



FDA's Regulatory Role in Medical Isotope Production

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What's FDA's Role in this?

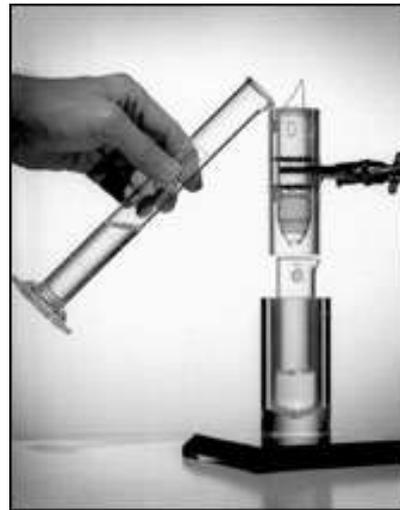
In 2007 the National Academy of Sciences (NAS) asked this question of FDA. There was confusion regarding FDA's regulatory requirements when switching from Highly Enriched Uranium (HEU) to Low Enriched Uranium (LEU) and other non-HEU methods for the manufacturing of medical isotopes.

Medical Isotope Production Without Highly Enriched Uranium- 2009



The Mo99/Tc99m Generator

- Developed in 1958 by the national labs.
- Came into wide spread medical use in the early 1960's.
- Mo99/Tc99m passes through column with “pure” Tc99m coming out



Regulation of Medical Radioisotopes

- Regulated by the Atomic Energy Commission (AEC) until 1975.
- In 1975 the AEC split into:
 - the modern day NRC, and
 - the Energy Research and Development Administration (ERDA), which later evolved into today's Department of Energy
- Since 1975, the regulatory oversight of all radiolabeled drugs is shared with the FDA.
- The licensed possession of the radioactive material remained an NRC statutory authority.

Food, Drug and Cosmetic Act (FDCA) - 1906

Statutes, codified as chapters, encompass a wide range of medical and consumer products, such as drugs, biologics, electronic product radiation, medical devices, and food processing.

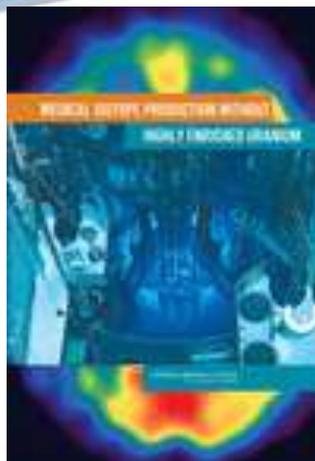
Product safety and efficacy are our concerns.

FDA consists of: (1 of 2)

- **Center for Drug Evaluation and Research (CDER) – Radiopharmaceuticals**
- **Center for Devices and Radiological Health (CDRH) – Medical Devices – accelerators, brachytherapy sources, etc.**
- **Center for Biologics Evaluation and Research (CBER) – Blood Irradiators**
- **Center for Food Safety and Nutrition (CFSAN) – Food irradiators**

FDA consists of: (2 of 2)

- **Center for Veterinary Medicine**
- **National Center for Toxicological Research**
- **Center for Tobacco Products**
- **Office of Regulatory Affairs – FDA’s field operations -
Inspections**



- Surprisingly accurate in predicting 2012 use of Tc99m (~14.9 million procedures in the US in 2012!)
- Missed the target in other areas.
- But this is the nature of such predictions and estimates, and is not intended as a criticism, as much as a warning that we must regard such estimates with respect, but also with a high degree of skepticism and uncertainty.

Table 5.1 Historical and Forecast- NAS 2009

	Total Nuclear (millions)	% Growth	Tc-99m procedures (millions)	Tc 99m % of Total NM	Growth Rate % Tc 99m	Tc 99m (millions)	Growth Rate % Tc 99m
- 2002	14.1	6.7	10.2	72.2	5.4	17.7	8.7
- 2003	15.3	8.3	10.7	70.0	5.0	19.1	8.0
- 2004	16.1	5.4	11.1	68.6	3.2	20.2	5.9
- 2005	16.9	4.7	11.3	66.8	2.0	21.1	4.6
- 2006	17.7	4.7	11.7	66.0	3.5	22.1	4.5
- 2007	18.7	5.8	12.1	64.5	3.4	23.0	4.0
- 2008	19.8	6.0	12.6	63.5	4.4	24.3	5.5
- 2009	21.1	6.4	13.2	62.7	5.0	25.7	6.1
- 2010	22.4	6.1	13.8	61.5	4.2	27.1	5.3
- 2011	23.8	6.3	14.3	60.2	3.9	28.5	5.1
- 2012	25.3	6.3	14.9	59.1	4.3	30.0	5.2

- NOTES: Data on procedures and doses are rounded from the original source. The 2002–2005 data are historical estimates; 2006–2012 data are forecast estimates.
- SOURCE: Bio-Tech Systems (2006, Exhibit 1-10).

My interpretation of results

- Over estimated growth of positron emission tomography (PET).
- Unexpected recession.
- The complexity of using alternative tests.
- The dynamics of evidence based medicine and reimbursement policies.

Alternative Tests are not simple substitutes for Tc99m.

- NM procedures (Th-201, Rb-82, N-13 ammonia)
- Fluoroscopic Angiography (real time X-ray imaging of heart)
- Computed Tomography Angiography (CTA)-emerging cardiac imaging procedure
- Magnetic Resonance Angiography
- Ultrasound
 - Doppler
 - Intravascular Ultrasound
- Non-Imaging Tests (Patient Risk factors, EKG, blood tests, etc.)

There was serious concern and confusion over FDA's regulatory requirements.

- Some predicted FDA delays of months and years due to conversions from HEU!
- Some predicted FDA would require clinical trials!
- The committee was confused, and predicted delays of: **“4 months and as long as 18 months depending on the quality of the application and issues raised by the FDA during the review process.”**

Experience to date

- Several DMFs for Mo-99 production have been reviewed and accepted within one week of submission.
 - DMFs are normally reviewed only when referenced as part of an application, not sooner.
 - **Mo99 DMF's, however, are reviewed upon receipt.**
 - DMFs are reviewed to determine whether they are acceptable to support a particular use, they are not approved or disapproved.
- There have been similar experiences with supplements to NDA's (sNDA), a more substantive document than a DMF. Ultimately the review times really depend on the scope and quality of the submission.

DHHS' presence here is to further clarify our Regulatory Mission Relevant to Mo99

- Tomorrow FDA's Ravi Kasliwal will discuss Tc99m drug quality and purity issues as related to current good manufacturing practice (cGMP).
- After my presentation Dan Duvall of the Centers for Medicare and Medicaid (CMS) will discuss Q9969 and other reimbursement issues.
- If nothing else, I hope you come away with an appreciation that this is a complex subject, with difficult and uncertain answers, and future predictions should be treated with a healthy skepticism.

Regulations, Research, Approval, and the Drug Master File (DMF)

- Research Phase for a drug involves the
 - Investigational New Drug Application (IND)
- NDA: New Drug Application
- sNDA: Supplement – changes to an NDA, (amendments describe IND changes).
- DMF- Drug Master File

Regulations relevant for medical isotope manufacturing?

**TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER C--DRUGS: GENERAL**

PART 210 CURRENT GOOD MANUFACTURING PRACTICE IN MANUFACTURING, PROCESSING, PACKING, OR HOLDING OF DRUGS; GENERAL

21 CFR PART 211 CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS

Research

Can take many years!

- Preclinical (Animal studies)
- Phase 0 – Microdosing human trials (may not always require an IND)
- **IND (Phase I, II, III)- Should only take 2- 4 years!**
- Phase IV Trials – Post market studies after approval

The clinical trial must scientifically demonstrate efficacy and safety.

- Clinical Research under an Investigational New Drug (IND) Application
 - Phase I- Safety “n ~ 20 – 80”
 - Phase II- Efficacy “n < several hundred”
 - Phase III- Large scale studies for benefit – risk, dosing, and physician labeling information
 - “n ~ several hundred to several thousand”

Timeline for a New Drug Application (Biological License Application)

- **NDA or BLA review process takes:**
 - 6 – 10 months (statutory)
 - **Fast Track Options Exist for new drugs where no such drug exists**

**If a drug is approved in another country
what is its status in the US?**

**FDA approves drugs for use in the U.S.
independent of whether or not that drug has
been approved elsewhere in the world.**

Fees*

Application Fee for NDA ~ \$1.8 M
Without clinical data ~ \$920 K

These statutes are upgraded periodically. Exceptions exist, e.g. fee can be waived for Orphan Drugs, and until recently there was no fee for generic drugs.

***Prescription Drug User Fee Act (PDUFA), we now have user fees for Medical Devices (MDUFA), and the Generic Drug User fee Act of 2012 (GDFUA)**

Reasons for a Drug Master File

- Maintain confidentiality of proprietary information.
- Permit review of information by reviewers at FDA to support applications submitted by more than one applicant, e.g. Company A and Company B may receive Mo99 from same Reactor C.

Drug Master File

“A Drug Master File (DMF) is a submission to the Food and Drug Administration (FDA) that may be used to provide confidential detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drugs. The submission of a DMF is not required by law or FDA regulation. A DMF is submitted solely at the discretion of the holder.”

How does this apply in our situation?

For Mo-99, a drug master file (DMF) may be filed for how it is produced, including the composition of the target material, the irradiation process, and the chemical separation of the Mo99 from the irradiated uranium target material. This is considered proprietary information.

A DMF may be amended when this information changes, e.g. when converting target material from highly enriched uranium (HEU) to low enriched uranium (LEU). If the DMF is already part of an approved NDA, the change must be submitted as a supplement to the NDA (sNDA).

Access to the DMF is through a Letter of Authorization (LOA)

- The LOA grants two things:
 - Grants FDA authority to review the DMF.
 - Grants the authorized party the right to incorporate the information in the DMF by reference into their overall manufacturing process.
- The DMF normally will be reviewed **ONLY** when it is referenced in an application.
- FDA is currently reviewing Mo-99 associated DMF's immediately upon receipt, with review times on the order of weeks, depending on quality of submission.

For additional information

- Go to www.fda.gov
- Search on “Drug Master File”, or any other subject...

and pay close attention to Ravi Kasliwal’s presentation tomorrow afternoon.

Questions and Answers

For additional questions you may email
Orhan.Suleiman@FDA.HHS.GOV



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Supplemental Slides for any questions that
may arise

How much does a Tc99m procedure cost?

- Total reimbursement is about \$700 range.
 - Physician fee ~\$300 - \$400
 - Everything else is bundled ~\$300 - \$400
 - Radiolabeled drug = Radioisotope + drug (kit)
- Current Federal Supply Schedule Costs for Mo99/Tc99m Generators is on the order of a few dollars 10 mCi of Tc99m.
 - 1 Ci (~\$1100), 10 Ci (~\$3000), 18 Ci(~\$5000)
- To encourage preferential procurement of non-HEU Tc99m, in January, 2013, CMS (Centers for Medicare and Medicaid Services) started reimbursing \$10 per procedure for using non-HEU Tc99m. The CMS code is Q9969.

How many production runs must a manufacturer perform to demonstrate manufacturing quality?

....the Food and Drug Administration (FDA) supplemental New Drug Application approval process requires three full-scale production runs of Mo-99 on the equipment that will be used for commercial production.

Examples of the testimony given to the NAS committee?

“A consultant.....who has long experience with the FDA approval process estimated it would take a minimum of about 4–6 months after submission of the necessary paperwork and cost about \$84,000 to obtain approval for using Mo-99 from a new LEU-based process at the MURR reactor (MURR, 2006).”

“A current Mo-99 producer told the committee that not all FDA approvals require long lead times. This producer obtained emergency approval of a backup Mo-99 supply in less than a week.”

What is Q9969?

- In January, 2013, reimbursement code for additional \$10 reimbursement by CMS (Centers for Medicare and Medicaid Services) for using non-HEU Tc99m.
- This is an extra \$10 in addition to the normal reimbursement for the entire imaging exam, which costs about \$700 range.
- Current Federal Supply Schedule Generator Costs:
1 Ci (~\$1100), 10Ci (~\$3000).18 Ci (~\$5000)

“Perhaps the most striking aspect of the presentations was the vast difference in what industry representatives expected from the FDA—a complex, tedious, expensive, and unpredictable process—and the simple, straightforward, and readily achievable approval process described by the FDA presenter.”*

*NAS 2009

Further confusion

“It is especially difficult for the committee to see how the FDA would ever require clinical trials as part of an sNDA for a new Mo-99 source. Clinical trials would be a useless exercise in any case because they can be used to detect only gross adverse drug effects.”*

*NAS 2009

In General, the report was accurate, addressing the uncertainties they were dealing with!

“If LEU-based Mo-99 can be produced with similar chemical characteristics similar to HEU-based Mo-99—and current experience in Argentina and Australia indicates that it can—it is hard for the committee to see any rational basis for expectations of substantial delays in FDA approvals if producers submit high-quality sNDAs and work with FDA staff throughout the approval process.”*

How much does a Tc99m procedure cost?

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 - Physician fee ~\$300 - \$400
 - Everything else is bundled ~\$300 - \$400
 - Radiolabeled drug = Radioisotope + drug (kit)
- Current Federal Supply Schedule Costs for Mo99/Tc99m Generators is on the order of a few dollars for 370 MBq (10 mCi) of Tc99m.
- The drug portion of the Tc99m- labeled drug, using an FDA approved “kit” varies depending on the drug.
- To encourage preferential procurement of non-HEU Tc99m, in January, 2013, CMS (Centers for Medicare and Medicaid Services) started reimbursing \$10 per procedure for using non-HEU Tc99m. The CMS code is Q9969.