CMC Requirements for an Investigational New Drug Application (IND)

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Two Topic Imaging Workshop:
Manufacturing of Positron Emission Tomography (PET) Radiopharmaceutical Products
April 14, 2010
Natcher Conference Center, NIH, Bethesda, MD

Outline of Presentation

- General Requirements for CMC
- IND Resources
- Application to PET Drugs
- CMC in Multi-Center IND Clinical Trials
- Areas of CMC for Special Attention
- On Preparation of the CMC Section

General Requirements for CMC

- A section in the IND describing the composition, production and controls of the drug substance and drug product (21 CFR 312.23(a)(7))

- FDA recognizes that the amount of this information will vary with the Phase of the IND, the dosage form, duration of the investigation and amount of information otherwise available

- But, in each Phase of the IND, there is to be sufficient CMC information to ensure identity, strength, quality and purity of the investigational drug

General Requirements for CMC

- As IND development progresses, and scale of production increases to expand the clinical investigation, additional CMC information is to be submitted in information amendments to supplement that in the initial submission

- In Phase 3, the studies should be conducted with product for which the method of production and specifications are essentially in final form – so that if and when the IND reaches the NDA stage, CMC in support of the NDA will be fully developed

IND Resources

- Regulations: 21 CFR 312
- Guidance:
  - Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs
    - http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071597.pdf
  - INDs for Phase 2 and Phase 3 Studies Chemistry, Manufacturing, and Controls Information
    - http://www.fda.gov/downloads/Drugs/Guidance/ComplianceRegulatoryInformation/Guidances/ucm070567.pdf
  - IND Meetings for Human Drugs and Biologics Chemistry, Manufacturing and controls Information
    - http://www.fda.gov/downloads/Drugs/Guidance/ComplianceRegulatoryInformation/Guidances/ucm0cm070568.pdf

Application to PET Drugs

- Follow general guidance as listed for IND's as for any investigational new drug, but populate the CMC section, as applicable to PET drugs, and consistent with the Phase of the investigation

- For quality controls to assure identity, strength, quality and purity – see USP <823> Radiopharmaceuticals for Positron Emission Tomography

CMC in Multi-Center IND Clinical Trials

- Ensuring that the drug used in the clinical trials has the proper identification, strength, quality and purity "over its entire shelf-life," consistent with its suitability for human use, is the responsibility of the sponsor of the IND

  - Applies whether the drug is produced in a single facility or in multiple facilities participating in a multi-center clinical trial under IND

CMC in Multi-Center IND Clinical Trials

- Expectation – drug (under study) produced at all sites participating in the multi-center trials will have the same formulation, and meet a common set of specifications

- Production procedures, purity/quality of materials used, and analytical testing procedures should be similar at sites of production so that a uniformly consistent product is used across the multi-center trials

CMC in Multi-Center IND Clinical Trials

- CMC covering all facilities in the multi-center trials should be under central control of the IND (going back to the sponsor)
- Changes during the course of the IND handled through a formal documented process, e.g., a Change Control Protocol, or similar mechanism, to cover, e.g., changes to:
  - Purity/quality of materials
  - Production process
  - Analytical testing procedures; limits

CMC in Multi-Center IND Clinical Trials

- Sponsor needs to know the impact of changes on the drug product, so that
  - Identity of intended drug molecule remains the same, purification procedures still effective and purity profile of final product is not adversely affected

  - Analytical procedures for release of final product still able to determine if product meets acceptable limits

Areas of CMC for Special Attention

Assurance that each dose of drug produced for human use will contain the intended drug substance molecule requires a sound CMC program with careful attention to:

- Characterization of the drug substance molecule – that it is unambiguous, and selection of the compound to serve as reference standard is suitable for use in routine identification
- Control of materials used in its production – emphasis on precursor (final intermediate)
- Sound methodology for identification of the drug molecule

Areas of CMC for Special Attention

Characterization of the drug substance molecule –

- Include entire molecular entity, the non-radioactive moiety, the radionuclide and its site of attachment, and stereochemistry (if relevant)
  - Critical for routine identification (radiochemical identity)
  - Critical for a valid determination of radiochemical purity (must be stability-indicating – heightening importance of the analytical methodology, that it can provide meaningful and reliable information)

Areas of CMC for Special Attention

Selection of compound to serve as reference standard –

- Since the standard is used in an “indirect” identification methodology, its integrity (authenticity) and purity are critical – choice of standard needs to be made with care
  - Official standard (e.g., USP) – used “as is,”
  - Commercial – COA with evidence of integrity/purity
  - Prepared in house – control as for precursor

Areas of CMC for Special Attention

Control of materials in production of drug –

Precursor (final intermediate)

- Last compound in production before introduction of the radionuclide

- Since the drug is not isolated and characterized prior to formulation into the drug product, integrity and purity of precursor are critical to obtaining the intended drug molecule with as few impurities as possible

Areas of CMC for Special Attention

Control of materials in production of drug –

Precursor (final intermediate)

- If obtained commercially
  - Use Certificate of analysis (COA) and your criteria for its acceptance
  - Information on synthesis, if available (DMF)
  - Simple identity test, if available; qualification

Areas of CMC for Special Attention

Control of materials in production of drug –

Precursor (final intermediate)

- If prepared in-house
  - Provide description of synthesis
  - Characterization (such as MS, NMR, elemental analysis, HPLC) – provide data / interpretation
  - Your in-house acceptance criteria (identity, purity and quality) and analytical procedures

Areas of CMC for Special Attention

Sound methodology for identification of drug molecule -

- Drug molecule distinguished from precursor and from impurities generated in radiolabeling reaction

- Co-injection of standard with drug sample, as appropriate; provide justification of any proposed alternatives

- Establish criterion for acceptable match of retention times between standard and drug sample (e.g., RRT, percentage of retention time of standard)

Areas of CMC for Special Attention

Sound methodology for identification of drug molecule –

- Ensure acceptance criterion (congruence of retention times) will be unique for the intended drug molecule
  - May use orthogonal procedures of separation employing different separation mechanisms, such as reverse-phase vs. adsorption or ion-exchange
- Include system suitability test (SST) before routine analysis
  - SST acceptance criteria (e.g., compares with reference chromatogram, or complies with USP <621> criteria)

Areas of CMC for Special Attention

Other considerations –

- Stability – ensure integrity of drug molecule (e.g., radiochemical identity and purity) throughout preclinical and clinical studies
- Labels – must contain the statement (21 CFR 312.6(a)

"Caution: New Drug – Limited by Federal (or United States) law to investigational use."

On Preparation of the CMC Section

- Paginate sequentially, including appendices
- Include an index, listing all parts with page numbers where information can be found
- Whenever possible, use tables and flow diagrams for clear conveyance of information

On Preparation of the CMC Section

- Label chromatograms and spectra clearly
- Chromatograms
  - Label peaks for drug molecule and precursor
  - Label impurity peaks and discuss significance
  - Clarify unusual events (shoulders, split peaks, etc)
- Spectra (NMR, MS)
  - What do they mean; their interpretation

Conclusion

- The CMC section is, of course, expected to be a compilation of all the CMC information satisfying the requirements in 21 CFR 312.23(a)(7)

- But, it also embodies the "CMC plan" – critical to supporting the clinical studies – if well-thought out, well-structured and adherent to sound principles,
  - Will ensure safety
  - Bolster scientific quality of the drug product
  - Aid in obtaining reliable and interpretable results from the clinical studies

IND Questions?

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