Member-state field report and good-practice examples

Germany

Alexander Drzezga
Department of Nuclear Medicine
University of Cologne
& DZNE Bonn/Köln
& Forschungszentrum Jülich INM-2
& Committee Radiological Protection in Medicine
of the German Commission on Radiological Protection (SSK)

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This project has received funding from the European Commission under Service Contract N° ENER/2022/NUCL/SI2.869532.0

Conflicts of Interest

- Research support: Siemens Healthineers, Life Molecular Imaging, GE Healthcare, AVID Radiopharmaceuticals, Sofie, Eisai, Novartis/AAA
- Speaker Honorary/Advisory Boards: Siemens Healthineers, Sanofi, GE Healthcare, Biogen, Novo Nordisk, Invicro, Novartis/AAA, Bayer Vital
- Stock: Siemens Healthineers, Lantheus Holding; Immunogen, Structured therapeutics
- Patents: Patent for 18F-JK-PSMA7 (Patent No.: EP3765097A1; Date of patent: Jan. 20, 2021).

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Topics

- Clinical application pathways for radiopharmaceuticals in Germany
- Scientific/trial application pathways for radiopharmaceuticals in Germany
- Specific issues/problems:
  - Multiple authorities/federal authorities (Ethics committee, Radiation protection authorities, drug approval agency)
  - BFS, dosimetry, radiation protection
  - BfArM, GMP regulations
- Recent recommendations of the radiation protection committee
- Suggestions/conclusions

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Involved authorities/federal agencies

Local IRB or centralized Ethics Committee (CTIS)

The Federal Institute for Drugs and Medicinal Products
(Bundesinstitut für Arzneimittel und Medizinprodukte)
BfArM

Federal Institute for Drugs and Medical Devices

Federal Office for Radiation Protection
(Bundesamt für Strahlenschutz)
BFS

Bundesamt für Strahlenschutz

District government (production license, notification, radiation protection regulation)

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Clinical application pathways for radiopharmaceuticals in Germany

Diagnostic drugs:

- **Approved drugs**
  - Drug provided "ready to use" (e.g. [18F]FDG from commercial provider)
    - *Within* approved indications (e.g. lung cancer)
    - *Outside* approved indications (off label use), e.g. dementia
  - Local labeling: Only precursor/kit approved, requiring labelling (e.g. most Tc-labelled tracers),
    - *Within* approved indications, e.g. cardiac perfusion imaging with Tc99m-Mibi
    - *Outside* approved indications (off label use) e.g. Tc99m-Mibi for parathyroid scintigraphy
    - **Controversy:** Is labelling = production? GMP standard required yes/no? Some centres in Germany forced to implement according infrastructure!
- **Non approved drugs**
  - Production license/AMRadV: production under responsibility of radiopharmacist, max. 20 patients/week, within one clinical unit.
  - §13/2b, production under direct professional responsibility of a physician for the purpose of personal use in an individual patient, e.g. numerous PET-tracers
    Controversy: level of required GMP-conformance?

Clinical application pathways for radiopharmaceuticals in Germany

Therapeutic drugs:

- **Approved drugs**
  - Drug provided "ready to use" (e.g. iodine-131, Pluvicto®, Lutathera®, SIRT) from commercial providers)
    - *Within* approved indications
    - *Outside* approved indications (off label use)
- **Non approved drugs**
  - Model of production license/AMRAD V NOT EXISTENT FOR THERAPY!
  - "Compassionate use" (approval already applied for)
  - §13/2b, production under direct professional responsibility of a physician for the purpose of personal use in an individual patient, e.g. numerous PET-tracers
    Controversy: level of GMP-conformance?

Scientific/trial application pathways for radiopharmaceuticals in Germany

- **Pathophysiology trials: (Diagnostic) drug is used to test a basic science hypothesis.**

  Required: Ethics/IRB approval, BFS approval, No BfArM approval, if the purpose of the trial is clearly not to study clinical value of a drug. **Controversy:** Production license required yes/no? Regional differences.

- **Established clinical application: Drug used according to established clinical application.**

  Required: Ethics/IRB approval, No BFS approval required, BfArM approval for the investigational drug not for diagnostic drug. **Controversy:** is there an "established use" of NON-approved drugs? BfArM approval required? GMP production license and IMPD etc.?

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Scientific/trial application pathways for radiopharmaceuticals in Germany

- **Companion diagnostics: Drug used as a companion diagnostic in a clinical therapy trial**

  Required: IRB/Ethics approval, BFS: Notification“only”, BfArM: approval for the investigational drug not for diagnostic drug. **Controversy:** what if NON-approved diagnostic drugs are employed as companion diagnostics? Full BFS and BfArM proposal/IMPD?

- **Original drug trial: Radiopharmaceutical itself in the centre of a clinical trial**

  Required: Ethics/IRB approval, BFS: full proposal, BfArM: GMP manufacturing license etc. If diagnostic drug part of the proposal, approval also required for diagnostic drug.

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Notification, full proposal or no proposal?

Radiation application within established health care

no proposal required

Radiation exposure = companion diagnostics

Subjects of legal age

Inclusion only of subjects suffereing from a disease to be treated

Application of radiation is NOT matter of the research

Application represents established clinical routine procedure

Decision „regular health care“ by expert physician with radiation protection expertise

Notification

If one question „no“:

Full proposal

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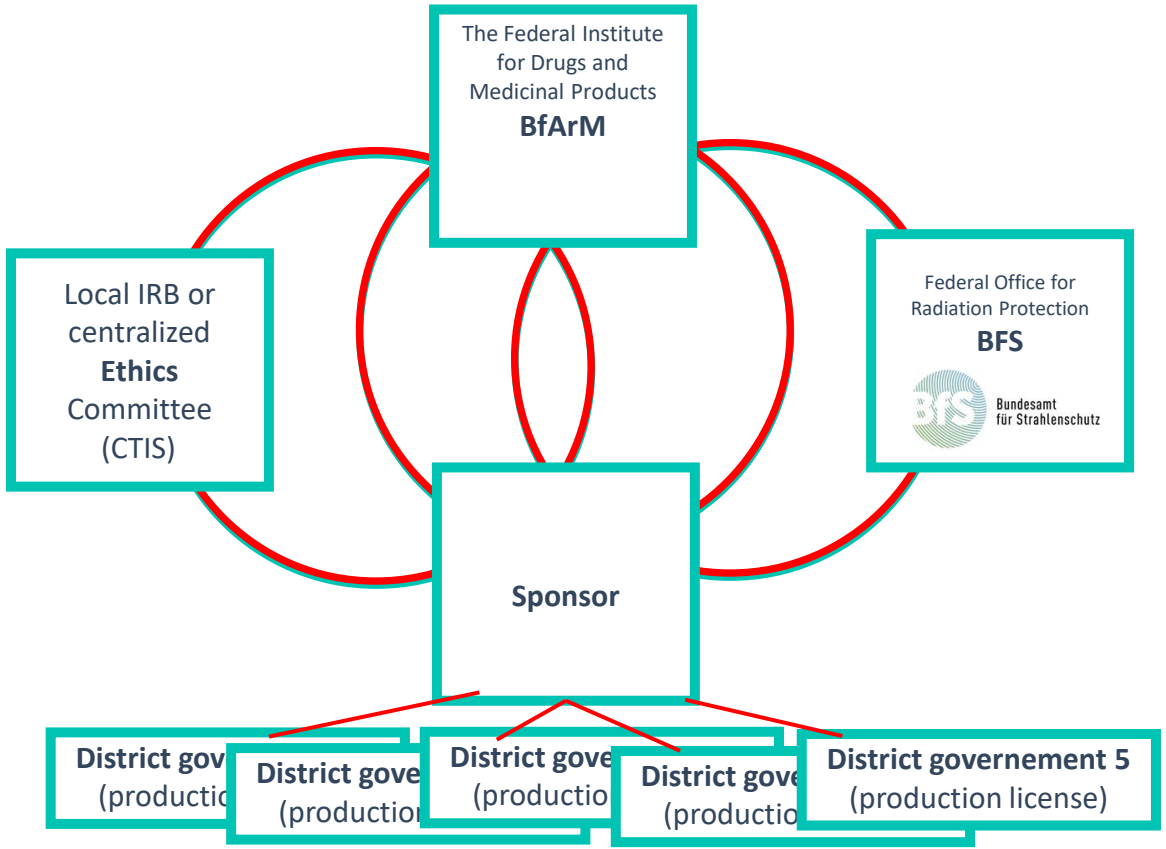
Issues: Multiple involved authorities/circularity



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Issues

GMP regulations

- Heterogeneity internationally but also regionally between German countries!
- Non-clarified situation with regard to labeling/production in trials and in clinical routine

  Controversies: Production license required for basic science trials yes/no?, required for clinical trials (in Germany only?). In multicenter-trials, do all involved centers require individual production license of their regional government, different standards leading to delays.

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Issues

BFS/Radiation protection/dosimetry requirements

- Involvement of another independent authority with specific opinions, in part judging again basic aspects of the trial, statistical questions, etc. Time-consuming, check for completeness 21 days, content review 90 days.
- In international comparison, relatively higher requirements e.g. with regard to dosimetry, follow-up periods, dose limits etc.

Controversies: Dosimetry originally required to ensure treatment safety (in initial approval trial/phase 1 trial), or in all trials (phase 2-3), or even always required for clinical use (notification procedure)? What extent of dosimetry is required (at one cycle, at every cycle, one whole body or up to 3 wholebody examinations)?

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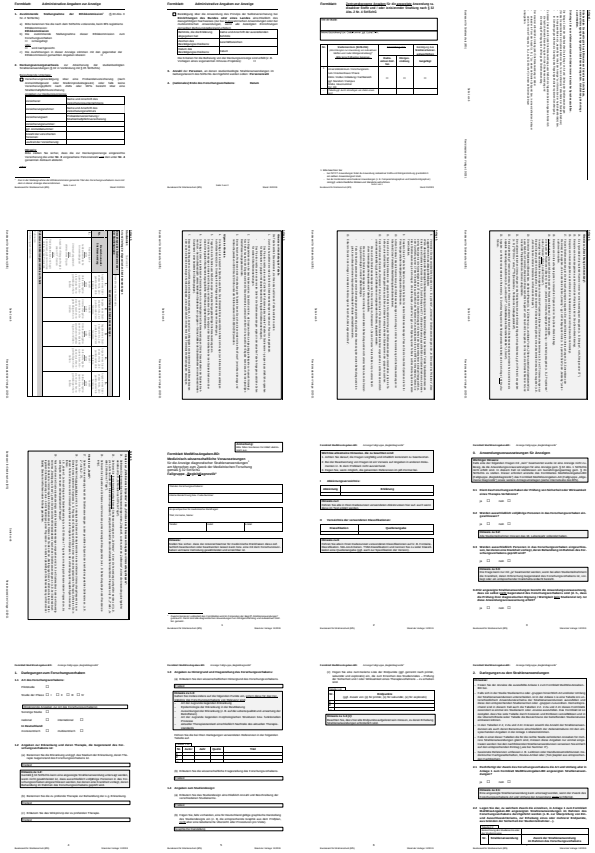
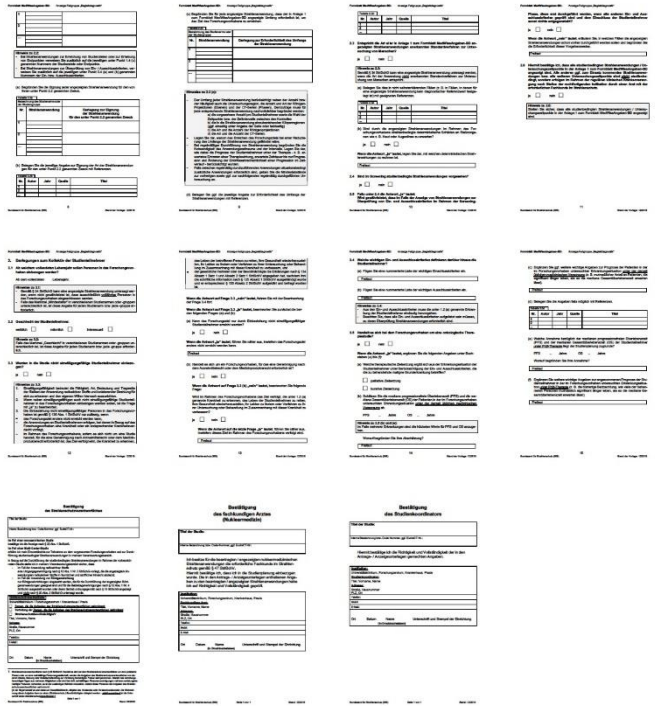
Issues Paperwork





Simple notification-procedure (companion diagnostics) **27 pages** template raw

Issues Paperwork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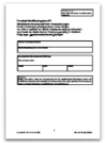
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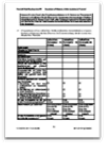
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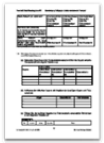
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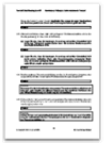
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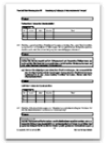
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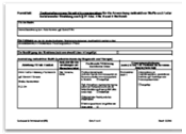
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Regular application: **35 pages** (raw) template, without patient information and clinical trial protocol

Issues Dosimetry

- Oncol. Radionuclide-therapy (RNT) ≠ thyroid therapy: **Maximum** not **minimum** possible dose
- RNT ≠ external beam therapy (EBT): For EB therapy-planning **in advance** to ensure sufficient tumor-dose and limit surrounding tissue damage. RNT= Prior to therapy, only dose-approximation by diagnostic scans. Radionuclide-therapy (RNT) targets multiple (not single) lesions. **Post-therapy dosimetry** regularly NOT resulting in change of management. Limitation systemic (not local) healthy organ function, measurable by organ function parameters
- RNT-Dose escalation by repeated cycles rather than adjustment of individual cycle doses
- Package insert of approved therapies (Lutathera, Pluvicto) does NOT suggest dosimetry
- Dosimetry is burdensome: 3 times after each cycle = 18 whole body examinations (&CT), radiation exposure, patient discomfort, repeated visits and exhaustion of capacities.

➔ Extensive post-therapy dosimetry in oncological RNT meaningful for first approval, for non-standard concepts or in case of pre-existing functional impairment of critical organ (medical reasons).

(Negative) Examples

- **DIAN trial:** Carriers of genetic mutation considered “healthy”, thus dose limitation for PET-imaging, trial cancelled in Germany by sponsor.
- **Vision trial:** Slow administrative processes (e.g. differences in regional standards for production license etc), trial closed before German centres could include subjects.
- **Enable trial: “**Randomization” led to judgement as a clinical trial (BfArM), not considered as a minimal interventional trial (despite only application of approved diagnostic radiotracer once in patients with immediate clinical value).
- **NeoRay trial:** Extended follow-up periods for dose-limiting toxicity required only in Germany, trial cancelled in Germany by sponsor
- **Amypad trial:** Approved tracer, only in Germany ”extension of indication” suggested because subjects with subjective cognitive decline were included, thus BfArM approval required.

Recommendations of the SSK (German Committee on Radiological Protection in Medicine)

Download-Link:

https://www.ssk.de/SharedDocs/Beratungsergebnisse/EN/2022/2022-09-22_Nuklide_in_der_Nuklearthерapie.pdf

Effect		
	Radiopharmaceutical	Metabolites
Name of radiopharmaceutical	[^{177}Lu]Lu-PSMA-617; [^{177}Lu]Lu-PSMA-I&T	-
Biological action of the radiopharmaceutical	Binds with the PSMA-bearing extracellular vesicles, followed by internalisation	-
Biodistribution/specific accumulation in	Prostate cancer cells and their metastases	-
Non-specific/non-target accumulation dominant in	Kidneys, liver, salivary glands, tear glands, proximal duodenum	-
Known common side effects (> 10 %)	Nausea/vomiting, haemototoxicity, fatigue	-
Rare severe side effects	-	-

Dose/dosimetry	
Typical effective dose per therapy session per patient (per administration)	0.44 Gy at 7.4 GBq
Typical effective dose (total for all patient cycles)	2.64 Gy after 6 cycles
Dose-limiting organ	Bone marrow, sometimes also kidney (both are potentially dose-limiting)
Intended dose target region	Unknown
Required pre-therapy dosimetry and imaging	Target identification required (PSMA-targeted PET/CT, PET/MRI or SPECT/CT)
Required post-therapy dosimetry and imaging	Determination of the dose rate upon discharge, post-therapy radiotracer scintigraphy, additional imaging optional between therapy cycles, quantification optional, dosimetry during 1st cycle for approx. seven days (variable protocols)

Exposure of surroundings/employees/environment by patient	
Radioactive excretion by patient	
Excreted nuclides	Lutetium-177
Excretion modes	Renal/urine, low gastrointestinal/faecal
Excretion route most relevant for radiation protection	Renal
Typical duration of excretion relevant for radiation protection	2 to 3 days
Handling of excrement in hospital and post-hospital	Waste water treatment plant (decontamination plant) (in hospital) Post-hospital: Advise patients to collect pads or similar for several days; ideally flush the toilet multiple times after use
Radiation emitted by patient post-treatment	
Emitted radiation type (% α, % β, % γ)	Patient emits almost exclusively γ
Type(s) of radiation emitted by patient most relevant to radiation protection	γ
Anatomic focal points of radiation (where present)	Metastases, kidneys during first few days
Typical duration of radiation relevant for radiation protection emitted by patient	Approx. 3 days
Necessary radiation protection measures in hospital and post-hospital	Therapy ward with waste water treatment plant (decontamination plant) Post-hospital: Toilet hygiene, keeping distance from vulnerable persons

Suggestions

- Approval of Radionuclides and of Kits, process of their combination not “production” but “Radiolabelling” ← specific regulatory entity requiring notification of the government and certain production characteristics (GMP light). Possibly for SPECT and PET tracers.
- Introduction of a regulated “AMRadV” type pathway for local production of therapeutic radiotracers with a production license in a dedicated clinical unit.
- Combination of Ethics/Medicine approval/Radiation protection assessment in one central process (common decision). ONE proposal, ONE answer.
- International standardization (not following the strictest possible interpretation).
- Limit dosimetry requirements to a reasonable amount. Phase I clinical trials and for selected cases where individualized therapy is meaningful in clinical routine (medical decision).

Thank you very much for your attention!

University of Cologne
Nuclear Medicine/IRE
Dr. Ph. Krapf

University of Rostock
University of
Prof. Dr. B.J. Krause, Univ- of Rostock

SSK A2

Authors SSK Recommendation:
- Prof. Dr. Dr. Dr. h. c. Andreas Bockisch, Universitätsklinikum Essen
- Prof. Dr. Andreas Buck, Universitätsklinikum Würzburg
- Prof. Dr. Wolfgang Burchert, Universitätsklinik der Ruhr-Universität Bochum Bad Oeynhausen
- Prof. Dr. Alexander Drzezga, Universitätsklinikum Köln
- Prof. Dr. Alexander Haug, Medizinische Universität Wien
- Prof. Dr. Ken Herrmann, Universitätsklinikum Essen
- Prof. Dr. Jörg Kotzerke, Klinikum der TU Dresden
- Dr. Jens Kurth, Universitätsmedizin Rostock
- Prof. Dr. Marianne Patt, Universitätsklinikum Leipzig
- Prof. Dr. Kambiz Rahbar, Universitätsklinikum Münster

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