Decision Making And Clinical Nuclear Medicine

A PHARMACIST’S PERSPECTIVE

Mark Soffing  PharmD, MBA, MS, RPh, BCNP

soffing.apha@gmail.com

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In order to make this presentation more substantive, I have included a number of supporting slides in the presentation available on-line that we will not have time to cover today. I trust you will find this useful.

The slides actually covered today will be noted by an asterisk ( * ) in the Title.
Objectives

Upon completion of this activity, the participant will be familiar with:

- Current trends in nuclear pharmacy in the US, Canada and Europe.
- Impact of regulatory agencies
- Economic impact on nuclear medicine.
- Changing landscape of radiotracers: Are there more on the horizon?

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Topics for Discussion

- Tracer Availability and Cost
  - Supply Chain, etc

- Regulatory Issues
  - NARM
    - Decommissioning
    - Radiation Protection & Exposure Limits
  - FDA
    - Critical Path
    - Drug Approvals
    - Regulation of PET Agents

What remains on the Horizon?
Isotope shortage threatens millions of medical diagnostic tests

Hospitals and clinics in the U.S. are preparing for a shortage and a price increase of medical isotopes after the Chalk River nuclear reactor in Ontario, Canada, was temporarily shut down for repair. The reactor is one of only five in the world that supply molybdenum-99 used in many diagnostic tests for cancer, heart disease and other illnesses. "About 8 million of our studies are imperiled because that reactor is offline," SNM President Robert Atcher said.

Source: SNM SmartBrief
Historical Timeline for US $^{99}$Mo Supply

- 1967 - MURR begins production of $(n, \gamma)$ Mo-99 for Mallinckrodt Nuclear Co.
- 1977 - MURR increases Mo-99 production for MediPhysics Inc.
- 1984 - MURR ceases Mo-99 production.
- 1980 - Cintichem, Inc. begins production of fission product Mo-99 and is the single U.S. supplier.
- 1989 - Cintichem reactor develops leak and is closed.
- 1991 - DOE purchased Cintichem technology, equipment and DMFs for production of Mo-99, I-125, X3-133.
- 1991 - DOE identified Omega West Reactor at LANL as proposed backup supply facility and constructs processing facility.
- December 1992 - Omega West Reactor at LANL develops leak and is closed.
- Until 1993, two Canadian reactors, operated by Atomic Energy of Canada Limited (AECL) at the Chalk River site (located about 100 miles from Ottawa, Canada), were available to produce Mo-99.
- 1996 – DOE selects Annular Core pulse reactor at Sandia National Lab. to become backup supply facility and constructs processing facilities. Project never completed.
- 1998 – Canadian MAPLE reactors were scheduled to open, but remain shutdown today due to fundamental design flaw.
- 2006 – MURR initiates efforts to become supplier of Mo-99.
- 2008 – Decision made to discontinue work on MAPLE 1 & 2.
* Worldwide $^{99}$Mo Production

- Canada NRU
- Belgium BR2/ Mol
- France Osiris/ Orphee
- Netherl. HFR/ Petten
- South Africa Safari I/ Pelindaba
- Australia OPAL/ Lucas Heights
- Brazil IEA-R1
- India/ Cirus
- Dhruva
- Indonesia
- GA Siwabesyy MPR
- Korea
- Hanaro
- Peru
- RP-10
- Russia/ IR 8
- WWR-M

Laboratories

- Canada Tyco Healthcare/ Petten
- Netherlands IRE/ Fleurus
- South Africa NTP/ Pelindaba
- Australia Ansto
## Major Facilities for Mo-99

<table>
<thead>
<tr>
<th>General Informations</th>
<th>MDS Nordion</th>
<th>IRE Fleurus</th>
<th>Mallinckrodt Medical</th>
<th>Necsa/NTP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Country</strong></td>
<td>Canada</td>
<td>Belgium</td>
<td>Netherlands</td>
<td>South Africa</td>
</tr>
</tbody>
</table>
| **Research Reactor for target irradiation** | 1. NRU (Canada)  
(2. Maple I and II (Canada)) | 1. BR-2 (Netherlands)  
2. Osiris (France)  
3. HFR (Netherlands)  
4. HFR (France)) | 1. HFR (The Netherlands) | 1. Safari I (South Africa) |
| **Capacity (% of world demand)** | 40%[^1] | 20%[^1]-30%[^2] | 25%[^1] | 10%[^1]-15%[^2] |
| **Production[^3]** | 5000 – 6000Ci/batch (several batches per week) | 10 000Ci/week | 10 000Ci/week | 8000Ci/week |

[^1]: Henri Bonet and Berbard David; National Institute for Radioelements (IRE) - Fleurus - Belgium and Bernard Ponsard; Nuclear Research Centre (CEN-SCK) - Mol - Belgium; Production of Mo\(^{99}\) in Europe: Status and Perspectives, ENS RRFM 2005; Transaction Session 1, 9\(^{th}\) International Topical Meeting; Research Reactor Fuel Management; April 2005

[^2]: Charles D. Ferguson, Tahseen Kazi, Judith Perera: Commercial Radioactive Sources: Surveying the Security Risks; Occasional Paper No.11; Monterey Institute of International Studies, Center forNonproliferation Studies; January 2003

[^3]: IAEA-TECDOC 1051; Management of radioactive waste from \(^{99}\)Mo production; November 1998
* ⁹⁹Mo Production With HEU Targets

Nuclide has impact on nuclear arms control:

- Danger of nuclear proliferation through use of nuclear weapons material HEU (highly enriched uranium)
  - Reactor fuel
  - Target material
- Interference with verification of the CTBT (Comprehensive Nuclear-Test-Ban Treaty)
- 95-99% of all ⁹⁹Mo is produced by irradiation of highly enriched uranium (HEU) targets
- less than 5 % of the global ⁹⁹Mo production is derived from the irradiation of low-enriched uranium (LEU) targets

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Conversion from HEU to LEU

- IAEA Coordinated Research Projects (CRP) “Production of Mo-99 Using LEU Fission or Neutron Activation”
- Provide interested countries with access to non-proprietary technologies and methods to produce Mo-99
  - using LEU foil or LEU mini-plate targets
  - utilizing \((n,\gamma)\) neutron activation, e.g. through the use of gel generators

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## Non-HEU Technologies for Mo-99

<table>
<thead>
<tr>
<th>LEU Technology</th>
<th>Origin of technology</th>
<th>Potential producers</th>
<th>Current/future production scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEU dispersion plate targets</td>
<td>CNEA (Argentina) (initiated by ANL)</td>
<td>CNEA (Argentina) ANSTO (Australia)</td>
<td>Small/large</td>
</tr>
<tr>
<td>LEU foil target and modified Cintichem process</td>
<td>BATAN (Indonesia) (initiated by ANL)</td>
<td>USA (MURR), Romania, Chile, Pakistan, Libya</td>
<td>Small/large</td>
</tr>
<tr>
<td>Gel-technology (activation of Mo)</td>
<td>India</td>
<td>Kazakhstan, Romania</td>
<td>Small/medium</td>
</tr>
<tr>
<td>Homogenous reactors</td>
<td>USA (initiated by ANL)</td>
<td>BWXT (USA)</td>
<td>None/large</td>
</tr>
</tbody>
</table>
N A R M ?

“Naturally-occurring & Accelerator-produced Radioactive Material”

10 CFR Part 170--Fees for Facilities, Materials…

A new fee category 3.S. has been proposed which would include fees for production of accelerator-produced radioactive material.

This would include PET Nuclear Pharmacies.

– Application fee $5,100; and Annual license fee $11,600

– NRC anticipates ~25 new applications will be received for this new 3.S category
NRC & Radiation Protection

- Revise and achieve alignment with 2007 International Commission on Radiological Protection (ICRP) recommendations found in Publication 103; effectively lowering the occupational dose limit to 2 rem (20 mSv) per year.

- Accept that Advisory Committee on Reactor Safeguards (ACRS) continue to provide adequate protection of the health and safety of workers, the public, and the environment.
NRC & Decommissioning Cost

- Letter of Credit
  - Example: Self shielded negative ion cyclotron
    12 MeV > $150,000-500,000
  - Price depends on the State
- Impacts company’s ability to borrow to some degree
- Does not require actually depositing money into an account (that is also acceptable to NRC)
- Bunker style cyclotrons—more expensive
- Washington University JSW and CS-15 positive ion cyclotrons, located in vaults remote from personnel
  - > $500,000-600,000 each
**United States Pharmacopeia (USP) Chapter <797>**

**Aseptic Technique**

The technique for manipulations of compounded sterile products and parenteral preparations that prevents contamination.

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Why do we give medications parenterally?

- Patients who are not able to take medications by mouth
- Need for rapid action of the medication as in emergency situations
- Medication not available in a suitable dosage form to be given by mouth
- Patients with difficulty absorbing medications
* Importance of Aseptic Technique

– Parenteral administration bypasses the skin and gastrointestinal tract, the body’s natural barriers to infection.

– Giving a patient a contaminated product can cause serious adverse effects including DEATH.

– Parenteral medications account for >40% of all medications administered in institutional practice.
Gowning Up for Patient Safety

Does This Outfit Make Me Look Heavy?
Environmental Conditions

Must have a buffer area or anteroom

Air quality ISO Class 8 (class 100000)

ISO class 5 environment for the preparation area

Inlaid ceiling panels impregnated with a polymer (impervious and hydrophobic)
  - Caulked around each perimeter to seal to support frame.
  - Lighting fixtures to be smooth, flush mounted and sealed

Preparation for cleanroom gowning:
  - Remove Outer jackets, Makeup, Jewelry.
  - Scrub hands and arms to the elbow

Non shedding uniform
  - Knee length coat fitting snugly at the wrist; zip or snap closure
  - Coveralls fitting snugly at the wrist, zip or snap closure

Shoe covers, Hair covers, Face Masks, Gloves (powder free)
Definitions

Contamination – any effect or action that has a negative impact on a product's integrity making it unfit for use

- Chemical composition
- pH
- Sterility (e.g. microorganism contamination)
- Pyrogenicity
- Biological or therapeutic potency
- Physical appearance
- Particulate matter (e.g. dust, glass or precipitation)
Sources of Product Contamination

- People (most common)
  - Touch contamination
  - Generation of particulates from shedding cells or hair
- Supply air
  - Heating Ventilation and Air Conditioning (HVAC)
- Infiltration
  - Particles from adjacent spaces (e.g. anteroom)
- Internal generation
  - Walls, floors, ceilings, packaging, equipment

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*When does FDA get involved?*

- **Preclinical (voluntary) phase**
  - animal testing
  - Pre-IND guidance:
    - Subpart E, Fast Track, Orphan designations
- **Clinical development phase**
  - IND
- **NDA review**
- **Marketing phase**
  - ADR surveillance
  - new uses, product changes, withdrawals
How does FDA guide drug development?

- Written guidances
  - Regulations, guidelines (incl. ICH), guidances
  - Regulatory letters
  - (Statute, Congressional Reports)
- Face-to-face meetings
  - Pre-IND, EOP2a, EOP2, as-needed
- FDA Advisory Committee meetings
- Podium presentations

1 Website - www.fda.gov
What comprises FDA guidance?

- Standards
  - chemistry and manufacturing controls (CMC)
  - preclinical animal toxicology requirements
  - ethics of human clinical trials
  - documentary requirements for INDs, & NDAs
  - Electronic records (21 CFR part 11)
- Clinical trials
  - safety
  - effectiveness
  - trial design
How many guidances / are they binding?

GUIDANCES
(http://www.fda.gov/cder/guidance.htm)
- 344 guidances (final/draft, FDA/ICH), 3/31/00

Guidance documents:
- Cannot legally bind FDA or the public
- Recognizes value of consistency & predictability
- Because a company wants assurance

Staff will apply statute & regulations consistently
## Industry Pipeline Estimates: An Abundance of Molecules

### New Drug Activity - Products in Clinic or Filed

<table>
<thead>
<tr>
<th>Company</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSK</td>
<td>113</td>
</tr>
<tr>
<td>Sanofi+Aventis</td>
<td>98</td>
</tr>
<tr>
<td>Pfizer</td>
<td>84</td>
</tr>
<tr>
<td>Novartis</td>
<td>65</td>
</tr>
<tr>
<td>Roche</td>
<td>52</td>
</tr>
<tr>
<td>Merck</td>
<td>44</td>
</tr>
<tr>
<td>BMS</td>
<td>36</td>
</tr>
<tr>
<td>AZN</td>
<td>32</td>
</tr>
<tr>
<td>Lilly</td>
<td>28</td>
</tr>
<tr>
<td>Abbott</td>
<td>26</td>
</tr>
<tr>
<td>Bayer</td>
<td>24</td>
</tr>
<tr>
<td>Takeda</td>
<td>22</td>
</tr>
<tr>
<td>S-Plough</td>
<td>17</td>
</tr>
</tbody>
</table>

### The Critical Path Conundrum: Managing the Portfolio

*SG Cohen March 2004*
Where Have All the New Drugs Gone?

“FDA cleared just 17 NMEs in 2002, the lowest number since 1984. Total NMEs approved in 2005 was 18, the worst tallies in a generation.”

“FDA approved 39 NMEs in 1997; no fewer than 7 of these drugs were subsequently withdrawn from the market”
More Spending

Less Apparent Productivity and Innovation

10 Year Trends in US Biomedical Research Spending

10 Year Trends in Number of Approvals of New Molecular Entities by FDA
* Reasons for Poor Productivity

- The easy drug therapies have already been discovered and developed
- Genomics and Proteomics
  – many new targets not well understood…yet
- High throughput screening – too many highly selective drug candidates?
  - promise of selective therapy not yet realized
- Public expects absolute safety and promised efficacy

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Reasons for Poor Productivity

- Regulators demanding more evidence of safety and efficacy
- Regulators mandating tighter quality standards in manufacturing, analysis, data management, patient privacy
- Costs of drug development keep rising
- Business demands on return on investment not compatible with long-term investment in drug development
- Shortage of patients for some clinical trials extend timeframes
The Problem: Predictability

How to select the few “winners” from the abundance of new molecules coming out of discovery?

– Failure rate is 40% in phase 2 for drugs completing phase 1

Why do many promising molecules fail for lack of effectiveness in phase 3?

– Failure rate is 50% in phase 3 for drugs completing phase 2

Data from Dr. Peter Kim, President of Merck, PhRMA, and McKinsey & Co.

“...if accomplished, the new tests and tools developed under the critical path initiative will modernize the drug development process by 2010…”

Safety Medical Utility Industrialization

Note: PhRMA, BIO and 21 Patient Groups Signed on to Support Critical Path
* What is the “Critical Path”?

- There is a “critical path” stretching from candidate identification to commercial product.
- Involves serial evaluation of product performance through preclinical testing and clinical evaluation.
- FDA’s Critical Path Initiative focuses on the science used for these evaluations.
FDA Critical Path Initiative

Regulatory Opportunities & Challenges of Imaging as a Drug Development Tool

1. Imaging is a key technology for assessing, accelerating the development of, and guiding the use of new therapeutic options

2. The Agency believes that synergy between current drug development programs and current imaging techniques can be created for drug development to work in a more cost effective manner.
Driver for Industry to Seriously Commit to Critical Path Concepts

“We are an industry with a 98% failure rate.....The only thing we have to do to double our success rate is to drop our failure rate by 2%”

Hank McKinnell, Pfizer CEO, at http://www.bio-itworld.com, 2/14/06
Guiding Principles of Critical Path

- Collaborative efforts among government, academia, industry and patient groups
- Infrastructure and "toolkit" development
  --- not product development
- Build support for academic science bases in relevant disciplines
- Build opportunities to share existing knowledge and databases
FDA Expectations for PET

- Result of over 10 years of consideration of the issue.
  - FDA timing of the proposal reflects increasing numbers of PET drug production facilities and PET imaging facilities.
- While FDA has established product-specific cGMPs for other industries—thermally processed low-acid foods in hermetically sealed containers and acidified foods—this is the Agency’s first foray into type-specific drug cGMPs.
- FDA has proposed to apply different requirements for investigational and research PET drugs.
  - Allows greater flexibility in the production of these drugs, many of which will not have commercial potential.
**PET cGMP Overview**

- Part 212 generally applicable to all PET drug products for human use, FDA has proposed to apply different requirements for investigational and research PET drugs.
  - Allows greater flexibility in the production of these drugs, many of which will not have commercial potential.
  - IND and research PET drugs would meet cGMP by adhering to USP 28 Chapter <823>
    - Provisions are generally less specific and explicit than the proposed requirements.
    - Proposal for comment requesting public & industry feedback for more appropriate standards to apply to IND and research PET.
* Exploratory IND: Improves Efficiency

- Exploratory IND studies enable faster, cheaper route to clinic - but not necessarily faster, cheaper route to market
- FDA may be more enthusiastic than industry (again)
- Microdose strategy has limitations, but popular in EU
- Sub-therapeutic dosing studies may provide more value
  - Particularly for early-stage biotech companies
# PET Products on the Horizon

<table>
<thead>
<tr>
<th>IMAGING OPPORTUNITY</th>
<th>AGENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncology (Renal Cancer)</td>
<td>Iodine-124 cG250</td>
</tr>
<tr>
<td>Oncology (Apoptosis)</td>
<td>Fluorine-18 Aposense</td>
</tr>
<tr>
<td>Neurology (Alzheimer’s)</td>
<td>Fluorine-18 AV-45</td>
</tr>
<tr>
<td>Cardiology (Myocardial Perfusion)</td>
<td>Fluorine-18 BMS747158</td>
</tr>
<tr>
<td>Bone</td>
<td>Fluorine-18 NaF</td>
</tr>
<tr>
<td>I-124Iodide</td>
<td>Iodine-124 NaI</td>
</tr>
</tbody>
</table>

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Topics for Discussion

Again, if much of this seemed to sound like barriers to progress,

PLEASE FORGIVE ME !!!!!

The government will be expanding to meet the needs of an expanding government…
What Can We Do?

- In order to study HEU, detailed information would be required.

- Unfortunately, companies and governments are very cautious in providing any data
  - Protect proprietary interests in light of a highly competitive isotope production market
  - General sensitivity of the nuclear industry regarding public scrutiny.

- Information about national demand for molybdenum-99 is pivotal. Since this is the most widely used medical isotope, the amount of irradiated HEU / LEU could be estimated from its consumption rate.
What Can We Do?

Do We Need ICRP Alignment?

- **YES**: When changes to NRC regulations may be merited;
- **NO**: When a technical basis exists for instances where exceptions to ICRP Publication 103 continue to be appropriate;

Submit comments that our regulatory framework for radiation protection is sound.
What Can We Do?

- Recognize that FDA clinical guidances are increasingly based on *principles of clinical pharmacology*
- Understand distinction between FDA “guidance” and “regulation”
  - value added vs barrier
  - national “treasure” vs “national nuisance”
- Value of FDA guidance is related to the quality of sponsor data and preparation
- Thoughtful Filing of that IND / NDA / ANDA
  - “biologic” vs “drug” vs “PET drug” vs “generic”
- Product lifecycle & cost-erosion protection
What Can We Do?

- Read FDA proposals and draft guidance and send any written comments your organization has, if you choose to do so, to FDA by the comment due dates.
- When submitting comments, please be specific.
- State if you are for or against the proposed or direct final rule, and why.
- Use reasoning, logic, and good science.
What Can We Do?

- Ensure all comments are relevant.
- State why the rule is inappropriate.
- Provide a challenge to the rule’s underlying premise or state why the rule is ineffective or unacceptable.
- Issues should be serious enough to warrant a substantive response from the agency, and should sufficiently challenge the agency’s view that the rule is needed.