

Overview of CDER Nonclinical Resources and Guidance for Approaching First-in- Human (FIH) Studies in Oncology

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Overview



- Where to start
- What we are looking for
- Potential Pitfalls
- For your consideration

Nonclinical Review



Pharmacology (MOA)

Pharmacokinetics

Toxicology

Nonclinical data

→ Role of nonclinical is front-loaded

You've your great idea, now what



- You've identified a target
- You've shown that your drug affects that target
- You've shown activity in an in vivo tumor model
- Is that enough? What's next?



Start with the Guidances



- **[ICH S9: Nonclinical Evaluation for Anticancer Pharmaceuticals](#)
- **[ICH S9 Nonclinical Evaluation for Anticancer Pharmaceuticals Questions and Answers](#)
- [ICH S6: Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals \(and its Addendum\)](#)

Typical Recommendations for Anticancer Drugs



- ICH S9 explains basic recommendations for anti-cancer drugs
 - 28-day GLP-compliant toxicology studies in 2 species
 - For biologics (see ICH S6 and its addendum), if scientifically justified, a single GLP study in a pharmacologically relevant species is often acceptable
 - ❖ Primary data used to determine starting dose for FIH trials



Tip: Can initially submit *draft* tox reports with signed histopathology reports

Special Consideration of Immune-Activating Drugs



- ICH S9 includes exception on standard toxicology-based methods for starting dose of immune agonists:
 - “For biopharmaceuticals with immune agonistic properties, selection of the start dose using a minimally anticipated biologic effect level (MABEL) should be considered.”
- MABEL approach relies heavily on pharmacology studies
- Use the **totality of data** to justify the proposed FIH dose

Saber H et al., 2016, Regul Toxicol Pharmacol, 81:448-456
Saber H et al., 2017, Regul Toxicol Pharmacol, 90:144-152

DHOT Publications on FIH Dose Selection



- An FDA oncology analysis of immune activating products and first-in-human dose selection. PMID: 27743776.
- An FDA oncology analysis of CD3 bispecific constructs and first-in-human dose selection. PMID: 28887049.
- An FDA oncology analysis of antibody-drug conjugates. PMID: 25661711.
- An FDA oncology analysis of toxicities associated with PBD-containing antibody-drug conjugates. PMID: 31325532.
- Pharmacokinetic models for first-in-human dose selection of immune-activating products in oncology. PMID: 38561147.

DHOT = Division of Hematology Oncology Toxicology

What are my endpoints?



- The CFSAN Redbook
 - Detailed descriptions of toxicological endpoints to include
 - Large array of study types (gene- to chronic tox)

CFSAN = Center for Food Safety and Applied Nutrition (FDA)

Key Endpoints in GLP Tox Studies



- Mortality
- Clinical Observations
- Body Weight
- Food Consumption
- ECG (non-rodent)
- Ophthalmology
- Hematology
- Clinical Chemistry
- Gross Pathology
- Organ Weights
- Histopathology
- Toxicokinetics

-Additional endpoints as needed (e.g., cytokines)

Good Laboratory Practice



- GLP ≠ study with good controls, endpoints
- GLP = these things, but also details about archiving, study conduct, responsibility
- GLP is described in the Code of Federal Regulations ([21 CFR part 58](#))

GLP cont.

- Consider the CRO or conducting lab
- Make sure they can format the data in SEND (*Standard for Exchange of Nonclinical Data*)
 - Single dose toxicity, repeat-dose toxicity, and carcinogenicity studies for commercial INDs initiated after December 17, 2017; Technical Rejection Criteria now active
 - [Study Data Standards Resources](#)
- MUST plan ahead! (schedule far in advance)
- These studies can be expensive but foundational

GLP cont.

- If you have questions/uncertainty about GLP study design:
 - Consult an expert first
 - Request a pre-IND meeting with FDA before initiating the study
 - We can provide general feedback on major red flags and missing endpoints

What else is recommended for FIH study?



- Depends on your product
- Proof-of-concept/MOA data
 - [Content and Format of Investigational New Drug Applications \(INDs\) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products](#)
- Screening data
- Concentration response data
- Immunomodulators: In vitro Cytokine Release Assays
- Safety Pharmacology (hERG; in vivo endpoints)



Stumbling Blocks/Pitfalls



- Common *nonclinical* reasons for going on hold in oncology:
 - Concerns with FIH starting dose and/or dose escalation
 - Missing studies/supporting information
 - Severe toxicity
 - [An FDA analysis of clinical hold deficiencies affecting investigational new drug applications for oncology products. PMID 31678263.](#)
- Starting dose: Scale by BSA (mg/m²) for small molecules/ADCs; body weight (mg/kg) for large biologics ([BSA conversions; Table 3](#))
- GLP-related: *Need signed pathology report*
- Provide data supporting selection of pharmacologically relevant species for biologics/oligonucleotides



Special Considerations and Additional Resources



| Radiopharmaceuticals | <ul style="list-style-type: none">• <u>Oncology Therapeutic Radiopharmaceuticals: Nonclinical Studies and Labeling Recommendations Guidance for Industry</u> |
|----------------------|---|
| ADCs | <ul style="list-style-type: none">• <u>ICH S9 Q&A</u>; <u>Saber H, Leighton JK. 2015</u>; <u>Saber H et al., 2019</u> |
| Novel excipients | <ul style="list-style-type: none">• <u>FDA Guidance for Industry: Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients</u> |
| Botanicals | <ul style="list-style-type: none">• Consider how your product differs from what has been given to humans previously• <u>Botanical Drug Development Guidance for Industry</u> |

Request a Pre-IND Meeting!



- INTERACT meeting
 - FDA input on unique challenges; use of novel alternative methods (NAMs)
- Type B pre-IND meeting
 - Follow-up opportunities available
- Provide enough data that we can answer your question(s)- don't submit full study reports
- We won't agree to specific starting dose at pre-IND

Summary



- There is a lot of nonclinical data needed to open an IND
- Let ICH S9 be your starting point
- Invest in good GLP tox studies
- Seek out a regulatory consultant if needed
- Request a pre-IND meeting!

Closing Thought



***Use these tips to improve your nonclinical package for your next FIH IND submission for oncology indications**

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