Novartis Development

*What are the **specific regulatory challenges** for radiopharmaceuticals compared to non-radioactive pharmaceuticals*

*How is this **impacting** your company when **developing innovative** radiopharmaceuticals*

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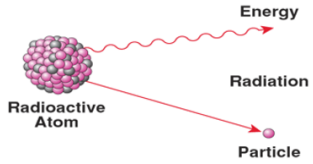
Context and problem statement

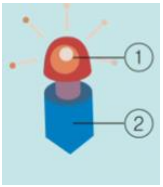
Specific aspects of Radiopharmaceuticals due to their radioactive nature do not fit into the current regulatory framework.

- ***Context**:*
  - Highly varied interpretations how to apply existing framework for non-radioactive pharmaceuticals
  - Different requirements regionally and even on a country level in EU
- ***Challenge**:* Not having a harmonized framework is a major hurdle for a globally operating pharmaceutical industry and threat to innovation
- ***Proposal**:* Achieve harmonization – one key opportunity is the ongoing review of the EU pharmaceutical legislation that could enable the usage of other regulatory vehicles such as ASMF and aQMF

Example draft definitions: Regulating Radionuclides according to their different role in the Radiopharmaceuticals



Radiopharmaceuticals for diagnostic (or related) or for therapeutic use



Radionuclide

Carrier molecule/ ligand

Radionuclide radiopharmaceuticals

Radionuclide is active substance e.g.:

Diagnostic	Therapeutic
^{123}I for thyroid cancer as chloride salt in tablet form	^{131}I for thyroid cancer as chloride salt in tablet form
^{82}Rb for cardiac imaging as chloride, injection of eluate from a generator	^{223}Ra for prostate cancer as chloride as solution for injection
^{99m}Tc for various specific indications as sodium pertechnetate, injection of eluate from a generator	

Complex radiopharmaceuticals

Radionuclide bound to carrier molecule/ligand e.g.:

Diagnostic	Therapeutic
^{18}F fluciclovine for prostate cancer	^{131}I meta-benzylguanidine for neuroblastoma
^{68}Ga gozetotide for prostate cancer	**^{177}Lu** vipivotide tetraxetan for prostate cancer
^{99m}Tc sestamibi for various specific indications	^{90}Y ibritumomab tiuxetan for Lymphoma

How are radionuclides presently regulated?

Regulatory question	EU	US
Is **kit-radiolabelling** a manufacturing step?	**Depends** on local interpretation	**No** Kit-radiolabling is clearly differentiated from manufacturing (compounding)
How are **radionuclides for radiolabeling** purposes regulated?	As **Medicinal Product Indication** «for radiolabelling purposes»; **not to be used on its own**	As **Drug Master File** According to the role of the radionuclide being a part of the active substance and not the active substance itself

How do these differences impact global rapiopharmaceutical companies?

Radionuclide for radiolabelling purposes regulated as medicinal product:

Radionuclide manufacturers need to:

- Submit a full dossier including non-clinical and clinical data, even though they are only responsible for the quality of what becomes a part of the active substance
- Conduct Pharmacovigilance for a product which is never adminsistered by itself, and there is no way to find out what carrier molecule it is bound to (at least if there are no approved kits which is the case for Lutetium-177 or Cupper-64)

RLT manufacturers need to:

- Include more detailed documentation on the radionuclide as being a regulated as medicinal product is interpreted by some countries that it **cannot be seen as «starting material»**
  - Need for different IMPDs in different countries for a global study; additional risk to conduct studies in Europe under the EU CTR

Conclusion

- Radiopharmaceuticals have high logistical complexities; not having a harmonized regulatory environment adds unecessary hurdles
- A safe and effective regulatory framework exists for key aspects like kit-radiolabelling (US and CH) and regulation of radionuclides for radiolabelling purposes (US)
- The update of the EU legislation is a key opportunity to harmonize the regulatory framework across European countries
  - ASMF/aQMF certification pathway is expected to achieve the following important criteria to protect patient safety:
    a. Good and clearly regulated oversight by Health Authorities
    b. Strict quality requirements maintained including sterility requirement