Preclinical safety testing of diagnostic and therapeutic radiopharmaceuticals - regulatory requirements

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Contents of talk

• General preclinical safety testing requirements (ICH)
• US and EU radiopharmaceutical regulations
• ICH microdose approach
• Swissmedic summary recommendations
Drug safety testing

Is the molecule too toxic to develop?

Is it likely to be safe in patients?
At what dose?

Any unexpected toxicity in clinical trials?

Is drug still safe in real-life clinical practice?
Early drug development

Safety questions:

• Is the candidate mutagenic or cytotoxic *in vitro*?

• What are the probable toxicity target organs?

• Are drug metabolism and pharmacokinetics (DMPK) adequately characterized (target exposure, toxic metabolites)
Early drug development

**In silico:**
Activity / toxicity related to chemical structure & physico-chemical properties

**In vitro:**
Subcellular systems, cell lines & primary cells

**In vivo:**
Short-term animal studies, "conventional" endpoints, DMPK
Preclinical safety studies

Is there any unacceptable toxicity?
What should the human starting dose be?
Preclinical safety: questions

**Toxicology**
What are the toxicity target organs? Are toxic effects reversible?
Is the drug mutagenic, carcinogenic or toxic to reproduction?
Are there adverse effects on cardiovascular, neurological or respiratory function?
Are there any toxic metabolites?
Are there any toxic impurities in production batches for clinical use?

**Toxicokinetics**
How are toxic effects related to dose and systemic concentrations?
Which enzymes are involved in the drug’s metabolism?
What are the metabolites and what is their activity on- and off-target?
Are there species differences in absorption, distribution, metabolism, and excretion?

**Preclinical questions**
What information is to be included in the Investigator's Brochure?
What (additional) safety endpoints need to be monitored in human trials?
What is the proposed human starting dose and its margin of safety?
What is the proposed human dose escalation step size?
### ICH nonclinical toxicity/safety study guidance

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**All toxicology/safety studies according to GLP**
Nonclinical safety study timing

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<th>Lead optimization</th>
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Radiopharmaceuticals - regulations and legislation

Decristoforo & Schwarz, 2011
Decristoforo & Schwarz, 2011
Investigational New Drug Application (IND) and Exploratory IND (eIND)

If the compound, labeled or unlabeled, has never been previously administered to humans, the US FDA requires an Investigational New Drug (IND) Application.

Whether an exploratory IND (eIND) or a full IND needs to be submitted, depends on the mass of drug administered.

If the administered dose complies with the definition of a microdose, i.e. "less than 1/100th of the dose of a test substance calculated (based on animal data) to yield a pharmacological effect of the test substance with a maximum dose of ≤100 μg or, in the case of biologics, ≤30 nanomoles", an exploratory IND submission is supported, which requires reduced preclinical safety and toxicology testing.

Wagner & Langer 2011
Radioactive Drug Research Committee (RDRC)

For radiolabeled compounds which have been used in humans before, and for which there is no intent to commercialize, approval from the "Radioactive Drug Research Committee" (RDRC) is considered sufficient to initiate clinical research studies.

The RDRC assesses the pharmacological and radiation dose administered in a clinical study. This usually requires whole-body dosimetry estimations in e.g. non-human primates, prior to initiating a phase 0 PET microdosing study.

Wagner & Langer 2011
Investigational New Drug Application (IND)
[21CFR312.23]

Pharmacology and toxicology information:

- Adequate information about pharmacological and toxicological studies of the drug involving laboratory animals or in vitro, on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations.

- The kind, duration, and scope of animal and other tests required varies with the duration and nature of the proposed clinical investigations.

[21CFR315.6 for drugs, 21CFR601.35 for biologics]
Investigational New Drug Application (IND)

To establish the safety of a diagnostic radiopharmaceutical, FDA may require, among other information, the following types of data:

(i) Pharmacology data,

(ii) Toxicology data,

(iii) Clinical adverse event data, and

(iv) Radiation safety assessment.

[21CFR315.6 for drugs, 21CFR601.35 for biologics]
Investigational New Drug Application (IND)

Radiation safety assessment:

• Must establish the radiation dose by radiation dosimetry evaluations in humans and appropriate animal models.

• The maximum tolerated dose need not be established.

[21CFR315.6 for drugs, 21CFR601.35 for biologics]
FDA has recently released new guidance for industry on nonclinical testing for "late radiation toxicity". This testing is not a legal requirement, but will probably be requested in practice.
Purpose

• aid in identifying at-risk organs
• establish a margin of safety for late radiation toxicity
• quantify potential organ sparing when dose fractionation is used
• compare organ tolerance doses for radiopharmaceutical therapy to the published tolerance doses for conventionally fractionated high dose rate radiotherapy

Study timing

• Should ideally be completed and analysed before phase 2 dose escalation toxicity trials are initiated in patients.
Nonclinical Evaluation of Late Radiation Toxicity for Therapeutic Radiopharmaceuticals (2011)

**Species**
The most appropriate species is chosen based on human dosimetry and pharmacokinetic data using tracer doses.

**Dosing schedule**
should mimic the anticipated clinical trials, in terms of amount of injected radioactivity, number and frequency of doses, and dosing interval.

**Doses**
- at least four dose levels to produce no, mild, moderate, and severe late radiation toxicity
- include cold formulation control (equivalent to the highest mass dose) to distinguish radiation from pharmacological effects
- express doses as radiation absorbed dose to the critical organs.

**Duration**
Animals should be monitored for late radiation toxicity for at least 1 year after dosing.
Decristoforo & Schwarz, 2011
"Medicinal products" are defined by Directive 2001/83/EC as "...prepared industrially or manufactured by a method involving an industrial process...".

The Clinical Trials Directive 2001/20/EC, Article 2 (d), provides the following definition for an Investigational Medicinal Product (IMP): "a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form."

Radiopharmaceuticals which may be classified as IMPs include radiolabelling kits, radionuclide generators and radionuclide precursors.
The following are NOT considered to be IMPs:

1. Any medicinal product prepared in a pharmacy in accordance with a medical prescription for an individual patient ("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 ("officinal formula").

3. Medicinal products intended for research and development trials [i.e. not for disease diagnosis or treatment].

4. Intermediate products intended for further processing by an authorized manufacturer.

5. Any radionuclides in the form of sealed sources [German version says opposite!!].

6. Whole blood, plasma or blood cells of human origin, except for plasma which is prepared by a method involving an industrial process.

7. Any advanced therapy medicinal product...which is prepared on a non-routine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient.

[Directive 2001/83/EC, Article 3]
EU Investigational Medicinal Product (IMP)

Medicinal products used in clinical trials but which are not the subject of the clinical trial, are also classified as non-Investigational Medicinal Products. They include:

- concomitant and rescue/escape medication (e.g. patient-controlled iv morphine for pain),
- challenge agents (e.g. methacholine broncospasm challenge),
- tools to assess a relevant clinical trial endpoint (e.g. PET radiopharmaceutical to measure primary endpoint effect of an IMP on organ function).

• Manufacturing of non-IMP [NIMPs] must be authorised by the competent authority of the Member State.

• Member States must ensure that national traceability and pharmacovigilance requirements as well as the specific quality standards for NIMPs are equivalent to those provided for at Community level.

[Directive 2001/83/EC, Article 3]
EU Investigational Medicinal Product (IMP)

Safety documentation requirements for radiopharmaceuticals

[radionuclide generators, kits, radionuclide precursor radiopharmaceuticals and industrially prepared radiopharmaceuticals] :

• Standard requirements for medicinal products
  [= ICH M3(R2) for preclinical safety]

• Radiation dosimetry
  - Organ/tissue exposure to radiation;
  - Absorbed radiation dose estimates for a given route of administration according to a specified, internationally recognised system.

[Directive 2001/83/EC]
EU Investigational Medicinal Product (IMP)

Safety documentation requirements for radiopharmaceutical precursors

• Information on effects of free radio-nuclide in the patient (due to poor radio-labeling efficiency or in vivo dissociation of the radio-labeled conjugate).
• Information on occupational hazards, i.e. radiation exposure to hospital staff and to the environment.
• Information on chemical toxicity and disposition of the ‘cold’ nuclide
• Mutagenicity studies on the radionuclide are not considered to be useful

[Directive 2001/83/EC]
ICH M3(R2) (2009)

Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization For Pharmaceuticals
ICH M3(R2) includes recommendations on "micro-dose" nonclinical safety studies which may be applicable to radiopharmaceuticals.

Preclinical data requirements are less stringent than normal when a "micro-dose" approach is used.
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<th>Clinical:</th>
<th>Non clinical:</th>
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<tr>
<td>Dose to be Administered</td>
<td>Start and Maximum Doses</td>
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<tr>
<td><strong>Approach 1:</strong></td>
<td>Maximal and starting doses can be the same but not exceed a total accumulated dose of 100 μg.</td>
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<tr>
<td>Total dose ≤ 100 μg (no inter-dose interval limitations) <strong>AND</strong> Total dose ≤ 1/100&lt;sup&gt;th&lt;/sup&gt; NOAEL and ≤ 1/100&lt;sup&gt;th&lt;/sup&gt; pharmacologically active dose (scaled on mg/kg for i.v. and mg/m² for oral).</td>
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<td><strong>Approach 2:</strong></td>
<td>Maximal daily and starting doses can be the same, but not exceed 100 μg.</td>
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<td>Total cumulative dose ≤ 500 μg, maximum of 5 administrations with a washout between doses (6 or more actual or predicted half-lives) <strong>AND</strong> each dose ≤ 100 μg <strong>AND</strong> each dose ≤ 1/100&lt;sup&gt;th&lt;/sup&gt; of the NOAEL and ≤ 1/100&lt;sup&gt;th&lt;/sup&gt; of the pharmacologically active dose.</td>
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## M3(R2); Guidance on Nonclinical Safety Studies

### Table 3: Recommended Non-Clinical Studies to Support Exploratory Clinical Trials

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<td><strong>Dose to be Administered</strong></td>
<td><strong>Start and Maximum Doses</strong></td>
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<td>Approach 3</td>
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<tr>
<td>Single Dose Studies at Sub-therapeutic Doses or into the Anticipated Therapeutic Range.</td>
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M3(R2); Guidance on Nonclinical Safety Studies

a. General toxicity studies should be conducted according to GLP regulations.

b. See Ref. 10 for genotoxicity study design and dose selection.

c. 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.

d. 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.

e. In the absence of adverse effects in the clinical trial, escalation above this AUC can be appropriate if the findings in the toxicity studies are anticipated to be monitorable, reversible, and of low severity in humans.
Microdosing

Approach 1:
Total dose ≤ 100 μg (no inter-dose interval limitations)
AND
Total dose ≤ 1/100th NOAEL and ≤1/100th pharmacologically active dose

Pharmacology
*In vitro* target/receptor profiling and characterization of primary pharmacology in a pharmacodynamically relevant model to support human dose selection.

Toxicology
- Extended single dose toxicity study in one species, usually rodent, with evaluations 14 days post-dose to assess delayed toxicity and/or recovery.
- Genotoxicity studies are not recommended.
- For highly radioactive agents (e.g., PET imaging agents), appropriate PK and dosimetry estimates should be submitted.
Microdosing

Approach 2:
Total cumulative dose ≤ 500 μg, maximum 5 administrations with 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.

Pharmacology

\( \text{In vitro} \) target/ receptor profiling and characterization of primary pharmacology in a pharmacodynamically relevant model to support human dose selection.

Toxicology

• 7-day repeated-dose toxicity study in one species, usually rodent.
• Genotoxicity studies are not recommended.
• For highly radioactive agents (e.g., PET imaging agents), appropriate PK and dosimetry estimates should be submitted.
Topics under Harmonisation

The following areas of work have been undertaken by the GCC-DR:

Radiopharmaceuticals

- **Work Description**: Guidelines for basic requirements for registration of Radiopharmaceuticals. These Guidelines are intended to complement those already available for pharmaceutical products as well as those for sterile pharmaceutical products.

  - **Based On**:
    - European Association of Nuclear Medicine (EANM), Guidelines on Current Good Radiopharmacy Practice (cGRPP) in the Production of Radiopharmaceuticals, May 2006.

- **Status**: Under Discussion

Swissmedic has produced a useful guidance document ("Points to Consider", not legally binding) on the choice of preclinical studies which may be useful for obtaining marketing authorisation for diagnostic and therapeutic radiopharmaceuticals.

This is currently one of the only guidance documents available on preclinical safety testing of radiopharmaceuticals (ICH guidance is "under discussion").

https://www.swissmedic.ch/zulassungen/00153/00189/00197/01337/index.html?lang=en&download=NHzLpZeg7t,Inp6IOtU042l2Z6In1ad1IZn4Z2qZrnO2Yuq2Z6gpJCDdXx4gymym162epYbg2c_JjKbNoKSn6A--
Diagnostic radiopharmaceuticals

Class 1:
Chemical entities administered at tracer quantity levels that do not have the potential for eliciting a pharmacological response.

Establish human dose based on mathematical and/or physical models (i.e., phantoms), and acceptable radiation dosimetry estimates.

Class 2:
Substances containing biological materials at tracer quantity levels, but with potential for eliciting allergic type responses.

Evaluate the risk of sensitization to the agent (which is reduced by high specific activity, i.e. low protein dose with high radioactive dose).

Class 3:
Substances with potential for a pharmacological response.
Potential risks reduced by high specific activity.

Establish minimum pharmacologically active dose, and minimum radioactivity dose needed for satisfactory imaging.
Therapeutic Radiopharmaceuticals

Studies should be designed to assess:

a) the *in vivo* stability of the radionuclide complex;

b) the animal biodistribution of the radionuclide;

c) the potential chemical toxicity;

d) the radiation exposure of tissues.
Summary

Data required to establish preclinical safety of radiopharmaceuticals include:
- in vitro target/receptor profiling including pharmacodynamics
- pharmacokinetics
- potential chemical toxicity including antigenicity
- radiation exposure of tissues
- late radiation toxicity

For diagnostic radiopharmaceuticals, safety is determined by the margin between
- the dose evoking pharmacologic activity or antigenicity, and
- the minimum radioactivity dose needed for satisfactory imaging.

For therapeutic radiopharmaceuticals, safety is determined by the margin between
- the dose exceeding organ tolerance or inducing late radiation toxicity, and
- the minimum efficacious dose
Questions?

ABOUT US

SCAHT was founded with the vision to contribute to the creation of a safer and healthier environment by advancing the science of human toxicology.

The Centre provides expert advice and services in regulatory toxicology for the Swiss administrative authorities, the media, the general public and for third parties. The Regulatory Toxicology Group at SCAHT is responsible for delivering professional analyses. The Centre supports research in applied human toxicology and facilitates the exchange of multidisciplinary information and data. SCAHT contributes to education and training in human toxicology and encourages the recruitment of students and new members into the profession.
Additional material…
Diagnostic radiopharmaceuticals

**Acute toxicity** studies: may be necessary for Class 3.

**Repeat-dose** toxicity studies:
Class 1: Dose-ranging studies not generally necessary. Lower dose limit may be based on mathematical and/or physical models, and upper limit based on acceptable radiation dosimetry estimates.
Class 2: Because of the potential for antigenic response, the appropriate dose is the lowest protein dose with the highest radioactive dose (i.e. high specific activity).
Class 3: Upper dose limit is the mass dosage that could potentially elicit a clinically observable pharmacological response, and the lower limit is the minimum radioactivity dosage needed for a satisfactory image.

**Chronic toxicity, reproductive toxicity, carcinogenicity studies** are usually not necessary.
Therapeutic Radiopharmaceuticals

Single-dose toxicity:
These studies may give some indication of the likely effects of acute overdosage in man and may be useful for the design of toxicity studies requiring repeated dosing in the relevant animal species.

Reproductive function and foetal toxicity:
Studies may be required in certain cases, especially if the radiopharmaceutical is intended for repeated use in women of child-bearing potential. Otherwise the study on reproductive function may justifiably be limited to ascertaining the effect on fertility.

Mutagenic potential:
Characterization of the mutagenic potential of the non-radioactive equivalent of the product; may be limited to screening for gene and chromosome mutations.

Carcinogenic potential:
An evaluation of any carcinogenic potential of the substances involved must be presented. If no carcinogenicity tests are performed, this must be clearly indicated.
Radiation dosimetry estimates - software example

http://66.170.111.4/kidney_dosimetry_SNM_ss.cgi
A preclinical investigation of the saturation and dosimetry of 153Sm-DOTMP as a bone-seeking radiopharmaceutical.
Radiation dosimetry estimates - animal study example

Biodistribution
A physiological distribution test is prescribed, if necessary, for certain radiopharmaceutical preparations. The distribution pattern of radioactivity observed in specified organs, tissues or other body compartments of an appropriate animal species (usually rats or mice) can be a reliable indication of the expected distribution in humans and thus of the suitability of the intended purpose.

The preparation meets the requirements of the test if the distribution of radioactivity in at least two of the three animals complies with the criteria specified in the monograph.

e.g. Technetium (99mTc) exametazime complex injection:
"Biodistribution. Carry out the test as described under R3.1 Biological distribution using a set of three mice. At 5 to 10 minutes post injection not less than 1.5% of the injected radioactivity should be found in the brain, not more than 20% in the intestine, and not more than 15% in the liver."

e.g. Technetium (99mTc) tetrofosmin complex injection:
"Biodistribution. Carry out the test as described under R3.1 Biological distribution using a set of three guinea pigs as described. At 1 hour post injection not less than 1.5% of the injected radioactivity should be found in the heart."

http://apps.who.int/phint/en/p/docf