How to Choose the Maximum Recommended Safe Dose for First-Time-In-Human Clinical Trials

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Ready for Human Testing?

- Congratulations!
- But, how to choose an initial dose for human testing?
  - Several methods with mixed success and failure
  - Some guidance required, especially for IND studies

Guidance for Industry

Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

July 2005
Pharmacology and Toxicology

UCSF University of California San Francisco

CDDS

Legal Authority of FDA

	Laws	Regulations	Guidance
Who wrote?	Legislative	Executive	Executive (FDA)
Scope	Declaration of basic principles	Governmental interpretations of the laws	Clarification of laws and regulations in greater detail, i.e., *"current thinking"*
Binding	Yes	Yes	No
Example	*FDC Act* as amended	*CFR*	Guidance Documents

Typical Design for Phase I Studies

- Start from a very small dose, not likely to yield any beneficial or harmful effects
- Escalate dose by recruiting a small group of new subjects (e.g., 6A+2P)
- Closely observe subjects for any effects (good or bad)
- Conclude study if certain number or proportion of subjects develop unwanted effects (i.e., dose limiting toxicity)
- Assess tolerability, pharmacokinetic and/or pharmacodynamic profiles

Trade-off

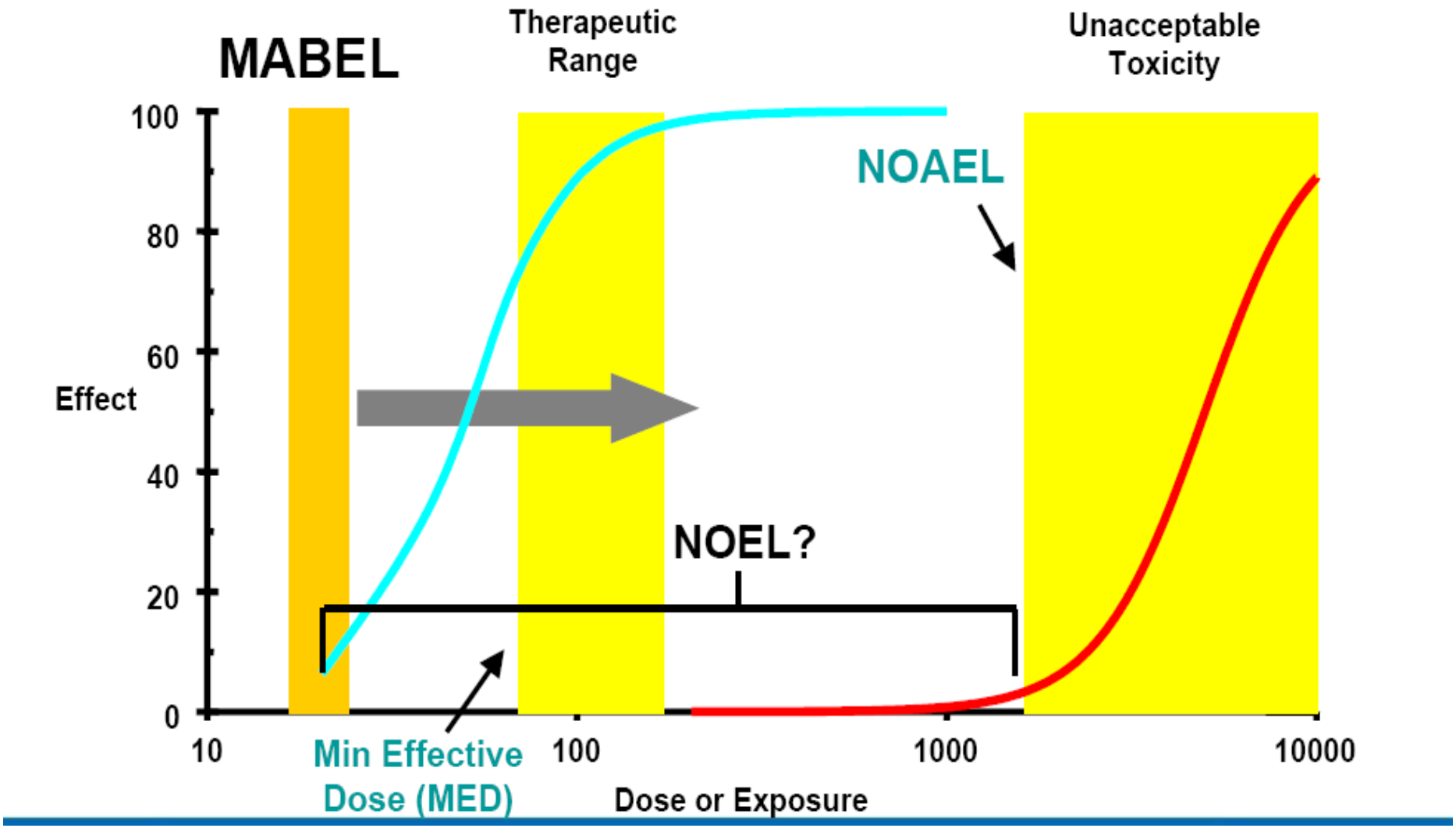
- Dose needs to be low enough to avoid toxicity at initial dose
- Dose needs to be high enough to allow reasonably rapid attainment of phase I trial objectives

Maximum Recommended Safe Dose (MRSD)

- 5 Steps using animal toxicity data
  - Determine No Observed Adverse Effect Level (NOAEL)
  - Convert NOAEL to Human Equivalent Dose (HED)
  - Select most appropriate species
  - Apply Safety Factor
  - Consider Pharmacologically Active Dose

No Observed Adverse Effect Level (NOAEL)

- The highest dose level that does not produce a significant increase in adverse effects (AEs) in comparison to the control group
  - AEs that are biologically significant should be considered (may not be statistically significant though)
  - NOAEL differs from NOEL (No Observed Effect Leve), i.e., ANY effect
- Calculate NOAELs for each species tested (at least three, with one being non-rodents)



Modified from Jennifer Sims, PhD, *Calculation of the Minimum Anticipated Biological Effect Level (MABEL) and 1st dose in human*

Human Equivalent Dose (HED)

- Convert NOAELs to HEDs based on body surface area
  - Assumes that there is a 1:1 relation between species when normalized to BSA
- Conversion based on body weight (Kg) available
- Conversion table for various species provided

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]

Most Appropriate Species

- Which species is most suitable for predicting what is expected to occur in humans?
  - ADME
  - Previous class experience
- In reality, this information is not likely to be available
  - Choose the most sensitive species, i.e., the lowest HED

Safety Factor

- Further safety net to address uncertainties
- Default safety factor is 10, i.e., divide HED by 10
- Increasing safety factor (i.e., >10)
  - Example: steep dose response curve, nonlinear PK, variable bioavailability, irreversible toxicity, limited animal data
- Decreasing safety factor (i.e., <10)
  - Example: known class, well characterized toxicity profile, NOAELs from animal studies with a longer duration than the proposed human studies

Pharmacologically Active Dose (PAD)

- PAD may be derived from appropriate PK-PD models (i.e., exposure-response relationship) in animal species
- Convert PAD to human equivalent active dose (HEPAD) using the conversion table
- Compare HEPAD vs. MRSD
  - If HEPAD < MRSD, consider further lowering MRSD

Example

NOAEL	calculation	HED
	mg/kg ÷ [$k_{mhuman}/k_{manimal}$]	
15 mg/kg in dogs	15 mg/kg ÷ 1.8 =	8 mg/kg
50 mg/kg in rats	50 mg/kg ÷ 6.2 =	8 mg/kg
50 mg/kg in monkeys	50 mg/kg ÷ 3.1 =	16 mg/kg

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$MRSD=HED_{dogs}/10$
$=0.8mg/kg$

Limitations of NOAEL/MRSD Approach

- Mechanical (i.e., strict algorithm based)
- Toxicity focused, less pharmacology incorporated
- Not applicable to endogenous hormones and proteins (i.e. recombinant clotting factors) used at physiological concentrations or prophylactic vaccines
- Not applicable to locally administered drugs
- Does not address dose escalation

Alternative Approaches

- Microdosing
  - Give a non-pharmacologic dose (i.e., <1/100) directly to humans
  - Next Regulatory Education Seminar (early 2008)
- Minimum Anticipated Biological Effect Level (MABEL)
  - Better to start with the lowest dose you think is active, rather than with the highest dose you think is safe
  - More conservative estimate
- PK-PD modeling using animal data

Conclusion

- Determination of an initial dose for FTIH studies is not easy, and case-by-case approach may be more appropriate
- However, conservative and consistent approach is required because safety is the most important factor from the regulatory perspective
- Several other options are available, but they need more experience