Joint WP4 & WP2 Workshop with Industry:

‘Compact Accelerators for Isotope Production’

26-27 March 2015, The Cockcroft Institute, STFC Daresbury Laboratory, Warrington UK

Outcomes of accelerators for isotope production workshop and promotion through networks

Vlad Skarda (STFC), Hywel Owen (Manchester), Dewi Lewis (Swansea)

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Workshop with industry organised jointly through WP4 (Accelerator Applications) and WP2 (Catalysing Innovation)

- **The workshop brought together industry, clinicians and academia to explore how accelerator technologies can be applied to future medical isotope production needs, including:**
  - 99mTc production methods
  - Novel compact accelerator technologies
  - Novel irradiation methods
- **The aim of the workshop**
  - **review the state of the art of novel accelerator technologies for production of radioisotopes for medicine - scientific committee**
  - **to explore future joint clinical/industrial/academic collaborative projects addressing the shortages in future radioisotope supply (KTT) – industry panel/discussion session.**
- *https://indico.cern.ch/event/366464/other-view?view=standard – programme and presentations (1)*

Promotion of the workshop (70 attendees)

- Why Knowledge and Technology Transfer (KTT) workshop with industry
  - **Knowledge/technology transfer activities help to form the links between the researchers and their institutes with industrial companies, through which the technical and scientific expertise is exchanged and ultimately transferred to industry.**
- Existing knowledge transfer networks - used to promote the workshop with industry.
  - EEN - The Enterprise Europe Network, helping small business to make the most of the European marketplace
  - HEPTech - Leading HEP technologies for industry Technology Transfer opportunities
  - STFC Innovations Club (~1500 academic and industrial members)
  - EuCARD-2 community and medical physics network (Manjit Dosanjh)
  - Targeted marketing - direct marketing and invitations

Scientific Programme Committee

- Chaired by Hywel Owen – Cockcroft Institute and University of Manchester
  - Ferrid Haddad – Arronax
  - Ulli Köster – Institut Laue Langevin
  - Dewi Lewis - University of Swansea
  - Steve Myers – CERN Office of Medical Applications
  - Alan Perkins – University of Nottingham
  - Bernard Ponsard – Association of Imaging Producers and Equipment Suppliers
  - Paul Schaffer – TRIUMF
  - Thierry Stora – CERN
- Included talks by industry, system and radioisotope manufacturers and end users (clinicians)
- There will be a separate report integrating the main points from the talk with the panel session

99mTc Background

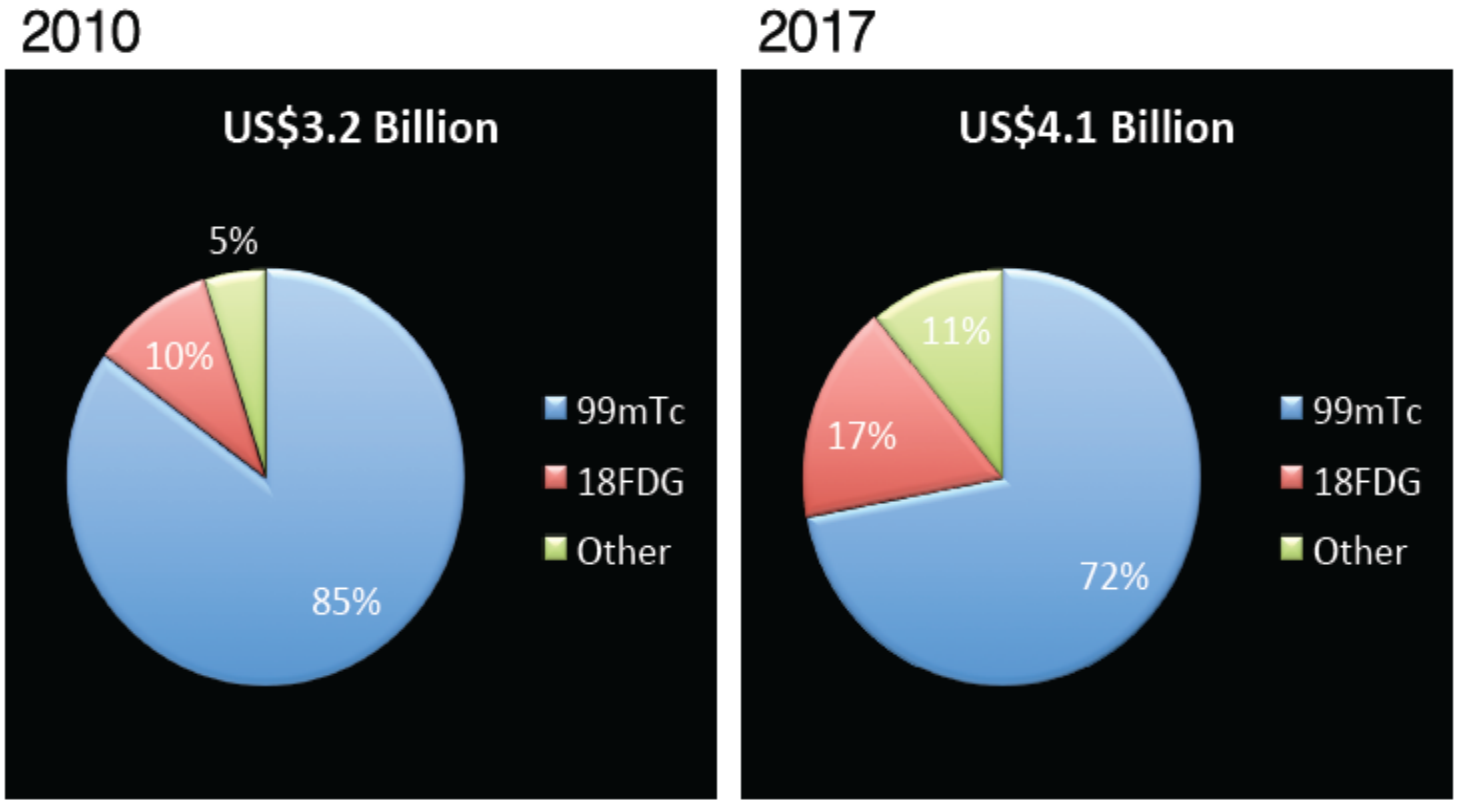
- **Hospital Imaging - Global demand 60M/year (19M USA, 21M Europe, 20 M rest of World)**
  1. Computed Tomography
  2. Nuclear Medicine (85% 99mTc)
  3. MRI

- **Technetium-99m (99mTc) - is a daughter product of molybdenum-99 and is the principal radioisotope used in medical diagnostics worldwide used in ~ 32 million procedures per year globally and accounts for 80 to 85% of all diagnostic investigations using Nuclear Medicine techniques.**

Investigation	Procedures (million)
Cardiac Imaging Tc-99m, T- 201	**12**
Bone Investigation Tc-99m	**10**
Lung Investigation Tc-99m	**5**
Thyroid, Imaging I-131 / I-123, Tc-99m	**5**

99mTc Background

Global Radiopharmaceutical Diagnostic Market (1,2,3)



1 Global Radiopharmaceuticals Market (PET/SPECT Imaging & Therapy) – Current Trends & Forecasts (2010 – 2015); MarketsandMarkets, August 2011
2 BMI - Business Monitor International Ltd, Molybdenum-99: Privatising Nuclear Medicine, Special Report 2011
3 Interim Report on the OECD/NEA High-Level Group on Security of Supply of Medical Radioisotopes, The Supply of Medical Radioisotopes, OECD 2012

Industry/Discussion Panel Members

- **Panel Members:** to explore future joint clinical/industrial/academic collaborative projects addressing the shortages in future radioisotope supply

  - Andreas Geisler - Siemens AG
  - Paul Hinton - Royal Surrey County Hospital, NHS
  - Michael Begg - Tesla Engineering Ltd
  - Jean-Michel Geets - IBA Group
  - Hywel Owen - University of Manchester/Cockcroft Institute
  - Ron Barack - Alliance Medical (Radiopharmacy Ltd)
  - Uno Zetterberg - GE
  - Paul Schaffer - TRIUMF
  - Richard Johnson - Best Cyclotron Systems
  - Bev Ellis - Radiopharmacy group, NHS Foundation Trust

- To aid the discussion and as a starting point, the panel members were asked to give their opinion on the following questions:

Industry/Discussion Panel Members

1. Introduce themselves and their position in the company
2. Outline the company's historical and present day operations in the area of accelerator production of radioisotopes including geographic territories is which the company is commercially active
3. What is the company's overall strategy for medical applications and how accelerators/ radioisotopes/radiopharmaceuticals fit into the corporate strategy?
4. What is the **market/company/R&D unmet need** that they are currently aiming to address
5. What do they consider the major market constraints to be and which are the most prominent competing technologies
6. Where and how do they manage their technology R&D and which organisations do they have collaborations with in this field
7. What kind of technologies/facilities /equipment/investment are required
8. Who within their company would be appropriate for contact any potential discussion on future collaboration
9. What recommendations could they make for better collaborations between the company, Government and academic institutions to supply the market need?

Outcomes of panel discussion

Paul Hinton - Royal Surrey County Hospital, NHS, Guildford, UK - end user of radioisotopes :

He runs a very busy centralized nuclear pharmacy in the UK servicing 13 gamma cameras, 8 PET scanners including some mobile units.

- His nuclear pharmacy operates a hub & spoke system for a radius of 50 km in the UK.
- They also supply radioisotope scientific support in this region.

His major concerns are:

- the reliability of ^{99m}Tc supply in the UK,
- the lack of new radiopharmaceuticals being developed,
- the long duration needed for developing new imaging agents,
- the perception that the pharma industry is unwilling to invest in radiopharmaceuticals.

His main requirements would be:

- the licensing of new radio-therapeutic products,
- more investment in nuclear medicine,
- the setting up of PET+SPECT production facilities.

In this case he would expect the demand for ^{99m}Tc to continue to grow

Outcomes of panel discussion

Bev Ellis – Radiopharmacy Group, NHS Foundation Trust, Central Manchester University Hospitals UK:

Their center provides pharmacy service for distances up to 120 Km.

- Bev is a council member of the British Nuclear Medicine Society.
- She is extremely concerned about the security of supply of 99mTc.

She believes:

- that new production technologies will appear,
- but the use of the $^{99}Mo/^{99m}Tc$ generator will continue in the future.

A direct Tc cyclotron facility could work in the UK.

- But the timelines to complete are unpredictably long.
- The licensing times could take years, especially if clinical trials were demanded by the Regulator.
- Abbreviated licenses may be possible as is being tried in Canada where the Regulator is trying to be extremely cooperative
- Also the reliability of production and supply would have to be well proven.
- The shelf life of direct Tc would need close attention.
- Probably shelf-life of > 12 hours would be needed.

She noted that there is no collated market data available on the usage in the UK – only several ad-hoc surveys.

Outcomes of panel discussion

Jean-Michel Geets – IBA Group, Louvain la Neuve, Belgium

IBA's strategy is in the accelerator and radioisotope market - cyclotron production since 1985 is a core business covering the current needs of PET and SPECT worlwide

- IBA Molecular is essentially a different company concentrating on radiopharmaceuticals.
- **They prefer to provide integrated services/systems using the IBA IntegraLab approach:**
- **Cyclotrons/targets / chemistry / labs**

Future market needs/developments will be solid state RF, cost efficient superconductivity

Possible market constraints are – that it is a very mature technology, the products are complex and often there are no prototypes available.

- **Accelerator produced ^{99}Mo and ^{99m}Tc are new opportunities although the supply of generators is likely to continue.**

Market trends include - no O_2 or N_2 PET usage and possibly ^{68}Ga will erode the FDG market.

- **IBA usually has to build its own test accelerators and has to perform high beam tests – often with support from academic group.**

Damien Bertrand is the primary contact for setting up collaborations, J-M Geets would also be available

- For future collaborations, it is useful to know the people concerned beforehand.
- Timing for making proposal is critical – often IBA is approached at the last minute to provide input for 'calls for proposals'

Outcomes of panel discussion

- **Uno Zetterburg – General Electric Healthcare, Upsalla, Sweden**
  - Uno comes from the company's cyclotron manufacturing section in Sweden.
  - They try to supply a broad range of products.- largest number of PET installations worldwide
  - **Their strategy is to supply a complete range of PET products worldwide including cyclotron systems and radiopharmaceuticals**
  - **cyclotron world market continues at around 50 units per year - this is now a very mature market.**
- **Their vision is to bring complete , economical and simple PET to every hospital**

They operate numerous collaborations for radiopharmaceuticals

They rely on academic partners such as TRIUMF

Their major business 'threat' is Regulatory demands for radiopharmaceuticals

- Development could take 5 to 10 years
- **The largest constraint is the burden of clinical trials that is required**

They want better links with pharma companies

- Also they need improved relationship with the Regulators, also WHO etc.

GE values participation in these workshops.

Outcomes of panel discussion

- **Paul Schaffer – TRIUMF National laboratory, Vancouver, Canada**
  - Global demand for 99Mo/99mTc ~ 40 million doses/yr
  - 76,000 scans/day (>1 scan/second)
  - **Overall, ~5 gov't owned reactors supply >95% of global demand**
  - 30-40% of global 99Mo obtained from NRU in Canada
  - **Recent reactor outages: widespread shortages, cost fluctuations**
  - **Current economic model is insufficient for long term sustainability**

  They have a long-term symbiotic relationship with Nordion worth 1 to 2M$ per year whom they consider a partner and listen for strategic directions
  - **Current goal – to demonstrate routine, reliable, commercial-scale cyclotron production of 99mTc via 100Mo(p,2n) at each site in Canada and to obtain regulatory approval**
  - Use the resulting production data to validate the business plan
  - Future production will be from variety of sources (neutron, proton, electron) and will be market driven

  They need to pursue more involvements with academic institutions and to deliver a credible 'return on investment' to Canada
- **Current challenges: Quality Control** (impurities) **- Regulatory – Economic** (activity based economic model)

Outcomes of panel discussion

- **Ron Barack – Alliance Medical (Radiopharmacy)**

  Alliance's business in the imaging segment end of the industry and in the UK, working in collaboration with Cancer Research UK

  - **Imaging network** (PET tracers cyclotron manufacture, synthesis modules, dispensing PET tracers (mainly **18FDG**, mobile scanners)
  - This is where the value of return is highest

  Their programme combines radioisotope production with the clinical imaging

  - This is a programme in transition

  They are planning, but no decision made, on ^{99m}Tc production in the UK using cyclotron production

- **Analyzing operational considerations including targets, hot cell design, separation/chemistry and additional bankers needed for shielding**

Outcomes of panel discussion

- **Andreas Geisler - Siemens AG, Germany**
  - Andreas comes from Siemens Corporate Technology Research
  - **Siemens have 30,000 employees in R&D and spend 5% of their revenue**

  The market for Siemens is in medical cyclotrons.
  - **They do not develop radiopharmaceuticals**
  - **Products often take 5 to 10 years to develop.**

  Their business strategy is to address the challenges of the ageing population and to win greater access in developing countries
  - **They have several collaborations in the UK – Huddersfield, UCL, RAL**
  - They acknowledge that they cannot cover everything
  - Most of the PET development is in Knoxville USA.

Outcomes of panel discussion

- **Hywel Owen – University of Manchester and the Cockcroft Institute**
  - UK accelerator institutes trying to contribute in their areas of expertise
  - Matching skills to commercial demands, e.g., superconducting RF, high-gradient RF, novel accelerator designs (e.g. FFAGs)

  Strategy
  - Development of test infrastructures e.g. CLARA, EMMA, ALICE
  - Strong interest in building a UK accelerator applications centre
  - Using background of HEP and light source experience, moving towards applications development, for example X-band structures for security scanning, desing of FFAGs for medicine

  He took part in the national study for ^{99m}Tc production.
  - They are moving towards more commercial type applications developments, being more collaborative and doing less high energy physics work.

Outcomes of panel discussion

Michael Begg – Tesla Engineering Ltd, UK

- Tesla is an UK magnet building company, started in 1973, now with 250 people.
- **They provide accelerators, beam lines, magnets, coils with outlets in UK, US, Netherlands and China.**

Their business strategy is to be the OEM 'supplier of choice' and concentrating on their design and production capabilities.

- A key strength is their QA and process QC systems.
- **They have produced many magnets for small cyclotrons.**

They rely heavily on their reputation and getting new ideas from outside the company.

- They need talented people who can work together on different technologies.
- They use big software packages for design – ANSYS for mechanical structure and thermal calculations and OPERA for 3D electromagnetism computations.

They often install cryogenic systems into their products.

They rely on academics for ideas and always aim for 'leading edge' design.

- They will try to establish IP.

The main growth area is still in Europe and also with superconducting magnets.

Outcomes of panel discussion

Richard Johnson - BEST Cyclotron Systems, USA

- BEST started as a small North American company supplying sources and measurements systems
- **Today it is a large international company supplying many products including several cyclotron models**
- Ease of operation, Optimize energy of cyclotron and design for application, **Integrate targetry and radiochemistry**

Team Best supplies radioisotope production systems. Production targets, Radiochemical separation , Target material and target reprocessing , Site design licensing

Strategy

The company's strategy is to provide complete patient treatment facilities based on radiotherapy which still remains largely unmet around the world

- **This means combining nuclear medicine imaging with radiotherapy**
- Diagnostics and treatment care
- Dementia is a big problem
- They are keen to involve external experts

^{99m}Tc is a big opportunity, also ^{68}Ga will be widely used and they have a cyclotron model suitable for producing ^{82}Sr

99mTc – themes arising from the discussion

- There are systematic problems in the global supply chain for medical radioisotopes as 99Mo is at present produced exclusively in a small number of research nuclear reactors (from the fission of uranium-235 targets) most of which are >40 years old and some may cease production permanently at the end of 2015 and 2016 respectively
- **The economic model of medical radioisotope production is poorly developed** (difficult to recover the full cost of developing any new radiopharmaceutical to the level of marketing authorisation)
- The model of cyclotron-based manufacture of 99mTc from 100Mo is one that is being developed and evaluated e.g. in Canada and requires high-energy cyclotrons and investment in infrastructure
- **The radionuclidic purity of cyclotron-produced 99mTc is reasonably well understood**. Small amounts of 93Tc, 94mTc, 94Tc, 95Tc, and 96Tc impurities may be present in variable amounts
- **The position relating to the regulatory approval** of cyclotron produced 99mTc radiopharmaceuticals is unclear
- The radioactive waste implications of routine cyclotron production of 99mTc have not been quantified

Preliminary Conclusions

- **Accelerator technologies can potentially meet the demand of 99mTc, at least as a viable alternative to generators (**cyclotrons with sufficient energy > 19MeV are required)
- **This production route suits well to existing network of PET centres and medical cyclotrons in general, in spite of technological and regulatory challenges (**switch from cyclotrons tailor-made for massive 18F productions in big centres to smaller cyclotrons for point of demand full range of isotopes productions adapted to small hospitals)
- **In contrast to Canada, Europe has not invested substantially to progress this field as yet.**
- **Overall there is strong interest in developing very low energy accelerators for single patient PET doses, using a range of technologies – conventional & superconducting, magnets, RFQ accelerators, electrostatic generator etc.**
- The workshop was highly valued by all participants and contacts have been provided for the participants looking for future collaboration in this area
- **There will be a written report made publicly available where the detailed answers (also from the questionnaires) will be integrated with the presentations and the knowledge in the public domain to provide a concise document on the outcome of the discussions which took place at the workshop** (following the approval by all panel participants)

Thank you