Imaging using Radioconjugates: Overview, Global Quality Guidance and Regulatory Pathways

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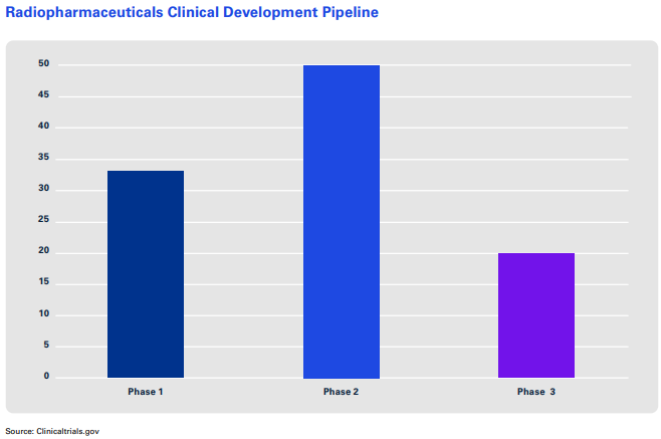
Context: Radioconjugate Growth Continues*

'In an increasingly challenging Life Sciences market, that demands better efficacy, safety and targeting, Radiopharmaceuticals have the potential to deliver on all three.'



PLUVICTO®
lutetium Lu 177 vipivotide tetraxetan
INJECTION FOR INTRAVENOUS USE

Xofigo®
radium – 223 dichloride

LUTATHERA®
(lutetium Lu 177 dotatate)
injection, for intravenous use

The global Radiopharmaceuticals market is set to reach nearly **$14bn** by 2033, growing 8-10% year-on-year.

> 100 interventional CTs

ca. $2B global sales in 2023

growth set to continue!

**'Leveraging Opportunities in Radiopharmaceuticals', KPMG, 2024*

A Brief Introduction to Theranostics

Visualization of tumour burden:

'treat what you see'.

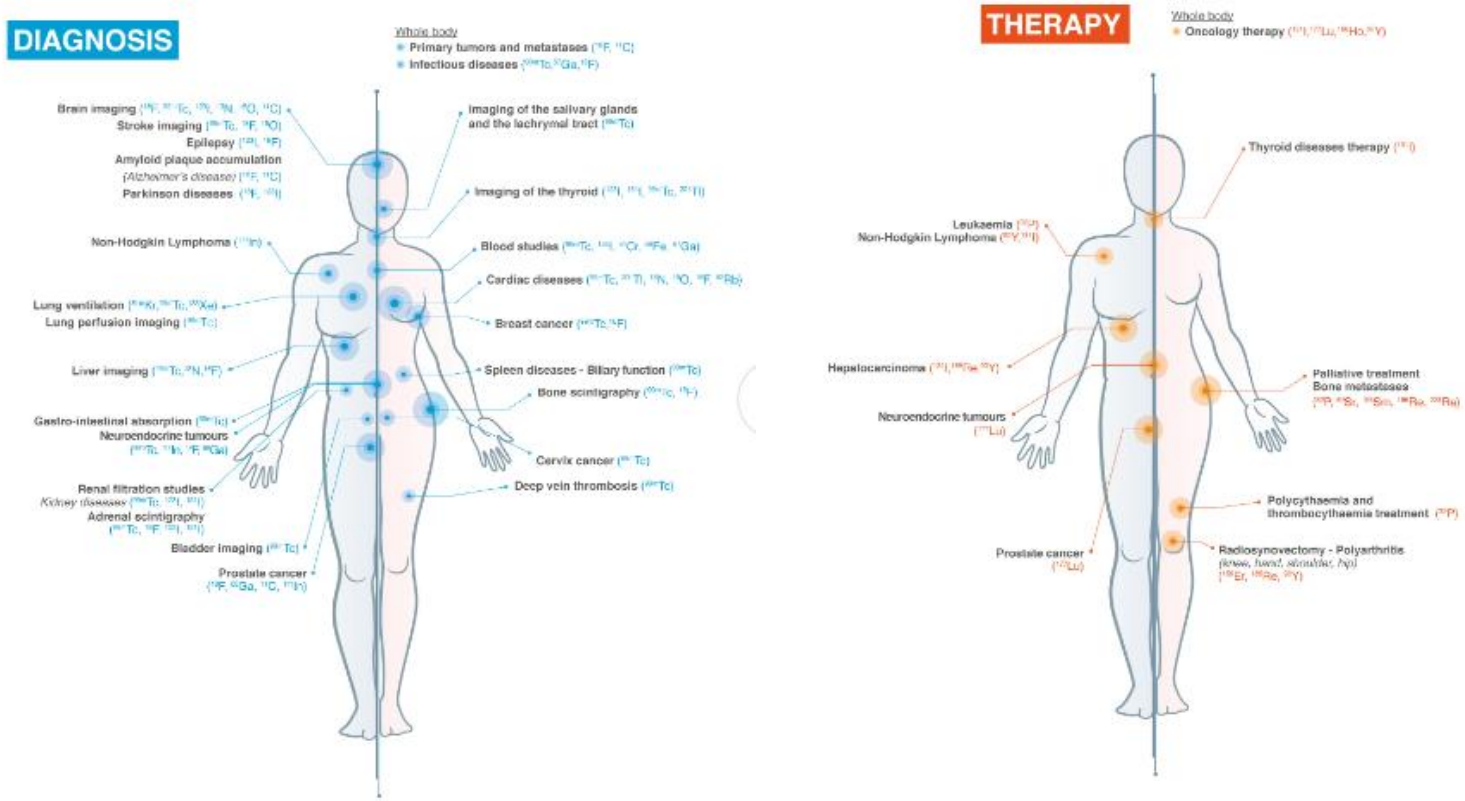
Repeat imaging enables assessment of the effect that therapy has had on target expression

- **Clinical value** is that it can help:
  - HCPs choose the best drug for each patient based on their tumour characteristics
  - HCPs monitor the response to the treatment and adjust the dose or switch to another drug if needed
  - reduce the side effects of the treatment by minimising the exposure of healthy cells to radiation
- **Potential to significantly improve patient experience *via* personalized care**

Adapted from: Bodei, L., Herrmann, K., Schöder, H. *et al.* Radiotheranostics in oncology: current challenges and emerging opportunities. *Nat Rev Clin Oncol* **19**, 534–550 (2022). https://doi.org/10.1038/s41571-022-00652-y

A Brief Introduction to Theranostics

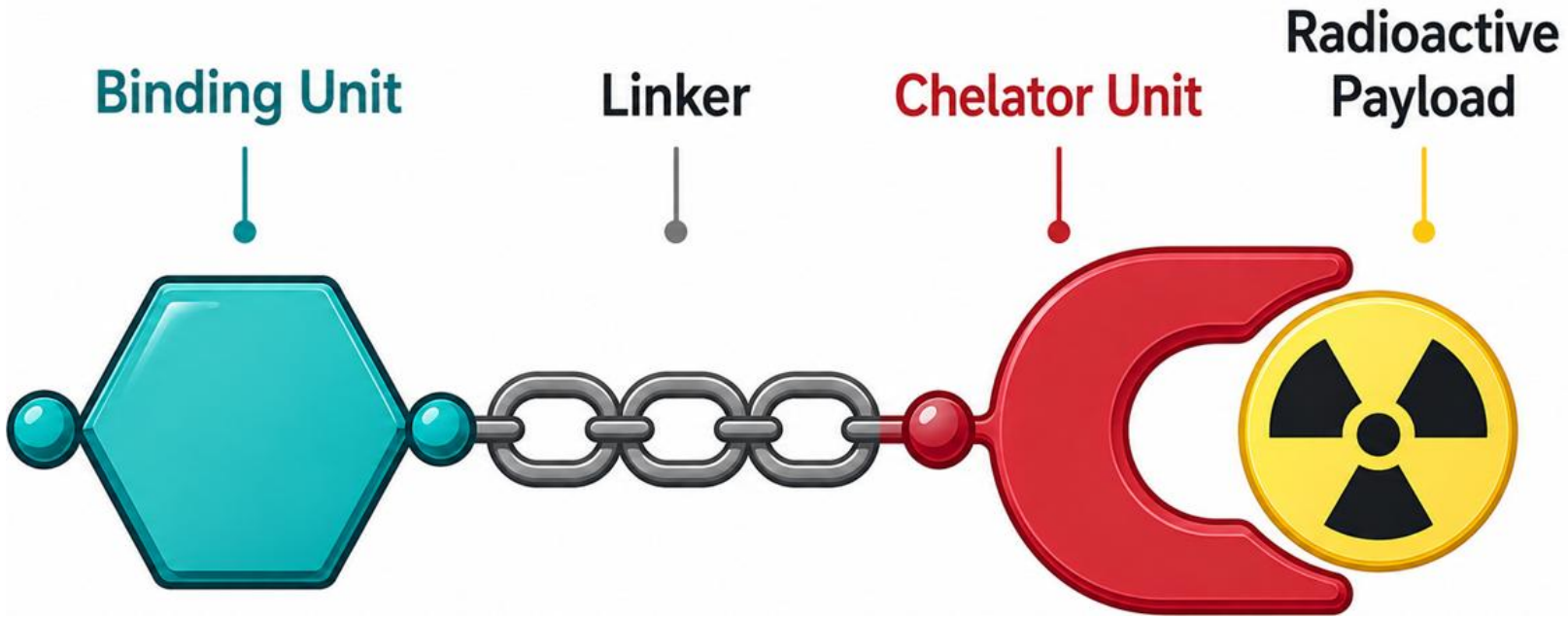
Multitude of radiopharmaceuticals available for diagnosis and therapy:



Opportunity for next-generation theranostics: expand into new targets and tumor types beyond GPCRs and PSMA by leveraging novel ligands (small molecules, antibodies, engineered scaffolds).

https://nuclearmedicineeurope.eu/nuclear-medicine/

Design of Targetted Radiotherapies



Typically consist of a:

- biological or synthetic targeting entity (vector)
- synthetic linker
- synthetic chelator unit that coordinates the radionuclide
- radionuclide (selected depending on application in imaging or therapy)

mAb-based RCs: General Structure and Preparation

Some structural similarity with ADCs:

- Antibody is conjugated to a DNA damaging agent *via* a synthetic linker

Also manufactured in a similar way:

- mAb and linker-chelator assembled separately
- Conjugated together
- Radiolabelling step (by treatment with appropriate metal salt) then unique for RCs.

Design of Theranostic Pairs

Properties of the targeting molecule in a theranostic pair needs to be carefully balanced to be effective in both diagnostic and therapeutic phases of treatment.

Radionuclide selection:

- Diagnostic: long path length to enable imaging
- Therapy: short path length to maximise energy delivered to tumour cells **but** minimise damage to surrounding tissue.
- **For the ligand:**

Targetting Properties	Application	
	Diagnostic	**Therapeutic**
Specific binding to target	X	X
Kinetics of target binding	Rapid	Persistent
High affinity for target	X	X
High accumulation at target site	X	X
High in vivo stability	X	X
Other:	• Fast clearance from circulation • Excretion mainly *via* urinary pathway	• Homogeneous tissue distribution • Very low off-target accumulation

Adapted from: Dr. Jacopo Millul, *Radioligand Therapy – Basic Course The choice of the targeted molecule (C6)*, https://elearning.eanm.org/course/rlt-academy/lesson/1186

Design of Theranostic Pairs

Adapted from: Selection of radioisotopes for imaging and therapy ordered from short to long half-life, matching the in-vivo half-life of small molecule, peptide, protein, and monoclonal antibody targeting agents. https://www.nature.com/articles/s41571-022-00652-y

TARGETTING VECTOR

Small Molecule / Peptide → Small Proteins → Engineered Ab Fragments → Antibodies

RADIONUCLIDE

0-20 h	30-90 h	150-200 h	240-500 h	RN Half Life / USE
^{18}F, ^{68}Ga ^{44}Sc, ^{149}Tb* ^{64}Cu*, ^{86}Y	^{89}Zr			PET
^{99m}Tc ^{123}I	^{111}In ^{67}Ga ^{67}Cu*	^{177}Lu*	^{233}Ra*	SPECT
^{64}Cu* ^{188}Re	^{104}Rh ^{67}Cu* ^{90}Y, ^{186}Re	^{177}Lu* ^{161}Tb ^{131}I		BETA
^{212}Bi ^{211}A1 ^{149}Tb*			^{225}Ac ^{227}Th ^{233}Ra*	ALPHA

* Indicates where the same RN has potential applications in both imaging and therapy (depending on dose)

SPECT *vs.* PET Imaging

SPECT and PET are tomographic nuclear imaging techniques that detect radiation from administered radioactive tracers and use these signals to visualize biological processes in the body.

SPECT PRINCIPLES

- Direct measurement of gamma emissions from the chosen radionuclide.
- Two gamma detectors are placed opposite each other. Each detector generates a 2D image of the radioactivity distribution. By acquiring multiple 2D images at various angles, a 3D image can be computed.
- Emitters used include: ^{99m}Tc, ^{67}Ga, ^{111}I

PET PRINCIPLES

- Detects gamma rays emitted when a positron and electron collide in the body.
- Gamma rays are detected by a ring of detectors that is surrounding the patient. The detected gamma rays can be reconstructed into 3D images.
- Emitters used: ^{18}F, ^{68}Ga, ^{11}C

Source: https://www.tracercro.com/resources/blogs/spect-vs-pet-in-drug-development/

SPECT *vs.* PET Imaging

	SPECT	PET
RESOLUTION	7 – 15 mm	2 – 6 mm
QUANTITATIVE?	LIMITED	YES
MULTPLE RADIOTRACERS?	YES	NO
ACQUISITION TIME	LONG	SHORT (DYNAMIC IMAGING VIABLE)
RN PRODUCTION METHOD	GENERATOR	CYCLOTRON
EQUIPMENT & RN AVAILABILITY	WIDESPREAD	LIMITED

Source: https://www.tracercro.com/resources/blogs/spect-vs-pet-in-drug-development/

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Both technologies capable of visualising relatively low quantities of the imaging agents.

For imaging agent development, some programmes may therefore qualify for microdosing clinical trial pathways offered in different regions.

Source: https://www.tracercro.com/resources/blogs/spect-vs-pet-in-drug-development/

Basis of E2E Control Strategy: mAb-based RC

EMA Guidance: Radiopharmaceuticals based on Monoclonal Antibodies, 3AQ21a, 1991

EU Legal Basis for Radiopharmaceuticals: 2001/83/EC (Medicinal Products for Human Use)

Gives the following definitions:

9. *Radionuclide precursor:*

Any other radionuclide produced for the radio-labelling of another substance prior to administration.

7. *Radionuclide generator:*

Any system incorporating a fixed parent radionuclide from which is produced a daughter radionuclide which is to be obtained by elution or by any other method and used in a radiopharmaceutical.

8. *Radionuclide kit:*

Any preparation to be reconsitituted or combined with radionuclides in the final radiopharmaceutical, usually prior to its administration.

6. *Radiopharmaceutical:*

Any medicinal product which, when ready for use, contains one or more radionuclides (radioactive isotopes) included for a medicinal purpose.

EU Legal Basis: 2001/83/EC (Medicinal Products for Human Use)

Gives the following definitions:

Relevant for centrally-manufactured TRPs

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Quality Guidance for mAb-Based RCs

- EMA (1992): *Radiopharmaceuticals based on Monoclonal Antibodies*
- FDE (1997): *Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use*
- CDE journal article (2025): *Considerations for quality study of recombinant protein-based radiopharmaceuticals [draft guidance also currently under review]*

Quality Attributes Unique to RNs and RCs

Attribute	Why?	How measured?
Radionuclidic Identity	Confirms correct RN is present	Gamma Spectroscopy - emission peaks (keV) are specific to desired RN
Radionuclidic Purity	Measures % desired RN present *vs.* other-RNs	

Comparison of Production Routes: Example for ^{225}Ac

Technology	Th-229 Generator*	Accelerator (Th-232)	Accelerator (Ra-226)**
Primary radioisotopic impurities to consider	None	Ac-227	Ac-226 and daughters (Ac-227 trace)
Primary radionuclide impurities to consider	Th-229 Ra-225	Th-232 spallation products	Ra-226 (Ra-225 trace)
Primary chemical impurities to consider	Iron, zinc, copper decay products (e.g. Bi-209)		
Sterility / endotoxin controls	Depends on source and manufacturing process?		

*primary production route for clinical trial supply to date

** developing technology

https://www-pub.iaea.org/MTCD/publications/PDF/TE-2057web.pdf
https://www.actineer.com/actinium-225/production-routes

Radionuclidic purity by different production routes:

Product Information

Isotope Program, US Department of Energy

NIDC | NATIONAL ISOTOPE DEVELOPMENT CENTER
MANAGED BY THE U.S. DEPARTMENT OF ENERGY ISOTOPE PROGRAM

Specifications — Actinium-225 (Thorium-229 Decay Product)

Half-Life/Daughter	9.920 days to francium-221
Decay	Decay Radiation Information (NNDC)
Chemical Form	Solid actinium nitrate
Radionuclidic Purity	>99% Ac-225 by activity
Production Route	Decay of thorium-229
Processing	Produced by ion exchange chromatography
Primary Container	Glass screw top V-vial in nonreturnable container
Availability	Routinely available (weekly); order far in advance due to limited supply
Unit of Sale	Millicuries

Other Information

https://www.isotopes.gov/sites/default/files/2025-07/Actinium-225%20%28Thorium-229%20Decay%20Product%29%20Product%20Information.pdf

Product Information

Isotope Program, US Department of Energy

NIDC | NATIONAL ISOTOPE DEVELOPMENT CENTER
MANAGED BY THE U.S. DEPARTMENT OF ENERGY ISOTOPE PROGRAM

Specifications — Actinium-225 (Accelerator-Produced)

Half-Life/Daughter	9.920 days to francium-221
Decay	Decay Radiation Information (NNDC)
Chemical Form	Solid actinium nitrate
Radionuclide Purity	≥99% by activity (gamma spectroscopy), not including Ac-227 or daughter isotopes; ≤2% Ac-227 at shipment (value extrapolated from earlier runs)
Production Route	Proton bombardment of natural thorium target
Processing	Separated by ion exchange and solvent extraction
Primary Container	Glass screw top V-vial in nonreturnable container
Availability	Routinely available every three weeks
Unit of Sale	Millicuries

Other Information

https://www.isotopes.gov/sites/default/files/2025-03/Actinium-225%20%28Accelerator-Produced%29%20Product%20Information.pdf

Quality Attributes Unique to RNs and RCs

Attribute	Why?	How measured?
Radiochemical Identity	Confirms correct RC is present	Chromatography, *e.g.* HPLC
Radiochemical Purity	Measures % desired RC present *vs.* all other structure-related radioactive impurities	

Quality Attributes Unique to RNs and RCs

Attribute	Why?	How measured?
Radioactive Concentration	Radioactive concentration per mL DP at (TOC) – **used by HCPs for dose calculation**	Dose Calibrator (units: Bq/mL or Ci/mL)
Specific Activity	Measures radioactivity per unit targeting vector at TOC – key for consistent antigen binding and biodistribution	Calculated test (radioactive concentration / vector concentration)

Regulatory Expectations: Other RC Components

- For ADCs, industry experience has been:

Drug-Linker Intermediate

- Small molecule guidance generally applied
- Common expectation from HA's that quality follows the same standard as a synthetic drug substance, rather than an intermediate
- Many markets apply synthetic classifications (& data requirements) for post approval changes to the drug linker (US, EMA, HC, SG, TGA)

Antibody Intermediate, Drug Substance & Drug Product

- Existing large molecule guidance applies
- Expectation that antibody follows the same requirements/standard as a biological drug substance

- Likely that this will also track for RCs to some extent

Health Authority Review Experience to Date

Review questions from initial INDs heavily focussed on the properties of the mAb!

However, the following RC-specific topics were also raised:

- Appropriate characterization testing of the unconjugated and conjugated mAb is required to understand any potential changes in physicochemical / biological properties following conjugation
- Appropriate (two-tiered) reference standards should be established for the unconjugated and conjugated mAb based upon this data
- In-use / compatibility studies required for DP prior to patient dosing
- Ensuring that the time of calibration provides sufficient activity for a patient dose throughout the shelf life of the DP.

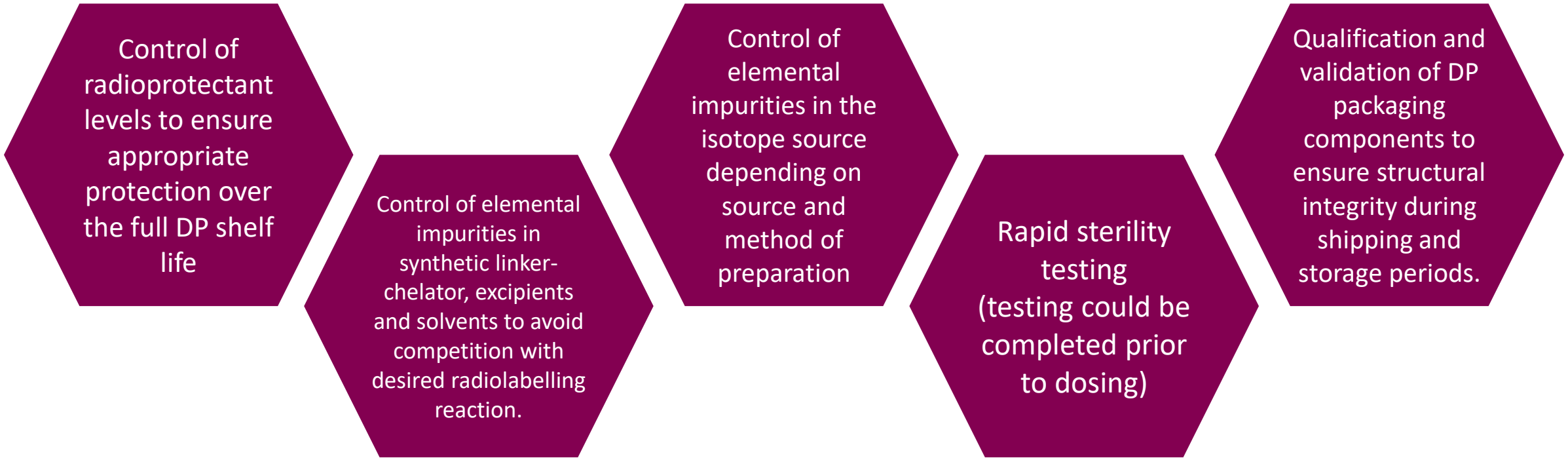
Health Authority Review Experience to Date

Non-hold questions included the additional RC-specific considerations:

- Control of radioprotectant levels to ensure appropriate protection over the full DP shelf life
- Control of elemental impurities in synthetic linker-chelator, excipients and solvents to avoid competition with desired radiolabelling reaction.
- Control of elemental impurities in the isotope source depending on source and method of preparation
- Rapid sterility testing (testing could be completed prior to dosing)
- Qualification and validation of DP packaging components to ensure structural integrity during shipping and storage periods.

Health Authority Review Experience to Date

Non-hold questions included the additional RC-specific considerations:



Overall: no issues flagged that aren't already covered in the guidance documents referenced earlier in the presentation!

Acknowledgements

- Dawn Spiller
- Mark Fielding

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