^{224}Ra standardization:
radiopharmaceutical perspective

International Workshop on Standards and Measurements for Alpha Emitting Nuclides in Therapeutic Nuclear Medicine

22 - 23 February 2024

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Radspherin

- **Current status:** clinical phase 2b trials - mid-2024
- Produced and analysed in **Oslo, Norway**
- Delivered ready-for-use to several sites in **Norway, Sweden, Belgium, Spain,** and expanding**.**

Gro Hjellum
Chief Operating Officer

Roy Hartvig Larsen, PHD
Chairman

Øyvind Bruland, Prof. emerit. MD, PhD
Board member

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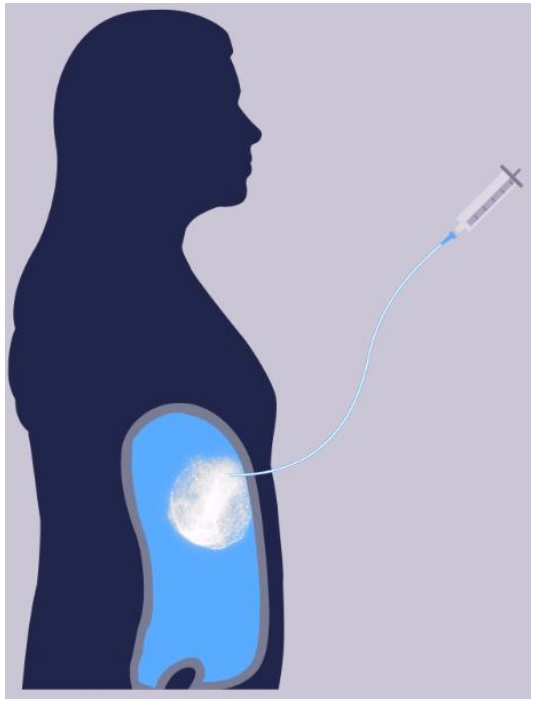

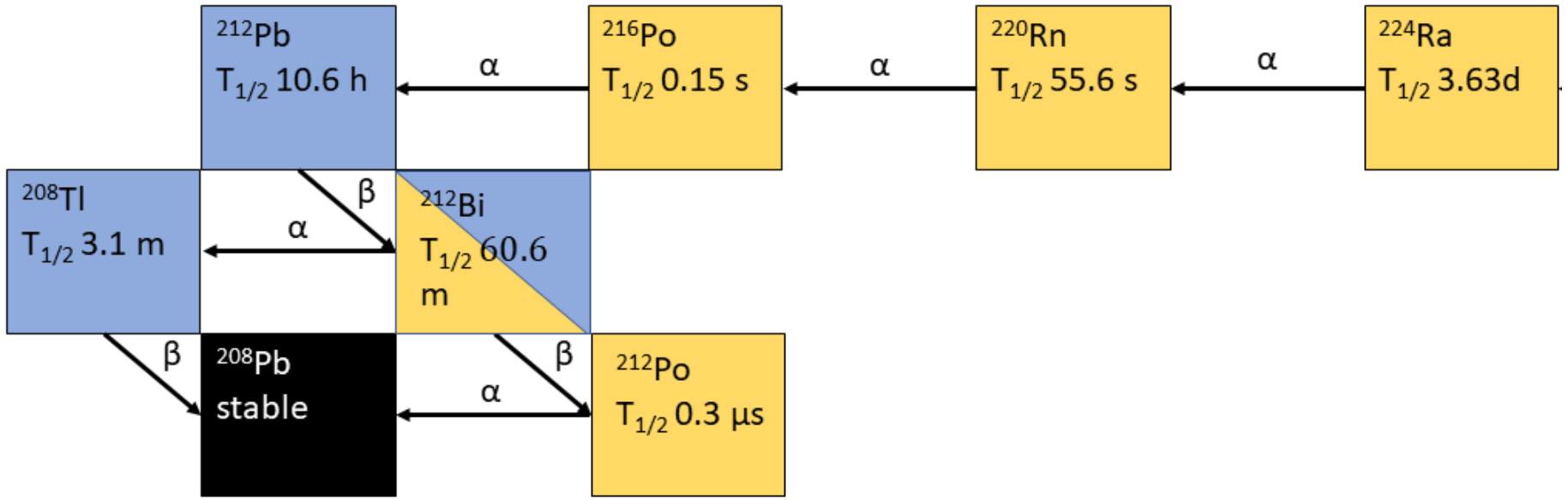

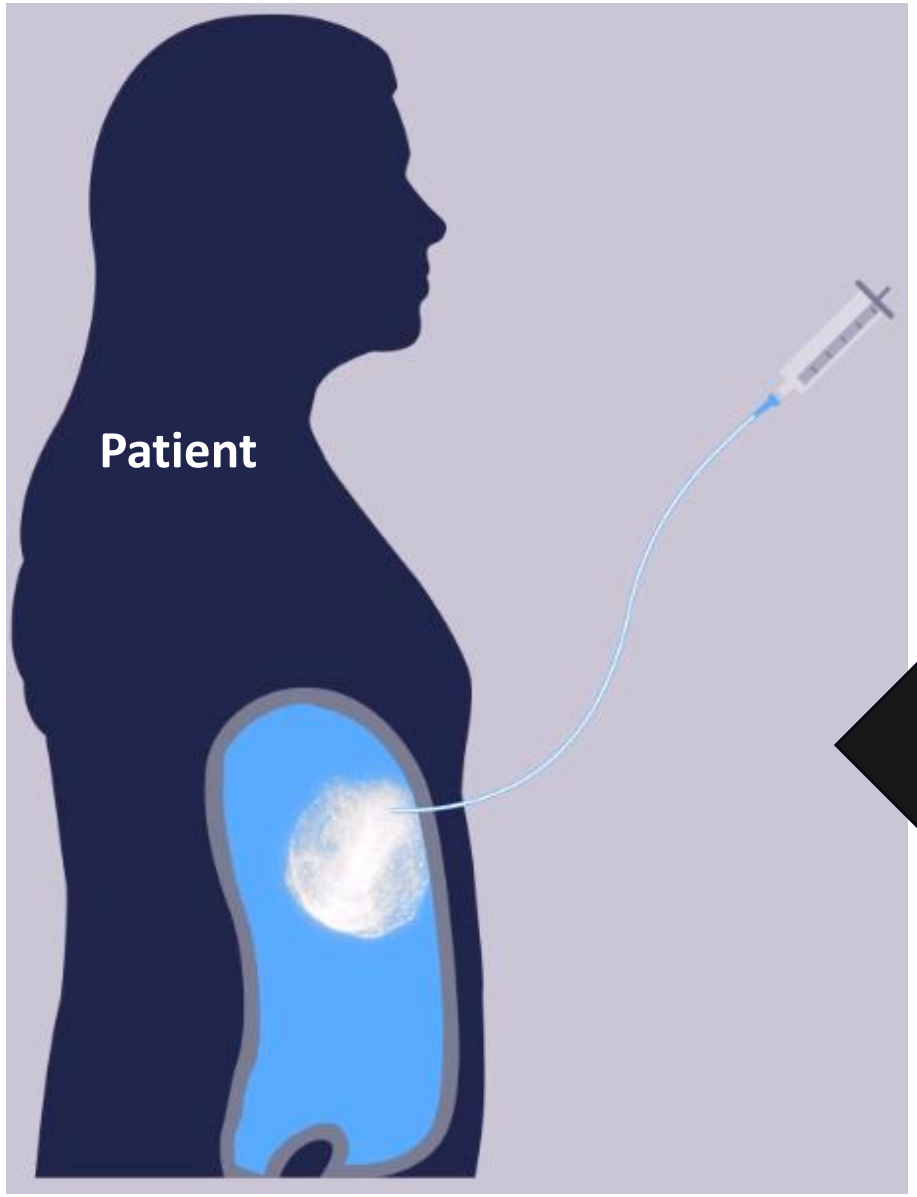

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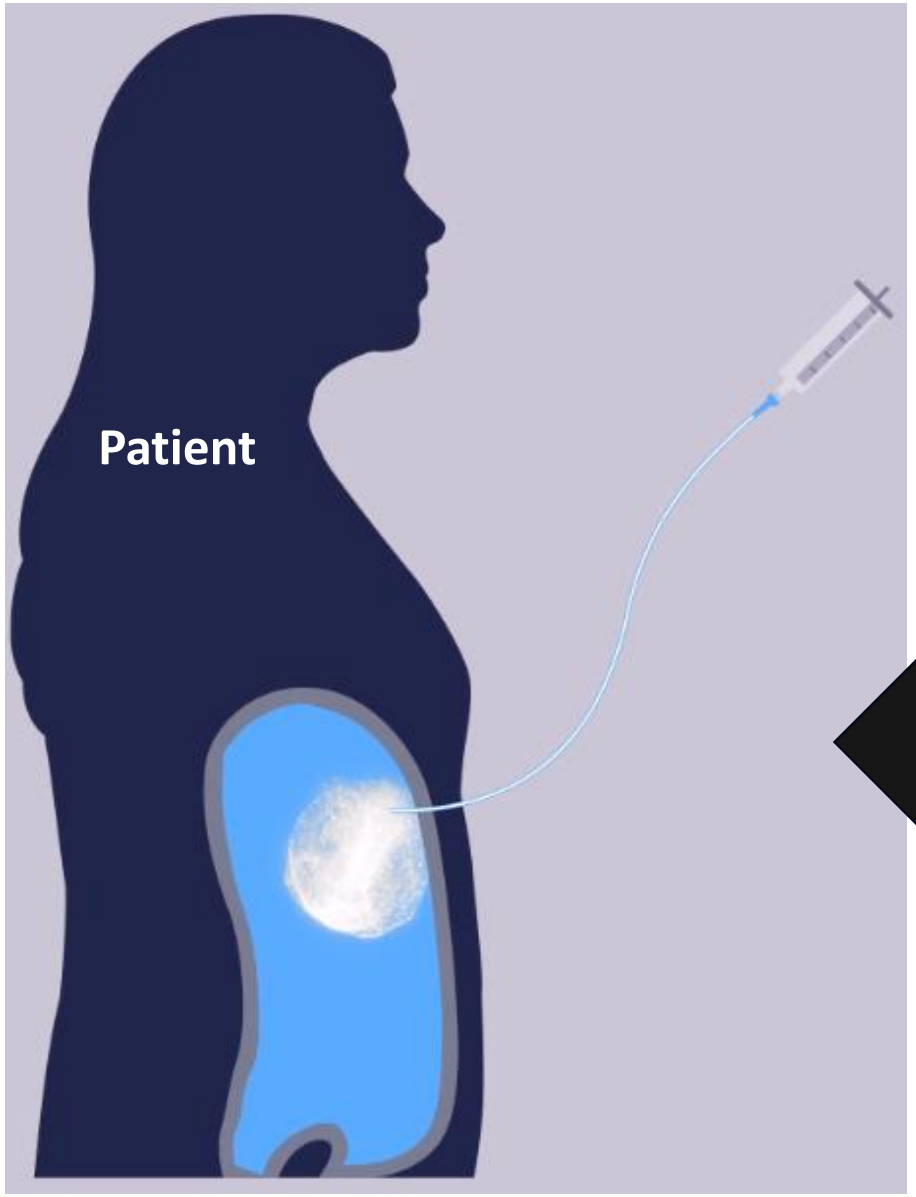
Clinics

Quality control

Production



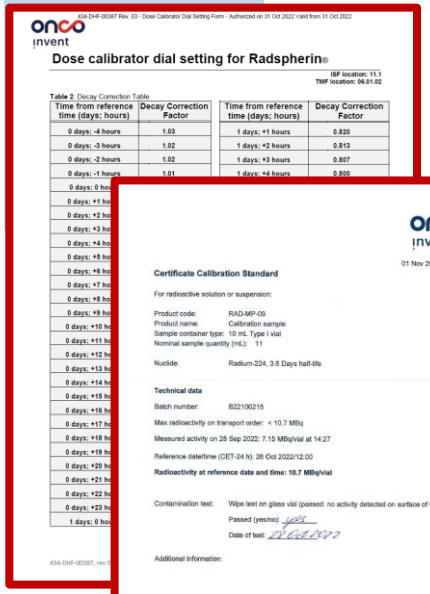
Clinics

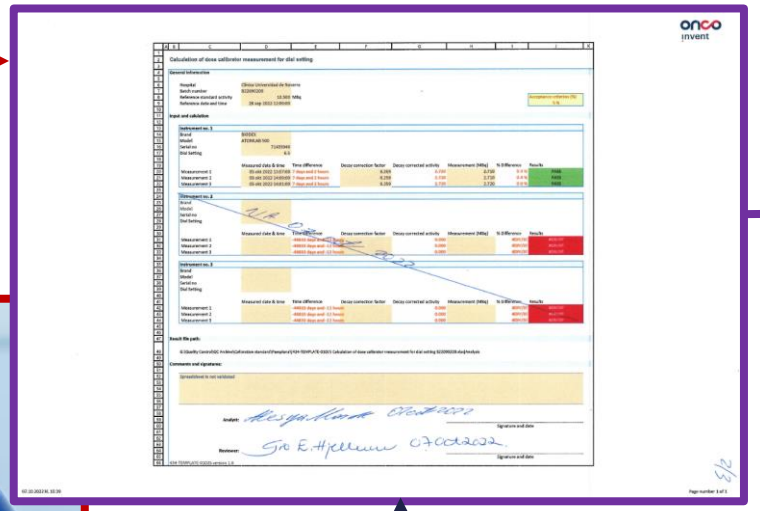
Clinics

1) The dose **calibrators on clinical sites can be** of **different** models and vendors (Atomlab from Biodex, IBC-Lite/VDS from Comicer, VIK from Veenstra, etc.). They are diverse, but very typical.
2) **Dial settings in clinics are set under Oncoinvent supervision**. According to our standard, “All affirmative measurements should be found within 5% of the decay corrected activity”
3) In practice, the results are within 2,5%.

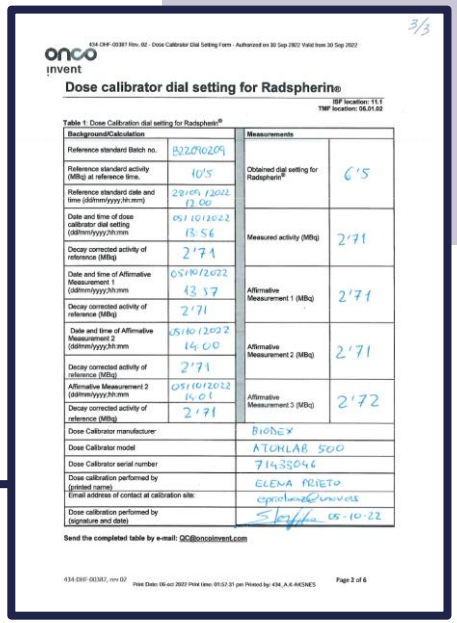
Calibration standard

Quality control





Clinics



Quality control

Calibration standard

Certificate Calibration Standard

For radioactive solution or suspension:

Product code: RAD-MP-09
Product name: Calibration sample
Sample container type: 10 mL Type I vial
Nominal sample quantity (mL): 11

Nuclide: Radium-224, 3.6 Days half-life

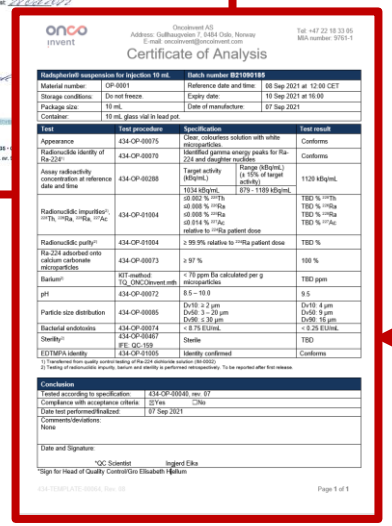
Technical data

Batch number: B22100215
Max radioactivity on transport order: < 10.7 MBq
Measured activity on 28 Sep 2022: 7.15 MBq/vial at 14:27
Reference date/time (CET-24 h): 26 Oct 2022/12:00
Radioactivity at reference date and time: 10.7 MBq/vial

Contamination test: Wipe test on glass vial (passed: no activity detected on surface of vial)
Passed (yes/no): yes
Date of test: 28/09/2022

Additional information:

Oncoinvent AS
Alesya Maruk
Senior Quality Control Scientist
Contact information:



Certificate of Analysis

Radspherin® suspension for injection 10 mL		Batch number B21090185	
Material number:	OP-0001	Reference date and time:	08 Sep 2021 at 12:00 CET
Storage conditions:	Do not freeze.	Expiry date:	10 Sep 2021 at 16:00
Package size:	10 mL	Date of manufacture:	07 Sep 2021
Container:	10 mL glass vial in lead pot.		

Test	Test procedure	Specification		Test result
Appearance	434-OP-00075	Clear, colourless solution with white microparticles		Conforms
Radionuclidic identity of ^{224}Ra[1]	434-OP-00070	Identified gamma energy peaks for ^{224}Ra and daughter nuclides		Conforms
Assay radioactivity concentration at reference date and time	434-OP-00288	Target activity (kBq/mL)	Range (kBq/mL) (± 15% of target activity)	1120 kBq/mL
		1034 kBq/mL	879 - 1189 kBq/mL	
Radionuclidic impurities[2]: ^{227}Th, ^{225}Ra, ^{223}Ra, ^{227}Ac	434-OP-01004	≤0.002 % ^{227}Th ≤0.008 % ^{225}Ra ≤0.008 % ^{223}Ra ≤0.014 % ^{227}Ac relative to ^{224}Ra patient dose		TBD % ^{227}Th TBD % ^{225}Ra TBD % ^{223}Ra TBD % ^{227}Ac
Radionuclidic purity[1]	434-OP-01004	≥ 99.9% relative to ^{224}Ra patient dose		TBD %
Ra-224 adsorbed onto calcium carbonate microparticles	434-OP-00073	≥ 97 %		100 %
Barium[2]	KIT-method: TQ_ONCOinvent.mth	< 70 ppm Ba calculated per g microparticles		TBD ppm
pH	434-OP-00072	8.5 – 10.0		9.5
Particle size distribution	434-OP-00085	Dv10: ≥ 2 µm Dv50: 3 – 20 µm Dv90: ≤ 30 µm		Dv10: 4 µm Dv50: 9 µm Dv90: 16 µm
Bacterial endotoxins	434-OP-00074	< 8.75 EU/mL		< 0.25 EU/mL
Sterility[2]	434-OP-00467 PE: QC-159	Sterile		TBD
EDTMPA identity	434-OP-01005	Identity confirmed		Conforms

1) Transferred from quality control testing of the Ra-224 distribute solution (IM-0002)
2) Testing of radionuclidic impurity, barium and sterility is performed retrospectively. To be reported after first release.

Conclusion		
Tested according to specification:	434-OP-00040, rev. 07	
Compliance with acceptance criteria:	☑Yes	☐No
Date test performed/finalized:	07 Sep 2021	
Comments/deviations: None		
Date and Signature:		

*QC Scientist Ingjerd Elka
*Sign for Head of Quality Control/Gro Elisabeth Hjellum

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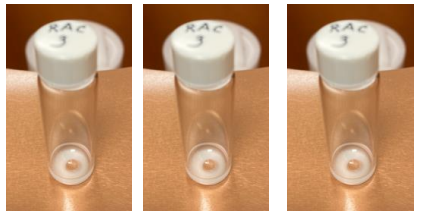
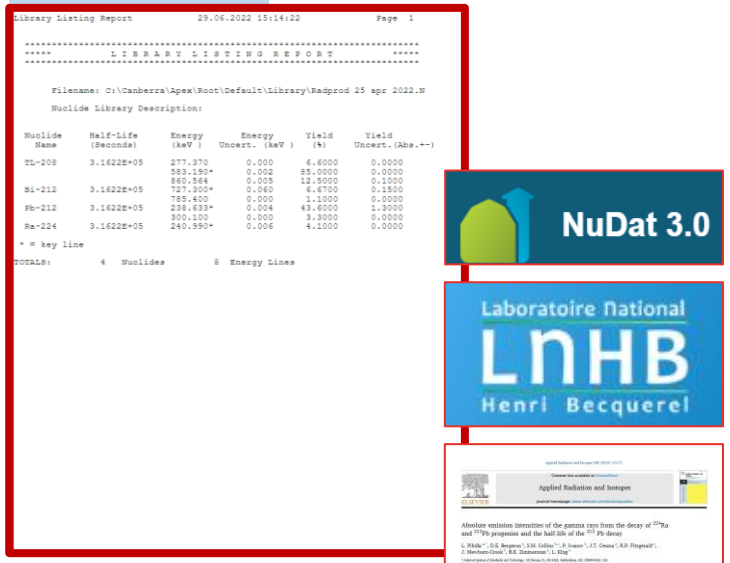


Quality control

Analytical method: instrument


Library Listing Report 29.06.2022 15:14:22 Page 1

***** L I B R A R Y L I S T I N G R E P O R T *****

Filename: C:\Canberra\Apex\Root\Default\Library\Radprod 25 apr 2022.N

Nuclide Library Description:

Nuclide Name	Half-Life (Seconds)	Energy (keV)	Energy Uncert. (keV)	Yield (%)	Yield Uncert.(Abs.+-)
Tl-208	3.1622E+05	277.370	0.000	6.6000	0.0000
		583.190*	0.002	85.0000	0.0000
		860.564	0.005	12.5000	0.1000
Bi-212	3.1622E+05	727.300*	0.060	6.6700	0.1500
		785.400	0.000	1.1000	0.0000
Pb-212	3.1622E+05	238.633*	0.004	43.6000	1.3000
		300.100	0.000	3.3000	0.0000
Ra-224	3.1622E+05	240.990*	0.006	4.1000	0.0000

* = key line

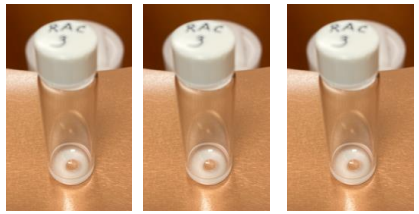
TOTALS: 4 Nuclides 8 Energy Lines

NuDat 3.0

Laboratoire National LNHB Henri Becquerel


Applied Radiation and Isotopes

Absolute emission intensities of the gamma rays from the decay of ^{224}Ra and ^{212}Pb progenies and the half-life of the ^{212}Pb decay



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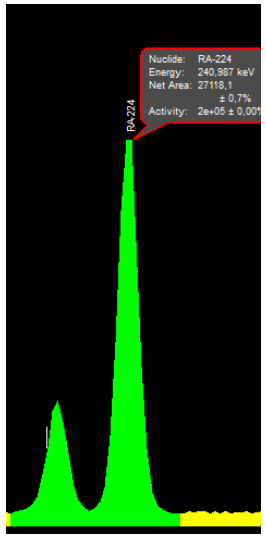
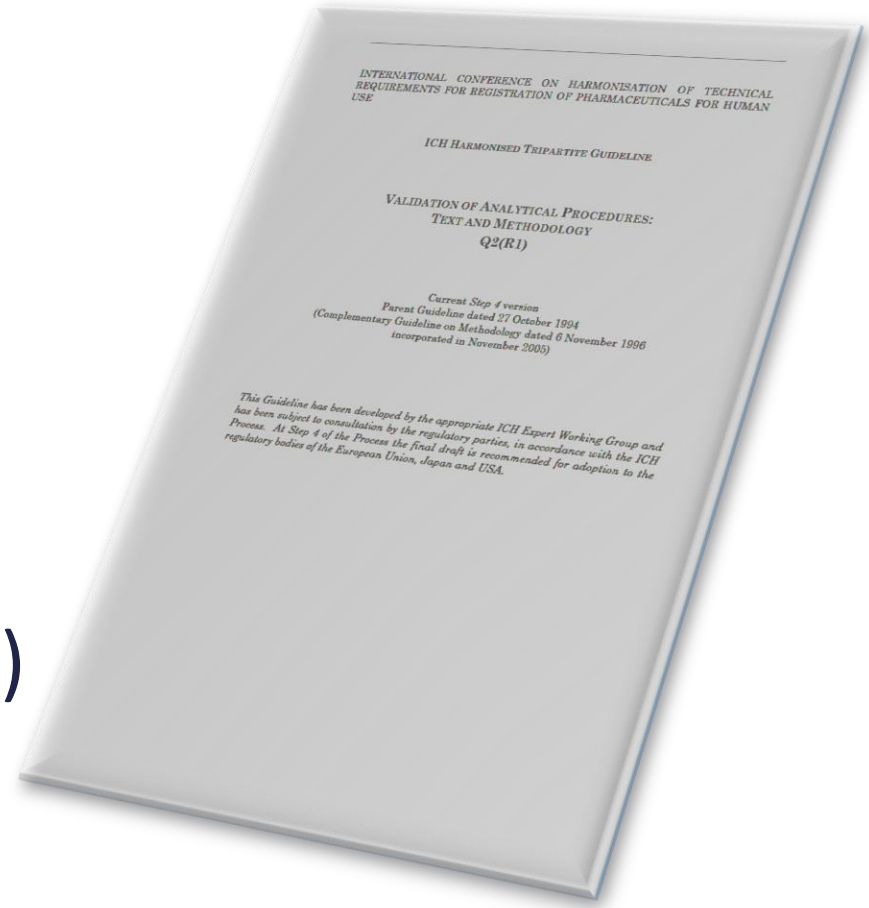
Quality control

Analytical method: parameters



- Sample preparation
- Geometry
  - Sample size (volume)
  - Distance from detector
- Counting time
- Sample size (activity -> dead time)
- Interferences (e.g., ^{212}Pb)



INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

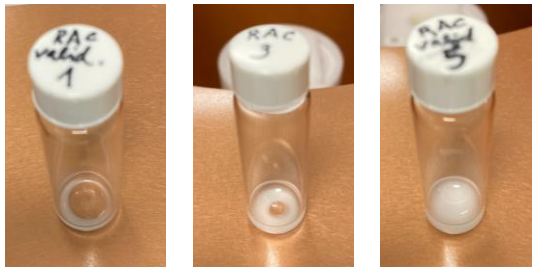
VALIDATION OF ANALYTICAL PROCEDURES: TEXT AND METHODOLOGY
Q2(R1)

Current Step 4 version
Parent Guideline dated 27 October 1994
(Complementary Guideline on Methodology dated 6 November 1996
incorporated in November 2005)

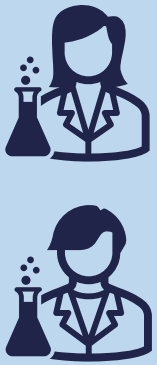
This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

Quality control

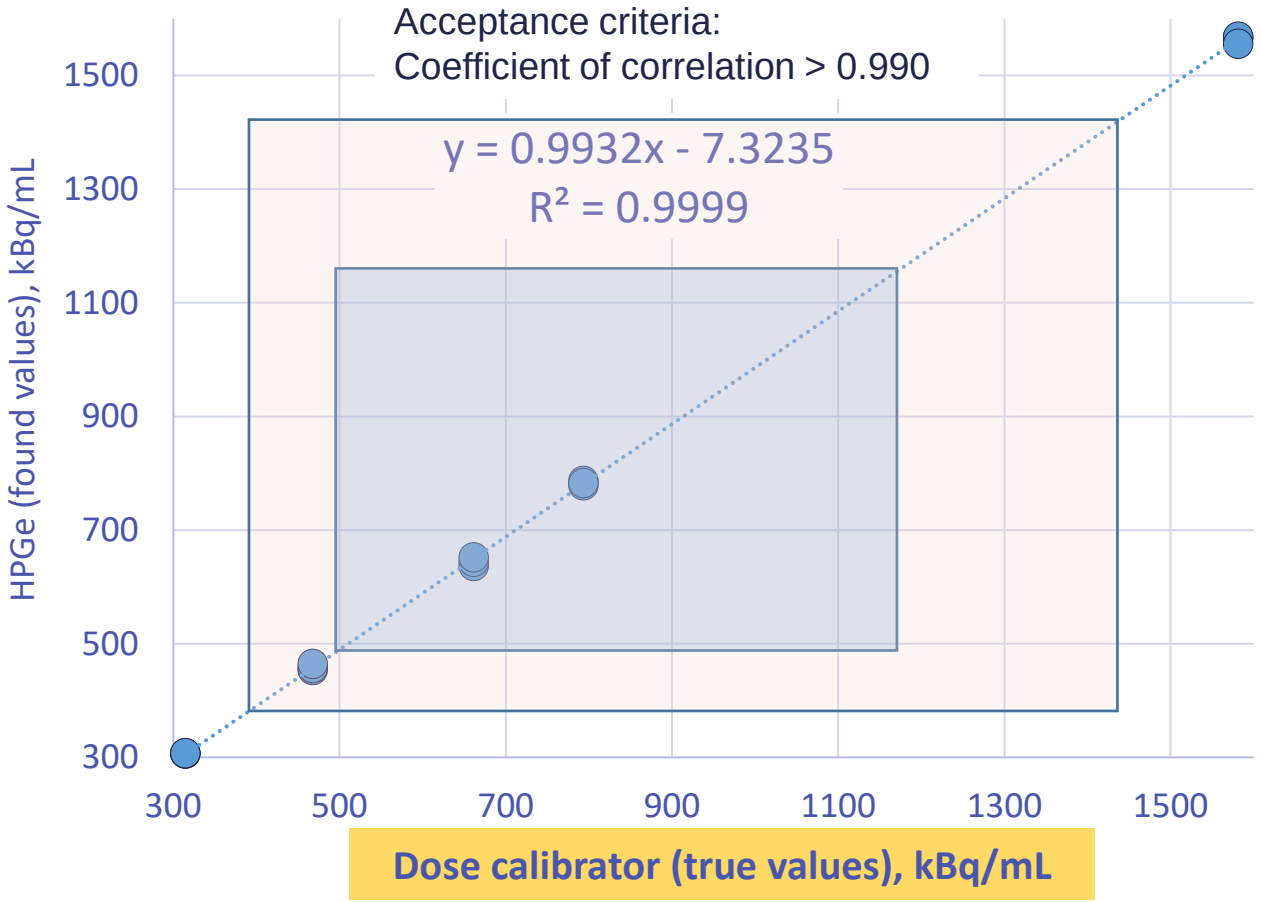
Analytical method: validation



Quality control



Analytical method: validation

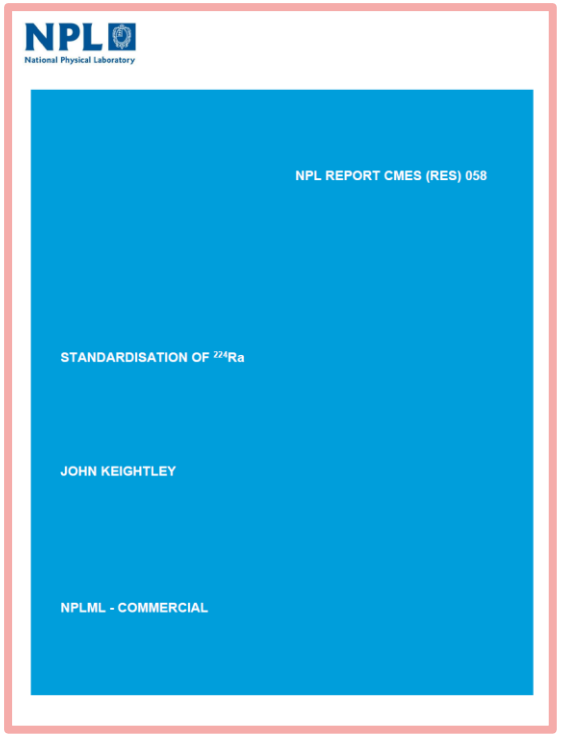


Parameter	Possible values	Acceptance criteria	Result
Range, kBq/mL (2 days after HPGe measurements ≈ reference date and time)	**502-1189**	**400-1400**	**314-1581**
Range, kBq/mL (on HPGe measurements date)	735-1742	590-2090	461-2316

Quality control

Analytical method:

true values – standardization – traceability



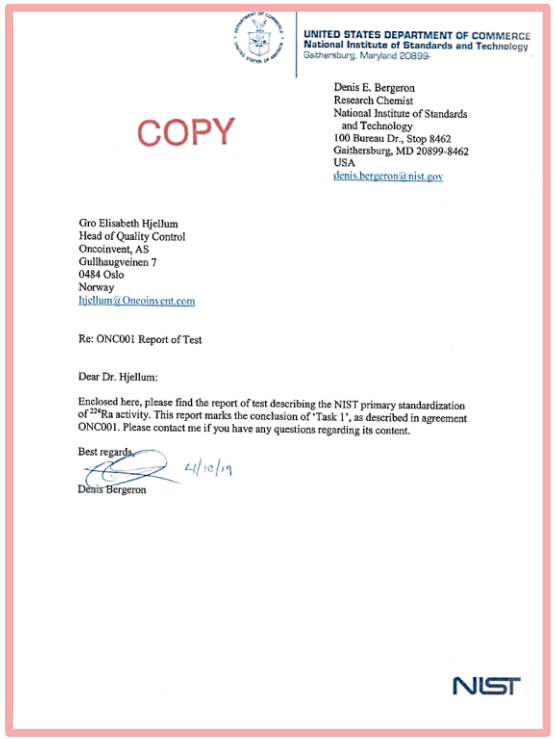
NPL
National Physical Laboratory

NPL REPORT CMES (RES) 058

STANDARDISATION OF ^{224}Ra

JOHN KEIGHTLEY

NPLML - COMMERCIAL



UNITED STATES DEPARTMENT OF COMMERCE
National Institute of Standards and Technology
Gaithersburg, Maryland 20899

COPY

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Re: ONC001 Report of Test

Dear Dr. Hjellum:

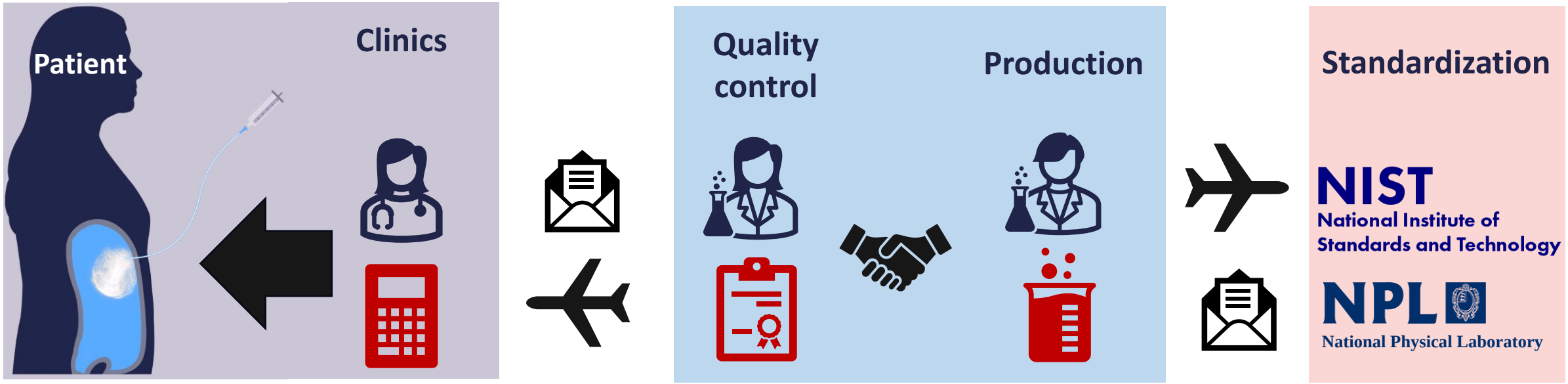
Enclosed here, please find the report of test describing the NIST primary standardization of ^{224}Ra activity. This report marks the conclusion of "Task 1", as described in agreement ONC001. Please contact me if you have any questions regarding its content.

Best regards,

Denis Bergeron

NIST

Complete chain of production, control and use



Questions?