



Nonclinical Safety & Toxicity Assessment of New Molecular Entities & Modified Existing Agents

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Focus

- Nonclinical studies needed to support clinical investigations under IND for optical imaging combination products
- Nonclinical perspectives on optical imaging agents combination products applications submitted by sponsors
- Potential device-related toxicities are evaluated by CDRH and will not be covered in this talk

Goals of Nonclinical Investigation

- Identification of target organs
- Characterization of pharmacology and toxicology
- Specific outcomes
 - ✓ Initial starting dose
 - ✓ Dose escalation scheme
 - ✓ Monitoring schemes
 - ✓ Nonclinical studies tailored to meet the needs

Fluorophore:

- Unapproved Dyes
- Approved/Unapproved Dyes combined with
 - Investigational New Molecular Entity
 - Approved small molecule/Biologics
 - Biologics at advanced stage of development
- Enzyme activated Products
- Nanoparticles (Gold, Silica, & Iron Oxide)

Diverse Nature of Optical Imaging Combination Products is Self Evident

Therefore, nonclinical
requirements have to be tailored
to meet the needs

Regulatory Flexibility

- Existing regulations allow for flexibility for nonclinical requirements
- Not often utilized
- ✓ Sponsors may not want to meet with FDA early in development
- ✓ FDA believes there is value in early dialog and agreement

Please Note!

If a Sponsor determines that nonclinical pharmacology or toxicology studies are not needed, at any stage of development and provides adequate justification, FDA is prepared to grant a waiver (21 CFR 312.10)



Nonclinical Assessment of New Molecular Entities

Recommended Studies

Studies Required Before Phase 1 for Optical Imaging IND (small molecules):

- Proof of Concept studies
- Safety Pharmacology: Major organs and organ systems
- TK/PK (ICH guidances)
- Expanded single dose toxicity study (may be combined with repeat dose toxicity study to save cost)
- Special toxicology (e.g. phototoxicity, route irritancy, blood compatibility)
- In vitro genotoxicity studies (not required for microdose)

Studies Required Before Phase 2 for Optical Imaging IND (small molecules)

- Short Term Repeat Dose Toxicity Study
- Genotoxicity Studies (not required for microdose)
- Request for waiver of reproductive and developmental toxicity studies before phase 3 if applicable

Nonclinical Assessment of Modified Existing Agents

To save time and resources, FDA strongly advises that sponsors communicate with the Agency prior to study initiation

Nonclinical Requirements

- No new nonclinical study
- Bridging toxicity study (If issues with dye or other components)
- Letter of Authorization to reference nonclinical studies from other sponsors
- Public data (NCI, NIH)

Biologics Optical Imaging Combination Products

- Most were previously investigated either as approved therapeutic biologics or as investigational therapeutic biologics at advanced stages of development hence relatively well characterized and may require fewer (or even no) new studies
- If not, immunogenicity, cross reactivity and other studies may be required. Best to contact review Division

Nonclinical requirements for route, dose or population change for approved agents

Case by Case Basis, we strongly encourage early communication and dialog with review Division

Outcome

- A more focused nonclinical safety evaluation
- Early communication with the Review Division to optimize nonclinical program
- A flexible approach that allows innovative products to move safely and quickly through nonclinical development

Pertinent Guidances

- Developing Medical Imaging Drugs and Biological Products:

Part 1: Conducting Safety Assessment:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078930.pdf>

- Investigational New Drug Applications: Exploratory IND Studies

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078933.pdf>

- Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073246.pdf>

- Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM074957.pdf>



Thank You!

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