

Submission and Approval of Molybdenum-99 (Mo-99) Information to Food and Drug Administration (FDA)

Molybdenum-99 Topical Meeting
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Ravindra K. Kasliwal, Ph.D.
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD

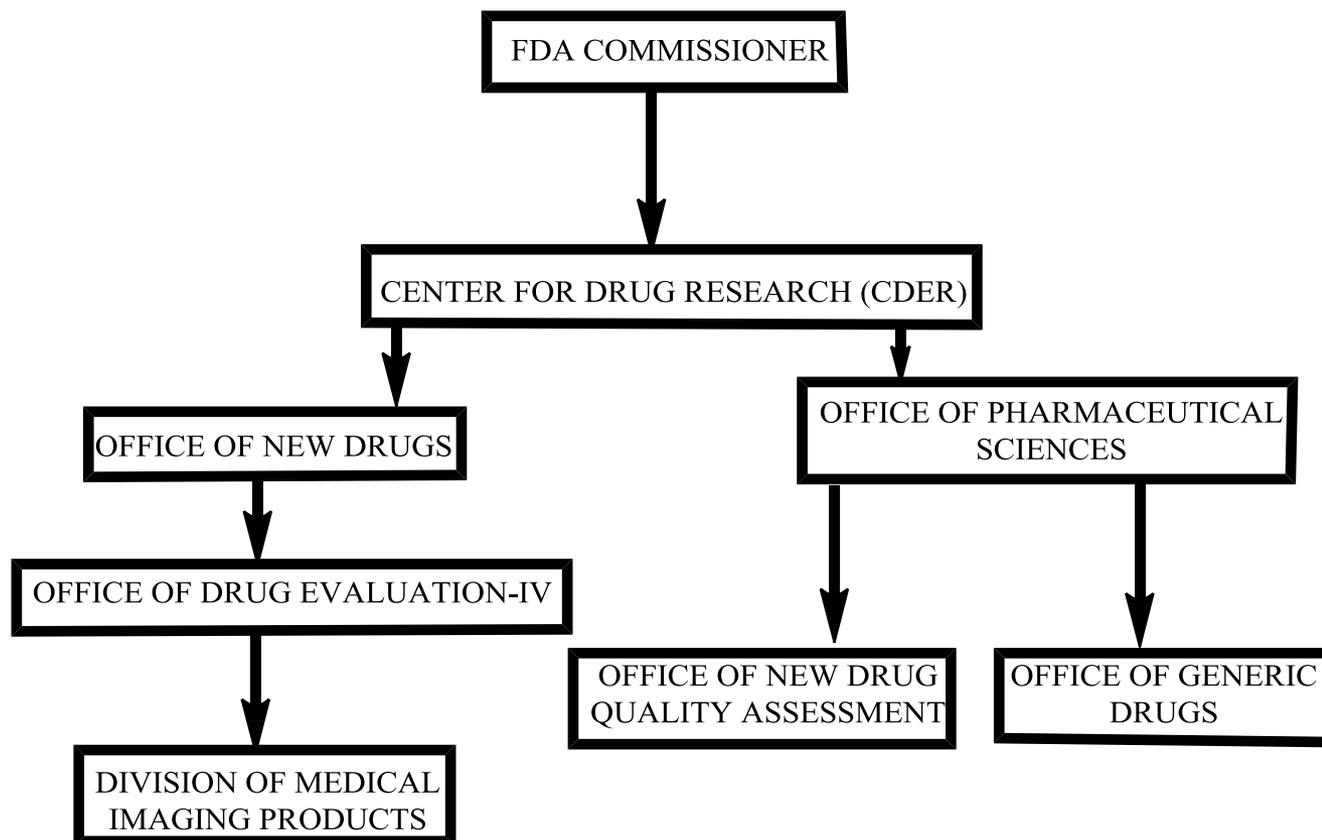
Objectives

- FDA/CDER Overview
- Molybdenum-99 [Mo-99] Production
 - Relationship to Technetium 99m (Tc 99m)
- Regulatory Process for Approval of
 - Mo-99
 - Technetium Tc 99m Injection
- Submission Process
- Communication

Food and Drug Administration (FDA)

- 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.
- FDA is also responsible for advancing the public health by helping to speed innovations that make medicines more effective, safer, and more affordable and by helping the public get the accurate, science-based information they need to use medicines and foods to maintain and improve their health.
- FDA Website: www.fda.gov
 - For Consumers and Patients
 - For Health Professionals
 - For Scientist and Researchers
 - For Industry

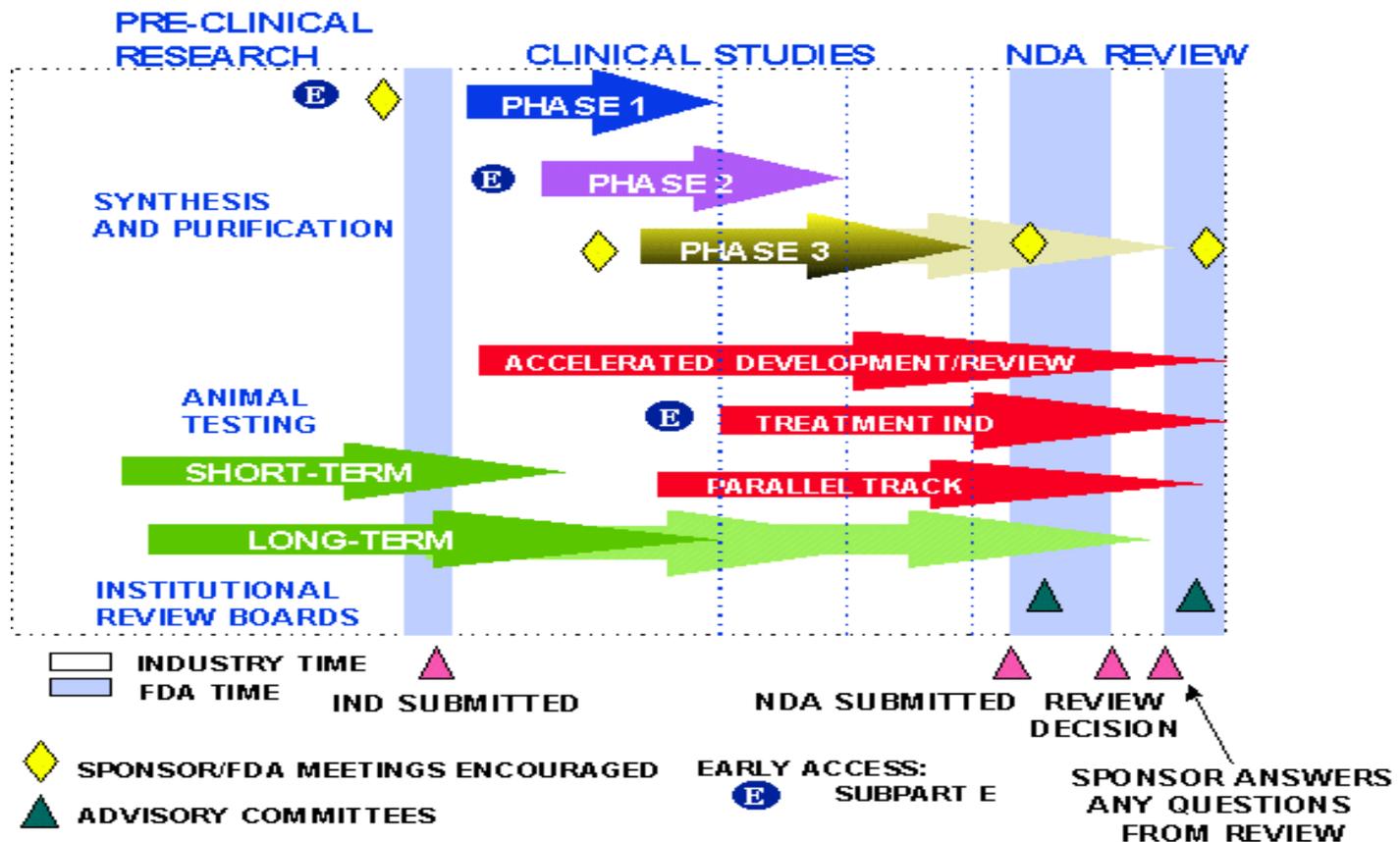
Human Drug Quality Assessment in FDA



Center for Drug Evaluation and Research (CDER)

- Promote and protect public health by assuring that safe and effective drugs are available to Americans.
 - Minimize risk while maximizing benefit
 - Promptly and efficiently reviewing clinical drug research and taking appropriate action on the marketing of human drugs in a timely manner.
- Activities are authorized by Food, Drug and Cosmetic Act.
- Regulates:
 - Product approvals
 - Drug manufacturing standards including the current Good Manufacturing Practice (cGMP)
 - OTC and prescription drug labeling
- CDER Web site: <http://www.fda.gov/Drugs>
 - Guidance and drug information

New Drug Development and Review Process



Medical Isotope Production and Regulation

- FDA regulates medical isotope drug products.
- Drug - Identity, strength (potency), quality and purity that has been shown to be safe and effective.
- Regulates the methods used in, or the facilities or controls used for manufacture, processing, packing, or holding of a drug.
 - Regulates radioactive drug products, active ingredients and precursors (intermediates)
 - Regulates the radionuclide production
 - e.g. Tc 99m, Mo-99
 - Regulate drug product production
 - e.g. Tc 99m sestamibi kit
- FDA needs sufficient data to support that new manufacturing processes does not affect product quality and purity.

Tc99m Vs Mo 99

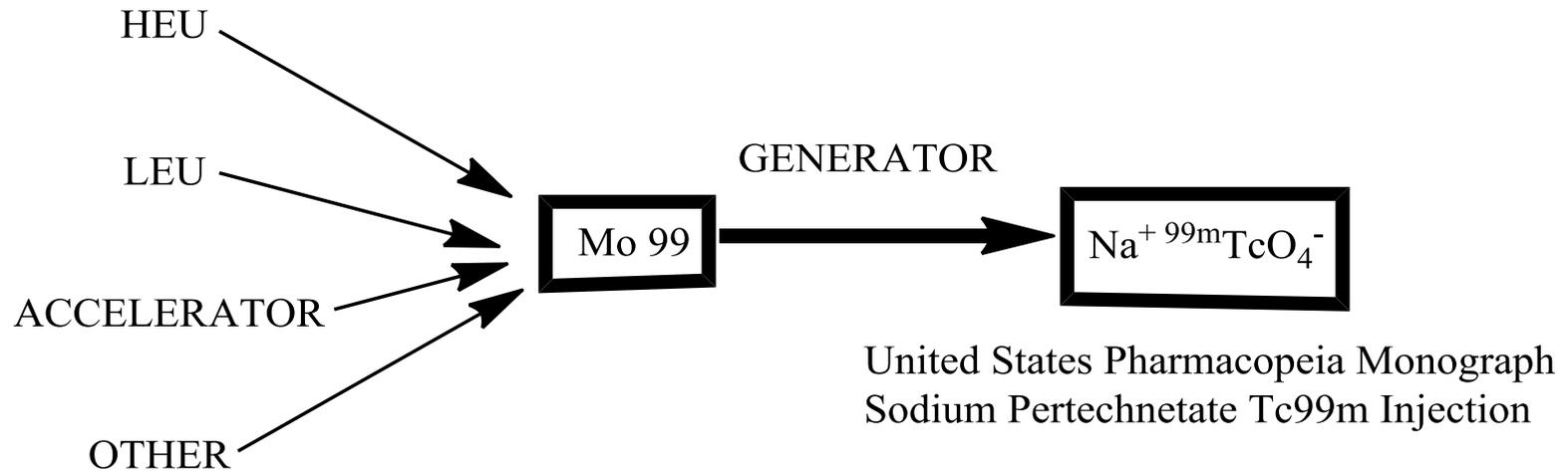
- Approved drug products are Tc 99m drugs (Drugs @FDA)
 - [TECHNECOLL](#) (TECHNETIUM TC-99M SULFUR COLLOID KIT)
 - [TECHNELITE](#) (TECHNETIUM TC-99M SODIUM PERTECHNETATE GENERATOR)
 - [TECHNESCAN](#) (TECHNETIUM TC-99M OXIDRONATE KIT)
 - [TECHNESCAN GLUCEPTATE](#) (TECHNETIUM TC-99M GLUCEPTATE KIT)
 - [TECHNESCAN HIDA](#) (TECHNETIUM TC-99M LIDOFENIN KIT)
 - [TECHNESCAN MAA](#) (TECHNETIUM TC-99M ALBUMIN AGGREGATED KIT)
 - [TECHNESCAN MAG3](#) (TECHNETIUM TC-99M MERTIATIDE KIT)
 - [TECHNESCAN PYP KIT](#) (TECHNETIUM TC-99M PYROPHOSPHATE KIT)
 - [TECHNETIUM \(99m Tc\) FANOLESOMAB; NEUTROSPEC](#) (TECHNETIUM (99m Tc) FANOLESOMAB; NEUTROSPEC)
 - [TECHNETIUM TC 99M ALBUMIN AGGREGATED KIT](#) (TECHNETIUM TC-99M ALBUMIN AGGREGATED KIT)
 - [TECHNETIUM TC 99M DIPHOSPHONATE-TIN KIT](#) (TECHNETIUM TC-99M ETIDRONATE KIT)
 - [TECHNETIUM TC 99M GENERATOR](#) (TECHNETIUM TC-99M SODIUM PERTECHNETATE GENERATOR)
 - [TECHNETIUM TC 99M HSA](#) (TECHNETIUM TC-99M ALBUMIN KIT)
 - [TECHNETIUM TC 99M MAA](#) (TECHNETIUM TC-99M ALBUMIN AGGREGATED KIT)
 - [TECHNETIUM TC 99M MPI MDP](#) (TECHNETIUM TC-99M MEDRONATE KIT)
 - [TECHNETIUM TC 99M SESTAMIBI](#) (TECHNETIUM TC-99M SESTAMIBI KIT)
 - [TECHNETIUM TC 99M SULFUR COLLOID](#) (TECHNETIUM TC-99M SULFUR COLLOID)
 - [TECHNETIUM TC 99M TSC](#) (TECHNETIUM TC-99M SULFUR COLLOID KIT)
 - [TECHNETIUM TC-99 SESTAMIBI](#) (TECHNETIUM TC-99M SESTAMIBI KIT)
 - [TECHNETIUM TC-99M MEBROFENIN](#) (TECHNETIUM TC-99M MEBROFENIN KIT)
 - [TECHNETIUM TC-99M PENTETATE KIT](#) (TECHNETIUM TC-99M PENTETATE KIT)

- Mo 99 – not an approved drug product
 - Intermediate
 - Regulated as its quality may have an impact on the final Tc 99m solution

Technetium Tc99m Sodium Pertechnetate

- Produced in Generator System from Mo-99
 - Where does Mo-99 come from?
 - Nuclear Reactor
 - Irradiation of HEU targets
 - Irradiation of LEU targets
 - Solution based Uranium irradiation
 - Neutron activation – High flux reactor
 - $^{98}\text{Mo} (n, \gamma) ^{99}\text{Mo}$
 - Accelerator Production –
 - From Mo-98 [$^{98}\text{Mo} (n, \gamma) ^{99}\text{Mo}$]
 - From Mo-100 [$^{100}\text{Mo} (\gamma, n) ^{99}\text{Mo}$; $^{100}\text{Mo} (n, 2n) ^{99}\text{Mo}$]
 - Other?

Alternate Sources Mo-99



Considerations for Reactor Irradiation Processes and Production

- Define Starting Material
- Target fabrication and specifications
 - Composition, dimensional specs, acceptance criteria, etc.
- Describe Manufacturing facility and Process
 - Critical process parameters and process controls
- Data on irradiation runs
 - One run under commercial conditions.
- Irradiation conditions
 - E.g., thermal neutron flux, comparative flux if alternate sites involved, 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
- Hold-up times and conditions (before irradiated target is processed)

Considerations for Reactor Irradiation Processes and Production

- Purification process
- Data for separate irradiation and purification runs
- Composition of Mo-99 solution
 - Target product profile
- Specifications of Mo-99
 - Radiochemical identity and purity, radionuclidic purity profile, radionuclidic impurities, etc.
 - European Pharmacopeia monograph

Considerations for Reactor Irradiation Processes and Production

- Information on generator
 - If Mo99 quality is different – can existing approved generator handle different quality Mo99 to give equivalent Tc 99m solution?
- Three lots of generators
 - Prepared from separate Mo-99 lots
- Include different generator size
 - e.g., 1, 3, 5 Ci, or other appropriate size
- May use bracketing when many different size generators produced

Considerations for Reactor Irradiation Processes and Production

- Release results on three lots of technetium Tc 99m generators
 - Analyses on generator eluate.
 - Conformance to United States Pharmacopeia Sodium Pertechnetate Tc 99m Injection monograph.
 - Radionuclidic impurities, other than indicated in USP monograph, need assessment for safety and justified.

Considerations for Reactor Irradiation Processes and Production

- Reconstitute three commonly used radiopharmaceutical kits with eluate from one of the generator runs
 - Recommend including anionic, cationic and neutral
 - Of the kits chosen, include at least one from the more demanding types, e.g., MAG3.
 - Radiolabeling efficiency
- Test for radiochemical characteristics, e.g., radiochemical purity.

Considerations for Accelerator Production Process

- Cyclotron / Linear Accelerator used
- Define Starting Material
- Target
 - Molybdenum enrichment and specifications
 - Target fabrication and specifications
- Irradiation parameters
- Purification process (manufacturing)
- Mo-99 qualification
 - Composition of solution
 - Release specifications
 - Preparation of technetium Tc99m generators
 - Release testing of generators
 - Radiopharmaceutical kit performance

Regulatory Process for Approval

- The applicant must notify FDA about each change in each condition established in an approved application beyond the variations already provided for in the application.
- The holder of an approved application under section 505 of the act must assess the effects of the change before distributing a drug product made with a manufacturing change.
- Existing New Drug Application (NDA)
 - Supplement existing NDA
 - Approval of a “new” sourced Mo-99
 - Mo-99 manufacturing information
 - Contained in NDA
 - Contained in Drug Master File (DMF) -LOA
- New NDA
 - Include manufacturing information in NDA

Drug Master File (DMF)

- “A 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.”
- If a manufacturer holds a DMF that you would like to reference, you should ask them to provide you with a letter of authorization (LOA), which you must include with (and reference in) your application and list on your Form 356h.
- LOA from the DMF holder grants the FDA authorization to refer to information in their DMF during the review of your application (e.g., NDA, ANDA).

Drug Master File (DMF)

- A DMF may be submitted for how Mo-99 is produced.
- 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).

Drug Master File (DMF)

- DMF submission is not a requirement
 - Information may be submitted in an application or a DMF
- DMF may be submitted for Moly-99 manufacturing
- DMF should be amended when processes change e.g., when conversion from HEU to LEU
- Maintain confidentiality of proprietary information
- Permit review of information by reviewers at FDA to support applications submitted by more than one applicant

Drug Master File (DMF)

- The regulatory requirements for a DMF
 - 21 CFR 314.420
- Guidance:
 - <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm122886.htm>
- DMF submission address:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville MD 20705-1266

Communication

- Discussion (meeting) with FDA is recommended prior to Moly-99 related submission
- Contact:
 - youbang.liu@fda.hhs.gov



Thank You

Questions?