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A regulators perspective on clincal trials using new radionuclides

Anna-Caterina Senn, Rolf Hesselmann
Federal Office of public Health FOPH, Radiation Protection Unit

The PRISMAP Radiolanthanides Workshop
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Disclaimer

This presentation reflects personal opinions and experiences gained during my time at FOPH (BAG)

The FOPH – Radiation protection unit

What do we do?

- Licensing in nuclear medicine, research facilities, industry, laboratories, schools/universities… using sealed and unsealed radioactive sources and devices emitting ionizing radiation
- Surveillance activities in all these areas
  - on-site presence during inspections
  - technical discussions and coaching
  - administrative surveillance
  - Radiation safety and source security
- Measures and projects aimed at optimizing radiation doses for patients and staff
- Radiation protection training
- **Radiopharmaceutical products**
- Radioactive waste

New radiopharmaceuticals

Definition

What is a **new** radiopharmaceutical (RP) from a regulatory perspective?

- Compounds that have **neither a marketing authorization nor a monograph in the EP**
- A radiopharmaceutical containing a **new radionuclide is always a new RP**

If you plan to use a new RP in a clinical trial (first in human use), **additional efforts** regarding the assessment and evaluation of the justification are required.

Applications for clinical trials involving radiopharmaceuticals

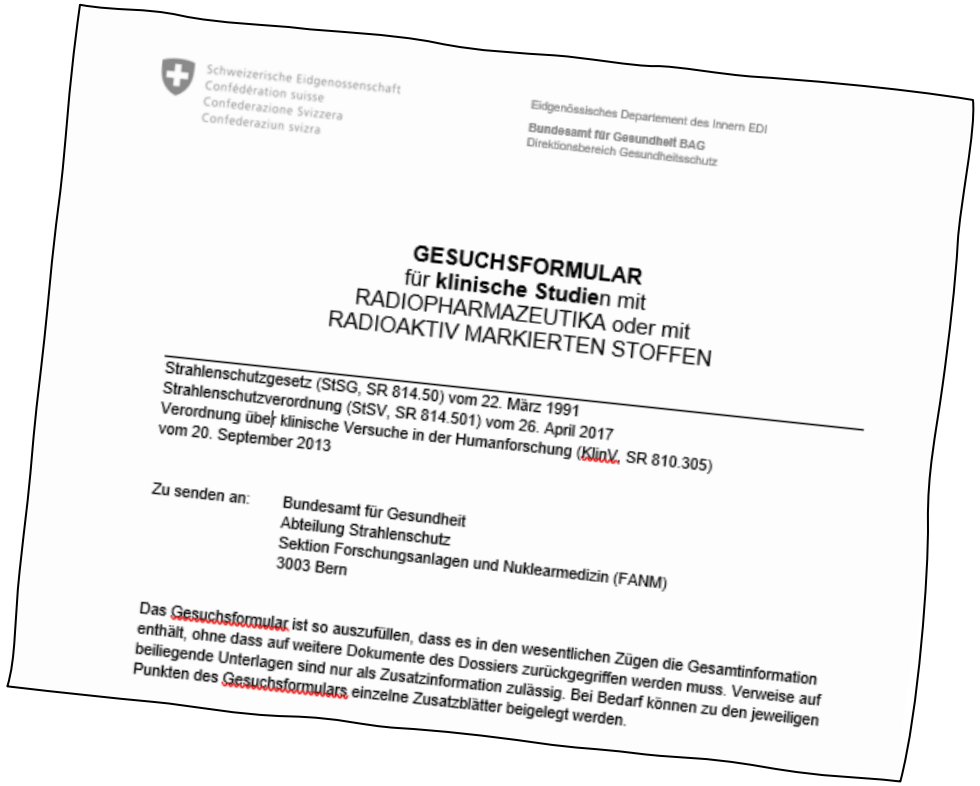
Application for a clinical trial involving an RP in Switzerland

How it usually works

Clinical trials in category C

Entire documentation for the trial is submitted to **Swissmedic**, the responsible **Ethics Committee** and the **FOPH** **at the same time:**

- Swissmedic: Clinical Trial Application
- FOPH: Informationen zum Strahlenschutz bei klinischen Studien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GESUCHSFORMULAR
für **klinische Studie**n mit
RADIOPHARMAZEUTIKA oder mit
RADIOAKTIV MARKIERTEN STOFFEN

Strahlenschutzgesetz (StSG, SR 814.50) vom 22. März 1991
Strahlenschutzverordnung (StSV, SR 814.501) vom 26. April 2017
Verordnung über klinische Versuche in der Humanforschung (KlinV, SR 810.305) vom 20. September 2013

Zu senden an: Bundesamt für Gesundheit
Abteilung Strahlenschutz
Sektion Forschungsanlagen und Nuklearmedizin (FANM)
3003 Bern

Das Gesuchsformular ist so auszufüllen, dass es in den wesentlichen Zügen die Gesamtinformation enthält, ohne dass auf weitere Dokumente des Dossiers zurückgegriffen werden muss. Verweise auf beiliegende Unterlagen sind nur als Zusatzinformation zulässig. Bei Bedarf können zu den jeweiligen Punkten des Gesuchsformulars einzelne Zusatzblätter beigelegt werden.

Swissmedic: KLV portal or postal mail (eDok structure)

FOPH: contact Str-Radiopharmazeutika@bag.admin.ch

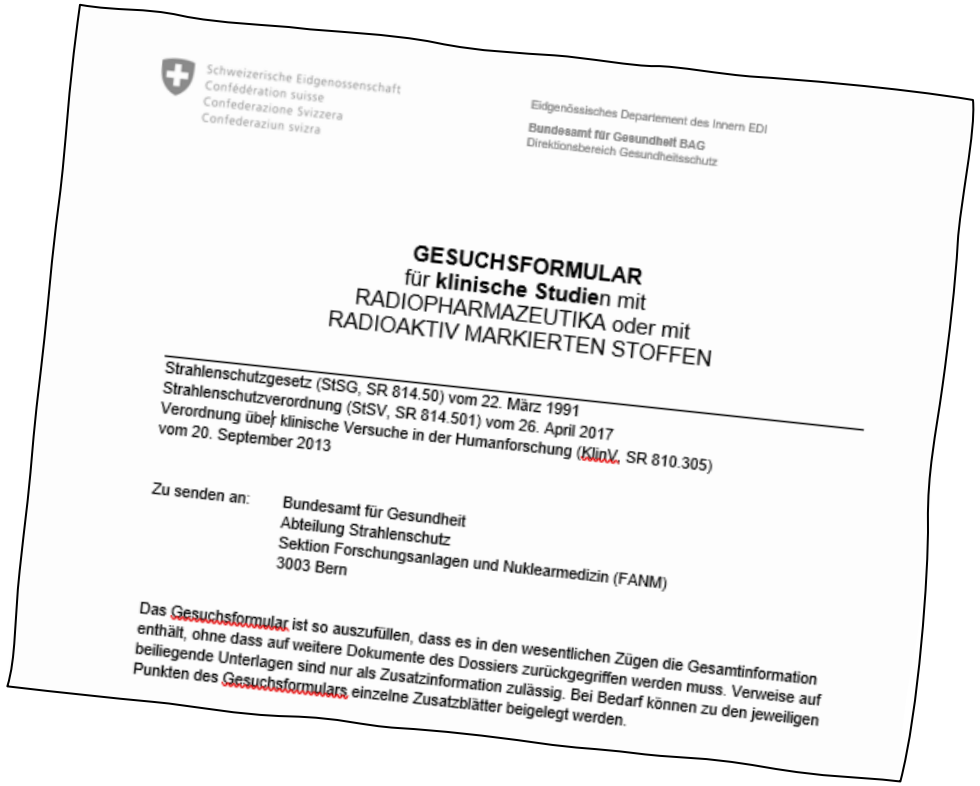
Application for a clinical trial involving an RP in Switzerland

How it usually works

Clinical trials in category C

Swissmedic:
verifies whether the quality and safety of the RP is guaranteed

FOPH (Radiation Protection Division)**:**
issues an opinion regarding radiation protection.



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Application for a clinical trial involving an RP in Switzerland

How it usually works

As soon as a study is submitted to Swissmedic, the official time limits come into effect:

- **«Formal check»: within 7 days**, receipt of application is confirmed; the applicant is informed of any formal flaws in the documentation.
- **Decision: within 30 days** of receipt of the complete application. Time limit can be extended for another 30 days, e.g., if the pharmaceutical is applied to human beings for the first time.

The FOPH is not issuing a separate response, but is providing its comments within the statement of Swissmedic.

- **The same time limits apply for the FOPH**

Application for a clinical trial involving an RP in Switzerland

How it could be optimized for new RPs

Assessment and evaluation of the justification for new RPs might require

- a dialogue between the FOPH and the sponsor and other partners involved and
- a literature review by the FOPH

➢ **More time for a thorough review to increase the quality of the response by the FOPH.**

What can **you** do to increase the quality of the response of FOPH?

➢ Seek **scientific advise** from FOPH **prior to submission** to Swissmedic

You can do this by writing us an e-mail (Str-Radiopharmazeutika@bag.admin.ch), no formal process ist required.

Application for a clinical trial involving an RP in Switzerland

How it could be optimized for new RPs

Why shoud you contact the FOPH prior to submission?

- **Quality and completeness of the dossier** can be assessed without the pressure of deadlines
- **Possible pitfalls** can be identified at an earlier stage (e.g., regarding the production of the radionuclide precursor, radiation safety, licencing, GMP…)
- It enables the experts at FOPH to expand their **knowledge on new nuclides**
  - **Add relevant literature** on (pre-)clinical data
  - Add information on the **reasoning** behind the trial setup

https://realkm.com/

GMP and non-GMP production

GMP/non-GMP production

Issues and questions regarding new RPs **in clinical studies**

Can you use a **non-GMP radionuclide solution as starting material** for manufacturing of an IMP?

What is commonly practiced today with known radionuclides?

Radionuclide and chemical precursors are often bought in **API quality** or have even a market authorisation (also excipients)

→ Especially for **new radionuclides**: feasibility not immediately obvious

GMP/non-GMP production

Issues and questions regarding new RPs **in clinical studies**

EudraLex Vol. 4 Part II: API manufacturing

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

- Production of **API Starting Material is not subject to GMP**
- **Nuclear transformations** are not listed → supports exclusion from GMP requirement

GMP/non-GMP production

Issues and questions regarding new RPs **in clinical studies**

EudraLex Vol. 4 Annex 3: Manufacture of Radiopharmaceuticals (Introduction)

Type of manufacture	*Non - GMP **	*GMP part II & I*	
Radiopharmaceuticals PET Radiopharmaceuticals Radioactive Precursors	*Reactor/Cyclotron Production*	*Chemical synthesis*	*Purific steps*
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**.*

The **manufacturer of the final radiopharmaceutical** should **describe and justify** the steps for manufacture of the active substance and the final medicinal product and which GMP (part I or II) applies for the specific process/manufacturing steps.

GMP/non-GMP production

Issues and questions regarding new RPs **in clinical studies**

Extract from Annex 3, PIC/S Guide (PE 009-17), **August 25, 2023**

Principle

The manufacture of radiopharmaceuticals should 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 iii. This annex is also applicable to radiopharmaceuticals used in clinical trials.

GMP/non-GMP production

Extract from Annex 3, PIC/S Guide (PE 009-17), **August 25, 2023**

INTRODUCTION

3. This guideline is applicable to …. the following types of products:

- Radiopharmaceuticals
- Positron Emitting (PET) Radiopharmaceuticals
- Radioactive Precursors for radiopharmaceutical production → **means GMP Part I applies in principle**
- Radionuclide Generators

Chemical precursors are not mentioned! → GMP Part II possible

GMP/non-GMP production

Issues and questions regarding new RPs **in clinical studies**

Every finished product manufacturing starts from an API (or several)

A **licensed pharmaceutical manufacturer** can transform an API starting material into an API by

- defining **specifications**;
- **quality control tests**
- own **processing** before it enters the API manufacturing step.

Knowledge about **potential impurities** is required and a **convincing risk analysis** must be provided by the **producer** of the API starting material. It is not sure that an authority will accept this approach.

If a starting material is produced as API or has even a market authorization, the **control requirements are reduced**.

GMP/non-GMP production

Issues and questions regarding new RPs **in clinical studies**

To avoid lengthy discussions and a potential non-approval, we recommend to validate **new radionuclides** as **API materials**

Why?

- Not all quality control tests can be performed on a radionuclide solution before application to humans
- Consumer (e.g. local radiopharmacy) cannot take **responsiblity for quality assurance**

→ A **well validated manufacturing process** for the radionuclide precursor is required

→ Manufacturers of new radionuclides should be supported (by PRISMAP?) in becoming **authorised active substance manufacturers**

From a regulatory perspective, a solution of registering the manufacturers of these new nuclides as authorised active substance would ease the justification on the applicants' side and the assessment by the authorities.

Thank you for your attention