA may be used for clinical application*

- *when prepared in clinical, authorized institution („Herstellungserlaubnis“ = Manufacturing Authorization)*
- *(only for diagnostic applications)*
- *if not used more than 20x per week*
- *when prepared under current scientific knowledge (cGMP)*

→ Inspectors have released specific interpretations of GMP (ZLG Memoire)

Medical Doctor can prepare RPs under his own responsibility following „the state of the art“ (GMP?), exemption in German drug law: **AMG §13 Abs. 2b**

Physician`s individual treatment



Article 5

1. A Member State may, in accordance with legislation in force and to fulfil special needs, exclude from the provisions of this Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised health-care professional and for use by an individual patient under his direct personal responsibility.

Radiopharmacy specific legislation in Italy

Farmacopea Ufficiale-Addendum:
NORME DI BUONA PREPARAZIONE DEI RADIOFARMACI PER MEDICINA NUCLEARE
(came into force in 2011)
NM departments can prepare RPs based on European Pharmacopeia monograph following these rules

Decreto Legislativo 6 novembre 2007
Laboratories from the public health system might prepare "experimental radiopharmaceuticals" out of industrial GMP if they follow the Good Radiopharmaceutical Practices of the Italian Pharmacopoeia

Extending Officinal Preparations and exemption from Manufacturing Authorization

5

Radiopharmaceuticals in Spain

- No magistral/officinal preparation for i.v. allowed
- Radiopharmacies only allowed to prepare radiopharmaceuticals *from* licensed kits and generators/radionuclides

Restrictive interpretation of access to unlicensed Medicines

Products without MA only be used :
- within a Clinical Trial

Or:
- PET radiopharmaceuticals under the following conditions

- Prepared in the authorised radiopharmacy units with non-profit use and in centres linked to the National Health System.
- established clinical and quality data (or CT application approved):
- Submission of a extensive dossier
- Full GMP inspectio

6

Some other national specifics

- Radiopharmaceuticals in hospitals under the responsibility of hospital (radio)pharmacist
- Radiopharmacist`s specialisation
- EANM GRPP for in-house preparation

- **Lets ask**

7

No specific exemptions

Use of Radiopharmaceutical only

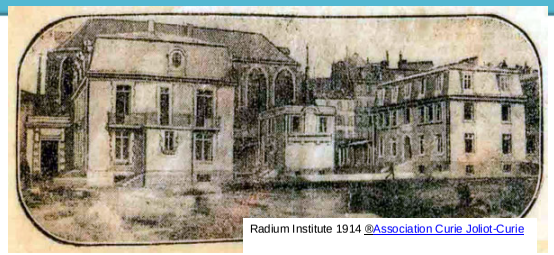
- Based on marketing authorization
- Within approved clinical trials

- No excemption

and……

8

- Is marketing authorisation always required?
- On which basis can radiopharmaceuticals be used without marketing authorisation and outside clinical trials?
- Do I have to follow GMP?



Radium Institute 1914 @Association Curie Joliot-Curie

→ What is the situation in your country?

9

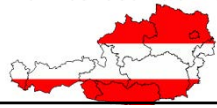
Radiopharmaceuticals in the Austrian Pharmaceutical Legislation

-1989 first time included in the legislation

- Strong lobbying of the Austrian Society of Nuclear Medicine in the implementation phase (Orgis, Füger)

Resulting in several specific Exemptions in relation to Radiopharmaceuticals

-Exemptions from Marketing Authorisation (Ministerial approval for distribution when there is a monograph, Import from unlicensed RPs from abroad)



AND….

10

Specific Exemption for Radiopharmaceuticals from Manufacturing Authorization

§62: For Manufacturing Sites of Pharmaceuticals Operating Regulations have to be in place (implementing **Manufacturing Authorization, Inspection** and **GMP requirement**)

No manufacturing sites are:

- Pharmacies
- Army
- **Nuclear Medicine Institutes or Labs** Preparing **Radiopharmaceuticals for immediate use**…….
- …….

So…… No GMP??

11

GMP or non-GMP…. Are we the only ones?

Pharmaceutical Preparation and Manufacturing requirements in the Austrian Legislation

- Arzneimittelbetriebsverordnung AMBO → Industrial Manufacturing, „full GMP“
- Apothekenbetriebsordnung → Pharmacy Practice

To decide

Risk Analysis Scheme of the Austrian Competent Authority

Based on: Distribution, Formulation, Process, Batch Size, Risk of Drug Substance
In analogy to the Council of Europe Resolution CM/Res AP(2011)13

12

Further Reading

- Decristoforo C, Mikolajczak R, et al. To be GMP or not to be- a radionuclide's question. EJNMMI Radiopharm Chem. 2025 Jul 10;10(1):42. doi: 10.1186/s41181-025-00369-0.
- Moya E, Cerrato C, Bedoya LM, Guerra JA. Radiopharmaceutical small-scale preparation in Europe: will we be able to harmonize the situation? EJNMMI Radiopharm Chem. 2024 Sep 5;9(1):64. doi: 10.1186/s41181-024-00281-z.
- Estrella Moya Sánchez. Quality in Non-Licensed Radiopharmaceutical Products: Are We Achieving the Goal? 2021 DOI: 10.5772/intechopen.99388
- Justyna Pijarowska-Kruszyna et al. Radiopharmaceutical Precursors for Theranostics 2021 DOI:10.5772/intechopen.95438
- Clemens Decristoforo & Serge K. Lyashchenko. Radiopharmaceutical legislation, In: Nuclear Medicine and Molecular Imaging Volume 1, 2022, Pages 274-279
- Neels O, Patt M, Decristoforo C. Radionuclides: medicinal products or rather starting materials. EJNMMI Radiopharm Chem. 2019 Aug 20;4(1):22. doi: 10.1186/s41181-019-0074-3
- Korde A et al. Practical considerations for navigating the regulatory landscape of non-clinical studies for clinical translation of radiopharmaceuticals. EJNMMI Radiopharm Chem. 2022 19;7(1):18. doi: 10.1186/s41181-022-00168-x.
- Schwarz SW & Decristoforo C. US and EU radiopharmaceutical diagnostic and therapeutic nonclinical study requirements for clinical trials authorizations and marketing authorizations. EJNMMI Radiopharm Chem. 2019 May 22;4(1):10. doi: 10.1186/s41181-019-0059
- Decristoforo C, Penuelas I, Patt M, Todde S. European regulations for the introduction of novel radiopharmaceuticals in the clinical setting. Q J Nucl Med Mol Imaging. 2017 Jun;61(2):135-144. doi: 10.23736/S1824-4785.17.02965-X.

GMP of PET radiopharmaceuticals

Susanne Geistlich, MPharm is RP and head of QA at the Center for Radiopharmaceutical Sciences at Paul Scherrer Institute (PSI) and ETH Zurich, Switzerland. She is responsible for the manufacture of PET- and therapeutic radiopharmaceuticals at both these sites. The sites operate in an academic setting and make available novel radiopharmaceuticals for clinical trials be it from own research of the institutions or in co-operation with industry partners. Lately the manufacture of Formula Products for patients of nearby nuclear medicines clinics became of interest, too. The ETH GMP lab has access to the on-site medical cyclotron and focuses on ^{18}F PET tracers whereas the PSI GMP lab specializes in the manufacture and distribution of labeled peptides with ^{68}Ga for diagnosis or ^{177}Lu and recently also ^{161}Tb for therapy. The studies range from first-in-human trials to phase II studies, commercial manufacture is out of scope of these labs. She holds an EANM Certificate as Radiopharmacist.

Before joining the Schibli lab at PSI / ETHZ she was a RP in a small pharmaceutical enterprise where she gained a broad understanding of pharmaceutical rules and regulations, pharmaceutical manufacture including distribution and marketing authorization procedures.

The lecture has the following learning objectives:

1. Students gain an over-sight and understanding of regulations /guidance resources to be considered in the manufacture of non-kit radiopharmaceuticals. They are able to select the relevant guidance.
2. Students understand where GMP starts in the manufacture of non-kit radiopharmaceuticals.
3. They know important GMP elements for the manufacture of non-kit radiopharmaceuticals and the role of risk analysis in the life cycle of a drug product.
4. Students know about the frequent pitfalls towards batch release and strategies to improve process reliability.
5. Students understand specific provisions in the technical release of radiopharmaceuticals and associated risks.

Summary of the lecture:

PET GMP is the title of the lecture – what exactly is meant by it in regulatory terms?

In search of clarification, we find information in these published guidelines:

- EudraLex Vol.4, GMP I, Annex 3: Manufacture of Radiopharmaceuticals, Brussels, 01 September 2008
- EANM Radiopharmacy Committee, cGRPP-guidelines, version2 March 2007(§)

(§): superseded by the newest publication of 2021:

- Guideline on current good radiopharmacy practice (cGRPP) for the small-scale preparation of radiopharmaceuticals, EJNMMI Radiopharmacy and Chemistry volume 6, 2021
- 5.19. EXTEMPORANEOUS PREPARATION OF RADIOPHARMACEUTICALS, Pharm. Eur. 04/2016:51900

- PIC/S GUIDE TO GOOD PRACTICES FOR THE PREPARATION OF MEDICINAL PRODUCTS IN HEALTHCARE ESTABLISHMENTS, PE 010-4, 1 March 2014

Result: The cGRPP guidelines by EANM radiopharmacy committee of 2007 discriminated the *in-house* preparation of radiopharmaceuticals prepared from licensed kits on the one hand and PET radiopharmaceuticals on the other hand. In fact not only PET products were covered by the term PET radiopharmaceuticals, but also any radiopharmaceutical that was prepared in-house and NOT being a licensed kit. The latest version of these guidelines published in 2021 covers the *small-scale preparation* of radiopharmaceuticals using licensed generators and kits and the *more complex preparation of small-scale radipharmaceutical products (SSRP) from non-licensed starting materials, often requiring a purification step and sterile filtration"*.

In parallel, there is also the relatively new monograph 04/2016:51900 of the Pharm. Eur., which covers "both kit-based preparations (from licensed and unlicensed kits) and unlicensed preparations containing radionuclides for positron emission tomography (PET), single photon emission computed tomography (SPECT) or for therapeutic applications". These products are "prepared on-site on a regular basis, typically as doses for a few patients based on specific clinical needs (extemporaneously prepared radiopharmaceuticals, EPRs)". On-site preparation here refers to healthcare establishments.

Whenever radiopharmaceuticals are manufactured in a commercial, industrial scale or for clinical trials, then EudraLex Vol.4 guidelines do apply.

<u>Where does GMP start for the materials/processes applied in the manufacture?</u>

These are the guidance resources that can help in the clarification:

- EudraLex Vol.4, GMP II
- EudraLex Vol.4, GMP I, Annex 3: Manufacture of Radiopharmaceuticals, Brussels, 01 September 2008

Active Pharmaceutical Ingredients (API) must be manufactured under GMP, i.e. compliant with EudraLex Vol.4 GMP II in a site having a GMP license. PET drug manufacture is a continuous process that usually starts in the late stage of API manufacture and the chemical precursor is not necessarily the API starting material when all steps of the precursor synthesis are considered. A possible decision about the GMP entry point will be discussed in the lecture on the example of an ^{18}F-PET tracer manufactured for clinical trials.

Very recently, the EU Clinical Trial Regulation No. 536/2014 became finally applicable and will have effects on manufacturers of radiopharmaceuticals for clinical trials – no manufacturing license should be needed for diagnostic RPs under certain conditions. Also it is stated that there is no GMP requirement for active substances of investigational medicinal products. It is not yet clear how these interesting new aspects will be put into practice.

<u>Important GMP elements</u>

The important GMP elements are easily found in the EudraLex GMP I and the PIC/S guide PE-010 where the main chapters have to be considered and also the relevant annexes, most prominently annex 1, 3, 8, 11, 15, 16 and 19, in case of Investigational Medicinal Products (IMPs) also consider

annex 13. These are very general guidelines and need to be put in practice considering e.g. the type of products, the scale of the manufacture, number of staff, age of equipment and regulatory category of products as well as local inspector's approach.

One very prominent and helpful tool to scale these general guidelines is Risk Assessment. Detailed guidance and a selection of risk assessment methods are found in ICH HARMONISED TRIPARTITE GUIDELINE QUALITY RISK MANAGEMENT Q9, 9 November 2005, *Annex I: Risk Management Methods and Tools*. Mind that basic GMP requirements, e.g. releasing all materials used for product manufacture cannot be waived by risk analysis. I will provide an example for risk assessment by FMEA (Failure Mode and Effects Analysis) in the lecture.

Most of the radiopharmaceuticals are injectable drugs and need to be sterile and non-pyrogenic. In order to guarantee each and every batch produced be sterile, multi-level preventive measures need to be in place. They involve facility and equipment design, staff members, selection of starting materials and sterile filters. Because the sterility test takes not less than 2 weeks, the result of the test is always too late to be considered for the release of the product but is still useful as process control.

Main benefit of applying GMP elements throughout the manufacture of medicinal products is providing high probability to yield compliant products. Process reliability is definitely a major issue of the manufacture of non-kit radiopharmaceuticals. Key factors are people, instruments, materials and root cause analysis to define effective CAPAs (Corrective and Preventive Action) whenever deviations or out-of-specification results occur. Supportive tools that use augmented reality features are currently in development and might improve total process reliability by easing training, providing expert technical support in real time and ultimately also prevent the operators from errors in critical steps of the production or quality control.

<u>Specific provisions when releasing radiopharmaceuticals:</u>

PET radiopharmaceuticals are of very short half-lives, which creates several difficulties towards a well-assessed, safe release of the products. Short and robust methods and well-trained operators are a precondition, especially for the HPLC method. Repetition in case of malfunction of the equipment or error of the operator may be crucial for releasing the product in its useful shelf life. Time for release is always short but all QC results, batch record and any deviation need be evaluated before release for application. Shipment to distant customers is often done in bond, i.e. QC and release are performed while the product is shipped. In case of OOS results, there need be measures in place to safely prevent the clinic from applying a non-conforming product. Written confirmation not having used the batch concerned is suggested.

It should be clearly defined what test results are evaluated for the conditional release. Post release tests are reported in the final release documents of the product.

If therapeutic products with longer half-lives are produced, e.g. ^{177}Lu-products, shipment in bond should be avoided whenever possible and the post release testing minimized.

<u>Take-Home messages:</u>

1) When planning GMP related actions always make sure to assess the regulatory status of the PRODUCT you intend to manufacture and identify the guidelines to consider.

2) If EudraLex Vol4. is applicable then also investigate precursor material and it's GMP status.
3) Risk assessment is important for all scales of production, also for small-scale. Make sure to use risk assessment also in case of changes and deviations. Make sure to keep risk analysis up-dated over the life cycle of a product or facility.
4) When something goes wrong and also if it goes almost wrong, investigate and try to find the root-cause to design effective CAPAs.
5) Training of staff and communication of important information to all staff is important to succeed frequently in the "just-in-time" mode of manufacture / preparation.
6) Robust methods and equipment are crucial in PET- and therapeutic products manufacture.
7) Shipment in bond needs solid agreements between manufacturer and customer to reliably being able to prohibit the application of the product.

PET GMP

Susanne Geistlich, Radiopharmacist and RP

POSTGRADUATE EUROPEAN RADIOPHARMACY COURSE / Module I Pharmacy
August 27, 2025

Learning Objectives

1. Know what regulations /guidance resources should be considered in the manufacture of non-kit radiopharmaceuticals
2. Understand where GMP starts in the manufacture of non-kit radiopharmaceuticals
3. Know important GMP elements for the manufacture of non-kit radiopharmaceuticals and the role of risk analysis in the life-cycle of a drug product
4. Pitfalls in the manufacture and prevention strategies
5. Releasing radiopharmaceuticals: about fundamental differences in comparison to standard pharmaceuticals

PET GMP – what is the relevant definition and guidance ?

PET Radiopharmaceuticals

- Definition:
  Positron Emission Tomography; emitters of ß⁺, annihilation, 511keV coincidence γ-rays for quantification of PET radiopharmaceutical distribution in the body

- Widely-used radionuclides / half-lives

^{18}F	110 min
^{11}C	20 min
^{68}Ga	68 min
^{13}N	10 min
^{15}O	2 min
^{82}Rb	75 sec

for clinical PET-tracer synthesis

In search of PET GMP definition / *EudraLex Volume 4 (I)*

Manufacture of Radiopharmaceuticals

Principle

The manufacture of radiopharmaceuticals shall be undertaken in accordance with the principles of Good Manufacturing Practice for Medicinal Products Part I and II. This annex specifically addresses some of the practices, which may be specific for radiopharmaceuticals.

Note i. Preparation of radiopharmaceuticals in radiopharmacies (hospitals or certain pharmacies), using Generators and Kits with a marketing authorisation or a national licence, is not covered by this guideline, unless covered by national requirement.

→ Preparation using **licensed** generators and kits is not covered by the Annex 3

PET Kit: SomaKit TOC (Dotatate; EMA: 08/12/2016) and Locametz (PSMA-11; EMA: 09/12/2022) / GalliaPharm (EZAG) & Galli Ad (IRE Elit)

Ref: EudraLex Volume 4, Annex 3 Manufacture of Radiopharmaceuticals, Brussels, 01 September 2008

In search of PET GMP definition / *EudraLex Volume 4 (II)*

3. This guideline is applicable to manufacturing procedures employed by industrial manufacturers, Nuclear Centres/Institutes and PET Centres for the production and quality control of the following types of products:

- Radiopharmaceuticals
- Positron Emitting (PET) Radiopharmaceuticals
- Radioactive Precursors for radiopharmaceutical production
- Radionuclide Generators

Type of manufacture	*Non - GMP **	*GMP part II & I (Increasing) including relevant annexes*			
Radiopharmaceuticals PET Radiopharmaceuticals Radioactive Precursors	*Reactor/Cyclotron Production*	*Chemical synthesis*	*Purification steps*	*Processing, formulation and dispensing*	*Aseptic or final sterilization*
Radionuclide Generators	*Reactor/Cyclotron Production*	*Processing*			

** Target and transfer system from cyclotron to synthesis rig may be considered as the first step of active substance manufacture.*

→ No separate, specific requirements for PET drugs

Ref: EudraLex Volume 4, Annex 3 Manufacture of Radiopharmaceuticals, Brussels, 01 September 2008

In search of PET GMP definition / current *EANM resources*

- → Guidelines
  - → Nomenclature
  - → Cardiovascular
  - → Central nervous system
  - → Musculoskeletal system
  - → Respiratory system
  - → Gastro-intestinal system
  - → Nephro-urinary system
  - → Endocrine system
  - → Oncology
  - → Inflammation/Infection
  - → Paediatric
  - → Therapy
  - → Dosimetry
  - → Physics, instrumentation & data analysis
  - → Radiopharmacy
  - → Preclinical and translational nuclear medicine

GUIDELINES

Radiopharmacy

- EANM guideline on quality risk management for radiopharmaceuticals (2022)
- EANM guideline for harmonisation on molar activity or specific activity of radiopharmaceuticals: impact on safety and imaging quality (2021)
- Guideline on current good radiopharmacy practice (cGRPP) for the small-scale preparation of radiopharmaceuticals (2021)
- EANM guideline on the validation of analytical methods for radiopharmaceuticals (2020)
- Guidance on validation and qualification of processes and operations involving radiopharmaceuticals (2017)
- Position paper on requirements for toxicological studies in the specific case of radiopharmaceuticals (2017)
- Guidance on current good radiopharmacy practice for the small-scale preparation of radiopharmaceuticals using automated modules: a European perspective (2014)

https://www.eanm.org/publications/guidelines/radiopharmacy/

In search of PET GMP definition / *EANM (2007)*

[redacted]

cGRPP-guidelines, version2 March 2007
EANM Radiopharmacy Committee

PART B. Guidelines on Current Good Radiopharmacy Practices (cGRPP) for Positron Emission Tomography (PET) and other Locally Prepared Radiopharmaceuticals*

** These guidelines are meant to cover the in house preparation of radiopharmaceuticals, which are not kit procedures and also the in house preparation of kits. For simplicity in the text they will collectively be covered by the term PET radiopharmaceuticals*

In search of PET GMP definition / *EANM (2021)*

Abstract

This guideline on current good radiopharmacy practice (cGRPP) for small-scale preparation of radiopharmaceuticals represents the view of the Radiopharmacy Committee of the European Association of Nuclear Medicine (EANM). The guideline is laid out in the format of the EU Good Manufacturing Practice (GMP) guidelines as defined in EudraLex volume 4. It is intended for non-commercial sites such as hospital radiopharmacies, nuclear medicine departments, research PET centres and in general any healthcare establishments. In the first section, general aspects which are applicable to all levels of operations are discussed. The second section discusses the preparation of small-scale radiopharmaceuticals (SSRP) using licensed generators and kits. Finally, the third section goes into the more complex preparation of SSRP from non-licensed starting materials, often requiring a purification step and sterile filtration. The intention is that the guideline will assist radiopharmacies in the preparation of diagnostic and therapeutic SSRP's safe for human administration.

Keywords: cGRPP, GMP, Radiopharmaceuticals, Radiopharmacy

Guideline on current good radiopharmacy practice (cGRPP) for the small-scale preparation of radiopharmaceuticals, EJNMMI Radiopharmacy and Chemistry volume 6, 2021

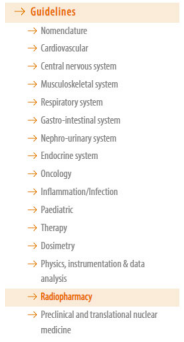
In search of PET GMP definition / *Summary*

What are the appropriate guidelines to consider?

1) Licensed Kits and Generators: EANM / national / not covered by EudraLex Vol 4
2) Establishment and customers:
   small scale and in-house (health care establishments) / not for clinical trial: EANM / EP / PIC/S / national
3) Small scale and for clinical trial: EudraLex Vol 4
4) Licensed products / industry: EudraLex Vol 4

This lecture is about (SS)RP from non-licensed starting materials that need sterile filtration; i.e. analytical method development and process validation are needed, too!
Therapeutic products are also covered.

Remember other helpful resources of EANM



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What are main differences of the EANM cGRPP vs EudraLex Vol.4?

Topic	EudraLex Vol.4	cGRPP
Legally binding	YES	NO, but close to PIC/S PE 010-4
GMP manufacturing license	YES	NO
Safety / radiation protection	NO	YES
Qualified person	YES	Responsible person for radiopharmaceuticals (RPR)
Independent QC/Production	YES, strictly	Reflecting small teams, exemptions possible
Aseptic work-space	Always grade A with B background, isolators	Grade A in C possible, grade C sterile filtration ok if assembly of unit was done in grade A
Sterility testing	All parenteral products	Not in case of "long-lived" isotope products, alternatives as e.g. process simulation
Release of starting materials	Every container to be tested for at least identity (all parenterals)	Visual and CoA-control, critical starting material released by test synthesis

ETH zürich

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Susanne Geistlich | 06.09.2023 | 14

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What are main differences of the EANM cGRPP vs EudraLex Vol.4?

Topic	EudraLex Vol.4	cGRPP
Legally binding	YES	NO, but close to PIC/S PE 010-4
GMP manufacturing license	YES	NO
Safety / radiation protection	NO	YES
Qualified person	YES	Responsible person for radiopharmaceuticals (RPR)
Independent QC/Production	YES, strictly	Reflecting small teams, exemptions possible
Aseptic work-space	Always grade A with B background, isolators	Grade A in C possible, grade C sterile filtration ok if assembly of unit was done in grade A
Sterility testing	All parenteral products	Not in case of "long-lived" isotope products, alternatives as e.g. process simulation
Release of starting materials	Every container to be tested for at least identity (all parenterals)	Visual and CoA-control, critical starting material released by test synthesis

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Where does GMP start?

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Where does GMP start? (I)

3. This guideline is applicable to manufacturing procedures employed by industrial manufacturers, Nuclear Centres/Institutes and PET Centres for the production and quality control of the following types of products:

- Radiopharmaceuticals
- Positron Emitting (PET) Radiopharmaceuticals
- Radioactive Precursors for radiopharmaceutical production
- Radionuclide Generators

Type of manufacture	*Non - GMP **	*GMP part II & I (Increasing) including relevant annexes*			
Radiopharmaceuticals PET Radiopharmaceuticals Radioactive Precursors	*Reactor/Cyclotron Production*	*Chemical synthesis*	*Purification steps*	*Processing, formulation and dispensing*	*Aseptic or final sterilization*
Radionuclide Generators	*Reactor/Cyclotron Production*	*Processing*			

** Target and transfer system from cyclotron to synthesis rig may be considered as the first step of active substance manufacture.*

Ref: EudraLex Volume 4, Annex 3 Manufacture of Radiopharmaceuticals, Brussels, 01 September 2008

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Where does GMP start (II)

Table 1: Application of this Guide to API Manufacturing

Type of Manufacturing	Application of this Guide to steps (shown in grey) used in this type of manufacturing				
Chemical Manufacturing	Production of the API Starting Material	Introduction of the API Starting Material into process	Production of Intermediate(s)	Isolation and purification	Physical processing, and packaging

Increasing GMP requirements

EudraLex Volume 4, GMP II Basic Requirements for Active Substances used as Starting Materials, Brussels, 13 August 2014

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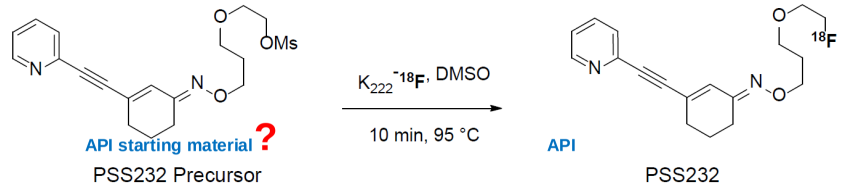
Example [^{18}F]F-PSS232 Manufacture (clinical trial medication)

The radiosynthesis of PSS232 is carried out by radiolabelling of the PSS232 precursor with fluorine-18. [^{18}F]Fluoride is obtained via the ^{18}O(p,n)^{18}F nuclear reaction by irradiation of a niobium target filled with [^{18}O]H_2O (98% enriched) using an in-house 18 MeV cyclotron. The product is isolated via HPLC and purified through a cartridge and finally immediately formulated for i.v. injection by passing the solution through a sterile filter.

An "Active Substance Starting Material" is a raw material, intermediate, or an active substance that is used in the production of an active substance and that is incorporated as a significant structural fragment into the structure of the active substance. An Active



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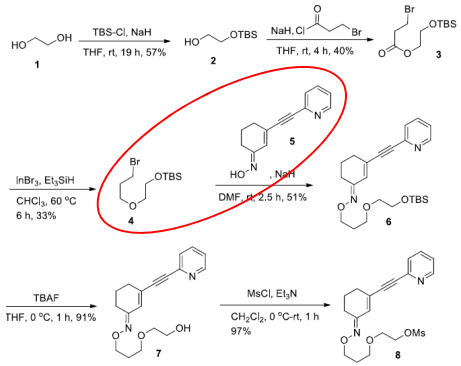
PSS232 Precursor Manufacture



What
- Expensive
- Labor intensive
- What is the benefit in terms of patient safety?
- Low mass product without pharmacological effect
- Precursor is well-characterized small molecule
- There is preparative HPLC purification of API and specs for chemical purity of Precursor.

⇨ Clinical Trial Regulation (EU) No 536/2014 does not require APIs for

GMP Exemption for PET IMPs (I) REGULATION (EU) No 536/2014

Non-industrial
Single state involvement

Article 61

Authorisation of manufacturing and import

1. The manufacturing and import of investigational medicinal products in the Union shall be subject to the holding of an authorisation.
2.
3.
4.

5. Paragraph 1 shall not apply to any of the following processes:

(b) preparation of radiopharmaceuticals used as diagnostic investigational medicinal products where this process is carried out in hospitals, health centres or clinics, by pharmacists or other persons legally authorised in the Member State concerned to carry out such process, and if the investigational medicinal products are intended to be used exclusively in hospitals, health centres or clinics taking part in the same clinical trial in the same Member State;

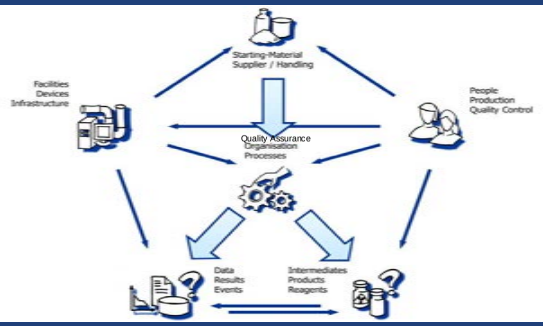
GMP Exemption for PET IMPs (II) REGULATION (EU) No 536/2014

If not used for marketing authorization

Manufacture of Investigational Medicinal Products EN

Annex 13 — Detailed Commission guideline of 8 December 2017 on the good manufacturing practice for investigational medicinal products pursuant to the second paragraph of the Article 63(1) of Regulation (EU) No 536/2014 EN (applicable as from the date of entry into application of Regulation (EU) No 536/2014 on Clinical Trials)

With regard to EudraLex, Volume 4, Part II, it should be noted that Regulation (EU) No 536/2014 does not lay down requirements for good manufacturing practice for active substances of investigational medicinal products. However, if a clinical trial is to be used to support the application for a marketing authorisation, Part II of EudraLex, Volume 4 would need to be considered.

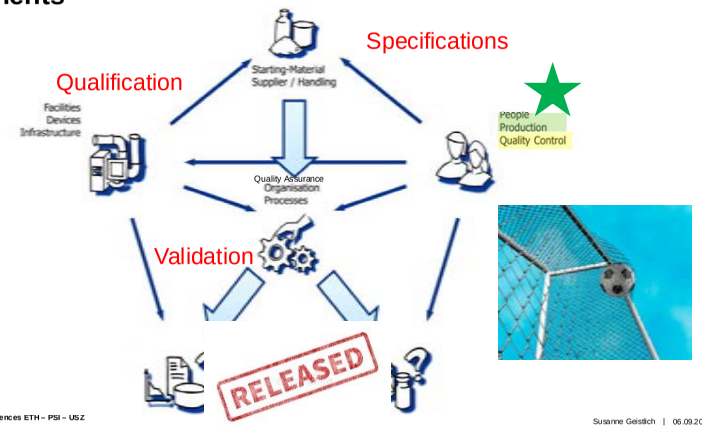


Important GMP Elements

Close-up to PET Production Lab (ETH Zurich)

Manufacture of an ^{18}F-tracer

GMP Elements



Pharm. Eur. Perspective for the extemporaneous preparation

Particular attention is to be paid to:
- qualified personnel with appropriate training;
- adequate premises;
- qualified and suitable equipment for production and analysis;
- validated procedures for all critical production and testing steps;
- environmental monitoring;
- appropriate documentation;
- procurement of materials and services used in the preparation;
- analytical methods / quality control.

Risks to the patient such as
- microbial contamination
- failure of chemical reactions
- malfunctioning of equipment
- inappropriate storage conditions

are controlled by an adequate Quality System

5.19. EXTEMPORANEOUS PREPARATION OF RADIOPHARMACEUTICALS, Pharm. Eur. 04/2016:51900

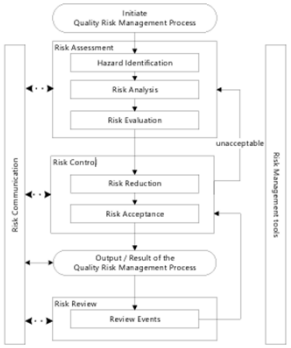
Risk Management – Key Tool e.g. Production Processes / Contamination Control

Risk = probability x severity of harm

In view of

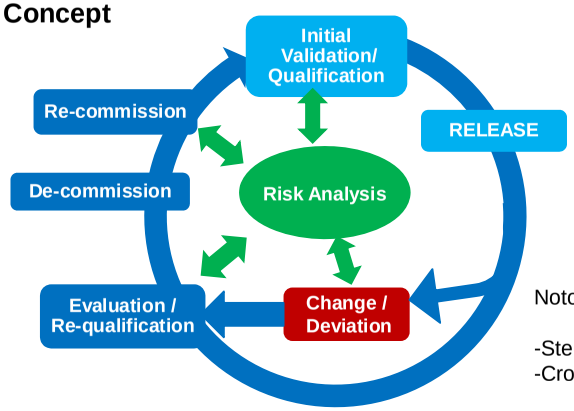
Patient Safety & Process reliability

- Analyze process
- Identify risks
- Reduce to acceptable level (measures)
- Review effectiveness



Flow chart from ICH HARMONISED TRIPARTITE GUIDELINE QUALITY RISK MANAGEMENT Q9, 10 Januar 2023

Life Cycle Concept



Notorious risks:

-Sterility (Annex 1!)
-Cross contamination

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Risk Analysis (e.g. FMEA *Failure Mode and Effects Analysis*)

Contamination Control

No	room/equipment	CR Class	Identified Risk	Danger / Effect	R_{ES} P	S	D	RPN	Suggested measure	R_{EM} P	S	D	RPN	Decision	Responsible person	Date	R_{RK} P	S	D	RF
1	all rooms	all CR Classes	contamination with chemicals by spillage	Hygene, crosscontamination, clean room grade may be in danger	2	3	2	12	Visible contamination is cleand immediately, being good practice in the labs	2	3	1	6	No more measures	N/A	N/A	2	3	1	6
8	all rooms	all CR Classes	Inlet air drop out	massive low pressure in the production lab, clean room grade in danger	1	4	3	12	alarm on the monitor for interpretation by operators plus alarm to central HVAC monitoring	1	4	1	4	Alarms to be installed	Stefan with Joseph	dd/mm /yy	1	4	1	4
4	all rooms	all CR Classes	pressure differentials are depending from a "zero-level-pipe" that may be malfunctioning	pressure differentials may be out of tune	3	4	4	48	The building has a "zero-level-pipe" already; functionality/stability needs to be tested before installation	1	4	4	16	"zero-level-pipe" to be tested AND HVAC installation to ensure that pressure differential between the air lock and the production of 10 Pa is allways ensured.	Joseph	dd/mm /yy	1	2	4	8

Legend:

P Probability	**4** = regularly (≥ 1/ week)	**3** = often (≤ 1/ week)	**2** = occasionally (≤ 1/ month)	**1** = rarely (≤ 1/ year)
S Severity	**4** = critical	**3** = rather critical	**2** = rather n.critical	**1** = n.critical
D Detection	**4** = impossible	**3** = difficult	**2** = mostly det.	**1** = always det.

RPN (Risk Priority Number) = P*S*D →
RPZ= ≤ 8 non critical
RPZ= 9 - 16 critical controlled - measures are optional
RPZ= ≥ 17 critical - needs measures

ICH HARMONISED TRIPARTITE GUIDELINE QUALITY RISK MANAGEMENT Q9,10 Januar 2023, *Annex I: Risk Management Methods and Tools*
EANM Guideline on "EANM guideline on quality risk management for radiopharmaceuticals", 2022

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Impacts on Product Sterility

- Facility and Equipment guarantee adequate clean room
- Personnel training, gowning and process simulation (media fill)
- Starting material is of low bioburden
- Sterile filters are tested for integrity / downstream sterile and non-pyrogenic materials only

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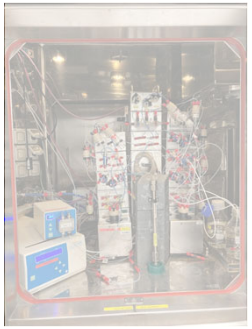
Types of synthesis modules in our labs

EZAG Modular-Lab PharmTracer
^{68}Ga / ^{177}Lu products



EZAG Modular-Lab Standard R&D
^{18}F-tracers

ORA Neptis Perform
^{18}F-tracers

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Preparation and setting up a synthesis module for ^{18}F-tracer

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Process Reliability

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Topic of Concern: Process Reliability

Survey of 24 months (Augmenticon)

Synthesis-platform Tracer / no. of batches	Process Reliability	Reasons for batch failures
EZAG Modular-Lab PharmTracer/ ^{68}Ga-PSMA-11 / total batches 164	98%	o Analytical HPLC defect; no result o Artefacts in analytical HPLC; RCP 93% o SCX cartridge retains most of the activity
EZAG Modular-Lab Standard R&D ^{18}F-PSS232 / total batches 16	81%	o Analytical HPLC defect; no result o Cyclotron defect; no product o Synthesis module defect; no product
ORA Neptis perform ^{18}F-AV1451 / total batches 51	96%	o HLB cartridge failure; consequence poor yield o Human error -> too many tasks besides the batch production

Instruments / Consumables / Human error

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Main factors for batch failure (Augmenticon's root cause analysis)

Root Cause Analysis

Based on ca. 10'000 batches produced for a commercial PET tracer

- Revealed three major areas leading to batch failures
  - 1/3 Human errors (deviation from established procedures)
  - 1/3 Equipment failures (cyclotrons, synthesis modules)
  - 1/3 Consumable defects (cassettes, filters, reagents)
- Insider experience shows that > 50% of equipment failures and consumable defects go back to improper handling and must be attributed to human errors

Augmenticon: augmented reality featured solutions, www.augmenticon.ch

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Problem Statement

- Radiopharmaceutical manufacturing faces multiple challenges leading to reliabilities ranging between 75% for novel and complex compounds to 98.5% for routine products like FDG
- Challenges arise from:
  - Just-in-time production (no time to fix issues)
  - Stressful work environments (noise, radioactivity, nightshift)
  - High staff turnover
  - High level of expertise required in various area:
    - GMP → aseptic processing
    - Equipment → cyclotron, synthesis module, dispenser, analytical
    - Product specific → Preparation of reagents, operation of equipment

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Operator Guidance & Control by an Expert

- Operator performs radiopharmaceutical synthesis wearing smart glasses
- Expert supervises all activities (video/ audio) and provides instructions via audio or AR overlays (e.g. red arrow or text)
- Interaction can be documented incl. photos or videos recorded with smart glasses during the operation




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Classical measures to improve process reliability (I)

Aim: FIRST-TIME RIGHT and PRO-ACTIVE attitude

People
- Training: learn from the best
- Work atmosphere, supportive team
- Expertise matches responsibility and competence

Quality Assurance
- Root cause analysis of deviations and errors
- Involve whole team or communicate to all for prevention of re-occurence

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Classical measures to improve process reliability (II)

Instruments
- Qualified and robust
- Regular preventative maintenance
- Treat them well all the time, fix minute problems instantly

Materials
- Line clearance and preparation (mise-en-place)
- Buy from reliable suppliers
- File complaint with supplier if material defect suspected

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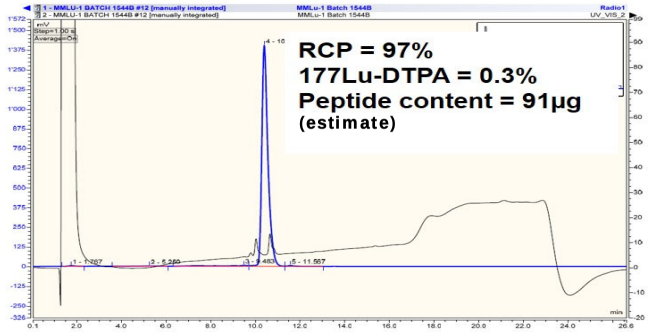

Special Rules for Technical Release of Radiopharmaceuticals

Releasing PET products (I)

Extremely short shelf life of products needs some adaptations for release procedures that are exotic in the pharmaceutical industry.

Nevertheless, quality of products must be conclusive before releasing:

- QC data and results reviewed
  Time constraint – errors need be corrected before issuing the release certificate

Short and **robust** methods may be essential

- Manufacture protocol reviewed, IPC assured
- Any deviations assessed for criticality before releasing the product for application

Releasing PET products (II)

Shipment in bond

- Define what parameters must be tested for application of product
- Measures for assuring that product is not used BEFORE release
- Have all contact details available to communicate with the appropriate persons in case of release problems / delays

Releasing PET products (III)

Conditional Release

Common post release parameters:

- Sterility
  Sample sent to contract lab after decay
  Test duration 14 days -> process control
  -> filter integrity test, environmental monitoring, media fills
- Radionuclide purity
  Only after decay of main activity (e.g. ^{68}Ge in ^{68}Ga after > 48h)
- (Endotoxins)
- (Residual solvents by GC)

Questions

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Registration of medicinal products and general rules for distribution

Barbara Byrne Habič, MPharm, is a Regulatory Affairs Manager at the Agency for Medicinal Products and Medical Devices of the Republic of Slovenia (JAZMP).
Throughout her 18-year employment at JAZMP, she has specialized in the regulation of medicinal products for human use. With formal training and experience in medicinal product analysis and control, she initially joined JAZMP as an assessor responsible for the pharmaceutical part of medicinal product dossiers.
Over the years, she has been actively involved in various national and mutual recognition/ decentralised procedures for obtaining marketing authorisations, including radiopharmaceuticals. In these roles, she has served as both a project manager and an assessor of product information.
Additionally, she contributes to the process of identifying and classifying interchangeable medicinal products for human use and oversees the classification of products based on their supply status (prescription or non-prescription). She is also a member of a working group established under the Slovenian Ministry of Health, which participates in negotiations within the Council of the European Union on the proposal for the revision of pharmaceutical legislation.

The lecture has the following learning objectives:

1) Students are able to make a distinction among community acts adopted by the Community institutions according to their legal effects.
2) Students are able to explain the structure and content of the documentation for obtaining marketing authorisation and identify that the marketing authorisation is also required for radionuclide generators, kits for radiopharmaceutical preparation, radionuclide precursor radiopharmaceuticals and industrially prepared radiopharmaceuticals.
3) Students are able to determine which product legal type is suitable in specific circumstances and interpret situations in relation with data and market exclusivity.
4) Students are able to discuss that identical requirements demonstrating the quality, safety and efficacy of medicinal product apply to different marketing authorisation procedures.
5) Students are able to explain that main objective of the Paediatric Regulation is to improve the health of children in the European Union by facilitating the development and availability of medicines for children from birth to less than 18 years.

6) Students are able to explain the aim of incentivising development and marketing of medicines for very rare diseases, since all persons suffering from rare diseases have the same rights as their fellow citizens to safe and effective therapies.
7) Students are able to demonstrate that general provisions for medicinal products are not adequate for radiopharmaceuticals and are able to discuss where the legislation has additional requirements for radiopharmaceuticals, e.g. product information (SmPC, PL and labelling).

Summary of the lecture:

Introduction

The lecture "*Registration of medicinal products and General rules for distribution*" ensures an overview of the European regulatory system for human medicines, including the legislation, the different routes for obtaining a marketing authorisation for the European market and European network. Norway, Iceland and Liechtenstein form the EEA with the 27 Member States of the European Union. These countries have, through the EEA agreement, adopted the complete Union acquis on medicinal products and are consequently parties to the Union procedures.

The framework of pharmaceutical legislation

The pharmaceutical legislation of the European Union has consistently pursued the twin objectives: the protection of public health and the free movement of medicinal products. The framework of pharmaceutical legislation originated over 50 years ago, in 1965 with the publication of Directive 65/65/EEC, known also as first directive. The EU legal framework for medicinal products for human use is intended to ensure a high level of public health protection and to promote the functioning of the internal market, with measures which moreover encourage innovation. It is based on the principle that the placing on the market of medicinal products is made subject to the granting of a marketing authorisation by the competent authorities.

Community authorisation procedures are in place since the mid-90s and in addition the system is supported by a Community regulatory agency in charge of providing the EU institutions with scientific advice on medicinal products: the European Medicines Agency (EMA).

The requirements and procedures for the marketing authorisation for medicinal products for human use, as well as the rules for the constant supervision of products after they have been authorised, are primarily laid down in Directive 2001/83/EC and in Regulation (EC) No 726/2004.

In addition, various rules have been adopted to address the particularities of certain types of medicinal products and promote research in specific areas: e.g. orphan medicinal products (Regulation (EC) No 141/2000) and medicinal products for children (Regulation (EC) No 1901/2006).

To facilitate the interpretation of the legislation and its uniform application across the EU, numerous guidelines of regulatory and scientific nature have additionally been adopted, for example a detailed explanation of the marketing authorisation procedures and other regulatory guidance intended for applicants is contained in Volume 2 (Notice to Applicants).

Medicinal products on the market

A medicinal product may only be placed on the market in the European Economic Area (EEA) when a marketing authorisation has been issued by the competent authority of a Member State for its own territory (national authorisation) or when an authorisation has been granted in accordance with Regulation (EC) No 726/2004 for the entire Union (an Union authorisation). The marketing authorisation holder must be established within the EEA. The European system offers several routes for the authorisation of medicinal products:

- The centralised procedure is compulsory for products derived from biotechnology, for orphan medicinal products and for medicinal products for human use which contain an active substance authorised in the Community after 20 May 2004 (date of entry into force of Regulation (EC) No 726/2004) and which are intended for the treatment of AIDS, cancer, neurodegenerative disorders or diabetes.
- Applications for the centralised procedure are made directly to the European Medicines Agency (EMA) and lead to the granting of a European marketing authorisation by the Commission which is binding in all Member States.
- The mutual recognition procedure, which can be applied for most conventional medicinal products, is based on the principle of recognition of an already existing national marketing authorisation by one or more Member States.
- The decentralised procedure, which was introduced with the legislative review of 2004, is can also be used for most conventional medicinal products. Through this procedure an application for the marketing authorisation of a medicinal product is submitted simultaneously in several Member States, one of them being chosen as the "Reference Member State". At the end of the procedure national marketing authorisations are granted in the reference and in the concerned Member States.
- Purely national authorisations, which are still available for medicinal products to be marketed in one Member State only.

When granting marketing authorisation competent authorities issue the decision together with the Summary of product characteristics, Labelling and Package leaflet, prepared in accordance with defined structure and guidelines.

EMA is in the process of implementing the ISO standards for the identification and description of medicinal products (IDMP) to facilitate the reliable and consistent exchange of medicinal product information and help to ensure wide interoperability across global regulatory and healthcare communities.

Orphan medicinal products

Orphan medicinal products are intended for the diagnosis, prevention or treatment of life-threatening or very serious conditions that affect no more than 5 in 10,000 people in the European Union. Patients suffering from rare diseases deserve access to the same quality of medicinal products as other patients within the European Union. Since only a very small number of the population is affected by these diseases, the pharmaceutical industry has been reluctant in the past to invest in the research and development of medicinal products to treat them. In response to this situation and to stimulate the research and development of orphan drugs, in year 2000 the EU introduced new legislation with the aim of providing incentives for the development of orphan and other medicinal products for rare disorders.

The EU Regulation on orphan medicinal products (Regulation (EC) No 141/2000) establishes a centralised procedure for the designation of orphan medicinal products and puts in place incentives for the research, marketing and development of orphan medicinal products.

The Regulation also sets up a Committee for Orphan Medicinal Products (COMP), which is responsible for the scientific examination of applications leading to the designation of an Orphan Medicinal Product.

Currently, over 260 orphan medicines have a valid marketing authorisation, issued by the European Commission.

Medicines for children

The Paediatric Regulation sets up a system of requirements, rewards and incentives together with horizontal measures to ensure that medicines are researched, developed and authorised to meet the therapeutic needs of children. The Regulation was seen as a response to the absence of sufficient numbers of suitable, authorised medicinal products to treat conditions in children in the European Union.

The key objectives of the Regulation are:

- to ensure high-quality research into the development of medicines for children.
- to ensure, over time, that the majority of medicines used by children are specifically authorised for such use.
- to ensure the availability of high-quality information about medicines used by children.

The Regulation also establishes the Paediatric Committee, which is responsible for providing opinions on the development of medicines for use on children.

Wholesale Distribution of medicinal products

Member states must ensure that only medicinal products with a marketing authorisation in accordance with Community law are distributed in their territory. Good distribution practice (GDP) describes the minimum standards that need to be met to ensure that the quality and integrity of medicines are maintained throughout the supply chain. Wholesalers need to fulfil minimum requirements regarding premises, equipment, staff and obligations to obtain the distribution authorisation. They have public service obligation: to guarantee

permanently an adequate range of medicinal products on the market. They need to establish tracing system to enable finding faulty products and recall of medicinal product.

Pharmacovigilance
Pharmacovigilance is the science and activities, relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem. Primary focus is post-marketing surveillance of Medicinal Products to ensure patients are continuously getting safe and effective Medicinal Products since certain side effects may emerge only when medicine has been used in a large number of patients, for a long period of time and with other medicines.
EU law requires each marketing authorisation holder, national competent authority and EMA to operate a pharmacovigilance system. The National Competent Authority monitors the safety profile of the products available on the market and takes appropriate action where necessary (marketing authorisation may be changed, suspended, revoked, or withdrawn).

Conclusion
The presentation covers several areas in relation to regulatory practice and challenges within the European regulatory network. This presentation is to be beneficial to all those working in regulatory and medical affairs. To the other students the presentation is intended as first-hand information on legislation and processes which enable the marketing of quality, safe and effective medicines.

Take home messages:
Compliance with EU regulations is essential: The registration and distribution of medicinal products in the EU require strict adherence to regulatory guidelines and standards to ensure quality, safety, and efficacy of medicinal products.

Companies seeking authorisation must compile comprehensive documentation, including pharmaceutical and clinical data, to support the quality, safety, and efficacy of their medicinal products.

The centralized procedure, managed by the European Medicines Agency (EMA), provides a unified route for marketing authorization of medicinal products across the EU and enables access to the entire EU market. Mutual recognition procedure, decentralised procedure and national authorisation enable marketing of medicinal product in selected concerned member states.

EU regulations aim to harmonize distribution rules, ensuring that authorized medicinal products can be freely distributed within the EU, enhancing patient access to treatments while maintaining stringent quality and safety standards.

Robust pharmacovigilance systems are in place to monitor the safety profile of medicinal products after authorization. Reporting of adverse events and suspected side effects enables continuous evaluation and risk-benefit assessment to protect patient safety.

References (further reading):

• Directive 2001/83/EC
• Regulation (EC) No 726/2004
• Regulation (EC) No 141/2000
• Regulation (EC) No 1901/2006
• Regulation (EC) No 1234/2008
• Eudralex - Volume 1 - EU pharmaceutical legislation for medicinal products for human use
• EudraLex - Volume 2 - Notice to applicants and regulatory guidelines for medicinal products for human use
• Community Register of medicinal products for human use
• The coordination group (CMDh) procedural guidelines
• European Medicines Agency' scientific and regulatory information

Useful links

• Heads of Medicines Agencies: http://www.hma.eu/
• European Medicines Agency – EMA: http://www.ema.europa.eu/ema/
• European Commission – DG Sante: https://commission.europa.eu/about-european-commission/departments-and-executive-agencies/health-and-food-safety_en
• EU legislation: http://ec.europa.eu/health/documents/eudralex/index_en.htm
• Community Register: https://ec.europa.eu/health/documents/community-register/html/index_en.htm

REGISTRATION OF MEDICINAL PRODUCTS AND GENERAL RULES FOR DISTRIBUTION

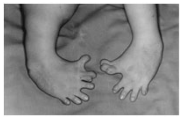
Sabina Zalar, Mpharm, Lidija Dobrota, Mpharm,
Barbara Byrne Habič, Mpharm, spec.

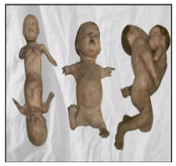
DISCLAIMER

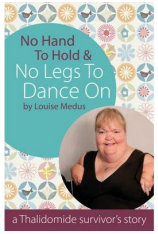
The views and opinions expressed in the following PowerPoint slides and during the presentation are solely those of the author and should not be taken as official statement of the institution where the presenter is employed.

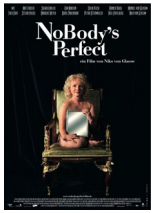
CONTENT

WHY AUTHORISE MEDICINAL PRODUCTS?









I. EU AND LEGISLATION

EU MEMBER STATES - HISTORY

Year	MS
1958	**Belgium, France, Germany, Italy, Luxembourg, Netherlands** „European Coal and Steel Community 1952", the signing of the Treaties of Rome (EEC, Euratom, in 1957) and the birth of the European Parliament.
1973	**Denmark, Ireland, United Kingdom**
1981	**Greece**
1986	**Portugal, Spain**
1995	**Austria, Finland, Sweden**
2004	**Cyprus, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, Slovakia, Slovenia**
2007	**Bulgaria, Romania**
2013	**Croatia**
2016-2020	Brexit (Brexit referendum in June 2016; since 31 January 2020, the **UK** is no longer part of the EU).

EU MEMBER STATES - TODAY

28 → 27

The „EEA EFTA States":

LEGISLATION

The **EU legal framework for human medicines**:

- sets standards to ensure a **high level of public health protection** and the **quality, safety and efficacy** of authorised medicines.
- promotes the functioning of the **internal market**, with measures to encourage innovation.
- is based on the principle that a **medicinal product requires a marketing authorisation** by the competent authorities **before being placed on the market**.

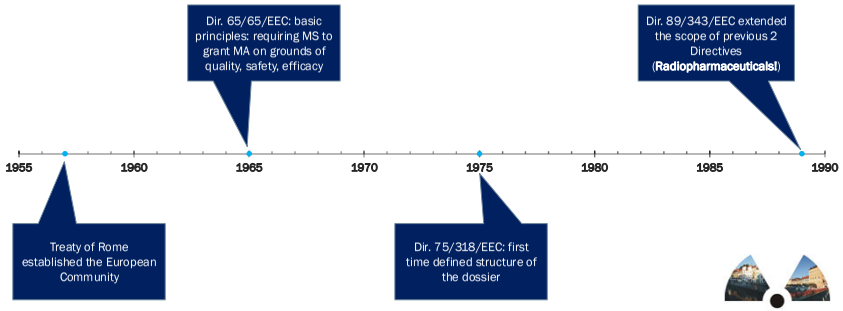
EudraLex - EU Legislation:
https://health.ec.europa.eu/medicinal-products/eudralex_en

Body of European Union legislation:
Volume 1 - *EU pharmaceutical legislation for medicinal products for human use*
https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-1_en

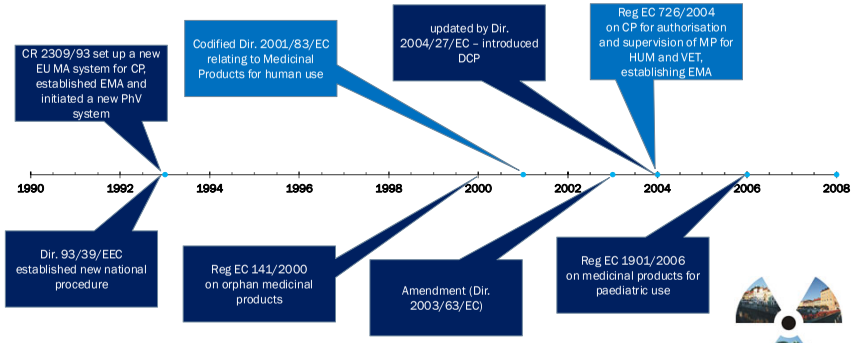
LEGAL ARCHITECTURE (HIERARCHY)

- **Legally binding acts ('hard law')**
  - **Regulation**: directly applicable in all Member States (MSs), it does not require any transposition by the national competent authorities (NCA).
  - **Directive**: must be transposed into the legal order of the MSs.
  - **Decision**: is a legal act binding the addressed subject – MS or natural or legal person.
- **Legally non-binding acts ('soft law')**
  - **Resolutions:** political act
  - **Guidelines**: prepared by scientific committees
    - **Notice to Applicants** is guidance adopted and published by the Commission.

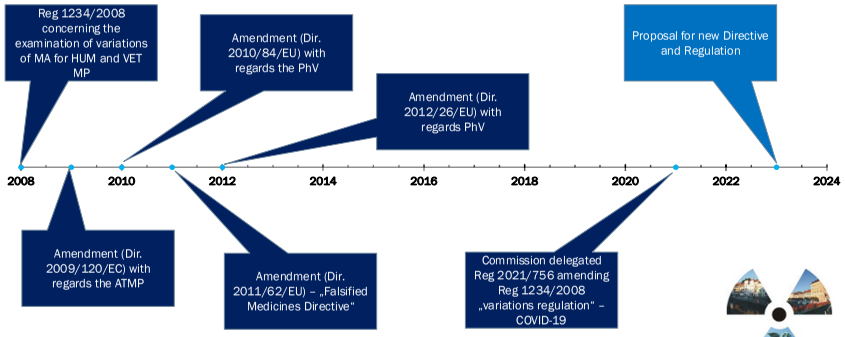
DEVELOPMENT OF LEGISLATION (1)



DEVELOPMENT OF LEGISLATION (2)



DEVELOPMENT OF LEGISLATION (3)



NEW LEGISLATION PROPOSAL

The revision aims to achieve the following main objectives:

- Make sure all patients across the EU have timely and equitable access to safe, effective, and affordable medicines
- Enhance the security of supply (address shortages) and ensure medicines are available to patients, regardless of where they live in the EU
- Continue to offer an attractive and innovation-friendly environment for research, development, and production of medicines in Europe
- Make medicines more environmentally sustainable
- Address antimicrobial resistance (AMR) and the presence of pharmaceuticals in the environment.

The revision is the first major review of the pharmaceutical legislation since 2004.

It will adapt the legislation to the needs of the 21st century.

II. COMPETENT AUTHORITIES (CA)

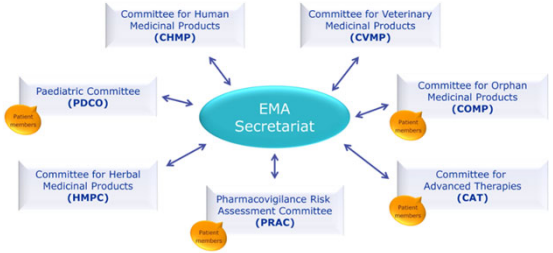
EU COMPETENT AUTHORITIES

Territorial scope	Scientific Assessment	Authorising body	Procedure
EU	European Medicines Agency (EMA)	**European Commission**	**Centralised** https://health.ec.europa.eu/medicinal-products/legal-framework-governing-medicinal-products-human-use-eu/authorisation-procedures-centralised-procedure_en
Concerned EU countries	National competent authorities (in case of disagreement additional assessment by the EMA)	**National authorities**	**Mutual Recognition, Decentralised, National** https://health.ec.europa.eu/medicinal-products/legal-framework-governing-medicinal-products-human-use-eu/authorisation-procedures-national-authorisation-procedures_en

EUROPEAN MEDICINES AGENCY

- Established in 1995 with CR 2309/93 as European Medicines Evaluation Agency – EMEA, responsible for coordinating the existing scientific resources put at its disposal by the competent authorities of the Member States for the evaluation and supervision of medicinal products.
- Reg EC 726/2004, laying down Union procedures for the authorisation and supervision of medicinal products for human and veterinary use, and establishing a European Medicines Agency, responsible for coordinating the existing scientific resources put at its disposal by Member States for the evaluation, supervision and pharmacovigilance of medicinal products.
- EMEA (also short for „Europe, Middle East and Africa") → EMA in Dec 2009
- 1995 - 2019: London, UK
- 1 March 2019 → Amsterdam, NL (relocation completed in 2020)

EMA SCIENTIFIC COMMITTEES



NATIONAL AUTHORITIES

NATIONAL AUTHORITIES

National competent authorities (NCAs) are responsible for the regulation of medicinal products for human and veterinary use in the European Economic Area.

The Heads of Medicines Agencies (HMA) is a network of the heads of the NCAs whose organisations are responsible for the regulation of medicinal products for human and veterinary use in the European Economic Area.

Agency for Medicinal Products and Medical Devices of the Republic of Slovenia was established on January 1, 2007, as an independent regulatory body, responsible for medicinal products and medical devices for human and veterinary use, in order to ensure the protection of public health.

III. STRUCTURE OF THE DOSSIER

- **Discovery and Development**
  - Basic research of disease mechanisms and targets, active substance discovery, research of promising compounds

} 3 – 6 years

- **Preclinical Studies**
  - laboratory and animal testing for basic safety findings
- **Clinical Trials**
  - Phase I - III -> safety and efficacy tested in humans

} 6 years

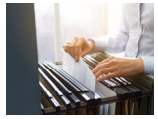
- **Competent Authority Review**
  - thorough review of submitted data to decide on approval

} 2 years

- **Post-Marketing Research and Safety Monitoring**
  - Phase IV -> continuous monitoring of safety

STRUCTURE OF THE DOSSIER

Common Technical Document - CTD

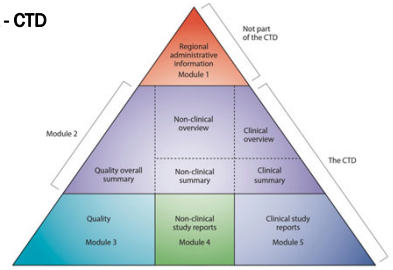


- The CTD (established in 2003) is an internationally agreed **format for the preparation of applications** (format for the data) to be submitted to regulatory authorities in the three ICH regions of Europe, USA and Japan
- It is intended to save time and resources and to facilitate regulatory review and communication.
- It gives **no** information about the content of a dossier and does not indicate which studies and data are required for a successful approval. Dossier will not necessarily be identical for all regions.

STRUCTURE OF THE DOSSIER

Common Technical Document - CTD

- ✓ Applicable for all types of MA applications (stand alone, generic,...)
- ✓ Applicable for all procedures (CP, MRP, DCP, NP)
- ✓ Applicable for all types of products (new chemical entities, radiopharmaceuticals, vaccines, herbals,...)



MODULE 1

1.0 Cover Letter

1.1 Comprehensive Table of Contents

1.2 Application Form

1.3 Product Information
- 1.3.1 SPC, Labelling and Package Leaflet
- 1.3.2 Mock-up
- 1.3.3 Specimen
- 1.3.4 Consultation with Target Patient Groups
- 1.3.5 Product Information already approved in the Member States
- 1.3.6 Braille

1.4 Information about the Experts
- 1.4.1 Quality
- 1.4.2 Non-Clinical
- 1.4.3 Clinical

1.5 Specific Requirements for Different Types of Applications
- 1.5.1 Information for Bibliographical Applications
- 1.5.2 Information for Generic, 'Hybrid' or Bio-similar Applications
- 1.5.3 (Extended) Data/Market Exclusivity
- 1.5.4 Exceptional Circumstances
- 1.5.5 Conditional Marketing Authorisation

1.6 Environmental Risk Assessment
- 1.6.1 Non-GMO
- 1.6.2 GMO

1.7 Information relating to Orphan Market Exclusivity
- 1.7.1 Similarity
- 1.7.2 Market Exclusivity

1.8 Information relating to Pharmacovigilance
- 1.8.1 Pharmacovigilance System
- 1.8.2 Risk-management System

1.9 Information relating to Clinical Trials

1.10 Information relating to Paediatrics

Responses to Questions

Additional Data

MODULE 2

Module 2: Common Technical Document Summaries
- 2.1 CTD Table of Contents (Module 2 – 5)
- 2.2 CTD Introduction
- 2.3 Quality Overall Summary — Quality
- 2.4 Nonclinical Overview — Safety
- 2.5 Clinical Overview — Efficacy
- 2.6 Nonclinical Written and Tabulated Summary
  - Pharmacology
  - Pharmacokinetics
  - Toxicology
- 2.7 Clinical Summary
  - Biopharmaceutics and Associated Analytical Methods
  - Clinical Pharmacology Studies
  - Clinical Efficacy
  - Clinical Safety
  - Synopses of Individual Studies

Summaries/Overviews must be prepared by suitably qualified and experienced persons (experts). The experts have to sign and add brief information on their educational background and specific expertise in a special section in Module 1.4.

MODULES 3, 4, 5

Module 3: Quality
- 3.1 Module 3 Table of Contents
- 3.2 Body of Data
- 3.3 Key Literature References

Quality

Module 4: Nonclinical Study Reports
- 4.1 Module 4 Table of Contents
- 4.2 Study Reports
- 4.3 Literature References

Safety

Module 5: Clinical Study Reports
- 5.1 Module 5 Table of Contents
- 5.2 Tabular Listing of All Clinical Studies
- 5.3 Clinical Study Reports
- 5.4 Literature References

Efficacy

MODULE 3

3.1	MODULE 3 TABLE OF CONTENTS
3.2	BODY OF DATA
3.2.S	DRUG SUBSTANCE
3.2.S.1	General Information
3.2.S.1.1	Nomenclature
3.2.S.1.2	Structure
3.2.S.1.3	General Properties
3.2.S.2	Manufacture
3.2.S.2.1	Manufacturer(s)
3.2.S.2.2	Description of manufacturing process and process controls
3.2.S.2.3	Control of materials
3.2.S.2.4	Controls of critical steps and intermediates
3.2.S.2.5	Process validation and/or evaluation
3.2.S.2.6	Manufacturing process development
3.2.S.3	Characterisation
3.2.S.3.1	Elucidation of structure and other characteristics
3.2.S.3.2	Impurities
3.2.S.4	Control of drug substance
3.2.S.4.1	Specification
3.2.S.4.2	Analytical Procedures
3.2.S.4.3	Validation of analytical procedures
3.2.S.4.4	Batch analyses
3.2.S.4.5	Justification of Specification
3.2.S.5	Reference Standards or Materials
3.2.S.6	Container Closure System
3.2.S.7	Stability
3.2.P	DRUG PRODUCT
3.2.P.1	Description and composition of the drug product
3.2.P.2	Pharmaceutical Development
3.2.P.2.4	Controls and critical steps and intermediates
3.2.P.3	Manufacture
3.2.P.3.1	Manufacturer(s)
3.2.P.3.2	Batch formula
3.2.P.3.3	Description of Manufacturing Process and Process Controls
3.2.P.3.4	Controls of critical steps and intermediates
3.2.P.3.5	Process validation and / or evaluation
3.2.P.4	Control of excipients
3.2.P.4.1	Specifications
3.2.P.4.2	Analytical procedures
3.2.P.4.3	Validation of analytical procedures
3.2.P.4.4	Justification of specifications
3.2.P.4.5	Excipients of human or animal origin
3.2.P.4.6	Novel Excipients *(ref to A 3)*
3.2.P.5	Control of drug product
3.2.P.5.1	Specification(s)
3.2.P.5.2	Analytical Procedures
3.2.P.5.3	Validation of Analytical Procedures
3.2.P.5.4	Batch analyses
3.2.P.5.5	Characterisation of Impurities
3.2.P.5.6	Justification of specification(s)
3.2.P.6	Reference Standards or Materials
3.2.P.7	Container Closure System
3.2.P.8	Stability
3.2.A	APPENDICES
3.2.A.1	Facilities and Equipment
3.2.A.2	Adventitious Agents Safety Evaluation
3.2.A.3	Excipients
3.2.R	REGIONAL INFORMATION
3.3	LITERATURE REFERENCES

MODULE 4

4.1 TABLE OF CONTENTS OF MODULE 4

A Table of Contents should be provided that lists all of the nonclinical study reports and gives the location of each study report in the Common Technical Document.

4.2 STUDY REPORTS

The study reports should be presented in the following order:

4.2.1 Pharmacology
- 4.2.1.1 Primary Pharmacodynamics
- 4.2.1.2 Secondary Pharmacodynamics
- 4.2.1.3 Safety Pharmacology
- 4.2.1.4 Pharmacodynamic Drug Interactions

4.2.2 Pharmacokinetics
- 4.2.2.1 Analytical Methods and Validation Reports (if separate reports are available)
- 4.2.2.2 Absorption
- 4.2.2.3 Distribution
- 4.2.2.4 Metabolism
- 4.2.2.5 Excretion
- 4.2.2.6 Pharmacokinetic Drug Interactions (nonclinical)
- 4.2.2.7 Other Pharmacokinetic Studies

4.2.3 Toxicology
- 4.2.3.1 Single-Dose Toxicity (in order by species, by route)
- 4.2.3.2 Repeat-Dose Toxicity (in order by species, by route, by duration; including supportive toxicokinetics evaluations)
- 4.2.3.3 Genotoxicity
  - 4.2.3.3.1 In vitro
  - 4.2.3.3.2 In vivo (including supportive toxicokinetics evaluations)
- 4.2.3.4 Carcinogenicity (including supportive toxicokinetics evaluations)
  - 4.2.3.4.1 Long-term studies (in order by species; including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)
  - 4.2.3.4.2 Short- or medium-term studies (including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)
  - 4.2.3.4.3 Other studies
- 4.2.3.5 Reproductive and Developmental Toxicity (including range-finding studies and supportive toxicokinetics evaluations) (If modified study designs are used, the following sub-headings should be modified accordingly.)
  - 4.2.3.5.1 Fertility and early embryonic development
  - 4.2.3.5.2 Embryo-fetal development
  - 4.2.3.5.3 Prenatal and postnatal development, including maternal function
  - 4.2.3.5.4 Studies in which the offspring (juvenile animals) are dosed and/or further evaluated.
- 4.2.3.6 Local Tolerance
- 4.2.3.7 Other Toxicity Studies (if available)
  - 4.2.3.7.1 Antigenicity
  - 4.2.3.7.2 Immunotoxicity
  - 4.2.3.7.3 Mechanistic studies (if not included elsewhere)
  - 4.2.3.7.4 Dependence
  - 4.2.3.7.5 Metabolites
  - 4.2.3.7.6 Impurities
  - 4.2.3.7.7 Other

4.3 LITERATURE REFERENCES

MODULE 5

5.1 Table of Contents of Module 5

5.2 Tabular Listing of All Clinical Studies

5.3 Clinical Study Reports
- 5.3.1 Reports of Biopharmaceutic Studies
  - 5.3.1.1 Bioavailability (BA) Study Reports
  - 5.3.1.2 Comparative BA and Bioequivalence (BE) Study Reports
  - 5.3.1.3 *In vitro-In vivo* Correlation Study Reports
  - 5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies
- 5.3.2 Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials
  - 5.3.2.1 Plasma Protein Binding Study Reports
  - 5.3.2.2 Reports of Hepatic Metabolism and Drug Interaction Studies
  - 5.3.2.3 Reports of Studies Using Other Human Biomaterials
- 5.3.3 Reports of Human Pharmacokinetic (PK) Studies
  - 5.3.3.1 Healthy Subject PK and Initial Tolerability Study Reports
  - 5.3.3.2 Patient PK and Initial Tolerability Study Reports
  - 5.3.3.3 Intrinsic Factor PK Study Reports
  - 5.3.3.4 Extrinsic Factor PK Study Reports
  - 5.3.3.5 Population PK Study Reports
- 5.3.4 Reports of Human Pharmacodynamic (PD) Studies
  - 5.3.4.1 Healthy Subject PD and PK/PD Study Reports
  - 5.3.4.2 Patient PD and PK/PD Study Reports
- 5.3.5 Reports of Efficacy and Safety Studies
  - 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication
  - 5.3.5.2 Study Reports of Uncontrolled Clinical Studies
  - 5.3.5.3 Reports of Analyses of Data from More Than One Study
  - 5.3.5.4 Other Clinical Study Reports
- 5.3.6 Reports of Post-Marketing Experience
- 5.3.7 Case Report Forms and Individual Patient Listings

5.4 Literature References

IV. MARKETING AUTHORISATION LEGAL TYPES

APPLICATION TYPES

Directive 2001/83/EC	Type of legal basis
Article 8(3)	Stand alone application „Data and market exclusivity" for submitted data
Article 10(1)	generic application
Article 10(3)	hybrid application (generic with additional new data)
Article 10(4)	Biosimilar application
Article 10a	well-established use application (bibliographic literature)
Article 10b	fixed combination application
Article 10c	informed consent application

STAND ALONE APPLICATION

Independent full dossier in accordance with Article 8(3) of Directive 2001/83/EC

Directive 2001/83/EC requires that application to place a medicinal product on the market shall be accompanied by the documents with respect to prove its **Quality, Safety and Efficacy**, relating in particular to the results of:

- pharmaceutical (physico-chemical, biological or microbiological) tests,
- pre-clinical (toxicological and pharmacological) tests,
- clinical trials.

GENERIC APPLICATION

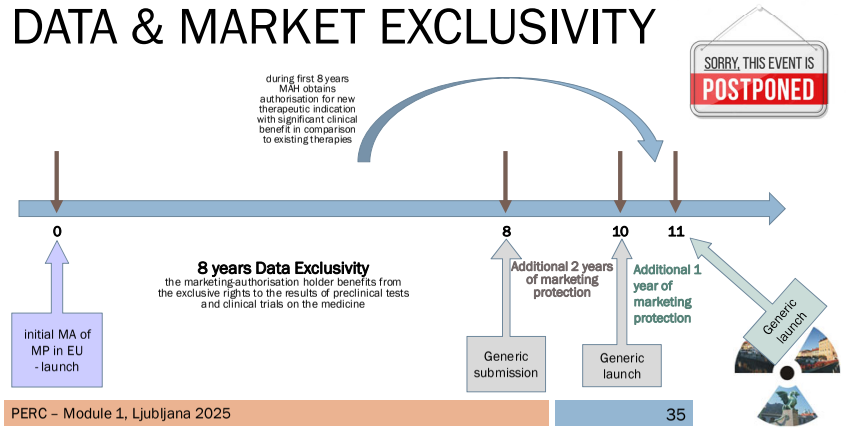
„Generic application" in accordance with Article 10(1) of Directive 2001/83/EC

'Generic medicinal product' shall mean a medicinal product which has:

- the **same qualitative and quantitative composition** in active substances
- the **same pharmaceutical form** as the reference medicinal product
- whose **bioequivalence** with the reference medicinal product has been **demonstrated** by appropriate bioavailability studies.

The various immediate-release oral pharmaceutical forms shall be considered to be one and the same pharmaceutical form.

DATA & MARKET EXCLUSIVITY

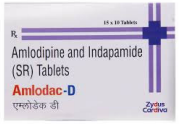


FIXED DOSE APPLICATION

„Fixed dose application" in accordance with Article 10b of Directive 2001/83/EC

In the case of medicinal products containing more active substances … but not used in combination for therapeutic purposes yet, the results of new pre-clinical tests or new clinical trials relating to that combination shall be provided in accordance with Art 8(3) but it shall not be necessary to provide scientific references relating to each individual active substance.

→ **for treatment of essential hypertension**



WELL ESTABLISHED USE APPLICATION

„Well established use" in accordance with Article 10a of Directive 2001/83/EC

- the applicant has to show and prove the „well-established medicinal use" within the Community for **at least 10 years** from the first systematic and documented use of the substance
- by means of bibliographic data only

Documentation:
All documentation – favourable and unfavourable published scientific literature

INFORMED CONSENT APPLICATION

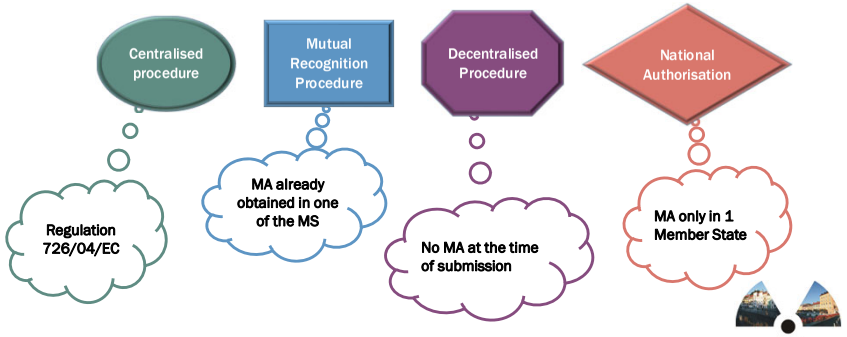
„Informed consent" in accordance with Article 10c of Directive 2001/83/EC

An informed consent application for a medicinal product is a marketing authorisation application based on a full reference to the dossier of another product (the reference product). It is possible when consent is given by the MA holder of the reference product. The new product is identical to the previously authorised reference product.

Documentation:
- Module 1 and
- Informed Consent letter

V. MARKETING AUTHORISATION PROCEDURES

MA PROCEDURES



NATIONAL PROCEDURES

Mutual Recognition Procedure

- based on the recognition of a pre-existing national marketing authorisation by one or more EU countries
- applicable to the majority of conventional medicinal products

Decentralised Procedure

the application for marketing authorisation is submitted simultaneously in several EU countries, one being chosen as the "Reference Member State"

National Authorisation

available for medicinal products sold in an individual EU country

NATIONAL PROCEDURE (NP)

- Strictly limited to medicines that will be marketed in 1 Member State only.
- The National Competent Authority is responsible for granting a Marketing Authorisation for medicines placed on its market.
- Procedure no longer available for new active substances.
- A marketing authorisation is normaly granted for a period of 5 years → renewal → unlimited period.

National Authorisation

MUTUAL RECOGNITION PROCEDURE & DECENTRALISED PROCEDURE

for medicines with an existing MA

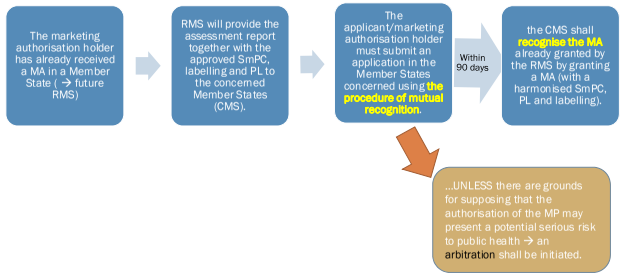
only if no MA previously granted

Scope

- May be used for all products except those which fall within the mandatory scope of the Centralised procedure.
- Obligatory for all medicines to be marketed in more than 1 Member State.
- Both procedures are based on the principle of mutual recognition.
- The applicant chooses the Reference Member State (RMS) and Concerned Member States (CMS).
- RMS evaluates documentation on behalf of CMS.

MUTUAL RECOGNITION PROCEDURE MRP

Applicable in cases where national authorisations are requested for the same medicinal product in more than one Member State, however:



MRP TIMELINE

Mutual Recognition

❑ 90 Days before submission	Applicant request RMS to update Assessment Report.
❑ Day -14	Documentation (with RMS AR) submitted to CMS, validation procedure follows.
❑ Days 0 to 30	Assessment and comments from Concerned member states (List of Questions).
❑ Days 30 to 60	Dialog between Reference Member State / Concerned Member States / Applicant

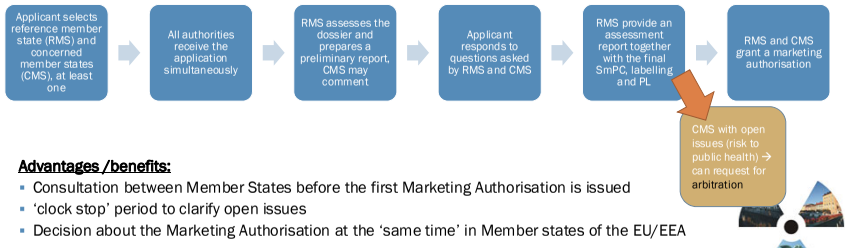
Conclusion of procedure → 60 days following day 0

- ✓ Granting of national MA in the Concerned Member States in **30** days
- ✗ Withdrawal of the application or
- ○ referral procedure (in case of potential serious risk to public health binding Commission Decision)

Prolongation of procedure for **additional 30 days** if CMS have remaining comments or „potential serious risk for public health".

DECENTRALISED PROCEDURE - DCP

Medicinal product has no MA at the time of application → applicant can choose procedure (NP or DCP, possibly CP)



Advantages /benefits:

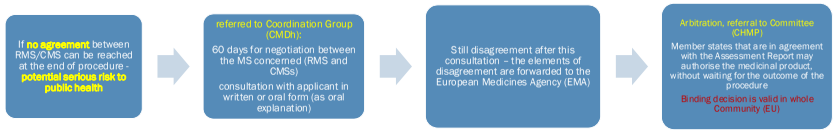
- Consultation between Member States before the first Marketing Authorisation is issued
- 'clock stop' period to clarify open issues
- Decision about the Marketing Authorisation at the 'same time' in Member states of the EU/EEA

DCP TIMELINE

Decentralised Procedure

Procedural steps	Timeline
1. Pre-procedural Step	Before day -14
2. Validation	Day - 14
3. Assessment step I	Days 0 – 119
⏱ Clock stop period up to 3 months	
4. Assessment step II	Days 120 – 210
5. Referral procedure (in case of Potential Seriuos Risk to Public Health); evaluation at the CMDh/CHMP	Days 270 or more
6. National step	Days 300 or more

MRP AND DCP – NO AGREEMENT



COORDINATION GROUP - CMDh

Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human

- Any question related to marketing authorisations of medicinal products **in two or more** Member States covers a variety of issues related to new applications, variations, renewals and pharmacovigilance activities
- The coordination group shall consider points of disagreement raised by Member States during mutual recognition or decentralised procedures
- The members of the CMDh nominated by the Member States, one per EU Member State, for a term of three years, which may be renewed.
- Secretariat provided by EMA

The **MRI Product Index** provides an overview of all medicinal products approved via MRP or DCP: https://mri.cts-mrp.eu/portal/home?domain=h

CENTRALISED PROCEDURE

- Laid down in **Regulation (EC) No 726/2004**
- **European Medicines Agency** is responsible for the scientific evaluation of the application for MA
- **European Commission grants** Authorisation
- the MAH can market the medicine and make it available to patients and healthcare professionals **throughout the EU (in all MSs & IS, NO, LI)** based on **a single marketing authorisation.**

CENTRALISED PROCEDURE

- **Mandatory** for:
  - Products derived from **biotechnology**
  - **advanced-therapy medicines** (i.e. gene therapy,...)
  - **Orphan** medicines (rare diseases)
  - Medicinal products for human use which contain a new active substance, intended for the treatment of **HIV/AIDS, cancer, diabetes, neurodegenerative diseases, auto-immune dysfunctions, viral diseases**.

- **Optional** for other medicinal products:
  - Generics of medicines authorised through the CP,
  - Constituting a significant therapeutic scientific or technical innovation, or
  - For which an EU authorisation would be in the interest of patients.

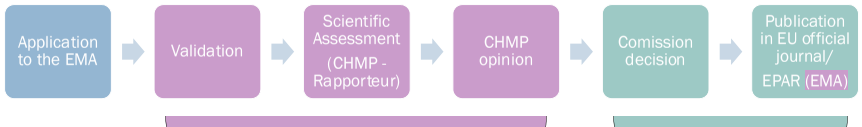
SCIENTIFIC COMMITTEE - CHMP

Committee for Human Medicinal Products **(CHMP)**

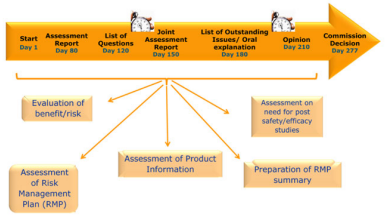
Members:
1 member nominated by each MS for a renewable period of 3 years
1 member nominated by the EEA-EFTA states (IS, NO, LI)
5 co-opted members (additional expertise, e.g. statistics, gene therapy)

Working parties and other groups for consultation on scientific issues
(QWP, BWP, BMWP, NcWP, Radiopharmaceuticals Drafting Group,...)

THE PROCESS



TIMELINE



Accelerated assessment
reduces the timeframe from 210 to **150 days** for CHMP to review a MA application and issue opinion if the product is of **major interest for public health and therapeutic innovation** (applicant needs to provide sufficient justification)
1st: **Soliris** in 2007, indicated in adults and children for the treatment of Paroxysmal nocturnal haemoglobinuria (PNH). Evidence of clinical benefit is demonstrated in patients with haemolysis with clinical symptom(s).
Up to today cca 115 MPs.

- evaluation procedure: **max 210 days** (clock stops possible at day 120 and day 180 if additional questions need to be addressed)
- within 15 days EMA forwards opinion to the → EC to start the **decision-making phase**
- Within 15 days EC sends draft implementing decision to the → Standing Committee on Medicinal Products for Human Use for review,
- In 15 days EU countries return their linguistic comments, in 22 days substantial ones.
- draft decision is adopted within **67 days** of the opinion of the EMA
- EC notifies MAH and publishes decision in the Union Register (https://ec.europa.eu/health/documents/community-register/html/index_en.htm).
- MAs are **valid for 5 years**. Renewal applications should be submitted to the EMA at least 6 months before expiry.

TYPES OF APPROVAL

Standard
- comprehensive data enable full evaluation of Quality, Safety and Efficacy
- 1st: GONAL-f in 1995: Anovulation (including polycystic ovarian disease, PCOD) in women, unresponsive to treatment with clomiphene citrate.

Conditional
- comprehensive clinical data have not been supplied, and are unlikely to be able to be provided
- the benefit risk balance is judged to be positive, because unmet needs will be fulfilled and the benefits of immediate availability outweigh risks due to the absence of the additional data
- valid for a renewable one year period; can be changed to standard
- must fulfil scope: **orphan drug, emergency threats** or **serious and life-threatening diseases**
- 1st: Arepanrix in 2010: Prophylaxis of influenza in an officially declared pandemic situation.

first COVID-19 vaccines authorised via CP

Exceptional Circumstances
- the applicant is unable to provide data on the efficacy and safety of the medicine (the indication is so rare that the applicant cannot reasonably be expected to provide comprehensive evidence or it is contrary to medical ethics to collect such information)
- must meet criteria: **rarity or medical ethics or state of scientific knowledge**
- 1st: Xigris in 2002: Xigris is indicated for the treatment of adult patients with severe sepsis with multiple organ failure when added to best standard care.

EPAR

European Public Assessment Report for all medicines authorised via centralised procedure (CP):

- Prepared by EMA secretariat and available at EMA website (e.g.: https://www.ema.europa.eu/en/medicines/human/EPAR/quadramet)

- Avalable in **all official EU languages**:
  - Summary for the public
  - List of all authorised presentations
  - Annex I Summary of Product Characteristics (SmPC)
  - Annexes IIA – IIE Manufacturers responsible for batch release, conditions or restrictions regarding supply and use, regarding the safe and effective use of medicine, specific obligations
  - Annex IIIA Labelling
  - Annex IIIB Package Leaflets (PL)

- In **English only**:
  - The scientific discussion,
  - Procedural steps before authorisation and
  - Steps taken and scientific information after authorisation

VI. MARKETING AUTHORISATION

MARKETING AUTHORISATION

A medicinal product may only be placed on the market in the European Economic Area (EEA) when a marketing authorisation has been issued by the competent authority of a Member State for its own territory (→ **national MA**) or when an authorisation has been granted in accordance with Regulation (EC) No 726/2004 for the entire Union (→ **Community/Union MA**).

The marketing authorisation holder (MAH) is responsible for marketing the medicinal product and must be established within the EEA (**Article 6 Directive 2001/83/EC).**

A marketing authorisation lays down the terms under which the marketing of a medicinal product is authorised in the EU.
A marketing authorisation is composed of:
- a **decision** granting the marketing authorisation issued by the relevant authority; and
- a **technical dossier** with the data submitted by the applicant in accordance with Articles 8(3) to 11 of Directive 2001/83/EC and Annex I thereto.

MARKETING AUTHORISATION

EUROPEAN COMMISSION

Brussels, 19.6.2015
C(2015)4317 (final)

COMMISSION IMPLEMENTING DECISION

of 19.6.2015

granting marketing authorisation under Regulation (EC) No 726/2004 of the European Parliament and of the Council for "Lumark - lutetium, isotope of mass 177", a medicinal product for human use

(Text with EEA relevance)

(ONLY THE DUTCH TEXT IS AUTHENTIC)

When granting marketing authorisation competent authority issues the decision together with Annexes (Product information).

The marketing authorisation must contain the **SmPC** according to Article 11 of Directive 2001/83/EC and the **labelling and the PL** according to Title V of Directive 2001/83/EC.

EU Databases with authorised medicinal products & Product Information (= SmPC, PL):
https://melclass.edqm.eu/links

PRODUCT INFORMATION

Summary of products characteristics (SmPC)
- o contains fundamental information for healthcare professionals on how to use the medicine

Package leaflet (PL)
- o usually placed inside the secondary packaging
- o it should describe everything the patient needs to know in patient friendly terms

Labelling
- o the wording on the primary and secondary packaging

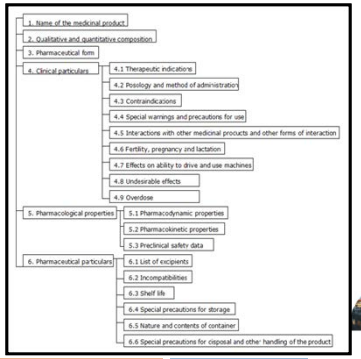
Guideline on how to draw up SmPC (in English) and practical advice in the form of templates on how to draw up the Product Information (in all EU languages) are provided to the applicant. They have been developed by the Quality Review of Documents (QRD) group, for centralised, decentralised and mutual recognition procedures (https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/product-information/product-information-templates-human).

SUMMARY OF PRODUCT CHARACTERISTICS

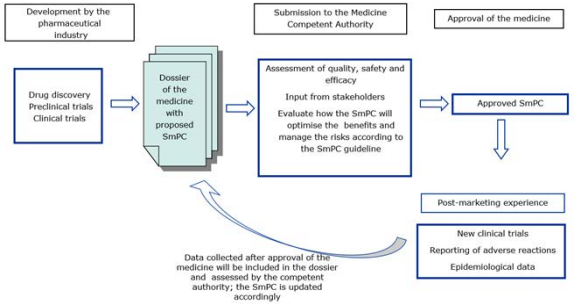
- Legal document, approved as part of the MA of each medicine.
- Information for healthcare professionals on how to use medicine.
- Information is updated throughout the life-cycle of the product as new data emerge.
- Information is presented according to a predefined structure. Some information may be suitable in different sections but cross-references are made to avoid repetitive information.

Essential information about the medicine:
- regarding the use
- benefits
- risks
- individualised care
- paediatric and elderly population
- organ impairment, concomitant diseases
- interactions

Pharmaceutical information:
- incompatibilities in 6.2
- shelf life in 6.3,
- precaution for storage, disposal and handling in 6.4 and 6.6



SmPC – HOW IS THE INFO PREPARED



SmPC – WHAT IS NOT INCLUDED

- Iformation on the scientific development which is available in the public assessment report
- Information in non-approved indications:
  - Because the MAH has not claimed the indication
  - An indication has been claimed but data did not demonstrate a positive benefit risk of the medicine; withdrawal or refusal AR provide available data
  - Exception in the paediatric group; the Paediatric Regulation aims to improve the information regarding this subgroup by providing all information on clinically relevant trials
- Specific issue for which data is lacking
- General advice on the treatment of particular medical conditions

SmPC – UPDATE

- The SmPC is a living document that requires an update when new relevant information emerges e.g.:
  - New adverse reactions observed after marketing of the product reported to the national competent authorities or the company
  - Following safety communication updates
- Pharmacovigilance legislation encourages participation of patients and healthcare professionals in reporting suspected adverse reactions

RADIOPHARMACEUTICALS

Definitions in Article 1 of Directive 2001/83/EC:

- **6. Radiopharmaceutical**: Any medicinal product which, when ready for use, contains one or more radionuclides (radioactive isotopes) included for a medicinal purpose.
- **7. Radionuclide generator**: Any system incorporating a fixed parent radionuclide from which is produced a daughter radionuclide which is to be obtained by elution or by any other method and used in a radiopharmaceutical.
- **8. Kit** : Any preparation to be reconstituted or combined with radionuclides in the final radiopharmaceutical, usually prior to its administration.
- **9. Radionuclide precursor**: Any other radionuclide produced for the radio-labelling of another substance prior to administration.

RADIOPHARMACEUTICALS

Marketing authorisation in paragraph 2 of Article 6 of Directive 2001/83/EC:

- The authorisation referred to in paragraph 1 shall also be required for **radionuclide generators, kits, radionuclide precursor radiopharmaceuticals** and **industrially prepared radiopharmaceuticals**.

Exception in Article 7 of Directive 2001/83/EC:

- A marketing authorization shall not be required for a radiopharmaceutical prepared at the time of use by a person or by an establishment authorized, according to national legislation, to use such medicinal products in an approved health care establishment exclusively from authorized radionuclide generators, kits or radionuclide precursors in accordance with the manufacturer's instructions.

Additional requirements in Article 9 of Directive 2001/83/EC:

- In addition to the requirements set out in Articles 8 and 10(1), an application for authorization to market a radionuclide generator shall also contain the following information and particulars:
  - a general description of the system together with a detailed description of the components of the system which may affect the composition or quality of the daughter nuclide preparation,
  - qualitative and quantitative particulars of the eluate or the sublimate.

RADIOPHARMACEUTICALS

Additional information for SmPC in Article 11 of Directive 2001/83/EC:

- Chapter 11.: full details of internal radiation dosimetry.
- Chapter 12.: additional detailed instructions for extemporaneous preparation and quality control, maximum storage time for intermediate preparation (e.g. eluate) or ready-to-use pharmaceutical.

Additional information regarding special labelling and instructions in PL in Article 66 and 67 of Directive 2001/83/EC include:

- **labelling of outer carton and container regarding safe transport of radioactive materials**
- label on the **shielding** regarding additional explaination of the codings on the vial and indicating time and date, the amount of radioactivity per dose or per vial and the number of capsules, or, for liquids, the number of millilitres in the container.
- labelling of **vial** with:
  - name or code of the medicinal product, including the name or chemical symbol of the radionuclide,
  - batch identification and expiry date,
  - international symbol for radioactivity,
  - name and address of the manufacturer,
  - amount of radioactivity as specified in paragraph 2.

Safety features (unique identifier and an anti-tampering device according to the Falsified Medicines Directive) don't apply to:

- radionuclide generators
- kits
- radionuclide precursors

...

VII. ORPHAN MEDICINAL PRODUCTS

ORPHAN MEDICINAL PRODUCTS

Regulation (EC) No. 141/2000 sets the basis with aims:

- stimulate research and development of medicinal products for life-threatening or very serious rare diseases by providing **incentives to sponsors**:
  - 10-years market exclusivity after authorisation,
  - fee reductions,
  - protocol assistance,
  - financial support for research.
- ensure access to treatment for patients suffering from rare diseases

Regulation establishes **COMP - The Committee for Orphan Medicinal Products,** EMA's committee responsible for recommending orphan designation of medicines for rare diseases.

COMP

...is responsible for evaluating applications for orphan designation:

- → intended for medicines to be developed for the diagnosis, prevention or treatment of **rare diseases**
- → that are **life-threatening** or **chronically debilitating**
- → the **prevalence** of the condition in the EU must not be more than 5 in 10,000 or it must be unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development;
- → no satisfactory method of diagnosis, prevention or treatment of the condition concerned can be authorised, or, if such a method exists, the medicine must be of **significant benefit** to those affected by the condition.

The European Commission decides whether to grant an orphan designation for the medicine based on the COMP's opinion.

The COMP also advises and assists the EC on matters related to orphan medicines, including:

- developing and establishing an EU-wide policy;
- drawing up detailed guidelines;
- liaising internationally.

COMP

Committee for Orphan Medicinal Products **(COMP)**

Members:
a chairman (elected by COMP members)
1 member nominated by each of 27 MS
1 member nominated by the EEA-EFTA states (IS, NO, LI)
6 members nominated by the EC to represent patients' organisations and on EMA's recommendation

1st: Nexavar in 2006 (orphan designation granted 2004): for treatment of hepatocellular carcinoma and renal cell carcinoma

ORPHAN DESIGNATION

Since 2014, 1.793 medicines have been granted an orphan designation, 141 in 2024.

Medicinal products with orphan designation:
- Over 260 **active** orphan medicinal products with a MA
- Over 149 orphan designations of medicinal products holding a MA already **withdrawn or expired**

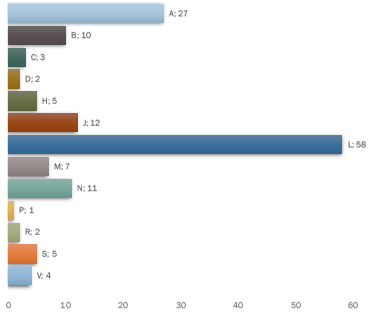
> 6000 rare diseases

ORPHAN DESIGNATION IS NOT AN AUTHORISATION

Orphan designation in the product lifecycle

Research and development	Marketing authorisation	Post-authorisation
Orphan incentives		
Applying for orphan designation		
Activities after orphan designation		
Submitting annual reports on medicine development		
Changing the name or address of a sponsor		
Removing an orphan designation		
Transferring a designation to a new sponsor		
	Applying for marketing authorisation	
		Market exclusivity

DISTRIBUTION BY THERAPEUTIC AREA



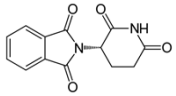
A	ALIMENTARY TRACT AND METABOLISM
B	BLOOD AND BLOOD FORMING ORGANS
C	CARDIOVASCULAR SYSTEM
D	DERMATOLOGICALS
H	SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS
J	ANTIINFECTIVES FOR SYSTEMIC USE
L	ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS
M	MUSCULO-SKELETAL SYSTEM
N	NERVOUS SYSTEM
P	ANTIPARASITIC PRODUCTS, INSECTICIDES AND REPELLENTS
R	RESPIRATORY SYSTEM
S	SENSORY ORGANS
V	VARIOUS

ORPHAN DESIGNATION

THALIDOMIDE

Since 2000 EMA has received 7 requests for orphan designation for thalidomide for treatment of:
- erythema nodosum leprosum (ENL) or type II lepra reactions (2, W)
- graft-versus-host disease (1, W)
- multiple myeloma (3, W)
- hereditary haemorrhagic telangiectasia (1, P)

On 20 nov 2001 thalidomide was granted orphan status for the treatment of multiple myeloma.
Less than 7 years later, thalidomide was authorised in the EU, on april 2008, and the MA is currently active.
In april 2018 the orphan designation status ended at the end of a 10-year period of market exclusivity (https://www.ema.europa.eu/en/medicines/human/EPAR/thalidomide-celgene)
Ongoing is the orphan designation for treatment of hereditary haemorrhagic telangiectasia (positive/published 31. 3. 2017)



VIII. MEDICINES FOR CHILDREN

MEDICINES FOR CHILDREN

Before 2007, many medicines authorised in Europe were not studied adequately or authorised in children → difficulties for prescribers and pharmacists treating children, patients and carers.

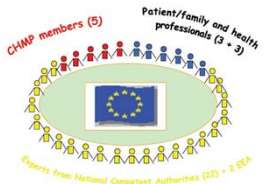
The Regulation (EC) **No. 1901/2006** introduced changes into the regulatory environment for paediatric medicines, to better **protect the health of children** in the EU, entered into force on 26th January 2007:

- established **Paediatric Committee** (PDCO) to provide objective scientific opinions on paediatric investigation plans (PIPs), development plans for medicines for use in children.
- facilitates the development and availability of medicinal products for use in the paediatric population
- places certain **obligations** on applicants, the main one being submission of data on the use of a medicinal product in children obtained in accordance with an agreed **paediatric investigation plan (PIP)** by EMA.
- provided that the requirements of Regulation are fulfilled, the applicants may be eligible for a **reward** (Title V of Regulation):
  - an extension of the supplementary protection certificate (SPC),
  - extension of market exclusivity, or
  - data/market protection.
- provides for a specific **authorisation for medicinal products developed exclusively for use in the paediatric population**: the paediatric use marketing authorisation – **PUMA** (Article 2.4 of the Regulation).

MEDICINES FOR CHILDREN

Members:
5 members of CHMP
1 member nominated by each of 27 MS
3 members representing patients' associations
3 members representing healthcare professionals

Paediatric Committee
(PDCO)



PAEDIATRIC USE MA - PUMA

- **PUMA is a dedicated marketing authorisation covering the indication(s) and appropriate formulation(s) for medicines developed exclusively for use in the paediatric population.**
- The PUMA was introduced by the Paediatric Regulation (Article 30) for medicines that are:
  - already authorised;
  - no longer covered by intellectual property rights (patent, supplementary protection certificate);
  - exclusively developed for use in children
- PUMA
  - may retain the existing brand name of the corresponding adult product
- The development of a PUMA must follow a paediatric investigation plan (PIP) (must discuss all paediatric subsets!), to be agreed by the Paediatric Committee (PDCO).
- **Buccolam (midazolam in buccal application form) has been first MP granted with PUMA in 2011. It is recommended for treatment of prolonged, acute, convulsive seizures in paediatric patients from 3 months to 18 years**
- Medicinal products that have received a PUMA benefit from the data and marketing protection periods set out in Directive 2001/83/EC (Article 38(2) of Regulation (EC) 1901/2006) → **10 years of market protection**

IX. WHOLESALE DISTRIBUTION

WHOLESALE DISTRIBUTION OF MEDICINAL PRODUCTS

- All activities consisting of procuring, holding, supplying or exporting medicinal products, apart from supplying medicinal products to the public.
- Activities carried out with manufacturers or their depositories, importers, other wholesale distributors or with pharmacists and persons authorized or entitled to supply medicinal products to the public in the Member State concerned
- Wholesalers have a **public service obligation**: guarantee permanently an adequate range of medicinal products to meet the requirements of a specific geographical area and to deliver the supplies requested within a very short time over the whole of the area in question.
- Member states shall ensure that **only medicinal products with a marketing authorisation** in accordance with Community law are distributed in their territory.

WHOLESALE DISTRIBUTOR

- To obtain the distribution authorisation in MS, applicants must fulfil the following minimum requirements :
  a) they must have suitable and adequate premises, installations and equipment;
  b) they must have staff, and in particular, a qualified person designated as responsible;
  c) they must undertake to fulfil the obligations under the terms of Art. 80 of Dir. 2001/83/EC.
- **Good distribution practice (GDP)** describes the minimum standards that need to be met to ensure that the quality and integrity of medicines is maintained throughout the supply chain:
  - medicines in the supply chain are authorised in accordance with EU legislation;
  - medicines are stored in the right conditions at all times (including during transportation);
  - contamination is avoided;
  - an adequate turnover of stored medicines takes place;
  - the right products reach the right addressee within a satisfactory time period.
- Tracing system in place enables finding faulty products and an effective recall procedure.

EudraGMDP is a publicly accessible EU database containing all wholesale distribution authorisations and details of registered importers and distributors of active substances in the EEA
http://eudragmdp.ema.europa.eu/inspections/displayWelcome.do

X. PHARMACOVIGILANCE

PHARMACOVIGILANCE FOCUS

- The specific aim has been defined by WHO as the science and activities, relating to the: **detection**, **assessment**, **understanding** and **prevention** of adverse effects or any other medicine-related problem.
- The European Medicines Agency (EMA) coordinates the European Union (EU) pharmacovigilance system and operates services and processes to support pharmacovigilance in the EU.

- **Primary focus = postmarketing surveillance.**
- **To ensure patients are continuously getting safe and effective Medicinal Products.**

WHY PHARMACOVIGILANCE?

- Before a medicine is authorised for use, evidence of its safety and efficacy is limited to the results from clinical trials, where patients are selected carefully and followed up very closely under controlled conditions.
- This means that at the time of a medicine's authorisation, it has been tested in a relatively small number of selected patients for a limited length of time.
- After authorisation the medicine may be used in a large number of patients, for a long period of time and with other medicines. Certain side effects may emerge in such circumstances.
- It is therefore essential that the safety of all medicines is monitored throughout their use in healthcare practice.

PHARMACOVIGILANCE SYSTEM

- EU law therefore requires each marketing authorisation holder, national competent authority and EMA to operate a pharmacovigilance system.
- The overall EU pharmacovigilance system operates through cooperation between the EU Member States, EMA and the European Commission.
- In some Member States, regional centers are in place under the coordination of the national competent authority.
- The Member State shall take all appropriate measures to **encourage doctors and other healthcare professionals to report suspected or unexpected adverse reactions** to the National Competent Authority.

THE ROLE OF NCA

- Each Member State has established a **PhV system** for the collection and evaluation of relevant information to the risk-benefit balance of Medicinal Product.
- monitors the safety profile of the products available on the market and **takes appropriate action where necessary**. As a consequence of such evaluations, a Marketing Authorisation may be
  - changed (amended SmPC, PL, labelling),
  - suspended,
  - revoked or
  - withdrawn.
- **ensures** that Healthcare Professionals, Patients/Consumers and the general public are **informed** of any significant changes and of any suspected safety concerns requiring vigilance.

PHARMACOVIGILANCE RISK ASSESSMENT COMMITTEE (PRAC)

- responsible for assessing all aspects of the risk management of medicines for human use
- activities include the **detection, assessment, minimisation and communication** relating to the risk of adverse reactions, while taking the therapeutic effect of the medicine into account
- recommendations on any questions relating to pharmacovigilance activities related to a medicine for human use
- agendas, minutes, signal recommendations are published

PHARMACOVIGILANCE

- to detect any rare or long-term adverse effects over a much larger patient population and longer time period than was possible during the Phase I-III clinical trials.
  - **"small" population:** may miss (very) rare adverse effects (<1/1,000)
  - **"short" term:** may miss adverse events that only develop after several years

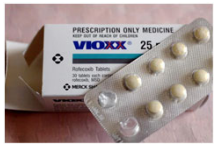
- Serious adverse effects discovered by Phase IV trials may result in a recall of the MP from the market. Past cases include cerivastatin (**Lipobay**) and rofecoxib (**Vioxx**).

PHARMACOVIGILANCE

- **Cerivastatin (Baycol, Lipobay)** was used to lower cholesterol and prevent cardiovascular disease. Cerivastatin was marketed by Bayer A.G. in the late 1990s.
- During post-marketing surveillance, 52 deaths were reported in patients using cerivastatin, mainly from rhabdomyolysis (rapid breakdown of skeletal muscle tissue due to traumatic injury) and its resultant renal failure.
- 2001: withdrawn from the market.

PHARMACOVIGILANCE

- **Rofecoxib was a nonsteroidal anti-inflammatory** drug (NSAID) developed by Merck & Co. to treat osteoarthritis, reutmathoid arthritis, acute pain conditions, and dysmenorrhoea (painful menstruation).
- Rofecoxib was approved and marketed under the brand name Vioxx.
- In 2004, Merck withdrew rofecoxib from the market because of concerns about increased risk of heart attack and stroke associated with long-term, high-dosage use.



Drug name	Drug class or use	Year first marketed	Year of withdrawal	Length of time on market (years)	Adverse reaction or safety concern
Rofecoxib	NSAID (COX-2 inhibitor)	1999	2004	5	Thrombotic events
Thioridazine	Neuroleptic (α-adrenergic and dopaminergic receptor antagonist)	1958	2005	47	Cardiac disorders
Valdecoxib	NSAID (COX-2 inhibitor)	2003	2005	2	Cardiovascular and cutaneous disorders
Rosiglitazone	Antidiabetic treatment (PPARγ agonist)	2000	2010	10	Cardiovascular disorders
Sibutramine	Treatment of obesity (serotonin-noradrenaline reuptake inhibitor)	1999	2010	11	Cardiovascular disorders
Oxyfrenaline	Sympathomimetic (non-specific β-agonist)	1961	2010	49	Cardiac disorders
Benfluorex	Anorectic and hypolipidaemic	1974	2009	35	Heart valve disease—Pulmonary hypertension
Clobutinol	Cough suppressant (centrally acting)	1961	2007	46	QT prolongation
Buflomedil	Vasodilator (α1 and α2 receptor antagonist)	1974	2011	37	Neurological and cardiac disorders (sometimes fatal)
Veralipride	Neuroleptic (and dopaminergic receptor antagonist)	1979	2007	28	Neurological and psychiatric disorders
Rimonabant	Treatment of obesity (cannabinoid receptor antagonist)	2006	2008	2	Psychiatric disorders
Carisoprodol	Muscle relaxant	1959	2007	48	Intoxication—Psychomotor impairment—Addiction—misuse
Acepromeazine + Acepromazine + Clorazepate	Hypnotic	1988	2011	23	Cumulative adverse effects—misuse—fatal side effect
Dextropropoxyphene	Opioid painkiller	~1960	2009	49	Fatal overdose
Nefazodone	Antidepressant	1994	2003	9	Hepatotoxicity
Ximelagatran/melagatran	Anticoagulant (thrombin inhibitor)	2003	2006	3	Hepatotoxicity
Lumiracoxib	NSAID (COX-2 inhibitor)	2003	2007	4	Hepatotoxicity
Sitaxentan	Antihypertensive (endothelin receptor antagonist)	2006	2010	4	Hepatotoxicity
Bufexamac	NSAID	~1970	2010	40	Contact allergic reactions

An investigation into drug products withdrawn from the EU market between 2002 and 2011 for safety reasons and the evidence used to support the decision-making

XI. CONCLUSION

Understanding and complying with the rules governing the production, distribution, and use of medicinal products is essential for pharmaceutical companies, wholesale distributors, and healthcare professionals, to safeguard public health and ensure the availability of safe and effective medicinal products.

- ✓ *High quality*
- ✓ *Safe*
- ✓ *Effective*

MORE INFORMATION

• Heads of Medicines Agencies
http://www.hma.eu/

• European Medicines Agency – EMA
http://www.ema.europa.eu/ema/

• European Commission – DG Sante
https://commission.europa.eu/about-european-commission/departments-and-executive-agencies/health-and-food-safety_en

• EU legislation
http://ec.europa.eu/health/documents/eudralex/index_en.htm

• Community Register
https://ec.europa.eu/health/documents/community-register/html/index_en.htm

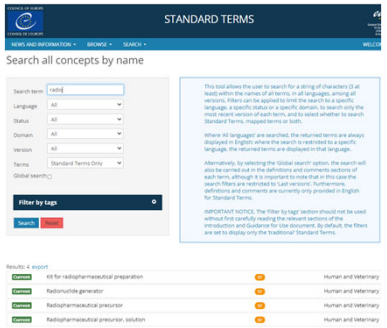
ABBREVIATIONS

- CP Centralised Procedure
- CMS Concerned Member States
- CR Council Regulation
- CTD Common Technical Document
- DCP Decentralised Procedure
- EC European Commission
- EMA European Medicines Agency
- EU European Union
- MA Marketing Authorisation
- MAH Marketing Authorisation Holder
- MP Medicinal Product
- MRP Mutual Recognition Procedure
- MS Member State
- NCA National Competent Authority
- NP National Procedure
- PL Package leaflet
- RMS Reference Member State
- Q, S, E Quality, Safety, Efficacy
- SmPC Summary of Product Characteristics
- WHO World Health Organisation

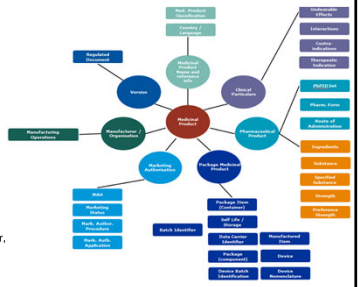
THX FAQ BTW ASAP BRB XOXO LOL PLZ ROFL! YOLO OMG! GR8

"I'm just waiting to see what you're making, so I can write some regulations for it."

RADIOPHARMACEUTICALS & EDQM



ISO IDMP



EMA is in the process of **implementing the standards** developed by the International Organization for Standardization (ISO) **for the identification of medicinal products (IDMP).**
The standards are being implemented in a phased programme based on the four domains of master data in pharmaceutical regulatory processes: **substance**, **product**, **organisation** and **referential** (SPOR) master data:

ISO IDMP standards specify the use of standardised definitions for the **identification and description of medicinal products** for human use;
→ to facilitate the reliable **exchange of medicinal product information** in a robust and consistent manner,
→ help to ensure wide **interoperability** across global regulatory and healthcare communities.

Legal basis: Commission Implementing Regulation (EU) No 520/2012 (articles 25 and 26).

Standards cover the following aspects to **describe a medicinal product for human use**:

- medicinal product name;
- substances;
- pharmaceutical product (route of administration, strength);
- marketing authorisation;
- clinical particulars;
- packaging;
- manufacturing.

ISO IDMP covers the **entire medicinal product lifecycle**, and all holders of marketing authorisations for medicines in the EU and EEA must submit information to the EMA on authorised medicines and **keep this information up-to-date**.

SOPs as a part of quality assurance documents: purpose, preparation and implementation

Assist. Dr. Jasna Omersel graduated 2006 from the Faculty of Pharmacy, University of Ljubljana, Slovenia. In 2006, after working in Pharmacy, she obtained the State Pharmacist Certification from the Ministry of Health of the Republic of Slovenia and commenced postgraduate education in the field of Clinical Biochemistry. Between 2006 and 2010 she was an active researcher in the Laboratory of Immunology at the University Medical Centre Ljubljana. She received scholarships from the Society for Development of Rheumatology Slovenia, World Federation of Scientists, and The Wood-Whelan Research Fellowships for her post-doctoral study. In January 2011 she defended her doctoral thesis: Posttranslational Modifications of Immunoglobulins as a Cause of Autoimmunity. As a postdoctoral fellow, in 2015, she obtained basic knowledge on study design and laboratory research on experimental autoimmune animal models at The Zabludowicz Center for Autoimmune Diseases in Israel. In 2024 she finished national specialist study program for certified qualification European specialist of Clinical Chemistry and Laboratory diagnostics, giving her a broad perspective on routine laboratory work, biochemistry methods and overview of standard operating procedures, from technical to administrative routine protocols.

She works as teaching assistant at the Faculty of Pharmacy Ljubljana, Department of Clinical Biochemistry. She supervises students´ practical laboratory work as part of courses: Immunology in Laboratory Diagnostics, Skin Immunology, Clinical Biochemistry, Clinical Chemistry and Biomedical Analysis at both graduate and postgraduate level. Her research interests include the study of mechanisms and molecular changes responsible for triggering autoimmune reactions leading to various autoimmune diseases, protein modifications, development of laboratory diagnostics tests, immunoreactivity cell tests. In March 2025 she became a head of Laboratory for Molecular Diagnostics at the Department of Clinical Biochemistry at the Faculty of Pharmacy.

<u>The lecture has the following learning objectives:</u>

1. Students are able to understand the value and function of SOPs in QA system and their importance to an organization.
2. Students are able to explain the benefits of SOPs implementation in pharmaceutical industry.
3. Students are able to recognize benefits of implementing SOPs in analytical/clinical laboratory.
4. Students are able to formulate a technical or administrative SOP.
5. Students are able to critically evaluate and revise SOPs at their organization.

Summary of the lecture:

Constant development and use of Standard Operating Procedures (SOPs) in everyday procedures is integral part of successful quality management system in many organisations. Due to the complex structure of the pharmaceutical industry, due to its own industry standards and governmental regulations, standardized procedures are necessary to achieve high standards throughout the whole lifecycle of the medicinal product. SOPs serve as a fundamental and foundational means of communication across all levels of the organization, enhancing success in this challenging and competitive environment. Not only in pharmaceutical industry but also in specialised analytical or medicinal laboratories, where medicinal products are being tested, prepared for their final application form or monitored in patients´ blood or body, SOPs are the main building blocks of a laboratory quality assurance framework. Furthermore, in the pharmaceutical industry, they help to assure quality, safety and efficacy of the medicinal product; in laboratory they are meant to ensure consistency, accuracy, and quality of data obtained from a specific analysis and to provide clinicians with reliable results supporting their patients´ diagnosis (Figure 1).

In the field of radiopharmaceuticals, quality assurance is of special importance because products are released before all the testing is done. According to valid cGRPP-guidelines (2021) ˝quality assurance represents the sum of all organised arrangements made with the objective of ensuring that medicinal products are of the quality required for their intended purpose˝. One part is also a good documentation practice. Supporting documents may be paper, electronic, or a combination of both. For a small scale radiopharmacy the cGRPP guidelines also specify the need for a responsible person for radiopharmacy with a list of responsibilities. One of them is also ˝approval of the procedures, specifications, processes and methods including related standard operating procedures.˝.

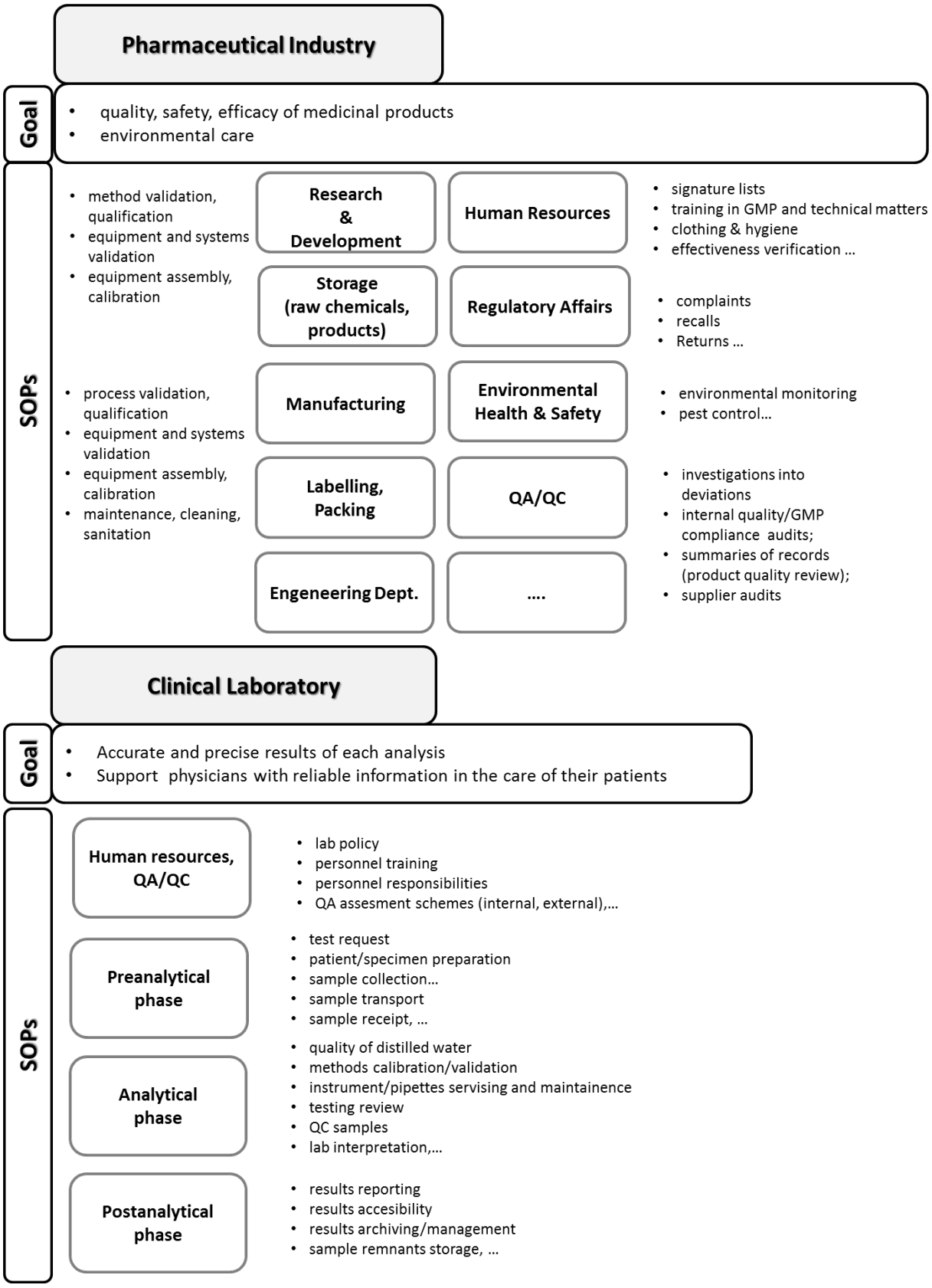


Figure 1: The areas of importance of SOPs in Pharmaceutical Industry and Clinical Laboratory.

1. Standard Operating Procedure

According to the cGRPP guidelines (2021): *˝Instructions and Standard Operating Procedures should be written and independently approved for each procedure or operation within the small-scale radiopharmacy. These operations include production, quality assurance and management aspects. SOPs should be reviewed at least every 2-3 years unless they require immediate revisions. There must be version control such that only currently approved version is accessible.˝*.

SOP is an authorized set of written instructions that document a routine or repetitive activity (method, procedure) followed by an organization.
They should be prepared and implemented in all following areas:
- where variations must be controlled,
- where safety risk is present,
- where numerous people perform the same procedure,
- where technical equipment permits variations,
- when management looks and evaluates continuous improvement,
- when objective feedback on performance is desired.

An SOP is a living and multipurpose document. It is intended to be used in everyday routine or research practice, to speed up personnel training and reduce or even prevent possible procedure mistakes. Finally, it also coordinates one procedure with another, so it can be kept as a record or used as a review. The development of an efficient SOP, reflecting critical activities in organization, should go through **several steps of creation**: SOP goal planning, drafting, internal reviewing, external reviewing, testing, posting at working place and archiving.

1.1. Types of SOPs

There are two basic types of SOPs: **(a) administrative/fundamental programmatic SOP**, which covers the instructions for various activities in the organization/laboratory (e.g. determines employee training needs, describes office/lab correspondence procedures, results archiving procedures (analytical study, patient files…) etc. It instructs how to initiate, coordinate, report results of a specific activity; (b) **technical SOP**, which instructs the user how to perform a specific analytical method in the lab or field, how to collect the sample to preserve its integrity or informs and leads user how to do things properly (e.g. data processing and evaluation, modelling, software programming, risk assessment, equipment operation).

1.2. Form, Formats and Writing Style of SOPs

Covering wide range of activities, it is well accepted that SOPs forms should be standardized, especially within an organization. The manufacturer instructions provided on product inserts are not really example of SOP. They instruct how to perform a method but do not include important information that is specific to laboratory policy, such as how to record results, sequence of testing, safety practice, ways of archiving, etc. However, there is no universal standard for SOP structure, but it should contain some required elements, organized in fixed structure. Sections can be added, organized or left out according to specific needs of the procedure or activity.
Suggested form of SOP structure:

(i) Standardized Header
(0) Tittle
(1) Purpose/Objective
(2) Scope
(3) Responsibility
(4) Terminology, Definitions, Abbreviations
(5) Related documents/Related SOPs
(6) Procedure/Method/Principle
(7) Archiving/ Records management
(8) References
(9) Appendices/Enclosures (checklists, QR code, equipment list, …)

(10) List of receivers (controlled copy)/ Distribution list
(11) Revision record/History of change

Standardized header and numbering system provide good transparency and traceability of organisation's technical procedures and administrative activities, also showing the flow of the information kept inside. Is should contain most important information. Complete standardized header would typically appear on the first page of a SOP; reduced standardized header includes a smaller version of the header (department name, page number, SOP tittle, SOP number, SOP revision number) and would appear on all other pages.

Writing style is of great importance; SOPs should be easy to read; language should be concise and clear, with short, explanatory sentences, usually in imperative form. SOP can be written in a simple step text format, which is a useful and powerful way to describe short routine processes. When procedures are longer, involve demanding tasks and sample or equipment handling, flowcharts and graphics should be included wisely to increase transparency. Many computer programmes and video technology software can help to design a creative SOP, understandable and helpful for the work at hand.

1.3 Management of SOP

The SOP development process is critical for a successful implementation. SOPs should be written by individuals knowledgeable with the activity and organisation´s internal structure. Usually these are field filed experts, however, personnel from a routine practice should be involved in a process of internal review. This will provide them with a sense of ownership and a commitment when management will use their ideas. SOPs need to remain current to be useful – regular update and re-approval is needed with changes tracked in Revision section. Also, guidelines propose a systematic review on a two-year periodic basis to assure procedures remain current, appropriate or withdrawn. The frequency of review should be indicated by management in Quality Management Plan, determining all responsibilities of the personnel connected to the SOPs.

2. Conclusion

Continual improvement is the core of quality management system, especially at the field of medicinal products and its controlled environment. However, it requires an organised system, commitment, planning, and participation of each individual. The bigger the company, the more complex its SOP management. SOPs should not be a policy, but readable written instructions, developed by working personnel for working personnel. This will help them to work with methods confidently, achieving high quality standards consistently. This, ultimately, will increase buy-in and empower workforce, reduce training costs and support quality goals of the organization.

Take home messages:

- SOPs are integral part of successful quality management system
- SOPs are concise written instructions that document a routine or repetitive activity
- SOPs ensure consistency, accuracy, and quality of data or a procedure
- SOPs should have standardized format within organisation
- SOPs are only of use if they are easily understood by new personnel, regularly updated, accessible on-site

References (further reading):

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STANDARD OPERATING PROCEDURES

SOPs AS A PART OF QUALITY ASSURANCE DOCUMENTS: PURPOSE, PREPARATION AND IMPLEMENTATION

Asist. dr. Jasna Omersel, mag. farm., EuSpLM
Faculty of Pharmacy, University of Ljubljana
Department of Clinical Biochemistry
Laboratory for Molecular Diagnostics

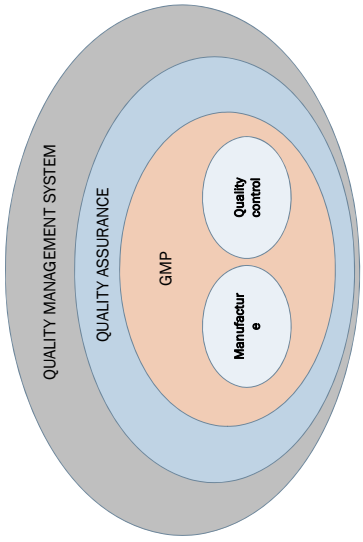
OUTLINE

1	SOP in quality management system
2	SOP in Pharmaceutical Industry and Clinical Laboratory
3	SOP creation process Forms and formats of SOP Management of SOP
4	Implementation of SOP SOP: Strengths and weaknesses

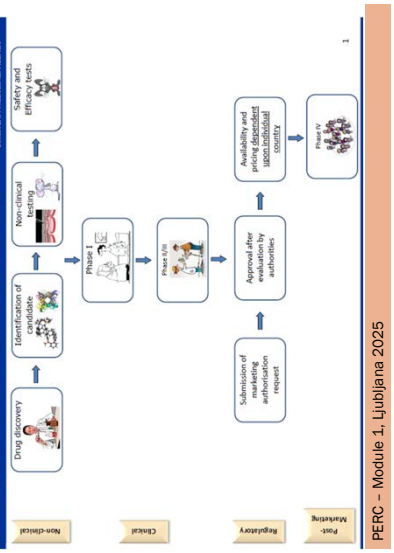
GOALS

- Upon successful completion of this training you will be able:
- Understand the value and function of SOPs in QA system and their importance to an organization
- Explain the benefits of SOPs implementation in pharmaceutical industry
- Recognize benefits of implementing SOPs in analytical/clinical laboratory
- Formulate a technical or administrative SOP
- Critically evaluate and revise SOPs at your organization

1. SOP IN QUALITY MANAGEMENT SYSTEM



2. SOP IN PHARMACEUTICAL INDUSTRY



Clinical Laboratory

Goal
- **Accurate and precise results of each analysis**
- **Support physicians with reliable information in the care of their patients**

SOPs

Human resources, QA/QC	Preanalytical phase	Analytical phase	Postanalytical phase
• lab policy • personnel training • personnel responsibilities • QA assesment schemes	• test request • patient/specimen preparation • sample collection... • sample transport • sample receipt, ... • quality of distilled water	• methods calibration/validation • instrument/pipettes servising and maintainence • testing review • QC samples • lab interpretation.... • results reporting	• results accesibility • results archiving/management • sample remnants storage. ...

SOPs connect all building blocks of QMS: organization and personnel, equipment, procurement, process control, biosafety and corrective and preventive actions.

Pharmaceutical Industry

Goal
- **quality, safety, efficacy of medicinal products**
- **environmental care**

SOPs

Research Development	Storage (raw chemicals, products)	Manufacturing	Labelling, Packing	Engeneering Dept.
• method alidation, qualification • equipment and systems validation • equipment assembly, calibration	• process validation, qualification • equipment and systems validation • equipment assembly, calibration • maintenance, cleaning, sanitation			

Human Resources	Regulatory Affairs	Environmental Health & Safety	QA/QC	....
• signature lists • training in GMP and technical matters • clothing & hygiene	• effectiveness verification ... • complaints • recalls , returns ...	• environmental monitoring • pest control...	• investigations into deviations • internal quality/GMP compliance audits; • summaries of records (product quality review); • supplier audits	

SOP IN QA OF RADIOPHARMACEUTICALS

According to the cGRPP guidelines (2021):

˝ Instructions and Standard Operating Procedures should be written and independently approved for each procedure or operation within the small-scale radiopharmacy. These operations include production, quality assurance and management aspects. SOPs should be reviewed at least every 2-3 years unless they require immediate revisions. There must be version control such that only currently approved version is accessible.˝.

3. SOP CREATION PROCESS

- **S**tandard **O**perational **P**rocedures

(protocol, instructions, worksheets, lab. operating procedures)

˝ SOP is an authorized set of written instructions that document a routine or repetitive activity (method, procedure) followed by an organization.˝

- Description of a administrative, technical and fundamental programmatic operational elements of an organization.
- Managed under a QA/QMP of organization.

1. Administrative/Fundamental programmatic SOP:

Covers the instructions for various activities in the organization/laboratory: how to initiate, coordinate, report results of the activity…:

- determine employee training needs,
- describe office/lab correspondence procedures
- results archiving procedures (analytical study, patient files…) ,…

2. Technical SOP

- **instructs the user how to:**
  - perform a specific analytical method in the lab or field
  - how to collect the sample to preserve its integrity, …
- **Informs and leads user how to do sth properly:**
  - data processing and evaluation (verification, validation),
  - modeling, software programming, risk assessment
  - equipment operation, …

- ***GOP*** *– global operating procedures*
- ***SOP*** *– standard operating procedures*
- ***WP*** *– working procedures*
- ***AP*** *– analytical procedures*

SOPs should be prepared and implemented in all following areas:

- where variations must be controlled
- where safety risk is present
- where numerous people perform the same procedure
- where technical equipment permits variations
- when management looks and evaluates continuous improvement
- when objective feedback on performance is desired

Where to start...

1. **Plan for results**
2. **Draft SOP** ⇒ decide about form and format
3. **Internal Review**
4. **External Review**
5. **Testing**
6. **Post**
7. **Train**

Parts/chapters of SOPs

(i) Standardized Header

(0) Tittle
(1) Purpose/Objective
(2) Scope
(3) Responsibility
(4) Terminology, Definitions, Abbreviations
(5) Related documents/Related SOPs
(6) Procedure/Method/Principle
(7) Archiving/ Records management
(8) References
(9) Appendices/Enclosures
(10)List of receivers (contolled copy)/ Distribution list
(11)Revision record/History of change

WHO recommendations

(0) Tittle
(1) Introduction
(2) Principle of method
(3) Specimen types, collection and storage
(4) Reagents, standards and control - preparation and storage
(5) Equipment, glassware and other accessories
(6) Detailed procedure
(7) Calculations, calibration curve
(8) Analytical reliabilities –(QC and Statistical assessment)
(9) Hazardous reagents
(10) Reference range and clinical interpretation
(11) Limitations of method (e.g. interfering substances and troubleshooting)
(12) References
(13) Date and signature of authorization
(14) (Effective date + Schedule for review)

***Clinical Laboratory Standards Institute**: CLSI document GP2-A5 2006*

SOP FORMS AND FORMATS

1. Writing style - basic rules :

- Concise, clear, step-by-step, easy-to-read format
- Present the information in an unambiguous, not overly complicated way
- Use the active voice and present verb tense, to clearly define the actions to take
- The term "you" should not be used, but implied in the text

"Keep it simple as possible, not a bit simpler."

2. Level of details: ?!

Give enough detail to eliminate significant variation to the procedure.
"SOP testing"!

3. Format:

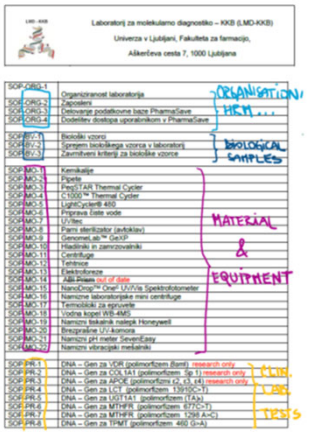
Many decisions	More than 10 steps?	Best SOP format
No	*No*	**Simple Text steps**
No	*Yes*	**Hierarchical/graphical**
Yes	*No*	**Flowchart**
Yes	*yes*	**Flowchart**

Adopted from: Stup. R..Standard Operating Procedures: A writing Guide. PennState Extensions

SOP CREATION PROCESS

Logo **Department Name**		**Page 1 of 5**
SOP number:	Revision number:	
SOP Tittle:		
Type of document: SOP	Valid from: Review date:	
Written by:	Signature:	Date:
Reviewed by:	Signature:	Date:
Approved by:	Signature:	Date:

Logo **Department Name**		**Page 1 of 5**
SOP number:	Revision number:	
SOP Tittle:		



SOP FORMS AND FORMATS

How and when to use different formats?

a) Simple step text format –
Used frequently but not neccesary the most appropriate one.

b) Hierarchical/graphical

c) Flowchart

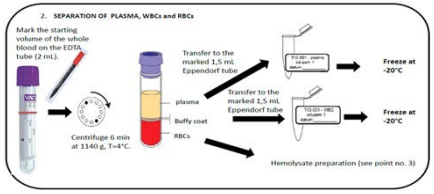
b) Hierarchical/graphical

e.g. Complex procedure

Pictures provide clarity and a "picture is worth a thousand words˝.

http://www.eanm.org/content-eanm/uploads/2016/11/tech_radiopharmacy.pdf

e.g. Complex procedure



c) Flowchart

e.g. Sequence action, quick decisions needed

e.g. Sequence action, repeating activity...

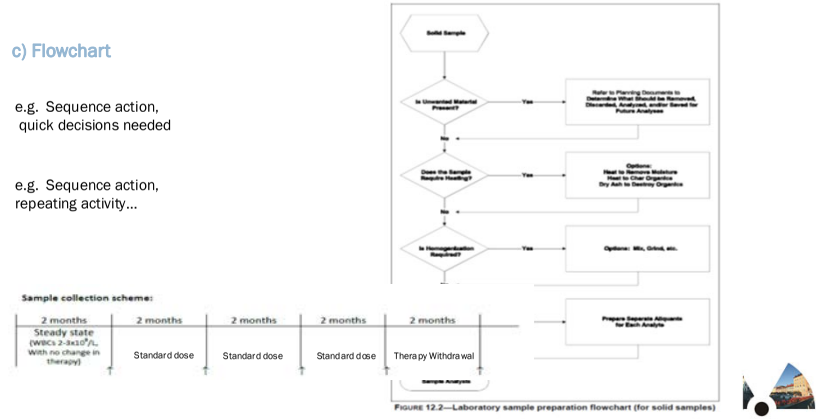


FIGURE 12.2—Laboratory sample preparation flowchart (for solid samples)

- Picture
- QR code : picture and video support *(as an Appendix)*
- Checklists table

e.g. Picture of the equipment

e.g. QR code

https://www.youtube.com/watch?v=JMfKgDoKJp0

SOP MANAGEMENT

"If it´s important enough to write, then it´s important enought to mantain and communicate."

- SOPs should be written by individuals knowledgeable with the activity
- regular update, re-approval (changes tracked in SOPs' Revision section)
- determine all responsibilities of the personnel connected to the SOPs
- a systematic review is needed (e.g. 2-3 years periodic basis , specified in Quality Management Plan)

Version	Effective Date	Description of the revision
02	10.9.2017	Change of sample storage, pg.3., section 3.1

- A Master Document should be created, the number and location of approved copies should be recorded.

SOP IMPLEMENTATION

1. Plan for results
2. Draft SOP
3. Internal Review
4. External Review
5. Testing
6. Post
7. Train

"Human nature dictates that people support what they help to create."

4. SOP STRENGHTS AND WEAKNESSES

PROBLEM	⇒	ACTION
• SOPs` overload	⇒	develop Quality manual
• SOPs not standardised	⇒	design and use ˝boilerplate SOP˝/SOP of SOPs
• SOPs not revised	⇒	develop Quality manual
• SOPs badly written	⇒	Your mission to critically evaluate, edit and implement!
• SOPs not used (!?!)	⇒	Value your team, engage them, accept their ideas - ... ⇒ implement

4. SOP STRENGHTS AND WEAKNESSES

1. **Ensure standardized processes that yield the same and consistent result even by different personnel.**
2. **SOPs ensure consistency, accuracy, and quality of data or a procedure**
3. Save time and mistakes.
4. Reduce training costs.
5. Empower workforce.
6. Get read and used.
7. Enable to delegate work.
8. Support quality goals, improve credibility and legal defensibility.
9. Used as a checklist in auditing procedures.

SOP is not a policy!
˝A policy tells you WHAT you will do, an SOP tells you HOW you will do it.˝

TRENDS

VS

Paper 1000

Digital

https://www.youtube.com/watch?v=C3L8EkjGzqo
https://www.youtube.com/watch?v=nM4DaB0bNWU

TAKE HOME MESSAGES

1. **SOPs are integral part of successful quality management system**
2. **SOPs are concise written instructions that document a routine or repetitive activity**
3. **SOPs ensure consistency, accuracy, and quality of data or a procedure**
4. **SOPs should have standardized format within organisation**
5. **SOPs are only of use if they are easily understood by new personnel, regularly updated, accessible on-site**

SSS : simple, short, step-by-step

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