May 9th, 2019 Val Benoit, Bâtiment du Génie Civil Quai Banning 6, 4000 Liège, Belgium







Medicinal (Drug) Product, MDP

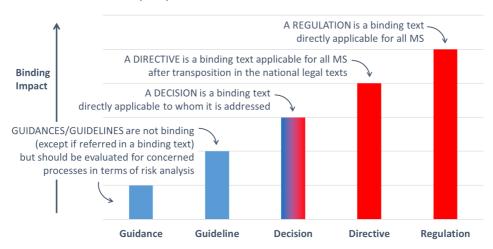


- DIRECTIVE 2001/83/EC
- Community code relating to medicinal products for human use
- Concerns mainly the licensed products (industrial products with marketing authorization)

Medicinal (Drug) Product, MDP



■ DIRECTIVE 2001/83/EC



3

Medicinal Product & Substance



Medicinal product:

- (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.

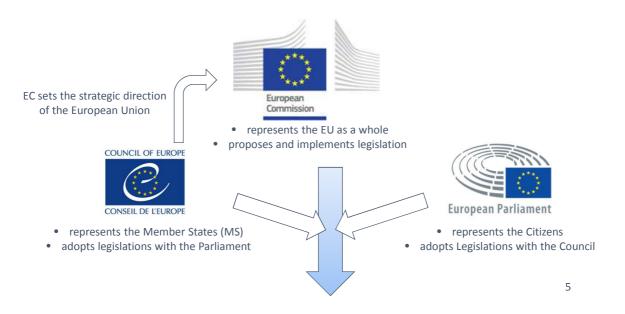
<u>Substance</u>: Any matter irrespective of origin which may be:

- human, e.g. human blood and human blood products;
- animal, e.g. micro-organisms, whole animals, parts of organs, animal, secretions, toxins, extracts, blood products;
- vegetable, e.g. micro-organisms, plants, parts of plants, vegetable secretions, extracts;
- chemical, e.g. elements, naturally occurring chemical materials and chemical products obtained by chemical change or synthesis.

Source: Directive 2001/83/EC

EU Institutions involved in legal processes





EU Institutions involved in drug quality





Directive 2001/83/EC



Does NOT apply to:

- Veterinary MDP
- Magistral formula (MDP prepared in a pharmacy in accordance with a prescription for an individual patient)
- Officinal formula (MDP prepared in a pharmacy in accordance with a pharmacopoeia recipe and intended to be supply to the pharmacy's patient)
- Investigational Medicinal (drug) Product (IMP)
- Any radionuclides in the form of sealed source (medical devices)

Source: Directive 2001/83/EC 7

Impacts of the directive 2001/83/EC



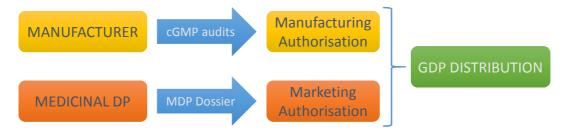
- A manufacturing authorization is required to produce MDP
- The Marketing Authorization (MA) is required for radionuclide generators, kits, radionuclide precursor radiopharmaceutical and industrially prepared radiopharmaceuticals (art. 6)
- A MA shall not be required for a radio-pharmaceutical prepared 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 (art. 7)
- The holder of a manufacturing authorization shall at least be obliged to comply with the principles and guidelines of good manufacturing practice for medicinal products and to use as starting materials only active substances, which have been manufactured in accordance with the detailed guidelines on good manufacturing practice for starting materials (art. 46)

Source: Directive 2001/83/EC 8

Impacts of the directive 2001/83/EC



- A manufacturing authorization is required to produce MDP
- The Marketing Authorization (MA) is required for radionuclide generators, kits, radionuclide precursor radiopharmaceutical and industrially prepared radiopharmaceuticals (art. 6)



Source: Directive 2001/83/EC

9

What about IMPs? Directive 2001/20/EC

- Manufacturing Authorization is also required
- GMP requirements are fully applicable for IMPs

- Today situation

.... and future Regulation EU 536/2014

Exception: GMP guidelines are <u>not</u> applicable and <u>no</u> manufacturing authorization is required:

- for 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

Source: Directive 2001/20/EC and Regulation EU536/2014

No EU GMP: does it mean no rules?



- For magistral and officinal preparations, no EU regulations nor directives enforce the EU GMP guidelines
- National Authorities publish "GMP like" local regulations, generally based on EU guidelines that are binding in a specific MS → Heterogeneity

Example: France, "Bonnes pratiques de préparation.

Chapitre 9: Préparations de médicaments radiopharmaceutiques"

http://ansm.sante.fr/var/ansm_site/storage/original/application/a5d6ae4b3d5fdee013ca463462b7b296.pdf

- Institutions and International organizations publish their non-binding views to guide the
 user in his tasks to achieve the preparation of medications with adapted quality for
 human use, e.g.:
 - PIC/S (Pharmaceutical Inspection Co-operation Scheme): "Guide to Good Practices for the Preparation of Medicinal Products in Healthcare Establishments"

https://www.picscheme.org/layout/document.php?id=156

 IAEA (International Atomic Energy Agency): "Good Practice for Introducing Radiopharmaceuticals for Clinical Use"

https://www.iaea.org/publications/10829/good-practice-for-introducing-radiopharmaceuticals-for-clinical-use

11

Summary



- The manufacture, preparation, distribution and use of radiopharmaceuticals in European Union are regulated by different directives and guidelines
- Radiopharmaceuticals are classified in the group of medicinal drug products
- The same laws as for non-radioactive products apply to radiopharmaceuticals. In addition, radiation protection rules apply.
- GMP are mandatory for licensed products and for investigational drug products
- "GMP like" guidelines are (should be) applied for other drug products (magistral and officinal formulae)

Eudralex: the repertoire for EC public health regulations

EudraLex - EU Legislation

* EudraBook V1 - May 2015 / EudraLex V30 - January 2015

PUBLIC HEALTH European Commission > DG Health and Food Safety > Public health > Eudralex **EUDRALEX**

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 >> Directive 2001/83/EC
- Volume 5 EU pharmaceutical legislation for medicinal products for veterinary u

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 >> cGMP
- 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 and advanced therapies are governed by specific rules.

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

13

Eudralex Volume 4: cGMP for Medicinal Products



Part I - Basic Requirements for Medicinal Products

- Chapter 2 Personnel (into operation since 16 February 2014)
- Chapter 3 Premise and Equipment (into operation since 1 March 2015) o See transitional arrangement for toxicological evaluation on page 1 of Chapter 3
 - Previous version
- Chapter 4 Documentation Page (January 2011)
- Chapter 5 Production (into operation since 1 March 2015)
- $\circ~$ See transitional arrangement for toxicological evaluation on pages 1-2 of Chapter 5 $\,$ Previous version
- Chapter 6 Quality Control | (into operation since 1 October 2014)
- Chapter 7 Outsourced activities (into operation since 31 January 2013)
- Chapter 8 Complaints and Product Recall (into operation since 1 March 2015)
- Chapter 9 Self Inspection

Part II - Basic Requirements for Active Substances used as Starting Materials

- Chapter 1 Pharmaceutical Quality System 📙 🚭 (into operation since 31 January 2013)
 Basic requirements for active substances used as starting materials 📔 (August 2014)
 - Part III GMP related documents
 - Site Master File 🔑 \cdots • Q9 Quality Risk Management 🔑
 - Q10 Note for Guidance on Pharmaceutical Quality System
 P
 - MRA Batch Certificate
 - . Template for the "written confirmation" for active substances exported to the European Union for medicinal products for human
 - · Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal
 - Guidelines of 19 March 2015 on the formalised risk assessment for ascertaining the appropriate good manufacturing practice for excipients of medicinal products for human use (all language versions are available here). A risk assessment as set out in these guidelines should be carried out for excipients for authorised medicinal products for human use by 21 March 2016.
 - Template for IMP batch release (applicable as from the date of entry into application of Regulation (EU) No 536/2014 on Clinical Trials)

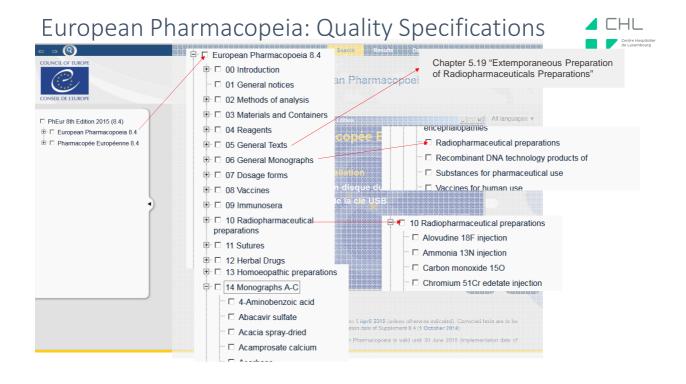
https://ec.europa.eu/health/documents/eudralex_en

cGMP: how to manufacture MDPs





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



European Pharmacopeia: impacts



• General text are NOT BINDING (= guidelines) except if they are referred in a monograph or enforced by another binding text.

Example: Chapter 5.19 "Extemporaneous Preparation of Radiopharmaceuticals Preparations"

• General Monographs are automatically BINDING.

01/2014:0125

Example:

RADIOPHARMACEUTICAL PREPARATIONS

Radiopharmaceutica

• Specific Monographs are automatically BINDING.

01/2014:1325

Example:

FLUDEOXYGLUCOSE (18F) INJECTION

Fludeoxyglucosi (18F) solutio iniectabilis



Source: EP 8.4 1

17

May 9th, 2019 Val Benoit, Bâtiment du Génie Civil Quai Banning 6, 4000 Liège, Belgium







Radiopharmaceutical: Medicinal Product?



Medicinal product:

- (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.

Radiopharmaceutical:

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

Source: Directive 2001/83/EC 19

Other definitions from 2001/83/EC



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.

Kit:

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

Radionuclide precursor:

Any other radionuclide produced for the radio-labelling of another substance prior to administration.

Source: Directive 2001/83/EC 20