# FDA Activities Promoting Mo-99 Production From non-HEU Processes

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# Introduction

- FDA Committed to Ensuring Availability of Tc-99m for Imaging Studies
- FDA Committed to Ensuring Safe, Effective and High Quality Isotopes
- FDA Committed to Fostering Transition from HEU to non-HEU for Production of Mo-99

# Food And Drug Administration (FDA)

- Estimated that it regulates 25% of every US dollar consumer spent every year
- Mission Statement:
  - The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation. The FDA is also responsible for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable; and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health.
- Websites:
  - FDA Homepage: http://www.fda.gov/
  - About the FDA: http://www.fda.gov/opacom/hpview.html

# Center for Drug Evaluation and Research

- Promotes the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of human drugs in a timely manner

- Protects the public health by ensuring that human drugs are safe, effective and high quality

# Medical Isotope Production and Regulation

- FDA regulates medical isotope drug products and the "active ingredients" and precursors
  - Regulate the radionuclide production
    - eg Tc-99m generator and Mo-99
  - Regulate drug product production
    - eg Tc-99m sestimibi kit
- FDA needs sufficient data to support new manufacturing processes

# *FDA role in facilitating domestic supply of $^{99}$Mo*

# FDA Role in Facilitating Domestic Supply of Mo-99

- Expedite all regulatory submissions and requests for advice meetings

  -Example – approval of LEU derived moly in days – involved Drug Master File (DMF) pre-submission

- Communicate clear regulatory expectations to permit early submissions and speedy review
- Encourage Diversification of Mo-99 Sourcing/Technologies

# FDA Role in Facilitating Domestic Supply of Mo-99

- Coordinate with other Gov't Agencies
  - Office of Science and Technology Policy
  - National Nuclear Security Administration
  - Nuclear Regulatory Commission
  - Organization for Economic Cooperation and Development/NEA/HLG-MR
- Collaborate Internationally with other Drug Regulatory Agencies
  - Health Canada
  - European Medicines Agency

# *Regulatory submission and review processes*

# Regulatory Submission Process

- pre-NDA (New Drug Application) meetings, IND (Investigational New Drug), NDA, ANDA (Abbreviated New Drug Application), post approval supplemental submissions
  - Pre-submission discussions encouraged
    - Development programs could be streamlined
  - IND submission for development program
  - A/NDA submission for marketing approval
  - Post approval submissions – changes to product process or controls
    - Prior approval required – major changes
    - Changes being effected – minor changes

# Regulatory Submission Process

- Existing New Drug Application (NDA)
  - Supplement existing NDA
  - Approval of “new” sourced Moly-99
  - Moly-99 manufacturing information
    - Contained in NDA
    - Contained in Drug Master File (DMF)
- New NDA
  - Include manufacturing information in NDA
- ANDAs – none thus far

# Regulatory Submission Process

- Submission process for LEU and New Technologies the Same
  - Data requirements may be greater for new processes due to different impurity profiles
  - Potential for different biodistribution may require additional data
  - Human Factors Assessment may be Needed for New Technologies Requiring New Manipulations and Labeling

# *Submission examples: information expected*

# Submission Examples

- New NDA

  -New technologies

  - Non-uranium derived Mo-99 requiring new generator design and use – labeling for safe use
  - Mo-99 derived from old or new technologies from new manufactures

- Supplemental Submissions

  -Prior approval

  - New target design/fabrication, irradiation site

  -Changes Being Effected

# Submission Example
# HEU to LEU Conversion

- Target fabrication and Specification
  - Composition, dimensional specs, acceptance criteria, etc.
- One irradiation run (may include separate targets)
- Irradiation parameters (thermal neutron flux,comparative flux if alternate site, bombardment time, temperature, etc.)
  - with target and ranges
- Placement of targets in reactor core & associated levels of neutron flux
- Size and composition of the target, e.g., how it will compare with commercial size
- Number of targets in reactor port
- Transport hold-up time and conditions

# Submission Example
# HEU to LEU Conversion

- Separate purification runs
- Specifications of Mo99 (also include radionuclidic purity profile, radionuclidic impurities, etc.)
  - European Pharmacopeia Monograph Specs
  - Note that Mo-99m from New Technologies may need different/additional specification due to impurities

# Submission Example
# HEU to LEU Conversion

- Three generator runs (including generator size depending
- Generator sizes (e.g., 1, 3, 5 Ci, or other appropriate size - bracketing

# Considerations for Irradiation Processes and Production

- Reconstitute 3 commonly used radiopharmaceutical kits (we recommend anionic, cationic and neutral) with eluate from one of the generator runs, and test for
  - Radiochemical characteristics, e.g., radiochemical purity.
  - Of the kits chosen, include at least one from the more demanding types.

# Considerations for Non-Irradiation Processes and Production

- Cyclotron
  - Define cyclotron energy level
  - Target fabrication
    - Moly enrichment
- Irradiation parameters
- Purification process
- Moly-99 qualification
  - Kit performance

# *Conclusion*

- Availability and stability of supply of $^{99m}$Tc:
  *Critical to public health*
- FDA actively monitors drug shortages:
  http://www.fda.gov/Drugs/DrugSafety/DrugShortages/default.htm
- FDA submission, review processes:
  - Communicative, cooperative, collaborative @ each step
  - Provide ample guidance:
    http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064979.htm

***Least burdensome, most timely approach to maintain product supply, safety, and effectiveness***

Thank You

Questions

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