Manufacturing Regulations for Imaging Radiopharmaceuticals in the United States

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An overview of the US regulatory environment for radiolabeled drugs

• Nuclear Regulatory Commission and Agreement States
• The Food and Drug Administration
• Research
  • Preclinical
  • Clinical Trials
• Marketing Approval
  • New Drug Application (NDA)
  • Manufacturing
• End User Ultimately Determines Drug Use
Radiolabeled drugs (Medicines) are regulated by more than one Agency in the United States.

• The Nuclear Regulatory Commission (NRC) licenses the possession and use of Radioactive material, or you may be licensed by one of 37 agreements states which have been delegated their authority by the NRC.

• The Food and Drug Administration (FDA), separate from the licensing of this radioactive material, must authorize these medical products (drugs or devices) for use in research, and before they can be marketed for sale in the United States.
Thirty Seven (37) NRC Agreement states license radioactive material rather than the NRC.
Nuclear Regulatory Commission

- Originally created as the Atomic Energy Commission (AEC) in 1954.

- The NRC licenses the possession and use of radioactive material, specifically source material, special nuclear material, and by-product material. Naturally occurring radionuclides such as radium were not regulated until recently, when the NRC was given authority for radium and other non-reactor produced but hazardous radionuclides.

- In 1963 the FDA began to require premarket approval of drugs following the thalidomide disaster, but FDA allowed the AEC to continue to regulate radiolabeled drugs.

- In the early 1970’s the FDA assumed the medical authority for radiolabeled drugs, as the AEC was reorganized into the NRC and the Energy Research and Development Administration (ERDA). ERDA later evolved into today’s Department of Energy.
FDA consists of multiple Centers: (1 of 2)

• Center for Drug Evaluation and Research (CDER) – Drugs, including all cancer drugs, and imaging drugs

• Center for Devices and Radiological Health (CDRH) – Radiation emitting electronic products, Medical Devices, and radiopharmaceuticals such as Y-90 microspheres.

• Center for Biologics Evaluation and Research (CBER) – Biologics, Blood products, Vaccines

• Center for Food Safety and Nutrition (CFSAN) – Food
FDA consists of:
(2 of 2)

• Center for Veterinary Medicine

• Center for Tobacco Products

• Office of Regulatory Affairs – FDA’s field operations - Inspections
Radiopharmaceuticals are not all regulated by the same Center

• Drugs, whose effect is chemical, such as the recent cancer therapeutic Ra-223 (Xofigo), and all of the imaging drugs are approved by CDER.

• Biologics, which occur naturally within the human body, such as antibodies are licensed by CBER. The CD-20 monoclonal antibodies for non-Hodgkins lymphoma, Bexxar (I-131) and Zevalin (In-111/Y-90), were originally approved by CBER, but that authority has since moved to the Oncology office in CDER.

• Some radiopharmaceuticals are considered medical devices because their effect is considered physical, such as Y-90 labeled microspheres for liver cancer. These are approved by CDRH.
FDA is responsible for human subject research associated with medical products

• Clinical research cannot be performed in the United States without prior approval by the FDA.

• The research must involve Institutional Review Boards.

• The research may be conducted under an Investigational New Drug (IND) application, a Radioactive Drug Research Committee (RDRC), or CDRH’s Investigational Device Exemption (IDE).

• Exemptions exist for certain types of studies, such as those not intended for new indications.
An Investigational New Drug (IND) application must have a sponsor

• The National Institutes of Health (NIH) is a major sponsor of research, along with industry sponsors.

• Individual researchers may also be sponsors.

• Not all research is conducted for eventual medical product approval, sometimes the research is simply for the sake of basic science.
The clinical trial must scientifically demonstrate efficacy and safety.

- Preclinical (Animal studies) before first in humans
- Phase 0 – Microdosing human trials (RDRC or eIND)

**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”

Phase IV- Post approval studies
New Drug Application (NDA)
(Go to: www.fda.gov and search on “NDA”)

NDA includes information such as, but not limited to:

Data from animal and clinical studies,
labeling information,
manufacturing information to ensure drug quality and purity,
chemistry, manufacturing and control (CMC) information,
pharmacokinetics, microbiology, statistics, etc.
New Drug Application (NDA) Deadlines
(Go to: www.fda.gov and search on “NDA”)

Within 30 days of filing an application FDA either accepts the application, or returns the application with a Refuse to File (RTF) determination. An RTF may actually save the sponsor time and money over the long run, but in the short term it is often a serious wake up call which identifies serious flaws in the application.

If the NDA is accepted, the application fee is cashed, and the review process begins.

A decision must be made by FDA within 6 months, although there is some flexibility in the process.

If the review proceeds satisfactorily, an inspection of the manufacturing site(s) is conducted prior to the final decision.
Accelerated Approval

• The drug must provide a benefit for a serious or life-threatening condition which lacks satisfactory alternative treatments.

• A surrogate endpoint must strongly suggest the product works.

• Final approval will depend on additional ongoing clinical studies.

• Sponsors usually voluntarily withdraw the product when the additional trials fail. In a 2011 oncology advisory committee meeting, it was reported that 10% of AA’s failed to confirm the benefit.
Imaging Rules
Regulations and Guidance

• Imaging Regulations 21 Code of Federal Regulations (CFR) Part 315 Diagnostic Radiopharmaceuticals

• FDA Imaging Guidances (voluntary standards)
  
  • Developing Medical Imaging Drug and Radiological Products Part 1: Conducting Safety Assessments (June 2004)
  
  • Developing Medical Imaging Drug and Radiological Products Part 2 Clinical Indications (June 2004)
  
  • Developing Medical Imaging Drug and Radiological Products Part 3 Design, Analysis, and Interpretation of Clinical Studies (June 2004)
  
• Clinical Trial Imaging Endpoint Process Standards (Guidance for Industry) DRAFT March 2015
Imaging: A Diagnosis or a Measurement

Diagnostic Accuracy depends on readers, their training, ROC analyses

Measurements will require:

A specific measurement protocol!

Standardization of the Imaging equipment and scan technique (SPECT, PET, X-ray, CT, MRI, US), which, in my opinion, is often not standardized.

Accurate, and precise measurement of the amount of drug (contrast agent or radiolabeled drug) administered.

Knowledge of the patient’s size, which will also affect the imaging metrics.
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.
These statutes are upgraded periodically (5 years), fees upgraded annually. Fees vary for medical devices and generic drugs. Exceptions exist, e.g. fee can be waived for Orphan Drugs (≤ 200K people).

*Prescription Drug User Fee Act (PDUFA), Medical Devices User Fee Act (MDUFA), and the Generic Drug User fee Act of 2012 (GDFUA)
Current Good Manufacturing Practice (cGMP) PET Guidance

- Go to: www.fda.gov
- Search on: PET CGMP
- Click on: PET Drugs-Current Good Manufacturing Practice (CGMP)
Which are the appropriate diagnostic tests for cardiac imaging? PET, SPECT, X-ray, MRI, US?

- NM procedures (Tc-99m, Th-201, Rb-82, N-13 ammonia)
- Fluoroscopic Angiography (real time X-ray imaging of heart)
Which are the appropriate diagnostic tests for cardiac imaging? PET, SPECT, X-ray, MRI, US?

- Computed Tomography Angiography (CTA) - X-ray cardiac imaging procedure
- Magnetic Resonance Angiography
- Ultrasound
  - Doppler
  - Intravascular Ultrasound
Which are the appropriate diagnostic tests for cardiac imaging? PET, SPECT, X-ray, MRI, US?

- Non-Imaging Tests (Patient Risk factors, EKG, blood tests, etc.)
Evidence based medicine - is a decision making process where the optimal decision for the patient is made based on science. Referral criteria or Appropriate use criteria are examples of this type of decision making process.

Value based medicine also considers cost and what value it will give the patient, will it make a difference?

This is timely today, because everyone’s role in medicine is undergoing transformational change.
Which tests are performed depends on many variables.

• Access: Local office, clinic, or hospital and which equipment and support staff?
• Which tests (imaging or non-imaging) will provide essential information?
• Radiation dose considerations?
• How much will it cost?
• Value of the test?
Thank You

If you have any questions, I will be here entire week...

or you can contact me, Orhan Suleiman, at:
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Additional Slides
Abstract (1)
Dx Tests and Costs in US (3)
Drug Master File (4)
How many production runs? (1)
Gallium Generator (1)
Abstract

The overall regulatory responsibilities of the US Food and Drug Administration will be presented, with emphasis on drug (medicine) approval, and specific emphasis on radioactive drugs. In the United States medical products cannot be marketed without prior FDA review. Imaging technology requires approval or clearance of medical devices, and a separate approval of the imaging drugs. These often require review by both the Center for Devices and Radiological Health, and the Center for Drug Research and Evaluation. One area of emphasis is manufacturing quality, and most recently the FDA established current good manufacturing practices for positron emission tomography (PET).
# Trends in Diagnostic Imaging*

1996 - 2010

<table>
<thead>
<tr>
<th>Modality</th>
<th>1996</th>
<th>2010</th>
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<tbody>
<tr>
<td>CT</td>
<td>52</td>
<td>149</td>
</tr>
<tr>
<td>MRI</td>
<td>17</td>
<td>65</td>
</tr>
<tr>
<td>US</td>
<td>134</td>
<td>230</td>
</tr>
<tr>
<td>NM</td>
<td>32</td>
<td>21</td>
</tr>
<tr>
<td>PET</td>
<td>0.24</td>
<td>3.6</td>
</tr>
</tbody>
</table>

Number of Annual Exams in the United States

• Computed Tomography (CT)* ~ 67 million
• Conventional R/F* ~ 293 million
• Interventional Fl* ~ 17 million
  ~4.6 million cardiac procedures
• Nuclear Medicine* ~ 18 million
  ~ 80% Tc99m = 14.4 million

• MRI** ~ 27-39** million
• Echo/Ultrasound** ~ 122-140** million

** Estimates for 2006 and 2010 using Smith-Bindman data, adjusted with NCRP CT data and Smith-Bindman CT/MRI and CT/US ratios.
What do these exams cost*?

<table>
<thead>
<tr>
<th>Exam</th>
<th>Physician</th>
<th>Hospital</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT 75574</td>
<td>$114</td>
<td>$222</td>
<td>$336</td>
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<tr>
<td>Fluoroscopy 93454</td>
<td>$259</td>
<td>$2587</td>
<td>$2846</td>
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<tr>
<td>MRI 75563</td>
<td>$143</td>
<td>$1154</td>
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<td>Ultrasound 93312</td>
<td>$102</td>
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<td>$696</td>
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<td>PET 78492</td>
<td>$89</td>
<td>$1311</td>
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<tr>
<td>SPECT 78452</td>
<td>$77</td>
<td>$1154</td>
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</tr>
</tbody>
</table>

*Centers for Medicare and Medicaid Services Database
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.
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.
These generators which produce positron emitters for PET imaging, are not approved for use in the United States, although there is ongoing clinical research.

A recent NRC issue addressed concerns that the potential up front NRC decommissioning financial deposits could be a barrier for obtaining an NRC license.