Production of radiopharmaceuticals for clinical and research uses

The European perspective

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The Rules
European players in (radio-) pharmaceutical legislation

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

Professional organisations
- PIC/S
- EANM
- AIPES
- .....
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 (RP)

Directive 2001/83/EG → Qualified Person,...
Directive 2003/94/EC → GMP
Directive 2004/27/EC → API according to GMP
CHMP/SWP/28367/2007 → First in human clinical trial guideline (EMEA)
Regulation (EC) No 1394/2007 → Advanced therapy regulation

The current challenge for PET-radiopharmaceutical development are pharmaceutical regulations, not radiation safety issues
Eudralex
The Rules Governing Medicinal Products in the European Union

Vol 1: Medicinal Products for Human Use
- Directives
  - 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

http://ec.europa.eu/health/index_en.htm
Good Manufacturing Practices

**Part I:** Basic Requirements for Medicinal Products

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**Part II:** Basic Requirements for Active Substances used as Starting Materials
# GMP: Annexes

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GMP Annex 3 (Radiopharmaceuticals)

March 2009

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

<table>
<thead>
<tr>
<th>Type of manufacture</th>
<th>Non - GMP *</th>
<th>GMP part II &amp; I (Increasing) including relevant annexes</th>
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<tr>
<td>Radiopharmaceuticals PET Radiopharmaceuticals Radioactive Precursors</td>
<td>Reactor/Cyclotron Production</td>
<td>Chemical synthesis</td>
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<tr>
<td>Radionuclide Generators</td>
<td>Reactor/Cyclotron Production</td>
<td>Processing</td>
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</table>

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

National Competence
Marketing Authorization in the European Union

- **Centralized Procedure**: Application and evaluation at EMA (London), valid throughout 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)
The Problems
EANM opinion

- **current EU legislation** on medicinal products is imposing excessive hurdles for the use of radiopharmaceuticals in particular those without marketing authorization

- The number of registered radiopharmaceuticals is limited


- In-house preparation of RPs has become more difficult...... In many countries the existing regulatory environment is definitely hampering the use the best possible radiopharmaceuticals available for our patients.

- The problem affects both the everyday clinical use and research applications and is especially important for academic centers, in which most of the research in this field is carried out in Europe, ......
EANM WG legislation

Problems

Lack of availability of radiopharmaceuticals for clinical use
Related to products potentially used in clinical routine that do not have marketing authorization, we propose to clarify and improve the regulatory framework for radiopharmaceuticals outside clinical trials, without marketing authorization (including off label use) in order to increase the routine availability.

Harmonization of standards for the small scale preparation of radiopharmaceuticals
To improve the current situation by harmonization of the standards for small scale preparations across Europe and that these are distinct from those required for industrial standards. This would also include harmonization of the standards required for small-scale preparation of radiopharmaceuticals for both routine clinical use and clinical trials.

Do you agree that these items are the most important issues to address?

Answer from National Societies YES
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
Common European standards for the preparation of radiopharmaceuticals?

Country C

Full GMP preparation of $^{99m}$Tc-radiopharmaceuticals

Country D

„On the bench“ preparation

→ Same Quality/Safety?
→ Same Costs?
PET Products – legal options


1. Magistral preparation:
   - “..Medical Prescription for an individual patient…”
   - “... prepared in a pharmacy..”

2. Officinal: same principles as above, when applied to established products l.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.
PET products as Magistral / Officinal products

- EU legislation may not have foreseen the preparation of *sterile parenteral products* in the context of Marketing Authorization

- GMP is an important issue: EANM has an internal best practice guideline, but no formal EU guideline
Legislation on Radiopharmaceuticals

What do we share in Europe?

- Regulations on industrial manufacturing (GMP)
- Regulations on registration and marketing authorization
- Regulations on clinical trials
- European Pharmacopoeia

What would we need?

- Individualize RP from other medicinal products
- Common regulations for:
  - Extemporaneous preparation of RP
  - PET RP compounding for in-house use
  - Inspection
EANM initiatives

• Guidelines on Current Good Radiopharmacy Practice (cGRPP) in the Preparation of Radiopharmaceuticals

• Guideline to regulations for radiopharmaceuticals in early phase clinical trials in the EU

• Postgraduate Programme for Responsible Person

• Guidelines on GMP issues and CT application in preparation

• Initiatives at congresses, meetings

• Commenting to legislation drafts and initiatives

• Talks/Contacts to EMA, DG`s in Brussels, PIC/S, EDQM

• Support to National Societies

• **WG Legislation**
Long half-life isotopes and ‘cold’ kits

- Industrially manufactured, controlled and distributed in a market, therefore ...
- A Marketing Authorisation is needed.
- Regarded entirely as ‘NORMAL’ medicines from a regulatory point of view


- The EC has said this will not change. There are already enough facilitating measures e.g. SME, Orphan, Assistance with Sc.Adv., Conditional, etc.
Short half-life

- In contrast to ‘normal’ products, Industrial manufacture, control and distribution is either very difficult or not possible. If intended for a named individual patient then Marketing Authorisation legislation may not apply.

- EANM would prefer a legal / regulatory framework where such products are **outside the requirements for Marketing Authorisations**

- Particular problems with PET products

- It is unlikely that the EC will create new provisions. However, it may be that the current legal framework can accommodate these problems

- Undecided at present.
PET Radiopharmaceuticals

• These products have raised many questions in the current regulatory framework, and are not definitively solved in the EU at the present time.
  – Is it industrial manufacture? Or magistral / officinal dispensing?
  – Where is the boundary between manufacturing and magistral preparation?
    • Is it commercialisation?
  – Is a Marketing authorisation mandatory?
  – If so, what are the data requirements for the dossier?
  – Alternatively, from the applicant’s side, how can this be avoided?
  – If there is no dossier, then at least GMP provisions should apply, yes?
  – But GMP provisions are only for large industry and are extremely onerous and are not suited to the preparation of PET products?

• **Standard questions from the Regulators:**
  – If there is no evaluation in the context of a Marketing authorisation, who is responsible for the quality, safety and efficacy of the product in patients?
  – Who is liable? Are we right to allow self-regulation in this context?
  – After all, these are products for intravenous injection in humans!
Guidelines for preparation of RP

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
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
Are complaints of professionals being heard?

- **Standardizing Radiopharmacy practice in hospitals:**
  - European Pharmacopeia: Chapter on Compounding of RP`s
  - PIC/S: Annex 3 to guidelines for healthcare establishments
  - Proposed Regulation on Clinical Trials
2009: Compounding of RP Working Party created

2011: Draft Chapter released for public consultation
European Pharmacopoeia

1. General Chapter on Radiopharmaceutical Preparation
2. Monographs for specific radiopharmaceuticals
3. General Chapters for pharmaceutical tests
4. Chapter Compounding of Radiopharmaceuticals (Draft)

Under the mandate from the Council of Europe (different from EU!!)

EDQM

(European Directorate of Quality of Medicines)
### Monographs PET-RPs, European Pharmacopeia

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New Regulation on Clinical Trials

Legislative Proposal published 17/07/2012 by European Commission (Health & Consumers)

Currently under subsidiarity scrutiny in National Parliaments

Waiting for approval (possible changes?) at the European Parliament
Modulation of impact assessment based on real risk to subject safety

GMP not requested for preparation of diagnostic RP for CT

Special requirements for labelling of primary packaging
Summary: Regulatory Aspects of PET Radiopharmaceuticals

- European regulations in particular related to pharmaceutical aspects of PET-RPs are manifold and complex

- Regulations are often subject to (national) interpretation resulting in a heterogenous situation in Europe

- GMP is a major challenge in fulfilling regulatory requirements

- Specific regulations and exemptions for RPs are rare, but would be required, recent developments such as General Chapter 5.19 "Compounding of RP" (Pharm Eur) may lead to a harmonized pan-european standard on RP preparation

- Most regulatory documents can be found on-line: EUDRALEX