Adaptive and Innovative Study Designs to Accelerate Drug Development from First-In-Human to First-In-Patient

Michelle L. Combs, PhD

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Definition of Adaptive Designs

- A clinical trial design that uses accumulating data to decide how to modify aspects of the study as it continues, without undermining the validity and integrity of the trial.[1]

- "…clinical trials can be designed with adaptive features (i.e. changes in design or analyses guided by examination of the accumulated data at an interim point in the trial) that may make the studies more efficient…"[2]

[1]Adaptive Designs in Clinical Drug Development : An Executive Summary of the PhRMA Working Group. Journal of Biopharmaceutical Statistics, 16: 275-283, 2006

[2] Food and Drug Administration: Center for Drug Evaluation and Research (CDER). Guidance for Industry - Adaptive Design Clinical Trials for Drugs and Biologics, Feb 2010

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Bayes Theorem

Represents updated degree of belief

Probability that the hypothesis confers upon the observation

Prior Probability

$$Pr(Hypothesis|Observation) = \frac{Pr(Observation|Hypothesis)*Pr(Hypothesis)}{Pr\ (Observation)}$$

Probability of the observation irrespective of any hypothesis

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Exploratory vs. Adequate and Well-Controlled Adaptive Designs

Adequate & Well Controlled Studies

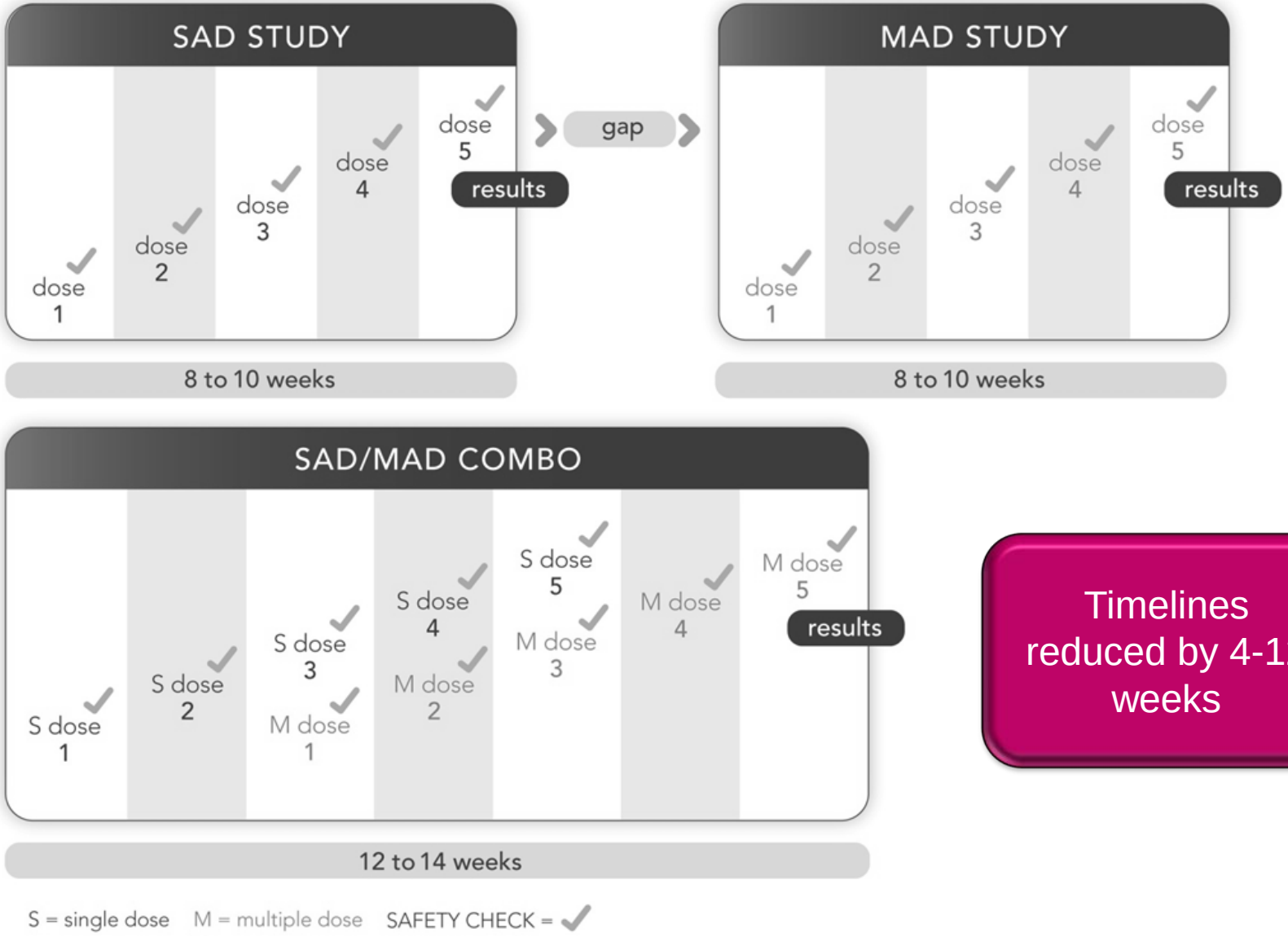
- Focus on avoiding increased rates of false positive study results (increased Type I error rate)
- Intended to support marketing a drug
- Because of potential for regulatory impact, primary focus of FDA guidance

Exploratory Studies

- Studies that do not rigorously control the Type I error rate
- Designed from the outset to allow changes in the design during the study based on interim examinations of data
- May have multiple endpoints to be considered in the results

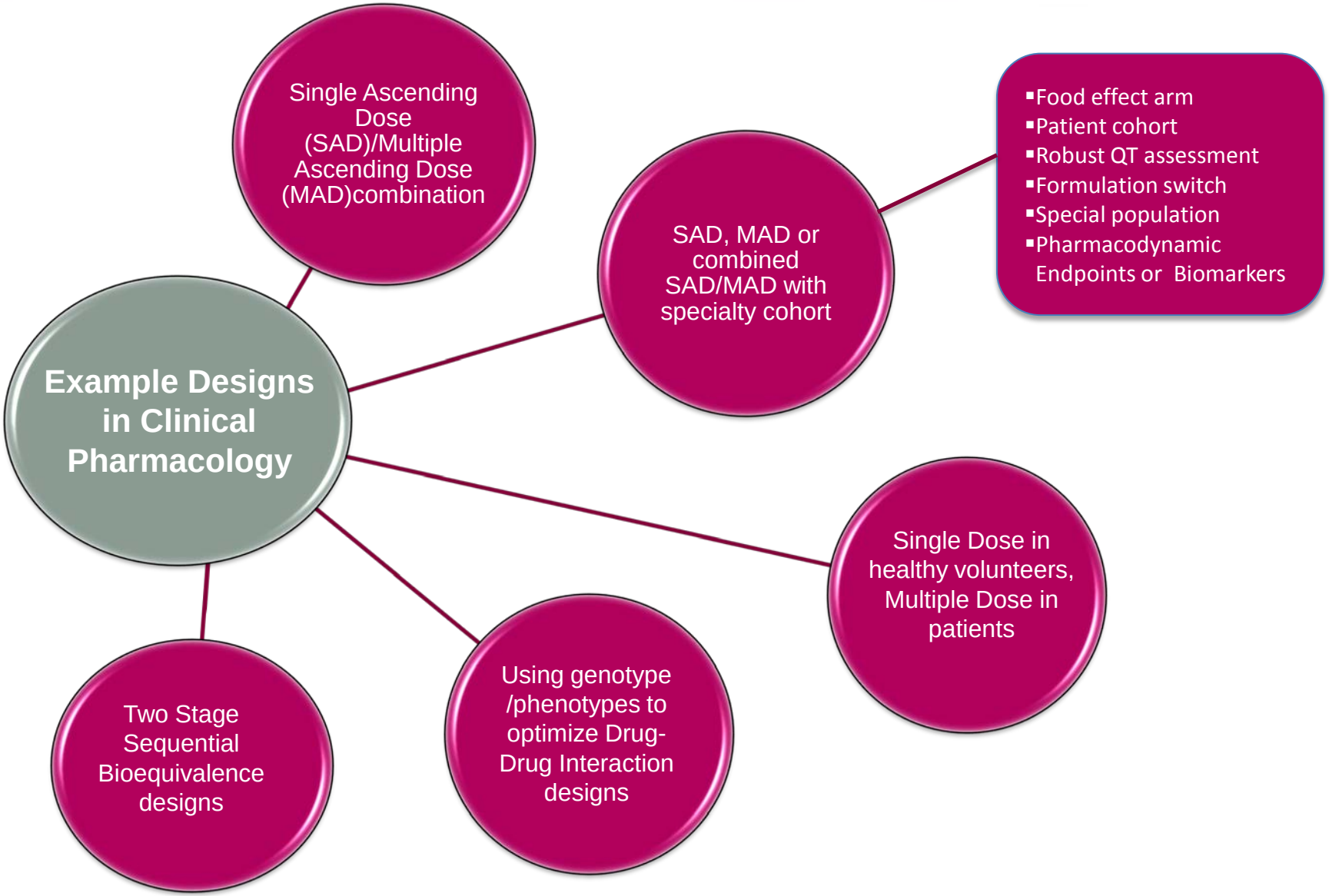
Exploratory studies are generally conducted earlier in the drug development program than the A&WC studies and have an important informative role in drug development.

SAD/MAD Combination Studies



Timelines reduced by 4-12 weeks

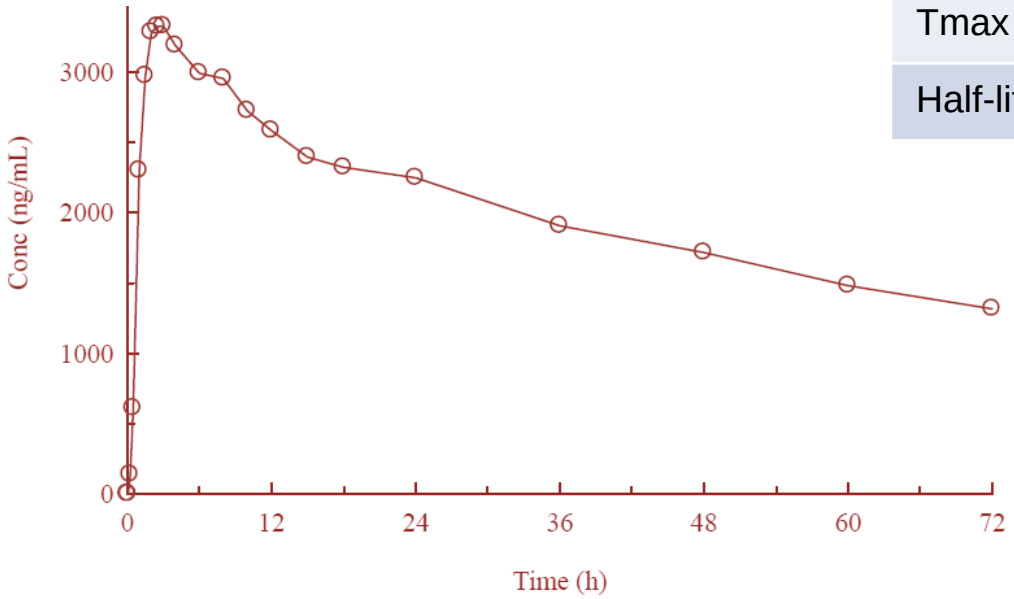
Adaptive Study Designs in Early Clinical Research



Case Study 1

Requested Design	Traditional SAD Sequential MAD	5 Cohorts Up to 5 Cohorts
Expected Half-life (from IB)	Mouse Monkey	~0.8 h 1.1 h
NOAEL		~40 mg/kg/day
Starting Dose	Calculated Selected	90 mg 50 mg

Cohort I



PK parameter	Cohort I
AUC0-t (ng/mL h)	133407
AUCinf (ng/mL h)	270000
Cmax (ng/mL)	3478
Tmax (h)	2.75
Half-life (h)	64

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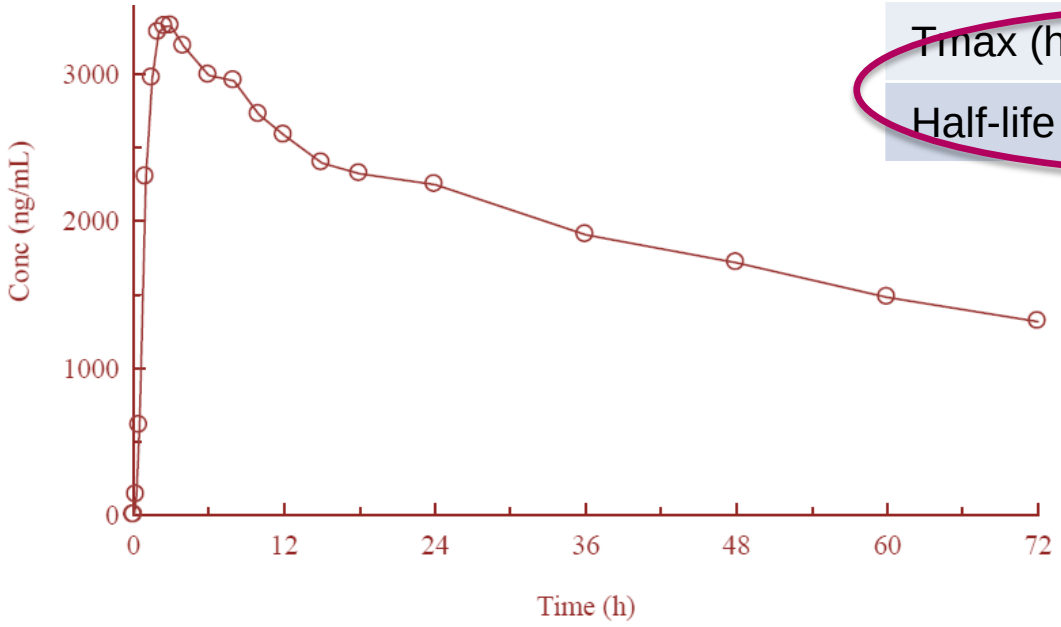

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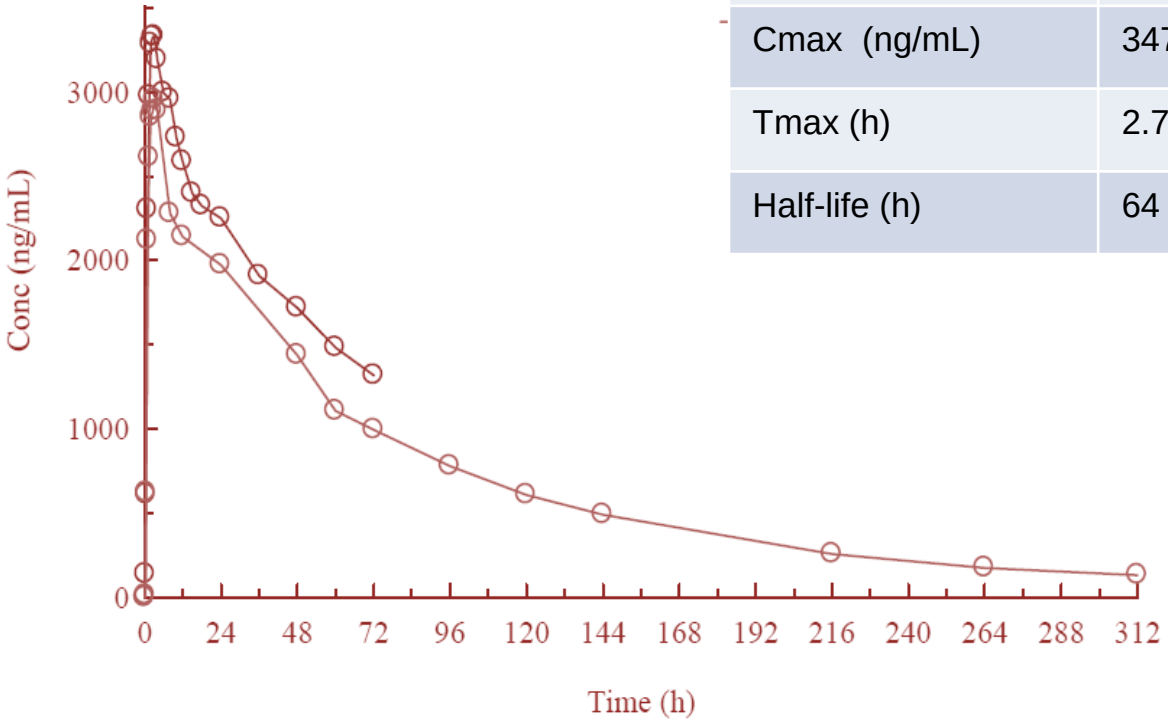
Cohort 2

PK parameter	Cohort I	Cohort 2
AUC0-t (ng/mL h)	133407	217344
AUCinf (ng/mL h)	270000	233302
Cmax (ng/mL)	3478	3035
Tmax (h)	2.75	3
Half-life (h)	64	80



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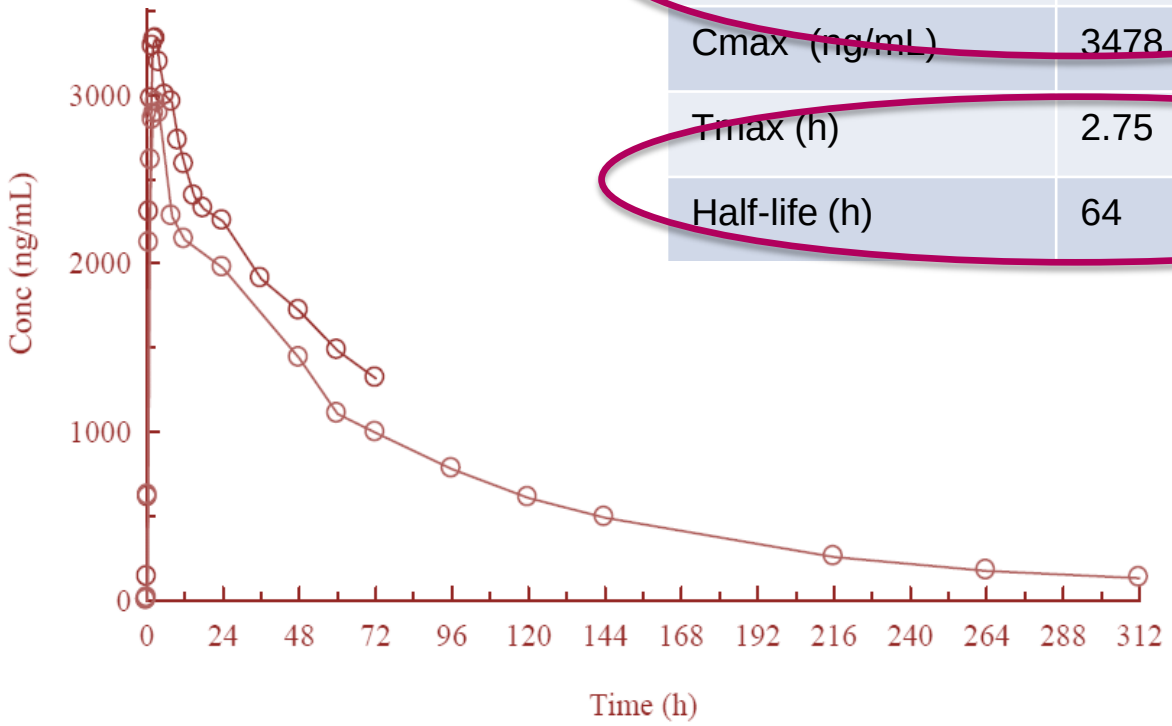

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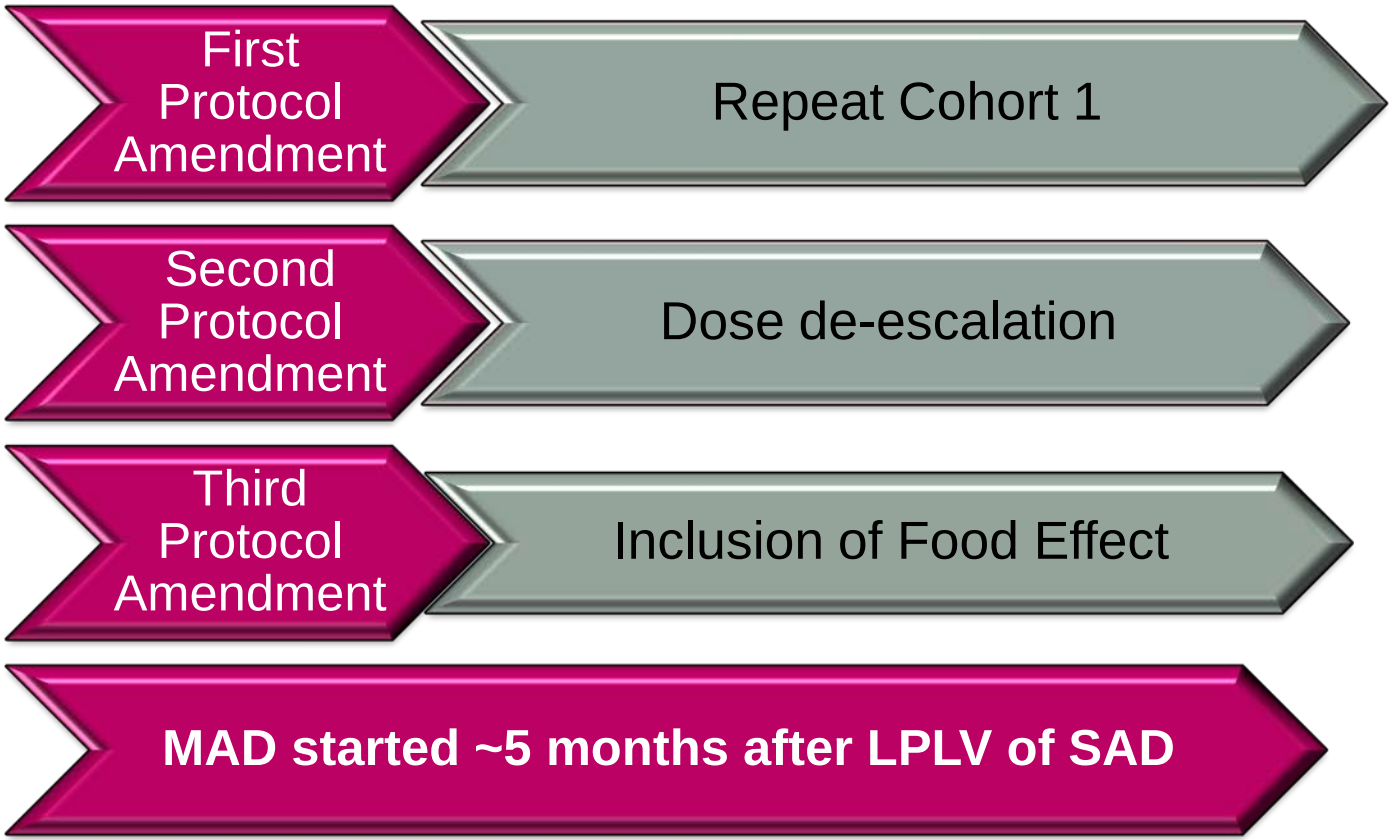
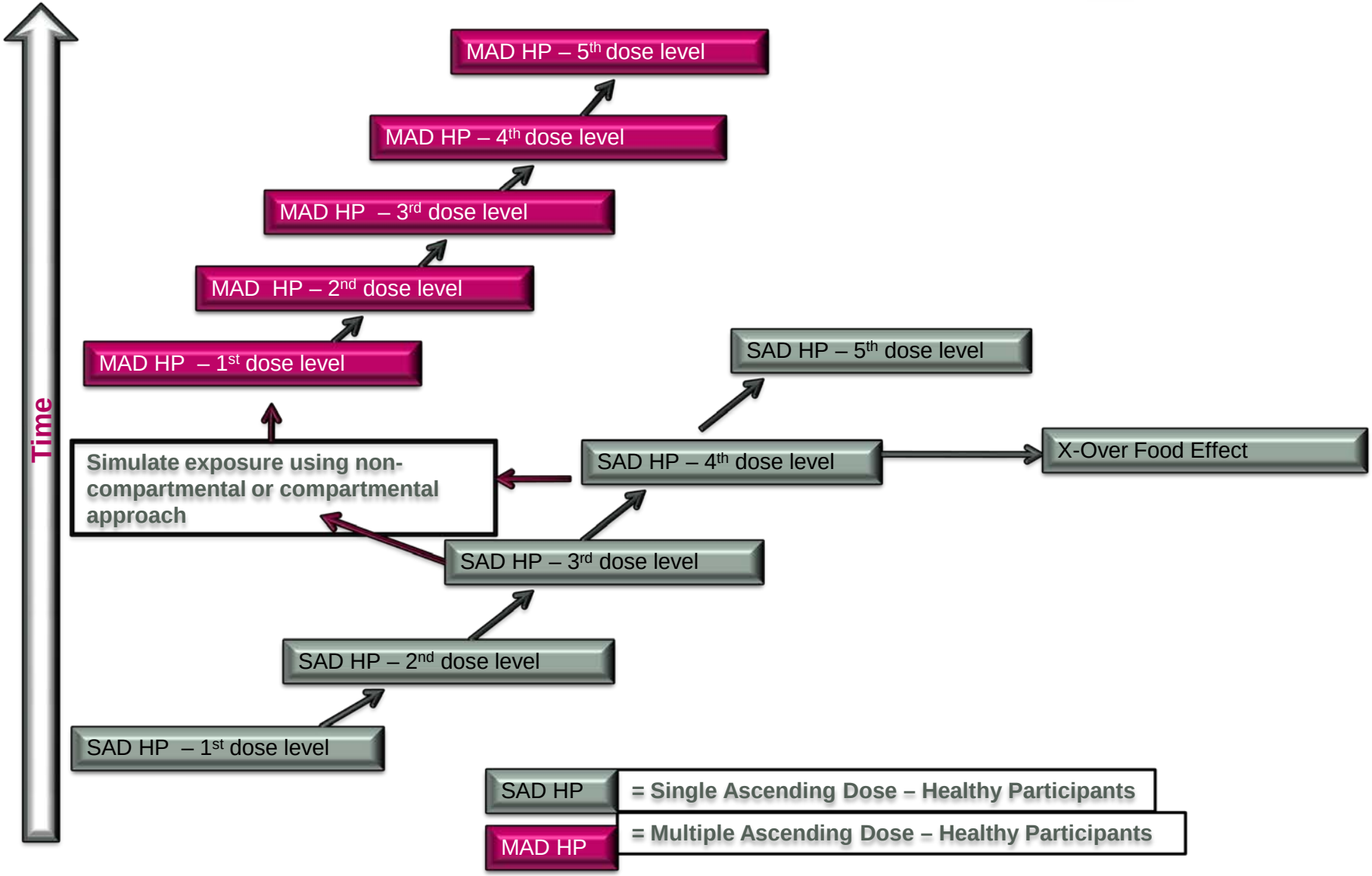
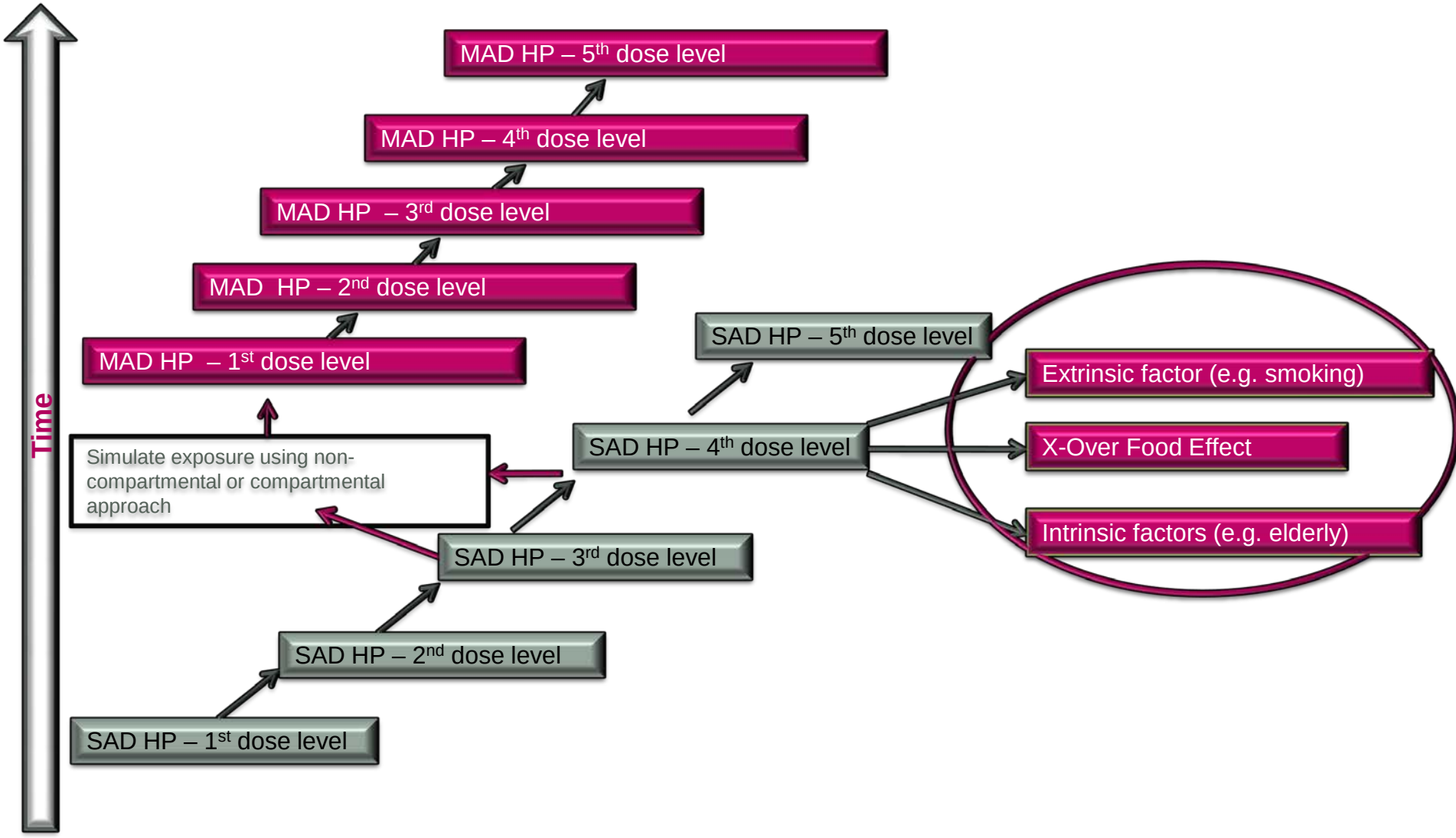
Case Study I Continued



Case Study 1 Redesigned



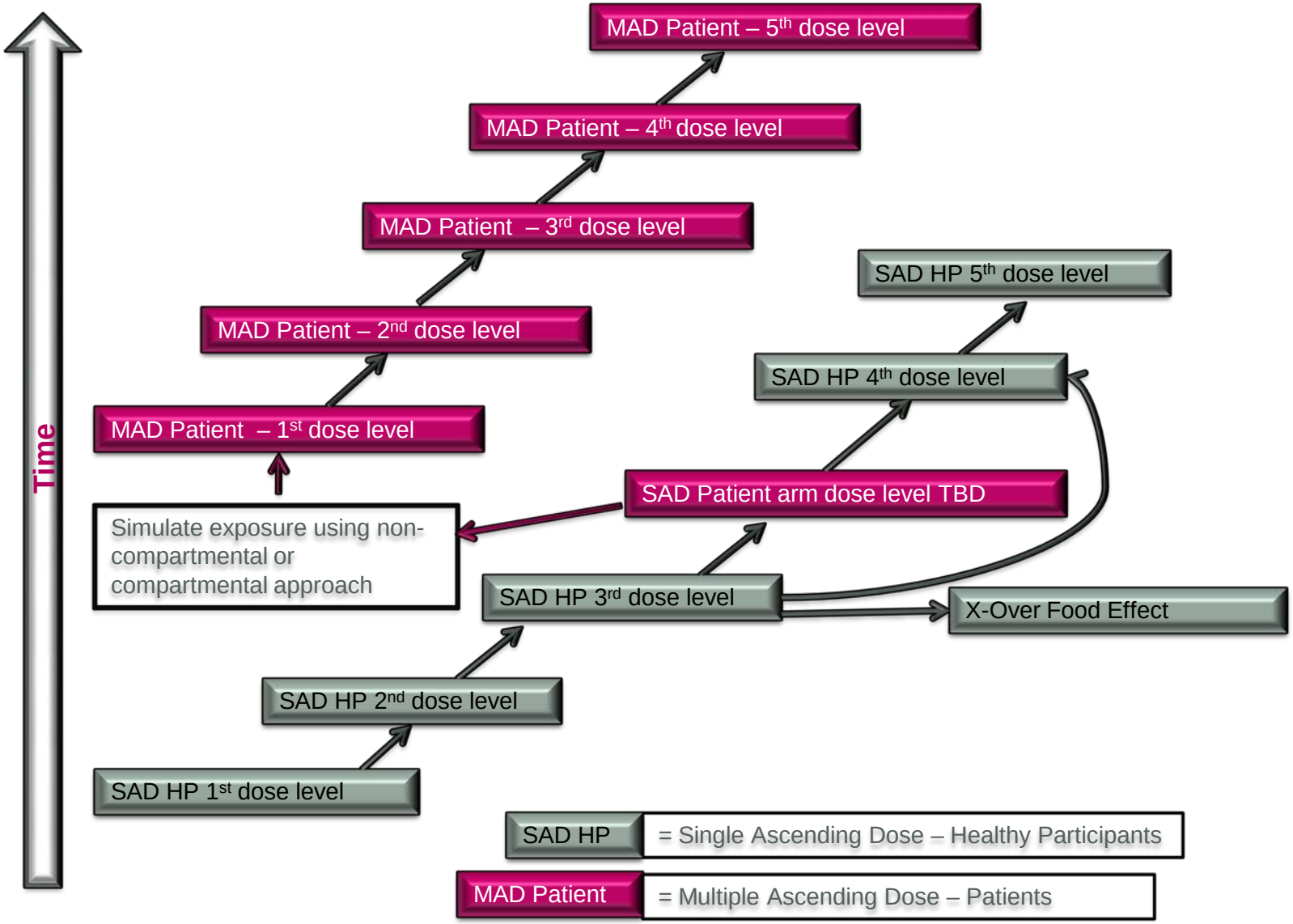
Optional Modifications (drug/therapeutic area specific)



Case Study 2

Requested Design	Combined SAD/MAD
Therapeutic Area	Endocrinology
Study Population	SAD: Normal Healthy MAD: Target Population

Case Study 2


Time
MAD Patient – 5th dose level
MAD Patient – 4th dose level
MAD Patient – 3rd dose level
MAD Patient – 2nd dose level
MAD Patient – 1st dose level
SAD HP 5th dose level
SAD HP 4th dose level
SAD Patient arm dose level TBD
Simulate exposure using non-compartmental or compartmental approach
SAD HP 3rd dose level
X-Over Food Effect
SAD HP 2nd dose level
SAD HP 1st dose level
SAD HP = Single Ascending Dose – Healthy Participants
MAD Patient = Multiple Ascending Dose – Patients

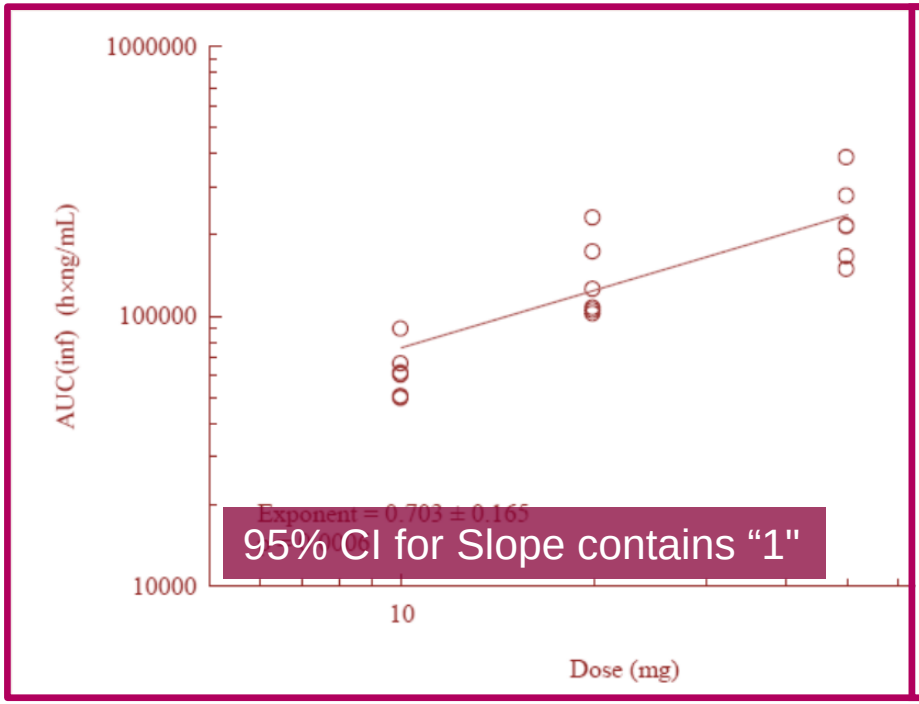
Adapting MAD Starting Point Based on Modeling Approaches

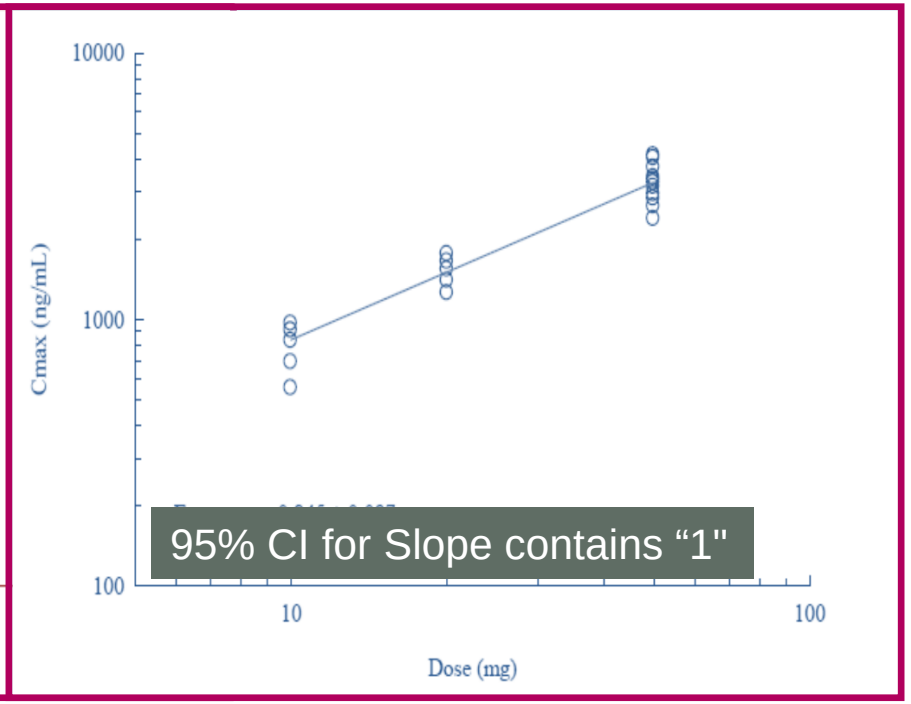
- Selecting MAD starting dose can be challenging
- Traditional approach has been to “ballpark” the MAD starting point well before any data collected or once SAD data available, taking ~30% of highest tolerated SAD dose level
- Modeling and Simulation using:
  - Non-compartmental approaches
  - Compartmental approaches

Non-Compartmental Approach

- Based on a minimum of three SAD cohorts to establish dose-proportional PK
  - Assumes proportionality continues throughout the dosage range
  - Assumes no time dependent PK changes (will be proven experimentally during MAD)

Linearity of Three Doses from Case Study I





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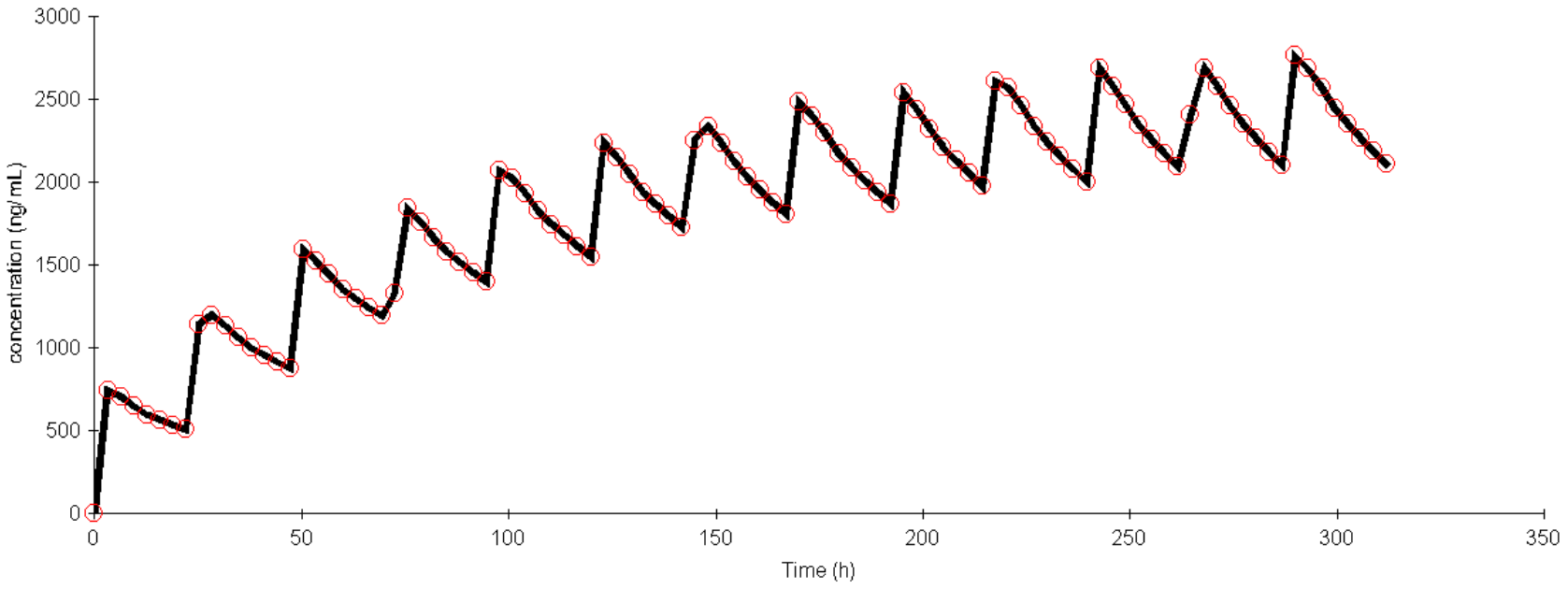
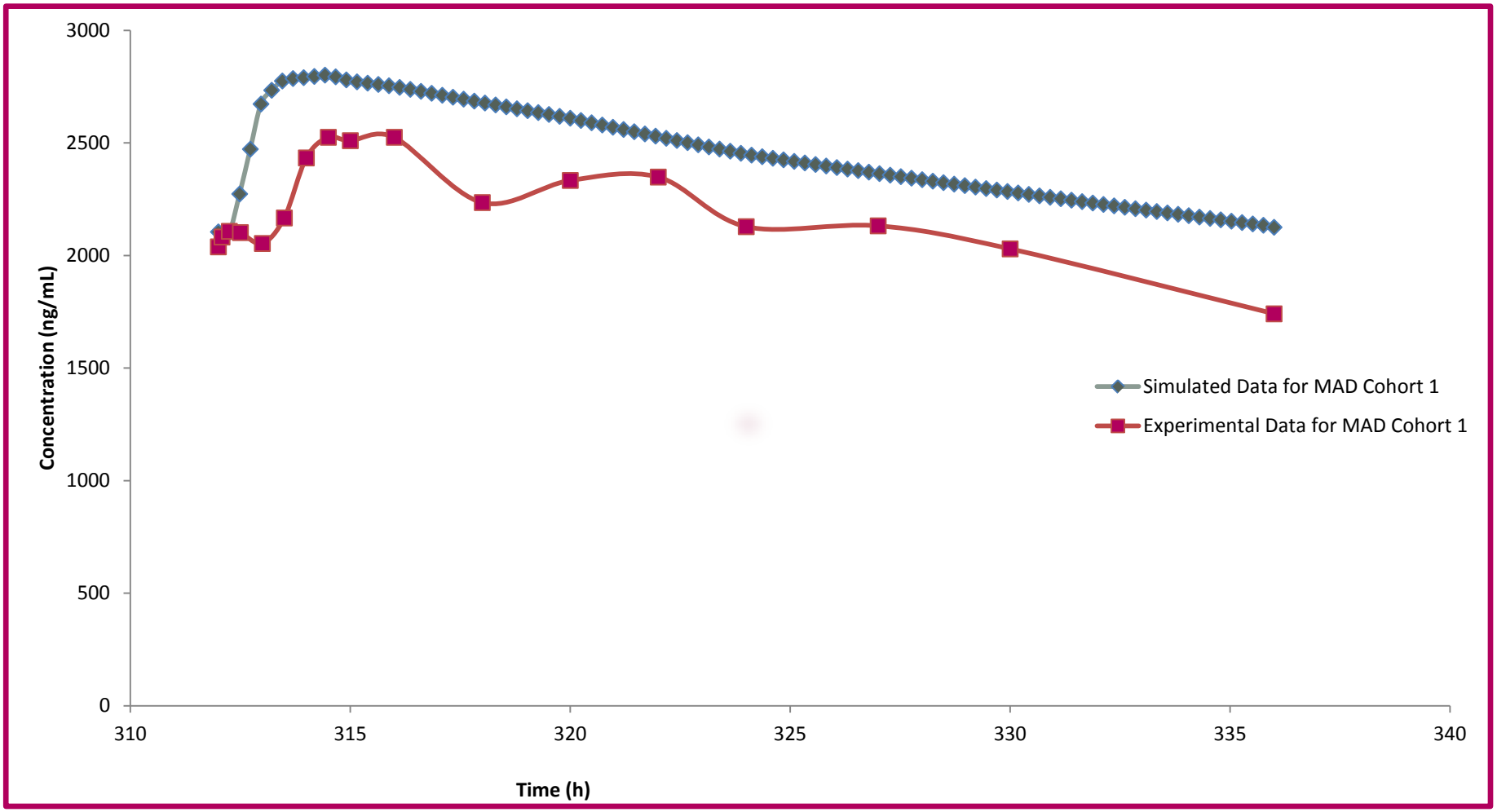
Simulating Using Non-Parametric Superposition: Rise to Steady-State



Non-Compartmental Simulated vs. Experimental Data



Mixed-Effect Modeling and SAD/MAD Studies

- Confirm assumptions of exposure and effect if available
- Fit PK/PD data and simulate various regimens to optimize the effect response
- Consider M&S analysis in modification of subsequent MAD cohorts

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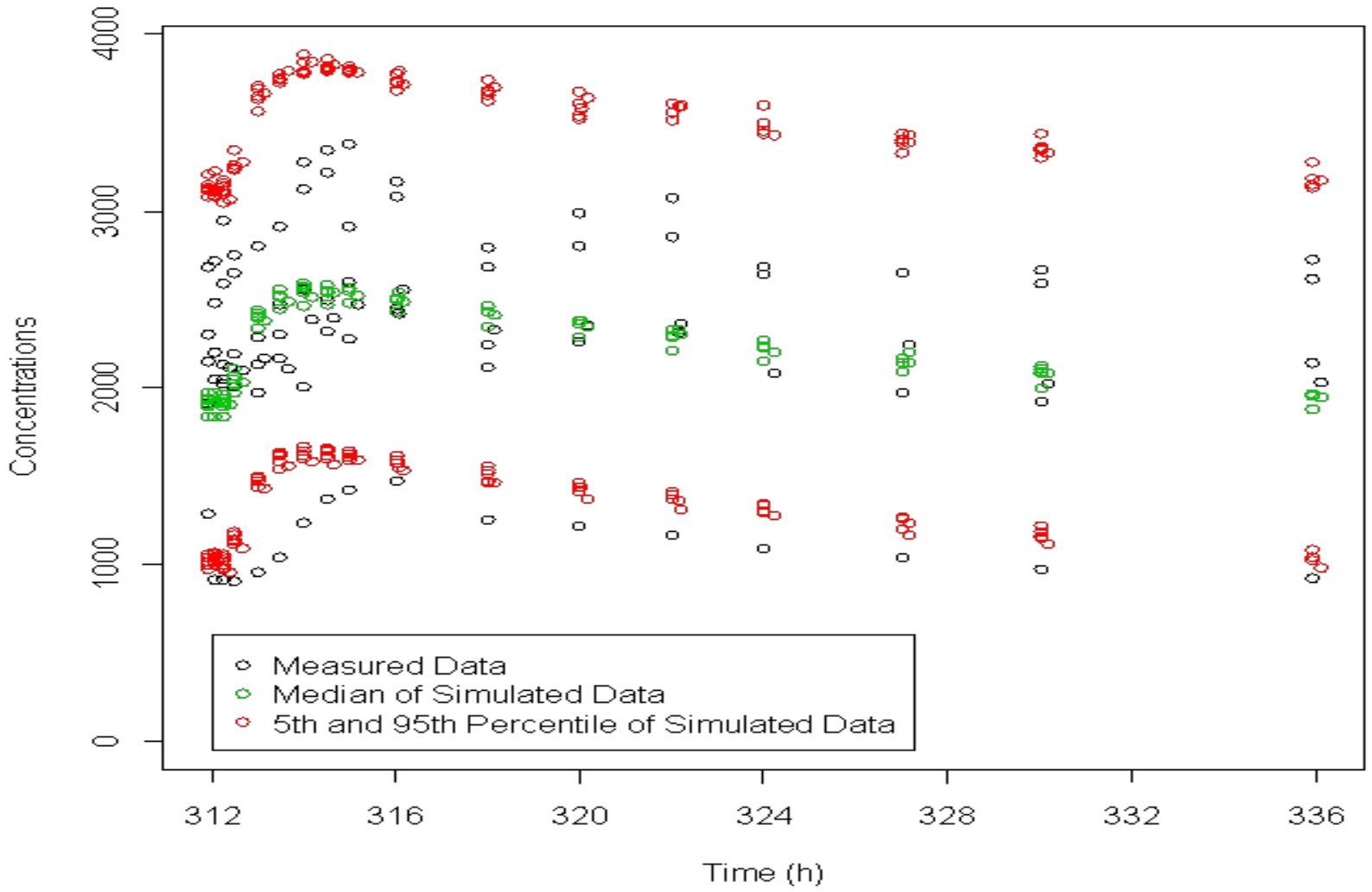
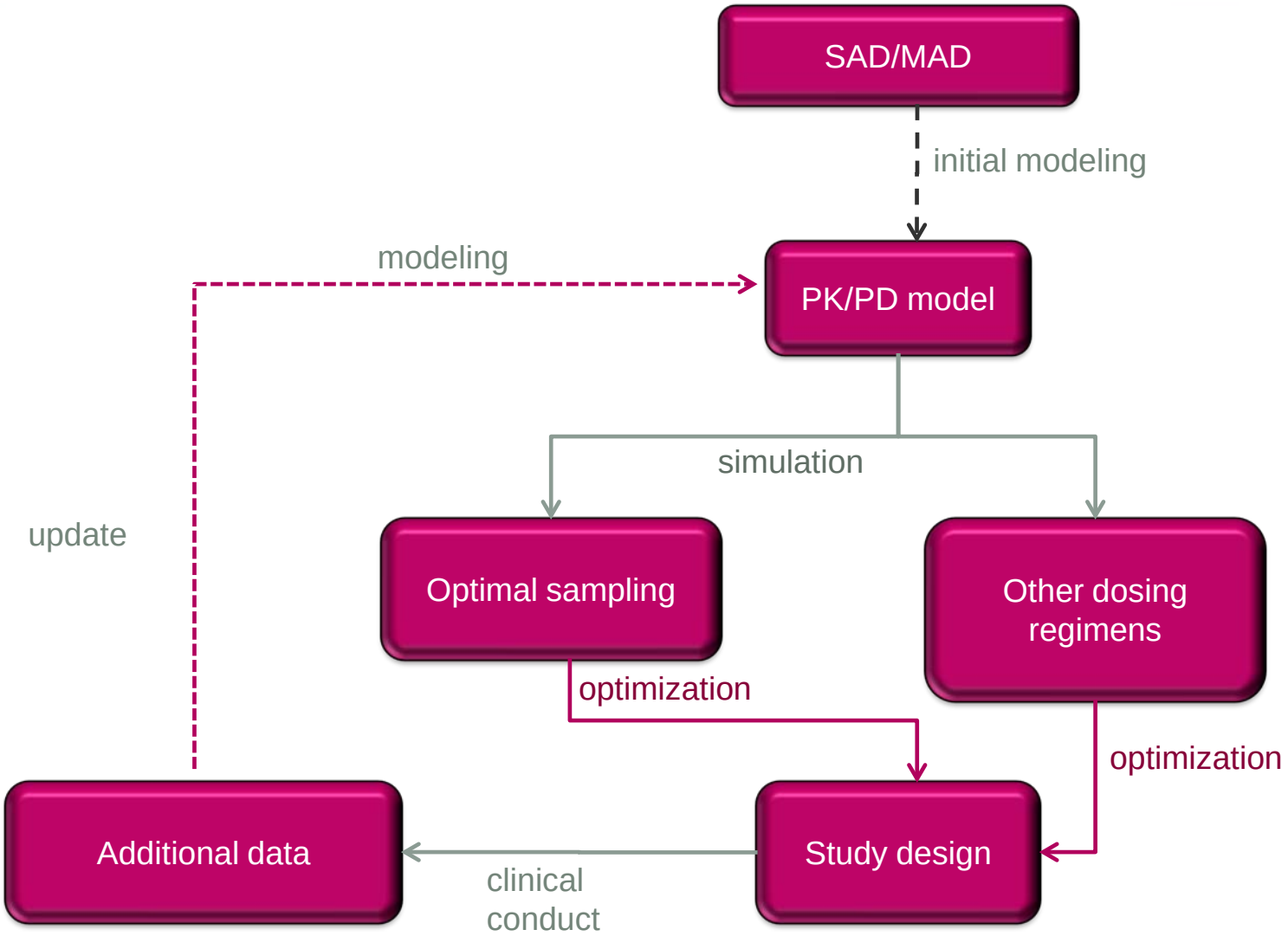
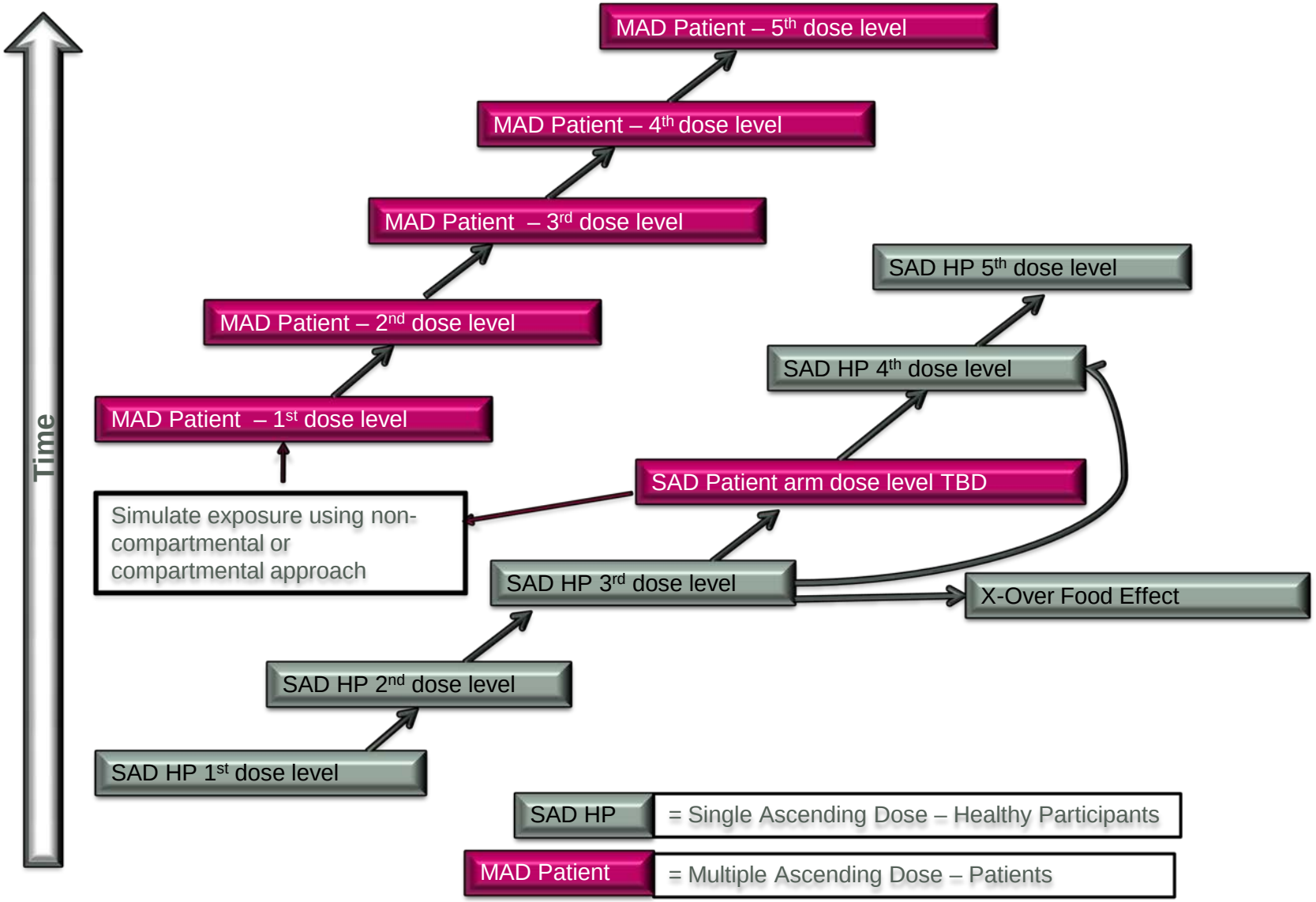
Simulated Multiple-Dose Curve from SAD Data



Benefits of Mixed-Effect Modeling Beyond SAD/MAD: "Learn & Confirm"



Case Study 2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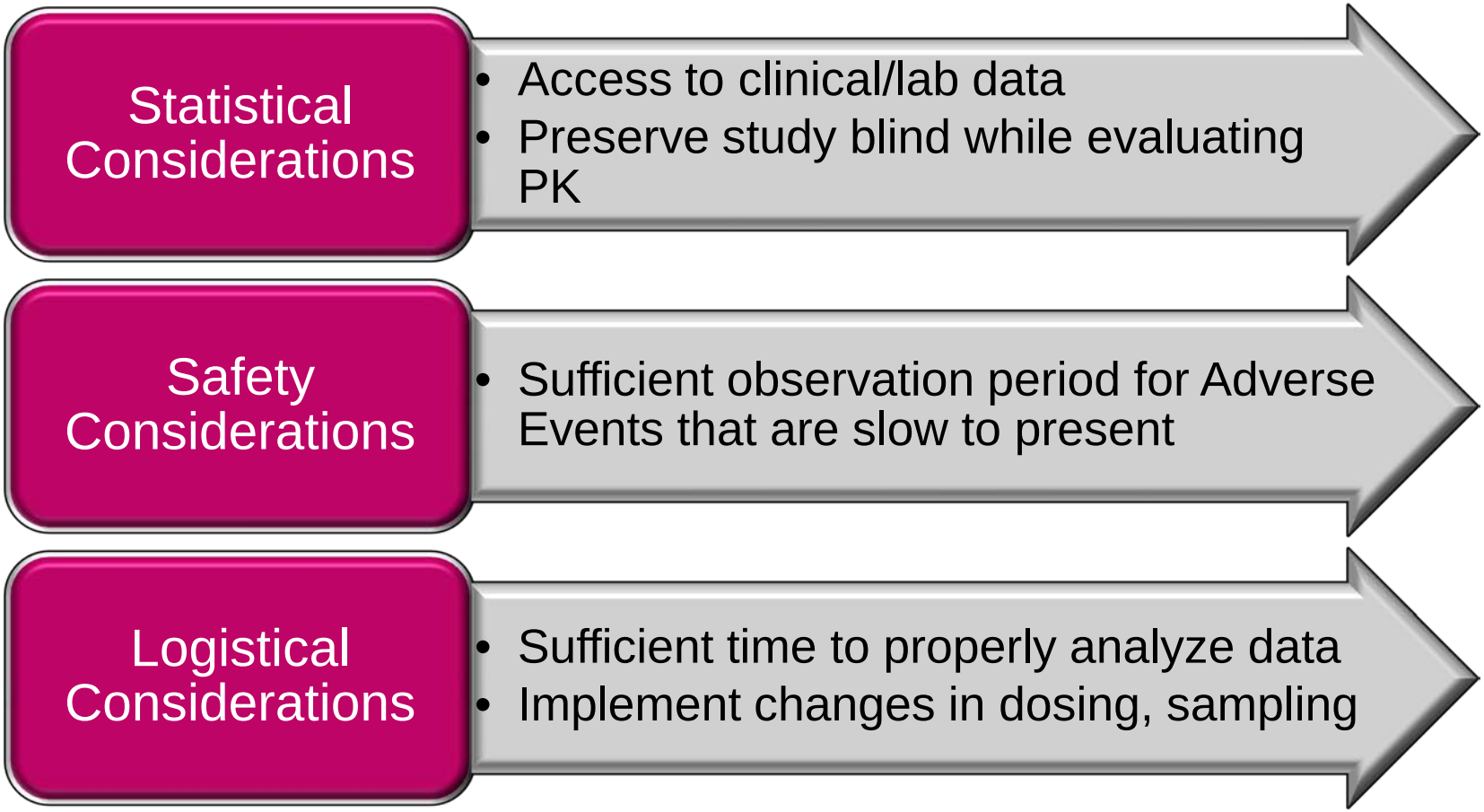
Practical Considerations



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