The IND Defined: A Regulatory Perspective

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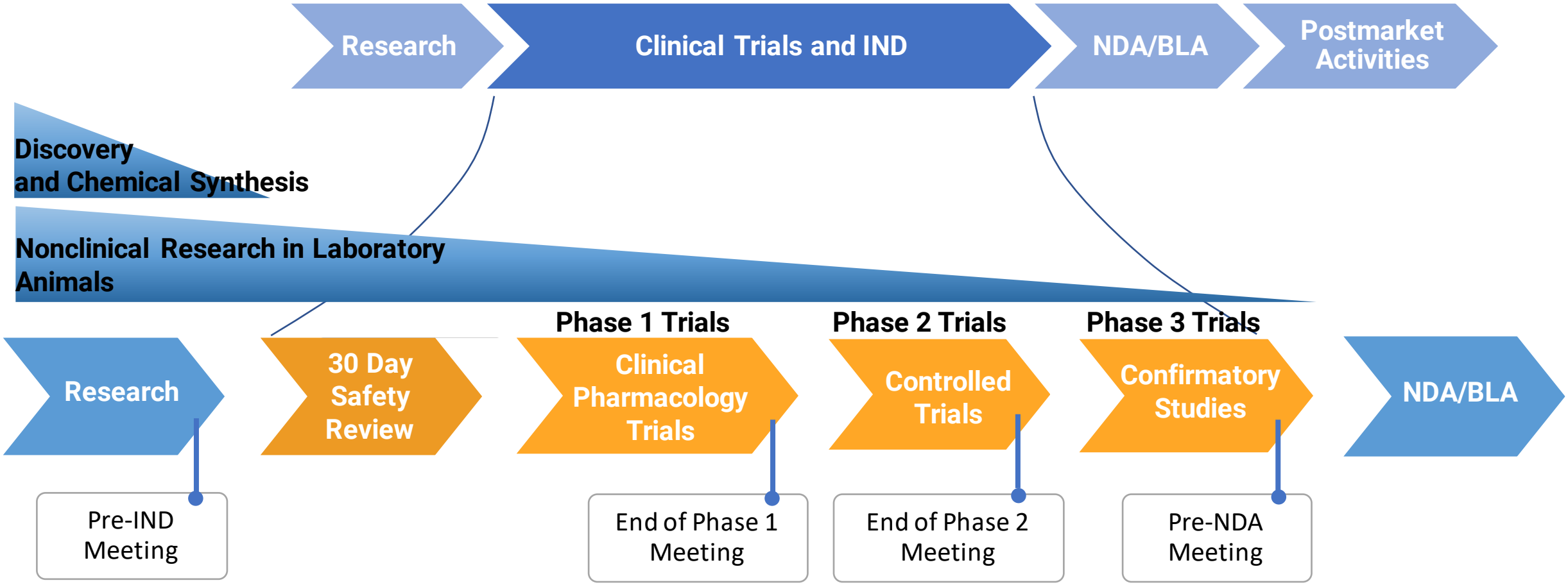
Agenda

- Overview of the drug development process
- Basics of the pre-IND meeting
- Basics of the IND review process
- The role of the nonclinical reviewer
- Nonclinical reasons leading to a clinical hold

Overview of the Drug Development Process



The Pre-IND

- Purpose of the pre-IND
  - Designed to facilitate and foster early communications between the FDA and sponsors
  - Identify any potential safety issues
  - Enable the timely initiation of clinical trials
  - Avoid conducting unnecessary nonclinical studies

- What is a pre-IND meeting?
  - Type B meeting; usually a written response only (WRO) or teleconference within 60 days of submitting a request
  - Opportunity for sponsors to ask the FDA questions pertaining to their nonclinical drug development program

- Should you request a pre-IND meeting?
  - FDA encourages all sponsors to utilize pre-IND meetings to discuss their nonclinical development program

The Pre-IND

- Pre-IND Briefing Package Contents (not inclusive)
  - Overall program synopsis, including a description of the clinical protocols
  - Description of the planned *in vivo* toxicology studies
  - Summary of the results for *in vitro* and *in vivo* toxicology studies
  - Notification if the animal rule is being considered
  - List of specific questions to be addressed by the Agency

- Advice provided by the FDA is based on the information provided in the briefing package

- Pre-IND timeframe
  - Sponsor must submit briefing package within 30 days of submitting meeting request
  - FDA has 60 days from receiving the meeting request to respond

Tips for Writing Pre-IND Meeting Questions

- Ask specific, well-phrased, direct questions
- Focus questions on specific areas
  - If the IND is for a first-in-human trial, avoid asking if the planned and completed studies will support an NDA/BLA; it is too soon in the process
- General questions are OK if they are relevant
- Share concerns and propose solutions
  - Ask the question you want answered
- Be clear - do not assume the FDA will know what you are talking about

The IND

- When is an IND required?
  - Use of a drug that is unapproved in the US
  - Use of an approved drug with a change in dosage or route of administration
  - Use of an approved drug in different patient populations

- Purpose of the IND review
  - Establish that a drug is reasonably safe and effective
  - Ensure all risk are adequately monitored and communicated to subjects in clinical trials

The IND Review Process

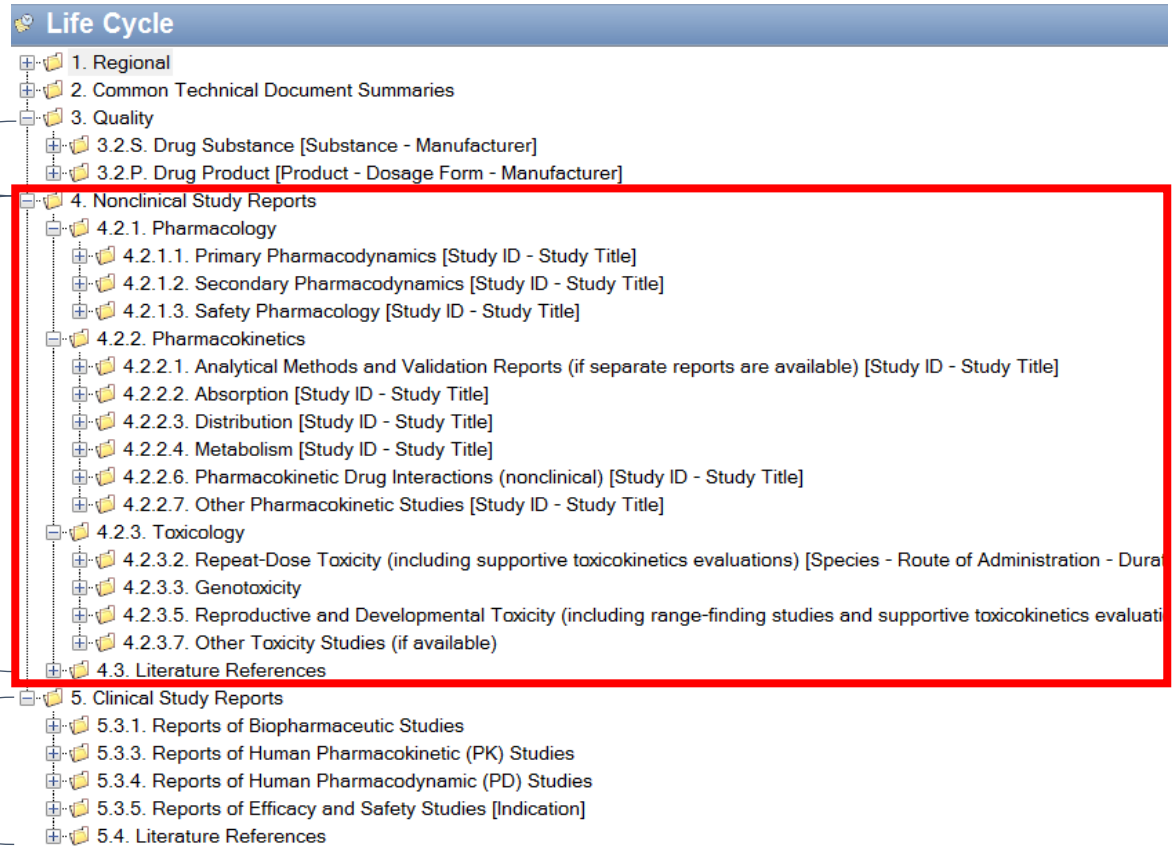
- The FDA has 30 calendar days to make a decision
- Near the end of the 30-day period, an internal safety meeting is held to discuss the IND application and reach a decision
- The multi-discipline review team decides whether or not the proposed trial is safe to proceed
- For the sponsor/investigator, no news is good news after 30 days

Contents of the IND

CMC Reviewer

Nonclinical Reviewer

Clinical and Clinical Pharmacology Reviewers



IND Nonclinical Content

- Pharmacology
  - Primary and secondary pharmacodynamics
  - Safety pharmacology (cardiovascular, respiratory, CNS)
- Pharmacokinetics/Toxicokinetics
  - Absorption, Distribution, Metabolism, Excretion (ADME)
- Toxicology
  - Single-dose toxicity
  - Repeat-dose toxicity
  - Genotoxicity
  - Carcinogenicity
  - Reproductive and developmental toxicity
  - Local tolerance
  - Special toxicology studies

Primary and Secondary Pharmacodynamics

Primary Pharmacodynamics

- Preliminary studies that help measure drug efficacy
- *In vitro* studies:
  - Receptor binding (affinity/selectivity for primary receptors)
  - Functional activity (agonist/antagonist)
- *In vivo* studies (examples of nonclinical pharmacology studies):
  - MPTP Parkinson's Disease model in monkeys
  - Obesity models in rodents
  - SHIV model in monkeys
  - Animal rule models (anthrax, smallpox, Ebola, etc.)

Secondary Pharmacodynamics

- Studies that help identify potential off-target effects of the drug
- Broad or targeted *in vitro* screens that identify potential secondary targets
  - Receptors
  - Channels
  - Enzymes
  - Transporters
- Additional animal studies or clinical monitoring may be requested

Pharmacokinetics (ICH S3B)

- Studies that assess how a drug is absorbed, distributed, metabolized, and excreted from the body (ADME)
- Generally conducted as single-dose studies in animals at non-toxicological dose levels
  - Supports nonclinical toxicology study doses
  - Helps predict human PK parameters

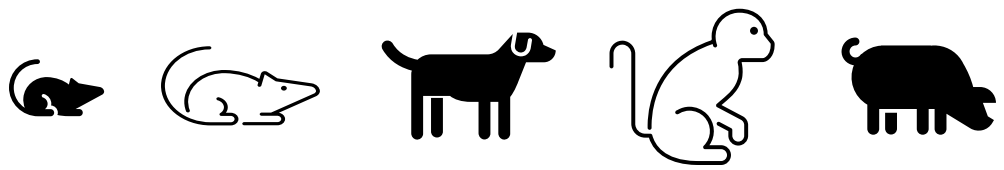
- Absorption:
  - How does formulation affect solubility/dissolution rate?
  - How does food affect oral dosing?
  - What is the bioavailability (amount of drug that is absorbed into the blood stream and survives the hepatic first-pass effect)?
- Distribution:
  - Where does the drug go? What organs?
  - Is it sequestered?
  - Does this correlate to organ toxicity or mechanism of action?
- Metabolism:
  - Are there any metabolites and what happens to them?
  - Are metabolites species-specific?
  - Are additional studies on metabolites needed?
- Excretion:
  - Are the drug/metabolites removed from the body? How much?
  - Through what pathway(s) (bile, urine, feces)?

Toxicokinetics (ICH M3R2, S3A)

- Toxicokinetics = pharmacokinetics in animal models at toxicological doses
- Usually integrated into the repeat-dose studies
  - Blood samples are collected usually after the first and last doses
  - Data are used to correlate drug exposure to toxic endpoints
- Common TK parameters:
  - C_{max} = highest concentration of drug, usually in plasma
  - AUC = total exposure to drug over a set time period (“area under the curve”)
  - $t_{1/2}$ = time required for clearance of 50% of the drug (“half-life”)
  - T_{max} = time at which C_{max} occurs
- Important considerations:
  - Does exposure increase with dose? Is the increase dose-proportionate?
  - Does the drug accumulate with repeat/increased doses?
  - How does route of administration affect exposure?
  - Does the formulation affect exposure?

Safety Pharmacology (ICH S7A, S7B, S6R1)

- Studies that identify potential adverse pharmacodynamic effects of a drug on normal physiological functions
- Cardiovascular (dogs, monkeys, minipigs)
  - Blood pressure, heart rate, electrophysiology, echocardiography, *in vitro* hERG assay
- Respiratory (rats, mice, dogs)
  - Respiratory rate, tidal volume, airway resistance, lung compliance
- Central nervous system (rats, mice)
  - Functional Observation Battery (FOB)
    - Qualitative – body position, reflexes, grooming, behavior, vocalization, gait, etc.
    - Quantitative - body temperature, grip strength, hindlimb splay, motor activity
  - Electroencephalogram
    - Seizure liability
    - Spectral analysis



Safety Pharmacology (ICH S7A, S7B, S6R1)

- Renal (not always conducted)
  - Water consumption and urine volume
  - Glomerular filtration rate and renal plasma flow
  - Electrolyte excretion and pH
- Gastrointestinal (not always conducted)
  - Emesis and nausea
  - Esophageal and intestinal transit time
  - Gastric emptying time and pH
  - Frequency of gastric contractions
- Typical study design
  - Single-dose
  - One control and 3 dose levels
  - Small groups or individual animals
  - May be combined and/or integrated into repeat-dose toxicity studies

Single-Dose Toxicology Studies (ICH M3R2, S6R1)

- Studies that assess the acute toxicity of a drug
  - Often conducted as dose-range finding (DRF) studies to determine the maximum tolerated dose (MTD) and inform dosing in repeat-dose toxicology studies
- Not always conducted according to GLP regulations
- May not be needed for initiation of clinical trials

Repeat-Dose Toxicology Studies (ICH M3R2, S9)

- Studies that determine the adverse effects of a drug in animals
  - Required to support initiation of clinical trials
  - Longer clinical protocols require longer repeat-dose studies
- The starting dose in humans is dependent on repeat-dose studies
  - Each study should have a well-defined NOAEL that is used to calculate safety factors
  - The highest non-severely toxic dose (HNSTD) may be used for anticancer drugs
  - The safety factors are calculated based on exposure and body surface area
- Typical Study Design:
  - Requires at least two species (rodent and non-rodent)
  - Both sexes should be evaluated
  - At least three dose levels and a control
  - Doses are selected based on *in vitro* and preliminary animal studies
  - Route of administration should be same as in clinical trial
  - Length of study is dependent on the duration of the proposed clinical trial
  - Should include a recovery period to assess reversibility

Repeat-Dose Toxicology Studies (ICH M3R2)

- Key parameters to be evaluated:
  - Mortality and clinical signs
  - Body weight and food consumption
  - Clinical pathology
    - Hematology
    - Serum chemistry
    - Clotting parameters
  - Urinalysis
  - Ophthalmology
  - Pathology
    - Gross pathology
    - Organ weights
    - Histopathology
  - Local tolerance
  - Toxicokinetics

- Recommended duration for repeat-dose toxicology studies

Table 1 Recommended Duration of Repeated-Dose Toxicity Studies to Support the Conduct of Clinical Trials

Maximum Duration of Clinical Trial	Recommended Minimum Duration of Repeated-Dose Toxicity Studies to Support Clinical Trials	
	Rodents	Nonrodents
Up to 2 weeks	2 weeks[a]	2 weeks[a]
Between 2 weeks and 6 months	Same as clinical trial[b]	Same as clinical trial[b]
> 6 months	6 months[b, c]	9 months[b, c, d]

Table 2 Recommended Duration of Repeated-Dose Toxicity Studies to Support Marketing

Duration of Indicated Treatment	Rodent	Nonrodent
Up to 2 weeks	1 month	1 month
>2 weeks to 1 month	3 months	3 months
>1 month to 3 months	6 months	6 months
>3 months	6 months[c]	9 months[c, d]

Repeat-Dose Toxicology Studies (ICH M3R2)

- Important considerations:
  - Were the studies conducted according to GLP requirements?
  - Is there a well-defined NOAEL? Does it provide an adequate safety factor?
  - Are the toxicities sex- or species-specific?
  - Are the toxicities dose-dependent? Are they reversible?
  - Are additional studies required?
  - What are the expected clinical toxicities? Are they monitorable?

Genotoxicology (ICH S2R1, S2B)

- Studies that assess the ability of a drug to induce genetic damage
  - Damage may induce mutations which may lead to carcinogenesis
  - Carcinogenesis may not be evident for many years
- Types of mutations:
  - Base-pair substitutions
  - Frameshift mutations
  - Additions and deletions
  - Chromosomal breaks and defects (clastogenicity)
- Additional considerations:
  - Location of damage (what genes are affected and are they critical?)
  - Extent of damage (will the damage be passed on to daughter cells?)
  - Repair mechanisms (is the damage repairable?)
  - Threshold (is there a dose below which no effects are observed?)

Genotoxicology (ICH S2R1, S2B)

- Bacterial reverse mutation assay (Ames test)
  - Used to identify base pair substitutions and frameshift mutations
- *In vitro* chromosomal aberration assay
  - Used to identify structural damage to and numerical changes in chromosomes/chromatids
- Mouse lymphoma assay (thymidine kinase assay)
  - Used to detect point mutations and chromosomal damage
- *In vivo* micronucleus assay
  - Used to detect chromosomal and mitotic spindle apparatus damage
- *In vivo* comet assay
  - Used to detect strand breaks, alkali-labile sites and DNA-DNA or DNA-protein adducts

Carcinogenicity (ICH S1A, S1B, S1C)

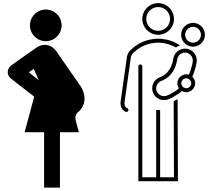
- Studies that assess the carcinogenic potential of a drug
- Required, generally prior to approval, for drugs that are administered for at least 6 months
  - Includes intermittent use for chronic/recurrent conditions
  - May not be needed if a drug is genotoxic
  - Not required for initiation of an IND
  - Typically conducted in rats and mice but transgenic mouse models may also be used
- Study protocol and study reports are thoroughly reviewed by internal biostatisticians and the Executive Carcinogenicity Assessment Committee (ECAC)

Developmental and Reproductive Toxicology (ICH S5)

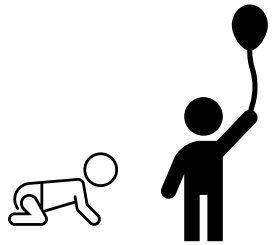
- Studies that evaluate the ability of a drug to adversely affect fertility, pregnancy and embryo-fetal/neonatal development
  - Difficult and unethical to study in humans
  - Data used for risk assessment in the product label

- Types of reproductive toxicology studies:
  - Fertility and early embryonic development (FEED)
  - Embryo-fetal development (EFD)
  - Pre- and post-natal development (PPND)

- Definitive studies not typically included in the initial IND package, but dose range-finding studies may be included



Juvenile Toxicology Studies (ICH S11)



- Studies that assess the effects of a drug on postnatal growth and development following neonatal to pre-adult exposure
- Conducted only when previous animal and human data are considered insufficient to support pediatric trials based on a weight of evidence
- Study design is similar to that of a repeat-dose toxicology study
  - What is the appropriate species?
  - How old are the animals?
  - What is the appropriate dosage?
  - What organs/systems are being targeted?

	Human	Rat	Dog	Cynomolgus Monkey
Neonate	Birth – 1 month	Birth – 7 days	Birth – 3 weeks	Birth – 4 months
Infant	1 – 24 months	7 – 21 days	3 – 6 weeks	4 – 6 months
Child	2 – 12 years	21 – 35 days	6 – 20 weeks	6 – 36 months
Adolescent	12 – 16 years	35 – 60 days	5 – 8 months	3 – 5 years

Special Toxicology Studies

- Immunotoxicology (ICH S8)
  - Studies that assess the effects of a drug on the immune system
    - Immunosuppression (increased cancer/infection risk)
    - Immunostimulant (hypersensitivity, autoimmunity)
  - Initial assessments (hematology, histopathology, unexplained infections) are evaluated in the repeat-dose toxicity studies. Additional assessments may also be made.
    - T cell-dependent antibody response (TDAR) assay
- Phototoxicoloy (ICH S10)
  - Studies that assess the potential of a photoreactive drugs, those that generate a reactive species following exposure to visible/UV light, to induce a light-induced tissue response
    - 3T3 neutral red uptake assay (*in vitro*)
- Abuse potential (Assessment of Abuse Potential of Drugs, Guidance for Industry)
  - Studies that assess the potential for CNS-acting drugs to cause abuse or dependence
- Mechanistic studies
  - Studies to further assess the mechanism of action or toxicity

SEND (Standard for Exchange of Nonclinical Data)

- Electronic Study Data Requirements:

SEND Requirement Dates for Nonclinical Studies Modelled in SEND : FDA Data Standards Catalog (Studies started after the following dates require SEND datasets)		
Study Types Modelled in SEND	**NDAs/BLAs**	**Commercial INDs**
Single Dose Toxicity, Repeat Dose Toxicity, and Carcinogenicity Studies	December 17, 2016 (SENDIG v3.0) March 15, 2019 (SENDIG v3.1)	December 17, 2017 (SENDIG v3.0) March 15, 2020 (SENDIG v3.1)
Cardiovascular and Respiratory Safety Pharmacology Studies	March 15, 2019 (SENDIG v3.1)	March 15, 2020 (SENDIG v3.1)
Animal Rule	March 15, 2022 (SENDIG AR v1.0)	March 15, 2023 (SENDIG AR v1.0)

- Technical Rejection Criteria
  - On September 15, 2021, if sponsors submit an IND without required SEND datasets for nonclinical studies the entire application will be rejected at the Electronic Submissions Gateway (ESG)
  - The FDA may Refuse To File (RTF) an NDA, BLA, or ANDA lacking required SEND datasets
  - Nonclinical studies not requiring SEND datasets need a Simplified ts.xpt file

Small Molecules vs. Large Molecules

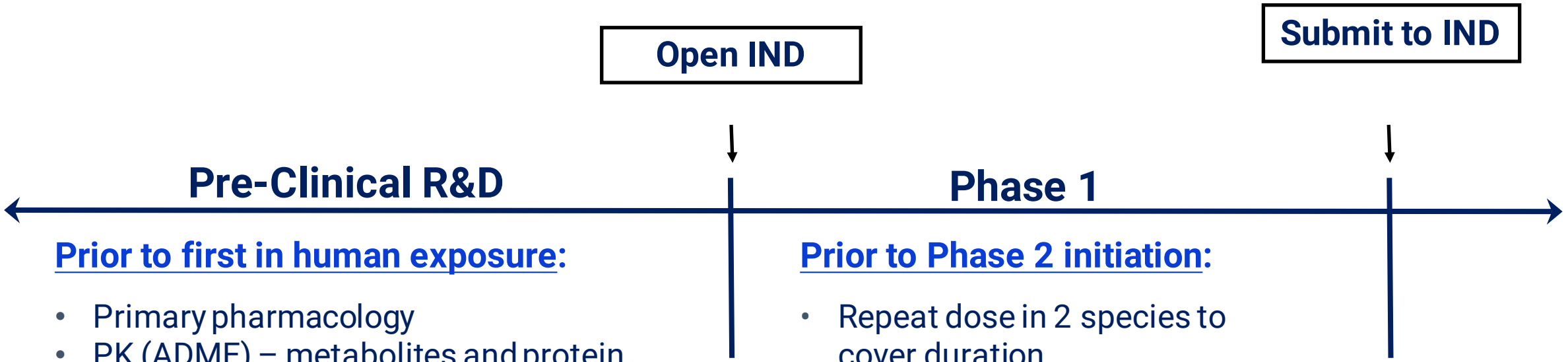
Small Molecules

- ICH M3R2 – chemicals and oligonucleotides
- Some PK/ADME
- Single- and/or repeat-dose toxicity studies in 2 species (rodent and nonrodent)
- Safety pharmacology
- Genotoxicity
- Local tolerance (depending on the route)
- Starting dose is 10-fold higher than the NOAEL

Large Molecules

- ICH S6R1 – mAbs, cytokines, recombinant plasma factors, growth factors, fusion proteins, enzymes, receptors, hormones, etc.
- Toxicity studies in 2 species but a single species may be justified under certain circumstances
- Tissue cross-reactivity (TCR) study to assess off-target binding and determine most appropriate species
- Measure immunogenicity
- Local tolerance
- No genotoxicity assessment
- Starting dose may be based on the minimally anticipated biologic effect level (MABEL)

Timeline of Nonclinical Development



Prior to first in human exposure:

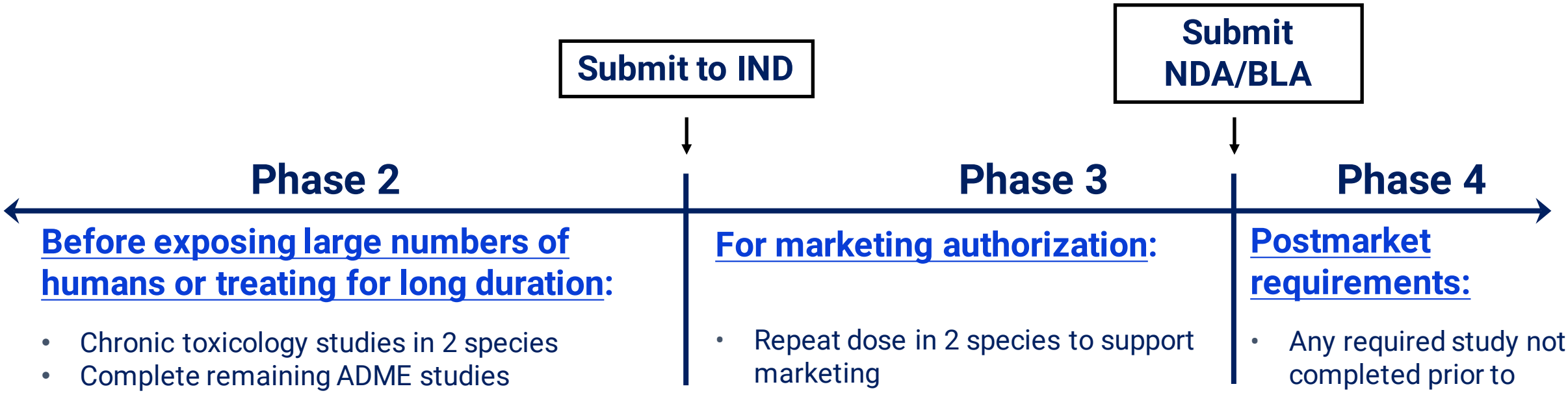
- Primary pharmacology
- PK (ADME) – metabolites and protein binding
- Safety pharmacology
- Single or short-term repeat dose study in 2 species
- *In vitro* genotoxicity

Prior to Phase 2 initiation:

- Repeat dose in 2 species to cover duration
- ADME
- Comparison of animal and human PK
- Genotoxicity (completed)
- Use of 2 forms of contraception for women of reproductive potential

***Note: It is possible to open the IND in Phase 2 or 3 as well, depending on the product.**

Timeline of Nonclinical Development



Before exposing large numbers of humans or treating for long duration:

- Chronic toxicology studies in 2 species
- Complete remaining ADME studies
- Characterization of human-specific metabolites, if necessary
- Fertility and early embryonic development (FEED) and Embryo-fetal development studies (EFD)
- Juvenile animal studies, if necessary

For marketing authorization:

- Repeat dose in 2 species to support marketing
- Carcinogenicity
- Pre- and post-natal development (PPND)
- Any remaining pharmacology/mechanistic studies to support NDA/BLA

Postmarket requirements:

- Any required study not completed prior to market authorization (e.g., carcinogenicity, DART, juvenile toxicity)

Role of the Nonclinical Pharmacology/Toxicology Reviewer

REVIEW
Evaluate all discipline related evidence, including field related opinions

RECOMMEND
Provide opinions based on expertise to those who make the final decision

COMMUNICATE
Both written (reviews) and oral (internal and industry meetings)

- Pre-IND
- New IND 30-day safety assessment
- Active IND study review (IND maintenance)
- Industry meetings
- Internal consults with clinical, CMC, and clinical pharmacology reviewers
- Consults with other FDA Centers (CDRH, CBER)
- Protocol assessments
- NDAs and Labeling
- Postmarket surveillance

Pharmacology/Toxicology Reviewer's Role in Meetings

- Pre-IND meetings
  - Ensure the Sponsor has proposed/conducted the appropriate nonclinical studies to determine if the drug is safe for administration to humans.
- 30-day safety meetings
  - Discuss potential human safety concerns based on the nonclinical findings.
  - Communicate any significant adverse effects or potential need for additional clinical monitoring.
  - Determine if the proposed trial is safe to proceed.
- End of Phase 2 meetings
  - Ensure all necessary nonclinical studies have been conducted to support a large clinical trial in the intended patient population.
  - Establish a timeline on any remaining studies needed for marketing authorization.
- Pre-NDA meetings
  - Confirm all necessary nonclinical studied needed to support an NDA/BLA are completed.

Other Areas that a Nonclinical Reviewer Must Consider

- CMC
  - Structural alerts or reactive groups of concern
  - Excipients, impurities, extractables and leachables
- Clinical Pharmacology
  - How exposure relates to toxicity
  - Comparison between the animal and human PK/TK data
- Clinical
  - Can potential toxicities be monitored in the clinic or will special monitoring be needed
  - Toxicities that are difficult to monitor in the clinic
    - Sudden death
    - Vasculitis
    - Genotoxicity and carcinogenicity
    - Impaired fertility or teratogenicity
    - Histopathological changes
    - Long-term toxicities

Nonclinical Reasons for a Clinical Hold

- Appropriate studies were not conducted to assess the drug's safety
- Study design was flawed
  - Insufficient number of animals
  - Inappropriate endpoints
  - Study duration not appropriate
- The toxicities present an unacceptable risk
- A NOAEL was not identified
  - Exception for oncological indications when the highest non-severely toxic dose (HNSTD) is used.
- The risks to humans outweighs any potential benefit

Summary

- Refer to ICH and FDA Guidance for Industry
- Guidance does allow for flexibility on a case-by-case basis
- Engage with the FDA

Thank You

Resources

- *FDA Guidance for Industry*
  - https://www.fda.gov/regulatory-information/search-fda-guidance-documents
- *ICH Guidelines*
  - https://www.ich.org/page/ich-guidelines