

Protocol for a CCRI(II) Key Comparison of ^{177}Lu

1. Introduction

There has been increasing interest during the past 10 years in the use of ^{177}Lu for radionuclide-based radiotherapy for certain types of cancers. Accurate administrations of drugs using this radionuclide require accurate standards against which instrumentation used in the clinics and radiopharmacies can be calibrated. Several new ^{177}Lu -based radiotherapy drugs are being investigated worldwide, which will cause an even greater need for such standards.

Lutetium-177 decays with three primary β branches ($E_{\beta\text{max}} = 176 \text{ keV}$, 385 keV , and 498 keV) and has two reasonably strong γ -rays at 113 keV and 208 keV , making it suitable for analysis using a variety of techniques, including coincidence counting.

To date, the only comparison of ^{177}Lu that has been carried out was a bilateral comparison (BIPM-R(II)-K1.Lu-177) conducted between the NIST and the PTB in 2000. In this case, both laboratories were able to submit ampoules to the SIR and report activity values based on liquid scintillation counting using the CIEMAT/NIST efficiency tracing method. The results indicated a difference of about 1.4 % in the SIR equivalent activity. The short half-life of the ^{177}Lu did not allow for follow-up studies to be performed.

Since 2000, several more NMIs have standardized this radionuclide. In order to establish a link between primary standards of β -emitters in the NMIs and the SIR, as well as to provide a means for laboratories to substantiate CMC claims for β - γ nuclides, a Key Comparison of ^{177}Lu is proposed. This proposal was initiated as an Action Item arising from a meeting of the Life Sciences Working Group (LSWG) of the International Committee on Radionuclide Metrology (ICRM), held in January 2007 and endorsed by the CCRI(II) in May 2007.

The short half-life of ^{177}Lu ($T_{1/2} = 6.647 \text{ d}$) requires careful planning on the part of the participating laboratories to ensure that the measurements are made in a timely manner and that the ampoules submitted to the SIR arrive with sufficient activity.

2. Comparison Protocol

Pilot Institute: National Institute of Standards and Technology (NIST)

List of possible participants:

NPL (UK)

PTB (Germany)

IFIN-HH (Romania)

LNE-LNHB (France)

NIST (USA)

BIPM (Sèvres)

IRMM (Geel)

NMISA (South Africa) and

ENEA (Italy)

Comparison Nuclide Solution: ^{177}Lu chloride containing nominally 74 MBq at time of shipment to be dispatched by NIST

Container: NIST-style ampoule supplied by NIST, to be transferred by each participant into BIPM ampoules for submission to the SIR

Mass: approximately 5 g

Chemistry: in carrier containing $1 \text{ mol} \cdot \text{L}^{-1}$ HCl and approx. 5 $\mu\text{g/g}$ of solution non-active LuCl_3

Recommended Nuclear Data: BIPM Monographie BIPM-5, Vol 2, pp 107-112.

2.1 Schedule

Distribution: It is proposed that the solutions will be prepared and distributed to participants during the first week of March, 2009. Measurements will need to commence upon receipt due to the short half-life of ^{177}Lu . Deadline for submission of all appropriate shipping, customs, and special handling information will be 16 January 2009 (6 weeks prior to anticipated shipment date).

Based on the assumption that the sources will be distributed in early-March, the following schedule for reporting is proposed:

Reporting deadline: 1 May 2009

Draft A sent to participants: 19 June 2009

Draft A acceptance deadline: 21 August 2009

Draft B sent to participants: 25 September 2009

Draft B acceptance deadline: 23 October 2009

2.2 Measurand: **The measurand for this exercise is activity per unit mass.**

2.3 For those participants within convenient distance to BIPM, an ampoule containing 3.6 g of solution should be sent for measurement in the SIR. The NIST will also undertake to do this. Because of the short half-life of the ^{177}Lu , it is likely that the ampoules will need to be sent to the BIPM for measurement in the SIR before the participants have completed their own measurements.

2.4 The starting date for this programme is 12 January, 2009.

2.5 The NIST shall be responsible for maintaining up-to-date key comparison status reports and shall transmit them to the Executive Secretary of CCRI(II)

2.6 Each participating institution is responsible for its own costs associated with the measurements, as well those for transportation and customs and any damage that may occur within its country. The costs associated with the organization of the comparison, preparing, calibrating, and shipping the ^{177}Lu comparison solutions will be borne by the NIST.

2.7 All results, method of standardization, associated uncertainties, and any additional requested information shall be transmitted to the NIST using the reporting forms to be provided. The NIST will send a copy of its own results to the Executive Secretary of the CCRI prior to receipt of any external results.

2.8 Participants must provide a list and evaluation of the principal components of the uncertainty budget based on the Guide to the Expression of Uncertainty in Measurement, published by ISO. In addition to the principal components of the uncertainty, common to all of the participants, individual institutes must add any other components they consider

appropriate. Uncertainties are evaluated at a level of one standard uncertainty and information must be given on the number of effective degrees of freedom, required for a proper estimate of the level of confidence, where this is appropriate.

2.9 Transport of the ^{177}Lu ampoules to the participants will be arranged by the NIST using their normal radioactive shipment arrangements. Immediately after receipt, the participating institute shall check for any damage to the samples and report this to the NIST.

2.10 If delays occur, the NIST shall inform the participants and revise the schedule, if necessary.

3. Preparation of the report on the comparison

The NIST is responsible for the preparation of a report on the comparison. The report passes through a number of stages before publication, and these are referred to here as draft A and draft B.

3.1 During the comparison, as the results are received by NIST, they are kept confidential by NIST until all the participants have completed their measurements and all the results have been received, or until the deadline for receipt of results has passed.

3.2 A result from a participant is not considered complete without an associated uncertainty, and is not included in the draft report unless it is accompanied by an uncertainty supported by a complete uncertainty budget. Uncertainties are drawn up following the guidance given in the technical protocol.

3.3 If, on examination of the complete set of results, NIST finds results that appear to be anomalous, the corresponding institutes are invited to check their results for numerical errors but without being informed as to the magnitude or sign of the apparent anomaly. If no numerical error is found the result stands and the complete set of results is sent to all participants.

3.4 The first draft, draft A, is prepared as soon as all the results have been received from and, if necessary, confirmed by the participants. It includes the results, uncertainties, standardization methods and experimental details transmitted by the participants, identified by name.

3.5 Draft A of the report is sent as soon as possible after completion of the comparison to all the participants for comment, with a reasonable deadline for replies. The date at which this draft is sent to the participants is taken to be the end date for the comparison and is subsequently referred to as such.

3.6 If any controversial or contradictory comments are received by NIST, they will be circulated to all participants and discussion continues until a consensus is reached.

3.7 Draft A is considered as confidential to the participants. Copies are not given to non-participants, and graphs or other parts of the draft are not used in oral presentations at an external Conference without the specific agreement of all the participants. (The results may be

the subject of an internal report if they are shown in relative terms and the names of participants hidden. At this stage, a participant may publish experimental techniques of special interest or new developments of a measurement method made in the frame of the comparison, as long as no information or comments are made about the comparison results.)

3.8 Note that once all participants have been informed of the results, individual values and uncertainties may be changed or removed, or the complete comparison abandoned, only with the agreement of all participants and on the basis of a clear failure of the travelling standard or some other phenomenon that renders the comparison or part of it invalid.

3.9 An institute that considers its result unrepresentative of its standards may request a subsequent separate bilateral comparison with the NIST or one of the other participants. This should take place as soon as possible after the completion of the comparison in progress. The subsequent bilateral comparison is considered as a new and distinct comparison.

3.10 On receipt of final comments from participants, the second draft, draft B, is prepared by the BIPM incorporating the agreed comments on the draft A and an Appendix regarding the comparison reference value and degrees of equivalence.

3.11 As the comparison will be linked to the SIR, the KCRV (in terms of SIR Equivalent Activity) will be determined by the BIPM and the Appendix will be produced by the KCWG, including the comparison results in the SIR master file, KCRV file and equivalence files.

3.12 The draft B is circulated through the participants. Once agreed, draft B is not considered confidential and may be the subject of a publication, with the exception of the Appendix containing proposals for the reference value and degrees of equivalence.

3.13 Draft B will be sent to the CCRI(II) for review and approval.

3.14 In the event that there is disagreement concerning the results or the interpretation of the results of a key comparison, and the disagreement cannot be resolved by the participants, by the key comparison working group or by the Consultative Committee, the matter is referred to the CIPM for decision.

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