Practical Applications of Radionuclidic Impurity with Apex-Guard™

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MIRION TECHNOLOGIES

Radiopharmaceutical Supply Chain

Radionuclidic Purity QA Measurements

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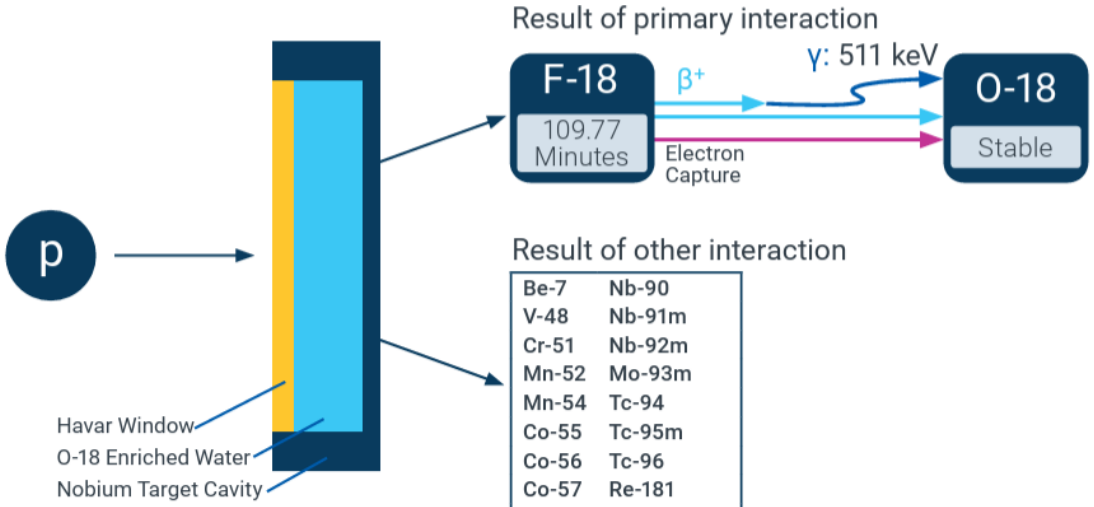
Examples of Radio-isotopes with Impurities of Concern

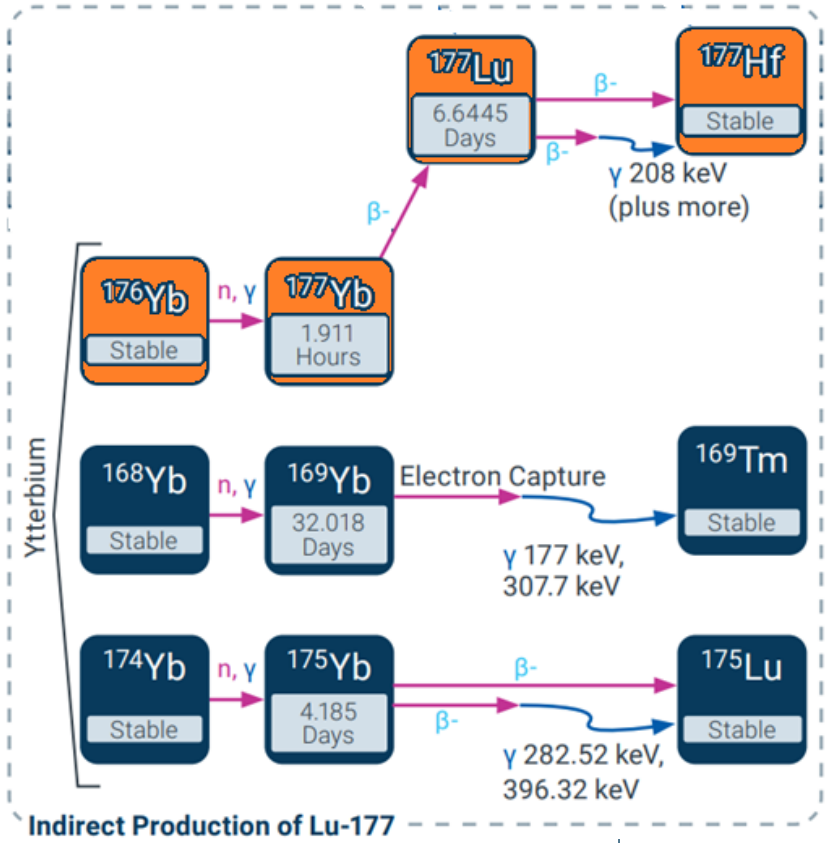
F-18 Production:

- Production is by proton bombardment of a O-18 enriched water in a cyclotron.
- Many potential impurities can be created as by-products



Lu-177 Production:

- Indirect production is by irradiation of Ytterbium with neutrons
- Impurities include Yb-169 and Yb-175



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Radionuclidic Purity Measurements

Objective

Determine if the activities of a set of radionuclide impurities are below a percent limit of the primary radionuclide activity. **This activity ratio is called the Radionuclidic Purity**.

Measurement

For impurity radionuclides: Gamma spectrometry (or potentially Alpha Spec, Mass Spec, or LCS)

For primary radionuclides: Gamma spectrometry or other

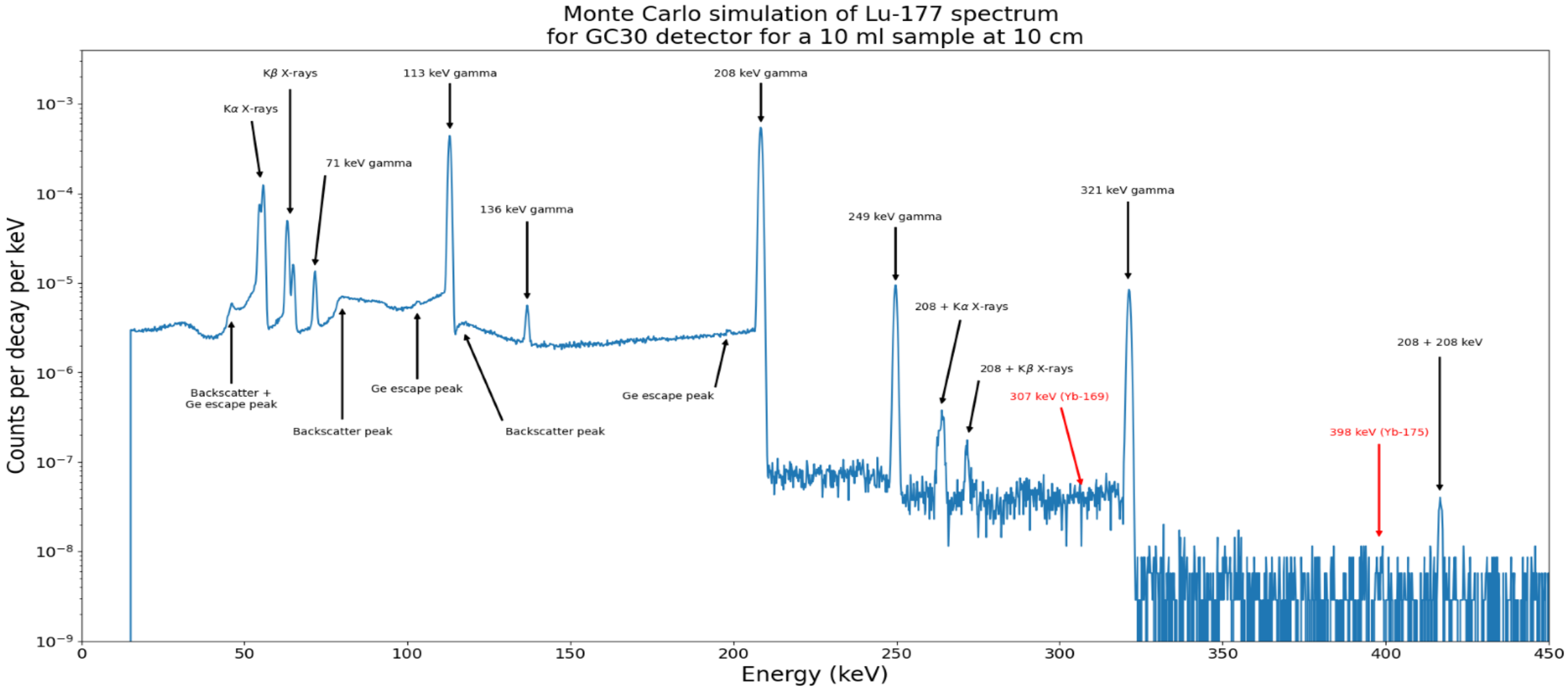
Challenges

Quantifying the Impurity Radionuclides (i.e., which emission lines to use in gamma spec)

Managing the measurement uncertainties

Reporting on radionuclidic impurity when the impurity is not detected.

HPGe Gamma Spectrum of Lu-177



Components of the Gamma Spectrometry Solution

SPECTROSCOPY SYSTEM

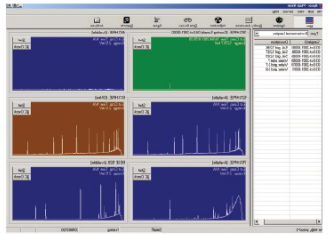
GENIE™ SPECTROSCOPY SUITE

- Instrument Control & Acquisition
- Gamma, Alpha, & QA/QC Analysis
- Interactive Reporting

APEX-GAMMA™ APPLICATION

Apex-Guard™ User Management

- Sample Definition Management
- Streamlined Counting Interface



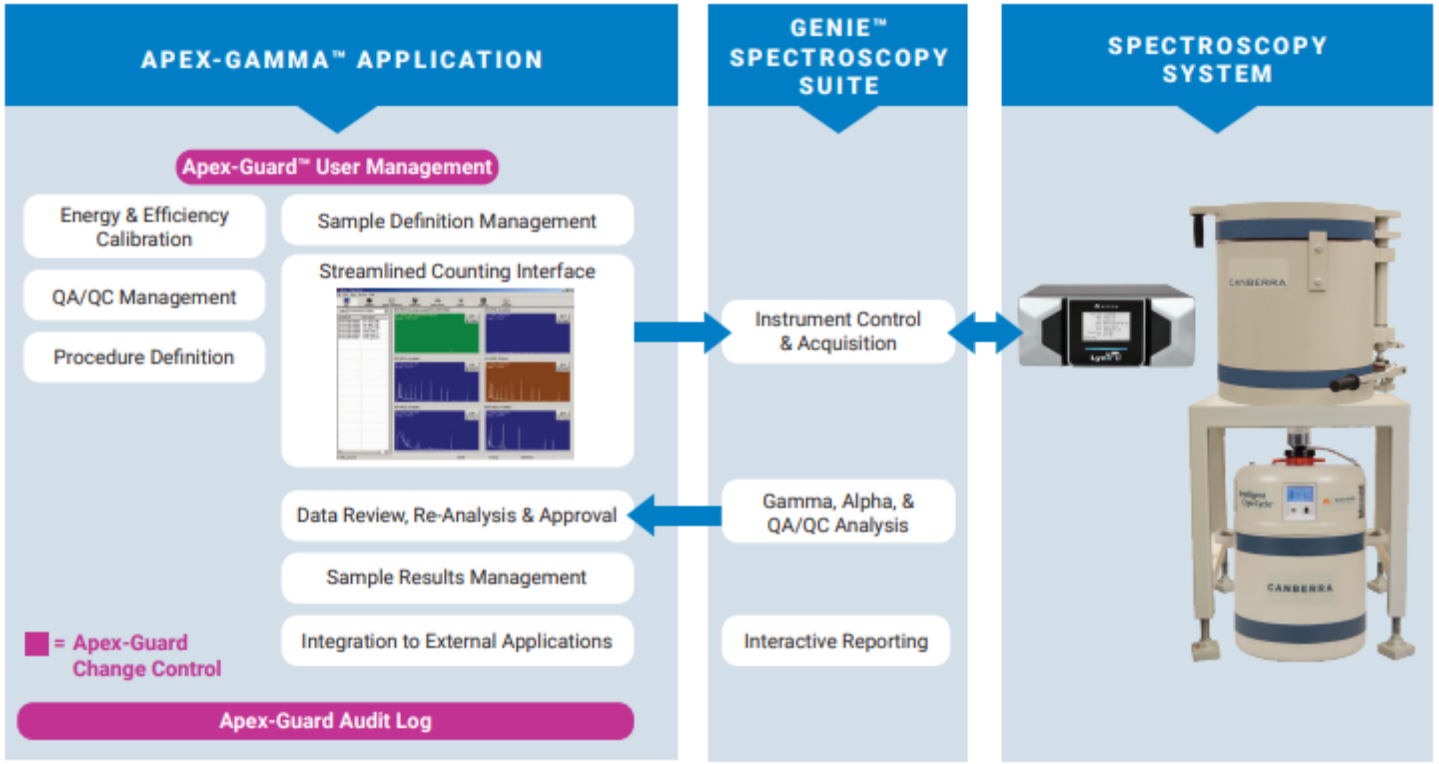
- Energy & Efficiency Calibration
- QA/QC Management
- Procedure Definition
- **Apex-Guard Change Control**
- **Apex-Guard Impurity Analysis and Reporting**
- Data Review and Approval
- Sample Results Management
- Automation Integration to External Applications
- **Apex-Guard Audit Log**

BIOTRAX QMS (EC² SOFTWARE)

- Quality Documentation Management
- Training and Instrument Compliance Management
- Inventory Management
- Batch Record Management
- Radionuclidic Purity QA Records

Apex-Guard Software: An Option with Apex-Gamma

- Developed to satisfy the evolving needs related to US FDA 21 CFR Part 11 Compliance
  - Part 11 Compliance is commonly required for radiopharmaceutical applications and samples with oversight by the FDA or similar local requirements
  - Part 11 Compliance is all about data integrity, specifically when applied to “electronic records”
- Builds on top of existing & mature Apex-Gamma product



Innovation at Work

Apex-Gamma Software: Advanced Spectroscopy Management

Sample Procedures
- Manage count parameters, analysis, reporting, and approval requirements

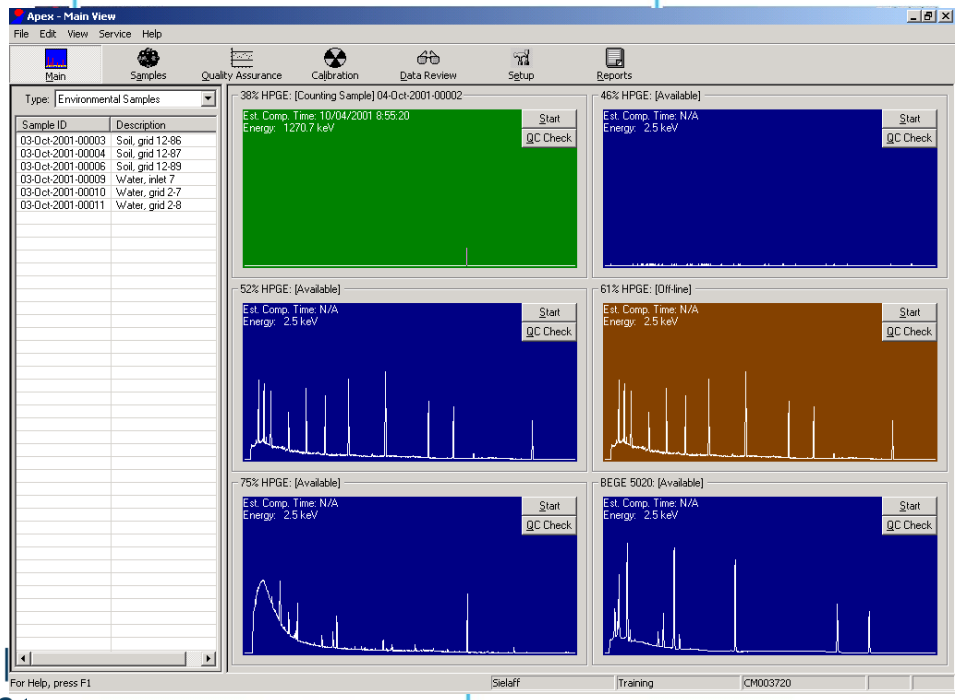
Sample Definition
- Define manually or import from LIMS system for greater efficiency gains

Sample Counting Interface
- Automated to reduce time, mistakes, and end user training requirements for operators

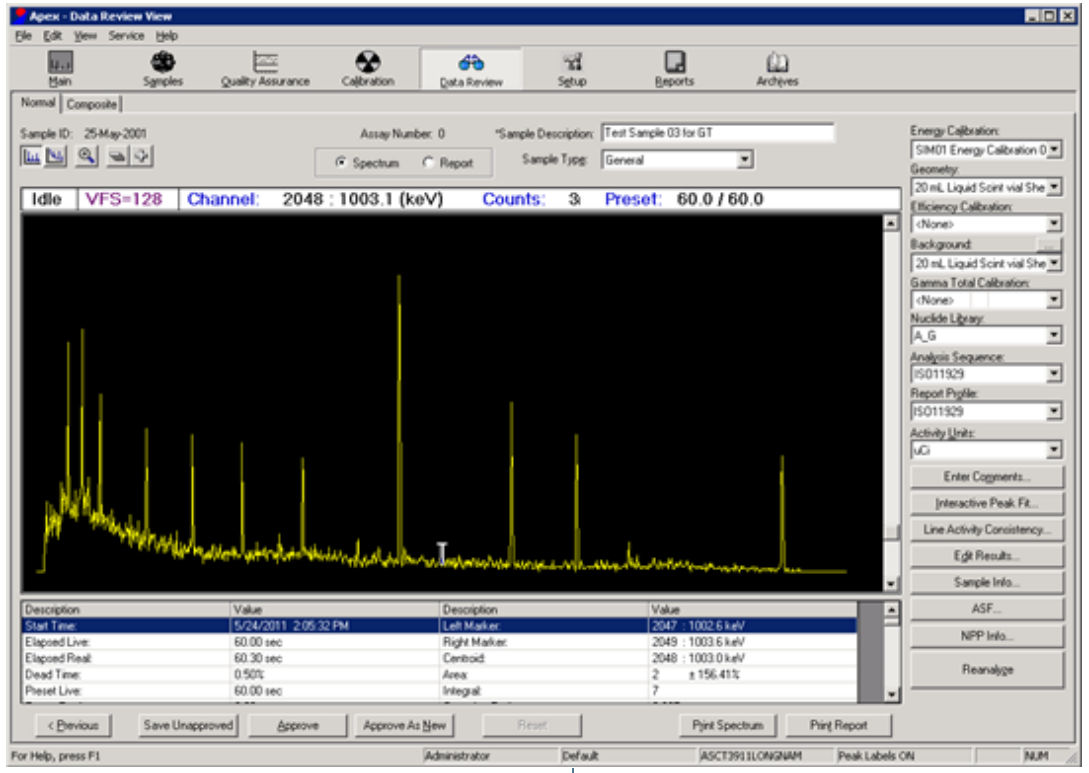
Data Review
- Dedicated environment to approve and/or reanalyze sample counts
- Powerful database search

Drag and drop logged-in samples to any available detector start count

"Estimated Completion Time" makes it easy to establish which detector is available next



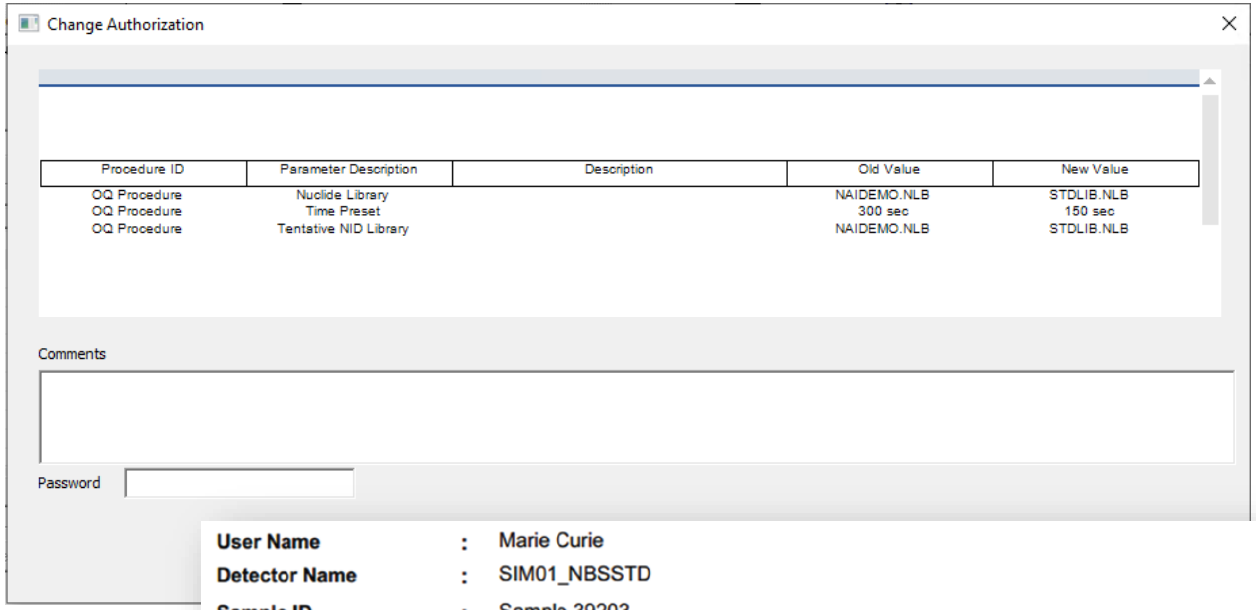
Color code shows detector availability at a glance.



Innovation at Work

Apex-Guard Data Integrity Features

- User-login management via Windows Credentials
- Auto logouts
- Granular Role-Based Security Features
- Change Control Authorization
- Powerful Audit Log
- Secured control outside of application
- Electronic Signatures for Change Review
- Enforceable Instrument QA
- Database driven records and analysis history



User Name : Marie Curie
Detector Name : SIM01_NBSSTD
Sample ID : Sample 39203
Description : Approve
Comments : Approving sample with nuclide library change

Sample ID	Parameter Description	Description	Old Value	New Value
Sample 39203	Sample State		Counted - Pending Review	Done - Fully Approved
Sample 39203	Nuclide Library		STDLIB.NLB	ANSI_GammaGuru.NLB
Sample 39203	Analysis No.		1	2

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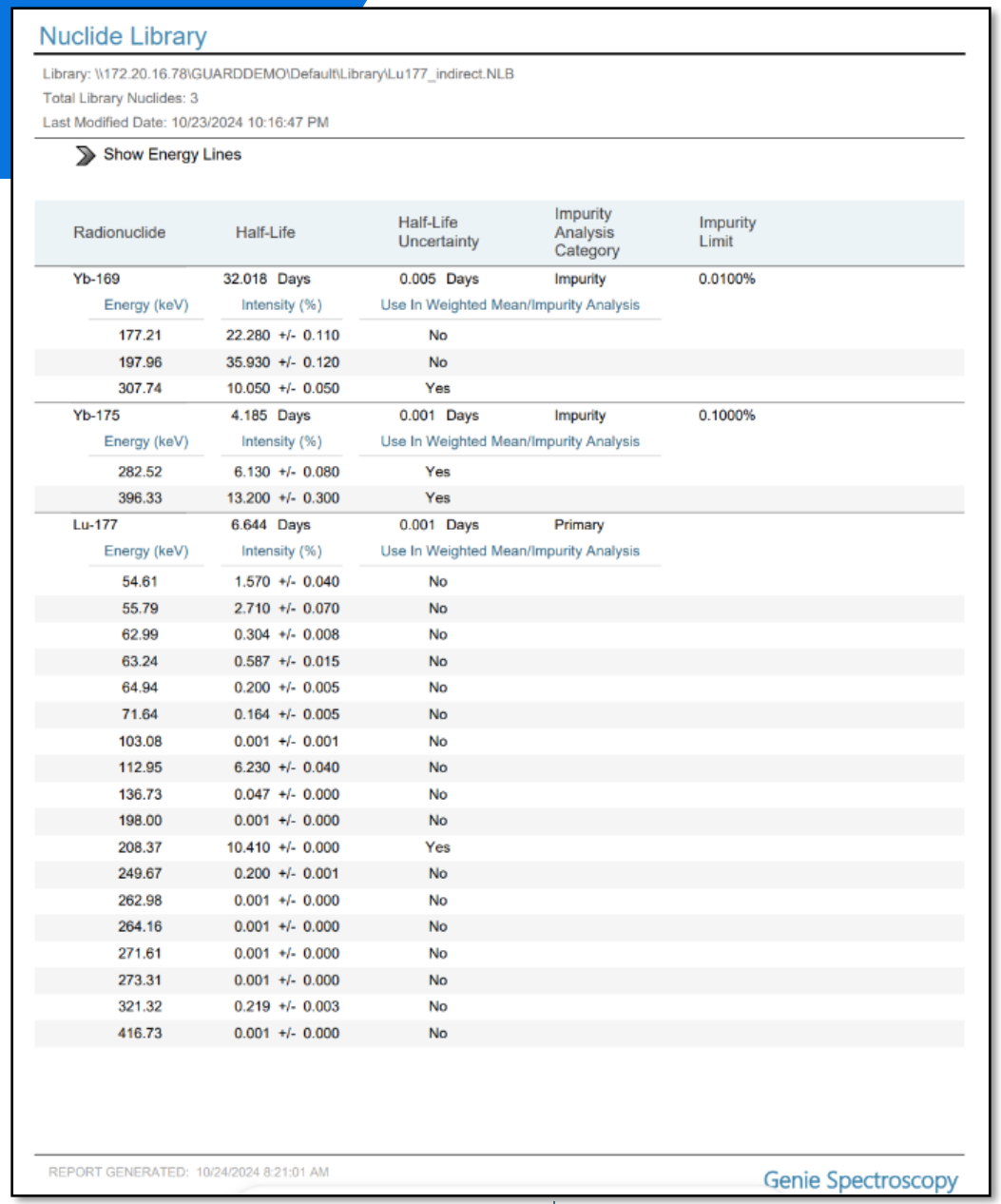
Apex-Guard Spectrum Analysis

APEX-GUARD PROCEDURE

1. Count Duration
2. Analysis
   - Peak Area Analysis
   - Nuclide Library Selection
   - Geometry (for efficiency calibration)
   - Activity, MDA, and Impurity Calculations
3. Reporting Selection
4. Approval Requirements
5. Scripting Components



Nuclide Library

Library: \\172.20.16.78\GUARDDEMO\Default\Library\Lu177_indirect.NLB
Total Library Nuclides: 3
Last Modified Date: 10/23/2024 10:16:47 PM

Show Energy Lines

Radionuclide	Half-Life	Half-Life Uncertainty	Impurity Analysis Category	Impurity Limit
Yb-169	32.018 Days	0.005 Days	Impurity	0.0100%
Energy (keV)	Intensity (%)	Use In Weighted Mean/Impurity Analysis		
177.21	22.280 +/- 0.110	No		
197.96	35.930 +/- 0.120	No		
307.74	10.050 +/- 0.050	Yes		
Yb-175	4.185 Days	0.001 Days	Impurity	0.1000%
Energy (keV)	Intensity (%)	Use In Weighted Mean/Impurity Analysis		
282.52	6.130 +/- 0.080	Yes		
396.33	13.200 +/- 0.300	Yes		
Lu-177	6.644 Days	0.001 Days	Primary	
Energy (keV)	Intensity (%)	Use In Weighted Mean/Impurity Analysis		
54.61	1.570 +/- 0.040	No		
55.79	2.710 +/- 0.070	No		
62.99	0.304 +/- 0.008	No		
63.24	0.587 +/- 0.015	No		
64.94	0.200 +/- 0.005	No		
71.64	0.164 +/- 0.005	No		
103.08	0.001 +/- 0.001	No		
112.95	6.230 +/- 0.040	No		
136.73	0.047 +/- 0.000	No		
198.00	0.001 +/- 0.000	No		
208.37	10.410 +/- 0.000	Yes		
249.67	0.200 +/- 0.001	No		
262.98	0.001 +/- 0.000	No		
264.16	0.001 +/- 0.000	No		
271.61	0.001 +/- 0.000	No		
273.31	0.001 +/- 0.000	No		
321.32	0.219 +/- 0.003	No		
416.73	0.001 +/- 0.000	No		

REPORT GENERATED: 10/24/2024 8:21:01 AM

Genie Spectroscopy

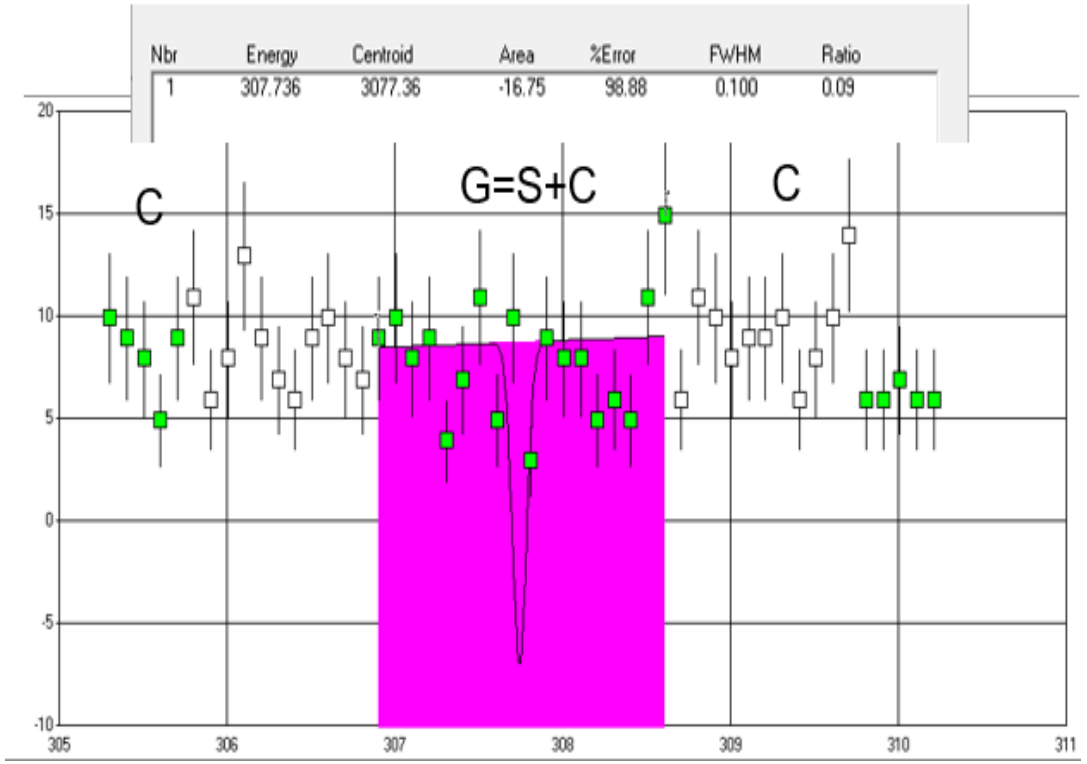
Reporting Peak Areas

Radionuclide identified in Spectrum

- (add photo of peak area reports)

➢ Peak Areas are determined with a measurement uncertainty

Radionuclide not identified in Spectrum



➢ Always possible to force a peak area

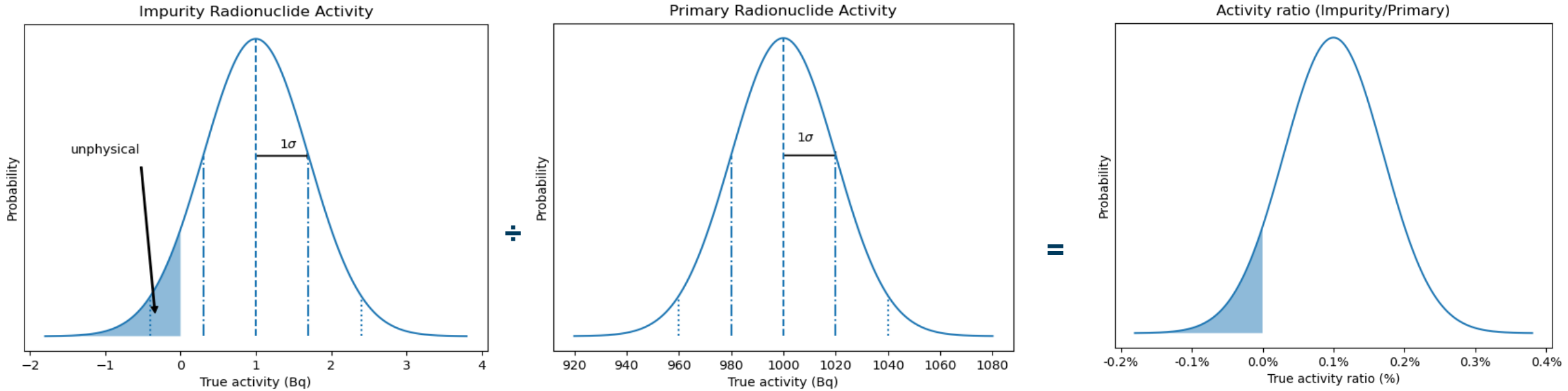
A New Algorithm: Determining a ratio *including uncertainties*

Consider a measurement of an impurity radionuclide and a primary radionuclide, each with an activity and activity uncertainty:

- The uncertainties of the activity measurements are normally distributed
- The measured value is the most likely value
- 68% probability that the true value is within the +/-1σ uncertainty of the measured value

Since the true value for the activities is not known, the true value of the impurity-to-primary activity ratio is not known either.

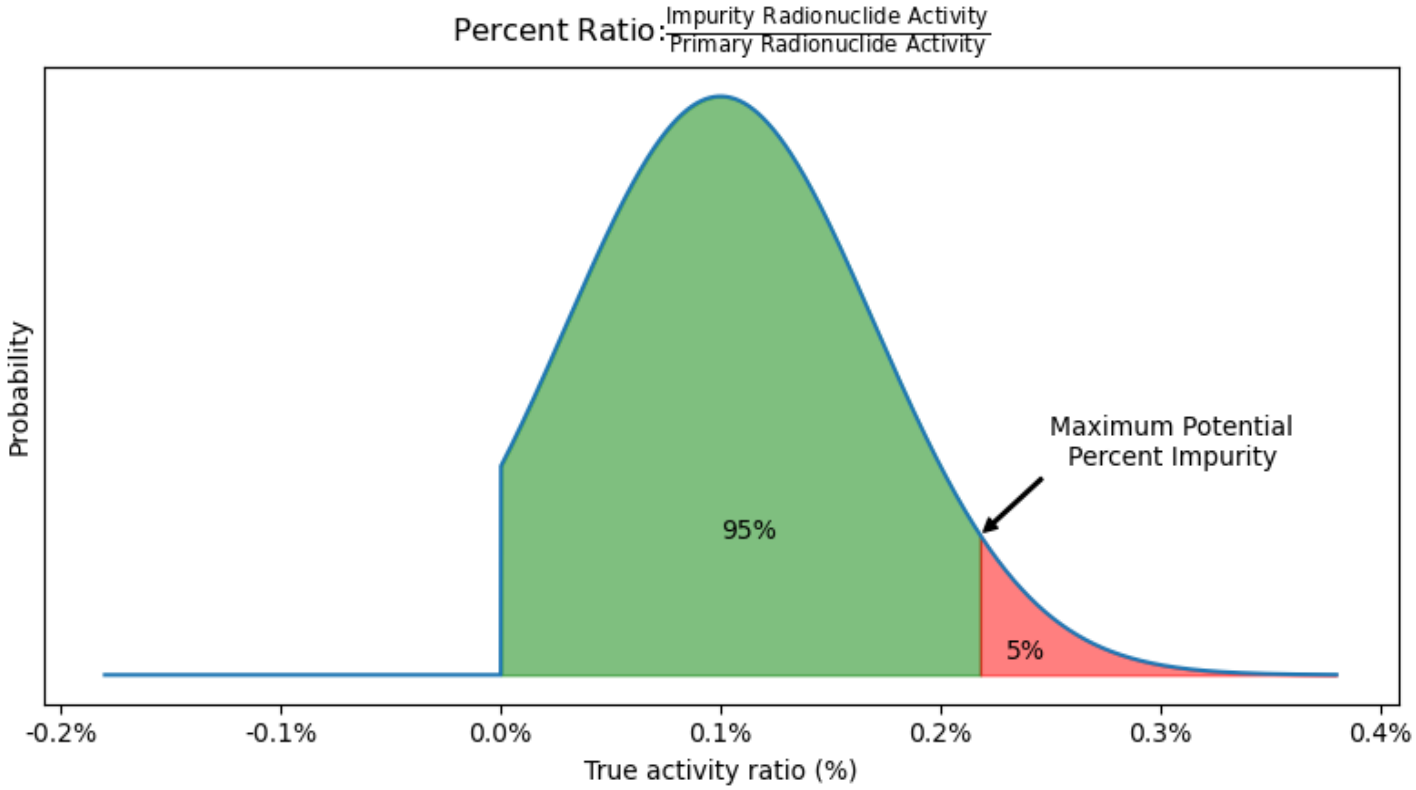
That said, it is known that the true radionuclide activity cannot be negative - although one may measure a negative activity.



A New Algorithm: Determining a ratio *including uncertainties*

The probability distribution of ratio of the two activity measurements provides a range of potential values for the true impurity ratio:

- The most likely value of the true impurity ratio is the calculated ratio of the measured activity values
- The possible true values of the ratio follows the probability distribution, which can be greater than the calculated ratio



Introducing the Maximum Potential Percent Impurity (MPPI) Value

- An impurity ratio value that is greater than the true activity ratio with 95%* confidence

  * This is the 1 – α confidence, which can be specified
- If the MPPI is less than or equal to a maximum impurity percentage, one can conclude that the impurity activity is less than this limit with at least 95% confidence.

Apex-Guard Impurity Analysis Results

Mirion Apex-Guard™ Software 10/4/2024 4:22:44PM Page 1 of 2

Analysis Report for Sample ID 12345
QA Measurement of Lu-177 Production

GAMMA SPECTRUM ANALYSIS

Sample Identification	: Sample ID 12345
Sample Description	: QA Measurement of Lu-177 Production
Sample Type	: Example
Sample Size	: 1.000E+00 units
Facility	: Default
Sample Taken On	: 10/4/2024 4:16:03PM
Acquisition Started	: 10/1/2024 1:29:10PM
Procedure	: Proc-A_Lu-177
Operator	: fred
Detector Name	: DET01
Geometry	: LSV at 10 cm
Live Time	: 3600.0 seconds
Real Time	: 3600.0 seconds
Dead Time	: 0.00 %
Peak Locate Threshold	: 3.00
Peak Locate Range (in channels)	: 1 - 16384
Peak Area Range (in channels)	: 1 - 16384
Identification Energy Tolerance	: 1.000 keV
Energy Calibration Used Done On	: 10/2/2024
Efficiency Calibration Used Done On	: 10/2/2024
Efficiency Calibration Description	: Efficiency Calibration Mixed Gamma
Sample Number	: 37
Analysis Number	: 1

10/4/2024 4:22:44PM Page 2 of 2

Analysis Report for Sample ID 12345
QA Measurement of Lu-177 Production

Radionuclide Impurity Report

MPPI Activity Reference: Activity of Primary Radionuclide only
Alpha Confidence: 5.000 %
Nuclide Library: LU177_INDIRECT.NLB

Reference Date: 10/4/2024 4:16:03PM

Radionuclide	Impurity Analysis Category	Activity (kBq/units)	Activity Uncertainty at 1.0 sigma	MDA / Reference Activity	Maximum Potential Percent Impurity	Percent Impurity Limit
Lu-177	Primary	4.547E+02	2.14E+00%	-------	------	------
Yb-169	Impurity	---------	---------	0.012%	0.005%	0.010%
Yb-175	Impurity	---------	---------	0.002%	0.001%	0.100%
Sum of Impurities :					0.006%	0.100%

>> Sample analysis results are below the specified radionuclide impurity limits at reference time 10/4/2024 4:16:03PM.

>> Minimum Radionuclidic Purity : 99.994%

The maximum potential percent impurity (MPPI) is the greatest relative percent activity of the impurity compared to the activity reference at the alpha confidence for this measurement, taking into account their respective uncertainties. There is a 95.00% probability that the true impurity percent is at or below the MPPI.

Apex-Guard Report Results

ACCEPTABLE RESULTS

10/4/2024 4:22:44PM Page 2 of 2

Analysis Report for Sample ID 12345

QA Measurement of Lu-177 Production

Radionuclide Impurity Report

MPPI Activity Reference: Activity of Primary Radionuclide only
Alpha Confidence: 5.000 %
Nuclide Library: LU177_INDIRECT.NLB

Reference Date: 10/4/2024 4:16:03PM

Radionuclide	*Impurity Analysis Category*	*Activity (kBq/units)*	*Activity Uncertainty at 1.0 sigma*	*MDA / Reference Activity*	*Maximum Potential Percent Impurity*	*Percent Impurity Limit*
Lu-177	Primary	4.547E+02	2.14E+00%	-------	------	------
Yb-169	Impurity	---------	---------	0.012%	0.005%	0.010%
Yb-175	Impurity	---------	---------	0.002%	0.001%	0.100%
Sum of Impurities :					0.006%	0.100%

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HIGH IMPURITY RESULT

10/4/2024 4:35:42PM Page 2 of 2

Analysis Report for Sample ID 12346

Impurity analysis at acquistion time and two weeks later

Radionuclide Impurity Report

MPPI Activity Reference: Activity of Primary Radionuclide only
Alpha Confidence: 5.000 %
Nuclide Library: LU177_INDIRECT.NLB

Reference Date: 10/18/2024 4:28:07PM

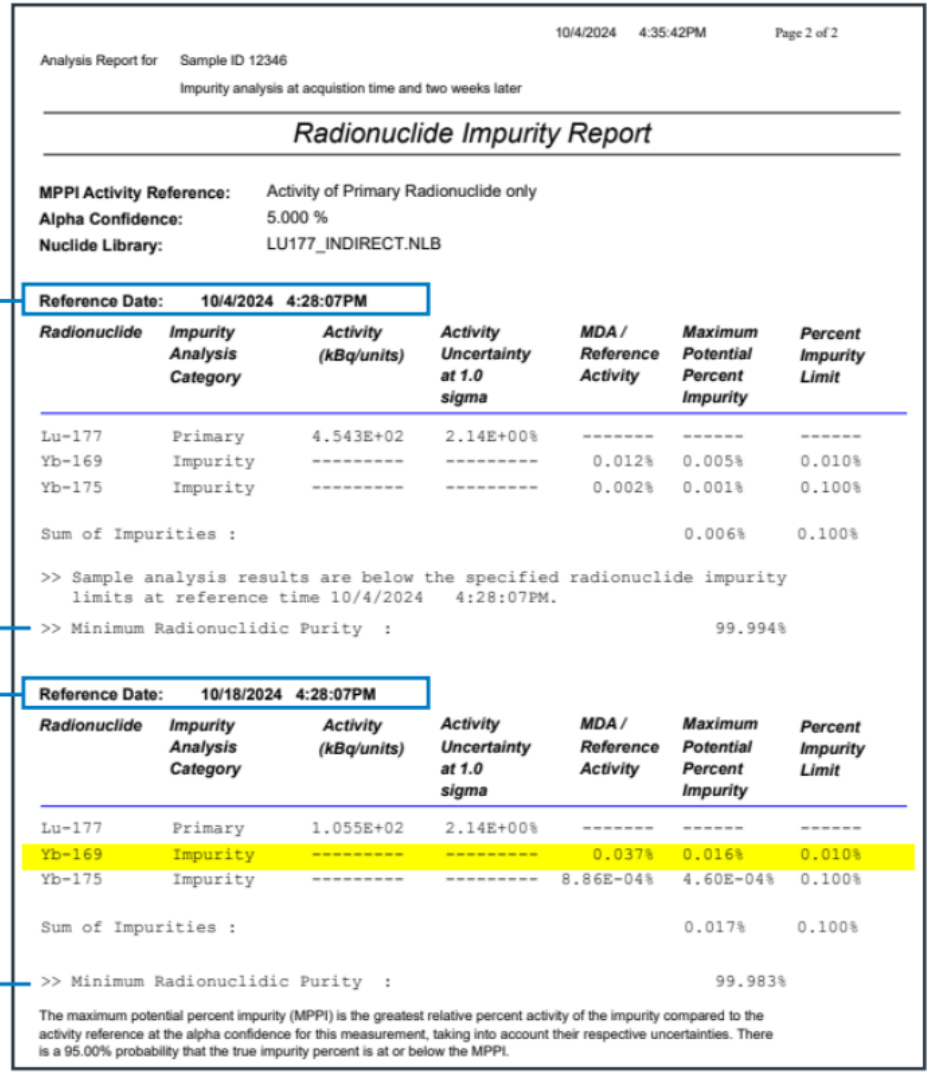
Radionuclide	*Impurity Analysis Category*	*Activity (kBq/units)*	*Activity Uncertainty at 1.0 sigma*	*MDA / Reference Activity*	*Maximum Potential Percent Impurity*	*Percent Impurity Limit*
Lu-177	Primary	1.055E+02	2.14E+00%	-------	------	------
Yb-169	Impurity	---------	---------	0.037%	0.016%	0.010%
Yb-175	Impurity	---------	---------	8.86E-04%	4.60E-04%	0.100%
Sum of Impurities :					0.017%	0.100%

>> Minimum Radionuclidic Purity : 99.983%

The maximum potential percent impurity (MPPI) is the greatest relative percent activity of the impurity compared to the activity reference at the alpha confidence for this measurement, taking into account their respective uncertainties. There is a 95.00% probability that the true impurity percent is at or below the MPPI.

Impurity Calculations at Two Reference Dates

- To configure, select the “Dual Counting” sample setup in the procedure
- When defining a sample, enter two reference dates (e.g., date of assay and future injection date)
- The Impurity Report will decay-correct the activities, MDAs, and MPPI to each reference date
- The assessment of impurity limits will be done for each date



10/4/2024 4:35:42PM Page 2 of 2

Analysis Report for Sample ID 12346

Impurity analysis at acquistion time and two weeks later

Radionuclide Impurity Report

MPPI Activity Reference: Activity of Primary Radionuclide only
Alpha Confidence: 5.000 %
Nuclide Library: LU177_INDIRECT.NLB

Reference Date: 10/4/2024 4:28:07PM

Radionuclide	Impurity Analysis Category	Activity (kBq/units)	Activity Uncertainty at 1.0 sigma	MDA / Reference Activity	Maximum Potential Percent Impurity	Percent Impurity Limit
Lu-177	Primary	4.543E+02	2.14E+00%	-------	------	------
Yb-169	Impurity	---------	---------	0.012%	0.005%	0.010%
Yb-175	Impurity	---------	---------	0.002%	0.001%	0.100%
Sum of Impurities :					0.006%	0.100%

>> Sample analysis results are below the specified radionuclide impurity limits at reference time 10/4/2024 4:28:07PM.

>> Minimum Radionuclidic Purity : 99.994%

Reference Date: 10/18/2024 4:28:07PM

Radionuclide	Impurity Analysis Category	Activity (kBq/units)	Activity Uncertainty at 1.0 sigma	MDA / Reference Activity	Maximum Potential Percent Impurity	Percent Impurity Limit
Lu-177	Primary	1.055E+02	2.14E+00%	-------	------	------
Yb-169	Impurity	---------	---------	0.037%	0.016%	0.010%
Yb-175	Impurity	---------	---------	8.86E-04%	4.60E-04%	0.100%
Sum of Impurities :					0.017%	0.100%

>> Minimum Radionuclidic Purity : 99.983%

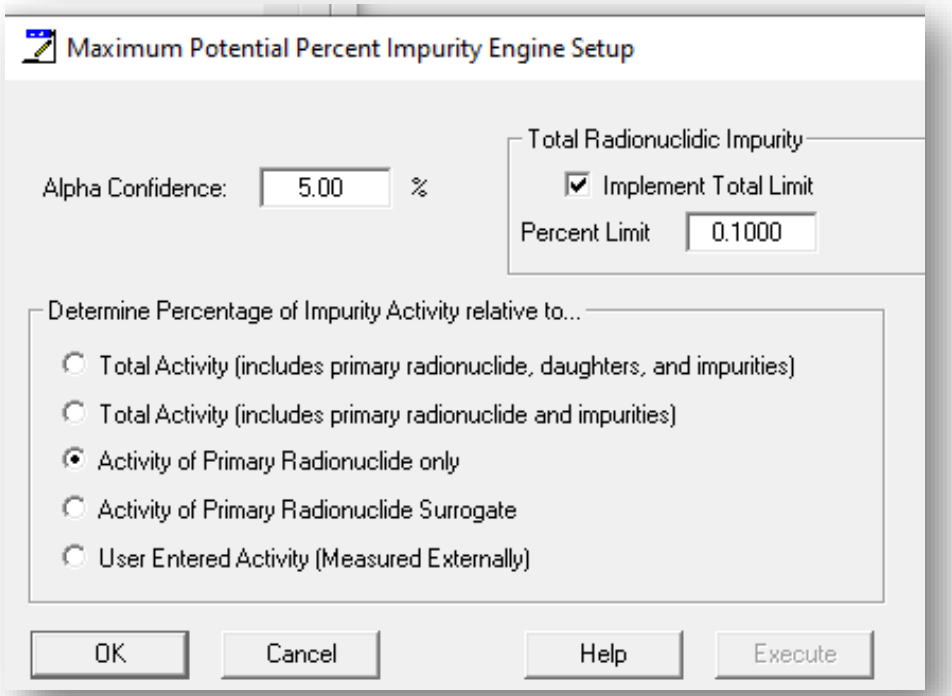
The maximum potential percent impurity (MPPI) is the greatest relative percent activity of the impurity compared to the activity reference at the alpha confidence for this measurement, taking into account their respective uncertainties. There is a 95.00% probability that the true impurity percent is at or below the MPPI.

Results for first reference date

Results for second reference date

Impurity Calculations using External Reference Activity

- An external reference activity can be measured with any equipment, such as dose calibrator
- Activity is entered at time of sample definition
- Assessment of impurities will be done using the external reference activity & activity uncertainty



4/24/2025 10:45:59AM Page 2 of 5

Analysis Report for F-18 Sample 001
48 hours after initial measurement

Radionuclide Impurity Report

MPPI Activity Reference: Activity (measured externally)
Alpha Confidence: 5.000 %
Nuclide Library: F-18_IMPURITIES.NLB

Sample Activity (Measured Externally)
Activity : 2.90E+01 µCi/units
Uncertainty : 2.34%
Description : Initial measurement of F-18 Sample 001

Reference Date: **4/21/2025 3:31:36PM**

Radionuclide	*Impurity Analysis Category*	*Activity (µCi/units)*	*Activity Uncertainty at 1.0 sigma*	*MDA / Reference Activity*	*Maximum Potential Percent Impurity*	*Percent Impurity Limit*
Be-7	Impurity	---------	---------	0.001%	8.74E-04%	------
V-48	Impurity	---------	---------	2.42E-04%	1.67E-04%	------
Cr-51	Impurity	---------	---------	0.002%	0.001%	------
Mn-52	Impurity	---------	---------	3.10E-04%	2.46E-04%	------
Mn-54	Impurity	---------	---------	2.62E-04%	1.69E-04%	------
Co-55	Impurity	---------	---------	0.002%	0.002%	------
Co-56	Impurity	---------	---------	2.57E-04%	1.73E-04%	------
Ni-56	Impurity	---------	---------	1.64E-04%	1.47E-04%	------
Co-57	Impurity	---------	---------	1.22E-04%	6.27E-05%	------
Ni-57	Impurity	---------	---------	8.20E-04%	5.68E-04%	------
Co-58	Impurity	---------	---------	2.25E-04%	1.38E-04%	------
Nb-92m	Impurity	---------	---------	2.83E-04%	1.95E-04%	------
Tc-95m	Impurity	---------	---------	2.08E-04%	1.24E-04%	------
Tc-96	Impurity	---------	---------	3.58E-04%	2.54E-04%	------
Re-182	Impurity	---------	---------	8.39E-04%	8.51E-04%	------
Re-184	Impurity	---------	---------	4.03E-04%	3.56E-04%	------

Sum of Impurities : 0.007% 0.100%

>> Sample analysis results are below the specified radionuclide impurity limits at reference time 4/21/2025 3:31:36PM.

>> Minimum Radionuclidic Purity : 99.993%

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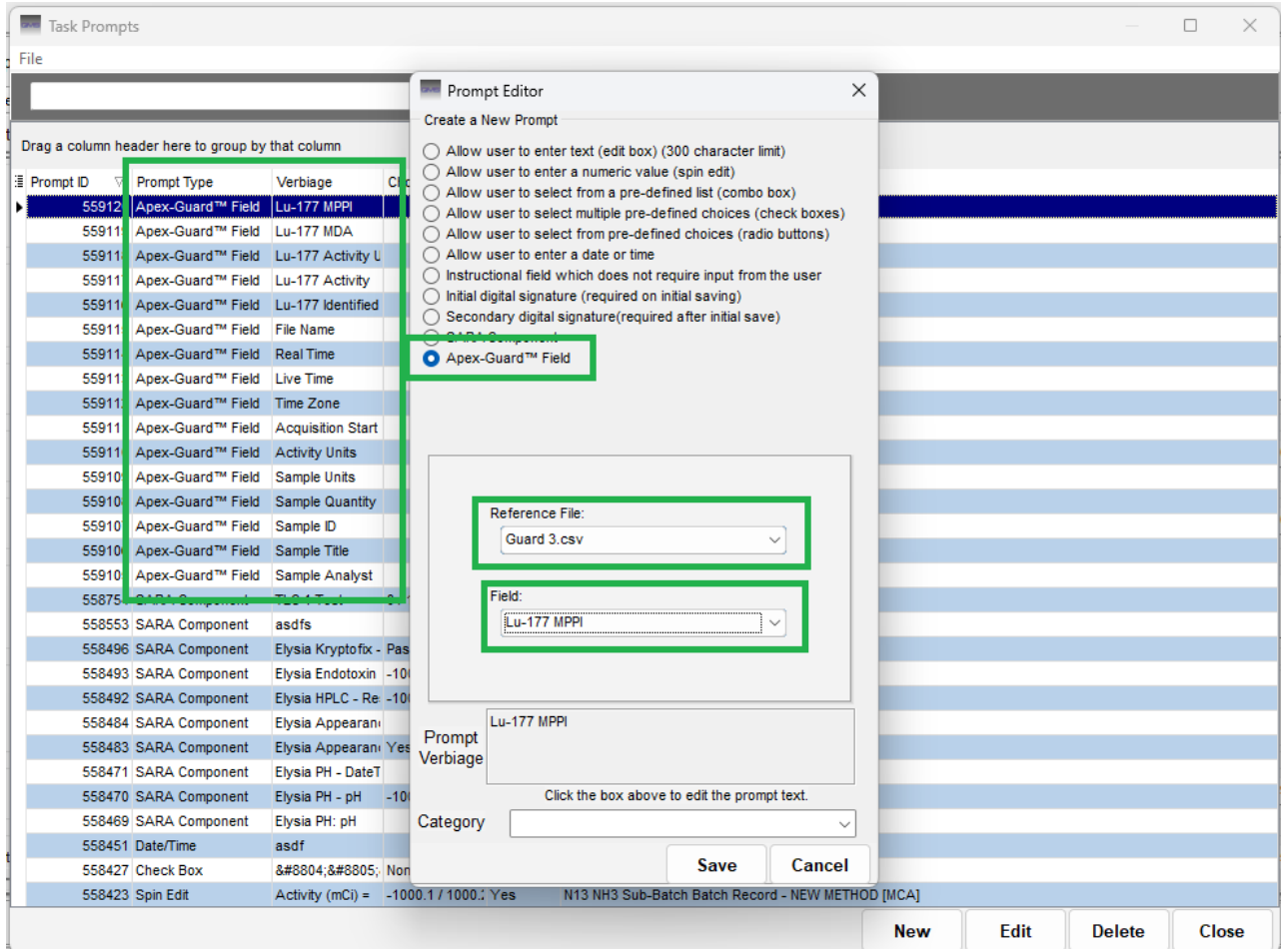
Closing the Loop: Storing results in BioTrax QMS

Apex-Guard to BioTrax QMS process

1. Use a scripting option (configured with the Apex-Gamma Procedure) to export results to CSV file
2. Configure preferred batch record options in BioTrax QMS Software
3. Import batch results into BioTrax QMS for review and QA records management.
4. Review results individually or as batch summary (next slide)



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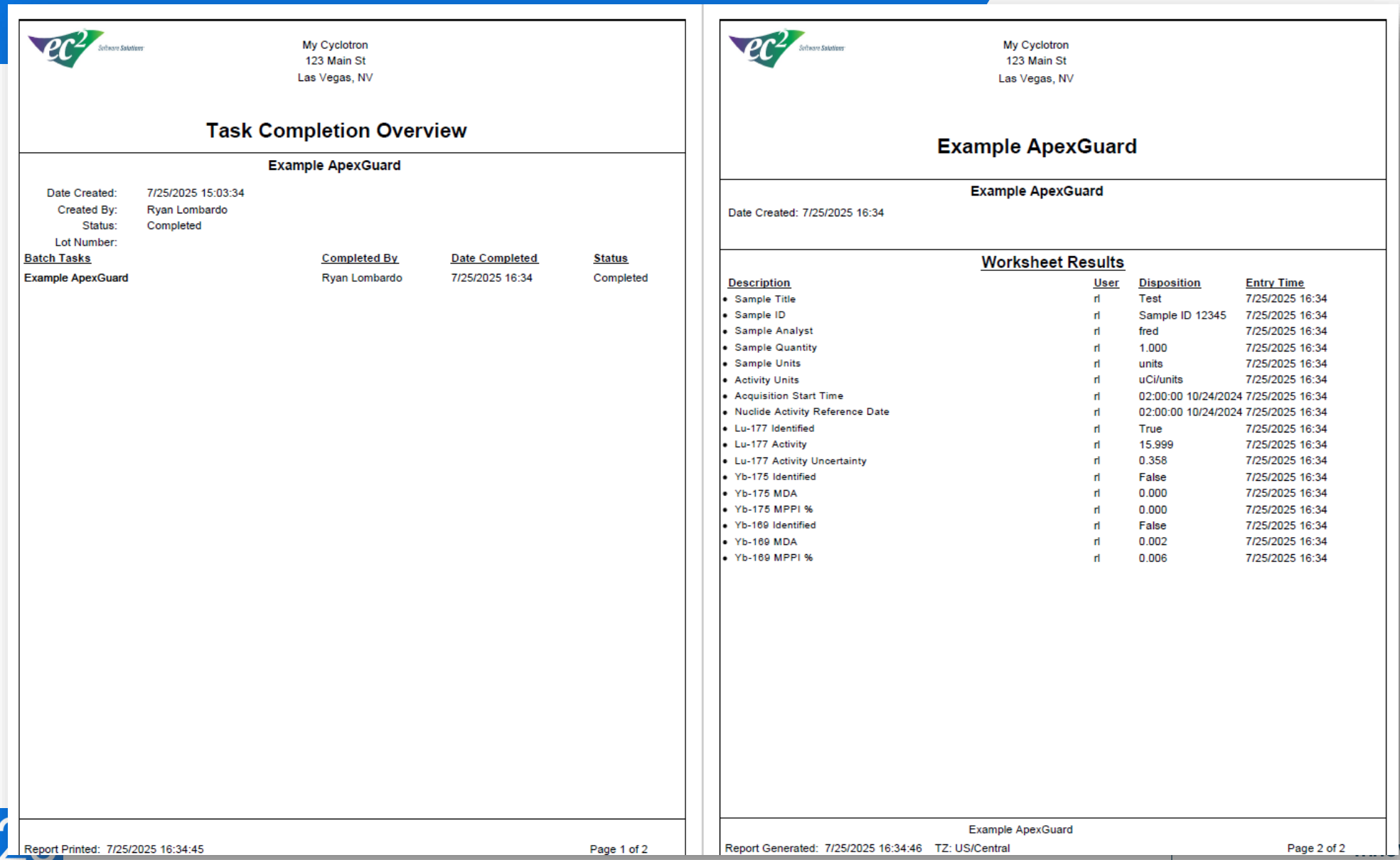
Radionuclidic Impurity Results in BioTrax QMS



My Cyclotron
123 Main St
Las Vegas, NV

Task Completion Overview

Example ApexGuard

Date Created: 7/25/2025 15:03:34
Created By: Ryan Lombardo
Status: Completed
Lot Number:

Batch Tasks	Completed By	Date Completed	Status
Example ApexGuard	Ryan Lombardo	7/25/2025 16:34	Completed

Report Printed: 7/25/2025 16:34:45 Page 1 of 2

My Cyclotron
123 Main St
Las Vegas, NV

Example ApexGuard

Example ApexGuard

Date Created: 7/25/2025 16:34

Worksheet Results

Description	User	Disposition	Entry Time
• Sample Title	rl	Test	7/25/2025 16:34
• Sample ID	rl	Sample ID 12345	7/25/2025 16:34
• Sample Analyst	rl	fred	7/25/2025 16:34
• Sample Quantity	rl	1.000	7/25/2025 16:34
• Sample Units	rl	units	7/25/2025 16:34
• Activity Units	rl	uCi/units	7/25/2025 16:34
• Acquisition Start Time	rl	02:00:00 10/24/2024	7/25/2025 16:34
• Nuclide Activity Reference Date	rl	02:00:00 10/24/2024	7/25/2025 16:34
• Lu-177 Identified	rl	True	7/25/2025 16:34
• Lu-177 Activity	rl	15.999	7/25/2025 16:34
• Lu-177 Activity Uncertainty	rl	0.358	7/25/2025 16:34
• Yb-175 Identified	rl	False	7/25/2025 16:34
• Yb-175 MDA	rl	0.000	7/25/2025 16:34
• Yb-175 MPPI %	rl	0.000	7/25/2025 16:34
• Yb-169 Identified	rl	False	7/25/2025 16:34
• Yb-169 MDA	rl	0.002	7/25/2025 16:34
• Yb-169 MPPI %	rl	0.006	7/25/2025 16:34

Example ApexGuard
Report Generated: 7/25/2025 16:34:46 TZ: US/Central Page 2 of 2

MPPI and MDA as a function of measurement time