The Role of Modeling & Simulation (M&S) in Regulatory Decision Making

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Disclaimer

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Outline

1. M&S Roles in Determining Clinical Doses
2. M&S Influence on Nonclinical Bioassay Study Designs
3. Dose-/Exposure-response Curves & Dose Escalation
4. Reformulations
5. Drug Accumulation Potential

Preclinical Data & Therapeutic Window Predictions

MABEL = Minimal Anticipated Biological Effect Level

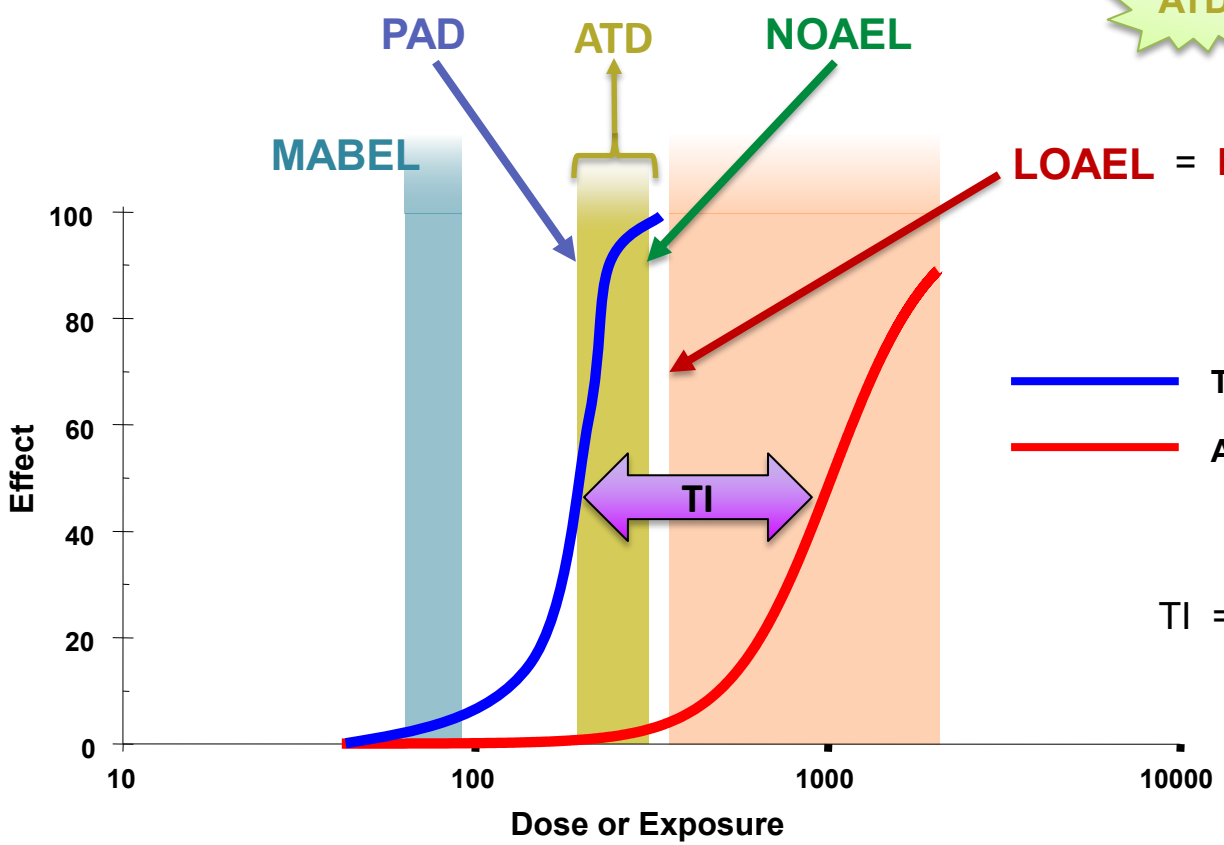
- *In vitro* pharmacology data from target cells from human and toxicology species
- Concentration-effect data from *in vitro* and *in vivo* studies
- Integrate data into PK/PD & PB/PK models, to predict pharmacological response in humans at multiple dose levels

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

M&S Plays an Important Role



PAD = Pharmacologically Active Dose

ATD = Anticipated Therapeutic Dose Range

LOAEL = **Lowest** Observed Adverse Effect Level

Therapeutic Pharmacology

Adverse Toxicity/Pharmacology

TI = **Therapeutic Index**

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

Toxicology vs. Pharmacology Endpoints

Toxicology Endpoints

- **NOAEL**
  - **Gold Standard** for First-In-Human (**FIH**) study Maximum Recommended Starting Dose (**MRSD**) Determinations
    - "…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)

Determine the 'Safety Factor'

➢ Standard Safety Factor = 10

1. Humans may be more sensitive to the PD activity
2. Some toxicities are difficult to assess in animals (i.e. headache, myalgia, mental disturbances)
3. Interspecies differences in ADME
   - Bioavailability may be higher or lower than anticipated in humans
     - Could be due to differences in absorption, clearance, excretion, &/or protein binding
4. Differences in target densities or affinities
5. 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

MRSD Flow Chart

Standard Parameters

- NOAEL in most appropriate species
  - Or MABEL/PAD if deemed appropriate
- Convert to Human Equivalent Dose (HED)
  - Allometric conversion to normalize to body surface area (BSA)

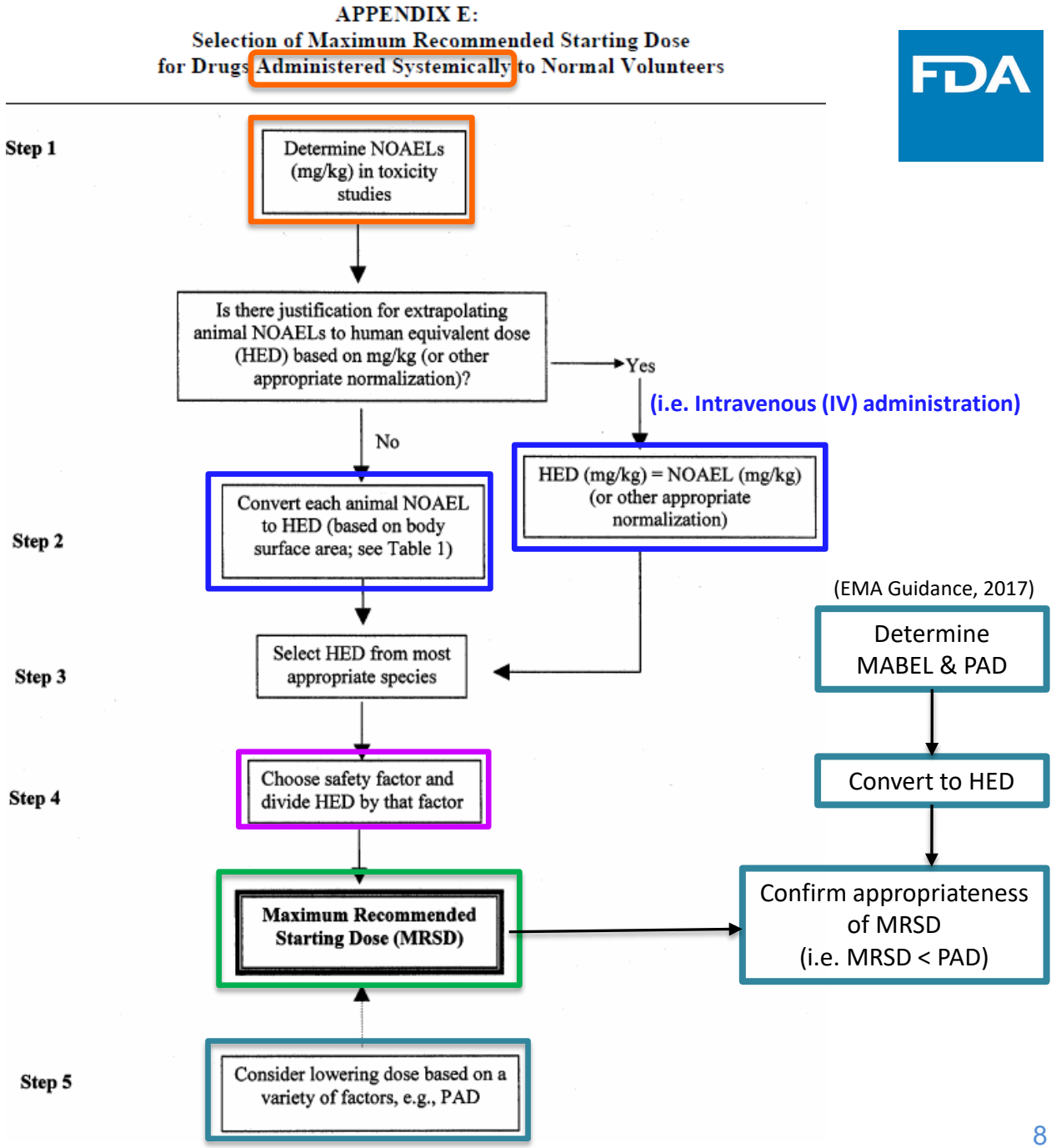
$$\text{HED (mg/kg)} = \frac{\text{Animal NOAEL (mg/kg)}}{\text{BSA Conversion Factor}} *$$

- Apply Safety Factor to calculate MRSD
  - Standard Safety Factor = 10

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

- Use Average Adult Human = 60 kg

$$\text{MRSD (mg/kg) X 60 kg} = \text{MRSD (mg)}$$



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

Determining MRHD

- Based on empirical nonclinical GLP toxicology and safety pharmacology studies
  - Reference ICH M3(R2) for nonclinical toxicity assessments
  - ➢ **NOT** based on PK or PB/PK modeling
- Take into account target saturation
  - Internal concentration at which complete inhibition or activation of the target is achieved
  - "…should be within the estimated human pharmacodynamic dose range"
- Can be limited by:
  - Highest dose tested in nonclinical studies
  - Insufficient margin of safety or exposure margin at the nonclinical NOAEL &/or LOAEL for significant adverse findings
    - Consider severity and reversibility of the finding(s)
    - Consider indication, patient population and severity of disease/disorder (e.g. life-threatening)
    - Determined on a **case-by-case basis**
- Healthy subjects: MRHD ≠ MTD
- Some Patient Populations (e.g. Advanced Cancer): MRHD may approach the preclinical MTD (MRHD = MTD)
  - Reference: ICH S9 for oncology patients, EMA 2017 Guidance

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High/Top Dose Selection: ICH M3(R2)

ICH M3(R2): Small Molecules

> ➢ *"… will normally be determined by **toxicological** conditions."*

Acceptable basis for high Dose selection for General Toxicity Studies include:

- MTD
- Maximum Feasible Dose (MFD)
- Saturation of exposure
  - including saturation of absorption (ICH S3A)
- Limit dose
  - For MRHD ≤1 g/day : 1000 mg/kg/day
  - For MRHD >1 g/day: 2000 mg/kg/day or MFD
- Exposure Margin
  - 50-fold margin based on exposure is generally sufficient

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

Can be limiting if actual PAD > **predicted PAD**

Necessary exploration of higher clinical doses to achieve efficacy

High/Top Dose Selection: ICH S6(R1)

ICH S6(R1): Biotechnology-Derived Products

Acceptable basis for high Dose selection for General Toxicity Studies include:

- The 5 toxicology, feasibility, and exposure bases described in ICH M3(R2)

- **PD endpoints**
  - The **higher** of the following 2 should be used:
    1. Dose that provides maximum PD effect
    2. Dose that provides 10-fold exposure to MRHD

  - **Supportive** use of PK/PD data & in vitro binding &/or pharmacological data

    Take into account species differences in target binding affinity, potency, exposure, etc.

➢ When to use:
- In vivo & ex vivo PD endpoints are not available
  - Little/no activity in animal species, correlating with little/no toxicities
- Significant differences in PK/PD and biology between animals and humans
  - Different Mechanism of Action

➢ When to use:
- Significant differences in PK/PD and biology between animals and humans
- Dose-limiting effects due to exaggerated pharmacology
  - Consider Dose-Response Relationship

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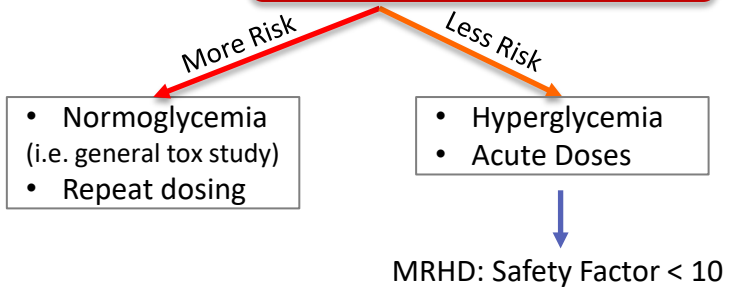
Linear Dose-/Exposure-Effect & Toxicity Relationship

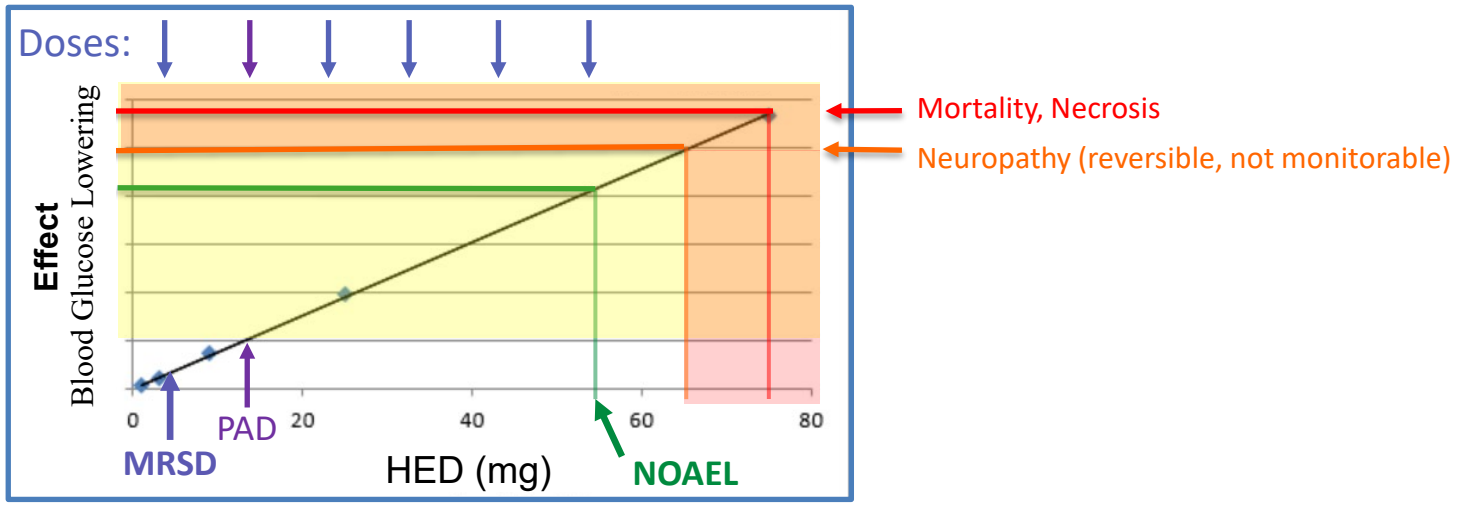
Indication: Type 2 Diabetes

Effect: Blood Glucose Lowering
(monitorable & treatable)

Toxicities: Hypoglycemia-related



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



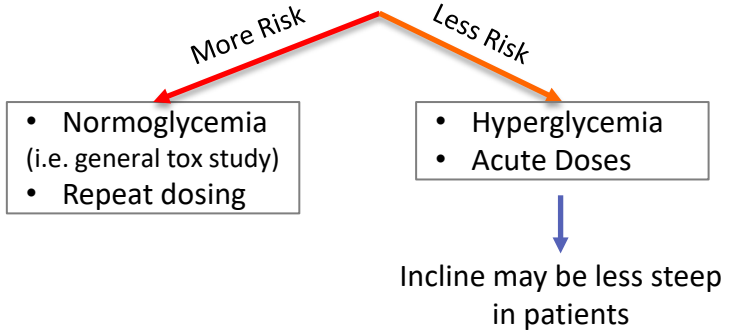
Linear Dose/Exposure-Effect & Toxicity → Linear, consistent rate of dose escalation

Exponential Dose-/Exposure-Effect & Toxicity Relationship

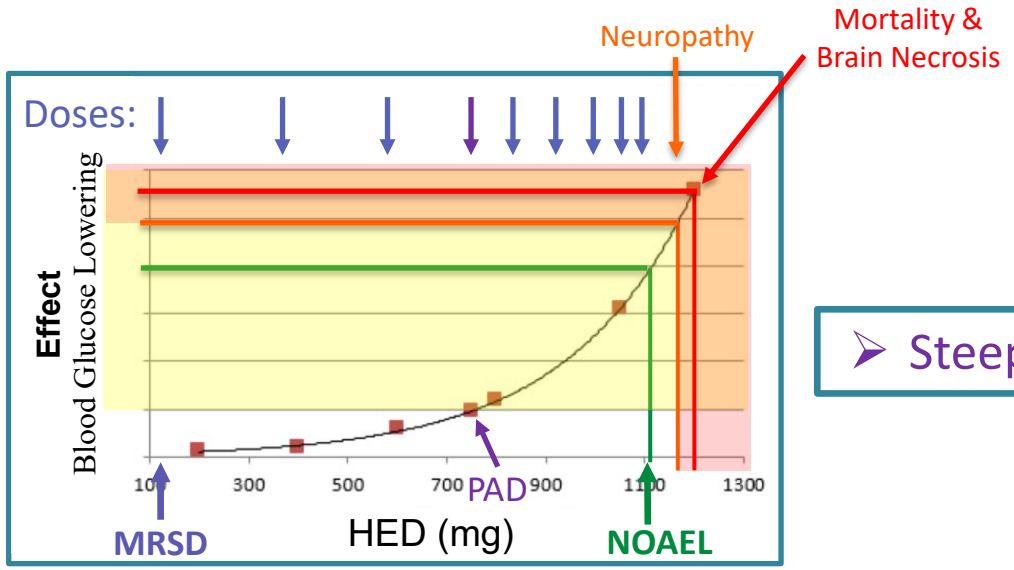
Indication: Type 2 Diabetes

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

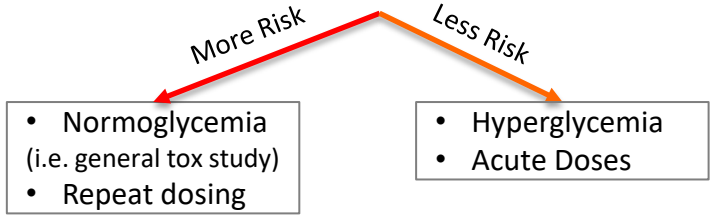
Decreased rate of dose escalation

Logarithmic Dose-/Exposure-Effect & Toxicity Relationship

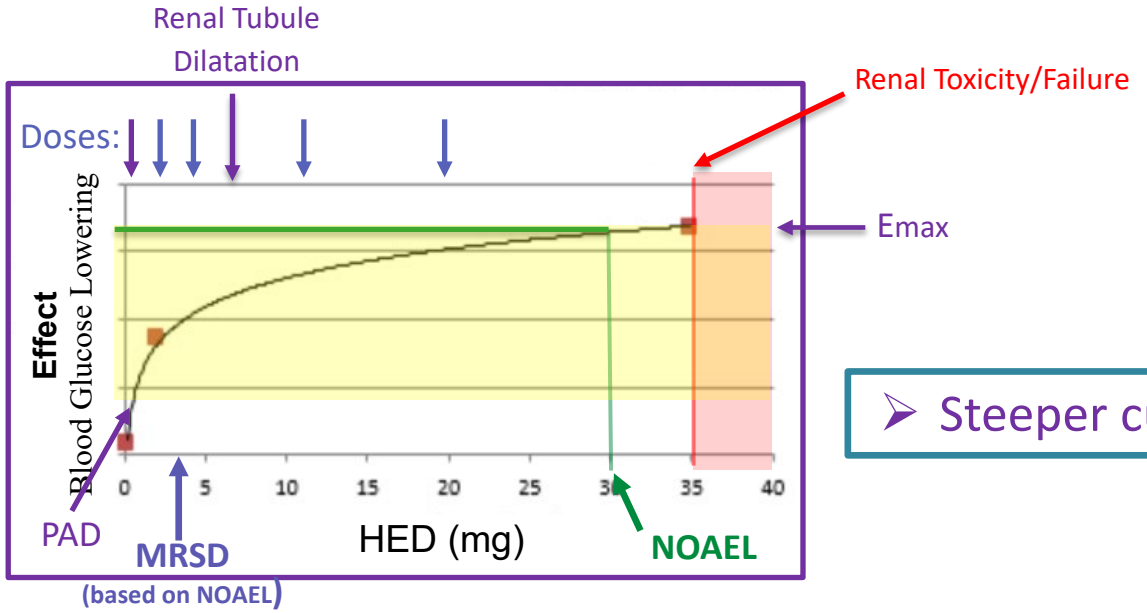
Indication: Type 2 Diabetes

Effect: Blood Glucose Lowering
(monitorable & treatable)

Toxicities: Hypoglycemia-related



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

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Formulation Changes

- M&S can be useful in formulation development
  - Modeling Bioavailability & Bioequivalence
- *"An adequate evaluation of the pharmacokinetics and absorption, distribution, metabolism, and elimination (PK/ADME) of the drug substance is recommended for new formulations."* – 2015 FDA Reformulations Guidance*
  - Note that additional nonclinical "Bridging" studies may be warranted
- For reformulations of approved products for extended-release formulations, an in vitro/in vivo correlation (IVIVC) may be useful as "*a surrogate for in vivo bioequivalence when it is necessary to document bioequivalence*" – 1997 FDA Extended Release Guidance**

* 2015 FDA Guidance for Industry: Nonclinical Safety Evaluation of Reformulated Drug Products and Products Intended for Administration by an Alternate Route

** 1997 FDA Guidance for Industry: Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations

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   - M&S information may be useful information for regulators

When Distribution & Accumulation may need "Special Consideration"

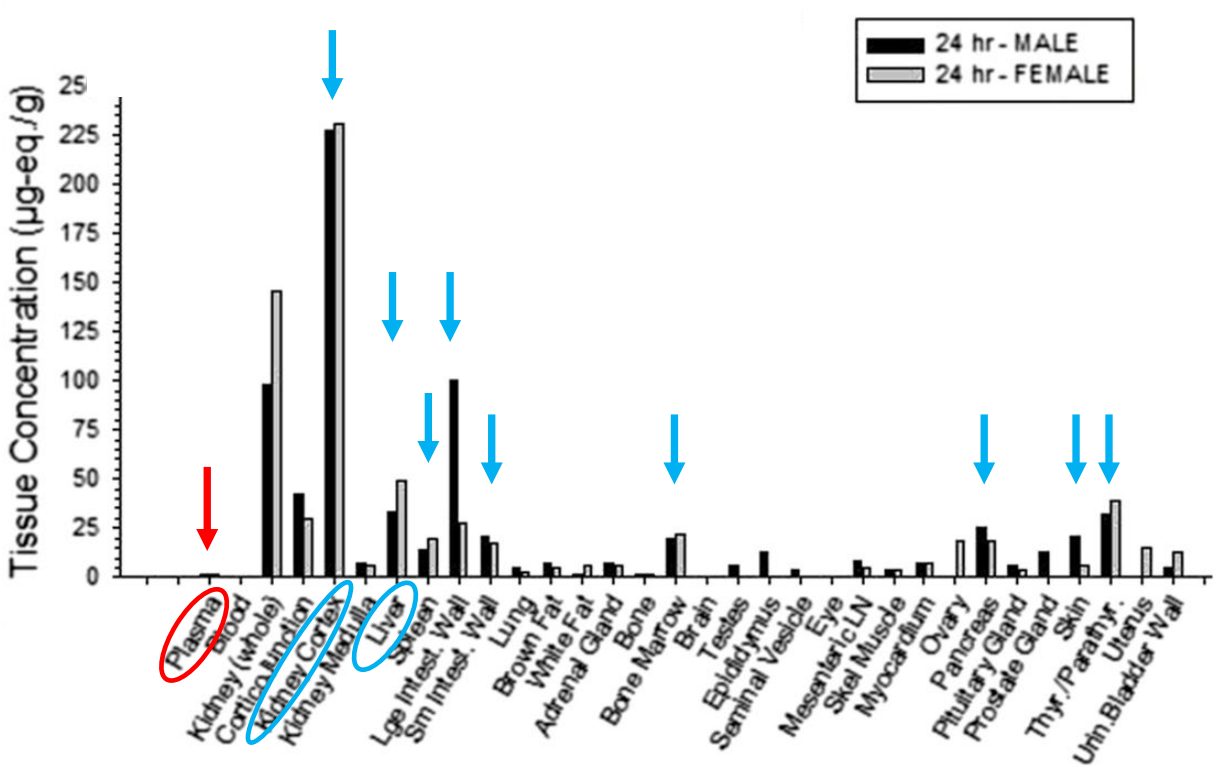
- Significant distribution to tissues with relatively slow clearance rates
  - if the clearance rate is significantly slower than the rate of uptake and frequency of administration
    - i.e. tissue half-life is longer than the plasma half-life and greater than the frequency of administration
    - e.g. fast distribution of oligonucleotide therapeutics ("oligos") in target tissues
  - Can lead to accumulation
- Increases in PD-related effects with repeat dosing may be secondary to significant distribution &/or accumulation in target tissues
- Concerns that preferential tissue distribution &/or accumulation could be related to tissue toxicity
  - Adverse toxicities affecting NOAEL determination
  - Dose-limiting toxicities
  - e.g. preferential distribution of oligos in target organs of toxicity
- Re-distribution of drug released from tissues can affect PK/TK parameters in other compartments
  - e.g. slow release of lipophilic drugs from fat compartments
  - e.g. slow re-distribution of oligos from target tissues, resulting in prolonged treatment durations to reach steady state plasma levels

Example: Systemic PS ASO Tissue Distribution

- Anti-sense oligonucleotide (ASO) with phosphorothioate (PS) backbone
  - Largest subclass of systemic Oligonucleotides

- Rapidly Removed from Plasma Due to Rapid Tissue Uptake
- Very Slow Tissue Clearance

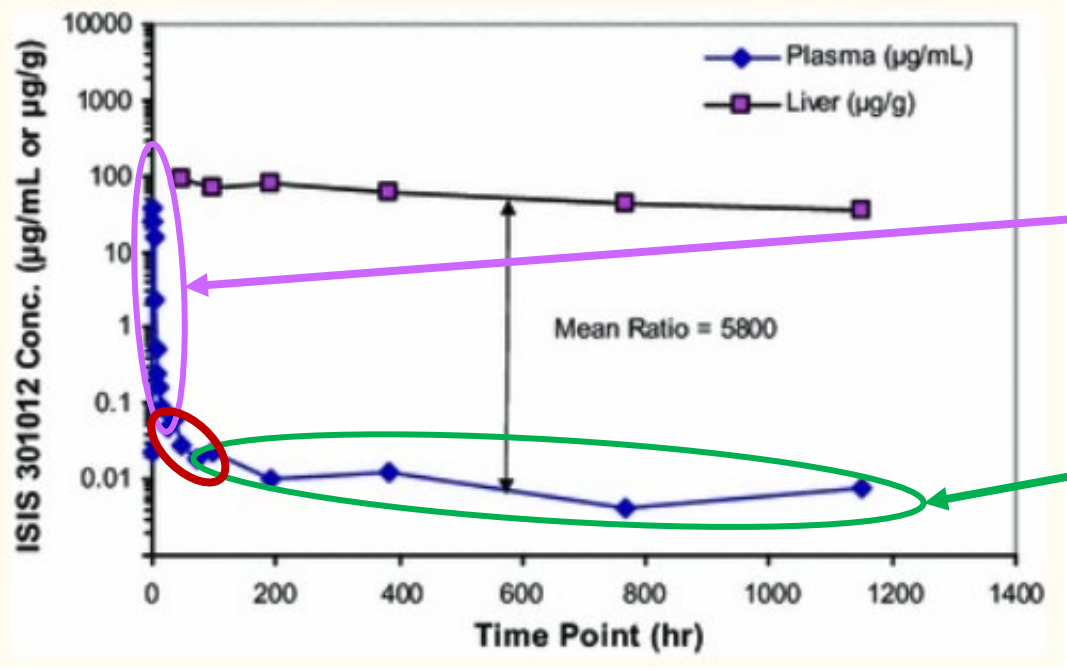
- Broad tissue bioavailability (>90%)
  - Kidney, Liver, Spleen, Intestine, Bone Marrow, Pancreas, Thyroid/Parathyroid, Lymph Nodes, skin,...
- Similar patterns of distribution
  - Conjugation to modifications can enhanced delivery to target organs (e.g. liver or kidney)
- Common Plasma PK Characteristics:
  - T_{max} = 0.5 to 4 h post-dose
  - ~5% of C_{max} by 24 h
  - High plasma protein binding
  - Rapidly taken up by tissues
- Slow tissue clearance
  - Tissue $t_{1/2}$ = ~2 weeks to ~2 months



Reference: Richard S. Geary, Daniel Norris, Rosie Yu, C. Frank Bennett, Pharmacokinetics, biodistribution and cell uptake of antisense oligonucleotides, *Advanced Drug Delivery Reviews*, Volume 87, 2015, Pages 46-51

Systemic PS ASO: Example Single-Dose Plasma PK

- Biphasic Plasma PK (SC & IV)
  1. Rapid rise & fall = Distribution Phase
     - Systemic exposure & Distribution to Tissues
  2. Very Prolonged return to baseline
     - Elimination phase



➢ Standard 3 Compartment Model (used for most drugs), may NOT be sufficient

➢ Species range: minutes to hours

$t_{½\alpha}$ = Distribution phase half-life (~1 hour)

Endocytosis into tissues

Exocytosis from tissues

$t_{½\beta}$ = elimination phase half-life (~31 days)

Redistribution-phase plasma conc. ⟷ (Equilibrium) Tissue conc.

➢ Species range: days to months

Reference: Richard S. Geary, Daniel Norris, Rosie Yu, C. Frank Bennett, Pharmacokinetics, biodistribution and cell uptake of antisense oligonucleotides, *Advanced Drug Delivery Reviews*, Volume 87, 2015, Pages 46-51

Physiologically Based PK Model

Is AUC exposure for dose margin determination still best??

PS ASO Single Dose:
Plasma C_{trough} achieved by 24 hours

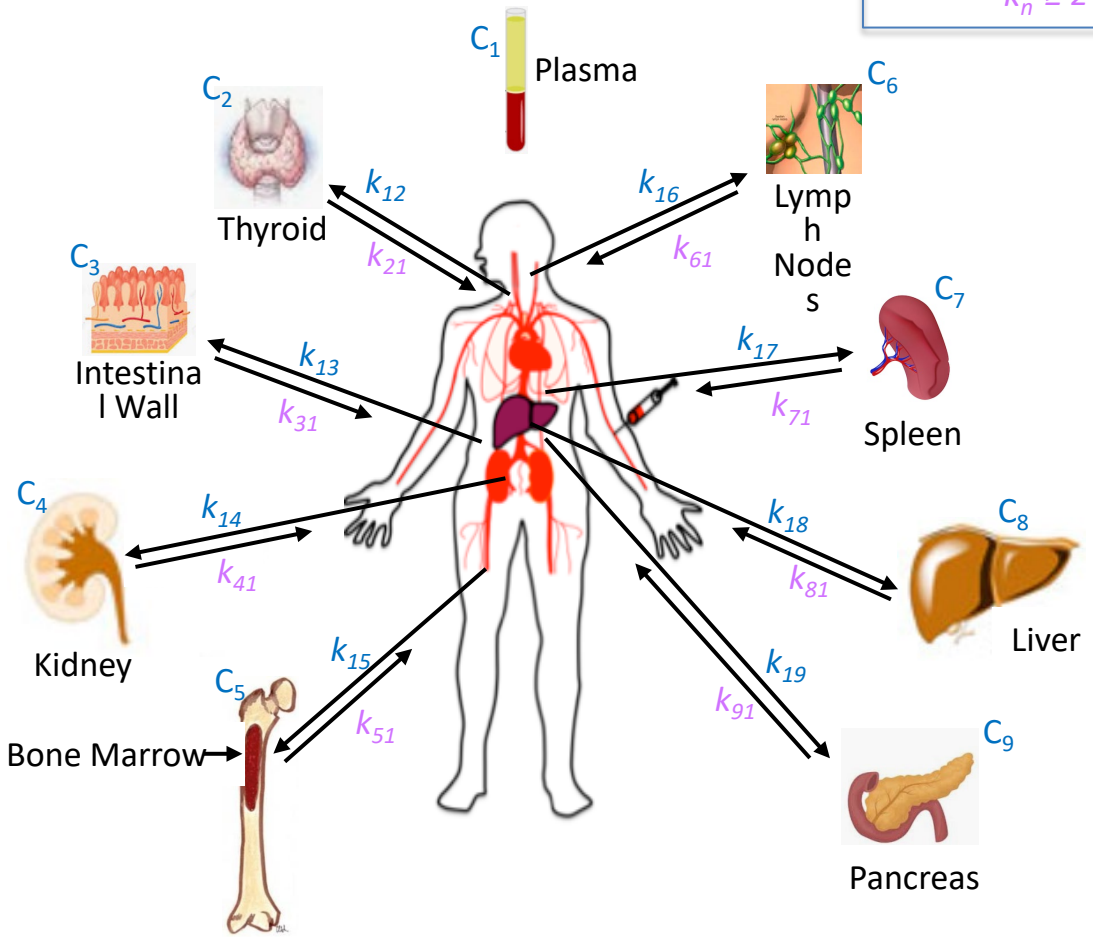
Tissue $t_{1/2}$: ~2 weeks – ~2 months

PS ASO Repeat Dosing:
Plasma $C_{trough,ss}$ achieved after ≥3 months

- Many variables & unknowns
  - Many Compartments
  - Many Different Rate Constants
- High degree of interspecies variability

➢ Impossible to Predict?

Rate Constants (k_n)
k_n < 24 h
k_n ≥ 2 weeks



Systemic PS ASO Drug Class: Steady-State

PK Observations:

- Plasma C_{trough} levels are used to identify steady-state (SS)
- Acute increases in plasma exposure levels with dosing are less informative
  - Do not necessarily reflect target tissue exposure levels
  - Cannot be assumed to be comparable between species

➢ Value of PS ASO Plasma AUC exposures for dose margin comparisons of toxicities in target tissues is limited

➢ What is the most appropriate alternative?

Phase 3 Clinical Trial Experience:

- 3-6 months to reach SS Plasma C_{trough}
  - ➢ No further impact from re-distribution
- 3-6 months to reach SS PD activity
- Plasma Elimination = 3-6 months
  - 3-6 months for PD activity return to baseline levels

➢ Prolonged time to achieve SS likely driven by significant Distribution & Accumulation effects

Systemic PS ASOs: Dose Margin Comparisons

- The toxicity in humans (for a particular class) is dependent on an exposure parameter that is highly correlated across species with dose on a mg/kg basis. For example, complement activation by systemically administered antisense oligonucleotides in humans is believed to be dependent upon Cmax (Geary et al., 1997). For some antisense drugs, the Cmax correlates across nonclinical species with mg/kg dose and in such instances mg/kg scaling would be justified.
  - 2005 FDA Guidance for Industry and Reviewers: Estimating the Safe Starting Dose in Clinical Trials for Therapeutics in Adult Healthy Volunteers

- C_{max} and BW bases are appropriate for the blood compartment

➢ What about drug-related toxicities in tissues?

Volanesorsen BSA Basis Determination

– Volanesorsen: systemically administered PS ASO

1. Contributing Factors
   - Short plasma exposures despite prolonged pharmacodynamic activity
   - Increases in C_{trough} values with repeat-dosing
     - influenced by release of drug from tissues
   - Prolonged tissue half-life
     - particularly in target organs such as kidney and liver
     - Likely contributor to observed organ toxicities
   - Complexities of oligonucleotide tissue pharmacokinetics and compartmentalization
     - Compartment multiplicity compounded by differences/unknowns related to tissue uptake, clearance, and redistribution
     - Have not and/or cannot been tested or fully characterized in humans

BSA = Most appropriate basis for organ tox

➢ Applicable to other drug products with significant PK/TK contributions due to Distribution &/or Accumulation??

➢ Decreased validity of comparability of AUC exposures between species, resulting in an unclear exposure relationship to humans

2. The interspecies comparison analysis conducted by Dr. Wang, wherein comparisons based on BSA correction were most appropriate for the approved systemic PS ASO Mipomersen
   - Reference: 2012 FDA Advisory Committee Meeting for Mipomersen

➢ Both the blood compartment & organ systems may contribute to the MOA

Summary

- M&S is useful in predicting clinical pharmacology (e.g. MABEL, PAD, ATD) prior to FIH trials
- Clinical doses (i.e. MRSD and MRHD) are determined based on empirical nonclinical data, **NOT** PK or PB/PK modeling
  - However, the M&S-derived pharmacology endpoints (e.g. MABEL, PAD) can be appropriate for MRSD determinations for some drug products
    - NOTE: Toxicological endpoints (e.g. NOAEL) remain the standard
  - MRHD is based on empirical nonclinical findings, not M&S, and can be limited by nonclinical bioassay high dose selections
    - However, M&S can play a role in providing supplementary information to support high dose selection for nonclinical bioassays of biotechnology-derived products
- Dose-/Exposure Effect Curves & Toxicity can inform dose escalation decisions for early phase clinical trials
- M&S can play an important role in reformulations and support bioequivalence submissions
- M&S information related to drug accumulation potential could be useful to regulators for some products

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Thank you for your attention!


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Back-up Slides

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)

MRSD: 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.