FDA Regulatory Update on Mo 99 produced by LEU and Novel Technologies

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Outline

- FDA regulates medical isotopes
- FDA facilitates Mo 99 LEU processes and non-HEU technologies
- FDA assessment process for LEU and non-HEU technologies
- Xe 133 and I 131 considerations
- Conclusion

Food And Drug Administration (FDA)

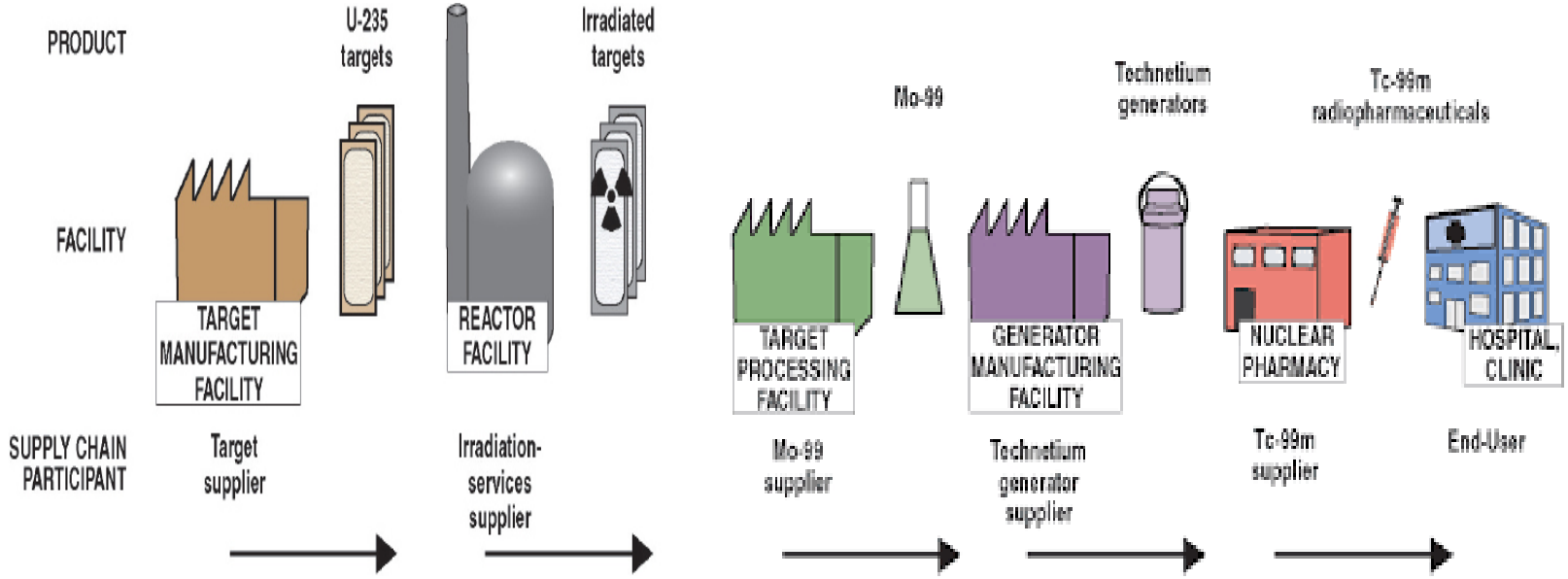
- Mission Statement:
  - The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation. The FDA is also responsible for advancing 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.
- Website:
  - FDA Homepage:
  - About the FDA: http://www.fda.gov

Medical Isotope Production and Regulation

- FDA regulates medical isotope drug products and the "active ingredients" and precursors
  - Regulates the radionuclide production
    - e.g., Tc-99m generator and Mo-99
  - Regulate drug product production
    - e.g., Tc-99m sestamibi kit
- FDA needs sufficient data to support new manufacturing processes

FDA's role in facilitating LEU technologies and domestic supply of ^{99}Mo

Mo 99 production from U 235: complex, fragile, global supply chain



National Academies of Sciences, Engineering, and Medicine. 2016. *Molybdenum-99 for Medical Imaging*. Washington, DC

FDA's 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

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FDA's 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

Radiogenix Approval 2018

505(b)(2) NDA: technetium 99 (Tc 99m) generator

- Significance of approval action
  - ↑ Tc-99m availability for use in medical imaging
  - 1st non-uranium source of Mo 99
  - 1st domestic source of Mo 99 in 30 years
- Achievements
  - innovations to achieve microbiologic and pharmaceutical quality assurance
  - inter-agency collaboration (DOE, NNSA, NRC)
- Public health benefits
  - ↓drug shortages, ↓nuclear proliferation risks

Regulatory submission and review processes

Regulatory Submission Process

- Pre-IND (Investigational New Drug), NDA (New Drug Application) meetings, IND NDA, ANDA (Abbreviated New Drug Application), post approval supplemental submissions
  - Pre-submission discussions encouraged
    - Development programs could be streamlined
  - IND submission for development program –*"INDs for Phase 2 and Phase 3 studies"*
  - **A/NDA submission for marketing approval**

  21 CFR 314.50

  21 CFR 314.50 (d) (1) Chemistry, Manufacturing and Controls section
  - Post approval submissions – changes to product process or controls
    - Prior approval required – major changes
    - Changes being effected – minor changes

    https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances

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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 Examples

- 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

User Manuals

- New technologies may include complex instructions for the end user. Safe use and delivery of the accurate dose consistent with clinical practice are critical
- Human Factors Studies account for end user ability to consistently and safely perform system manipulations according to labeling to deliver the drug
- Training and certification of end users may be necessary for complex technologies
- Interdisciplinary review of User Manuals for complex systems and Novel Technologies

Submission examples: information expected

Production of radionuclides

Technologies: Cyclotron, high energy accelerator, nuclear reactor, generator

Target → Radionuclide

- Include in the NDA application, or cross-reference a Type II Drug Master File for complete CMC information and supporting data.
  - Nuclear reaction describing the formation of daughter radionuclide from its parent
  - Decay modes, principal radiation emission and half-lives of the parent and daughter radionuclides.
  - Chemical form and composition of parent radionuclide - specifications.

Qualification Process

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

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

Comparability assessment Mo 99 *HEU to LEU Conversion or Novel Technology

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

*HEU: High Enriched Uranium

Comparability Tc 99m generator

- Three generator runs (including generator size) Generator sizes (e.g., 1, 3, 5 Ci, or other appropriate size – bracketing)
- USP Monograph for Na Tc 99m O_4
- Note that Sodium Tc 99m Pertechnetate solution derived from Mo 99m produced from New Technologies may need different specification due to impurity profile

Additional Considerations for Na Tc 99m O_4

- 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, radiolabeling efficiency
  - Of the kits chosen, include at least one from the more demanding types
  - Novel technology of Mo 99/Tc 99m includes successful reconstitution of all FDA approved, commercially available kits

Additional Considerations

- Available information on geographical location of ore/mine (starting material)
- Available information on mineral composition
- Risk assessment and levels of impurities after target processing in NDA applications

Radiolabelled drugs/New Technologies

- Comparability protocols in NDA applications: CMC(Quality) review includes drug product, microbiology, manufacturing facilities assessment
- Approval of a comparability protocol in a NDA application or PAS, facilitates implementation of new technology or manufacturing at multiple sites. Manufacturing data to support the technology from each site may be submitted as “Changes Being effected” if the manufacturing site is cGMP compliant. Facility assessment is re-evaluated at the time of submission.

Current Technetium Tc 99m Generators

- Contain Mo 99 produced from U-235
  - By 2021, approved processes to obtain Mo 99 from Low Enriched Uranium (LEU)
  - Short shelf life (2 weeks)
  - Leachables and microbiology assurance not significant challenges

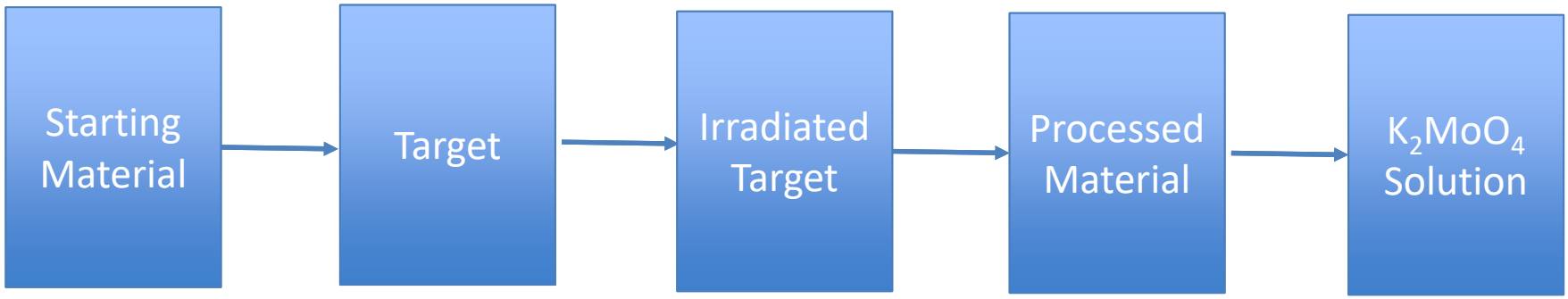
Novel Tc 99m generator (RadioGenix System)

- Is considered a generator and is classified as a drug (21CFR 310.3(n)).
- Is a complex generator that produces technetium Tc 99m injection, USP form **non-Uranium produced** Molybdenum 99 (Mo 99).
- Automated computer controlled system
  - Pumps, valves, fluid lines, shielded areas, reagents and control electronics (computer)
- Long "shelf-life" (re-certification date)
  - Unlike traditional Tc 99m generators may be eluted repeatedly for 1 year
  - Microbiology assurance a critical quality and safety attribute of Sodium Tc 99m Pertechnetate (Na Tc 99m O_4)

Potassium or Sodium Molybdate Mo 99

- Prepared domestically by novel process
- Prepared from Natural Mo 98

$^{98}Mo\ (n,\gamma)\ ^{99}Mo$



Summary: Public Health Benefits

- Enhance availability of Tc 99m for diagnostic use
  - strengthen, diversify Mo 99 supply chain
  - re-establish domestic sources of Mo 99
- Minimize threats of nuclear proliferation
  - advance non-uranium based manufacturing processes
  - progress also made on shift from high-enriched (weapons grade) to low-enriched uranium

Fission products, Xe 133 and I 131

- Xe 133 gas is used in lung ventilation
- Production information may be included in a DMF Type II (e.g., LEU Mo 99 process) or in the application
- Three production runs and isolation

I 131 products

- Approved as a diagnostic and Na ^{131}I to treat thyroid cancer and iobenguane ^{131}I to treat paragangliomas and pheochromocytomas
- Production process in a DMF Type II or in the application
- Non-fission technology
- Three production runs
- Three successful radiolabeling runs for radiolabeled I 131 products

Conclusion

- Availability and stability of supply of ^{99m}Tc, ^{133}Xe, ^{131}I :
  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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