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Preclinical Review

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Which studies are necessary to obtain a marketing approval?

- Extent of nonclinical testing depends on
  - product
    - new active substance or well established
    - radiodiagnostic or radiotherapeutic agents
  - indication (e.g. late stage cancer or other indication)
  - available clinical information, if not developed from the beginning

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General requirements are outlined in …

- WL Zulassung Radiopharmazeutika:
  - toxikologischen, pharmakokinetischen (und wo relevant, pharmakodynamischen) Eigenschaften des Radionuklids, des Trägermoleküls und der markierten Verbindung

- International guidelines
  - ICH M3(R2): *Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*
  - ICH S9: *Nonclinical Evaluation for Anticancer Pharmaceuticals*
  - FDA: *Nonclinical Evaluation of Late Radiation Toxicity of Therapeutic Radiopharmaceuticals*

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Examples of nonclinical data packages for approved products

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Case study for a radiodiagnostic
Amyvid (NAS)

- Background information:
  - Active substance: Florbetapir 18F (18F-AV-45), half-life of approximately 110 minutes by emitting a positron radiation of 634 keV, followed by photonic annihilation radiation of 511 keV.
  - Route of administration: intravenous
  - Indication: indicated for (PET) imaging of β-amyloid neuritic plaque density in the brains of adult patients with cognitive impairment who are being evaluated for Alzheimer's disease (AD) and other causes of cognitive impairment. Amyvid should be used in conjunction with a clinical evaluation. A negative scan indicates sparse or no plaques, which is not consistent with a diagnosis of AD.
- Approved by EMA (2013),FDA (2012) and Swissmedic (2014)

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Amyvid: nonclinical data package (source EPAR)

- Pharmacodynamics
  - in vitro studies/ publications
- Safety pharmacology
  - Safety Pharmacology (according to ICH guidelines to assess CNS and cardiovascular safety assessment)
- Pharmacokinetics: the pharmacokinetics of Amyvid has been investigated in vivo in mice, rats and Monkeys.

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Amyvid: nonclinical data package (source EPAR)

- Toxicity of AV-45 was evaluated with single-dose and repeat-dose studies in rats and dogs.

- The maximal dose levels chosen for testing in rats and dogs corresponded to 100 times the MHD (maximum human dose) for single-dose toxicity testing and 25 times the MHD for repeat-dose testing for 28 days.

- AV-45 produced no significant findings in single-dose and repeat-dose toxicity assays in rats and dogs at high multiples of the intended MHD.
- Genotoxicity was performed in vitro and in vivo testing systems
- No reproductive and developmental toxicity, immunotoxicity, and carcinogenicity evaluations were conducted

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Case study for a radiodiagnostic
Dopaview (well established)

- Well established use (Positiv-Liste von Swissmedic), EP Monograph

- It is an analogue of L-DOPA (L-3,4-dihydroxyphenylalanine), an endogenous aromatic amino acid that accumulates rapidly in target tissues particularly the striatum of human brain and is transformed into dopamine, a neurotransmitter from the catecholamine group.
- **Pharmacokinetics**

  The pharmacokinetic properties of radiolabelled L-DOPA has been evaluated in several animal species and it is also well known in humans. Biodistribution of [18F]-L-DOPA has been studied after intravenous administration in several animal species, including mice, rats and dogs.
- The toxicology and the radio toxicology of this compound are based **on the literature analysis**, and are confirmed by one additional GLP-regulated study in the mouse.

Source: Information for professionals

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Case study for a radiotherapeutic
Xofigo (NAS)

- Background information:
  - Active substance: radium Ra223 dichloride; alpha particle emitter with a physical half-life of 11.4 days.
  - Route of administration: intravenous
  - Indication: Xofigo is indicated for the treatment of adults with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastases

- Approved by EMA (2013), FDA (2013) and Swissmedic (2014)

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Xofigo: nonclinical data package (source EPAR)

- Pharmacodynamics
  - in vitro (3) and in vivo (4) studies/ publications
- Safety pharmacology
  - Effects of radium-223 chloride on vital organ functions [central nervous system, cardiovascular system (including ECG) and respiratory system] were investigated in several in vivo studies (rats, dogs).
- Pharmacodynamic drug interaction studies (2)
- Pharmacokinetics
  - The pharmacokinetics of radium-223 has been investigated in vivo in rats, mice and dogs, using the same formulation as the clinically intended.

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Xofigo: nonclinical data package (source EPAR)

- Toxicology
  - Single dose studies (mouse, rat, dog)
  - Repeat dose studies
    - Rat → once every 4 weeks x 4 + 12 months postdose
    - Rat → once every 4 weeks x 12 + 1 month postdose
    - Dog → once every 30-35 days x 6 + 35 days postdose
  - Not conducted
    - Genotoxicity/ Carcinogenicity: In general, radionuclides are considered to be genotoxic and carcinogenic.
    - Reproductive toxicity: In general, radionuclides induce reproductive and developmental effects.
    - Environmental Risk Assessment: Inorganic salts representing electrolytes are considered not to pose a risk to the environment

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For your information

- EMA/ Safety Working Party:
  - *Guideline on the non-clinical evaluation of radiopharmaceuticals*
  - Draft to be published for consultation Q3 2018

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Thank you!

Any questions?