PSI Center for Life Sciences

^{161}Tb Therapies for Clinical Trials

Experiences

David Schmid, Responsible Person
Clinical Drug Supply Group

Villigen, 4. September 2024

Agenda

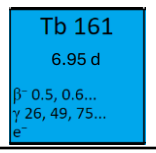
1 Why using ^{161}Tb in radio ligand therapy (RLT)?

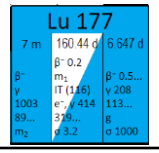
2 Translation of established research isotope ^{161}Tb to a novel clinical radioactive precursor

3 Manufacturing of drug products

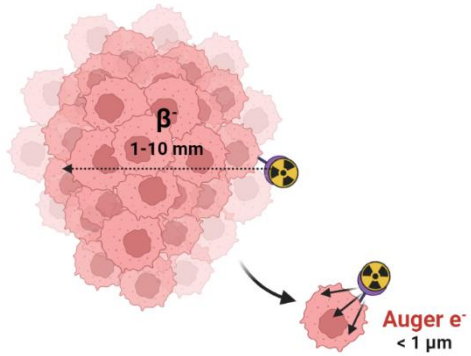
4 Current clinical studies with ^{161}Tb in Switzerland

Novel Radioisotope ^{161}Tb vs ^{177}Lu





Half-life	6.95 d	6.65 d
Decay mode	β^- (154 keV), **Auger** and **conversion e$^-$**	β^- (134 keV)
Photon emission for imaging	Yes	Yes
Main application	β^- therapy	β^- therapy
Decay to	Stable ^{161}Dy	Stable ^{177}Hf
Formation of stable DOTA complex	Yes	Yes

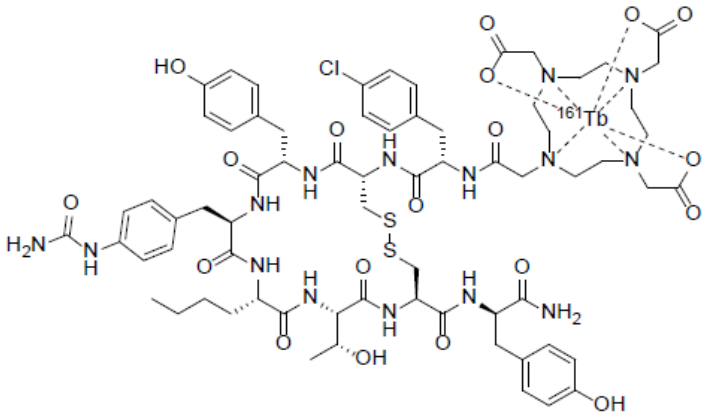


Type of radiation	β^-	**Auger e$^-$**
Linear Energy Transfer (LET)	ca. 0.2 keV/µm	4–26 keV/µm
Range in tissue	1–10 mm	< 1 µm
Best suited for treatment of	Tumor masses	Single cancer cells, micro metastases

Hypothesis: ^{161}Tb more powerful than ^{177}Lu?

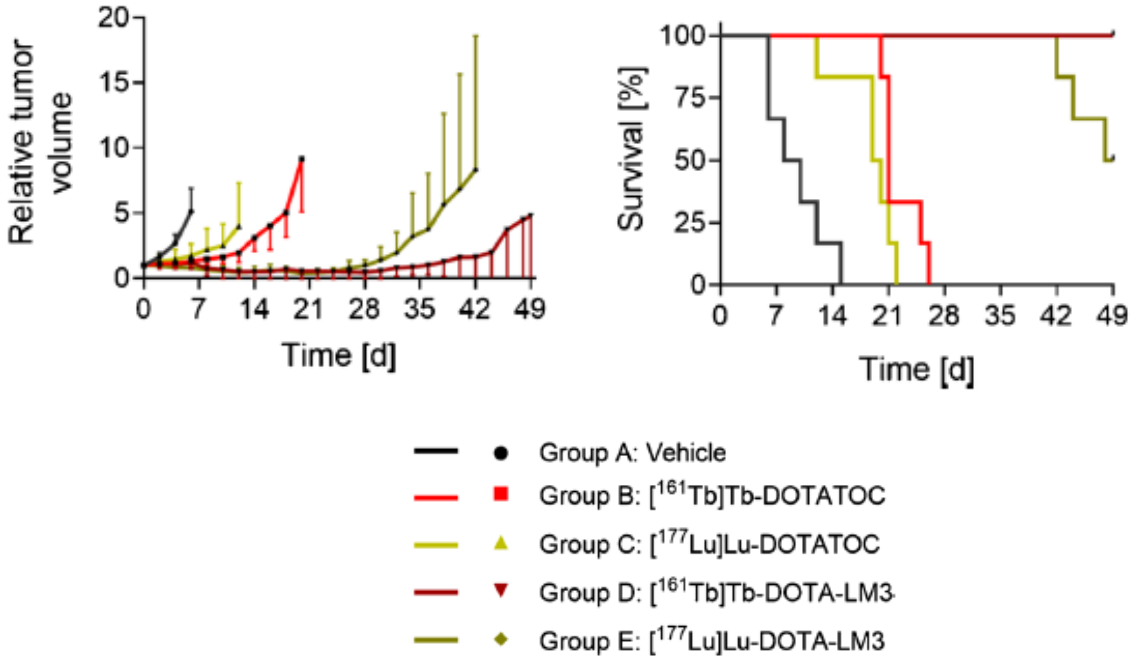
Müller *et al.*, Eur J Nucl Med Mol Imaging, 50, 3181-3184, 2023

Pre-Clinical Data of [^{161}Tb]Tb-DOTA-LM3



[^{161}Tb]Tb-DOTA-LM3

Somatostatin receptor antagonist for the treatment of neuroendocrine neoplasms



Results:

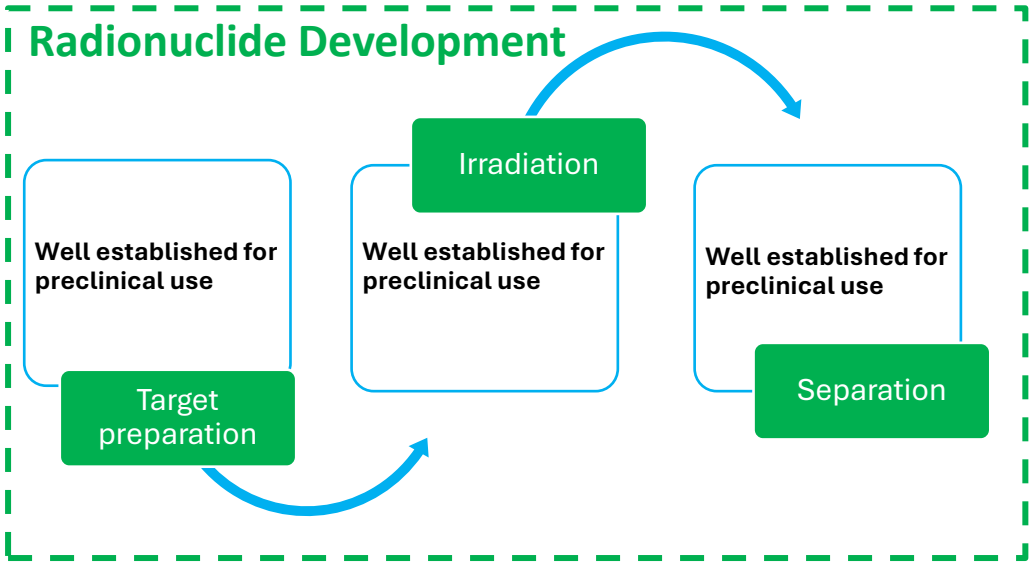
Superior efficacy in preclinical therapy studies compared to "gold-standard"

- ✓ [^{161}Tb]Tb-DOTATOC > [^{177}Lu]Lu-DOTATOC
- ✓ [^{177}Lu]Lu-DOTA-LM3 >> [^{177}Lu]Lu-DOTATOC
- ✓ **[^{161}Tb]Tb-DOTA-LM3 >>> [^{177}Lu]Lu-DOTATOC**

Borgna *et al.*, Eur J Nucl Med Mol Imaging, 49(4), 1113-1126, 2022

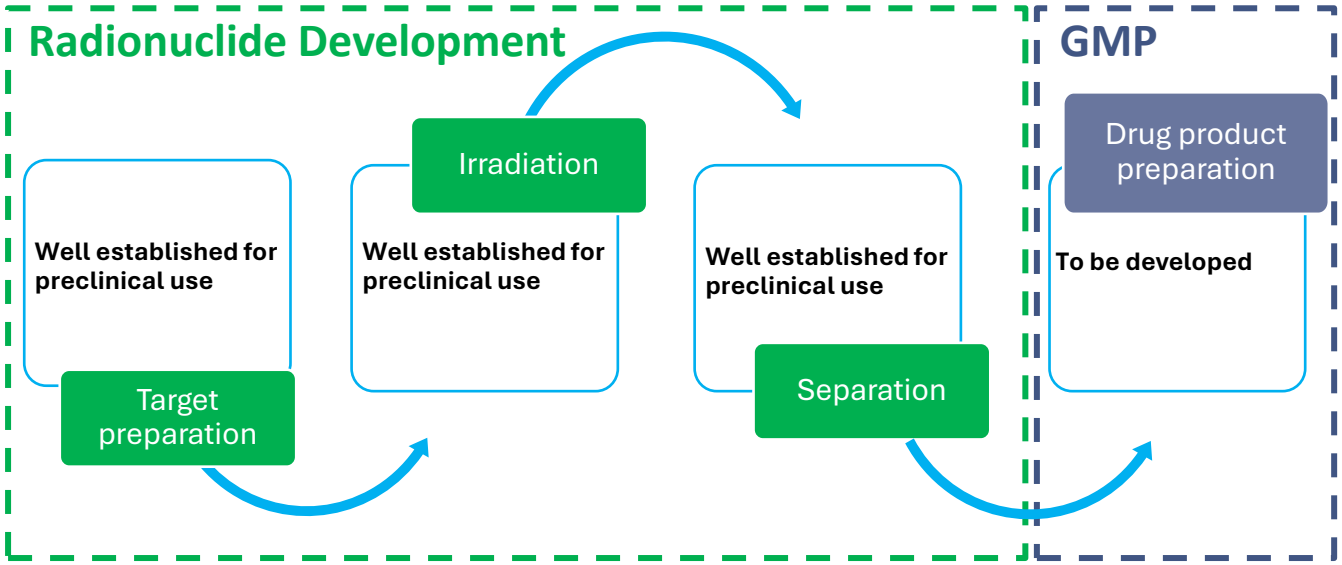
Manufacturing Strategy ^{161}Tb

- Well established process for manufacturing of ^{161}Tb for preclinical use



Manufacturing Strategy ^{161}Tb

- Well established process for manufacturing of ^{161}Tb for preclinical use
- Requirement to manufacture [^{161}Tb]Tb-DOTA-LM3 under Good Manufacturing Practice (GMP) for clinical trial



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EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines

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Introduction

Volume 4 of "The rules governing medicinal products in the European Union" contains guidance for the interpretation of the principles and guidelines of good manufacturing practices for medicinal products for human and veterinary use laid down in Commission Directives 91/356/EEC, as amended by Directive 2003/94/EC, and 91/412/EEC respectively.

Annexes

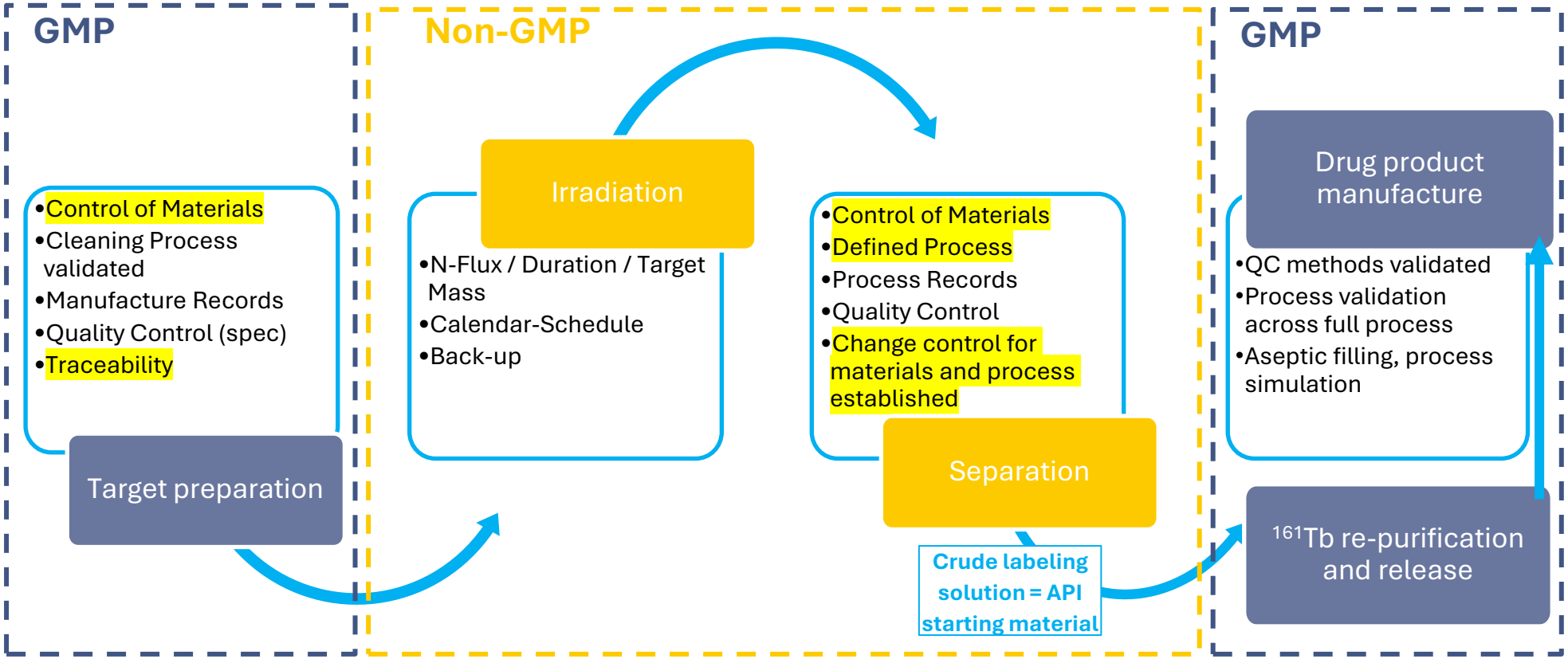
Annex 1	**New** - Manufacture of Sterile Medicinal Products - The deadline for coming into operation of Annex 1 is 25 August 2023, except for point 8.123 which is postponed until 25 August 2024 Manufacture of Sterile Medicinal Products (previous version)
Annex 2	**New** - Manufacture of Biological active substances and Medicinal Products for Human Use (into operation since 26 June 2018) Annex 2 is no longer applicable to Advanced Therapy Medicinal Products to which applies the Commission guideline on Good Manufacturing Practice for Advanced Therapy Medicinal Products, published in Part IV of Eudralex Volume 4 and operational as of 22 May 2018.
Annex 3	Manufacture of Radiopharmaceuticals
Annex 4	Manufacture of Veterinary Medicinal Products other than Immunological Veterinary Medicinal Products

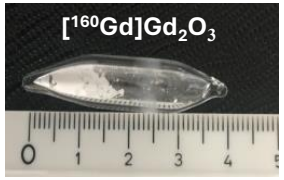
Type of manufacture	*Non - GMP **	*GMP part II & I (Increasing) including relevant annexes*			
Radiopharmaceuticals PET Radiopharmaceuticals Radioactive Precursors	*Reactor/Cyclotron Production*	*Chemical synthesis*	*Purification steps*	*Processing, formulation and dispensing*	*Aseptic or final sterilization*
Radionuclide Generators	*Reactor/Cyclotron Production*	*Processing*			

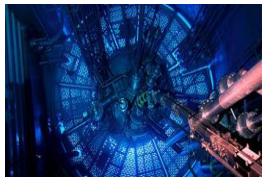
** Target and transfer system from cyclotron to synthesis rig may be considered as the first step of active substance manufacture.*

Manufacturing Strategy ^{161}Tb

- Set-up of EudraLex-compliant manufacturing strategy approved by Swiss health authority



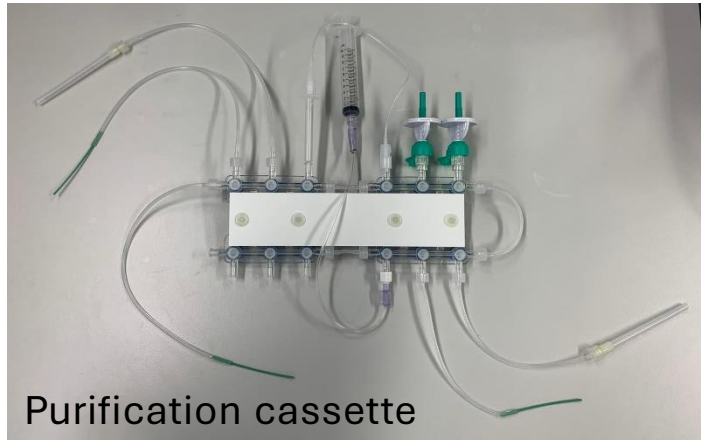


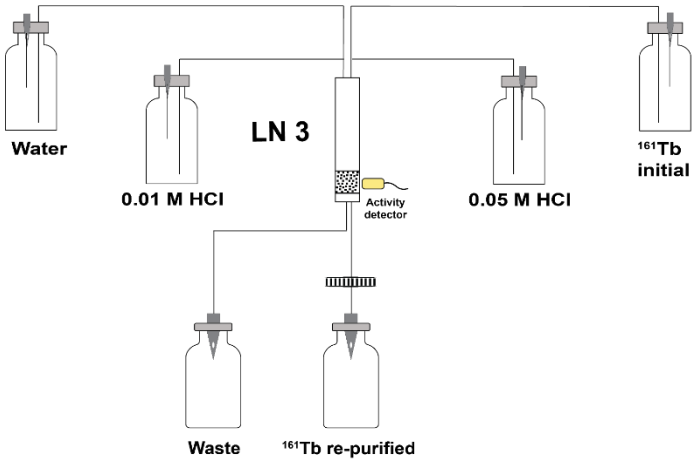


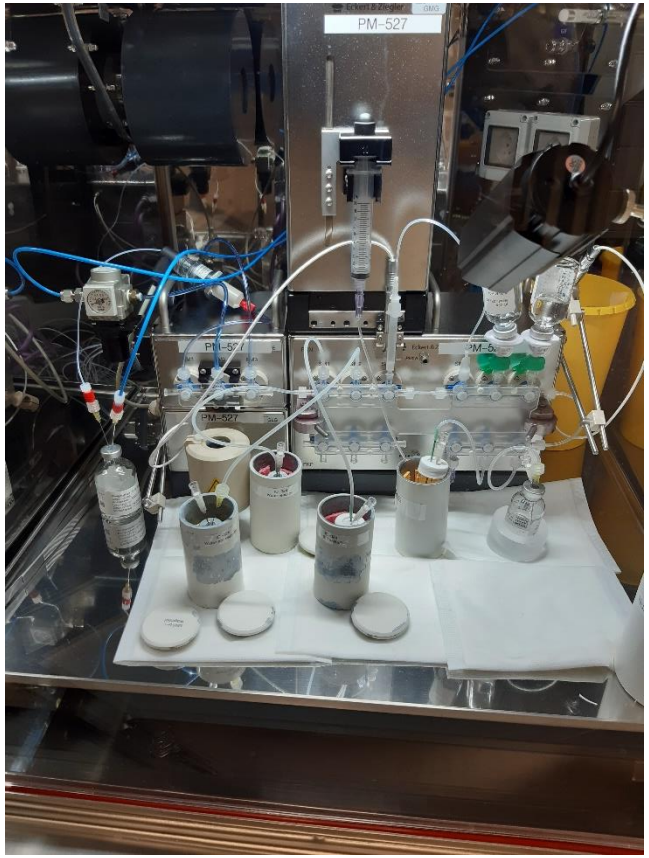
^{160}Gd(n,γ)^{161}Gd → ^{161}Tb

^{161}Tb re-Purification

- **Automated** purification process of crude ^{161}Tb labeling solution in grade C clean room, to give GMP-compliant, re-purified ^{161}Tb labeling solution


Purification cassette



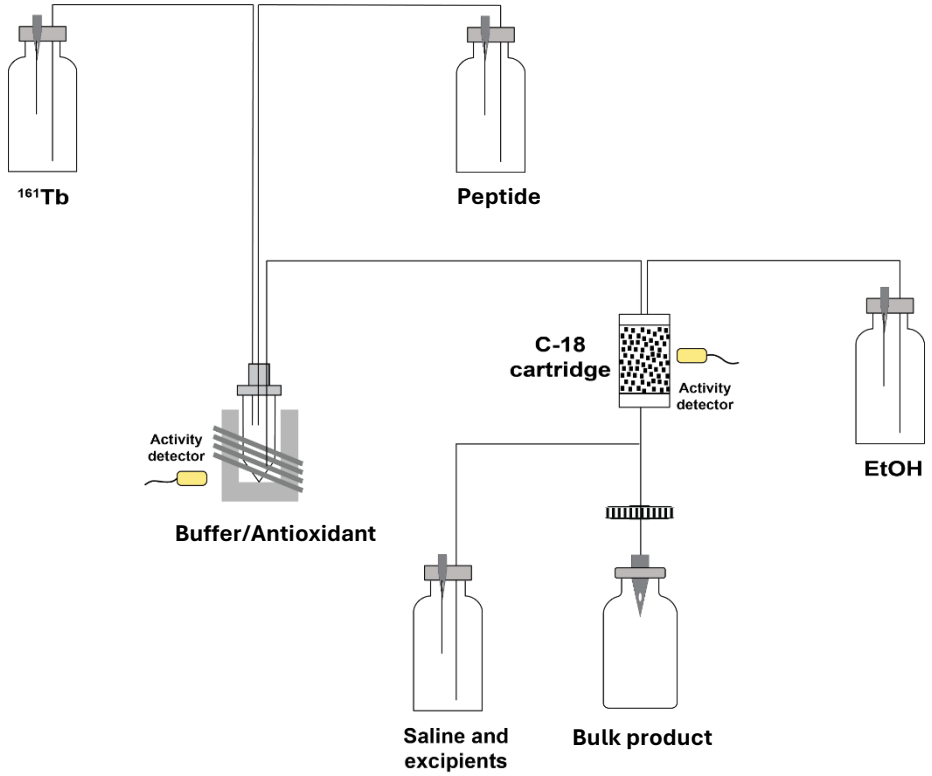


Purification set-up

Re-purification 0.5 – 50 GBq ^{161}Tb	
Elution flow rate	0.06 mL/min
Process time	2.5 h
Purification yield	ca. 90%
Final solution	[^{161}Tb]Tb^{3+} in 0.05 M HCl
Final volume	ca. 1.2 mL
Final pH	1 – 2

Manufacture of Drug Product

- Production of drug product in grade C clean room, using automated synthesis module and disposable cassettes
- Transfer of bulk product to dispensing hot cell (grade A), followed by sterile filtration and aseptic dispensing of patient vial



Quality Control of Drug Product

- Quality control
  - Appearance
  - Chemical purity/identity (HPLC)
  - Ethanol content (GC)
  - pH
  - Endotoxins
  - Radionuclidic identity
  - Radioactivity concentration
  - Filter integrity test
  - Radionuclidic purity (post release test)

- Release of drug product for application and shipment to clinical site

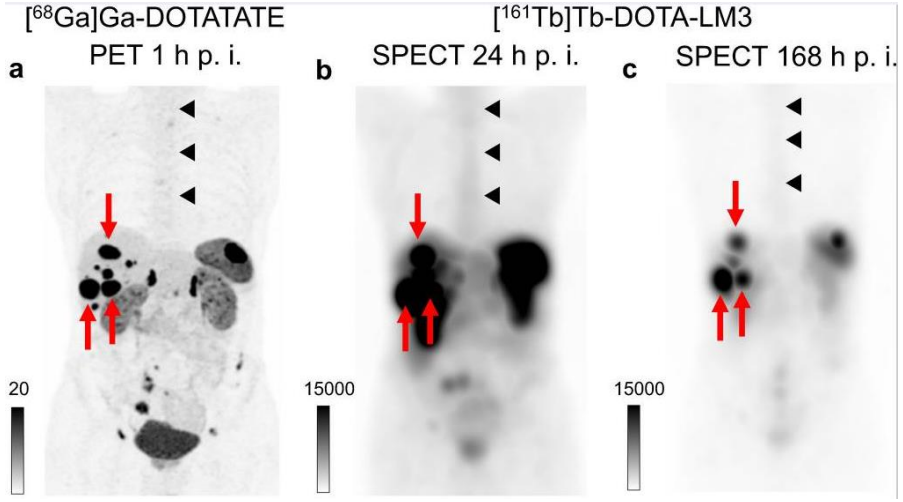
Parameter	Test / Limit	Result	PASS / FAIL
Properties			
Appearance (Solution)	Clear and colourless to slightly yellow solution, free of visible particles	Clear and colourless to slightly yellow solution, free of visible particles	PASS
pH (Test strips)	4.0 - 8.0	6.0	PASS
Minimum product volume	12 mL	16 mL	PASS
Identity			
Radonuclidic identity of ^{161}Tb	Typical gamma lines: 74.6 ± 1 keV 87.9 ± 1 keV 103.1 ± 1 keV 106.1 ± 1 keV	Complies	PASS
Retention time of [^{161}Tb]Tb-DOTA-LM3	Complies	Complies	PASS
Purity			
Radiochemical purity of [^{161}Tb]Tb-DOTA-LM3	≥ 95%	100 %	PASS
Limit Test of DOTA-LM3 and metal complexes	≤ 100 µg/patient dose	Complies	PASS
Limit Test of every unknown chemical impurity	≤ 100 µg/patient dose	Complies	PASS
Excipient			
Limit Test Ethanol	≤ 7%	Complies	PASS
Microbiological Tests			
Bacterial endotoxins	≤ 175 EU/patient dose	< 81 EU/patient dose	PASS
Content			
Radioactivity concentration at EOS [^{161Tb}]Tb-DOTA-LM3	28 – 92 MBq/mL	70 MBq/mL	PASS
Filter Integrity			
Bubble point test	≥ 2.86 bar (matrix based) **OR**	3.37 bar (matrix based)	PASS
	≥ 3.45 bar (water based)	N/A bar (water based)	

Clinical Trial with [^{161}Tb]Tb-DOTA-LM3 - Beta Plus Study

Phase 0A: Dosimetry

Comparator: [^{177}Lu]Lu-DOTATOC

- 1 GBq, max. 100 µg peptide
- 8 patients
- First patient: 17.04.2023
- Last patient: 27.02.2024



Fricke et al., Eur J Nucl Med Mol Imaging, 51, 2517-2519, 2024

Phase 0B: Dose escalation/peptide mass scaling

- 2–3 GBq, max. 100 µg peptide
- 2–3 GBq, 300–400 µg peptide
- Planned: 4–8 patients
- 4 treatment cycles
- Expected start: Q3/2024

ClinicalTrials.gov Identifier: NCT05359146

Universitätsspital Basel

Swiss National Science Foundation

Clinical Trial with [^{161}Tb]Tb-SibuDAB - PROGNOSTICS Study

PSI

PeRsOnalized theraGNOstics of metaStaTIC proState cancer

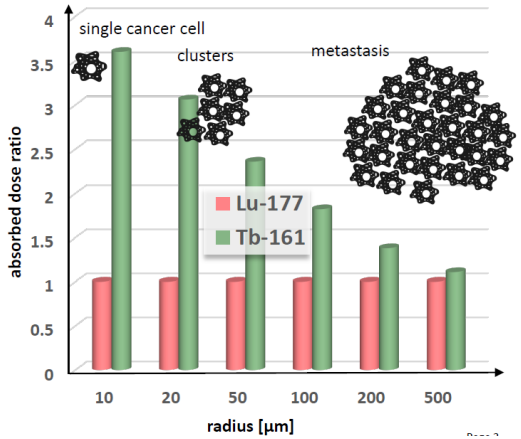
Phase 1A: Dosimetry

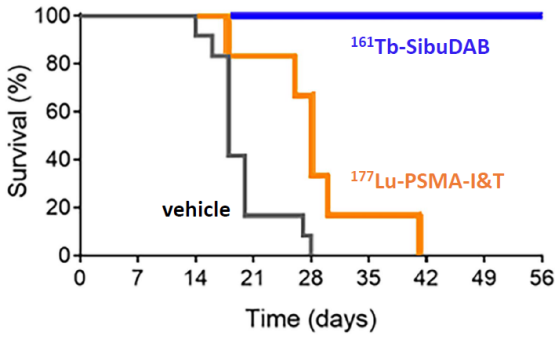
Comparator: [^{177}Lu]Lu-PSMA-I&T

- 1 GBq, ~ 200 µg peptide
- Planned: 10 patients
- First patient: 20.03.2024

Phase 1B: Dose escalation

- 2–5 GBq (tbd), ~ 200 µg peptide
- Planned: up to 15 patients
- 4 treatment cycles





Hypotheses

- *Disseminated micrometastases are not killed by ^{177}Lu-based RLT because of insufficient radiation dose deposition, leading to poor outcome*
- *Sibu-DAB combined with ^{161}Tb will kill micrometastases due to*
  - *> 3-times higher tumor accumulation than Pluvicto™*
  - *> 3-times higher radiation dose deposition due to ^{161}Tb*

Strategic Focus Area Personalized Health and Related Technologies

ETH zürich

University of Gothenburg

Universitätsspital Basel

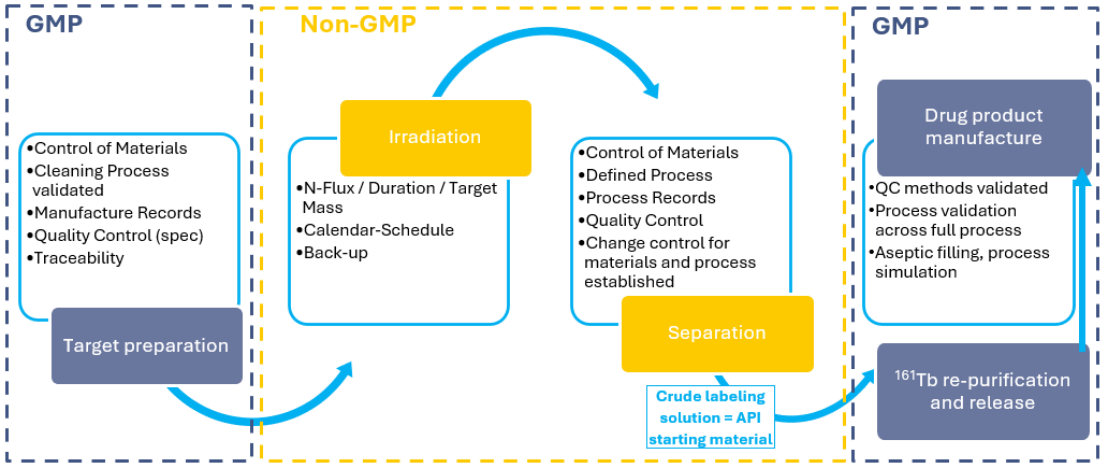
itm Passion for Precision

ClinicalTrials.gov Identifier: NCT06343038

Tschan et al., J Nucl Med., 64(10), 1625-1631, 2023

Conclusion

- Manufacturing strategy for clinical ^{161}Tb-radiotracers developed and approved by national health authority



- ^{161}Tb re-purification, to yield GMP-compliant labeling solution, developed and validated
- Manufacturing of [^{161}Tb]Tb-DOTA-LM3 and [^{161}Tb]Tb-SibuDAB established for use in clinical studies (Beta Plus and PROGNOSTICS study)

Acknowledgement

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Fan Sozzi-Guo

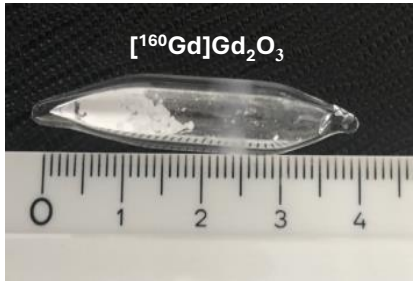
Radionuclide-Production and Maintenance group
Roger Geissmann
Muhamet Djelili

Prof. Damian Wild

Nuclear Medicine Department
Julia Fricke
Alin Chirindel

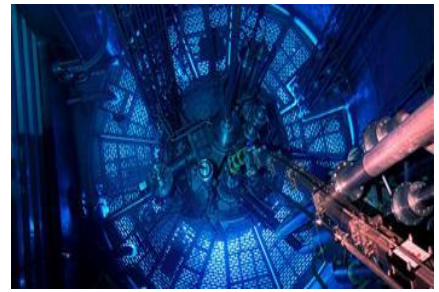
Backup Slides

Overview Logistics and Operations

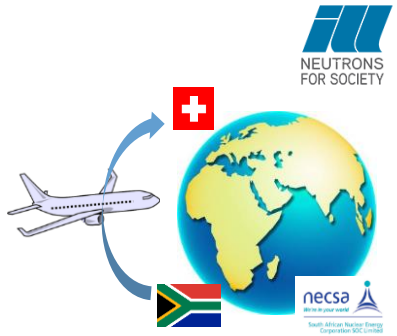


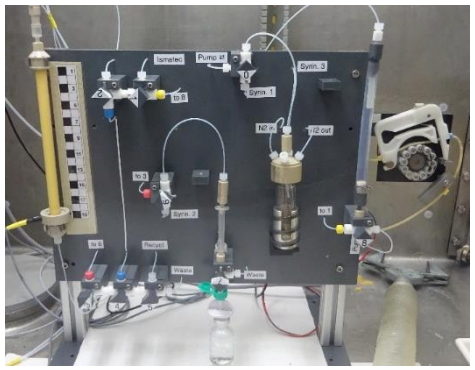
Target manufacture

Transport cold target to irradiation site



$^{160}Gd(n,\gamma)^{161}Gd \rightarrow {}^{161}Tb$
for 7 to 14 days (reactor/neutron flux)

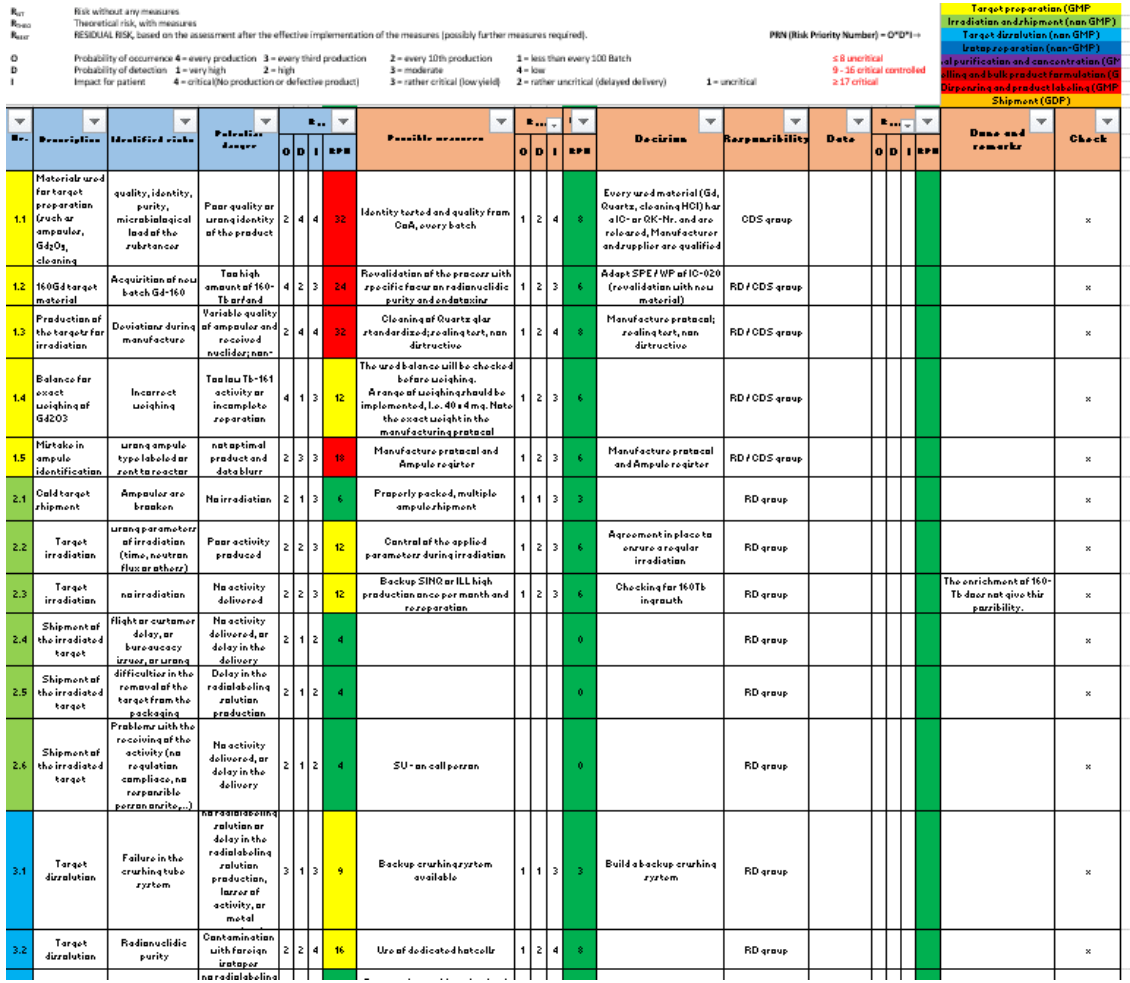




Chemical separation and processing

GMP:
1) Final purification
2) Labeling & formulation

Risk Analysis: Potential Risks to Patients and Process



R_{wo} Risk without any measures
R_{theo} Theoretical risk, with measures
R_{res} RESIDUAL RISK, based on the assessment after the effective implementation of the measures (possibly further measures required).

PRN (Risk Priority Number) = O*D*I →

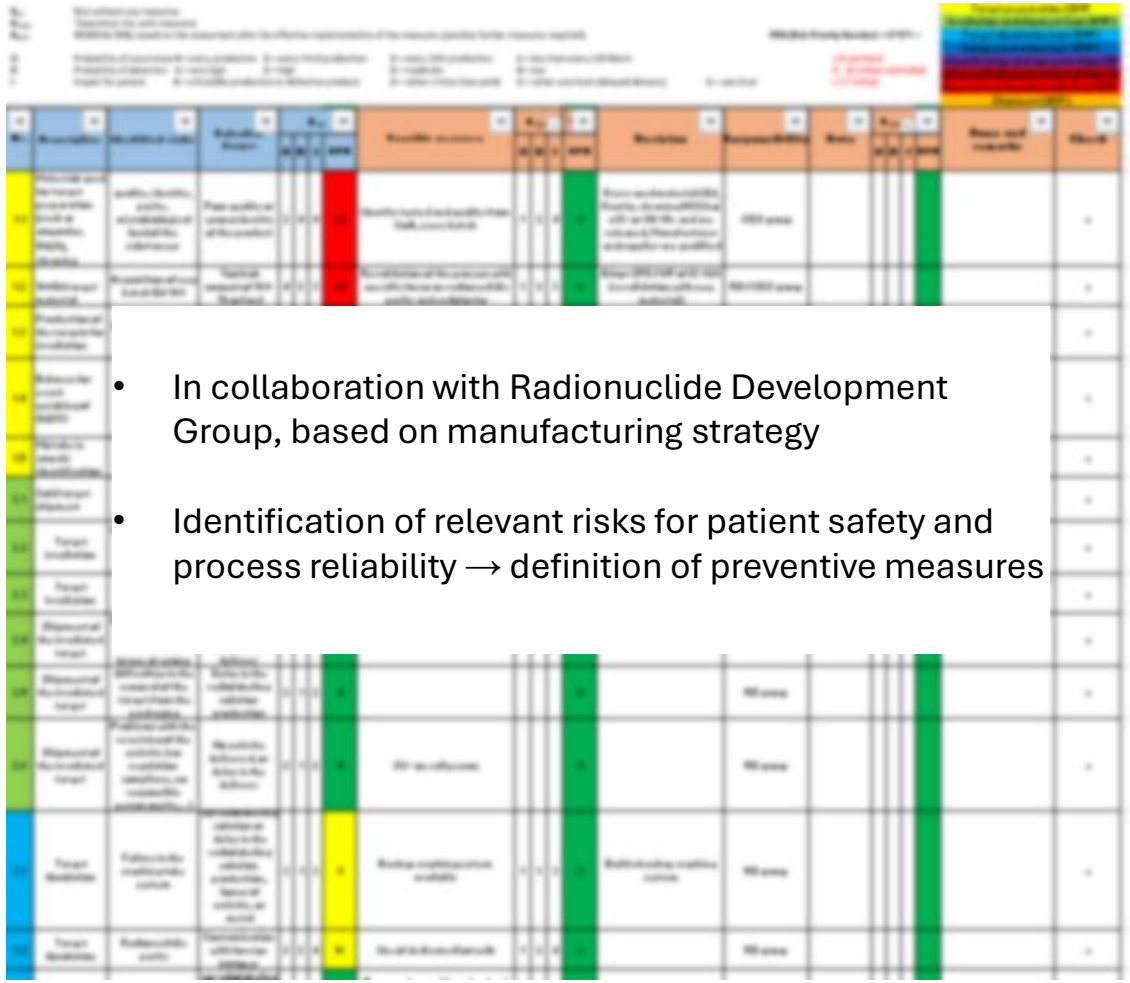
O Probability of occurrence 4 = every production 3 = every third production 2 = every 10th production 1 = less than every 100 Batch
D Probability of detection 1 = very high 2 = high 3 = moderate 4 = low
I Impact for patient 4 = critical(No production or defective product) 3 = rather critical (low yield) 2 = rather uncritical (delayed delivery) 1 = uncritical

≤ 8 uncritical
9 - 16 critical controlled
≥ 17 critical

Target preparation (GMP
Irradiation and shipment (non GMP)
Target dissolution (non GMP)
Isotope separation (non-GMP)
ial purification and concentration (GM
elling and bulk product formulation (G
Dispensing and product labeling (GMP
Shipment (GDP)

Nr.	Description	Identified risks	Potential danger	R_{wo} O	R_{wo} D	R_{wo} I	R_{wo} RPN	Possible measures	R_{res} O	R_{res} D	R_{res} I	R_{res} RPN	Decision	Responsibility	Date	R_{res} O	R_{res} D	R_{res} I	R_{res} RPN	Done and remarks	Check
1.1	Material used for target preparation (such as ampoules, Gd_2O_3, cleaning	quality, identity, purity, microbiological load of the substances	Poor quality or wrong identity of the product	2	4	4	32	Identity tested and quality from CoA, every batch	1	2	4	8	Every used material (Gd, Quartz, cleaning HCl) has a IC- or QK-Nr. and are released, Manufacturer and supplier are qualified	QDS group							×
1.2	160Gd target material	Acquisition of new batch Gd-160	Too high amount of 160-Tb and	4	2	3	24	Revalidation of the process with specific focus on radionuclidic purity and endotoxins	1	2	3	6	Adapt SPE / WP of IC-020 (revalidation with new material)	RD / QDS group							×
1.3	Production of the targets for irradiation	Deviations during manufacture	Variable quality of ampoules and received nuclides; non-	2	4	4	32	Cleaning of Quartz glas standardized; sealing test, non dirtructive	1	2	4	8	Manufacture protocol; sealing test, non dirtructive	RD / QDS group							×
1.4	Balance for exact weighing of Gd2O3	Incorrect weighing	Too low Tb-161 activity or incomplete separation	4	1	3	12	The used balance will be checked before weighing. A range of weighing should be implemented, i.e. 40 ± 4 mg. Note the exact weight in the manufacturing protocol	1	2	3	6		RD / QDS group							×
1.5	Mistake in ampule identification	wrong ampule type labeled or contra reactor	not optimal product and data blurr	2	3	3	18	Manufacture protocol and Ampule register	1	2	3	6	Manufacture protocol and Ampule register	RD / QDS group							×
2.1	Cold target shipment	Ampoules are broaken	No irradiation	2	1	3	6	Properly packed, multiple ampule shipment	1	1	3	3		RD group							×
2.2	Target irradiation	wrong parameters of irradiation (time, neutron flux or others)	Poor activity produced	2	2	3	12	Control of the applied parameters during irradiation	1	2	3	6	Agreement in place to ensure a regular irradiation	RD group							×
2.3	Target irradiation	no irradiation	No activity delivered	2	2	3	12	Backup SINQ or ILL high production once per month and re-separation	1	2	3	6	Checking for 160Tb in growth	RD group						The enrichment of 160-Tb does not give this possibility.	×
2.4	Shipment of the irradiated target	flight or customer delay, or bureaucracy issues, or wrong	No activity delivered, or delay in the delivery	2	1	2	4					0		RD group							×
2.5	Shipment of the irradiated target	difficulties in the removal of the target from the packaging	Delay in the radiolabeling solution production	2	1	2	4					0		RD group							×
2.6	Shipment of the irradiated target	Problems with the receiving of the activity (no regulation compliance, no responsible person on site,...)	No activity delivered, or delay in the delivery	2	1	2	4	SU - on call person				0		RD group							×
3.1	Target dissolution	Failure in the crushing tube system	No radiolabeling solution or delay in the radiolabeling solution production, losses of activity, or metal	3	1	3	9	Backup crushing system available	1	1	3	3	Build a backup crushing system	RD group							×
3.2	Target dissolution	Radionuclidic purity	Contamination with foreign isotope	2	2	4	16	Use of dedicated hot cells	1	2	4	8		RD group							×
			no radiolabeling																		

Risk Analysis: Potential Risks to Patients and Process



- In collaboration with Radionuclide Development Group, based on manufacturing strategy
- Identification of relevant risks for patient safety and process reliability → definition of preventive measures

Regulatory Requirements: GMP

[^{161}Tb]Tb-DOTA-LM3 for Phase 0 clinical trial.

- Requirement to manufacture [^{161}Tb]Tb-DOTA-LM3 under Good Manufacturing Practice (GMP)

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EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines

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https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-4_en

Risk Reduction Radionuclidic Impurities

- Pattern depending on the material and separation techniques (!)
- Proportion depending on the ingrowth, i.e. time dependant (!)
- Cannot be tested before releasing the drug product

Desired Reaction: $^{160}Gd(n,\gamma)^{161}Gd \rightarrow {}^{161}Tb$

Gd-isotope	Abundance in natural Gd [%]	Abundance in enriched ^{160}Gd [%]*
Gd-152	0.20	< 0.01
Gd-154	2.18	0.03
Gd-155	14.8	0.19
Gd-156	20.47	0.38
Gd-157	15.65	0.31
Gd-158	24.84	1.17
Gd-160	**21.86**	**97.92**

* Batch #2-96-O

Additional conversions may occur

Other Gd isotopes than ^{160}Gd:

$^{157}Gd(n,\gamma)^{158}Gd$

$^{158}Gd(n,\gamma)^{159}Gd \rightarrow$ **^{159}Tb**

Natural terbium traces:

^{159}Tb (n,γ)**^{160}Tb**

$^{160}Gd_2O_3$ enrichment grade and impurity profile very cruical for radionuclidic purity of ^{161}Tb

Risk Reduction Radionuclidic Impurities

- Transparency on the timelines (irradiation, separation), batch-wise
- Control over target material
- Change Control Agreement with Provider
  Ensures that process validation data remain valid over the life-cycle of drug product

OR

Measurement of radionuclidic impurities as a release test for radioactive precursor