Nonclinical Studies to Support Clinical Trials

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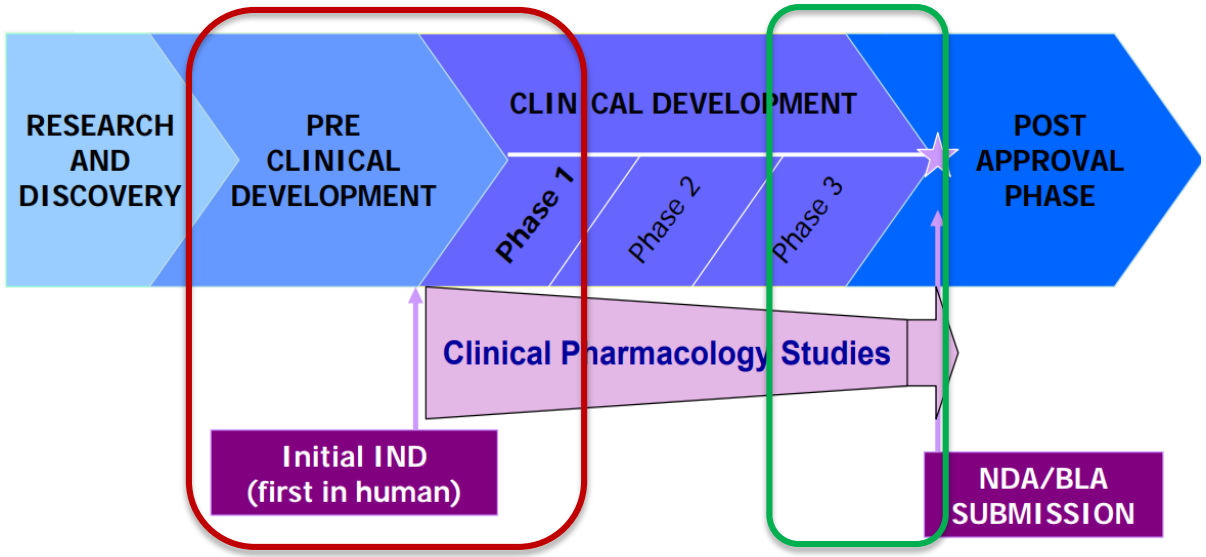
Scope of this Presentation

- Preclinical Program
  - Studies Required to Support first-in-human (FIH) Trials
  - Nonclinical Data Used in Early Phase Dosing Determinations
  - Outline of Nonclinical Studies Used to Support Late Phase Clinical Trials & Applications for Market Approval



- Early Phase Trials
  - Study Designs
  - Dosing Regimens

Outline

1. Preclinical Safety Assessments
2. Using preclinical data to determine appropriate FIH clinical doses
3. Dosing regimen considerations in Early Phase clinical trials
4. How indication can affect acceptable FIH dose determinations

Outline

1. Preclinical Safety Assessments
   - Nonclinical study recommendations to support FIH studies
     - Regulatory guidances: International Council on Harmonization (ICH), FDA, & European Medicines Agency (EMA)
   - Outline of nonclinical studies to support late phase clinical studies
2. Using preclinical data to determine appropriate FIH clinical doses
3. Dosing regimen considerations in Early Phase clinical trials
4. How indication can affect acceptable FIH dose determinations

Purpose of Preclinical Safety Assessment

➢ The overall purpose of preclinical safety program is three-fold

1. Hazard identification
2. Hazard characterization
3. Risk assessment

- Propose a safe FIH clinical dose
  - Determine Maximum Recommended Starting Dose (MRSD)
- Set safe clinical dosing limits
  - Define Maximum Recommended Human Dose (MRHD)
- May be used to guide other dosing decisions for FIH clinical trials
  - Pharmacokinetic (PK) / Pharmacodynamic (PD) modeling of nonclinical data can be used to predict clinical exposures
  - Nonclinical dose/exposure-response data can be useful in determining appropriate FIH dose escalation increments and dosing schedules

Regulatory Guidances: Nonclinical studies to support FIH trials

- ICH M3(R2): ICH Guidance for Industry: M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals (2010)
  - ICH M3(R2) Questions and Answers(R2) (2013)
  - Nonclinical studies to support FIH trials with **small molecules**
- ICH S6 & S6(R1): ICH Guidance for Industry: S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (1997/2010)
  - Nonclinical studies to support FIH trials with **biotechnology-derived products**, including biologics & recombinant peptides
- ICH S9: ICH Guidance for Industry: S9 Nonclinical Evaluation for Anticancer Pharmaceuticals (2010)
  - ICH S9 Questions & Answers (2018)
  - Nonclinical studies to support FIH trials with **oncology** products
- EMA Guideline (R1): Guideline On Strategies To Identify And Mitigate Risks For First-In-Human Clinical Trials With Investigational Medicinal Products (Revision 1, 2017)

"EMA 2017 Guidance"

  - Aligns with ICH M3(R2), S6(R1) and S9 guidances
  - Refers to ICH M3(R2), S6(R1) and S9 for design of safety pharmacology, PK/ADME, and toxicology studies

ICH M3(R2): Nonclinical Studies to Support Early Clinical Trials

- Pharmacodynamics
  - In vitro and/or in vivo studies
- Safety Pharmacology Studies
  - Core Battery: Cardiovascular (CV), Central Nervous System (CNS), & Respiratory assessments
    - ICH S7A and S7B
- PK/ADME (absorption, distribution, metabolism, & excretion)
  - In vitro plasma protein binding
  - In vitro metabolic data
- Genetic Toxicity Studies
  - Single clinical Doses
    - Gene mutation assay (i.e. in vitro Ames assay)
  - Multiple clinical Doses
    - Chromosomal damage in a mammalian system (i.e. in vitro chromosome aberration assay)
- General Toxicology Studies

ICH M3(R2): General Toxicology Studies to Support Early Clinical Trials

- **Acute Toxicology**
  - 2 species
    - 1 rodent + 1 non-rodent
  - Either single dose or repeat dose studies that test to a maximum tolerated dose (MTD)
- **Repeat-Dose Toxicology**
  - ≥2-week in 2 species
    - 1 rodent + 1 non-rodent

- Include most relevant species
  - pharmacologically active
  - Target distribution information is useful

- High Dose
  - MTD
  - Maximum feasible dose (MFD)
  - Saturation of exposure
  - Limit dose
    - ≤1 g/day : 1000 mg/kg/day
    - >1 g/day: 2000 mg/kg/day or MFD
  - Large exposure multiple
    - 50-fold margin based on exposure is generally sufficient

General Tox Study Duration ≥ Clinical Trial Duration

(Early Phase ≤ 6 months)

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

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

a. In the United States, as an alternative to 2-week studies, extended single-dose toxicity studies (see footnote c in Table 3) can support single-dose human trials. Clinical studies of less than 14 days can be supported with toxicity studies of the same duration as the proposed clinical study.

[Table 1, ICHM3(R2)]

Clinical MRHD is usually limited by toxicities or the High dose tested in animals

Can be limiting if predicted PD < actual PD, resulting in necessary exploration of higher clinical doses to achieve efficacy

Nonclinical Studies: Support Early Phase

ICH M3 (R2)
Small Molecules

- PD
- Safety Pharmacology
  - CNS, CV, respiratory
- PK & Protein Binding
- ADME
  - In vitro plasma protein binding
  - In vitro metabolic data
- General Toxicology
  - 2 species (rodent & non-rodent)
    - Acute &/or Repeat-dose
  - Duration ≥ Trial
- Genetic Toxicity
  - Gene mutation assay
  - Chromosomal damage in a mammalian system

Single dose FIH Trial

Multiple dose Trial

ICH S6 (R1)
Biologics

- PD
  - Relevant species*
- Safety Pharmacology
  - CNS, CV, respiratory
- PK
  - Protein Binding (if applicable)
- Some ADE ~~– Metabolism~~
- General Toxicology
  - 2* species (rodent & non-rodent)
    - * If possible
  - 2-week
    - Immunogenicity
    - Local tolerance
- ~~Genetic Toxicity~~

ICH S9
Oncology Products

- PD
  - Proof of concept (POC)
- PK
- General Toxicology
  - 2 species (rodent & non-rodent)
  - Incorporated Safety Pharmacology (CNS, CV, respiratory)
  - Genotoxic products: 1 species (usually rodent)
  - ➢ Similar schedules* to clinical use
- ~~ADME~~
- ~~Genetic Toxicity~~

* See Table 1, ICH S9

Nonclinical Studies: Support Late Phase (≥ Phase 3)

ICH M3 (R2)
Small Molecules

- PD
- Safety Pharmacology
- PK & Protein Binding
- ADME
- General Toxicology
  - 6 month rodent - **AND** -
  - 9 month non-rodent
- Genetic Toxicity
  - Complete prior to Phase 2
- Carcinogenicity
- Reproductive & Developmental Tox

ICH S6 (R1)
Biologics

- PD
- Safety Pharmacology
- PK
  - Protein Binding (if applicable)
- Some ADE ~~– Metabolism~~
- General Toxicology
  - ≤1 month in 2 species
  - Chronic 6 month rodent
    - **OR** – 6 month non-rodent
- Carcinogenicity
- Reproductive & Developmental Tox
- ~~Genetic Toxicity~~

ICH S9
Oncology Products

- PD
- PK
- ADME
- General Toxicology
  - 3 month in 2 species
  - Genotoxic products: 3 month in 1 species
    - ➢ Similar schedules* to clinical use
- Genetic Toxicity
  - Complete prior to marketing
- Reproductive & Developmental Tox
  - EFD studies only

Outline

1. Preclinical Safety Assessments
2. Using preclinical data to determine appropriate FIH clinical doses
   - Preclinical data & therapeutic window predictions
   - Acceptable MRSD
     - Toxicity Endpoints
     - PD Endpoints
3. Dosing regimen considerations in Early Phase clinical trials
4. How indication can affect acceptable FIH dose determinations

Preclinical Data & Therapeutic Window Predictions

NOAEL = No Observed **Adverse** Effect Level

* "…the highest dose level that does not produce a significant increase in adverse effects in comparison to the control group"

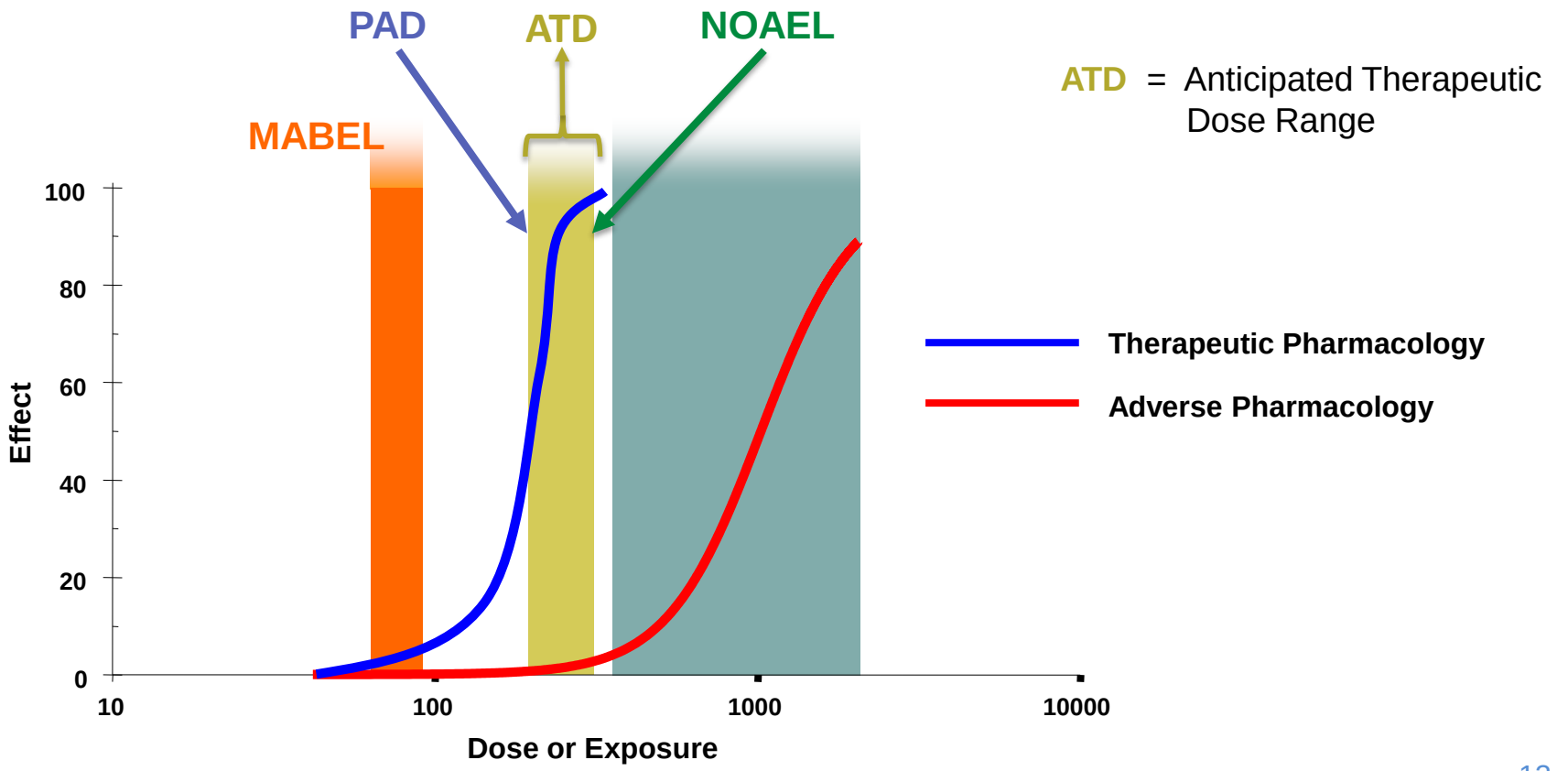
- Determined **empirically** in GLP toxicology and safety pharmacology studies in animals

MABEL = Minimal Anticipated Biological Effect Level

- *In vitro* pharmacology data from target cells from human and toxicology species
- Concentration-effect data from *in vitro* and *in vivo* studies
- Integrate data into PK/PD model (if feasible), to predict pharmacological response in humans at multiple dose levels

PAD = Pharmacologically Active Dose

ATD = Anticipated Therapeutic Dose Range



* (FDA Guidance for Industry: Estimating The Maximum Safe Starting Dose in Initial Clinical Trials For Therapeutics In Adult Healthy Volunteers)

Regulatory Guidances: Determining FIH Doses

- FDA Guidance for Industry: Estimating The Maximum Safe Starting Dose in Initial Clinical Trials For Therapeutics In Adult Healthy Volunteers (2005)

  "FDA 2005 Guidance"

  - Determining the **MRSD** to support FIH trials
- ICH M3(R2): ICH Guidance for Industry: M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals (2010)
  - ICH M3(R2) Questions and Answers(R2) (2013)
  - Nonclinical studies to support FIH trials with **small molecules**
  - Section VII: Exploratory Clinical Trials
- EMA Guideline (R1): Guideline On Strategies To Identify And Mitigate Risks For First-In-Human Clinical Trials With Investigational Medicinal Products (Revision 1, 2017)
  - **Chemical** & **biological** products
  - Nonclinical and clinical testing strategies, study design, quality
  - Determining **MRSD**, **dose escalations**, **MRHD**

FDA 2005 Guidance: Determining the MRSD

- Assumes Adult Healthy Volunteers
- Pertains to **small molecules** and **biologics**
  - ➢ Primarily for products with **systemic exposures**
  - – Does not apply to endogenous hormones and proteins used at physiological levels
  - – Does not apply to prophylactic vaccines
- Determine **MRSD** based on nonclinical toxicology endpoints
  - – Based on **NOAEL** in animals
  - – Most relevant species = usually most sensitive
  - – An algorithm is used to extrapolate the animal dose to a Human Equivalent Dose (**HED**)
- At the MRSD
  - – No adverse toxicity in humans
  - – Allow attainment of human tolerability, PD and/or PK profile data

Determine HED

Convert NOAEL to HED

- Allometric conversion to **normalize** to body surface area (**BSA**)

$$\text{HED} = \text{Animal NOAEL (mg/kg)} \times \left[\frac{\text{Animal weight (kg)}}{\text{Human weight (kg)}}\right]^{0.33}$$

-OR-

$$\text{HED (mg/kg)} = \frac{\text{Animal NOAEL (mg/kg)}}{\text{BSA Conversion Factor}}$$

Table 1: Conversion of Animal Doses to Human Equivalent Doses Based on Body Surface Area

Species	To Convert Animal Dose in mg/kg to Dose in mg/m^2, Multiply by k_m	To Convert Animal Dose in mg/kg to HED[a] in mg/kg, Either:	
		Divide Animal Dose By	Multiply Animal Dose By
Human	37	---	---
Child (20 kg)[b]	25	---	---
Mouse	3	12.3	0.08
Hamster	5	7.4	0.13
Rat	6	6.2	0.16
Ferret	7	5.3	0.19
Guinea pig	8	4.6	0.22
Rabbit	12	3.1	0.32
Dog	20	1.8	0.54
Primates:			
Monkeys[c]	12	3.1	0.32
Marmoset	6	6.2	0.16
Squirrel monkey	7	5.3	0.19
Baboon	20	1.8	0.54
Micro-pig	27	1.4	0.73
Mini-pig	35	1.1	0.95

[a] Assumes 60 kg human. For species not listed or for weights outside the standard ranges, HED can be calculated from the following formula:
HED = animal dose in mg/kg x (animal weight in kg/human weight in kg)$^{0.33}$.

[b] This k_m value is provided for reference only since healthy children will rarely be volunteers for phase 1 trials.

[c] For example, cynomolgus, rhesus, and stumptail.

(Table 1, FDA Guidance 2005)

Determine the 'Safety Factor'

➢ Standard Safety Factor = 10

- Humans may be more sensitive to the PD activity
- Some toxicities are difficult to assess in animals (i.e. headache, myalgia, mental disturbances)
- Interspecies differences in ADME
  - Bioavailability may be higher than anticipated in humans
- Differences in target densities or affinities
- Unexpected toxicities

➢ Validated experimentally

➢ Modifications may be justified

- Increase >10
- Decrease <10

Potential Safety Factor Justifications

➢ Standard Safety Factor = 10

Increase Safety Factor > 10

- Steep dose-response curve
- Severe toxicity at doses above NOAEL
- Non-monitorable toxicities
- Toxicities with no premonitory signs
- Irreversible toxicity
- Unexplained death
- Widely variable bioavailability in animals
- Non-linear PK
- Wide variability between species in doses or exposures eliciting toxicities
- Less than optimal nonclinical study design and/or conduct
- Novel therapeutic targets or drug class
- Animal models with limited utility

Decrease Safety Factor < 10

- Well-characterized drug class
  - established clinical dosing regimen
  - similar PK/ADME and toxicity profiles across species, including human.
- Toxicities are easily predicted, monitored, and are reversible.
- Dose-response for toxicity is not steep
- The NOAEL upon which the HED is based was determined in longer-term nonclinical studies
  - assumes that toxicities are cumulative
  - not observed early in the longer-term studies
- Toxicities are not likely to be translatable to humans
- Toxicities due to exaggerated PD effects in healthy animals, which are less of a concern in the indicated population.
  - If FIH human study is not in healthy volunteers

Determine MRSD

➢ Calculate MRSD

- HED at the nonclinical NOAEL
- Safety Factor
  - Standard = 10

$$\textbf{MRSD (mg/kg)} = \frac{\textbf{HED (mg/kg)}}{\textbf{Safety Factor}}$$

- Multiple by average healthy adult weight
  - Standard = 60 kg

MRSD (mg/kg) X 60 kg = MRSD (mg)

Toxicology vs. Pharmacology Endpoints

Toxicology Endpoints

- **NOAEL**
  - "…the highest dose level that dose not produce a significant increase in adverse effects in comparison to the control group" (FDA Guidance, 2005)
  - **Gold Standard** for **FIH** study **MRSD** Determinations
    - "starting point for determining a reasonably safe starting dose" (EMA Guidance, 2017)
    - "…an effect that would be unacceptable if produced by the initial dose…in a phase 1 clinical trial conducted in healthy volunteers" (FDA Guidance, 2005)
- LOAEL
  - Lowest Observed Adverse Effect Level
    - Not generally recommended for FIH study MRSD determinations in healthy subjects
- MTD
  - Maximum Tolerated Dose
    - "the highest dose that does not produce unacceptable toxicity"
    - Not generally recommended for FIH study MRSD determinations in healthy subjects

Pharmacology Endpoints

- MABEL
- **PAD**

➢ Consider appropriateness of a pharmacology endpoint for **Biologics**

- When to use:
  - There are no relevant nonclinical species
  - There are significant differences in PK/PD and biology between animals and humans
  - Different mechanisms of action are anticipated between species
  - There is limited cross-reactivity of the NME in animal species (i.e. antibody products)
  - Toxicities in animals from exaggerated pharmacological effects
    - No NOAEL identified (adverse effects at all doses)

"The **PAD** in these cases may be a more sensitive indicator of potential toxicity than the NOAEL and might therefore warrant lowering the MRSD" (FDA Guidance, 2005)

For antibodies, the MABEL-based approach always results in a smaller HED for the MRSD – (Suh, 2016)*

*Suh, Hoon Young et al. *Drug Design, Development and Therapy* 10 (2016): 4005–4016

EMA 2017 Guidance (Rev. 1)

- Nonclinical Toxicology & Pharmacology Endpoints
  - NOAEL should be determined in most relevant species
  - MABEL should be determined
  - PAD and/or ATD should be estimated
- MRSD
  - "Starting dose should be either related to the MABEL, PAD or NOAEL"
  - Reference ICH S9 for oncology patients
  - Reference ICH E11 for pediatrics
- MRHD
  - Based on PD, PK, and toxicity data [reference ICH M3(R2) for nonclinical toxicity assessments]
  - Take into account target saturation (when complete inhibition or activation of the target is achieved)
    - "…should be within the estimated human pharmacodynamic dose range"
  - Healthy subjects: MRHD ≠ MTD
    - exceeding MRHD may only be justified if risk mitigating measures are appropriate, but does not include MTD exploration
  - Patients: MRHD = MTD
    - "if applicable"

MRSD	
Healthy subjects	< PAD
Patients	≤ PAD

MRSD Flow Chart

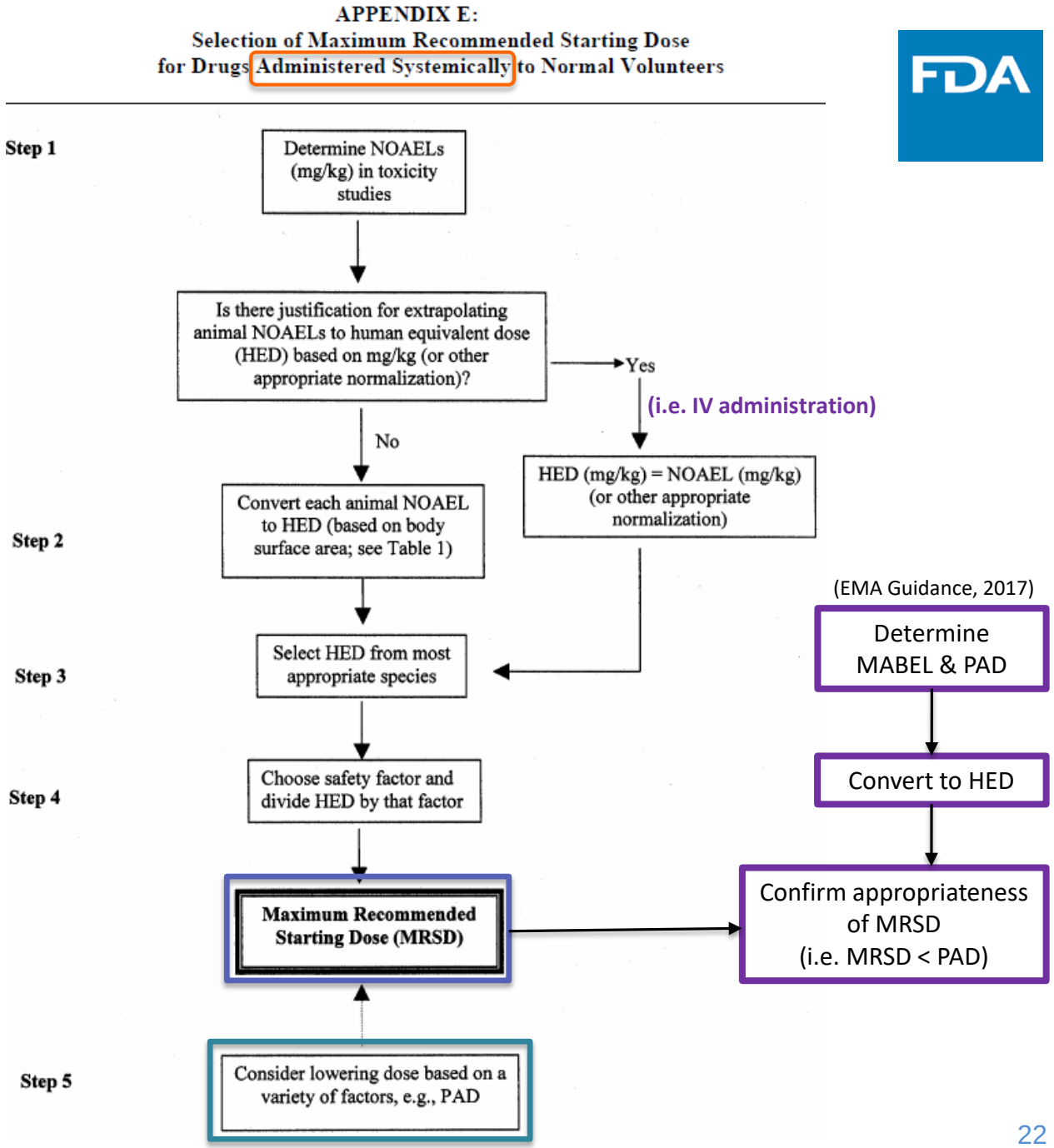
Standard Parameters

- NOAEL in most appropriate species
- BSA Allometric conversion to HED
- Safety Factor = 10
- Adult Human = 60 kg

$$\text{HED (mg/kg)} = \frac{\text{Animal NOAEL (mg/kg)}}{\text{BSA Conversion Factor}}$$

$$\text{MRSD (mg/kg)} = \frac{\text{HED (mg/kg)}}{\text{Safety Factor}}$$

MRSD (mg/kg) **X 60 kg = MRSD (mg)**



(FDA Guidance for Industry: Estimating The Maximum Safe Starting Dose in Initial Clinical Trials For Therapeutics In Adult Healthy Volunteers)

CDER's Experience

- NOAEL is the standard to determine starting dose for clinical trials
- MABEL is less frequently used by Sponsors for determination of FIH dose.
  - Often used for immunomodulators/activators
- MABEL, in general, has been used to determine starting dose in cases where…
  - there are no relevant species
    - i.e. biologics inactive in animals
  - when a NOAEL in animals could not be established
    - i.e. exaggerated PD-related adverse effects at all doses.
- For biologics, the NOAEL is still predominantly used to determine starting dose for clinical trials.
  - For biologics, CDER has no official preference
    - as long as the rationale for selection of the clinical starting dose is supported by sound scientific data.

Outline

1. Preclinical Safety Assessments
2. Using preclinical data to determine appropriate FIH clinical doses
3. Dosing regimen considerations in Early Phase clinical trials
   - Background: Early Phase clinical trials
   - Dosing regimen considerations
     - Based on preclinical PK & toxicology data
4. How indication can affect acceptable FIH dose determinations

Regulatory Guidances: Early Clinical Trials

- FDA Guidance for Industry: Exposure-Response Relationships – Study Design, Data Analysis, and Regulatory Applications. (2003)
  "FDA 2003 Guidance"
  - Determining **dose escalations**

- EMA Guideline (R1): Guideline On Strategies To Identify And Mitigate Risks For First-In-Human Clinical Trials With Investigational Medicinal Products (Revision 1, 2017)
  - Determining **MRSD**, **dose escalations**, **MRHD**

- ICH (E8) Guidance for Industry: General considerations for clinical trials (1997)

- ICH (E4) Guidance for Industry: Dose-Response Information to Support Drug Registration (1994)

➢ Focus: How preclinical data can guide dosing regimen decisions

Background: Early Clinical Trial Objectives

- Primary Objectives
  - Assess safety & tolerability
    - Characterize Dose-Limiting Toxicities (DLT)
    - Identify the maximum dose with an acceptable safety profile
  - Characterize clinical PK parameters
    - Exposure parameters (AUC, C_{max}) and drug half-life
    - Variability, linearity, dose-exposure relationship (i.e. dose-proportionality)
    - Steady-state parameters (accumulation, time-dependency)
- Secondary Goals
  - Evaluate absorption/bioavailability, metabolism, and excretion of the compound
  - Investigate PD activity
    - Monitor for biomarker endpoints (i.e. blood glucose levels, protein levels, etc.)

ICH E8: General considerations for clinical trials

FDA Guidance for Industry: Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications (2003)

Background: Common Early Clinical Trial Designs

- Randomized, placebo-controlled, studies in healthy volunteers
  - May include patients in cases with anticipated adverse toxicities
    - i.e. advanced cancer patients or HIV patients
- Dose-escalation studies
  - Stand-alone SAD FIH study
    - Can use a crossover design
      - wash-out period of ≥5 half-lives between administration, based on preclinical PK data half-life
  - MAD follow-up study
    - Dosing duration limited by the duration of nonclinical toxicology studies
  - Combined SAD/MAD FIH study
    - Part 1 = SAD portion ("Phase 1a")
    - Part 2 = MAD portion ("Phase 1b")
    - PK, PD, & safety data for each dose should be reviewed prior to proceeding with additional SAD or MAD cohorts at the same dose.
    - Parallel evaluations at lower doses are acceptable (EMA Guidance, 2017)
- Food Effect Study
  - Assess PK after a standardized test meal

Dose Range in Early Clinical Trials

- Dose range should identify the lowest effective dose
  - MRSD based on preclinical toxicology data
    - Lower starting doses are acceptable

- Dose range should identify the highest safe and effective dose
  - MRHD based on preclinical toxicology data
    - NOT based on PK modeling

Dose Escalation in Early Clinical Trials

- Should allow reasonably rapid attainment of the trial objectives (tolerability and PK)
- "The dose increment between two dose levels should be guided by the dose/exposure-toxicity or dose/exposure-effect relationship defined in the non-clinical studies and adapted following review of emerging clinical data from previous cohorts." (EMA Guidance, 2017)
- The rate of escalation can be slowed after the first observation of toxicity or PD activity
  - especially if a narrow therapeutic window and/or serious adverse toxicity was observed in nonclinical studies
- Rate of dose escalation based on preclinical findings and expectations, including drug half-life
  - Based on monitorability of potential serious/irreversible effects

Linear Dose/Exposure-Effect & Toxicity Relationship

Indication: Type 2 Diabetes

Effect: Blood Glucose Lowering
(monitorable & treatable)

Toxicities: Hypoglycemia-related

More Risk

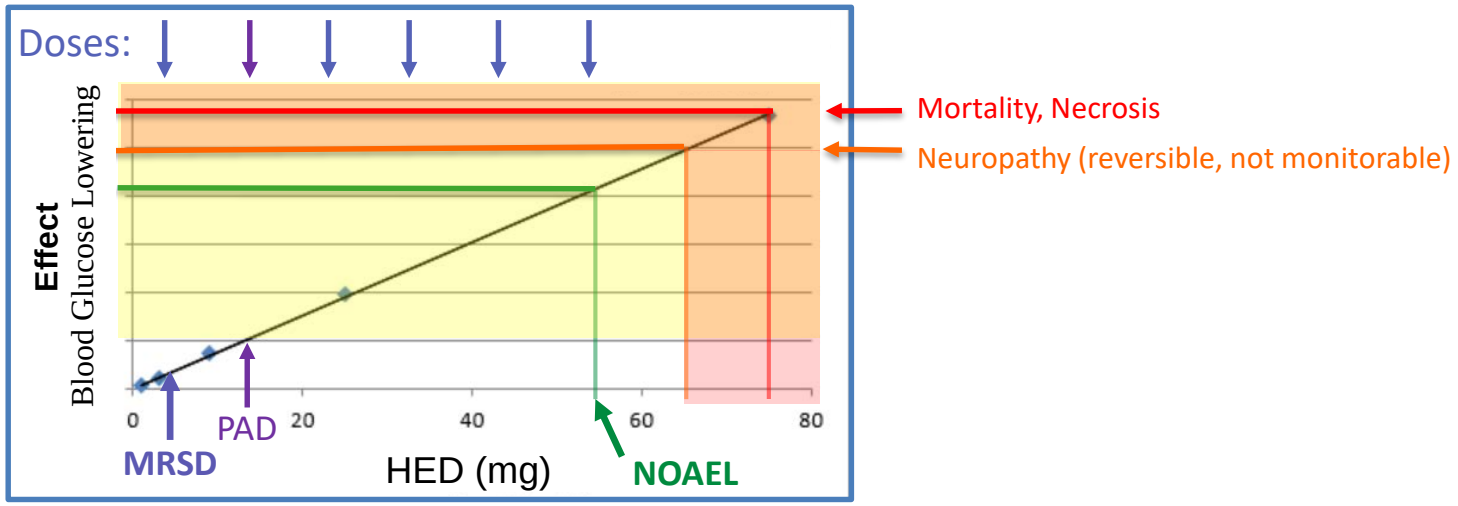
- Normoglycemia
(i.e. general tox study)
- Repeat dosing

Less Risk

- Hyperglycemia
- Acute Doses

MRHD: Safety Factor < 10

Linear example: Common hypoglycemia-related toxicities with anti-diabetic agents



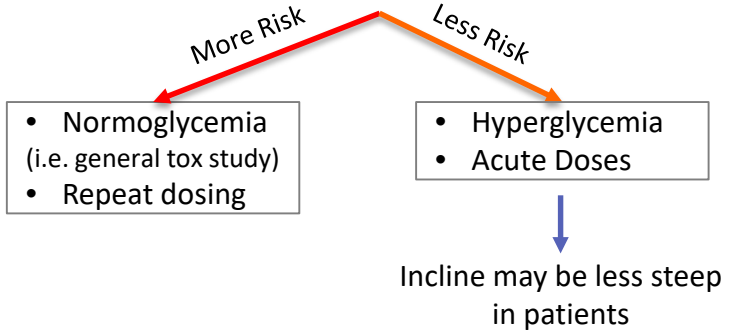
Linear Dose/Exposure-Effect & Toxicity → Linear, consistent rate of dose escalation

Exponential Dose/Exposure-Effect & Toxicity Relationship

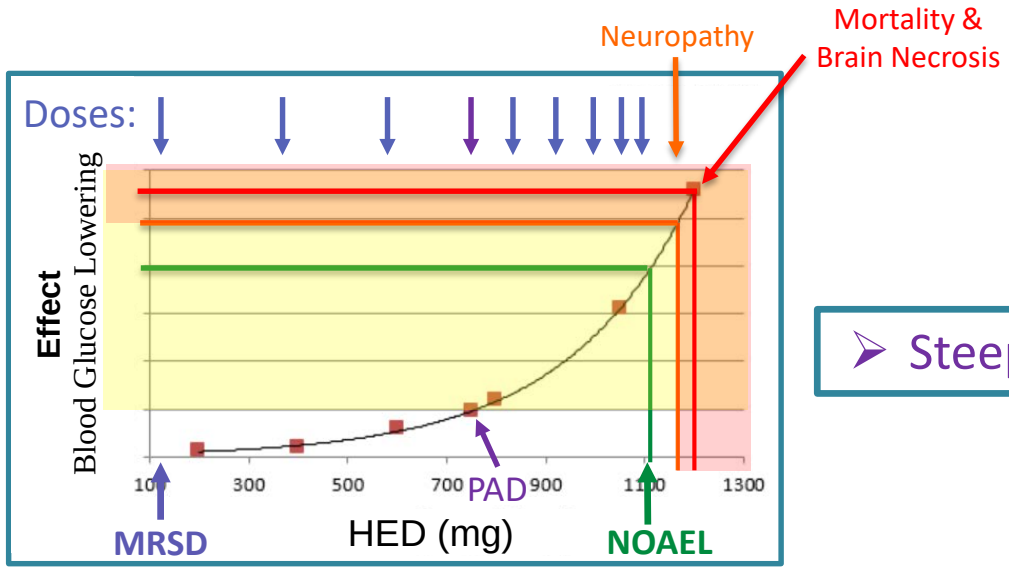
Indication: Type 2 Diabetes

Effect: Blood Glucose Lowering
(monitorable & treatable)

Toxicities: Hypoglycemia-related



Exponential example: Glucokinase Activator (GKA)
- regulates glucose homeostasis at the intracellular level



➢ Steeper curve = slower rate

Exponential Dose/Exposure-Effect & Toxicity → Initial rapid rate of dose escalation

Approach NOAEL

Decreased rate of dose escalation

Logarithmic Dose/Exposure-Effect & Toxicity Relationship

Indication: Type 2 Diabetes

Effect: Blood Glucose Lowering
(monitorable & treatable)

Toxicities: Hypoglycemia-related

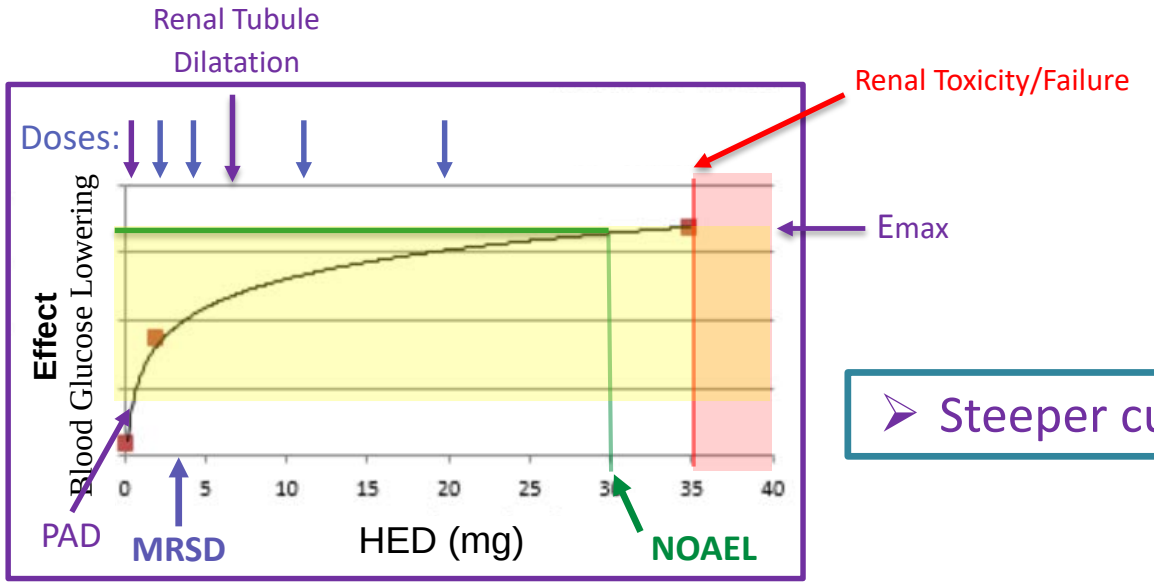
More Risk

- Normoglycemia
(i.e. general tox study)
- Repeat dosing

Less Risk

- Hyperglycemia
- Acute Doses

Logarithmic Example: Sodium-glucose cotransporters (SGLT1/2) Inhibitor
- prevent renal glucose reabsorption back into the bloodstream



➢ Steeper curve = slower rate

Logarithmic Dose/Exposure-Effect & Toxicity → Initial slow rate of dose escalation

↓ Approach Maximum Effect (Emax)

Increased rate of dose escalation

MAD Dosing Regimens

- MRHD limited by nonclinical toxicology data
  - NOT based on PK modeling
  - Initial MRHD based on BSA
    - once clinical PK data is available, switch to AUC basis
- Dosing duration
  - limited by the duration of **nonclinical** toxicology studies
- Usually the same (or reasonably similar) **dosing schedule** evaluated in nonclinical studies
  - i.e. daily, weekly, monthly, etc.
- Follow-up MAD studies
  - Dose levels, dosing increments, and schedule based on SAD study data
- For combined SAD/MAD FIH studies
  - Initially proposed dose levels, increments and schedule for the MAD portion may be based on **preclinical** data based on **BSA** (as done for SAD protocol)
  - May allow for modification based on SAD PK data at preceding dose(s)

Outline

1. Preclinical Safety Assessments
2. Using preclinical data to determine appropriate FIH clinical doses
3. Dosing regimen considerations in Early Phase clinical trials
4. How indication can affect acceptable FIH dose determinations
   - Indication-specific guidances
   - Oncology products
     - Determining the **MRSD** for oncology FIH clinical trials
     - Dosing schedules for oncology Phase 1 trials
     - Oncology Phase 1 dosing regimens

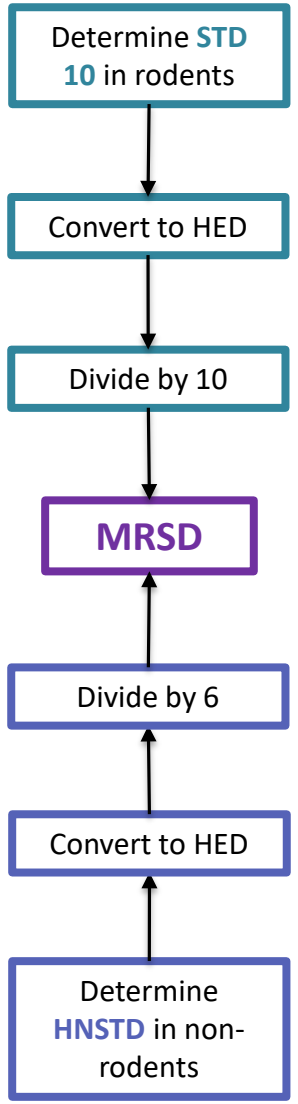
Indication-Specific Regulatory Guidances

- Oncology ICH S9: ICH Guidance for Industry: S9 Nonclinical Evaluation for Anticancer Pharmaceuticals (2010)
  - ICH S9 Questions & Answers (2018)
- Indications wherein human efficacy studies are not ethical or feasible
  - Animal Rule FDA Guidance for Industry for Product Development Under the Animal Rule (2005)
- Many indication-specific FDA Guidances
  - Broad range of diseases & disorders
    - Chronic & Acute
    - Genetic & Acquired
    - Common & Rare
  - Dozens more planned for development
  - Dozens have been withdrawn

➢ FDA Guidances: https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

ICH S9: MRSD for FIH Oncology Trials

- Patients with advanced cancer only
- Small Molecules
  - MRSD based on toxic findings in animals
  - STD 10: Severely Toxic Dose in 10% of rodents
    - **MRSD = 1/10th STD 10**
  - HNSTD: Highest Non-Severely Toxic Dose in non-rodents
    - "…the highest dose level that does not produce evidence of lethality, life-threatening toxicities or irreversible findings."
      - **MRSD = 1/6th HNSTD**



ICH S9: MRHD & Dose Schedule for FIH Oncology Trials

- MRHD
  - Not limited to highest dose tested in nonclinical studies
  - Patients can be dosed to an MTD or an optimal biological dose (OBD)

- Dose Schedule
  - The nonclinical dosing schedule should be similar to the clinical schedule or be justified (e.g. based on PK, PD, etc.)
  - **1-month** dosing in animals is typically sufficient to allow **continuous** dosing in patients
  - Results of general toxicology studies can also guide dose escalation

Table 1: Examples of Treatment Schedules for Anticancer Pharmaceuticals to Support Initial Clinical Trials

Clinical Schedule	Examples of Nonclinical Treatment Schedule[1,2,3,4]
Once every 3-4 weeks	Single dose
Daily for 5 days every 3 weeks	Daily for 5 days
Daily for 5-7 days, alternating weeks	Daily for 5-7 days, alternating weeks (2-dose cycles)
Once a week for 3 weeks, 1 week off	Once a week for 3 weeks
Two or three times a week	Two or three times a week for 4 weeks
Daily	Daily for 4 weeks
Weekly	Once a week for 4-5 doses

(ICH S9, Table 1)

Summary

- Preclinical Assessments are useful for guiding Early Phase clinical trials
  - Toxicology endpoints are the standard for determining the FIH MRSD and MRHD
  - Pharmacology endpoints may be used to determine the FIH MRSD
    - Drug class, toxicities, and PD activity must be considered on a case-by-case basis
  - Nonclinical PK, PD and toxicity data can be useful for estimating appropriate FIH dosing increments, intervals between dosing, and dosing schedules for Early Phase trials
- The FDA 2005 Guidance and the EMA 2017 Guidance are complimentary
- Indication can drive preclinical program requirements and dosing decisions for Early Phase trials
  - Stay up-to-date on current FDA Guidances

    https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm
  - Stay up-to-date on current ICH Guidances

    http://www.ich.org/products/guidelines.html

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Thank you for you attention!

Questions?


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Back-up Slides

ICH S6(R1): Nonclinical studies to support FIH trials for Biologics

- Pharmacodynamics
  - In vitro and in vivo studies
    - Identification of relevant species
- Safety Pharmacology Studies
  - Core Battery: Cardiovascular, CNS, respiratory system assessments
- PK/ADME
  - Metabolism not required
  - "some information on absorption, disposition, and clearance" in relevant models prior to Phase 1
- Genetic Toxicity Studies
  - Not required
- Toxicology Studies
  - ➢ Clinical studies ≤7 days: 2-week
  - Immunogenicity
  - Local tolerance

EMA Guidance Rev 1 (2017): Nonclinical studies to support FIH trials

- Pharmacodynamics
  - In vitro using animal & human-derived material
  - In vivo using relevant animal models
- Safety Pharmacology Studies
  - References ICH M3(R2), S6(R1), S9 (oncology products), and safety pharm guidances S7A & S7B
- PK/ADME
  - References ICH M3(R2), S6(R1) & systemic exposure guidance S3
- Genetic Toxicity Studies
  - Not described
- Toxicology Studies
  - References ICH M3(R2), S6(R1), S9 (oncology products)

ICH S9:
Nonclinical studies to support FIH trials for Oncology Products

- Patients with advanced cancer
  - ICH M3(R2) guidelines required for studies in healthy volunteers
- Pharmacodynamics
  - Proof of principle in an appropriate model
- Safety Pharmacology Studies
  - Stand-alone studies only needed if "specific concerns" exist with "significant additional risks"
- PK/ADME
  - PK parameters can facilitate dose selection in Phase 1 studies
    - Note that ADME studies can be done in parallel with clinical development
- Genetic Toxicity Studies
  - Not require until NDA submission
- Toxicology Studies
  - ID a MTD and DLT
  - 1 rodent + 1 non-rodent
    - Genotoxic drugs: 1 species may be sufficient
  - Assessment of CV, respiratory and CNS organ functions

ICH M3(R2): General Tox studies supporting exploratory trials

Standard Single Dose FIH studies

- see Approach 3, ICH M3(R2)
- Dosing into the anticipated therapeutic range
  - Max dose ≥ PAD (Pharmacologically Active Dose)
- Preclinical Toxicology studies
  - 2 species
    - 1 rodent + 1 non-rodent
  - Types of studies
    - 2 Acute
    - 1 Acute + 1 Repeat-dose
    - 2 Repeat-dose

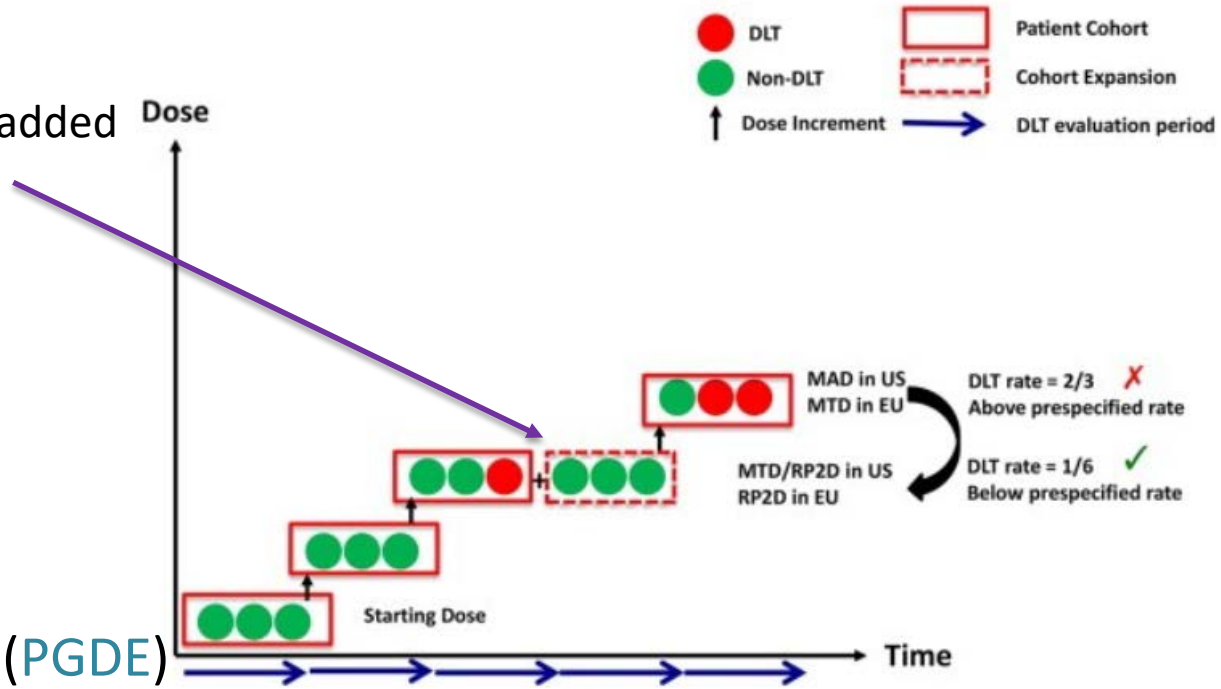
Exploratory Microdose Trials

- Max dose ≤ 1/100th PAD
- Max dose ≤ 1/100th NOAEL (No Observed Adverse Effect Level)
- Dose ≤ 100 μg
  - see Approach 1, ICH M3(R2)
  - Preclinical Toxicology studies
    - Extended single dose tox study in 1 species
- Up to 5 doses of ≤ 100 μg each
  - see Approach 2, ICH M3(R2)
  - Total ≤ 500 μg
  - Washout period of ≥6 half-lives
  - Preclinical Toxicology studies
    - 7-day repeat-dose tox study in 1 species

Examples of Common Oncology FIH SAD Dosing Regimens

- Standard '3+3' Design
  - Identify the MTD based on DLT
  - 3 patients tested at each dose level
  - If DLT in 1 of 3 patients, 3 additional subjects are added to that dose level
  - Dose with DLT in 2 of 3 patients exceeds the MTD
  - Next lower dose = MTD
- Continual Reassessment Method (CRM)
  - Target level of toxicity
  - Dose modification at each step
    - re-calculation based on Bayesian principles
- Pharmacokinetically guided dose escalation (PGDE)
  - Target AUC level
  - Real-time PK measurement and analysis
  - Dose modification at each step (Modified Fibonacci scheme)
- Accelerated Titration
- Etc…

Oncology '3+3' FIH Study Design



(Cook et. al., *Molecular Oncology*. 2015;9(5):997-1007)