# IND-Enabling Nonclinical Packages for Rare Diseases

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# Back to Regulatory Affairs Basics: What is an IND?

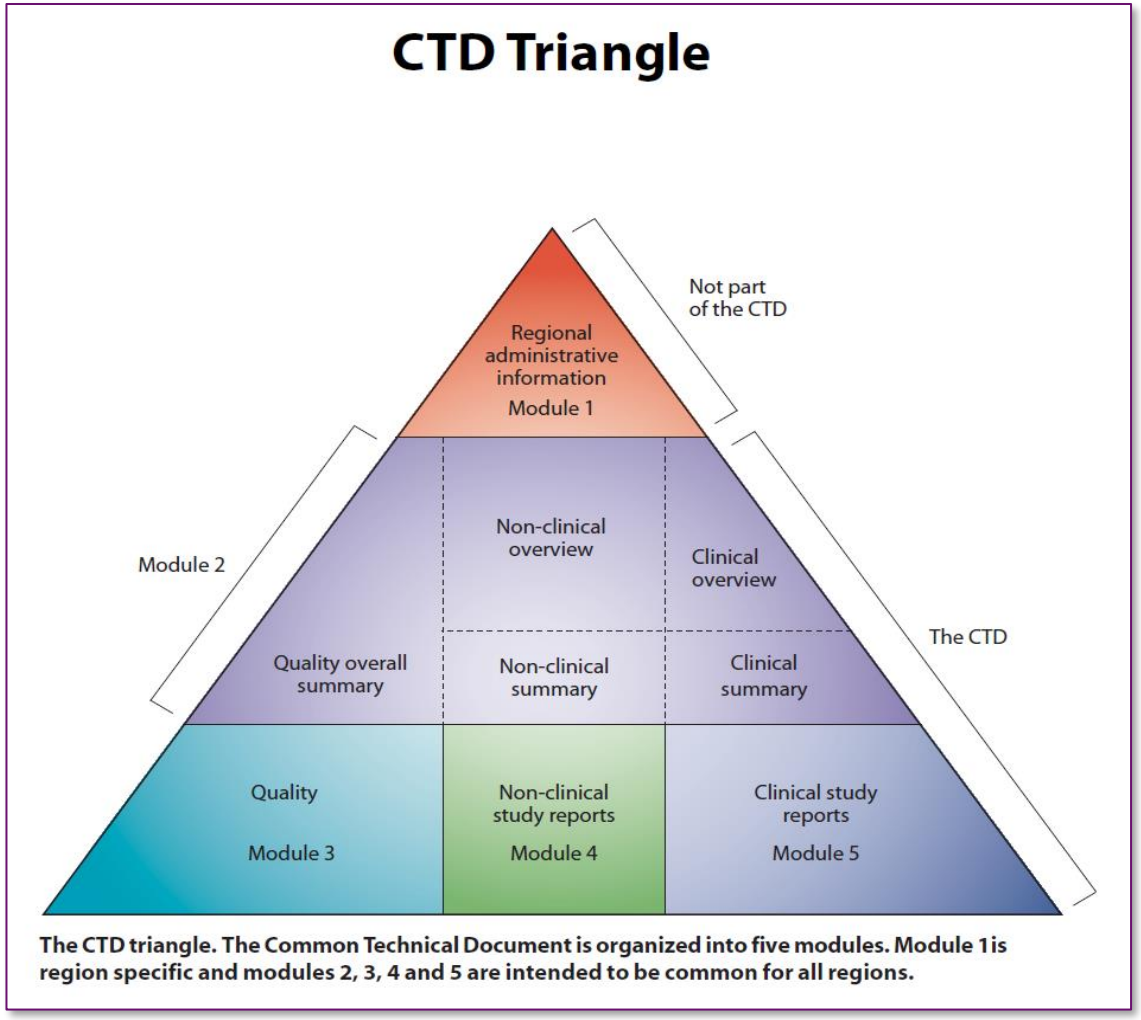
**CTD: Common Technical Document** structure

The aim of an investigational new drug application (IND) is to obtain approval from FDA to perform clinical trials of an investigational medicinal product (IMP) in humans in the US.

The IND follows the common technical document (CTD) structure developed by ICH and requires very detailed product and development data such as manufacturing, nonclinical, any previous clinical data.

It is required to provide comprehensive source documentation, including study reports.

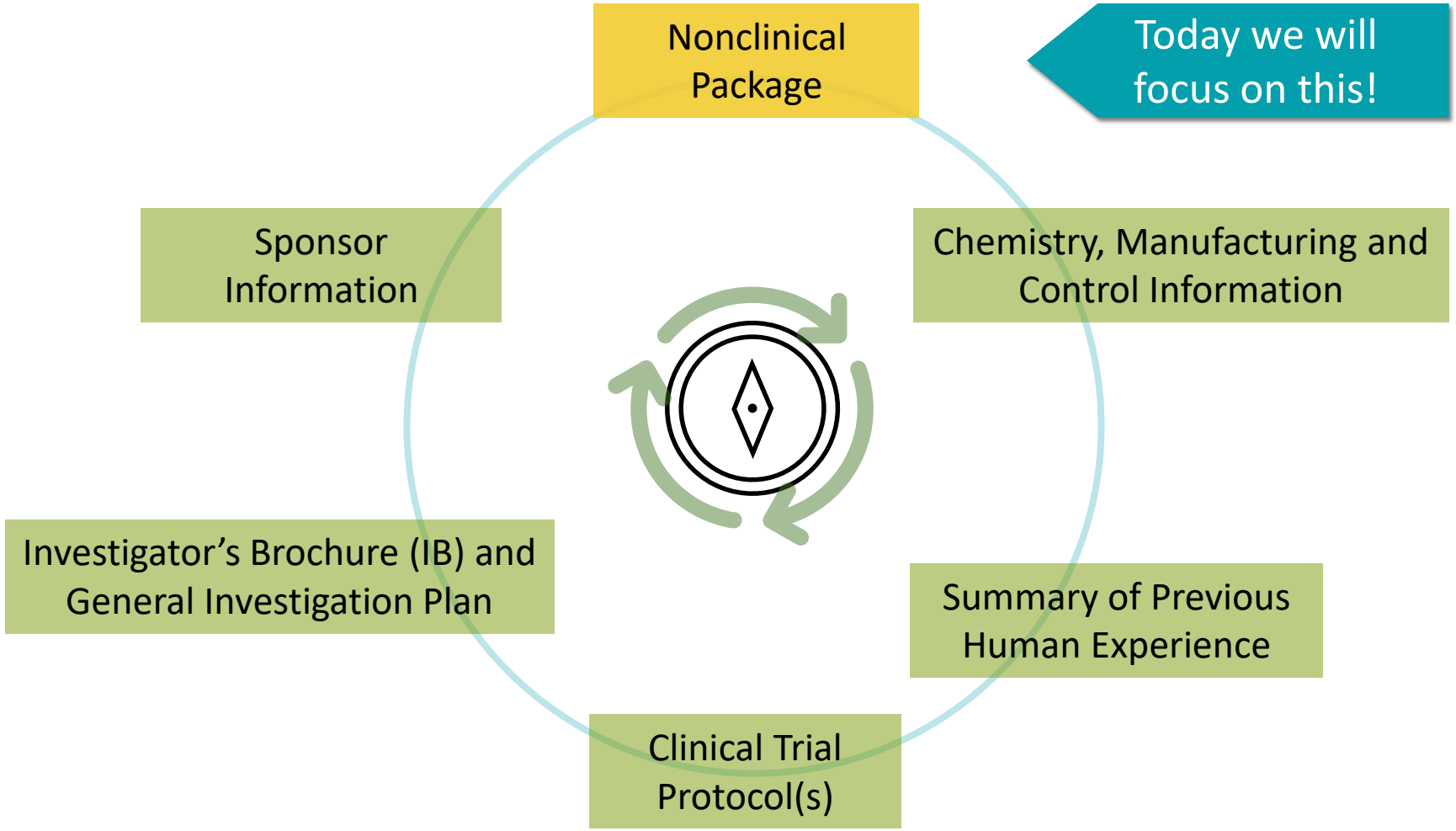
**Essentially, the IND is the way to share with the FDA what you know about your drug and how you want to test it clinically; the FDA's primary focus is safety at this stage**



The CTD triangle. The Common Technical Document is organized into five modules. Module 1 is region specific and modules 2, 3, 4 and 5 are intended to be common for all regions.

CTD guide in ICH M4: https://ich.org/page/ctd

# IND Content.


Nonclinical Package
Today we will focus on this!
Sponsor Information
Chemistry, Manufacturing and Control Information
Investigator's Brochure (IB) and General Investigation Plan
Summary of Previous Human Experience
Clinical Trial Protocol(s)

# Goals of IND-enabling nonclinical package.

Technical data package justifying why clinical investigation is warranted, based on:

- Demonstration of proof-of-concept (POC) effects in animals (if possible)
- Characterization of drug **pharmacology** (***effect***), **pharmacokinetics** (***exposure***), and **toxicology** (***safety/tolerability***)
  - Demonstrate ***exposure: effect*** relationships and how this resolves to dose ("PKPD")
  - Define efficacious and toxic dose range → therapeutic index (TI)
  - Predict efficacious dose, regimen and safe starting dose
- Inform clinical trial design (e.g., dosing, monitoring, biomarkers)
- Assure drug is reasonably safe to begin human testing

Consider that: **IND application is just *first* step of journey, additional studies needed as clinical development progresses**

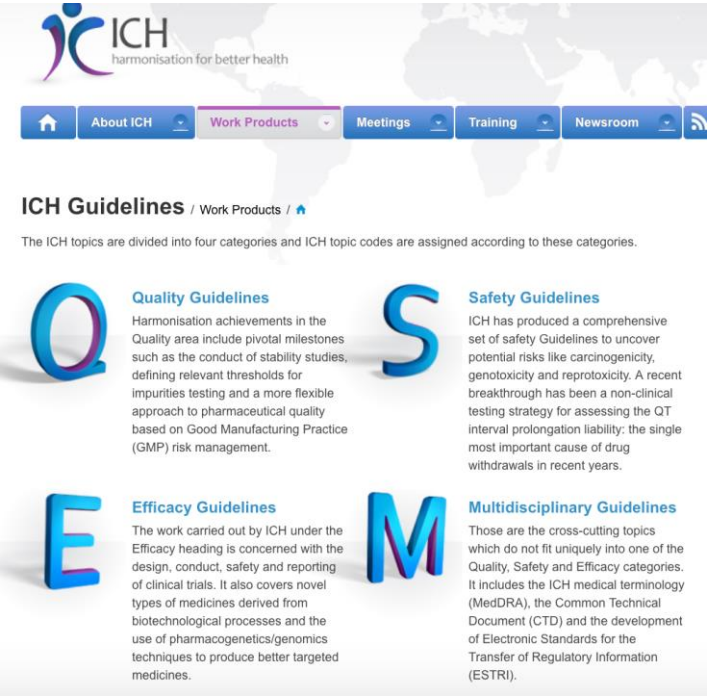
# IND-enabling packages for Broad v Rare Disease Indications.

**Examples of contrasting drug development and regulatory challenges that set rare disease apart from broader indications:**

| Broad Indication (e.g. Glucose-lowering; Diabetes) | Rare/Ultra-Rare Indication (e.g. CNS neurodegenerative) |
|---|---|
| Pharmacological MoA likely well researched and understood, with translatable animal models | Pharmacology not always understood, animal models of disease may not provide good translation to human disease |
| Likely joining a competitive marketplace, meaning rich natural history and RWE that supports efficacy claims | Little/no RWE puts strain on efficacious dose requirements, adds huge pressure to discover functional biomarkers |
| Ample market comparators to set pharmacology and safety criteria that may be able to guide clinical development | With little/no RWE, translation of animal pharmacology challenging and may not convert to appropriate dose range |
| Large and accessible patient population | Small patient population which may experience diverse disease symptomology and response |
| Healthy adult volunteer study to establish route of administration and tolerability limits | Likely want to start testing patients immediately at-risk, may have limited options based on drug modality |
| Precedented regulatory pathway with Health Authority expectations well defined | This is improving with dedicated Rare Disease guidance, agencies being flexible to program needs |

# Examples of Regulatory Guidance Used to Guide Nonclinical Programs.

## International Conference on Harmonization (ICH) (www.ich.org)




## ICH guidance established to harmonize expectations across Europe, Japan, and US

- ICH M3(R2) Nonclinical safety studies for the conduct of human clinical trials
- ICH S6(R1) Preclinical safety evaluation of biotechnology products
- ICH S5a Detection of toxicity to reproduction for medicinal products
- ICH S2b Standard battery of genotoxicity testing
- ICH S7a Safety pharmacology studies for pharmaceuticals
- ICH S11 Nonclinical safety testing in support of Pediatric pharmaceuticals
- ICH 12 Biodistribution considerations for gene therapy

## FDA guidance

- Estimating maximum safe starting dose in initial clinical trials

## Global and rare disease specific guidance also available

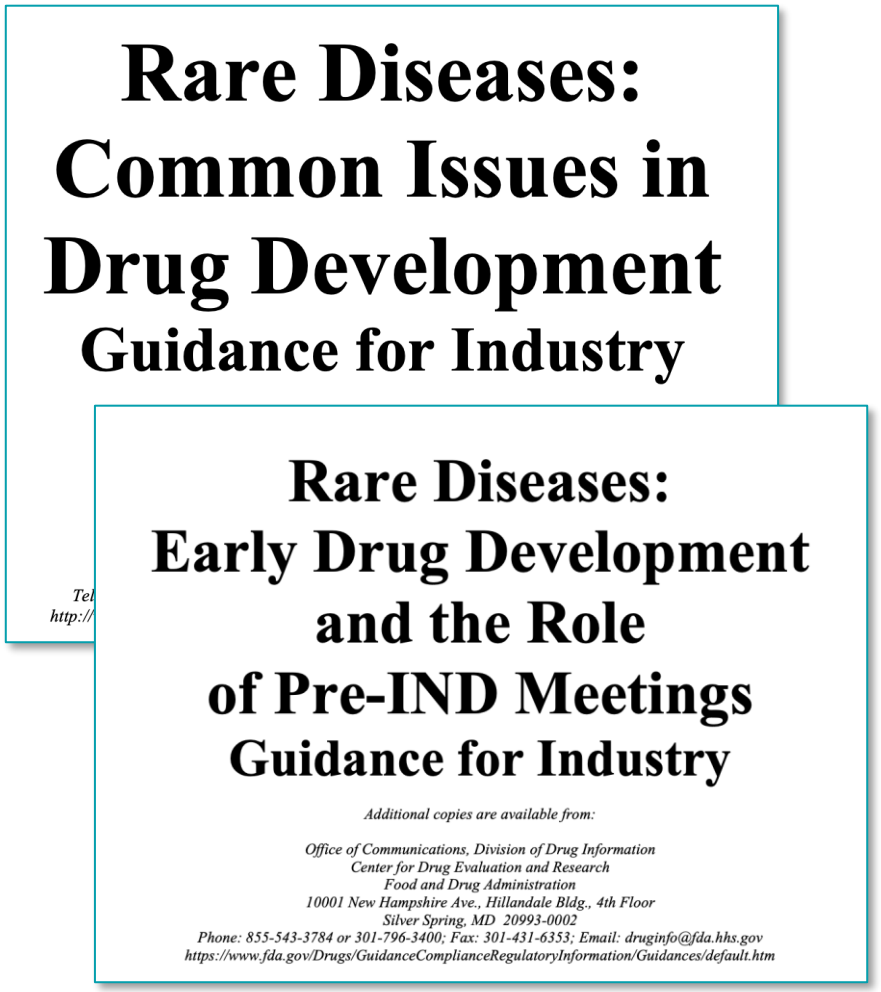
Some flexibility for serious and life-threatening rare diseases,
an abbreviated or deferred nonclinical program may be appropriate

# FDA Guidance for Industry – Rare Diseases: Common Issues in Drug Development.

## Key Takeaways for Nonclinical IND-enabling packages:

- **Information on disease natural history, understanding of the pathophysiology and drug's proposed MoA**

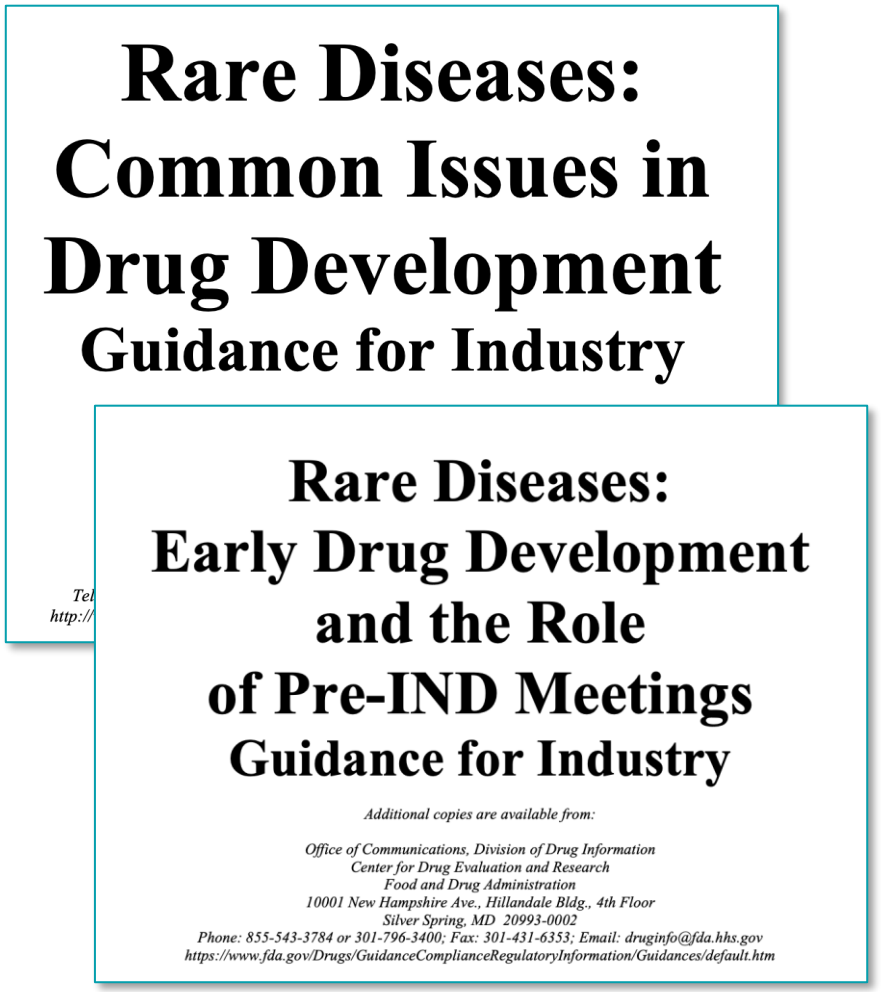
- **PharmTox considerations to support clinical investigation should include:**
  - **Endpoints** / biomarkers and outcome assessments
  - A means to establish **safety and efficacy** (NOAEL and MED)
  - **Drug manufacturing** considerations, and toxicological coverage of impurities / formulation / route of administration
  - Particularly relevant when **repurposing/expanding** existing indications



# FDA Guidance for Industry – Rare Diseases: Common Issues in Drug Development – *Focus on Nonclinical Studies*.

**Guidance advises that nonclinical package adheres to ICH M3 principles:**

- Tox info (In vitro/vivo) required before enabling FIH
- Contribute to better understanding of the MoA
- Important to the design of the early-stage clinical trial, and inform starting dose level, dose escalation plan, dosing regimen, and route of administration
- Data may help guide patient eligibility criteria and safety monitoring procedures
- Tox Study design based on:  biology of the disease, expected pharmacology of the drug (including existing POC data),  support for proposed clinical design



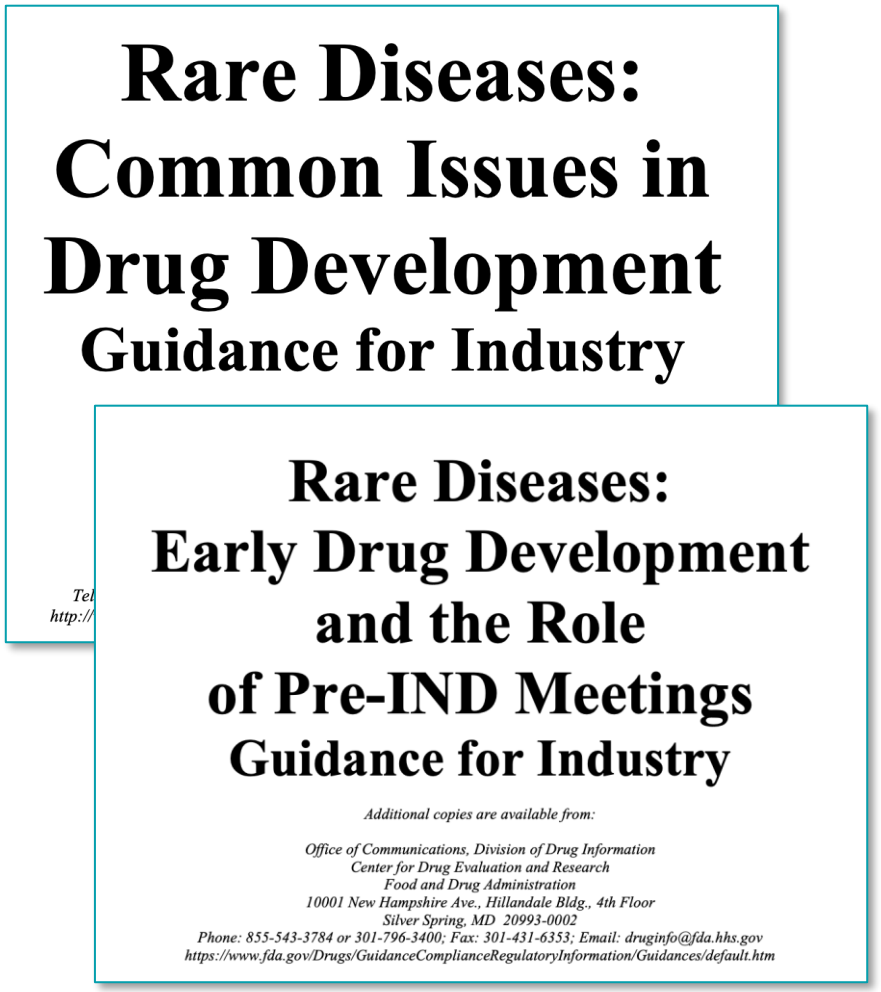
# FDA Guidance for Industry – Rare Diseases: Common Issues in Drug Development – *Focus on Nonclinical Studies*.

- **Default to use healthy animals, but can consider using animal models of disease for toxicology studies**
  - This usually will not substitute for all testing in healthy animals because of concern that the disease pathophysiology may obscure drug toxicity

- **FDA generally does not require testing for safety or pharmacology in animal model of disease**

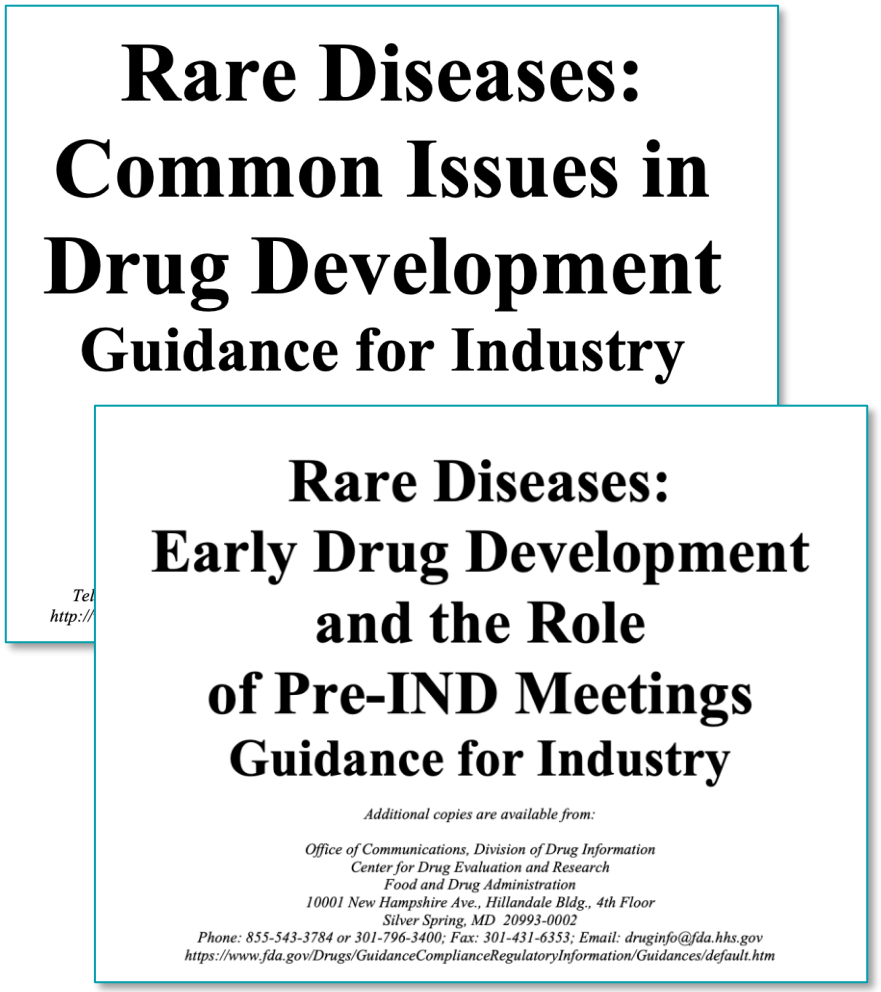
- **Although not a requirement, PharmTox testing in animal models may help evaluate long-lasting/irreversible adverse effects to describe the long-term risk/benefit differences**

- **FDA encourages sponsors to seek early communication v/v. pre-IND meetings**



# FDA Guidance for Industry – Early Drug Development and the Role of the Pre-IND Meeting.

- **Excellent opportunity to get feedback from FDA on package design and appropriateness**
- **FDA Guidance document provides many suggestions (helpful blueprint for your package design!)**
  - Consider ICH M3(R2) for guidelines that apply to all programs
  - Be prepared to discuss whether completed studies/proposed study plan are sufficient to support PoC and to inform safety of the drug before initiating FIH
- **Can use the meeting to discuss what additional studies may be necessary to support trials (eg duration of chronic studies, Development and Repro Tox, carcinogenicity)**



# Nonclinical studies should cover age of clinical population and duration of clinical study.

***Patient age*** **and** ***Study duration*** **are two important considerations that shape nonclinical studies:**

## Age of target population

- **Verifying that animals provide sufficient coverage to clinical population, and along with scaling dosing in animal models of disease when assessing pharmacology and tolerability**
- **Initial treatment in pediatric patients is at odds with conventional IND-enabling study planning (due to the assumption that early studies will be conducted in adults)**
    - Nonclinical studies must consider adding younger animals to study and/or selecting species that allow testing at younger ages
    - May be required to conduct standalone juvenile tox and DART earlier than typically expected

## Study duration

- **Without the option of healthy volunteer SAD to establish some treatment parameters, the risk/benefit aspects need to be well defined with a good escalation strategy that supports for starting and anticipated clinically efficacious dose**

# Key expectations for nonclinical package designs.

## Study designs should include:

- Species-justification - appropriate to characterize the test article, relevant to human
- Dose-justification - to establish safety margins above your anticipated starting or MED dose, and ‘stratify’ exposure:response relationship
- Duration that covers your initial clinical investigation needs (may be different for Rare indications)

## Study objectives should be able to describe:

- A sense of Therapeutic Index / safety margin
- Characterization of any dose-limiting toxicity, if possible, data on whether tox effects may be progressive
- Assessment of the translational relevance of the data
- Studies that enable testing in the appropriate patient population - age/gender

# Recommended Tox Study Durations (non-AAV) from ICH M3(R2).

**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** | **Non-rodents** |
| 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] |

How applicable are these to Rare?

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

| Duration of Indicated Treatment | Rodent | Non-rodent |
|---|---|---|
| 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] |

N.B., See footnotes **c** and **d** in Table 1.

# Differences in the types of Nonclinical Toxicology studies required to support clinical development may be driven by modality.

| | Small Molecules | Biologics | Gene Therapy |
|---|---|---|---|
| Short-term repeat dose studies | Up to 3 month to support FIH<br>2 species | Up to 3 month to support FIH<br>2 species | Single dose, followed to 3 months to support FIH (possibly 6 months for BLA); Biodistribution assessment included<br>1-2 species |
| Long-term (chronic) repeat dose studies | 6 month rodent and 9 month non-rodent as needed to support clinical duration | 6 month in single species as needed to support clinical duration | N/A |
| Safety Pharmacology | Core Battery (CNS, CV, Respiratory) to be completed prior to FIH | No dedicated studies, CV assessment included in short-term repeat dose tox studies | No dedicated studies at time of IND thus far required, but need to address as program progresses |
| Genotoxicity | Standard in vitro / in vivo test battery (gene mutation and chromosomal damage) usually completed prior to FIH (required to start phase II) | Not warranted | Not warranted in the typical way, but vector integration is a hot topic with HAs |
| Carcinogenicity | 2 species, usually long-term rodent bioassay, to be completed prior to NDA filing | Weight of evidence review to characterize risk; add-on nonclinical studies to mitigate risk or label inclusion; long-term rodent bioassay not generally warranted | Weight of evidence review to characterize risk, BUT tumorigenicity and HCCs are a hot topic with HAs |
| Reproductive toxicity | Fertility assessment (rodent), EFD (2 species) and PPND study (rodent) required at various stages of clinical development | Fertility assessment in repeat-dose study using mature NHP<br>ePPND study (NHP) required prior to filing | Likely need Fertility and EFD in one species<br>Risk of germline transmission needs to be considered if vector distributes and persists in gonads |

# Example nonclinical components of a AAV Gene Therapy IND package.

| Type of study | Model | Source |
|---|---|---|
| POC efficacy | G6pc$^{-/-}$ mouse | Literature |
| POC pharmacology study | G6pc$^{-/-}$ mouse | Sponsored in academic collaborator's lab (Non GLP) |
| GLP Toxicology/Biodistribution | WT mice | At CRO (GLP) |
| | | |
| In vivo activity assay to support product characterization | WT mice | At CRO (non GLP) |
| Secondary pharmacology to investigate HCC/HCA formation | Inducible liver specific KO mouse model | Sponsored in academic collaborator's lab (Non GLP) |

# Example nonclinical components of an ERT IND package.

| Type of study | Model | Source |
|---|---|---|
| In vitro Pharmacodynamics | Human MPS VII fibroblasts | In-house |
| POC pharmacology stud(ies) | MPS VII mouse | Sponsored in academic collaborator's lab (Non GLP); plus numerous publications referenced |
| Safety Pharmacology | CNS in rat; Respiratory in rat; CV as part of 6-month NHP tox | At CRO (GLP) |
| PK - absorption | SD rat; RD rat & NHP TK | At CRO |
| PK – distribution | SD & RD MPSVII mice; SD rat | At CRO; also referenced pubs |
| Non-GLP Toxicology – repeat dose | MPSVII mice | At CRO (non-GLP); plus at academic collaborator with addition of histopathology by CRO |
| GLP Toxicology – single dose | Rat | At CRO (GLP) |
| GLP Toxicology – repeat dose (chronic) | Monkey (juvenile) | At CRO (GLP) |

# Example nonclinical components of a small molecule IND package.

| Study Type / Duration | Route | Species | GLP Status |
|---|---|---|---|
| **Secondary Pharmacodynamics** | | | |
| Ex vivo creatine quantitation and brain imaging | IV infusion (1 hour) | WT and CrT KO Sprague-Dawley rat; Cynomolgus monkey | No |
| In vivo biomarker discovery | IV infusion (1 hour) | WT and CrT KO Sprague-Dawley rat | No |
| **Pharmacokinetics, Distribution, Metabolism and Excretion** | | | |
| Stability assessments | Cell culture; blood and plasma | C57/Bl6 mouse, Sprague-Dawley rat, Cynomolgus monkey and human | No |
| In vitro MetID | Cell culture; blood and plasma | C57/Bl6 mouse, Sprague-Dawley rat, Cynomolgus monkey and human | No |
| In vivo MetID | IV infusion (1 hour) | Sprague-Dawley Rat | |
| In vivo Mass Balance | IV infusion (1 hour) | Sprague-Dawley Rat and Cynomolgus monkey | No |
| CYP inhibition/induction (Drug-drug Interaction studies) | In vitro | Human | No |
| **Single-dose (Acute) Toxicity** | | | |
| Dose range finding tolerability | IV infusion (1 hour) | Adult Cynomolgus Monkey | No |
| **Repeat-dose Toxicity** | | | |
| 2-week repeat-dose toxicity (no recovery) | IV infusion (1-2 hour) | Adult Sprague-Dawley Rat and Cynomolgus Monkey | No |
| 3-month repeat-dose toxicity with 1-month recovery phase | IV infusion (1 hour) | Adult Sprague-Dawley Rat and Cynomolgus Monkey | Yes |
| **Safety Pharmacology** | | | |
| In vitro radioligand binding panel and functional assays | In vitro | Cell culture | No |
| In vitro hERG binding | In vitro | Cell culture | Yes |
| In vivo CV assessment | IV infusion (2hr) | Cynomolgus Monkey (integrated into repeat-dose toxicology) | Yes |
| In vivo neurological assessment | IV infusion (1hr) | Sprague Dawley Rat (integrated into repeat-dose toxicology) | Yes |
| In vivo CNS effect characterization | IV infusion (2-8 hours) | Cynomolgus Monkey | No |
| **Genetic Toxicology** | | | |
| Ames Assay: Bacterial Reverse Mutation Assay | In vitro | In vitro | Yes |
| Micronucleus Assay | In vitro | In vitro (note: in vivo micronucleus in rat also planned) | Yes |
| **Other Toxicology Studies** | | | |
| Phototoxicity Assessment | N/A | N/A | Non-GLP |
| Hemolytic Potential | In vitro | Ex vivo; Rat, Cynomolgus, Human Blood | Non-GLP |

# Conclusions and parting thoughts.

- Increasing discovery and diagnoses of rare diseases means there is no 'one size fits all' approach to development
- Regulatory guidance and general rules exist that help make development more consistent and predictable
- From nonclinical perspective, many programs will share common themes such as:
  - Balancing risk v benefit; using nonclinical data to inform and prioritize patient safety
  - Understanding your disease population and the overall clinical plan is important to the development of your nonclinical strategy
  - Plan to meet with regulatory authorities early to align on strategy, opportunities to accelerate development
    - For rare disease, the streamlining nonclinical plans may be possible, and some studies can be negotiated to conduct later in development and/or post-marketing
  - Investigative studies, e.g., with animal models of disease, can be incorporated into the overall nonclinical package, including the evaluation of safety
- Completion of nonclinical studies will gate initiation of clinical trials, and studies may also be conducted throughout the development process in parallel with clinical (including sometimes post-marketing)

# Appendix / Reference Material.

| Regulatory Affairs and IND -related |
| --- |
| Regulatory:  IND definitions, submission types |
| International Requirements;  US v OUS (including Canada and EU) |
| IND v Clinical Trial Application (CTA) |

| Nonclinical Study –related |
| --- |
| Types of Nonclinical Studies to Support Trials and Approval |
| GLP vs non-GLP study standards and requirements |
| Description of Studies per CTD Section; study design principles |
| Species selection and Study Design |
| Dealing with Drug Attrition |

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# Thank You

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# Appendix / Reference Material

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# What's an IND?

A review of the drug development process from non-clinical perspective

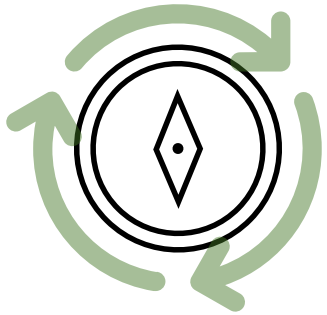
# IND Content.

Animal pharmacology, pharmacokinetics and toxicology studies

Today we will focus on this!

Sponsor Information

Chemistry, Manufacturing and Control Information



Investigator's Brochure (IB) and General Investigation Plan

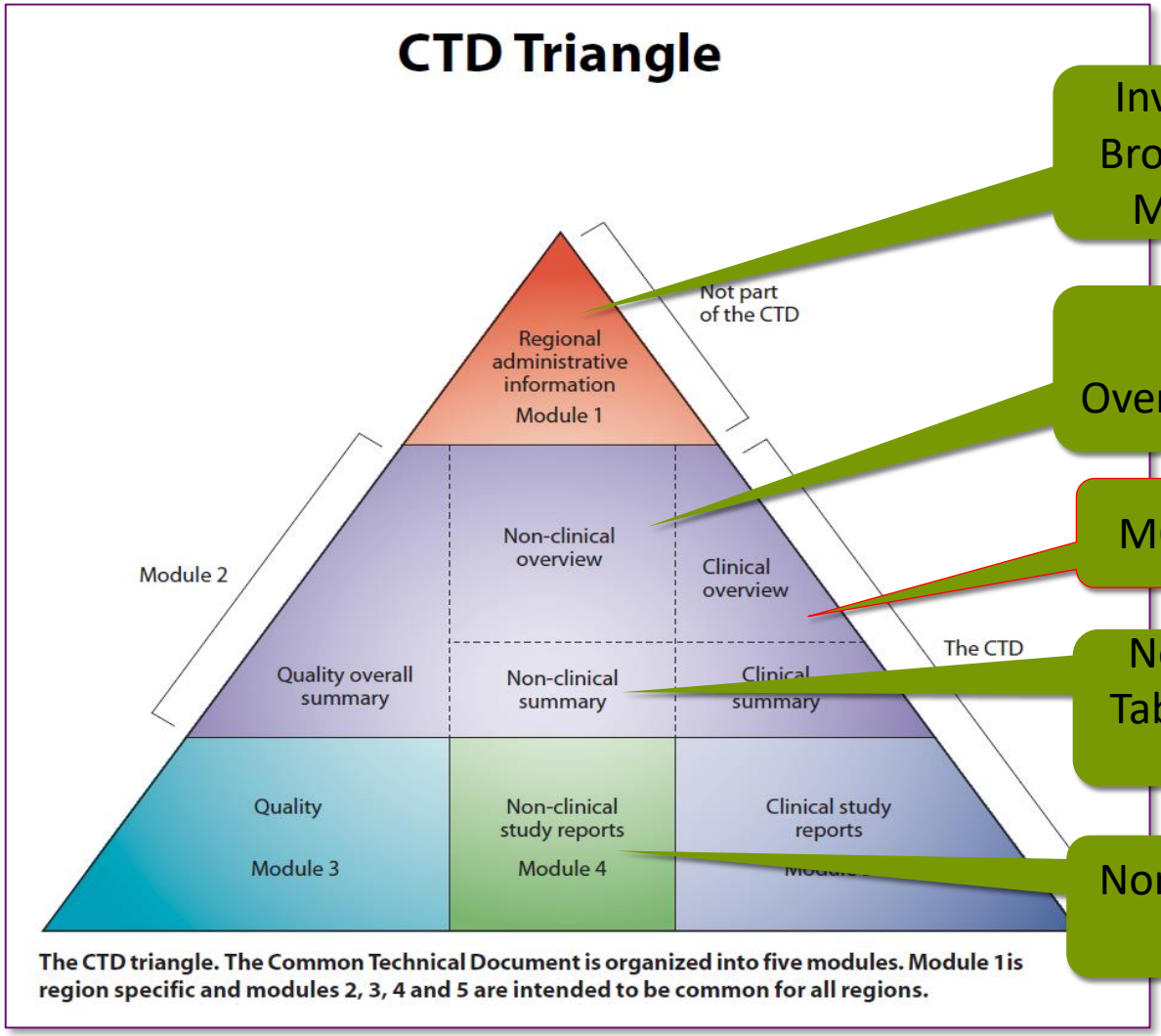
Summary of Previous Human Experience

Clinical Trial Protocol(s)

Nonclinical input valuable (and expected) in multiple sections:

- e.g., CMC and clinical input in **2.6.1 Nonclinical Introduction**
- nonclinical input into **2.5 Clinical MoA**)

# CTD: Common Technical Document structure.




Investigator's Brochure (IB) – Mod 1.1.16

Nonclinical Overview – Mod 2.4

Nonclinical expertise often required for MOA section too

MOA - Mod 2.5

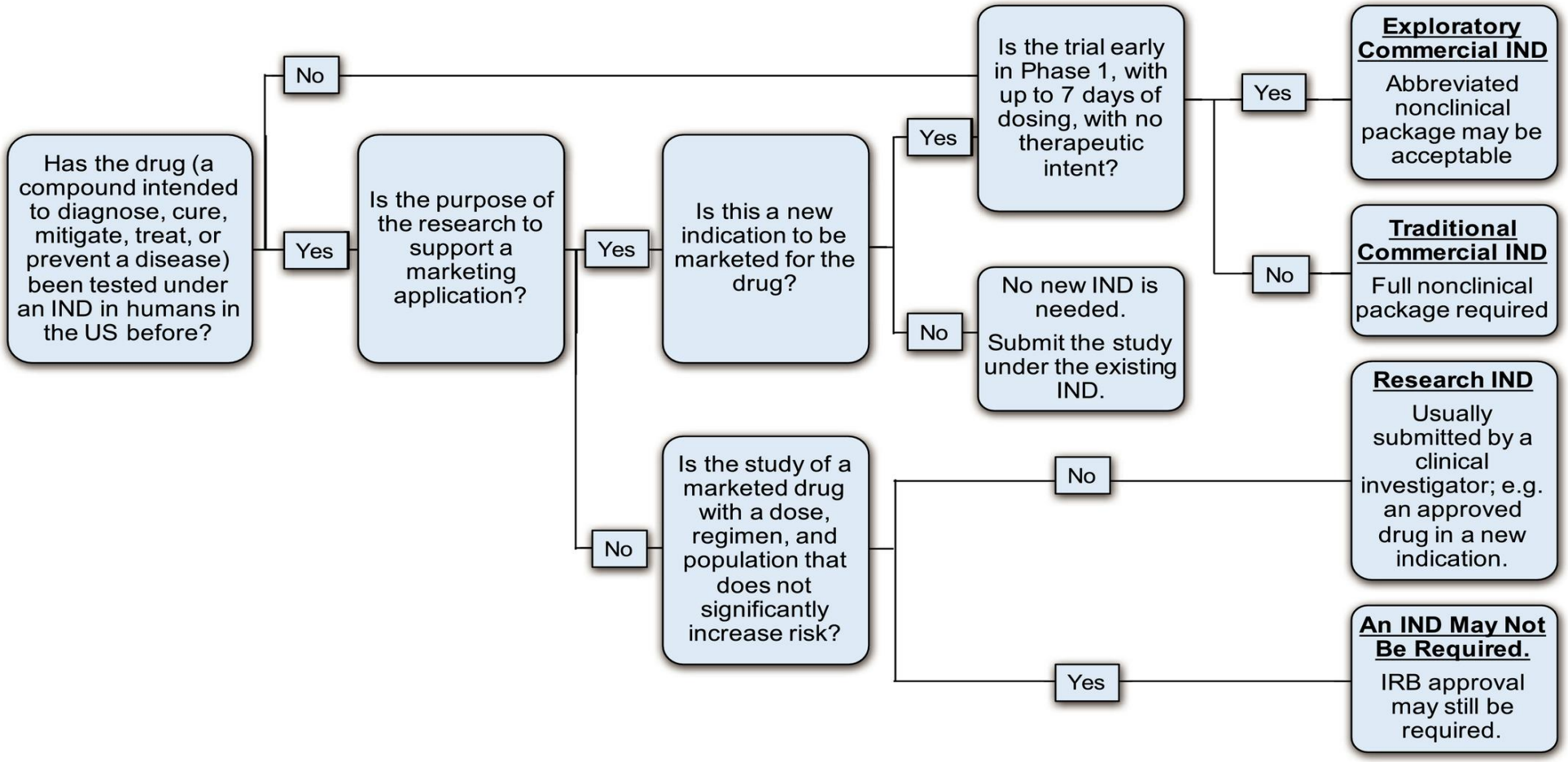
Nonclinical Written & Tabulated Summaries – Mod 2.6

Nonclinical Reports – Mod 4

CTD guide in ICH M4: https://ich.org/page/ctd

# Appendix: Paths to IND.

*Introduction to Investigational New Drug Applications and Clinical Trial Applications*






Clinical Translational Sci, Volume: 12, Issue: 4, Pages: 334-342, First published: 18 March 2019, DOI: (10.1111/cts.12635)

# Investigational New Drug (IND) Application.

**Some definitions**

- An **investigational new drug (IND)** is exempt from the premarketing approval requirements that are otherwise applicable and may be shipped lawfully for the purpose of conducting clinical investigations of that drug.
  - an IND provides an exemption from the New Drug Application (NDA) regulations, allowing you to ship your investigational drug across state lines in order to conduct clinical trials.

- An IND is submitted by a **Sponsor**, who assumes responsibility for initiating and overseeing a clinical investigation (study) or a series of clinical investigations.

- **Sponsors** are usually multi-person organizations such as pharmaceutical companies, academic groups, or government agencies. Occasionally, however, ***a Sponsor can be a single individual*** who initiates and conducts a clinical investigation with an unapproved drug (sometimes called a “Sponsor-Investigator”

# Types of INDs.

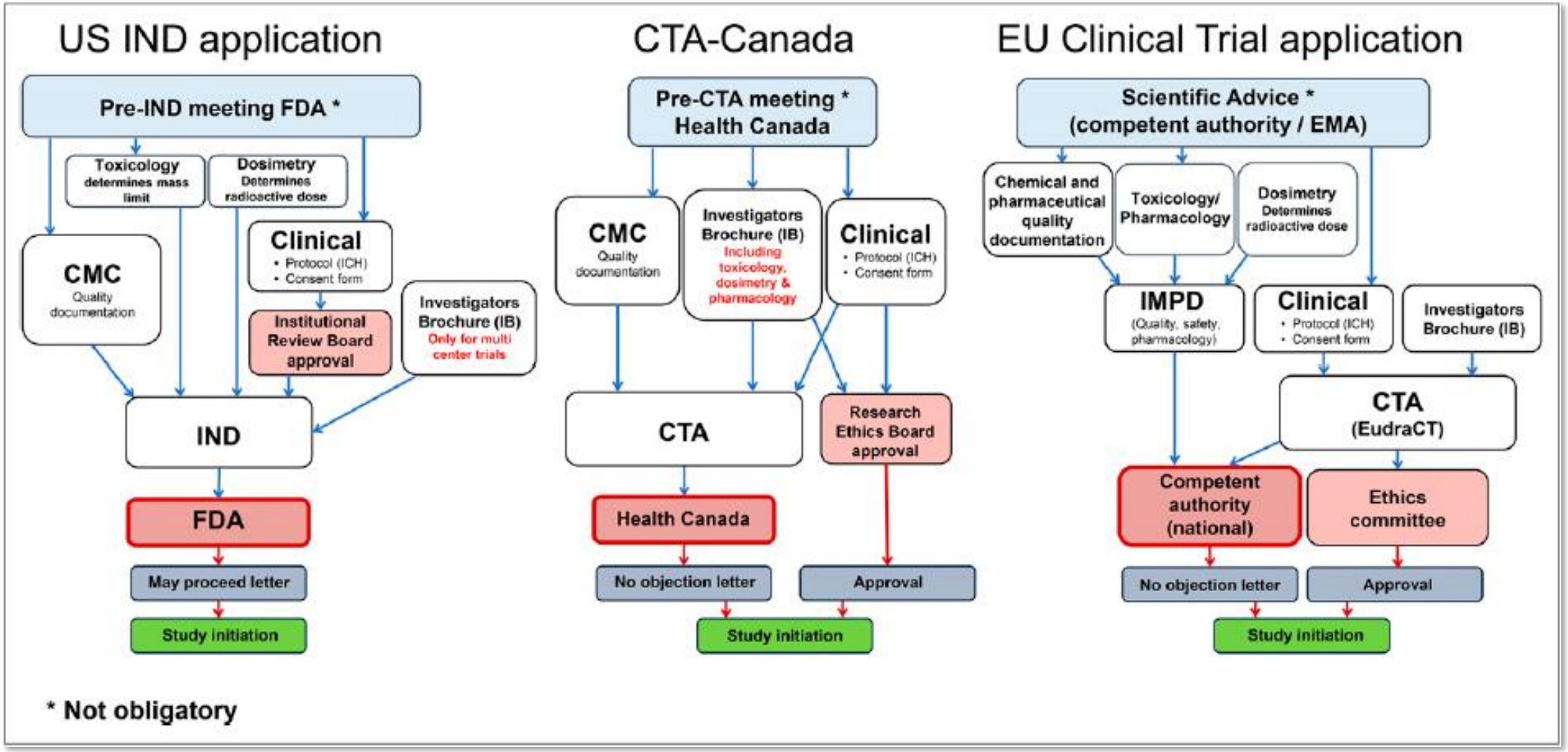
**Commercial and Research INDs are the two most common types of applications:**

- **Commercial INDs** are used when the ultimate goal is to seek approval to market a new drug. This may not be the case for advancing for n=1 (precision) type scenarios!
- **Research** (or "noncommercial") INDs are geared towards advancing scientific knowledge.
- There are several special subclasses of INDs that complement an IND's objective:
  - **Exploratory IND** – aka "Phase 0" or "micro dosing" clinical trial. Useful for refining drug PD or biomarker assays developing from nonclinical models. Often enables screening in human subjects, not for pivotal drug trials (and for discussion– risky/limited value for gene therapies)
  - **Emergency use IND** – for treatment of life-threatening with no acceptable treatment alternative and in which there is not sufficient time to obtain IRB approval
  - **Treatment IND** – for treatment of life-threatening/debilitating illnesses with investigational drugs, with no satisfactory alternative available, backed by ongoing trials in pursuit of marketing approval

# International Regulatory Requirements for Submissions

# Appendix: Outside US (OUS) Regulatory Submissions.

Note: today's discussion was very US (FDA)-centric, however other paths to clinical testing are available by region

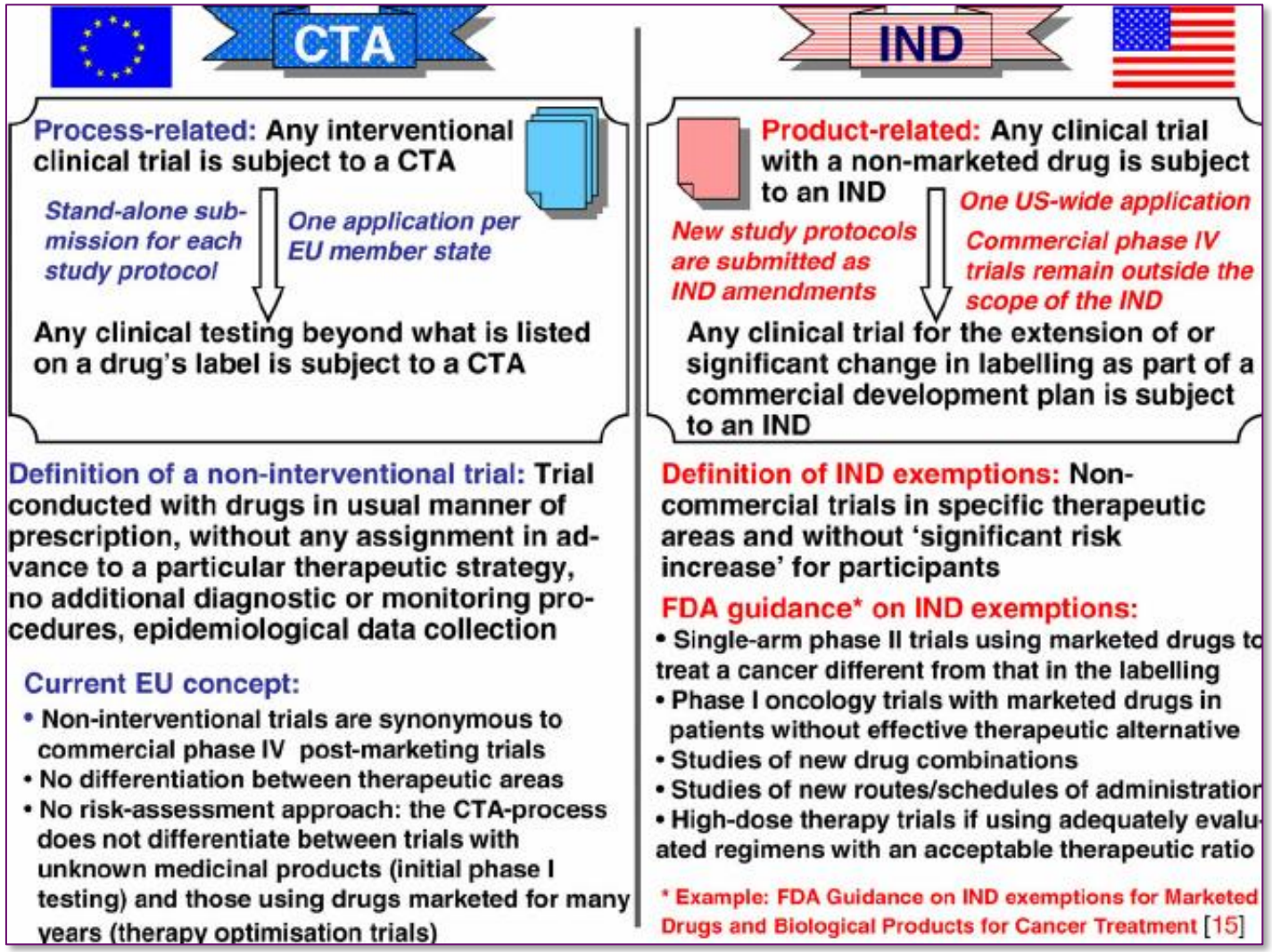





Schwarz S. J Nucl Med 2019; 60:158–166 DOI: 10.2967/jnumed.118.209460

# Appendix: Outside US (OUS) Regulatory Submissions.

- Note: this workshop is US-focused by design, and therefore FDA-centric.
- There is an IND "equivalent" used by other authorities (e.g., the CTA, IMPD)
- In general these documents leave space for nonclinical data summaries BUT THERE ARE EXCEPTIONS
- Team alignment is needed pre-submission to make sure relevant nonclinical data is available to support clinical development, trial initiation etc.






Hartmann M. The Clinical Trials Directive: How Is It Affecting Europe's Noncommercial Research? July 2006 PLoS Clinical Trials 1(2):e13 DOI:10.1371/journal.pctr.0010013

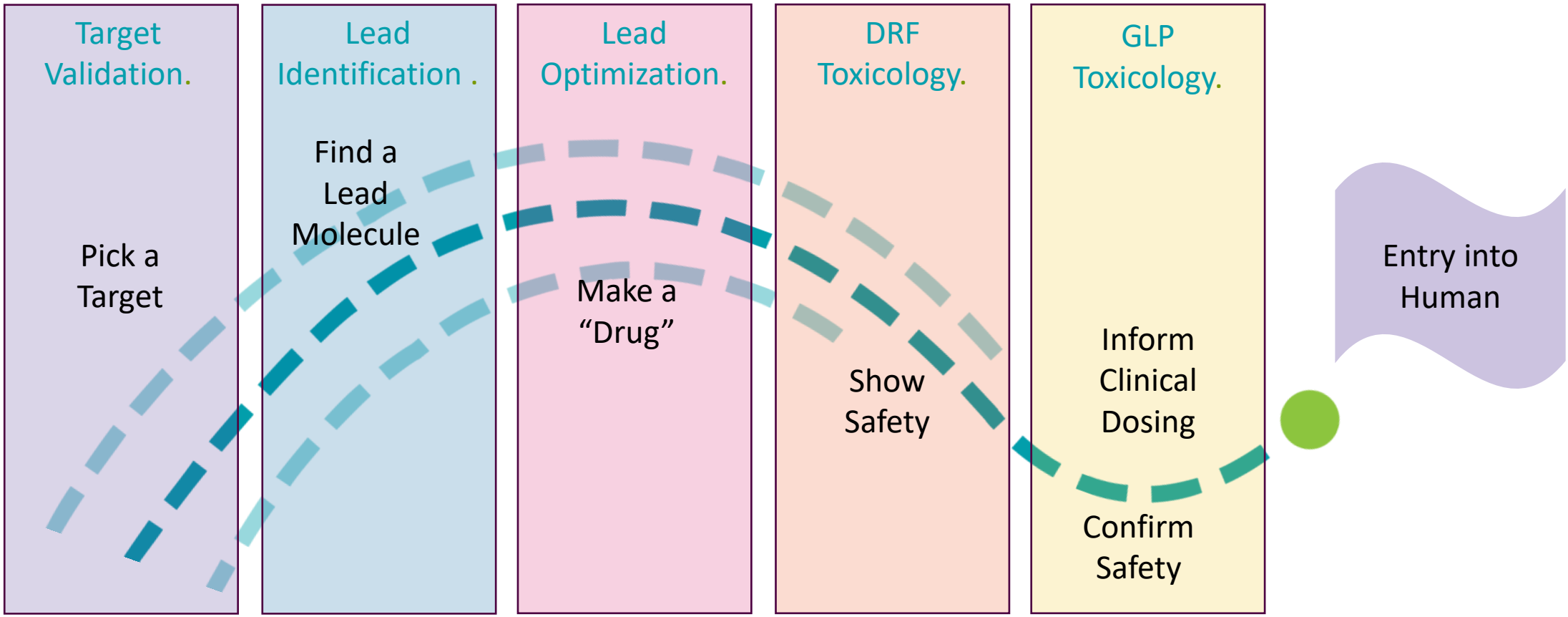
# Appendix: IND (US) v CTA (EMA).

- Both IND (US) and CTA (EMA) require the same basic data set to support initiation of clinical trials in humans
- Differences exist in the requisite documentation, review and approval process:
    - CTAs contain fewer documents than INDs, requiring less preparation time.
    - INDs have well-defined timelines to clearance (30 days); in contrast, there can be considerable variability in the approval process between each EU Member State's Health Authority and European Commission (e.g., parallel vs. sequential review, set or limited submission times, variable review lengths, etc.).
    - With INDs, there is no cost or time delay to amend or add new protocols (assuming sufficient nonclinical and CMC information are already present in the IND),
    - Substantial protocol amendments require CTA approval, and new protocols require new/separate CTAs.
    - CTAs do not carry potential risk for clinical hold like INDs do; the CTA is either approved (perhaps with mandatory changes) or rejected

Chiodin et al. Regulatory Affairs 101: Introduction to Investigational New Drug Applications and Clinical Trial Applications. Clin. Transl. Sci. (2019) 12, 334–342; doi:10.1111/cts.12635

"Homegrown"

# Typical Drug Development Paradigm.

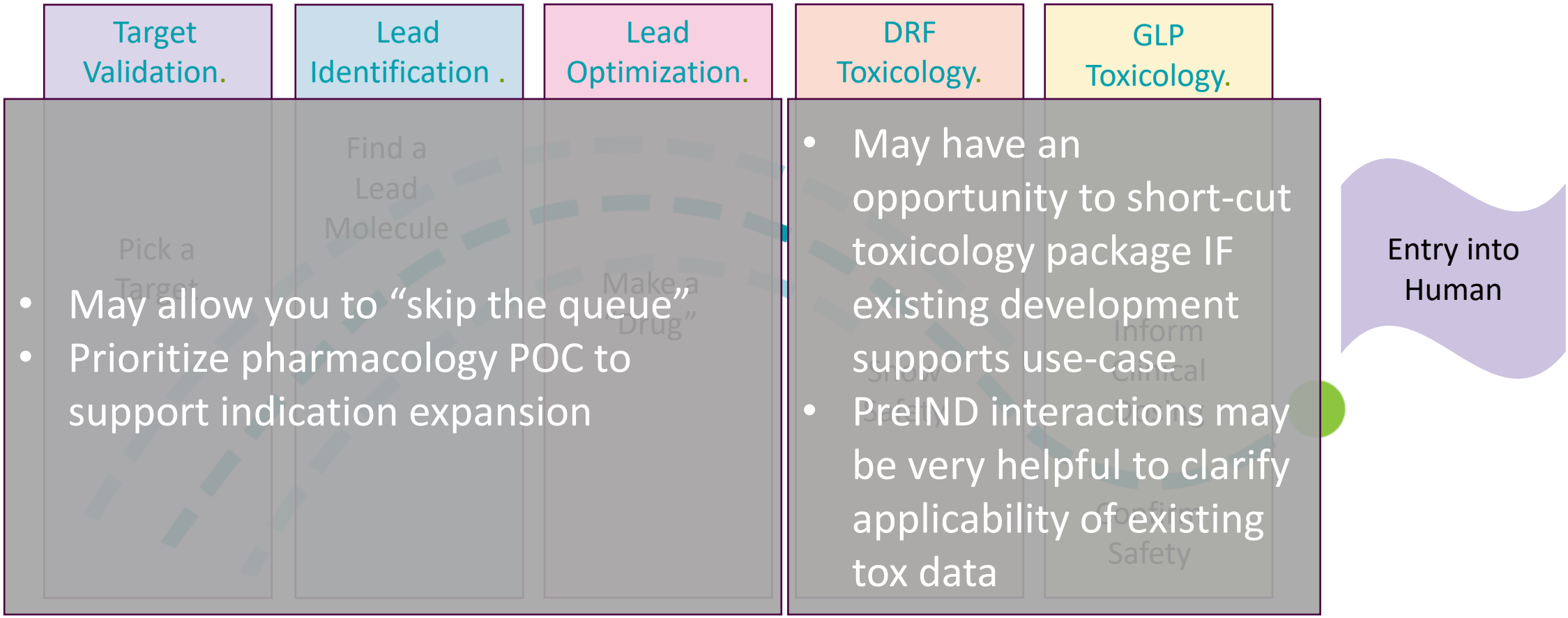





taken from Translating molecules into medicines, AAPS vol 25, 2017

"Repurposed"

# Typical Drug Development Paradigm.






taken from Translating molecules into medicines, AAPS vol 25, 2017

# Types of Nonclinical Studies to Support Clinical Trials and Approval

Key topics:  species selection, duration, GLP v nonGLP and disease models

# Where do I begin?

**“Begin with the end in mind”,  know what success looks like**

- Identify target patient population and unmet medical need
- Understand disease and drug target and biology
- Understand what is clinically meaningful and feasible
- Align (early) with clinicians on clinical trial design and objectives!
- Don’t ignore CMC and product quality!
- Understand precedence for similar drugs
- Understand GXP regulations

# GLP v nonGLP studies; quality compliance

**What do I need in my package and are nonGLP studies ok to include?**

- **GxP** – set of regulations and guidelines defining minimum quality and compliance standards across the drug industry
- **GLP** – good Laboratory practice, also include 'M' manufacturing, '**C**' clinical, '**D**' documentation etc
- "***Good Laboratory Practices***" – a response to numerous fraudulent / poorly conducted safety testing studies
  - Dangerous precedent, causing unnecessary harm due to exposures
  - Hurt the credibility of the entire field of safety testing; notorious IBT case, Alex Gross' "TBD" comment

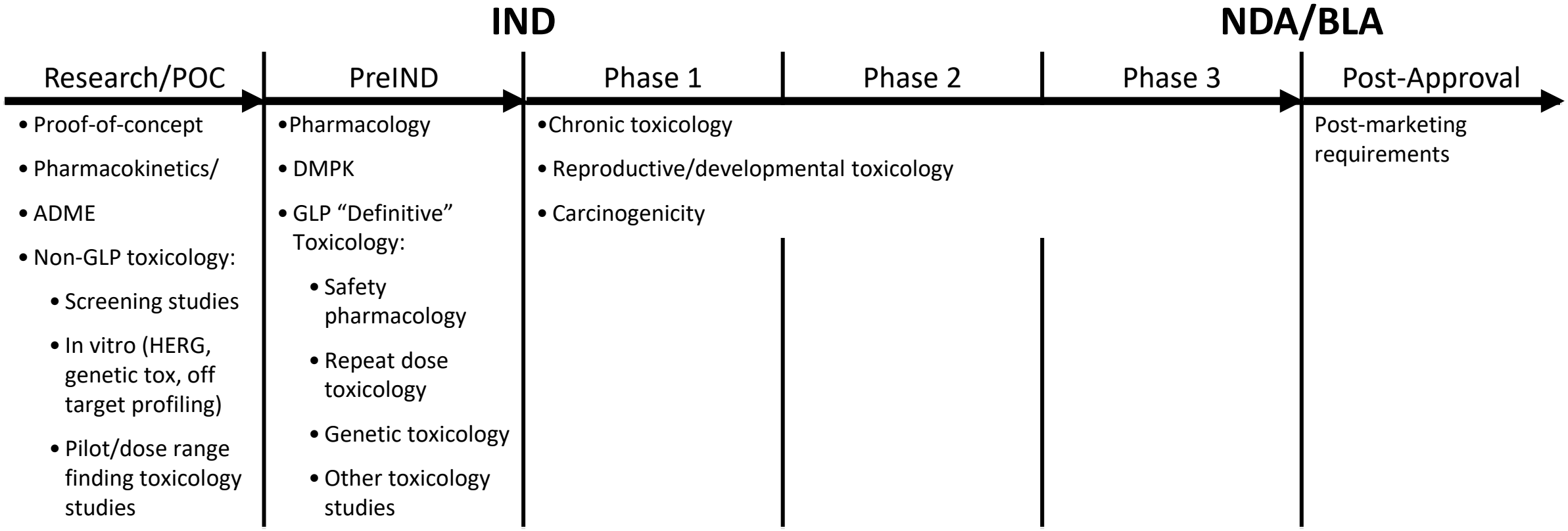
- In general, investigative studies (screening, PKPD, animal model) are conducted as nonGLP, which aids speed, iteration, cost

- "Pivotal" enabling studies, typically associated with toxicology/safety and manufacturing for clinical use, will be conducted as GLP

- Both study-types are often included in the CTD / IND

# Nonclinical Studies to Support Clinical Trials and Approval.

Generic Scheme




Study design and timing can vary significantly depending on drug type / indication/ patient population

# Understanding the Target Population.

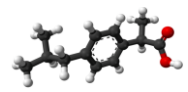
**Important factors to consider when setting the context:**

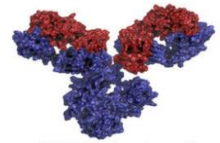
- **Target subjects**
  - Patients vs. healthy volunteers, male vs. female
  - Pediatric vs. adult vs. pregnant women vs. elderly
- **Unmet medical need**
  - Current standard of care suboptimal vs. no approved therapies
- **Impact of disease, life expectancy**
- **Disease-related constraints or limitations**

# Designing a nonclinical program.

## Selection of study type, species, and study design determined by multiple drivers

- Drug type, **mechanism of action**
- Known effects from similar classes of molecules, **platform** data (ASO, LNP, AAV etc)
- Knowledge from genetically modified or naturally occurring animal **disease models**
- Potential for **safety concerns** in disease setting that may translate clinically
- Target patient population (e.g., severity of disease, age, sex)
- Disease indication (**life threatening vs chronic**)





| Attribute | Small Molecule | Biologic |
|---|---|---|
| Size | Small<br>Low MW: ~<1 kD | Large<br>High MW: ~150 kD (e.g antibody) |
| Structure | Simple, well defined | Complex, can have post-translational modifications |
| Manufacturing | Chemical synthesis<br>Can make identical copy | Biological system, cultures of living cells<br>Comparable, not identical batches |
| Characterization | Easy | Difficult, mixture, can have variants |
| Stability | Relatively stable | Sensitive to storage/handling |
| Route of administration | Often oral | Typically injected/infused |
| Immunogenicity | Lower potential | Higher potential |
| Target specificity | Lower, promiscuous | High |
| Species specificity | Low | High |

# Pharmacology.

## 3 types of pharmacology studies:

**Primary pharmacology**: characterization of intended drug action; effects on biological targets (e.g., enzymes, receptors, etc.)

**Secondary pharmacology**: off-target or unintentional effects, important for predicting potential toxicities

Safety pharmacology: impact on vital organ systems acutely critical for life (i.e., cardiovascular, respiratory, central nervous systems)

- May be examined as standalone studies or components of toxicology studies

# Pharmacokinetic (PK) Studies.

***What happens to the drug when it enters the body?***

## Fundamental PK parameters

- ADME
  - Absorption – how does the drug get to the target
  - Distribution – where does the drug go (blood and tissues)
  - Metabolism – how does the body process the drug (relevant for small molecules only)
  - Excretion – how does the body get rid of the drug
- PK calculated from blood, plasma, or serum at various times after dosing to determine exposure, half-life, and clearance

## Objectives

- Predict therapeutic dose range in humans – what is the dose that is expected to provide benefit without causing any safety risk
- Estimate dosing interval for the clinical study -- how frequently to dose
- Explore dose-toxicity response relationship to estimate safe start dose in humans
- Estimate time to reversal of any biologic or toxic effects – how long until the drug clears once the patient stops taking the drug

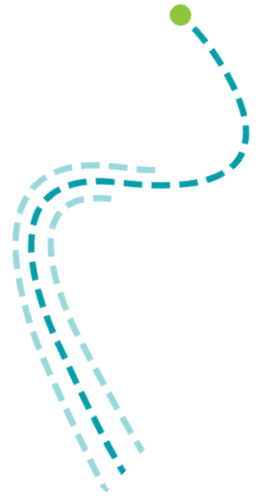
# Toxicology.

*Does the drug have undesirable effects and if so, under what circumstances and at what dose?*

- Key goals of the nonclinical toxicology program:
  - Identify potential hazards
  - Characterize toxic effects, target organs, dose/exposure relationships, “monitorability”, reversibility
  - Inform an initial safe starting dose and dose range for human trials
  - Inform clinical monitoring strategies
  - Understand therapeutic index (TI)

- Toxicology is a stepwise and iterative process
  - Inadequate toxicology information can hinder clinical development, and safety issues are the highest reason for failure in early development

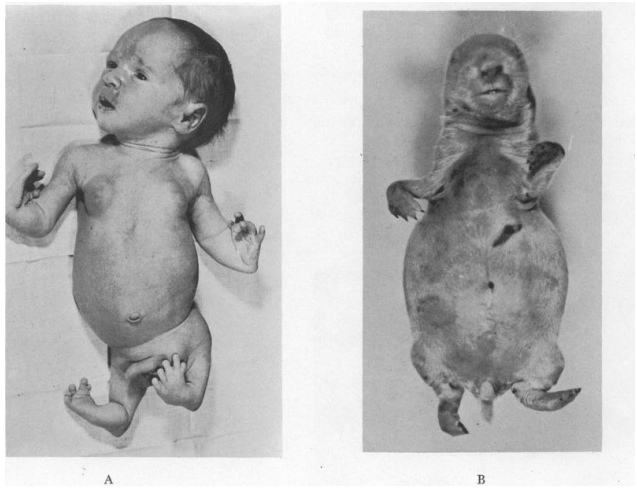
- Studies used to make claims of safety are conducted according to GLP (Good Laboratory Practices) regulations



# Why do we do toxicology studies?

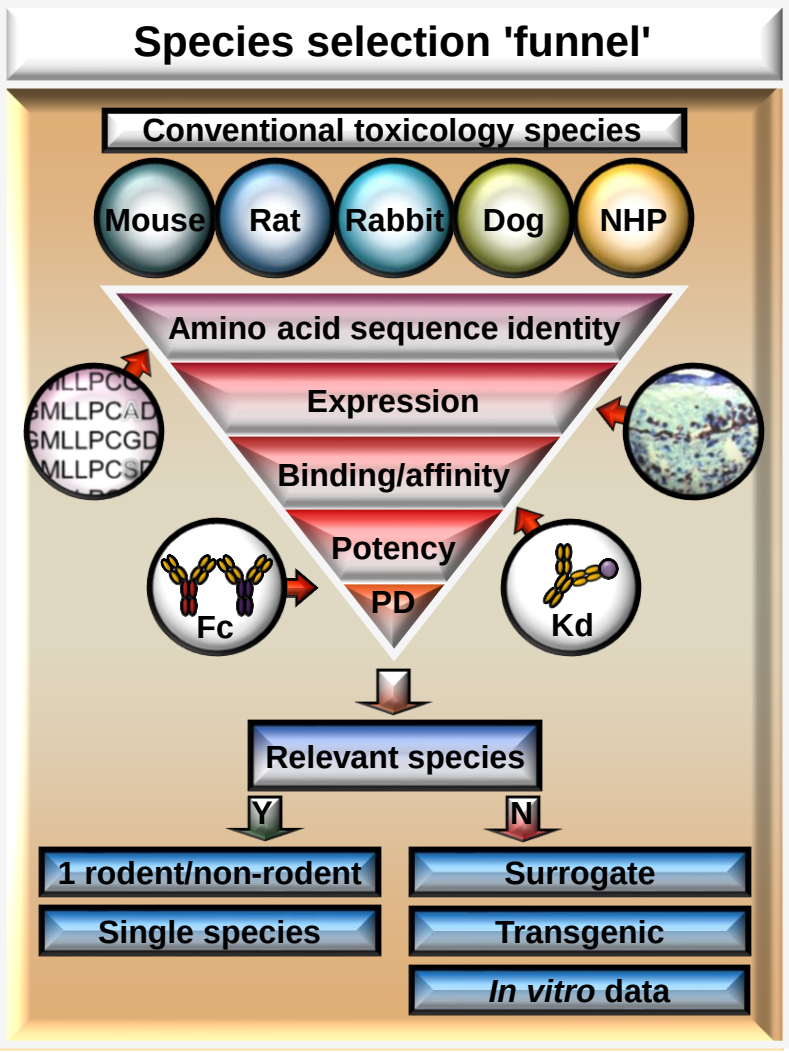
## Thalidomide Tragedy (1961-62)

- Thalidomide had been introduced an as a safe and effective hypnotic and antiemetic; it rapidly became popular for the treatment of “morning sickness” for pregnant women
    - At this time, animal studies were not performed to specifically look at safety during pregnancy
- Tragically, the drug proved to be a potent human teratogen that caused major birth defects in an estimated 10,000 children
    - Phocomelia was a characteristic feature
- This case led to the more rigorous safety testing now required by FDA & worldwide HAs



# Species selection and aspects of nonclinical study design

# Species Selection.




- **Toxicology studies should be conducted in relevant and responsive species; consider**
  - Species differences in metabolism, with a goal to cover potential human metabolites
  - Specificity for intended target and ability to respond to drug
- **Normal animals typically the default, but sometimes disease models needed/ appropriate**
- **The need to conduct toxicology studies in a relevant species can result in toxicology studies being conducted in a single species**
  - Studies in non-relevant models can be misleading and are discouraged

# Use of Animal Models of Disease for Safety Evaluation.

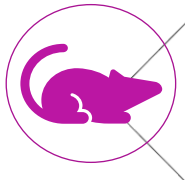
*Incorporating safety endpoints into nonclinical studies using a disease model can enhance the nonclinical package and add to the toxicology evaluation*

- Important to consider this prior to study start to incorporate ways to increase the quality/compliance

- Power and design the study to characterize
  - Disease pathology in the animal model (vehicle treated affected animals)
  - Toxicity of the drug candidate in normal animals (vehicle vs drug treated normal animals)
  - Toxicity of the drug candidate in the animal model (drug treated affected animals)
- Confirm dose formulation as is done for a GLP study
- Sample analysis (clinical pathology, PK) performed at a GLP-compliant lab, if possible
- Tissue evaluation
  - Necropsy with a Board-Certified Veterinary Pathologist present, if possible
  - Pathology samples sent to a GLP CRO for processing and evaluation
  - Pathology Peer-Review
- Study report prepared in a manner similar to a GLP study

# Species Selection Example for Small Molecule.

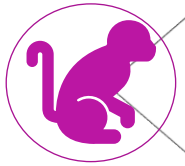
*Example of a small molecule prodrug being developed for creatine deficiency disease*



**Pharmacology: CRISPR-Cas9-mediated KO of the SLC6A8 gene** produced a functional disease model well suited for PK assessment. The lack of functional CrT protein in this model resulted in significantly lower whole brain levels of endogenous creatine (compared to wildtype animals). Demonstration that direct administration of d3-Creatine showed no brain accumulation verified that peripheral leakage from plasma across the BBB was not possible.

**Pharmacokinetics/DMPK:** Rats share a UX068 metabolite profile which is comparable to human. The development of a rat-based disease model provided a means to directly evaluate the PK of prodrug-mediated delivery of creatine to central and peripheral compartments, with important limitations due to the hyper rates of clearance of prodrug and Cr relative to those measured in non-rodents (and predicted clinically).

**Toxicology**: The rat is a relevant rodent species for predicting safety associated with repeat-administration of UX068 in humans and is considered acceptable for nonclinical toxicity testing by regulatory agencies. The rat is a suitable models for assessing tolerability to NCEs administered by both intravenous and oral routes. Toxicities observed in rat are consistent with those observed in cyno monkeys and to-date do not show any species-specific effects that may confound clinical risk assessment. The rat is considered an appropriate test system to evaluate the impact of effects from both acute and repeated administration at the clinical routes of administration being considered for UX068 (e.g. CNS effects associated with intravenous infusion administration; potential for systemic effects related to po dosing).



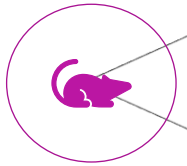
**Pharmacology:** Due to presence of functional CrT protein, the WT cyno is not well-suited to evaluate pharmacology. The cyno is an appropriate species to evaluate PK and toxicity/tolerability.

**Pharmacokinetics/DMPK: The cyno produces UX068 metabolite profile which is comparable to human.** PK profile of UX068 and half-life of creatine in cynomolgus monkey brain is anticipated to be similar and predictive of human. The kinetics and metabolism of UX068 in cynomolgus monkey, particularly as it relates to distribution across the BBB of the brain are expected to be more similar to those in human. Together these similarities enable the cynomolgus monkey to accurately predict PKPD translation to humans, thereby strengthening our understanding of the structural chemistry of the UX068 prodrug.

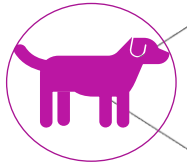
**Toxicology**: The cynomolgus monkey is a relevant non-rodent species for predicting safety associated with repeat-administration of UX068 in humans and is considered acceptable for nonclinical toxicity testing by regulatory agencies. The cyno is also a suitable models for assessing tolerability to NCEs administered by both intravenous and oral routes. The cynomolgus monkey is often used to assess acute CNS effects (a concern identified from intravenous infusion administration) and shows congruent systemic effects also observed in rats.

# Species Selection Example for mRNA Therapeutic.

*Example of an LNP-mRNA molecule being developed for a glycogen storage disease*

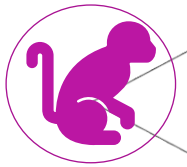


***Pharmacology**: Agl* knockout mouse model was generated through deletion of all exons after exon 5 in the *AGL* gene, resulting in deficient in expression of GDE (Liu et al. 2014).

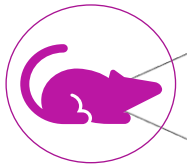


***Pharmacology***: GSD IIIa is a naturally occurring disease in the curly-coated retriever caused by a frameshift mutation resulting in defective GDE (Brooks et al. 2016).

***Toxicology***: the dog is a very sensitive preclinical species based on findings in GSD IIIa and normal Beagle dogs treated with UX053



***Toxicology***: the cynomolgus monkey is the most relevant species for predicting safety in humans based on physiologic and biologic similarities. UX053 PK is anticipated to be similar to human based on a comparison of the mRNA profile in monkeys to the human PK of the siRNA-LNP patisiran (Zhang et al. 2018).



***Toxicology***: rats are also considered an appropriate species for initial, shorter term, toxicity assessments, including CNS evaluations, in vivo genetic toxicity assays, and future reproductive and developmental toxicity studies.

# Appendix: example Nonclinical Program for an mRNA Therapeutic – Nonclinical Plan through Launch.

**Enable short-term repeat dosing in adults, followed by longer term dosing in pediatric patients and adults**

- UX053 is part of a larger mRNA-LNP platform that has benefitted from the nonclinical evaluation of previous oligonucleotide-LNPs, and will contribute data and learnings to future mRNA programs.
- The MoA of UX053 is complex, with properties that relate to biologics, small molecules, and/or gene therapy, and which leverages the same novel ionizable cationic lipid, ATX95, that is used in Arcturus' OTC program.
- The nonclinical program was designed to evaluate the pharmacology of UX053 in mouse and dog models of GSD IIIa, including UX053 biodistribution and impact on liver and muscle, and to evaluate the toxicity of UX053 in mice, rats, monkeys, and dogs.

**Phase 1/2**

**Enable IND w/ Short term RD**

Establish PoC, safety, tolerability, exposure profiles, and biodistribution following short term repeat dosing to support CL101

Leverage Weight of Evidence approach in IND suggesting dedicated juvenile tox studies are not required

Develop/validate bioanalytical assays to support PK/TK/PD & biomarker evaluations

**Phase 2b**

**Enable long term dosing**

Evaluate chronic toxicity of UX053 in a 9-month GLP study using V2.0 material, to support long- term dosing of adult and pediatric patients

Evaluate pharmacology and biodistribution of UX053 in *Agl* KO mice and GSD IIIa dogs following long term Q2W repeat dosing

**Phase 3**

**Enable BLA/MAA**

Evaluate the developmental and reproductive toxicity and carcinogenicity (TBD) of UX053

**Launch**

**Support Evidence Generation**

Conduct nonclinical evaluations to support additional evidence generation strategies (indication expansion, ISTs, next generation formulations, etc.) as applicable

# Considerations for toxicology study designs.

- Dose range-finding pilot studies (usually standalone, nonGLP)
- GLP repeat dose toxicology studies (“general toxicology”)
  - Species: Usually conducted in two species, a rodent and non-rodent
  - Dosing regimen, route of administration: “Mimic the clinic”
  - Duration: support duration of proposed clinical trials, “Stay ahead of the clinic”
  - Dose levels
    - Selected to define dose-response relationship
    - Maximum tolerated dose (MTD), maximum feasible dose (MFD), or 5-50X multiple over maximum intended clinical dose
    - No observable adverse effect level (NOAEL)
  - Endpoints: standard endpoints, toxicokinetics (TK), immunogenicity (if applicable), sometimes safety pharmacology endpoints, other endpoints based on target biology
  - Test article:
    - Material needs to be comparable to clinical material for pivotal GLP studies
    - Use of a homologous protein (“surrogate molecule”) considered in limited cases

# ”Other studies” to include in regulatory filings.

- Genetic toxicology battery:
  - Relevant for small molecules, organic linkers, and impurities, but not biologics (not expected to interact with DNA)
  - In vitro study to assess for mutagenicity, in vitro/in vivo detection of chromosomal damage
  - Important for consideration of future risk of carcinogenicity

- Tissue cross reactivity: monoclonal antibodies
  - Ex vivo immunohistochemistry (IHC) study conducted with panel of human tissues
    - May aid in identifying potential target tissues for toxicities

- Phototoxicity: small molecules

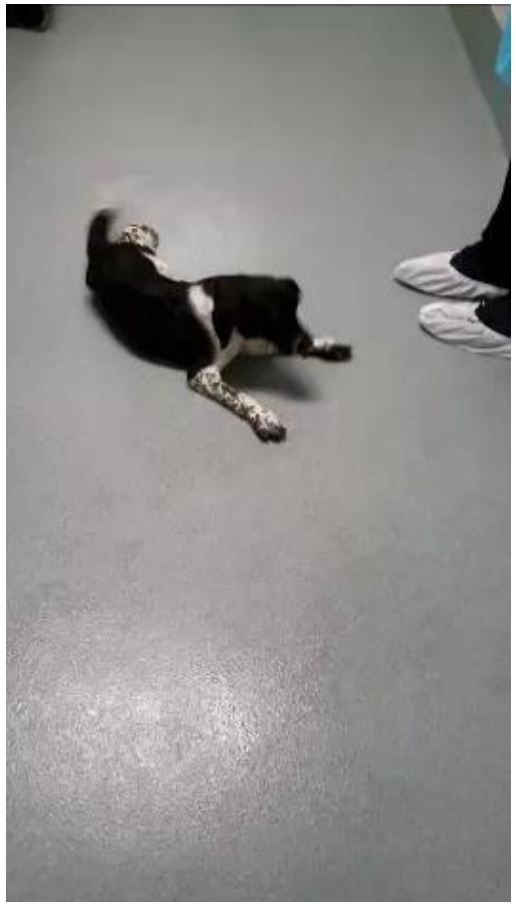
- Local tolerance at the injection site: usually assessed in repeat dose study

# Appendix: Primary Pharmacology Example using ERT.

*Mepsevii in a MPS VII dog model: 4/5 ERT treated, and 0/3 untreated animals could walk at 6 months, with assistance*

Control

Untreated MPS VII

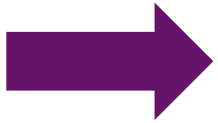


ERT Treated MPS VII (4mpk)

# Appendix - Primary Pharmacology Studies.

**Objectives:**

- Establish rationale for conducting trials in humans
- Establish pharmacodynamic (PD) markers of clinical efficacy
- Optimize dosing regimen
- Optimize route of administration
- Determine efficacious dose range



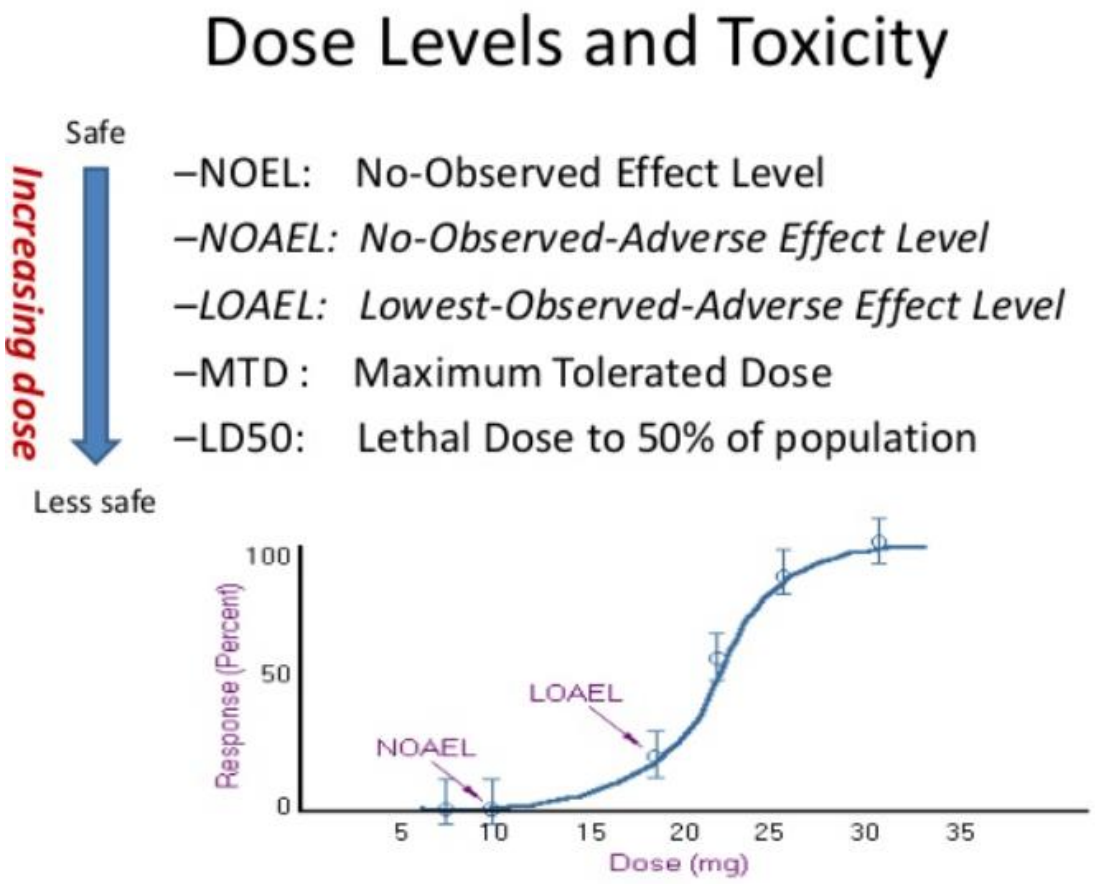
**Types of studies:**

- In vitro studies
  - Screen candidates for target affinity and selectivity
  - Conduct functional studies to determine potency
- In vivo studies
  - Evaluate efficacy in animal models of disease
  - Normal animals may also be useful

# Appendix - Safety Pharmacology Studies.

- Studies to assess potential undesirable effects on vital organ functions (i.e. cardiovascular, respiratory, central nervous system)
  - Typically, after single dose, but repeat dose sometimes important
  - In some cases (e.g. biologics), endpoints can be incorporated into repeat dose toxicology studies

# Appendix - Establishing a drug dose range for toxicity.




- Need to understand dose range (NOAEL to MTD)
- Independent of predicted efficacious doses
- Previous studies (e.g. pharmacology, PK, in vitro potency, similar molecules) can aid in determining a starting place
- *Note:* intentionally determining $LD_{50}$ is no longer required

**Adverse effect:** generally defined as an effect that would be unacceptable if produced by the initial dose in a healthy volunteer study

# Appendix -- SEND: Standard for Exchange of Nonclinical Data.

## What *IS* SEND?

- FDA standard data format & terminology
- Nonclinical safety data must be submitted to FDA in SEND format


## What is the *Scope* of SEND?

- The FDA Data Standards Catalog and Study Data Technical Conformance Guide outline FDA requirements for submission of SEND data
- FDA CDER currently requires SEND 3.1 for Single & Repeat Dose Toxicity Studies, Carcinogenicity, and Cardiovascular and Respiratory Safety Pharmacology studies. CDER will require SEND-DART 1.1 for Embryo-Fetal Development studies with study start dates on or after 15 March 2023
- FDA CBER will require SEND 3.1 for Single & Repeat Dose Toxicity Studies, Carcinogenicity, and Cardiovascular and Respiratory Safety Pharmacology studies with start dates on or after 15 March 2023.

## What is the *Goal* of SEND?

- Increase efficiency
- Improve quality of scientific data review by FDA reviewers
- Improve communication between FDA and the pharmaceutical industry

# Appendix – SEND resources.

- Study Data for Submission to CDER and CBER | FDA - Study Data for Submission to CDER and CBER | FDA
  - FDA Study Data Preparation Self-Check Worksheet - https://www.fda.gov/media/123098/download
  - Self-check Worksheet Instructions - https://www.fda.gov/media/123099/download

- Study Data Standards Resources - https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources
  - Study Data Technical Conformance Guide - https://www.fda.gov/media/153632/download
  - FDA Data Standards Catalog - https://www.fda.gov/media/156273/download

# Navigating through drug attrition, and other challenges

# How to navigate through ‘drug attrition’ issues.

Balancing broad population v precision-medicine based challenges

- Drug “attrition” – common “big pharma” topic, typical of large screening campaigns; fewer options for precision-drug development/ rare disease indications
- Common strategy is to begin safety assessment early in the development process, e.g., including toxicology endpoints in studies and/or testing wider dose-exposure-response relationships
- Risk v benefit equations are important considerations
- Drug terminations often associated with studies demonstrating low safety margin, off-target activity, unmonitorable and/or irreversible effects in animals (e.g., testicular tox)
- Leveraging platform and modality effects can help programs work through and de-risk issues’
- Real-world evidence (for drug repurposing and/or label expansion) may help gauge risks and establish a TI for your indication

| Modality | Signature Toxicity | Mitigation Options |
|---|---|---|
| AAV | Immunosensitivity | Prophylactic steroid, immune suppression; route |
| ASO | Thrombocytopenia, hepato– and renal toxicity | Dose-response / TI, sequence changes |
| Biologics (e.g., ERT) | Protein durability, neutralization | Infusion rates, ”dosing through” |
| LNP-mRNA | Immunogenicity, hepatotoxicity | Dose frequency, levels |
| Small molecule | Off-target effects, DILI | Dose reduction, regimen, route |

# Drug repurposing and label expansion (505b1 v b2 submission).

- Capitalizing on “beneficial” off-target effects, may support new indications / label expansions
- Incorporate real-world evidence and bridge missing pediatric indications, may reduce need for new testing
- Popular approach to fast-tracking submission, as data may be available to support bridging to new indication

| 505b1 “Stand-alone” submission | 505b2 path |
|---|---|
| • Contains full reports of investigations of safety and effectiveness that were conducted by or for the applicant or for which the applicant has a right of reference or use<br>  • Complete non-clinical package<br>  • Clinical pharmacology<br>  • Clinical safety and effectiveness data<br>  • CMC | • Contains full reports of investigations of safety and effectiveness, where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use<br><br>• Allows for flexibility in the characteristics of the proposed product without having to conduct studies on what is already known about the product |