Moly-99 Topical Meeting
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Eric P Duffy, PhD
Office of New Drug Quality Assessment
FDA/CDER

Presentation Overview

- FDA/CDER Overview
- Molybdenum-99 [Moly-99]Production
- Regulatory Process for Approval of
  - Moly-99
  - Technetium-99m
- Submission Process
- Communication

Food And Drug Administration (FDA)

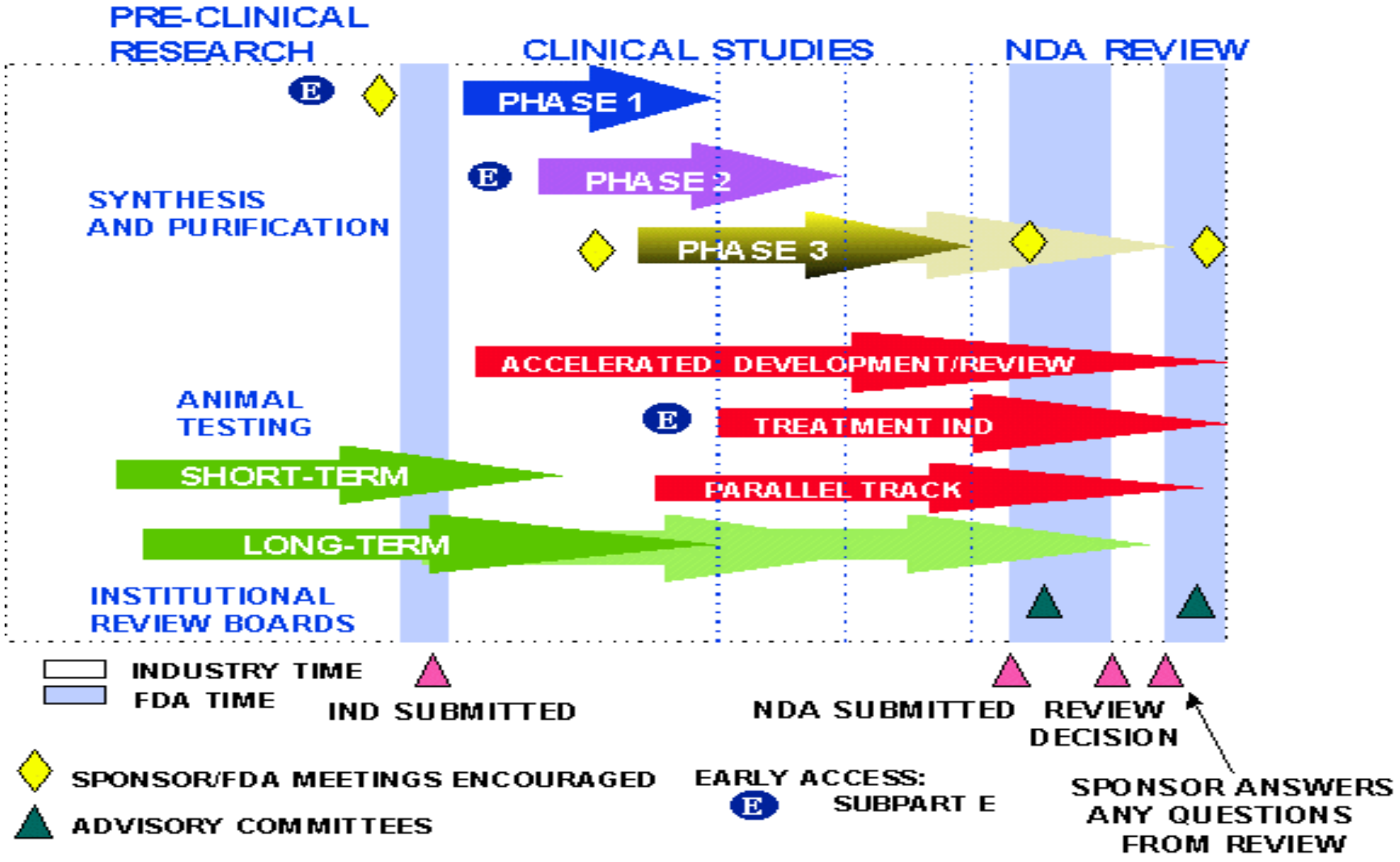
- Estimated that it regulates 25% of every US dollar consumer spent every year
- Mission Statement:
  - **The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, 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 and effective.

Drug Development Timeline



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

Technetium-99m

- Produced in Generator System from Molybdenum-99 [Moly-99]
  - Where does Moly-99 come from?
    - Irradiation of HEU targets
    - Irradiation of LEU targets
    - Solution based irradiation
    - Cyclotron from Mo-98
    - Cyclotron from Mo-100
    - Other?

Considerations for Irradiation Processes and Production

- Target fabrication and Specification
  - Composition, dimensional specs, acceptance criteria, 8etc.
- 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

Considerations for Irradiation Processes and Production

- Separate purification runs
- Specifications of Mo99 (also include radionuclidic purity profile, radionuclidic impurities, etc.)
  - European Pharmacopea Monograph Specs

Considerations for Irradiation Processes and Production

- three generator runs (including generator size depending
- generator sizes (e.g., 1, 3, 5 Ci, or other appropriate size)

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, e.g., MAG3.

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

Regulatory Process for Approval

- 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

DMFs

- “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.”

DMFs

A drug master file (DMF) may be filed for how molybdenum-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).

DMFs

- No legal or regulatory requirement.
  - Information may be in an application or a DMF
- DMF may be filed for Moly-99 manufacturing
- DMF should be amended when processes change eg 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

DMFs

- http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/default.htm
- DMF Guidance
  - http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073164.htm

Communication

- Prior to any Moly-99 related submission discussion with FDA is recommended
- Contact
  - eric.duffy@fda.hhs.gov
  - youbang.liu@fda.hhs.gov

Thank You

Questions?

FDA
10903 New Hampshire Ave
Silver Spring, Maryland 20993