2nd Conference on Radioisotopes Production and Utilization
And
11th Cyclotron Research Workshop

26-27 March 2015 - Monastir (Tunisia)

"Challenges of the regulatory body in implementing the legislations for the radiopharmaceuticals: efforts of IAEA"

Emilija Janevik

Goce Delcev University

International Atomic Energy Agency

Radiopharmaceuticals – Areas of activities

- Coordinated Research Products
- Technical Cooperation Projects
- Web based training module for medical cyclotron facility set up-completed

- Designing courses on GMP requirements for Radiopharmaceutical production – initiated

- **Addressing issues related to regulatory approvals for clinical deployment of radiopharmaceuticals – planned/initiated at concept level**

- Co-operation with International Bodies

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Capacity Building

Role in International Pharmacopoeia –WHO: Provides guidance on the quality and safety aspects of pharmaceutical products. Radiopharmaceutical Section is updated in collaboration with the IAEA. Monographs of new and emerging SPECT and PET radiopharmaceuticals being updated currently.

- **Quality Management Systems (QMS) and Good Manufacturing Practice (GMP) guidelines** with emphasis on training module development being developed.

- **PG level 'Certificate' and 'Masters' Radiopharmacy** programs through 'e-learning' and 'm-learning' with collaborating centres – Syllabi being worked upon.

Joint Training Initiatives in Blood Cell Labelling With ISORBE

IAEA Program implementation Mechanisms

Fostering relevant developments and dissemination of information

- Co-ordinated research projects (CRP)s
- Thematic meetings
- Technical documents
- Technology transfer, capacity building
- TC Projects- National, Regional, Inter-regional
- Building synergies-partnership, net-working
- Co-operation support to International initiatives

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European players in (radio-) pharmaceutical legislation

NATIONAL AUTHORITIES

- National regulations
- Licencing
- Inspection
- National Pharmacopeia
- Control laboratories

EUROPEAN UNION

EMA
(London)

- Medicinal products:
- Evaluation
- Supervision
- Pharmacovigilance

D.G. Health
(Brussels)

- Directives
- Regulations

PROFESSIONAL ORGANIZATIONS

- PIC/S
- EANM
- AIPES
- .....

COUNCIL OF EUROPE

E.D.Q.M.
(Strasbourg)

- European Pharmacopeia
- OMCL network

GMP
Marketing Authorisation
Quality

European laws and rules

Directives

Must be transposed to be effective

Regulations

Are immediately enforceable

Other rules

Decisions of the Council

Opinions

Recommendations

Regulatory documents of importance for Radiopharmaceuticals

Directive 2001/20/EC → "Clinical Trial Directive"

Directive 2001/83/EG → Qualified Person,...

Directive 2003/94/EC → GMP

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

The challenge for PET-radiopharmaceutical development are pharmaceutical regulations, not radiation safety issues

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Eudralex

The Rules Governing Medicinal Products in the European Union

http://ec.europa.eu/health/index_en.htm

Vol 1: Medicinal Products for Human Use

- **Directives**
  - **2001/83/EC**: Community code relating to medicinal products for human use (amended by directives 2002/98/EC, 2004/24/EC y 2004/27/EC)
  - **2003/94/EC:** laying down the principles and guidelines of (GMPs)
- **Regulations**
  - **1394/2007:** advanced therapy medicinal products (amends also dir. 2001/83)

Vol 4: GMPs

- **Part I:** Basic Requirements for Medicinal Products
- **Part II:** Basic Requirements for Active Substances used as Starting Materials
- **Annexes**

Vol 10: Clinical Trials

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Good Manufacturing Practices

Part I: Basic Requirements for Medicinal Products

Chapter 1	Quality Management (revision October 2005)
	Quality Management (revision February 2008) - Coming into operation by 01 July 2008
Chapter 2	Personnel
Chapter 3	Premise and Equipment
Chapter 4	Documentation
Chapter 5	Production
Chapter 6	Quality Control (revision October 2005)
Chapter 7	Contract Manufacture and Analysis
Chapter 8	Complaints and Product Recall (revision December 2005)
Chapter 9	Self Inspection

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

GMP: Annexes

Annex 1 Manufacture of Sterile Medicinal Products 01/03/2009
Annex 2 Manufacture of Biological Medicinal Products for Human Use
Annex 3 Manufacture of Radiopharmaceuticals 01/03/2009
Annex 4 Manufacture of Vet Med Products other than Immunological Vet Medicinal Products
Annex 5 Manufacture of Immunological Veterinary Medicinal Products
Annex 6 Manufacture of Medicinal Gases
Annex 7 Manufacture of Herbal Medicinal Products
01/09/2009
Annex 8 Sampling of Starting and Packaging Materials
Annex 9 Manufacture of Liquids, Creams and Ointments
Annex 10 Manufacture of Pressurized Metered Dose Aerosol Preparations for Inhalation
Annex 11 Computerized Systems
Annex 12 Use of Ionizing Radiation in the Manufacture of Medicinal Products
Annex 13 Manufacture of Investigational Medicinal Products
Annex 14 Manufacture of Products derived from Human Blood or Human Plasma
Annex 15 Qualification and validation
Annex 16 Certification by a Qualified person and Batch Release
Annex 17 Parametric Release
Annex 18 Good manufacturing practice for active pharmaceutical ingredients
Annex 19 Reference and Retention Samples
Annex 20 Quality Risk Management

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GMP Annex 3 (Radiopharmaceuticals)

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*			

Quite general, not specific for PET, tries to cover everything

Cross-References

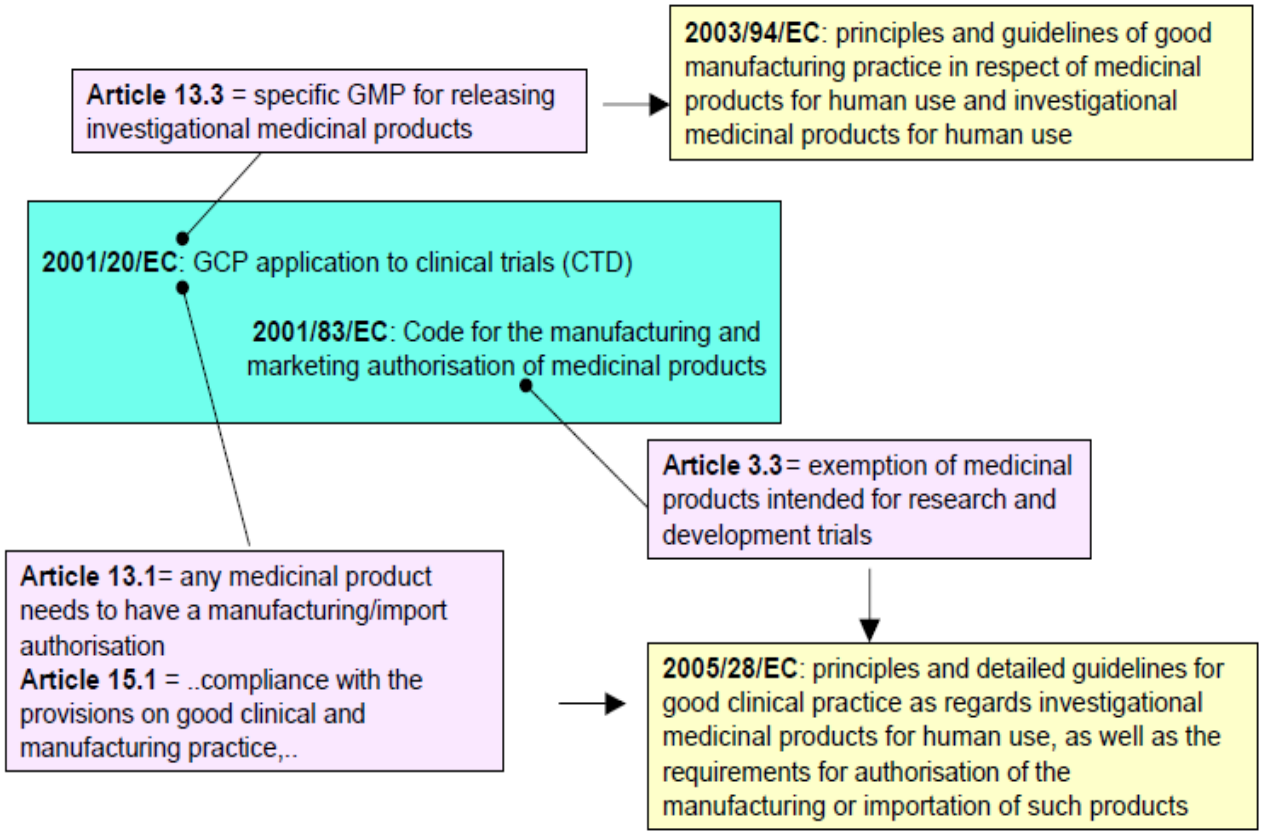

Fig. (4). Synoptic view of cross-references between issues on quality in Good Clinical Practice and specific regulations on medicinal products.

Regulatory basis for the use of radiopharmaceuticals

Marketing Authorisation

Clinical Trial

„Extemporaneous Preparation“ Compounding In-house

Directive 2001/83 (Medicinal Products for human use) as amended by 2004/27:

Directive 2001/20/EC
Directive 2003/94/EG
Directive 2005/28/EC

Marketing Authorization in the European Union

National agencies

- **Centralized Procedure:** Application and evaluation at EMA (London), valid troughout Europe, mandatory for therapeutic products for certain indications (oncology, NCE,..), not (yet) used for PET-RP

- **Decentralized:** Application in several countries, evaluation by one national „lead agency“, immediate authorization in all countries involved, „new“ not yet used for RP

- **National/ mutual recognition**: Licence granted in one country, then recognized in others, main route for PET-RP (FDG)

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Reasons why radiopharmacy in Europe is DIVERSE

- EU competences limited mainly to industrial matters
- Transposition of directives leaves room for interpretation and country-to-country variations
- Interpretations by individuals varies (inspectors, officials)
- History of (PET) RP in Europe is variable

National specifics in Radiopharmaceuticals

- Use of radiopharmaceuticals without marketing authorisation
- Standards of preparation (GMP, GRPP)
- Number of registered radiopharmaceuticals on the domestic market
- Related reimbursement issues
- Responsibilities
- Clinical Trial requirements

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PET Products – legal options

• *Ref. Directive 2001/83 as amended by 2004/27: Title II, 'Scope', Article 3:*

1. Magistral preparation:

- *"..Medical Prescription for an **individual patient**…"*
- *" … prepared in a **pharmacy**.."*

2. Officinal : same principles as above, when applied to established products I.e.- prepared according to the ***'..prescriptions of a pharmacopoeia..'*** e.g. a PhEur monograph . There are PhEur monographs for a number of PET products
If these aspects can be satisfied, then a Marketing Authorisation may not be needed.

3. Industrial manufacture ?:

Marketing Authorisation provisions apply only to products which are

- *"..**prepared industrially** or manufactured by a method **involving an industrial process**.."*

If this is not the case, then a Marketing **Authorisation** may not be needed.

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Alternatives to "Eudralex" GMP

cGRPP- Radiopharmacy Committee EANM

Guidelines for preparation of RP

cGRPP-guidelines, version2 March 2007
EANM Radiopharmacy Committee

GUIDELINES ON CURRENT GOOD RADIOPHARMACY PRACTICE (cGRPP) IN THE PREPARATION OF RADIOPHARMACEUTICALS

Part A. Guidelines on Current Good Radiopharmacy Practices (cGRPP) for kit-based Radiopharmaceuticals in Nuclear Medicine

PART B. Guidelines on Current Good Radiopharmacy Practices (cGRPP) for Positron Emission Tomography (PET) and other Locally Prepared Radiopharmaceuticals*

http://www.eanm.org/scientific_info/guidelines/gl_radioph_cgrpp.pdf

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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

Radiation Dose

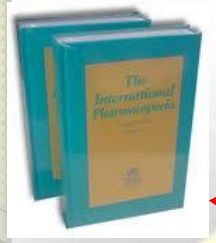
Each country has different :

- **Radiation dose limits including different critical values, also differing for patients and healthy controls**
- **Regulations in allowing healthy young women to participate**
- **Calculations of doses for multimodality imaging (adding PET and CT doses or approve separately)**

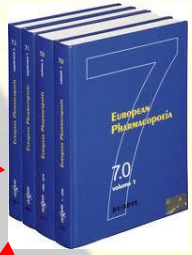
Harmonization

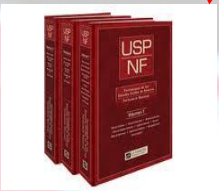
Efforts……..
Wishes……..
Needs……..

Pharmacopoeias



IAEA/WHO initiative





global harmonization

International Pharmacopoeia (Ph. Int.)	European Pharmacopoeia (Ph. Eur.)	United States Pharmacopoeia (USP)
General monograph **Annexes:** ▪ Terminology ▪ Table of physical characteristics	**General monograph**	**General monograph** ▪ Cobalamin Radiotracer ▪ Pharmaceutical Compunding – Sterile preparations ▪ Radioactivity ▪ Radiopharmaceutical Quality Control ▪ Assurance and compounding ▪ General Tests and Assays ▪ General Information Chapter
Specific monographs (27 monographs)	**Specific monographs (63 monographs)**	**Specific monographs (84 monographs)**
. **Methods of analysis** ▪ Physical and physicochemical methods ▪ Chemical methods ▪ Biological methods		

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Production Guidelines EANM / IAEA

„Strategies for Clinical Implementation and Quality Management of PET Tracers"

International Atomic Energy Agency Vienna, 2009

EANM: Draft Guidelines for Radiopharmacy
[Eur J Nucl Med Mol Imag (2003) 30:BP63–BP72]:

The Committee has adopted the strategy of starting to develop **"Draft guidelines for radiopharmacy"** for nuclear medicine laboratories and to adapt the

"Preliminary draft regulations on current good manufacturing practices for PET drugs" of the U.S. Food and Drug Administration

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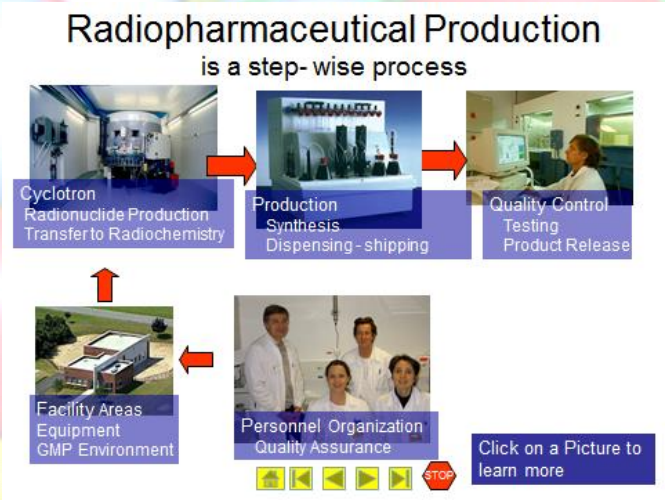
Education

Web-based Training Module on 'Radiopharmaceutical Production':

Cyclotron Facilities and FDG Radiopharmaceuticals Production

(In cooperation with BNL, launched in 2012)

http://www-naweb.iaea.org/napc/iachem/home.html



Virtual Course in Radiopharmacy

http://nucleus.iaea.org/HHW/Radiopharmacy/VirRad/index.html

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UNIVERSITY GOCE DELCEV STIP

China and other potential centers

University Diploma

STUDENT 2

STUDENT 1

University Diploma

University

University

University

University

University

IAEA

IAEA / University NETWORK

IAEA /Universities Certificate

WEB –page PLATFORM

On SITE

Enrolment of e-learning

University

+

IAEA / University NETWORK

+

Include:

THEORY

PRACTICE

Institutions in the countries Agreement with IAEA / University NETWORK

Approved

AUDIT using IAEA mission

ELABORATE
for compliance and accreditation of study programs in RADIOPHARMACY

August, 2014 година

Stip
Elaborate of second cycle of studies

CURRICULUM - RADIOPHARMACY
Faculty of Medical Science at the University "Goce Delchev" Stip

Study program: second cycle, RADIOPHARMACY

2 years, 120 ECTS

Diploma: Master of Radiopharmacy (NQF VIIB)

I SEMESTER	CREDITS
Basic (Applied) Pharmacy	8
Radiopharmaceutical Chemistry	8
Nuclear Physics, Radiation Safety & Regulations	6
Optional Theoretical Course - Faculty/Department - Group 1	4
Optional Theoretical Course - Faculty/Department - Group 1	4
Total number of credits	**30**

II SEMESTER	CREDITS
Radiopharmaceutical preparation	8
Quality control of radiopharmaceuticals	8
Nuclear Medicine - aspects of clinical practice	6
Optional Theoretical Course - Faculty/Department - Group 2	4
Optional Theoretical Course - Faculty/Department - Group 2	4
Total number of credits	**30**

III SEMESTER	
Radiopharmaceutical preparation - SPECT radiopharmaceuticals	5
Radiopharmaceutical preparation - PET radiopharmaceuticals	5
Radiopharmaceutical preparation - Therapeutic radiopharmaceuticals	5
Operation of a GMP facility	5
Quality control of radiopharmaceuticals	5
Clinical application of radiopharmaceuticals /NM	5

IV SEMESTER	
MASTER THESIS	30

Optional Theoretical Course - Faculty/Department - Group 1	Optional Theoretical Course - Faculty/Department - Group 2
Radiopharmacology Animal models, disease models, animal protection regulations , ethical issues Drug interventions and interactions/ adverse reactions Biopharmacy, radiotracer transport, pharmacokinetics, modelling	Radiopharmacy Management Quality Assurance and Product Performance Implications of Good Manufacturing Practice Regulations and Legal Aspects, Marketing Authorisations

PET centre in Skopje

Guverment of Republic of Macedonia . Ministry of Health, IAEA

Idea 2005…… supported by IAEA..

Plan, URS..2012… support IAEA experts for revision

Start building October 2013….

"Goce Delcev" University

24 Mars 2015

… continuous collaboration with IAEA

IAEA efforts:

regulatory body

legislations for the radiopharmaceuticals