

# Chemistry Related Deficiencies / Topics in PET Drug Applications

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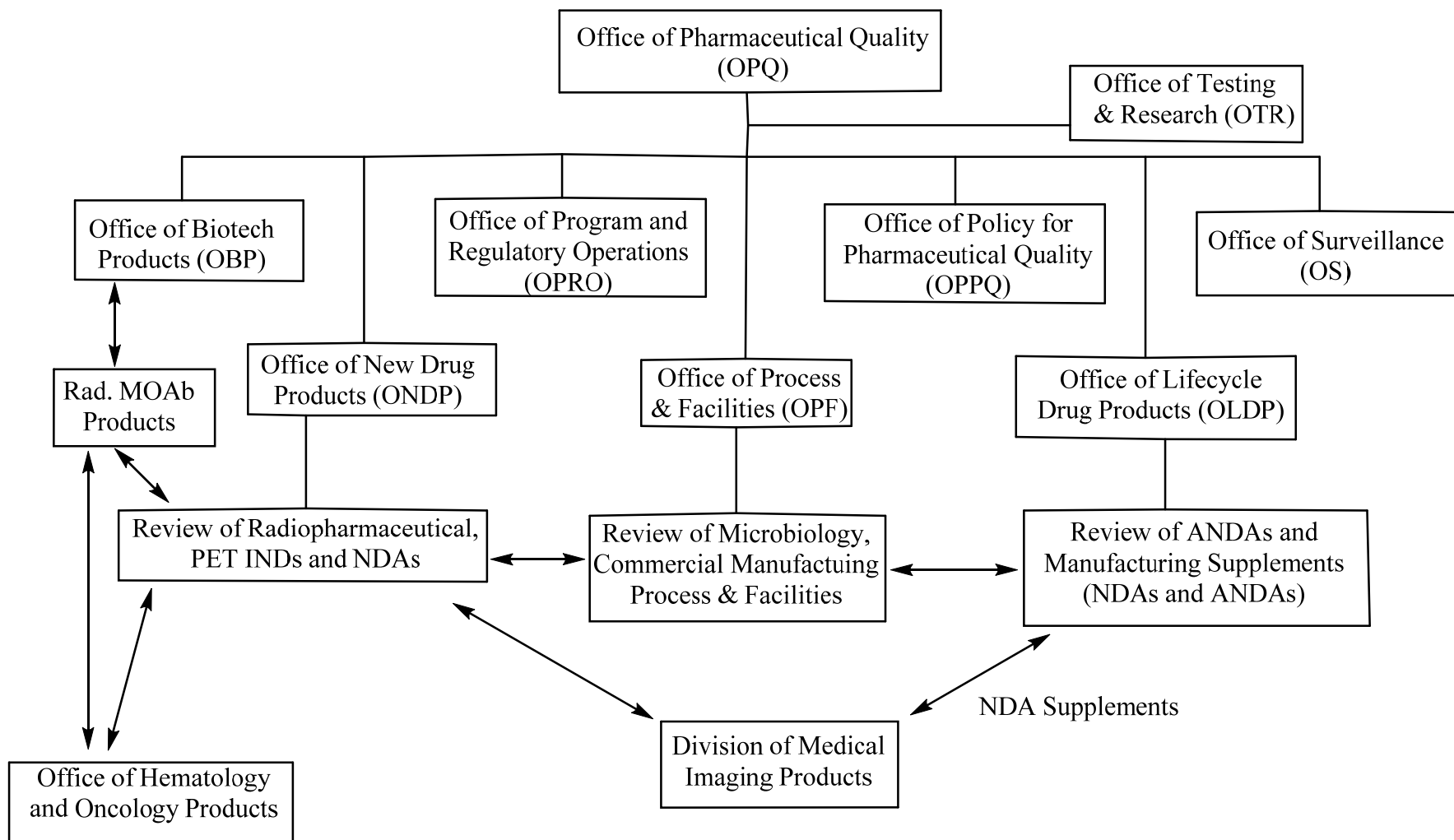


# OUTLINE

- How quality information for IND, NDA, ANDA and Supplement is reviewed
- IND, NDA, BLA and ANDA
- Drug characterization
- Manufacturing and testing facilities
- Manufacturing process
- Control of materials
- Precursor related information
- Radionuclide related information
- Radionuclide generators
- Radiolabeling procedure related information
- Drug product related information
  - Composition, strength reference time (unit dose / multi dose), excipients, specifications, analytical procedures/ validation, pharmaceutical development
- IND labeling
- Communication
- Conclusion



# Review of Chemistry, Manufacturing and Controls (CMC) Information for Radioactive Drugs



# Investigational New Drug (IND) Application



- **21CFR312 – IND Regulations**
- **21CFR 312.23 – IND Content and Format**
- **21CFR 312.23 (a)(7) – IND Chemistry, Manufacturing and Control Information**
- Animal Pharmacology and Toxicology Studies - Preclinical data to permit an assessment as to whether the product is reasonably safe for initial testing in humans. Also included are any previous experience with the drug in humans (often foreign use).
- Manufacturing Information - Information pertaining to the composition, manufacturer, stability, and controls used for manufacturing the drug substance and the drug product. This information is assessed to ensure that the sponsor can adequately produce consistent batches of the drug (i.e., batches that are similar to those used in preclinical studies).
- Clinical Protocols and Investigator Information - Detailed protocols for proposed clinical studies to assess whether the initial-phase trials will expose subjects to unnecessary risks. Also, information on the qualifications of clinical investigators, commitments to obtain informed consent from the research subjects, to obtain review of the study by an institutional review board (IRB), and to adhere to the investigational new drug regulations.



# New Drug Application (NDA)

- 21 CFR 314 - Applications for FDA approval to market a new drug or an antibiotic drug.
- 21CFR 310 – New Drugs.
- 21 CFR 310.4 (b) – Marketing approval for radioactive biological products must comply with 21 CFR 601.2(a) Provisions (e.g., mAb products)
- 21 CFR 314.50 – Content and format of an application.
- 21 CFR 314.50 (d)(1) – Chemistry, manufacturing and controls section.
- The NDA application is the vehicle through which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale and marketing in the U.S.
  - Whether the drug is safe and effective in its proposed use(s), and whether the benefits of the drug outweigh the risks.
  - Whether the drug's proposed labeling (package insert) is appropriate, and what it should contain.
  - Whether the methods used in manufacturing the drug and the controls used to maintain the drug's quality are adequate to preserve the drug's identity, strength, quality, and purity.

# Abbreviated New Drug Application (ANDA): Generics



- 21 CFR 314.92 – 21 CFR 314.99
- A generic drug product is one that is comparable to an innovator drug product in dosage form, strength, route of administration, quality, performance characteristics and intended use.
- All approved products, both innovator and generic, are listed in FDA's [Approved Drug Products with Therapeutic Equivalence Evaluations](#) (*Orange Book*).
- Generic drug applications are termed "abbreviated" because they are generally not required to include preclinical (animal) and clinical (human) data to establish safety and effectiveness.
- Generic applicants must scientifically demonstrate that their product is bioequivalent (i.e., performs in the same manner as the innovator drug).



# Submission of CMC information

- Preferred format for submitting an application, including CMC, is the Common Technical Document(CTD)
- Pharmaceutical Quality / CMC Guidance:
  - <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064979.htm>
- International Council on Harmonization (ICH) - Quality
  - <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm065005.htm>
- Generics – Guidance
  - <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064995.htm>



# Drug Substance in NDA –CTD

## (Precursor and Radioactive Drug Substance)

- **S.1 General Information: Nomenclature, Structure, General Properties**
- **S.2 Manufacture**
  - **Manufacturers**
  - **Description of Manufacturing Process and Process Controls**
    - **Flow Diagram**
    - **Process Narrative**
    - **Process Controls**
  - **Control of Materials**
    - **Starting Materials**
    - **Reagents, Solvents, Auxiliary Materials**
  - **Control of Critical Steps and Intermediates**
  - **Manufacturing Process Development**
- **S.3 Characterization**
  - **Elucidation of Structure**
  - **Other Characteristics**
    - **Physicochemical properties**
    - **Solid State Forms**
  - **Impurities**
    - **Types (organic, inorganic, residual solvents)**
    - **Classification (specified/unspecified, identified/unidentified)**
    - **Reporting, Identification and Qualification Thresholds**
    - **Acceptance Criteria**
    - **Qualification**
- **S.4 Control of the Drug Substance**
  - **Specifications**
  - **Analytical Procedures**
  - **Validation of Analytical Procedures**
  - **Batch Analyses**
  - **Justification for Specifications**
- **S.5 Reference Standards**
- **S.6 Container Closure System**
- **S.7 Stability**
  - **Stability Protocol and Data Evaluation**
  - **Forced Degradation/Stress Testing**
  - **Photo stability**
  - **Stability Summary and Conclusion**
  - **Post-approval Stability Protocol and Commitment**
  - **Stability Data**



# Drug Product in NDA -CTD



- **Drug Product**
- **P.1 Description and Composition**
- **P.2 Pharmaceutical Development**
  - Drug Substance
  - Excipients
  - Formulation Development
  - Manufacturing Process Development
  - Container Closure Suitability
- **P.3 Manufacture**
  - Manufacturer
  - Batch Formula
  - Description of Manufacturing Process and Process Controls
  - Control of Critical Steps and Intermediates
- **P.4 Control of Excipients**
- **P.5 Control of the Drug Product**
  - Specifications (release, stability, in-house)
  - Analytical Procedures
  - Validation of Analytical Procedures
  - Batch Analyses
  - Justification of Specifications
- **P.6 Reference Standards**
- **P.8 Stability**
- **P.7 Container Closure Systems**
  - Primary, Secondary, Functional and Non-Functional Secondary Packaging
  - Stability Protocol and Data Evaluation
  - Forced Degradation/Stress Testing
  - Photo stability
  - Stability Summary and Conclusion
  - Post-approval Stability Protocol and Commitment
  - Stability Data
- **Regional Information**
- **Executed Batch Records**
- **Comparability Protocols**
- **Method Validation Package**
- **Module 2 of CTD**
  - Quality Overall Summary



# Drug Substance

- **Inadequate characterization of the drug substance.**

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- Drug substance is the entire molecule, including the radionuclide.
  - Include radionuclide and stereochemistry aspects in the name.
  - Include relevant stereochemistry in structural drawing.
- Include general properties, resulting from non-radioactive portion and those from radionuclides. Examples:
  - Radioactive emission, abundance and energy, and radioactive half-life.
  - Relevant physical properties such as partition coefficient, ionic charge and dissociation constants, etc.
  - Physical properties may be determined using the equivalent non-radioactive reference standard.



# Manufacturers

- **Manufacturer is not ready for inspection or information is inadequate.**
- 
- All the information pertinent to the manufacture of the non-radioactive portion of the drug substance molecule, the radionuclide and its incorporation into the drug substance should be provided.
  - Include name, address and responsibility of each facility involved in the manufacturing or testing.
    - Include manufacturer for the non-radioactive portion of the molecule (e.g., starting material to non-radioactive precursor).
    - Include manufacturer for the radionuclide (e.g., target to radioactive intermediate).
    - Include the source of the target(s), the names and addresses of the facility(s) where the target(s) are irradiated, processed and tested.
    - Include manufacturer of the radioactive molecule (may be same as drug product for radioactive drugs).
    - Provide actual location where manufacturing or testing occurs – No P.O. Box for manufacturing / testing facility.
    - Include contract manufacturers and contract laboratories.



# Manufacturing Process

- **Inadequate details of the manufacturing process or process controls**

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- Include detailed flow diagram and procedural narrative of radioactive and non-radioactive portions of the process.
- Include description of procedures employed to incorporate the radionuclide into the molecular framework to produce the drug substance, along with the procedures used in its purification.
- For radiopharmaceutical kits where the drug substance is produced by reconstitution, a full description of the procedure of reconstitution should be provided.



# Manufacturing Process

- The scale up and holding times, as related to radiolysis (radioactive degradation of the drug substance) associated at high radioactive concentration, should be evaluated and validated, as appropriate.
- Details of the analytical procedures used in in-process testing should be included.



# Control of Materials

- **Starting materials are not specified.**
  - **Specifications for starting material are not provided.**
- 
- Specify starting material for the radionuclide (e.g., the target used for irradiation).
  - Specify starting material for non-radioactive precursor.
  - Include specifications for all starting materials.
  - Targets:
    - Source of the target, isotopic composition, isotopic and chemical purity.
    - Description / specifications for dimensions, if solid target is used.
    - A description of the target body (configuration, composition), and target windows if used. Information on the target windows, including thickness and composition.

[Methods of manufacture from starting material onwards must follow cGMP]

# Drug Substance - Precursor



- CMC information (e.g., Manufacturer, method of manufacture (synthesis), controls (specifications, test procedures), stability) not provided.
  - Lots to be used in clinical study not identified / data for Lot not provided.
- 
- Specify starting material(s).
  - Provide complete CMC information for the manufacture and control of the precursor (intermediate) – CTD drug substance format may be used.
    - Manufacturing and testing facilities
    - Synthesis, purification, in-process tests and controls.
    - Control of raw materials.
    - Reference standard.
    - Structure characterization data.
    - Impurity characterization.
    - Specifications
    - Analytical methods / validation data
    - Container closure system
    - Stability studies and data
    - Retest dating period.
- [Methods of manufacture from starting material onwards must follow cGMP]

# Radionuclide Intermediate



- **CMC Information for the radionuclide intermediate is inadequate.**

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- Include complete CMC information for the manufacture including purification and controls (starting from target) for radionuclide.
- Include radionuclidic purity of the radionuclide obtained from a supplier (accelerator or reactor-produced), including a list of the radionuclides present and their amounts.
- Include chemical form(s) of the radionuclide present and what is acceptable in relation to how the radionuclide will be used in the manufacturing process for the drug substance.
- Include chemical composition of the radionuclide solution.





# Radionuclide Intermediate

- Include chemical purity, including a list of both non-metal and metal impurities, and the amounts present.
  - Basis of chemical purity should be described in relation to the requirements of the manufacturing process to produce drug substance meeting its established chemical purity.
  - Assessment of formation of chemical as well as radiochemical impurities from the impurities present in radionuclide.
- Include procedures and criteria by which the radionuclide is accepted on the basis of chemical purity

# Multiple Sourced of Precursor or Radionuclide



- **Inadequate information to support alternate sources.**
- 
- Include CMC information for each material from each source.
  - If the material quality from alternate source is different from primary source (i.e., different purity, different impurities), an assessment of its impact on the drug substance / product quality should be provided.
  - Include qualification data that material from each source can provide drug substance / product of equivalent quality.

# Generator Produced Radionuclide



- Compete CMC information and supporting data should be provided (may be in Type II DMF): Target → Radionuclide.
  - 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.
  - Fabrication and specifications for target, target composition, target impurity controls.
  - irradiation parameters, irradiation facilities.
  - Production, processing and purification methods (including control of materials).
  - Chemical form and composition of parent radionuclide.
  - Specifications for parent radionuclide.
  - Assessment of impurities present including radionuclidic, radiochemical or chemical and their potential for contaminating the generator eluate.

# Generator Produced Radionuclide - continued



- Manufacture and control of generator components (hardware, software).
- Chemical form of the daughter radionuclide and its separation from parent. A detailed description of any column used, along with the packing material and principle of separation.
- Manufacture and controls for column.
- Manufacture and controls for eluent used for the generator.
- Manufacture of the generator (e.g., diagram of assembled generator with all components and their function, source of components, compatibility of components with the contacting fluids).
- Assurance of sterility of the generator over its shelf life.
- Release specifications for the generator (generally more extensive than performed at the user site); chemical composition of generator eluate.
- Quality control performed by user on eluate (e.g., testing for parent radionuclide breakthrough, test for any relevant chemical impurities).
- Activity-time kinetics of the parent-daughter pair and equilibrium, elution schedule and expiration date of the generator (stability studies).



# Qualification of Generators

- **Inadequate Generator qualification.**
- 
- Generally, all commercially available generators for the labeling of a kit product should be qualified.
  - Different generators must provide the radiolabeled product that has the same composition (i.e., same formulation as described in the package insert).
  - Specific generator may need to be identified in the product labeling.

# Reference Standard

## Drug Substance, Precursor, Impurity



- Reference standard or information is inadequate.
- 
- Used for identification, purity tests, analytical validation [e.g. accuracy, system suitability (e.g. chromatographic systems), assay.
  - Quality: appropriate to its use.
    - Highest purity that can be obtained through reasonable effort.
    - Thoroughly characterized to assure the identity, strength, and quality.
  - Characterized and evaluated for its intended purpose by additional procedures other than those used in routine testing.
  - Include lot number of the established primary reference standard lot.
  - Include description of the method of manufacture and purification.
    - If different, its impact on structure (including stereochemistry) should be discussed.



# Drug Substance Reference Standard

- If relevant, stereochemically pure reference standard (including for chelate) should be prepared.
- All the analytical data (characterization) must be derived from the specified lot.
- Include details of the analytical data and interpretation of the data.
- Include purity determination information for the lot.
- If a working lot of standard is used, procedures / specifications that will be used for establishing a working reference standard lot should be included.
- Specifications for the reference standards, to be used for replacing the reference standard lot when the supplies of the primary standard lot are exhausted, should be provided.
- Stability and storage information should be included.
- Procedure to requalify a reference standard should be included.



# Stability - Precursor

- Storage conditions should be defined.
- Stability studies should be conducted (both long term and accelerated) to support the shelf life under proposed storage conditions.
- Stability studies should be performed in the proposed container closure.
  - If multiple container closure systems are used (e.g., bulk or smaller amounts), stability should be determined under each type of container closure system.
- Photo-stability and other stress studies should be performed.



# Drug Product - Composition



- Inadequate description (identity) of components or composition of the finished dosage form.
- 
- Complete statement of the qualitative and quantitative composition should include the drug substance and all excipients.
    - Drug substance should be identified in terms of its radiochemical form, mass and the amount of radioactivity.
      - Mass amount may be indicated by specific activity (radioactivity per unit mass) along with the amount of radioactivity.
    - Excipients are intentionally added for specific purpose and should be included.
      - Process impurities are not excipients and should not be included.
    - Include container closure system (that contains and protects the dosage form, administration accessories, external packaging and container labeling).

# Drug Product – Composition

Kits to be reconstituted by users



- Include composition statements for:
  - Non-radioactive product (e.g., for the lyophilized powder in the reaction product).
  - For product after reconstitution with radionuclide solution.
- Composition of all kit components:
  - Reaction vial containing ligand and excipients.
  - Any separate vial containing buffer or diluent.
  - Syringes or other co-packaged components.
- Description of the radionuclidic solution used for reconstitution and its source.



# Strength Reference Time

(unit dose / multi dose)

- Multi dose product:
  - Strength (e.g., mCi/mL) is referenced to end of manufacturing time (e.g., EOS).
- Unit dose product (e.g., vial or prefilled syringe)
  - Strength is referenced to a defined calibration time.
  - The unit dose is filled with enough radioactive drug product solution to provide indicated strength at the calibration time.
  - Recommended dose to the patient should be considered in defining calibration time.



# Drug Product - Excipients

- **Excipient quality is inadequate / Controls for excipient quality is inadequate**
- 
- Include whether or not an excipient is compendial (USP / NF) grade.
  - Include specifications for identity, purity and quality for non-compendial excipients.
  - A compendial excipient must be tested using the compendial test methods.
  - Compendial specifications may not be adequate, may need additional controls (limits and test methods):
    - E.g., an excipient added prior to radiolabeling (chelation) may contain cationic metal impurities that might compete in the radiolabeling reaction.
  - Any ingredient being human or animal origin must be identified or statement provided that none of the ingredients are of human or animal origin.

# Control of Drug Product – Specifications.

- Specification is a list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the tests described.
- Changes in the specification after approval of the application may need prior approval by the regulatory authority.
- Justification should be presented for each procedure and each acceptance criterion included.
- Specified and unspecified impurities should be discussed.
  - Consider potential risks from a safety and efficacy perspective.
  - Potential sources of impurities and degradants, as well as those arising from radiolysis, should be investigated.



# Analytical Procedures

- **Inadequate details of the analytical method.**
- 
- Complete details including, materials and their quality used; equipment details; operating conditions used; preparation details of all solutions (standard, test sample and other solutions) and their use period (shelf life); system suitability solutions, tests and acceptance criteria; details of test procedures; formulae for calculations; how the results are analyzed and reported; reference chromatograms; reference spectra; etc.
  - An alternate analytical procedure may be proposed for use in lieu of the regulatory analytical procedure.
    - Both procedures should be included.
    - An alternate analytical procedure should perform at least equally to that of the regulatory analytical procedure.

# Analytical Procedures-Validation



- The analytical method is not suitable for the intended task or inadequate validation data.
- 
- The objective of validation of an analytical procedure is to demonstrate that it is suitable for its intended purpose and can provide accurate and precise results.
  - All relevant data collected during validation and formulae used for calculating validation characteristics should be submitted and discussed.
  - Well-characterized reference materials, with documented purity, should be used throughout the validation study.



# Analytical Procedures-Validation

- Guidance for Industry - Q2B Validation of Analytical Procedures: Methodology
  - <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073384.pdf>
- Guideline for Industry - Text on Validation of Analytical Procedures:
  - <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073381.pdf>





# Validation – Radiochemical Detector

- Specificity – method is specific and capable separating radiochemical species.
- Detector Linearity – should be linear over the range of detection (consider both the radioactive drug substance and free radionuclide present in small amount).
- Accuracy (recovery) – consider both the radioactive drug substance and free radionuclide present in small amount.
- Detection Limit / Quantitation Limit – what would be minimum radioactive concentration needed in the sample to achieve detection.
- Robustness – method is capable of performing under a variety of conditions.



# Analytical Procedures – System Suitability

- System suitability tests / acceptance criteria are inadequate or not present.
- 
- Each test procedure should have a system suitability test and acceptance criteria.
  - The system suitability tests and acceptance criterion for each should be proposed.
  - System suitability should assure that the analytical system (equipment, electronics, analytical operations and samples to be analyzed) is working as intended (as validated).
    - Should be performed prior to the analysis.
    - If system is running for prolonged time, the system suitability tests should bracket the analysis.
    - The sequence should be part of the procedure details.



# Pharmaceutical Development

- Include the development history of the manufacturing process, including the incorporation of the radionuclide.
- Any differences in the manufacturing processes or in-process controls between those for commercial production and pivotal clinical batches should be discussed.
- Any changes in the manufacturing process that may change the impurity profiles of the radionuclide, intermediates that affect the radionuclidic, radiochemical and/or chemical purity of the drug should be assessed for safety and efficacy.



# Pharmaceutical Development Formulation Related

- A summary of all the formulations used in clinical trials should be included.
- Any changes in the formulation subsequent to production of the clinical batches and the primary stability batches should be assessed for equivalency.
- Differences between the clinical trial formulations and the formulation of the drug product for marketing should be assessed and may need bridging studies.



# Container Closure

- The rationale for selection of the container closure system intended for use with drug product should be included.
- Glass may leach inorganic ions that may interfere with the radionuclide incorporation reaction in radiopharmaceutical kits during their reconstitution.
- Compatibility of the drug product with the container closure and any devices intended to be used with delivery of the product should be discussed.



# IND Labeling

- Container Label Must Contain (21 CFR 312.6(a))  
“Caution: New Drug – Limited by Federal (or United States) law to investigational use.”
- Should not contain other statements such as “Rx Only” or similar prescribing statements.



# Meetings Between FDA and Sponsors

Type	A	B	C
Confirmation of scheduling	14 days	21 days	21 days
Held no later than	30 days	60 days	75 days
Briefing package	With meeting request	1 month	1 month
Description, Comments	Dispute resolution, Clinical holds, Special Protocol Assessment (SPA), Post action meeting (3 months of the action)	preIND <sup>^</sup> , EOP1, EOP2, Pre NDA/BLA, REMS* or PMRs**	Any other than type A or B Can be granted as written response only (WRO)

\*Risk Evaluation and Mitigation Strategy    \*\* Post Marketing Requirements    ^ can be granted as WRO

- <https://www.fda.gov/downloads/drugs/guidances/ucm153222.pdf>



# Contacts

- For Pre-INDs, INDs, NDAs and NDA Supplements:  
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# Summary

- Drug applications are reviewed interactively with other disciplines.
- Drug substance related topics.
  - Non-radioactive precursor.
  - Radionuclidic intermediate.
  - Generator produced radionuclides.
- Drug product topics.
- Communication, meetings with FDA.

