Institution: University of Surrey

Unit of Assessment: 9 Physics

Title of case study: Correcting the global radiopharmaceutical standard for Xofigo® used for the palliative treatment of bone disease in metastatic prostate cancer

Period when the underpinning research was undertaken: 2014 – 2019

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Professor Patrick Regan	Professor of Radionuclide Metrology	1994 – present

Period when the claimed impact occurred: 2014 – 2020

Is this case study continued from a case study submitted in 2014? N

1. Summary of the impact (indicative maximum 100 words)

Almost 50,000 individuals are diagnosed every year with prostate cancer in the UK, with an estimated 400,000 living with the disease (Prostate Cancer UK, 2020). The radiopharmaceutical Xofigo® is approved in more than 40 countries (European Medicines Agency, 2020) for the treatment of prostate cancer with bone metastases and has been shown to increase life expectancy and quality of life significantly (Parker et al., *N Engl J Med* 2013; 369:213-223).

Professor Regan's group at the University of Surrey and the National Physical Laboratory (NPL) led research resulting in the re-evaluation of the primary calibration standards and the resetting of calibration factors for Xofigo® in more than 3,000 clinics worldwide.

2. Underpinning research (indicative maximum 500 words)

Xofigo® (radium (Ra-223) - dichloride) is a registered palliative therapy for prostate cancer patients with symptomatic bone metastases (http://bayer.com/en/innovation/research-development-drugs). Since radium is chemically similar to calcium, it binds selectively to areas of increased cell turnover in bone metastases. At these sites, the Ra-223 active material emits alpha particles which deposit their energy over a range corresponding to between 2 and 10 cell layers. The rapid slowing down and energy dispersion of these alpha particles causes double-strand DNA breaks, leading to a cytotoxic effect on tumour cells. Xofigo® is used in more than 3,000 clinics worldwide to provide life-extending treatments for patients with metastatic castration-resistant prostate cancer (CRPC). To ensure that patients are treated with the correct dosage, detailed information on the radioactive decay properties of this material are required. The accurate measurement of radium (Ra-223) dichloride activity is assured by adjustment of dose calibrators using the National Measurements Institute (NMI) traceable reference standard, which is provided to the licensee of the drug. The absolute accuracy of the traceable standard is the first point in the calibration chain and, if incorrect, results in potentially too high or too low doses of the drug being administered.

The high-precision nuclear decay data associated with the isotope-specific radioactive signatures for Ra-223 measured by Prof. Regan's group **[R1-R3]**, underpins the provision of an absolute primary calibration standard for dose application for Xofigo® and indeed all radiopharmaceuticals. Primary calibration standards are linked directly to clinic-based sources and the related ionisation chamber calibration factors which are needed to determine the dose administered to patients. It is crucial for public and clinical confidence in the quality assurance of such treatments that the clinic-based calibration factors are directly traceable to the primary standards held at NMIs, such as the National Physical Laboratory (UK) and the National Institute for Standards and Technology (NIST) in the USA. Cross-continental measurements need to be consistent when compared with each other and any other standards held at each NMI. **If they are inconsistent, different doses of Ra-223 may be administered to patients depending on where they are being treated.**

The precision radioactive decay data generated by Prof. Regan's group **[R1-R3]** led directly to the correction of the NIST-based standard for the first alpha admitting radiopharmaceutical approved for the treatment of metastatic castration-resistant prostate cancer. As a result, the clinic-based calibration factors were revised by more than 10% following the correction of the US-based standard held by NIST (see https://www.nrc.gov/docs/ML1526/ML15264B095.pdf). When compared to the previously claimed calibration accuracy of 0.3% (https://dx.doi.org/10.6028%2Fjres.120.004), this systematic shift/error of this magnitude could have led to significant over/under dosage of Xofigo® and a significant effect on ultimate patient outcomes (https://clinicaltrials.gov/ct2/show/results/NCT02023697).

Prof. Regan's group also conducted a range of measurements to provide the absolute nuclear decay data for other related, pre-clinical radiopharmaceutical nuclides, including thorium (Th-227) **[R2]**. This is particularly important as this radionuclide is used as a generator source for Ra-223, the active material used in Xofigo® **[R1, R2]**. This work was conducted using the same experimental analysis and interpretation techniques as Prof. Regan's STFC-funded studies into the decay signatures of radioactive nuclei for absolute standardisation **[R4, R5]** and the evolution of nuclear structure with changing proton and neutron numbers (e.g. **[R6]**).

3. References to the research (indicative maximum of six references)

[R1] "Direct measurement of the half-life of 223Ra", S.M. Collins, A.K. Pearce, K.M. Ferreira, A.J. Fenwick, **P.H. Regan**, and J.D. Keightley, Applied Radiation and Isotopes **99** (2015), p46-53. Doi: 10.1016/j.apradiso.2015.02.003

[R2] "The half-life of 227Th by direct and indirect measurements", S.M. Collins, S. Pommé, S.M. Jerome, K.M. Ferreira, **P.H. Regan**, A.K. Pearce, Applied Radiation and Isotopes **104** (2015), p203-211. Doi: 10.1016/j.apradiso.2015.07.001

[R3] "Precise measurements of the absolute γ-ray emission probabilities of 223Ra and decay progeny in equilibrium", S.M. Collins, A.K. Pearce, **P.H. Regan**, J.D. Keightley, Applied Radiation and Isotopes **102** (2015), p15-28. Doi: 10.1016/j.apradiso.2015.04.008

[R4] "Radionuclide Metrology and Standards in Nuclear Physics", **P. H. Regan**, S. M. Judge, J. D. Keightley A. K. Pearce, Nuclear Physics News, 28 (2018), p25-29. Doi: 10.1080/10619127.2018.1495482

[R5] "Investigation of γ-γ coincidence counting using the National Nuclear Array (NANA) as a primary standard", S.M. Collins, R. Shearman J.D. Keightley and **P.H. Regan**, Applied Radiation and Isotopes **134** (2018) p290-296. Doi: 10.1016/j.apradiso.2017.07.056

[R6] "Half-life measurements in 164,166Dy using γ− γ fast-timing spectroscopy with the v-Ball spectrometer", R. Canavan, M. Rudigier, **P.H. Regan** et al., Physical Review **C101** (2020) 024313. Doi: 10.1103/PhysRevC.101.024313

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4. Details of the impact (indicative maximum 750 words)

Research led by Prof. Regan's Nuclear Metrology Group (Surrey-NPL), identified a major discrepancy in the existing primary standardisation of the alpha-emitting radiopharmaceutical material Ra-223. High-precision radioactive decay data generated and validated by the Surrey-NPL group **[R1-R3]** was responsible for the 2015 revision to the National Institute of Standards and Technology (NIST) standard for the use of the castration-resistant prostate cancer therapy, Xofigo®. The calibration-factor correction was initiated following the identification of discrepancies between the existing radiological standards and the underpinning nuclear decay data by Prof. Regan's group **[R1-R6]**, some **two orders of magnitude greater than the acceptable range** with regards to primary standards. In clinical trials, larger dosages of Xofigo® have been shown to lead to increased radiological progression that caused treatment to be prematurely terminated (https://clinicaltrials.gov/ct2/show/results/NCT02023697). In such instances, such a large miscalibration error could have led to significantly poorer health outcomes for patients on Xofigo®.

Correcting the global radiopharmaceutical standard for Xofigo®: Nuclear decay data measurements by Prof. Regan's group highlighted a discrepancy in the pre-existing (2008) standard for the alpha-emitter Ra-223. This prompted a thorough evaluation by NIST who, after replicating the experimental work, confirmed an approximate +10% adjustment in the absolute calibration factor from their existing (2008) standard. The high-precision nuclear decay data, generated by Prof. Regan's group, led directly to the provision of the updated, corrected, absolute primary calibration standard.

On 11 March 2015, NIST published information regarding the revised primary standard for Ra-223 resulting in a numerical increase of 10.5% for the new primary standard. **[S1, S2]** This change was only to the numerical value of the quantity of Ra-223, as the actual amount of Ra-223 in the primary standard did not change. Thus, the work conducted by Prof. Regan and the NPL Nuclear Metrology Group provided the foundation and motivation for the upgraded standardisation for the Ra-223 radionuclide by NIST. This is confirmed by the statement in **[S1]** by the NIST group (as **[S3]**): *"As a result of a discrepancy involving our published secondary standards for 223Ra brought to our attention by colleagues at the National Physical Laboratory, we have undertaken a thorough review of our 2008 work and performed two large studies to re-standardize this radionuclide that will hopefully provide an explanation for the source of the discrepancy" and "This new primary standard is based on measurements made with methods that are more robust than those available in the original 2008 experiments."* **[S1]**

In March 2015, Bayer Pharmaceuticals Ltd notified the clinical community to this change in calibration dial factor standards following the revision of the (NIST) standard **[S4, S5]**. This required a simultaneous worldwide recalibration of all devices for measuring radiation dose carried out at more than 3,000 clinics worldwide. Bayer also stated that they would increase the numerical values listed on the package label by approximately 10%. That is, the labelling of the patient dose was updated from 50 kBq/kg of body weight to 55 kBq/kg of body weight, and product documentation was updated to read 110 kBq/ml (previously 1000 kBq/ml) and 6.6 MBq/vial (previously 6.0 MBq/vial). Bayer further stated that the revised standard for Ra-223 does not change the actual amount of Ra-223 dichloride being administered to patients and will therefore not impact the safety and efficacy of Xofigo® **[S5-S7]**.

Absolute, traceable radioactivity standards are vital in retaining public confidence in the application of every radiopharmaceutical in the medical arena worldwide. The discrepancy identified by Prof. Regan's group **[S1-S8]** in the universally accepted standard for the alpha-emitter Ra-223 highlights the need for a continuous evaluation of the radiopharmaceuticals currently in use worldwide and the potential impact on the future of cancer treatments.

5. Sources to corroborate the impact (indicative maximum of 10 references)

[S1]. B.E. Zimmerman et al., Revision of the NIST Standard for 223Ra: New Measurements and Review of 2008 Data, J. Res. Natl. Stand. Technol (2015) 120, 37-57. Doi: 10.6028/jres.120.004

[S2]. Revision of NIST published dial factor of 47.5(3) corrected by D.E. Bergeron et al. Applied Radiation and Isotopes 101 (2015) 10–14. Doi: 10.1016/j.apradiso.2015.03.008; refers to **S8** work by Keightley et al., from NPL-Surrey group.

[S3]. Referred to as 'S. Collins, National Physical Laboratory, data to be published, private communication (2013)', which was subsequently published as: S.M.Collins, A.K.Pearce, P.H.Regan, J.D.Keightley, Precise measurements of the absolute γ-ray emission probabilities of 223Ra and decay progeny in equilibrium, Applied Radiation and Isotopes Volume 102, (2015) 15-28. Doi: 10.1016/j.apradiso.2015.04.008

[S4]. Letter entitled 'Xofigo®: Change in NIST Standard Reference Material' from Bayer to the Healthcare Professional Community, https://assets.publishing.service.gov.uk/media/5537a3f0e5274a1575000023/Xofigo_DHPC_sent_19_March_2015.pdf.

[S5]. Notice from the US Nuclear Radiation Commission noting NPL role in identifying incorrect standard:
'DESCRIPTION OF CIRCUMSTANCES
In 2013, NIST was made aware of studies performed by the National Physical Laboratory (NPL) (the National Measurement Institute of the United Kingdom) in which an approximately 10 percent difference was found between NPL's activities obtained using several primary methods and those obtained with the calibration factors published by NIST from 2010. Subsequently, NIST performed additional testing using more robust methods than previously available to verify NPL's results and confirmed that activity

readings were lower than expected. On March 11, 2015, NIST published information regarding the revised primary standard for Ra-223 resulting in a numerical increase of 10.5 percent for the new primary standard.'
Text taken from 'Revision to the National Institute of Standards and Technology standard for Radium-223 and impact on dose calibration for the medical use of Radium-223 dichloride' https://www.nrc.gov/docs/ML1526/ML15264B095.pdf
https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/203971lbl.pdf

[S6]. Introduction of XOFIGO© in the UK (from 2014):
'Xofigo © (radium-223 dichloride), which has been hailed as a "huge step forward" in treating prostate cancer patients, is now available for the treatment of men with castration-resistant prostate cancer who have symptomatic bone metastases.
The drug was so successful in the trial phases that it was stopped early once it became clear that the drug was effective. The drug not only enabled men to live longer but when they are taking it they have fewer side-effects and less pain, giving them a better quality of life.'
'Prostate cancer is one of the most common cancers in men in the UK. In 2010, around 41,000 men were diagnosed with the disease. On average, 10-20% of prostate cancer patients develop castration-resistant prostate cancer (CRPC) within approximately 5 years of follow up and of those almost 84% have metastatic disease at the time of diagnosis.'
https://www.royalmarsden.nhs.uk/news-and-events/news/xofigo-radium-223-launches-uk

[S7]. Description of use and applications of XOFIGO© in the UK by Prostate Cancer UK
https://prostatecanceruk.org/prostate-information/treatments/radiotherapy-for-advanced-prostate-cancer

[S8]. Identification of errors of up to 18% in previously held NIST primary standard as identified by NPL group's primary standard work and revision of dial setting on ionisation chamber to 52.35(16) i.e. 0.3% uncertainty (see J. Keightley,et al., Standardisation of 223Ra by liquid scintillation counting techniques and comparison with secondary measurements.Appl.Radiat.Isot.95 (2015) 114–121. Doi: 10.1016/j.apradiso.2014.10.009; referred to in NIST correction for primary standard in S2).