



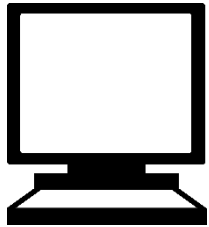
Actinium-225 (Ac-225) Radiopharmaceuticals

FDA Perspective – Chemistry, Manufacturing and Controls (CMC)

Ravi Kasliwal, Ph.D.
Office of New Drug Products
DNDC-3, Branch-6
Office of Pharmaceutical Quality
CDER/FDA

Pharmaceutical Quality

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



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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.

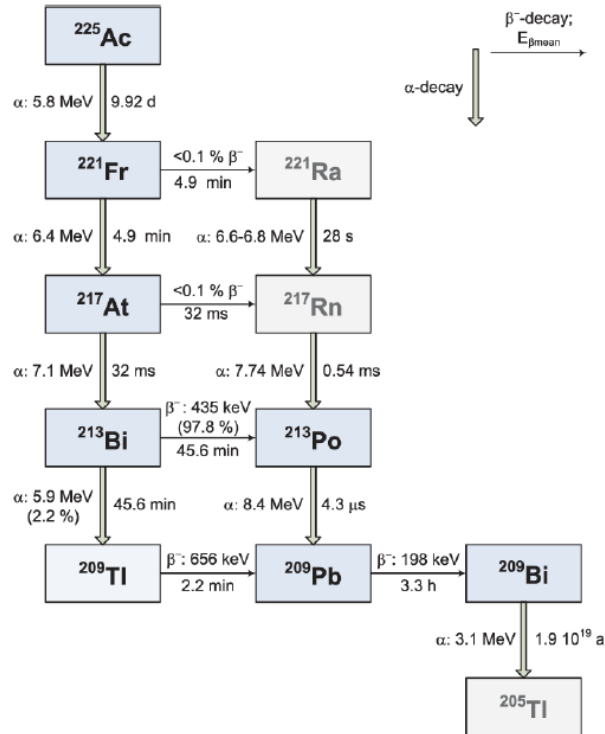
Pharmaceutical quality is

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

A close-up photograph of a person's hands. One hand is holding an orange plastic pill bottle, tilted to pour three white, oval-shaped pills into the palm of the other hand. The background is softly blurred, showing a person's arm in a blue sleeve.

It is what gives patients confidence in their medicine.

Actinium-225



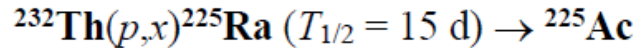
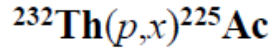
- Physical $t_{1/2}$ – 9.92 days
- Increasing clinical trials for radiopharmaceuticals containing Ac-225 for targeted alpha therapy
- Availability of Ac-225
 - For Ac-225 radiopharmaceuticals
 - For producing other isotopes (e.g., ^{213}Bi)

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



- 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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