Getting to First-in-Human Trials

for Small Molecules and Biologics

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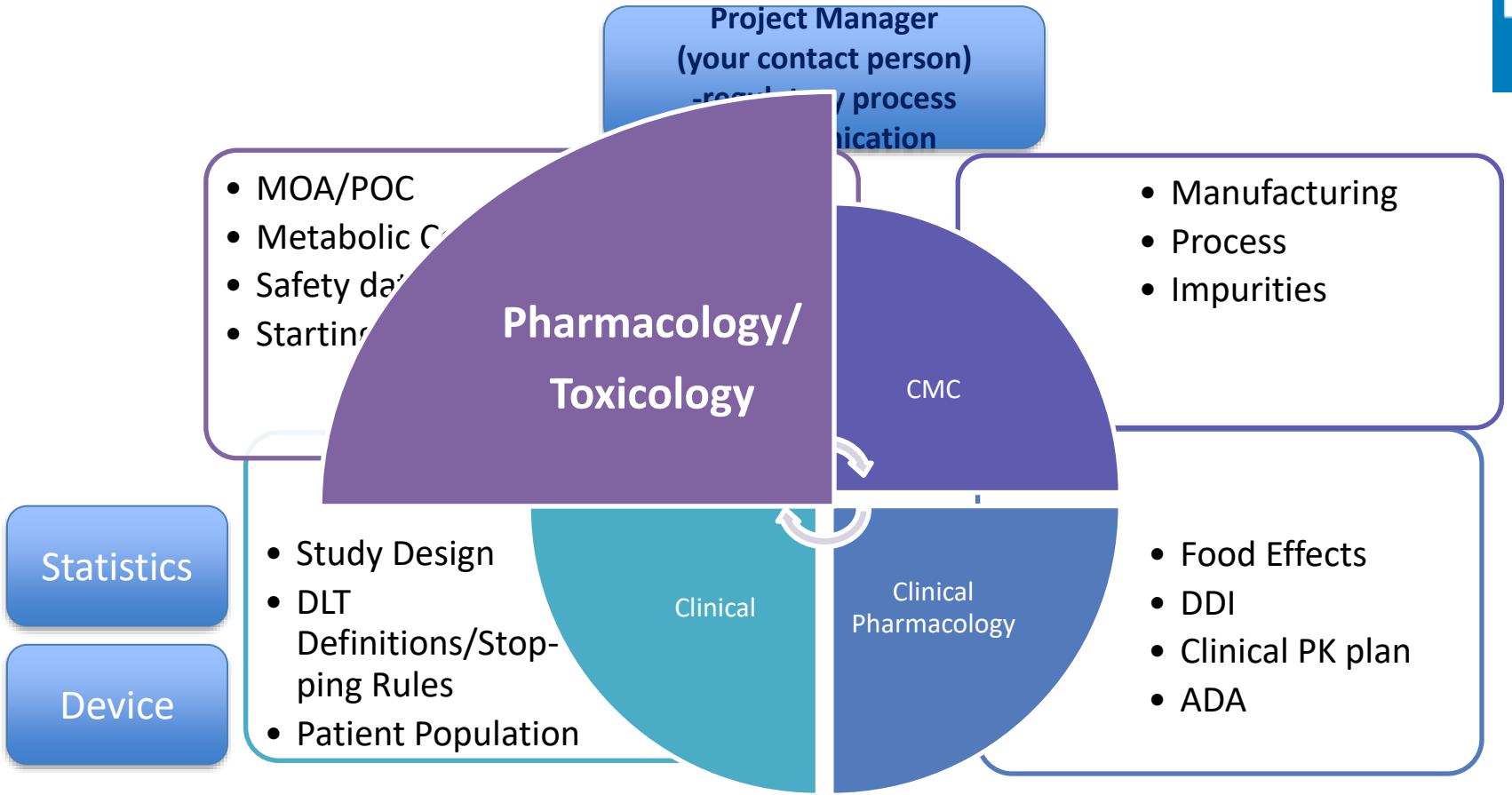
Overview

- Who is the team
- Where to start
- What we are looking for
- For your consideration

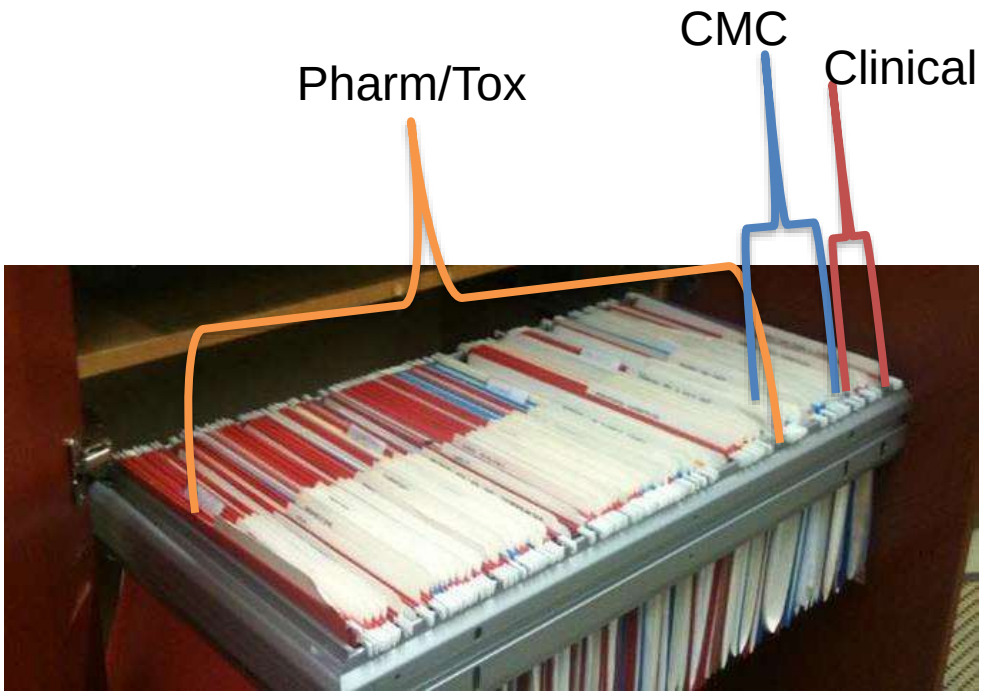
Abbreviations

- HNSTD-highest non-severely toxic dose
- STD10-severely toxic dose in 10% of animals
- MOA-mechanism of action
- POC-proof of concept
- MABEL-minimal anticipated biological effect level
- GLP-Good Laboratory Practice
- SEND-Standard for Exchange of Nonclinical Data
- ICH-International Council on Harmonization
- FIH-First-in-Human

Your Initial Team



Nonclinical is Front Loaded



You've had your great idea, now what

- You've identified a target
- You've shown that your drug effects 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
  - https://www.fda.gov/media/73161/download
- ICH S9 Nonclinical Evaluation for Anticancer Pharmaceuticals Questions and Answers
  - https://www.fda.gov/media/100344/download
- ICH S6: Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (and its Addendum)
  - https://www.fda.gov/media/72028/download
  - https://www.fda.gov/media/78034/download
- FDA Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trial for Therapeutics in Adult Healthy Volunteers
  - https://www.fda.gov/media/72309/download

Typical Requirements for Anticancer Drugs

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

Special Recognition of Immune-Targeting 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."
- The MABEL relies heavily on pharmacology studies

So what are my endpoints?

- The CFSAN Redbook
  - Detailed descriptions of toxicological endpoints to include
  - Large array of study types (genetox to chronic tox)
    - https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-and-other-stakeholders-redbook-2000#TOC

Key Endpoints in GLP Tox

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

Generally safety pharmacology endpoints are built into toxicology studies for oncology drugs

Stumbling Blocks

- Intersections with CMC
  - not having low enough dose formulations
  - not having data showing that you can deliver the right dose
  - a tox batch that is “too clean”
- GLP
  - Signed pathology report
- SEND

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)
  - https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=58

GLP-2

- Consider the CRO or conducting lab
- These studies are expensive
- These studies are also foundational
  - A bad study may not save you money
- Make sure they can format the data in SEND

What else do you need?

- Depends on your product
  - Screening Data—looking for other targets
    - Primary
    - Secondary
  - Concentration response data
  - Cytokine Release Assays in soluble and plate bound formats using primary human cells
  - Safety Pharmacology (hERG and in vivo endpoints)
  - Phototoxicity and Genetox (usually later in development)

Still have Questions? Pre-IND Meetings

- Can occur at different stages
  - Early development before the tox studies are done
  - Later when most of the questions are about study design
- You get one official PIND
  - But you can request additional kinds of meetings if needed

Pre-IND Considerations

- Provide enough data that we can answer the question
- Understand that we can't pre-review all the primary data
- Don't ask vague questions
  - "is my protocol ok?"

Case 1—SMKI-152

- SMKI-152 is a small molecule kinase inhibitor
  - The intended primary target is not novel, not first-in-class; 4 other targets (500 kinase panel); no additional hits
- Toxicology studies in 2 species (rat and dog)
  - Histopathology reports unsigned
  - STD10= 100 mg/kg ; HNSTD=6 mg/kg; proposed starting dose=75 mg

SMKI-152 Cont.

- Issue 1: Unsigned Pathology Reports
  - FDA sent an information request asking for the signed report
  - Sponsor was able to provide the report; problem resolved
- Issue 2: The tox studies don't support the proposed dose
  - The rat study showed no significant toxicity
  - The dog study showed clear toxicity and death; possible equivocal related dose
  - The dog can support a dose of ~40 mg; the Sponsor agreed to lower the dose
- Issue 3: The lowest formulation is 75 mg

Bio-101

- Bio-101 is a bispecific targeting CD3 and a target expressed on non-hematologic cells
- The Sponsor submitted an IND with no toxicology data and no primary pharmacology data
- There were references to pharmacology data in the literature and comparisons to an antibody with the same co-target.

Immediate Hold!

21 CFR 312.42(b)(1)(iv): Insufficient information to assess risks to human subjects

- Hold Comments from all disciplines
- Major Comments from Nonclinical:
  - Justify the lack of toxicology data or provide a GLP-compliant 28-day toxicology study
  - If there is no relevant species, provide human tissue cross reactivity data
  - Provide pharmacology data to support the selection of an appropriate starting dose

Complete Response

- The Sponsor submitted data showing that there was no relevant species
  - the product bound to the co-target but not the CD3 epitope in any species except chimpanzee
- No GLP-compliant tissue cross study, but there was a preliminary screen and information on expression of the co-target
  - FDA determined this was acceptable
- The Sponsor included dose comparisons to traditional antibodies with the same co-target and to a cellular therapy

Outcomes

- FDA still did not agree that the available data supported the proposed dose
  - The comparative data was to vastly different kinds of products
  - There was evidence of in vivo cytokine release and death
  - The argument for a safety margin based on lack of PBMC response in the presence of "normal" cells was not compelling, particularly because the co-target is widely expressed
- There was, however, sufficient in vitro data to set *a* dose
  - The EC50s in the activation assays were in the range of 10^{-4} nM
  - At a dose of 4.5ng/kg (approximately 112 ng) the predicted Cmax for Product A would be~ $2*10^{-4}$ nM; this was about 100x lower than the proposed dose of 11 ug

But the Sponsor remained on hold because of lack of sufficient CMC data regarding ability to adequately deliver the dose

- It is not our goal to find a reason to put your study on hold

Summary

- There is a lot of nonclinical data needed to open an IND
- Go to ICH S9 as a starting point
- Invest in good GLP studies
- Consider your nonclinical data before finalizing the initial clinical formulation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