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Development Strategy: IND-Enabling Nonclinical Package

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What's an IND?

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

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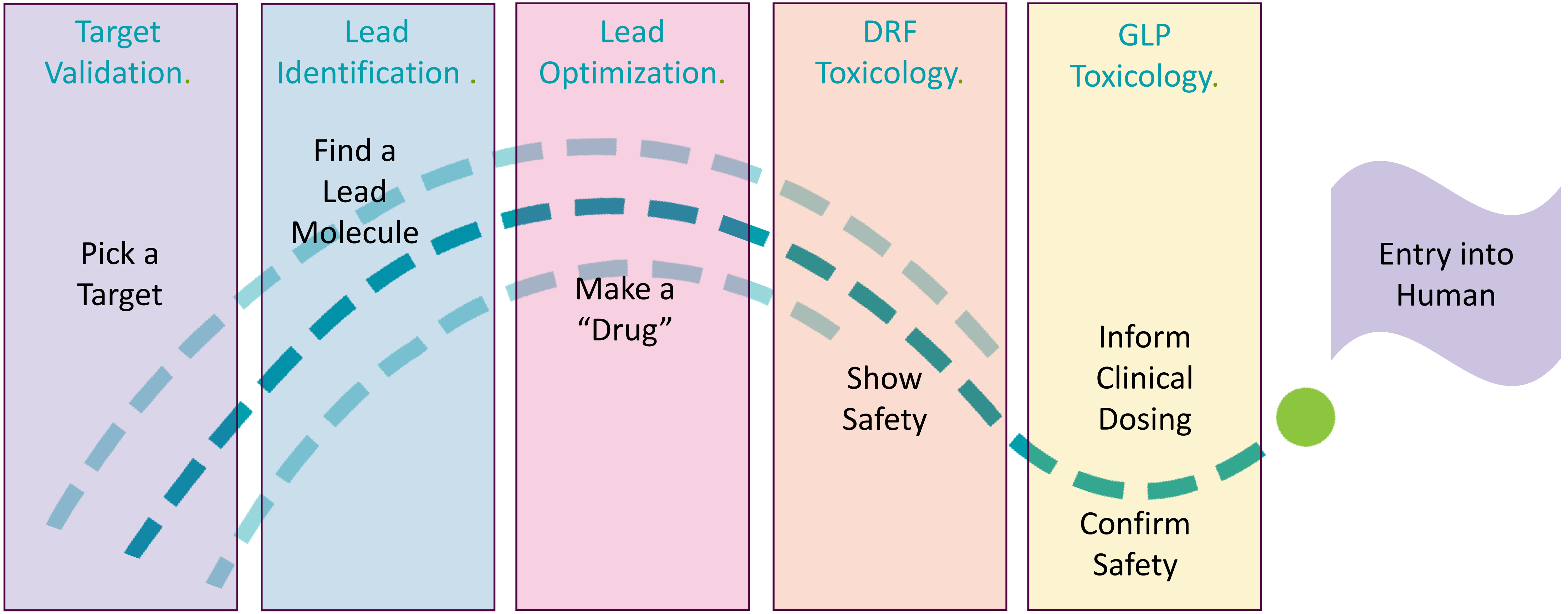
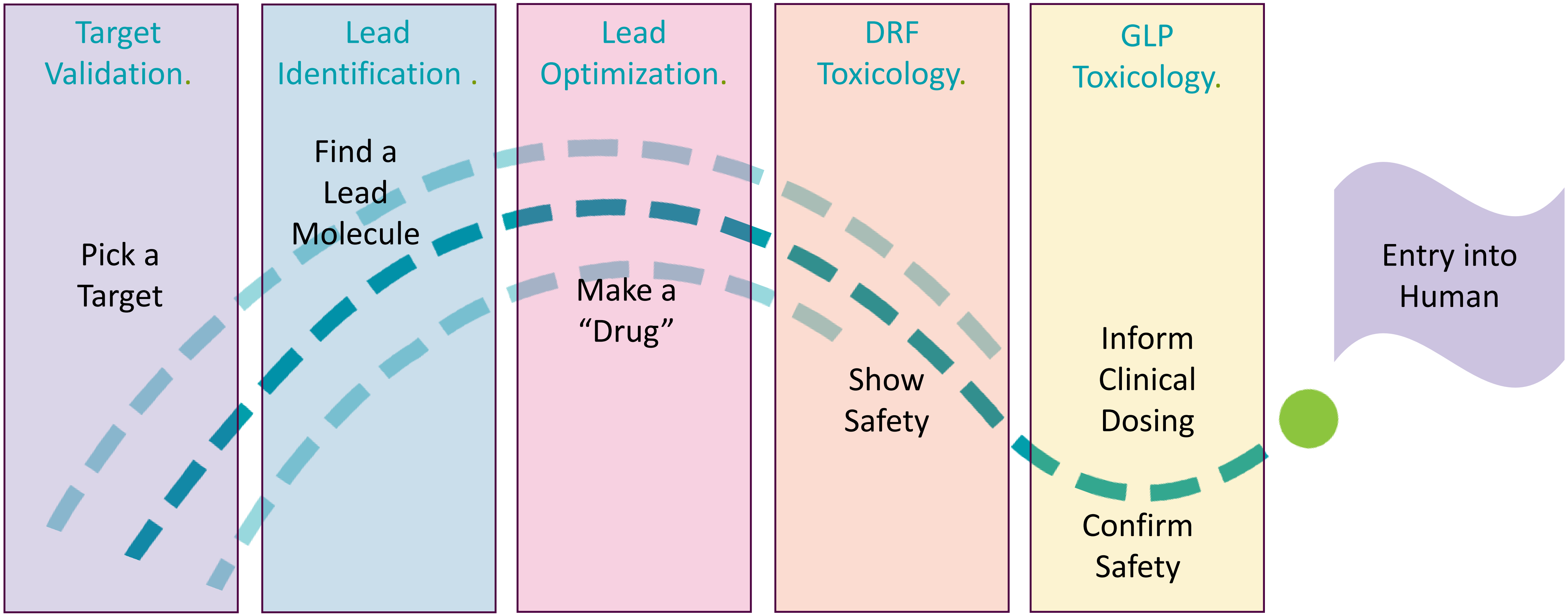
Typical Drug Development Paradigm.



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

”Homegrown”

Typical Drug Development Paradigm.



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

"Repurposed" Typical Drug Development Paradigm.

Target Validation.	Lead Identification .	Lead Optimization.	DRF Toxicology.	GLP Toxicology.

- May allow you to "skip the queue"
- Prioritize pharmacology POC to support indication expansion

- May have an opportunity to short-cut toxicology package IF existing development supports use-case
- PreIND interactions may be very helpful to clarify applicability of existing tox data

Entry into Human

Goals of IND-enabling nonclinical package.

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

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

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

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**)

What is an IND?

CTD: Common Technical Document structure

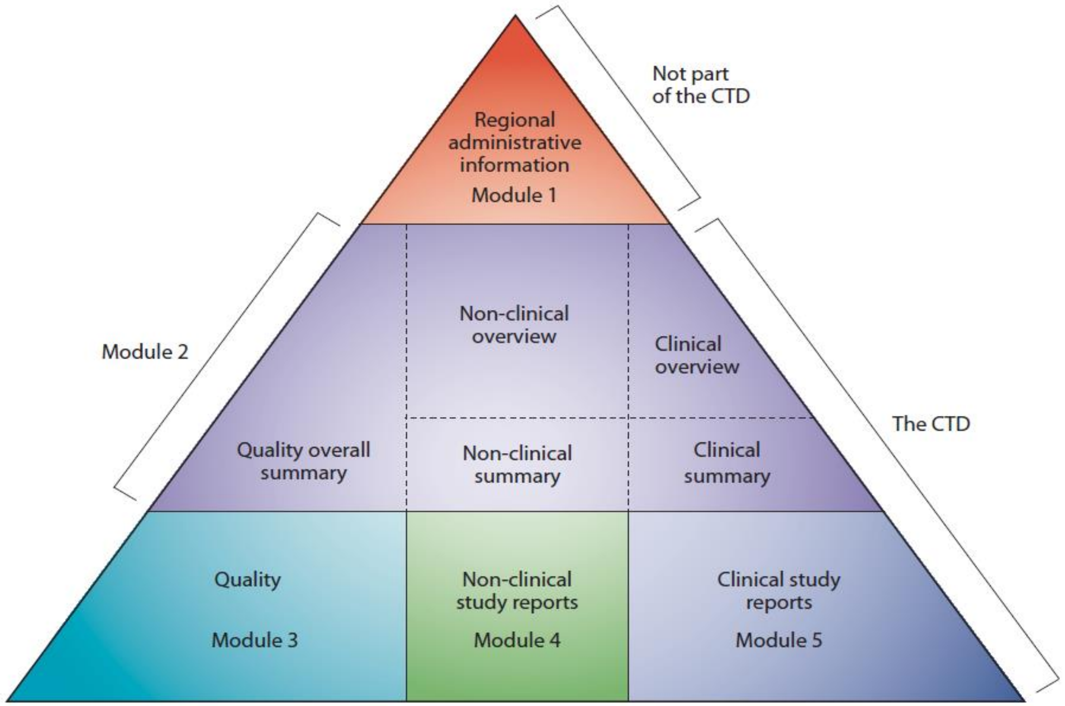
The aim of an investigational new drug application (IND) is to obtain approval from FDA to perform clinical trials of an investigational medicinal product (IMP) in humans in the US.

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

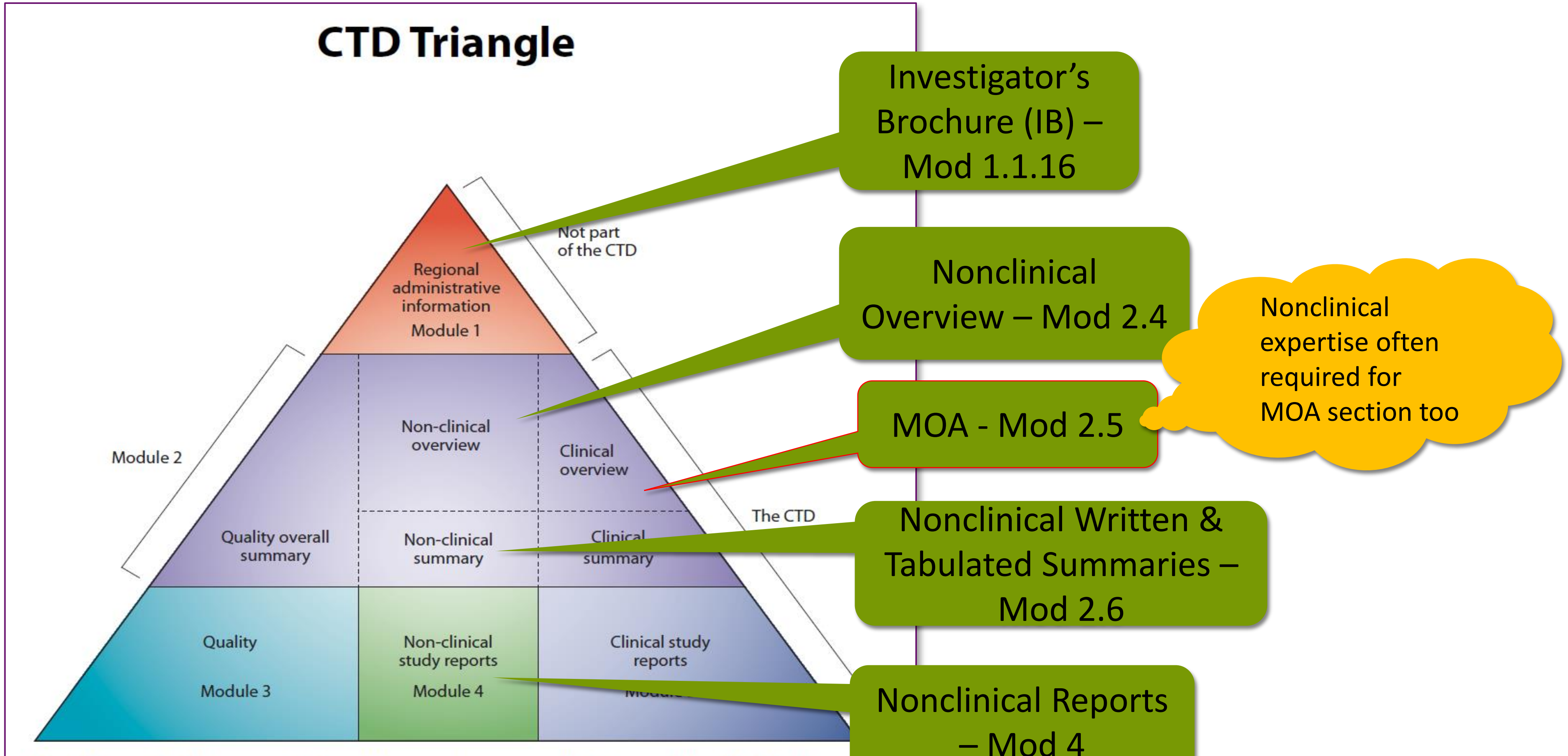
CTD Triangle



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

CTD: Common Technical Document structure.



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.

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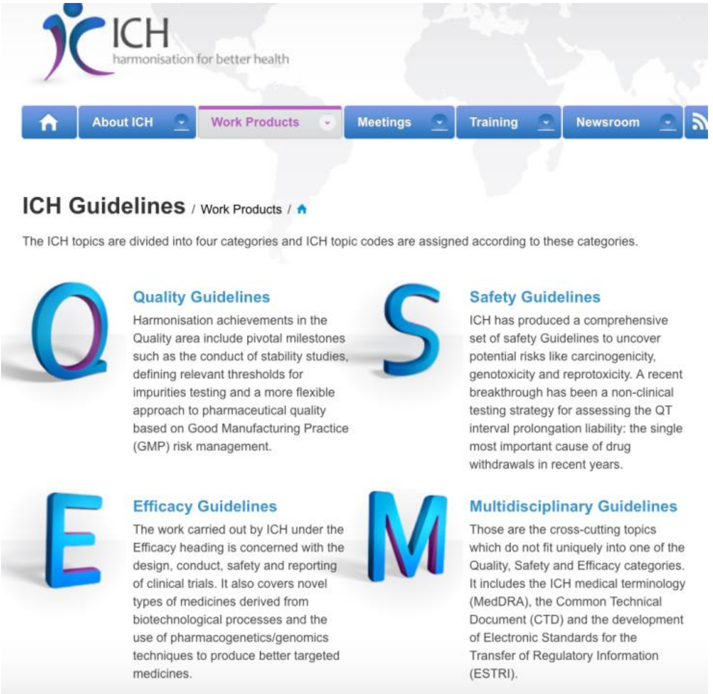
Examples of Guidance Used to Guide Nonclinical Programs.

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

Regulatory-speak ☑ , what next?

Nonclinical Studies to Support Clinical Trials and Approval

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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

IND | **NDA/BLA**

Research/POC
- Proof-of-concept
- Pharmacokinetics/
- ADME
- Non-GLP toxicology:
  - Screening studies
  - In vitro (HERG, genetic tox, off target profiling)
  - Pilot/dose range finding toxicology studies

PreIND
- Pharmacology
- DMPK
- GLP "Definitive" Toxicology:
  - Safety pharmacology
  - Repeat dose toxicology
  - Genetic toxicology
  - Other toxicology studies

Phase 1 | Phase 2 | Phase 3
- Chronic toxicology
- Reproductive/developmental toxicology
- Carcinogenicity

Post-Approval
Post-marketing requirements

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

Understanding the Target Population.

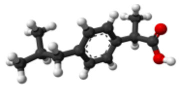
Important factors to consider when setting the context:

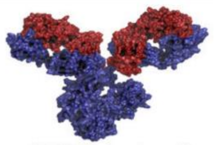
- **Target subjects**
  - Patients vs. healthy volunteers, male vs. female
  - Pediatric vs. adult vs. pregnant women vs. elderly
- **Unmet medical need**
  - Current standard of care suboptimal vs. no approved therapies
- **Impact of disease, life expectancy**
- **Disease-related constraints or limitations**

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 Low MW: ~<1 kD	Large High MW: ~150 kD (e.g antibody)
Structure	Simple, well defined	Complex, can have post-translational modifications
Manufacturing	Chemical synthesis Can make identical copy	Biological system, cultures of living cells 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

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Types of Nonclinical Studies to Support Clinical Trials and Approval

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

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

	Small Molecules	Biologics	Gene Therapy
Short-term repeat dose studies	Up to 3 month to support FIH 2 species	Up to 3 month to support FIH 2 species	Single dose, followed to 3 months to support FIH (possibly 6 months for BLA); Biodistribution assessment included 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 ePPND study (NHP) required prior to filing	Likely need Fertility and EFD in one species Risk of germline transmission needs to be considered if vector distributes and persists in gonads

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

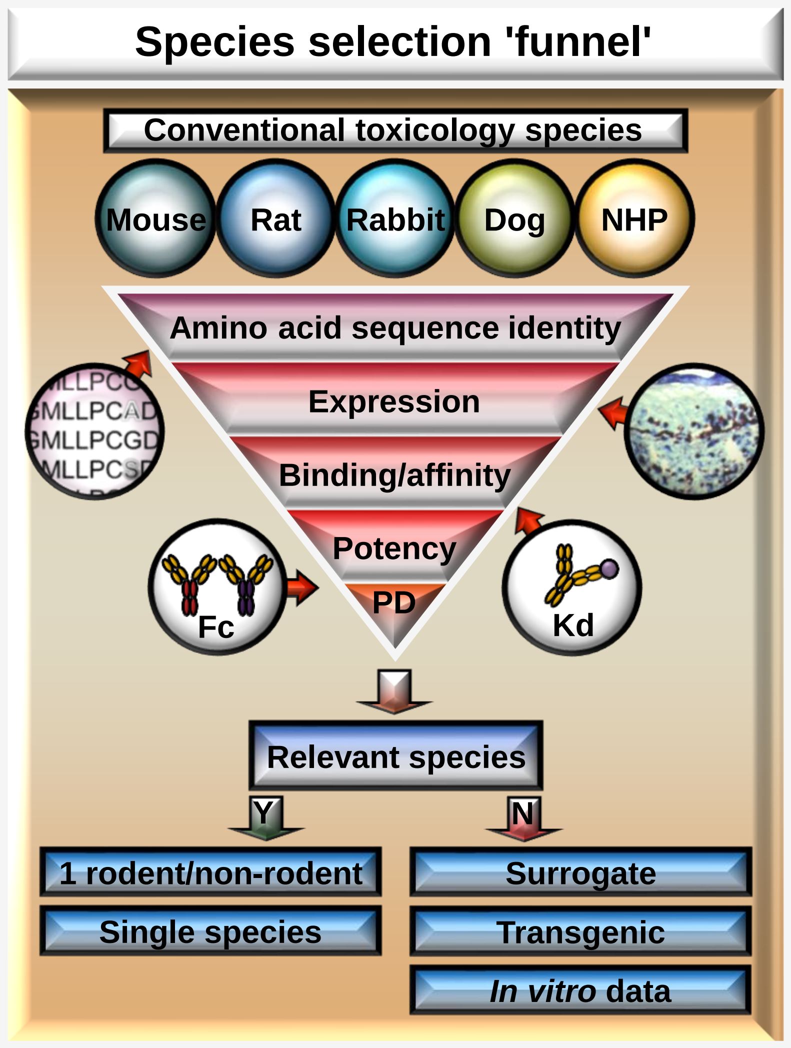
Why do we do toxicology studies?

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.

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

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Navigating through drug attrition, and other challenges

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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
  • Complete non-clinical package
  • Clinical pharmacology
  • Clinical safety and effectiveness data
  • 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
	• Allows for flexibility in the characteristics of the proposed product without having to conduct studies on what is already known about the product

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)

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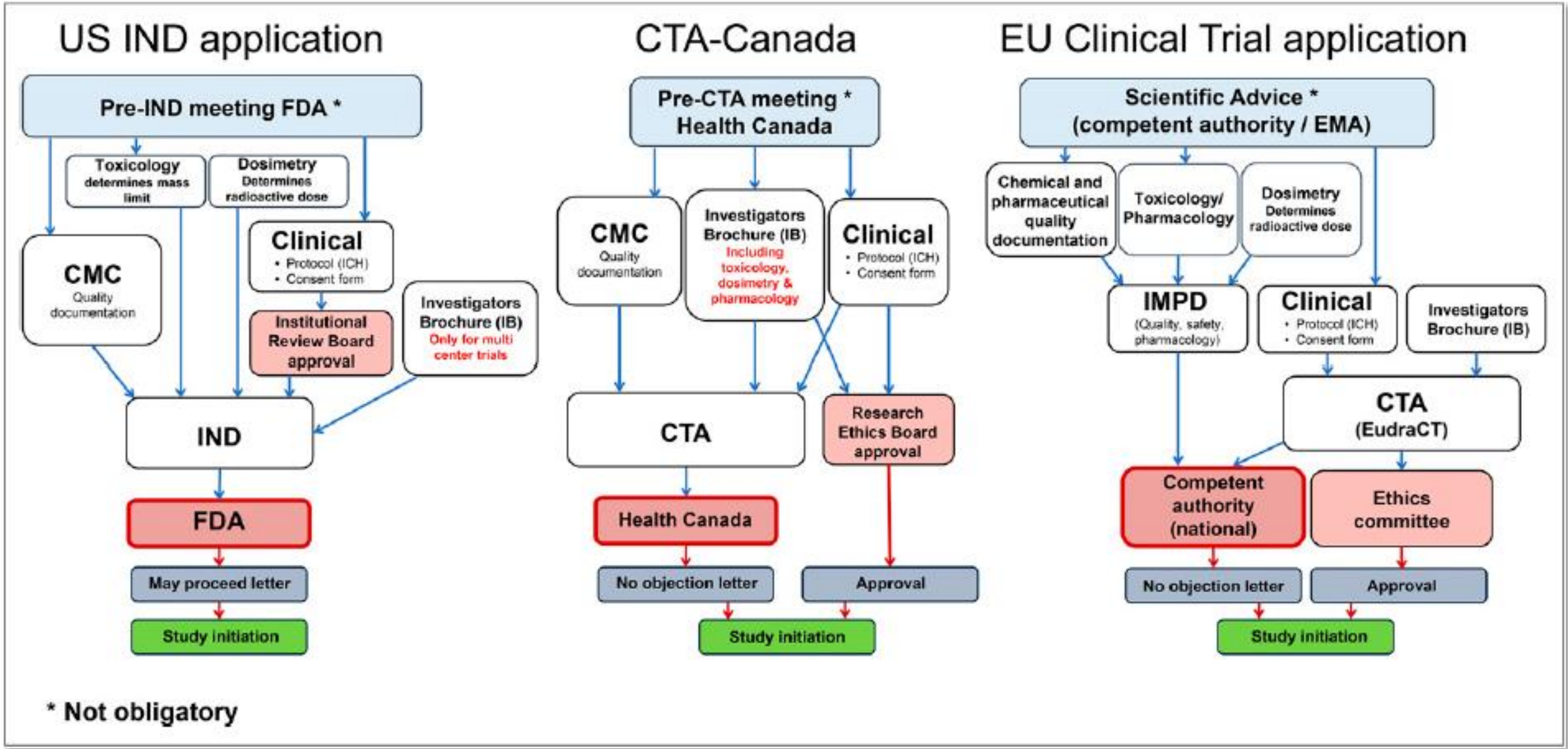
Thank You

Appendix

Appendix: Outside US (OUS) Regulatory Submissions.

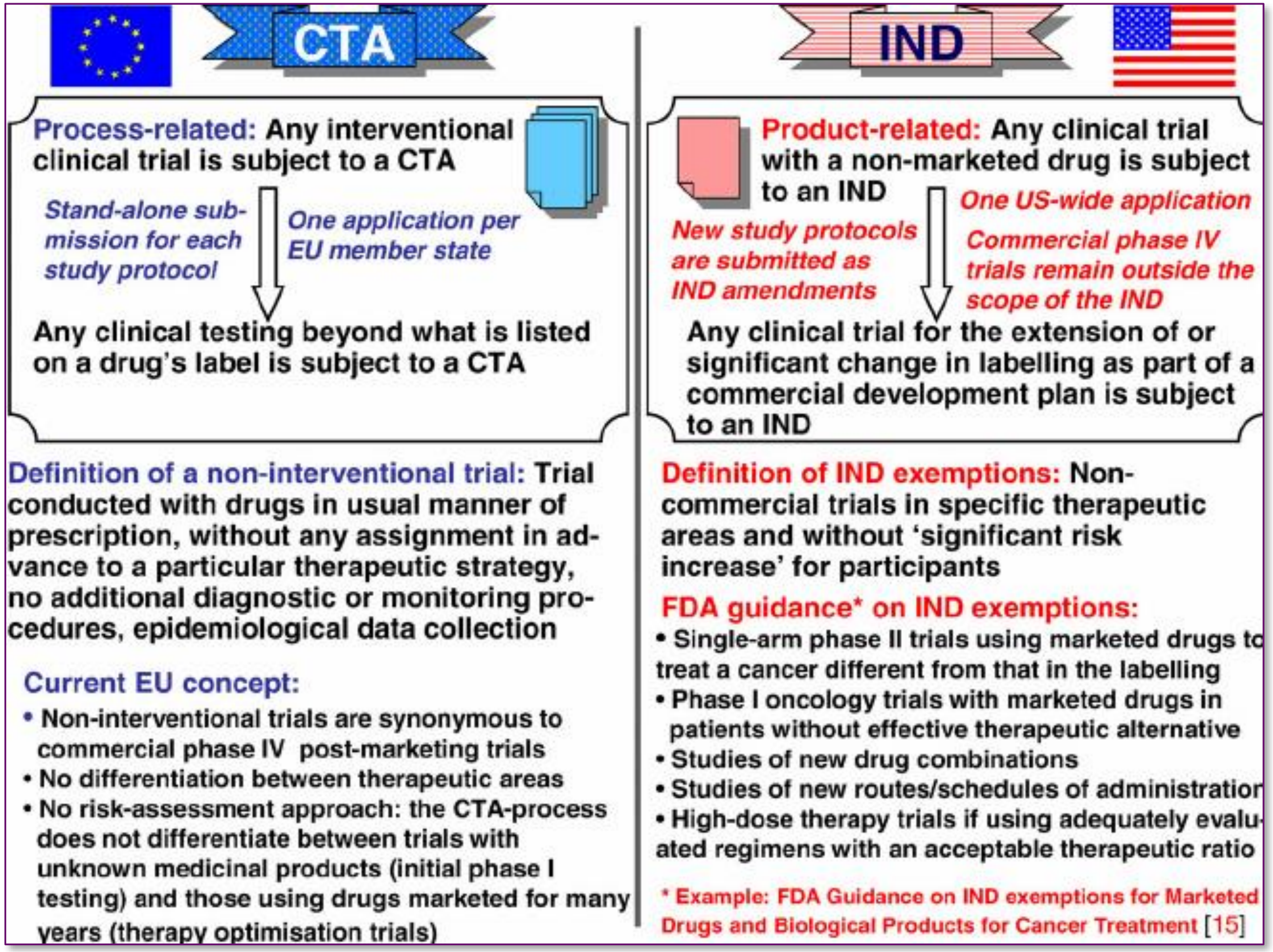
Note: today's discussion was very US (FDA)-centric, however other paths to clinical testing are available by region



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

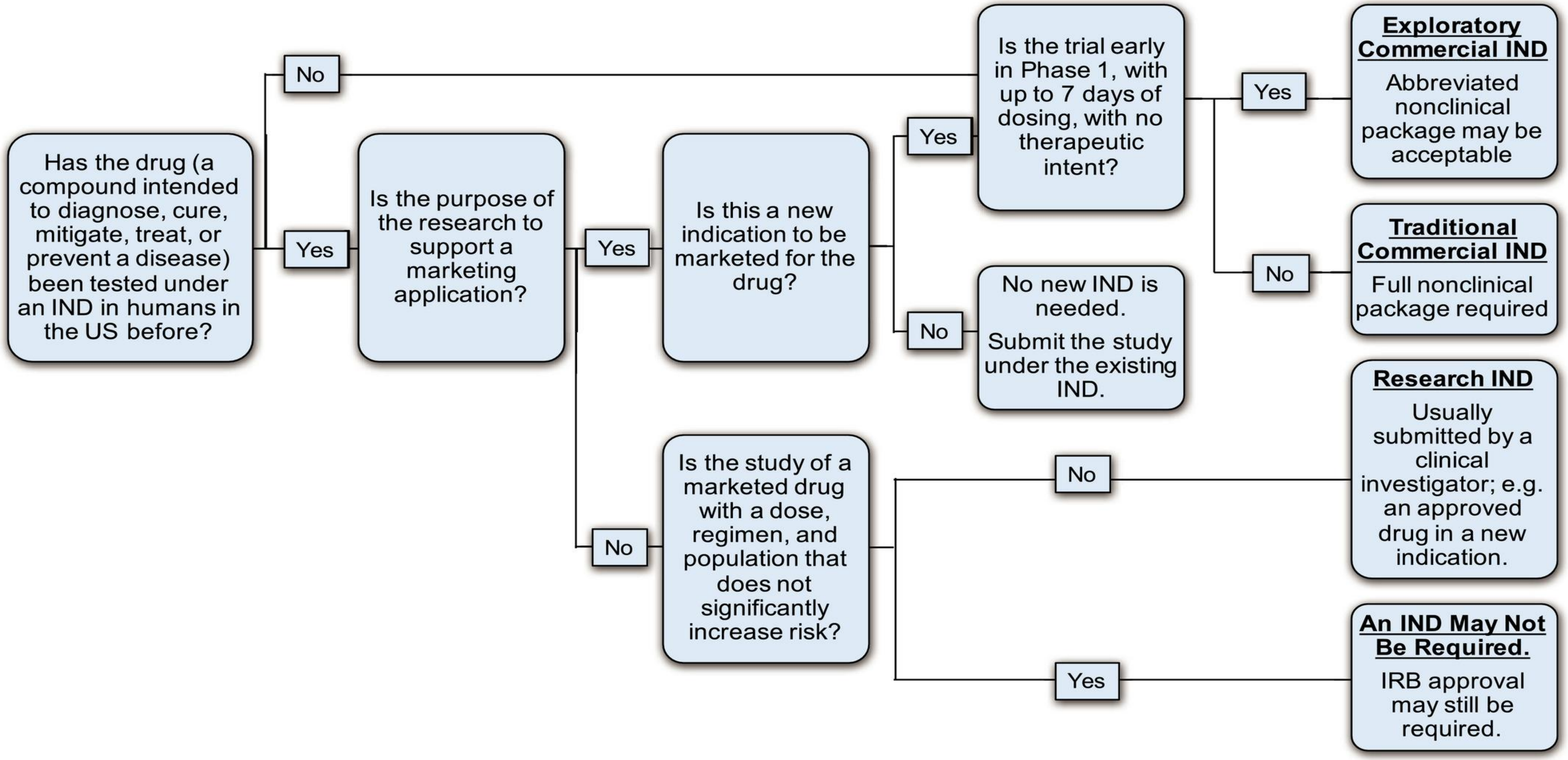
Appendix: IND (US) v CTA (EMA).

- 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

Appendix: Paths to IND.

Introduction to Investigational New Drug Applications and Clinical Trial Applications



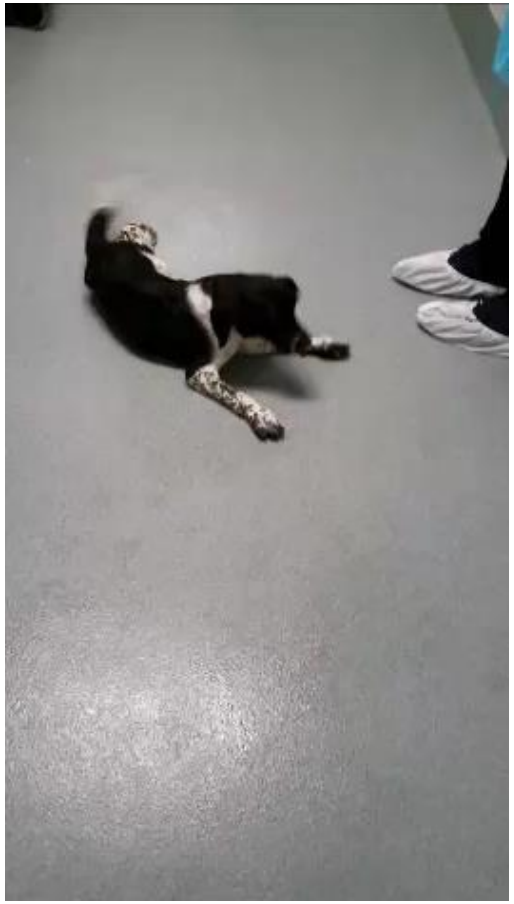
Clinical Translational Sci, Volume: 12, Issue: 4, Pages: 334-342, First published: 18 March 2019, DOI: (10.1111/cts.12635)

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

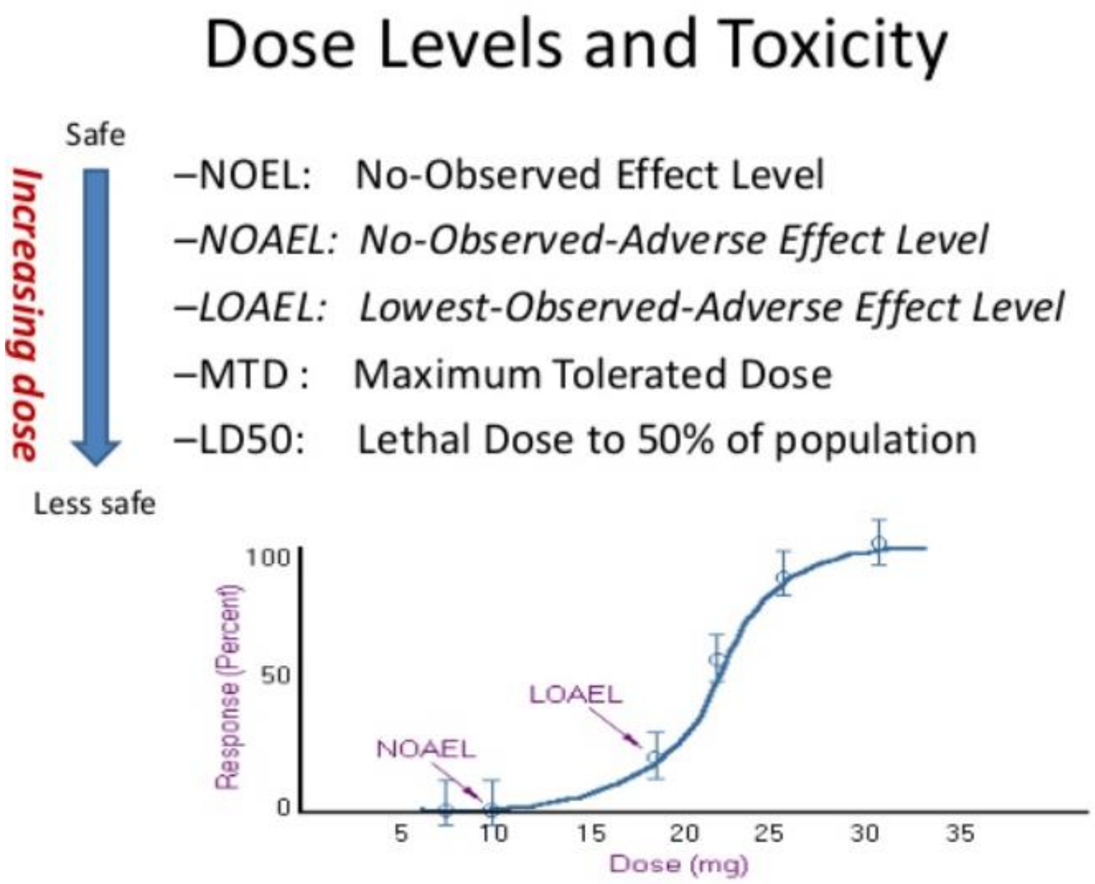
Types of studies:

- 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: example nonclinical components of a GT 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)

Appendix: example nonclinical components of an ERT (biologic) IND package (Mepsevii™ for MPS VII).

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)

Appendix: example nonclinical components of a small molecule IND package (UX068 for CTD).

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

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

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