Actinium-225 (Ac-225) Radiopharmaceuticals

FDA Perspective – Chemistry, Manufacturing and Controls (CMC)

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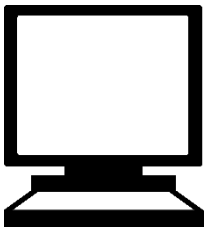
Pharmaceutical Quality

A quality product of any kind consistently meets the expectations of the user.



Pharmaceutical Quality

A quality product of any kind consistently meets the expectations of the user.

Drugs are no different.

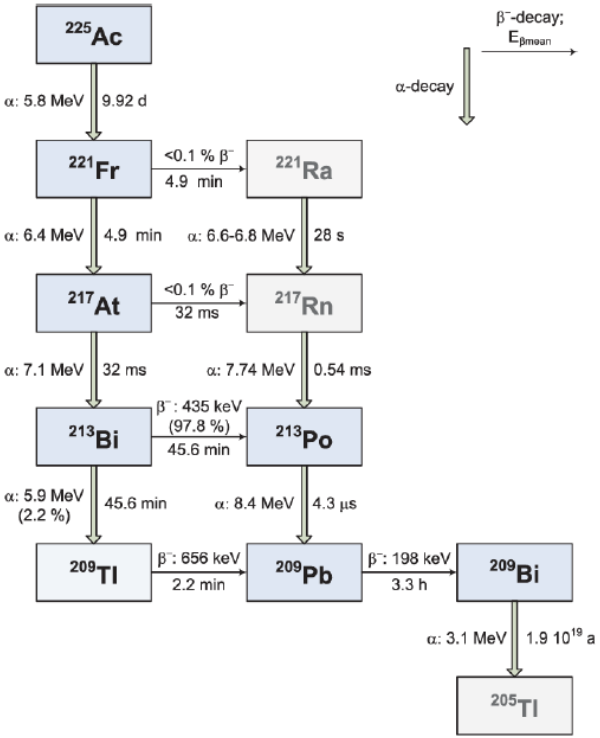
- Patients expect safe and effective medicine with every dose they take.

Pharmaceutical quality is

assuring *every* dose is safe and effective, free of contamination and defects.


It is what gives patients confidence in their medicine.

Actinium-225



- Physical $t_{1/2}$ – 9.92 days
- Increasing clinical trials for radiopharmaceuticals containing Ac-225 for targeted alpha therapy
- Availability of Ac-225
  - For Ac-225 radiopharmaceuticals
  - For producing other isotopes (e.g., ^{213}Bi)

Radioisotope Quality Issues in Ac-225

- New methods for Ac-225 production
  - Radionuclidic impurities – long lived
  - Multiple production methods – different impurities
- Radiolabeling process assessment
- Changing chemistry as Ac-225 decay chain progresses

Radionuclidic Impurities

- Reactor produced AC-225

$$^{232}\mathrm{Th}(p,x)^{225}\mathrm{Ac}$$

$$^{232}\mathrm{Th}(p,x)^{225}\mathrm{Ra}\ (T_{1/2} = 15\ \mathrm{d}) \rightarrow {}^{225}\mathrm{Ac}$$

- CMC information for the manufacture and controls of Ac-225
  - Should be submitted in a type-II DMF, which the radiopharmaceutical manufacture should reference
  - Include Letter of Authorization (LOA) in the application

- A variety of undesired radionuclides (impurities) are formed
  - Separated (process is validated)
  - Quantitated by validated methods

- Controlling and Reporting of impurities
  - Specified (identified) (e.g., Ac-227)
  - Each unidentified
  - Total Radionuclidic impurities

Radionuclide Impurity Results by Ac-225 Manufacturer

- Radionuclidic impurity results (actual amount present at a calibration date and time) should be included in the Certificate of Analysis (CoA) for the lot to the radiopharmaceutical manufacturer
  - Calibration date and time should be included in CoA
- Example:
  - Ac-227 (specified impurity)
  - Lot release acceptance criteria (specification): NMT 0.3% at calibration (of Ac-225 activity)
  - Result: 0.2% at calibration

Justification of Radionuclidic Impurities levels (example: Ac-227 levels in Ac-225)

- Additional production process related radionuclides do not form during radiolabeling / radiopharmaceutical manufacture
  - New radionuclide(s) may form the decay process
- The radiopharmaceutical manufacturer
  - Use the data from results provided in the CoA to determine the radionuclide impurity amount at the time of patient administration of the radiopharmaceutical dose
  - To assess effect radionuclide impurity on radiation dose to the patient for the radiopharmaceutical
  - To establish safety limits for radionuclidic impurities from preclinical for clinical trails and from clinical trials for marketing application
  - In establishing specification for radionuclide impurities, justifying the specification established

Radiolabeling Process Development

- Radiopharmaceutical manufacturer needs to know the specific activity (SA) value of the radiochemical lot (e.g., Actinium 225 nitrate)
  - Activity /mass at calibration
- SA enables determination of molar ratio of ligand to radiochemical to establish and control the radiolabeling process

Other Useful Information

- Date and time of manufacture
  - Use the information to establish acceptable use period for the radiochemical
  - Use the information to determine need to purify the radiochemical prior to formulation to get rid of decay products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