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*Translating Science to Medicine*

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

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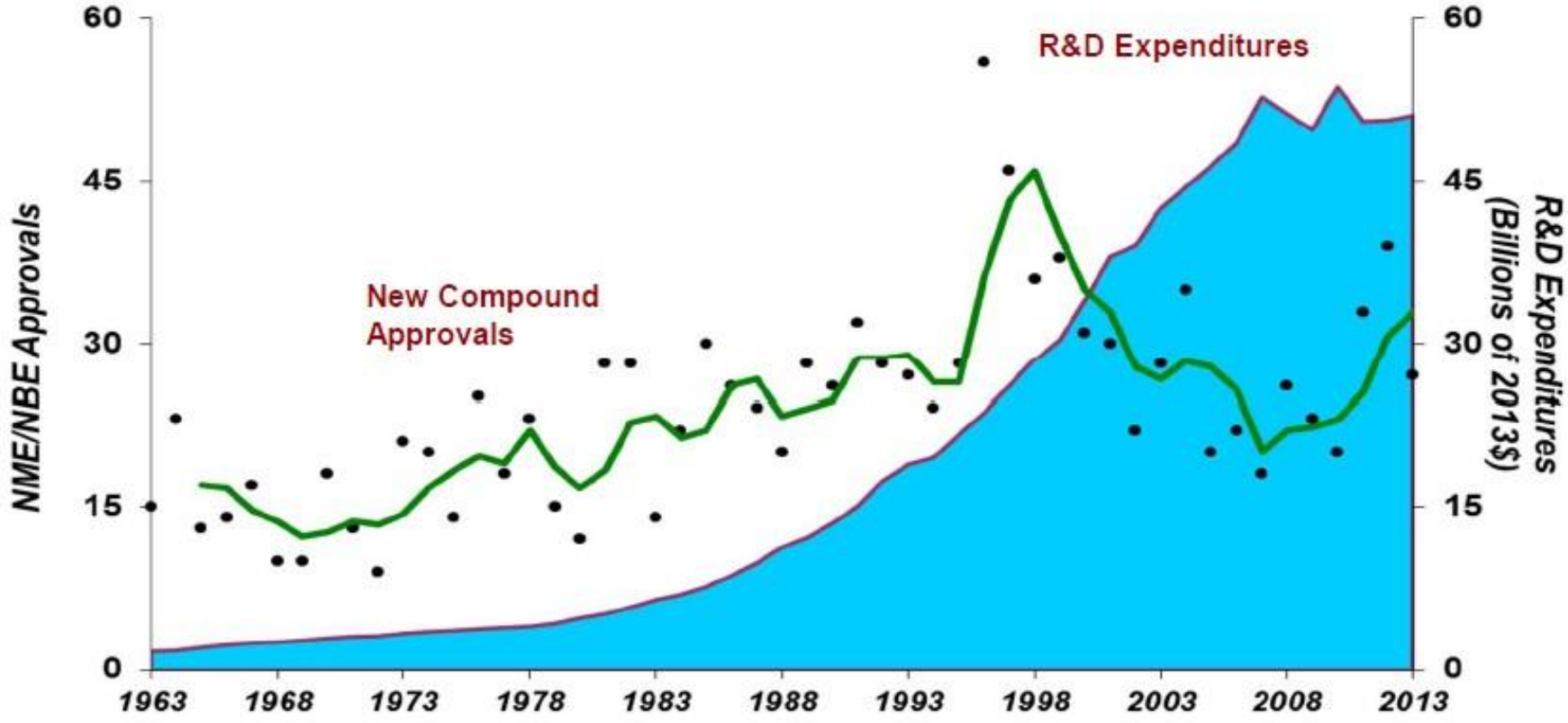
Vice President, Clinical Pharmacology Sciences

January 2020

# New Drug And Biologics Approvals/R&D Spending

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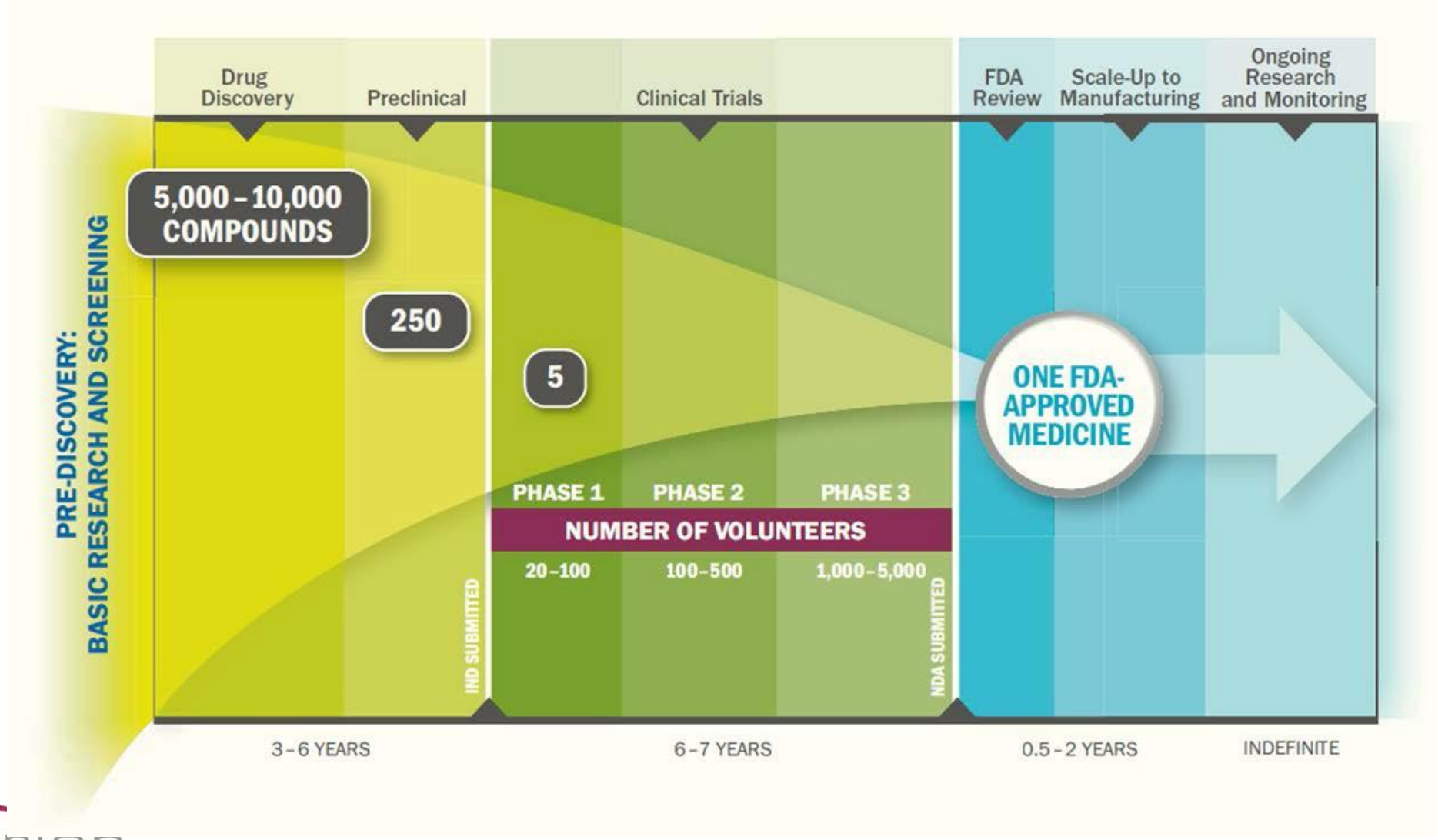
# Research & Development (R&D) Process: PhRMA 2013 Profile

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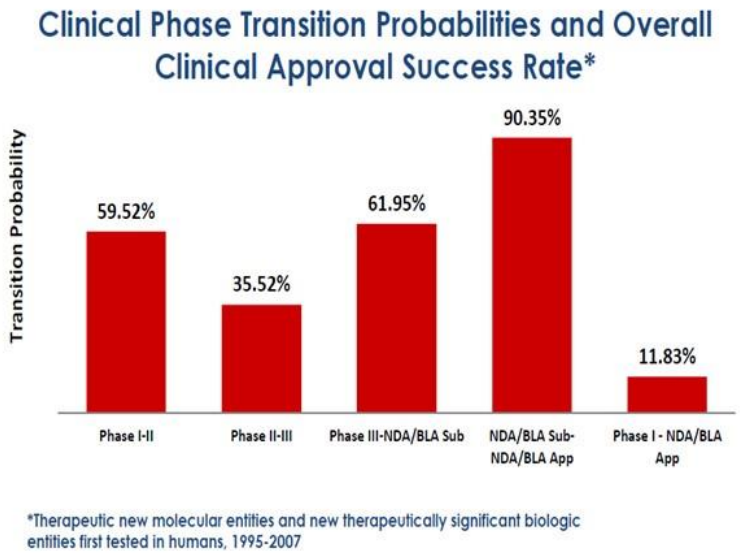
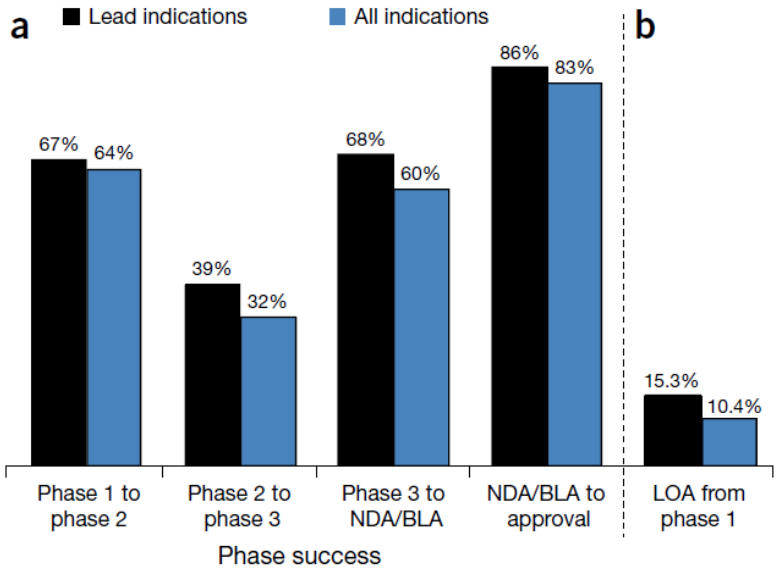
# Phase Transition Rates

## Tufts CDSS 2014




## Hays 2014

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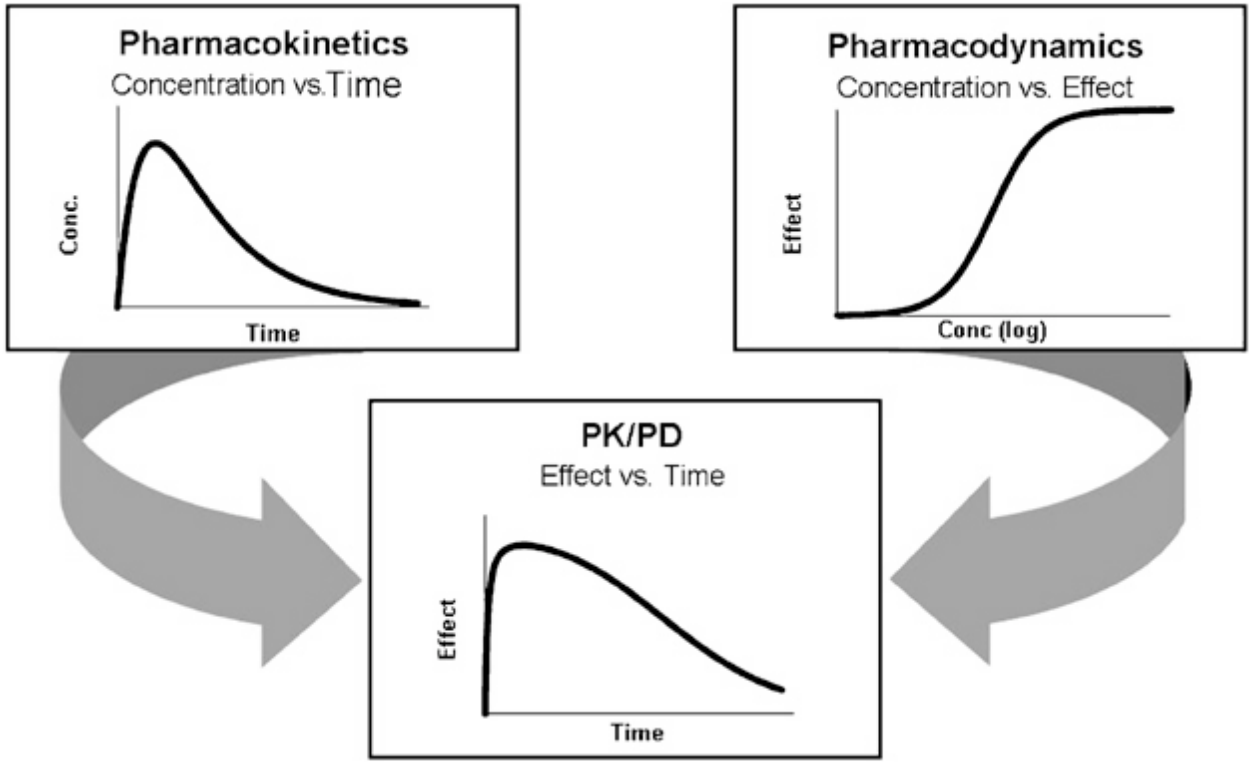
# Clinical Pharmacology

One of the fundamental assumptions of Clinical Pharmacology is the relationship between the **efficacy and toxicity** of a drug and the **concentration at the site of activity** of the drug.

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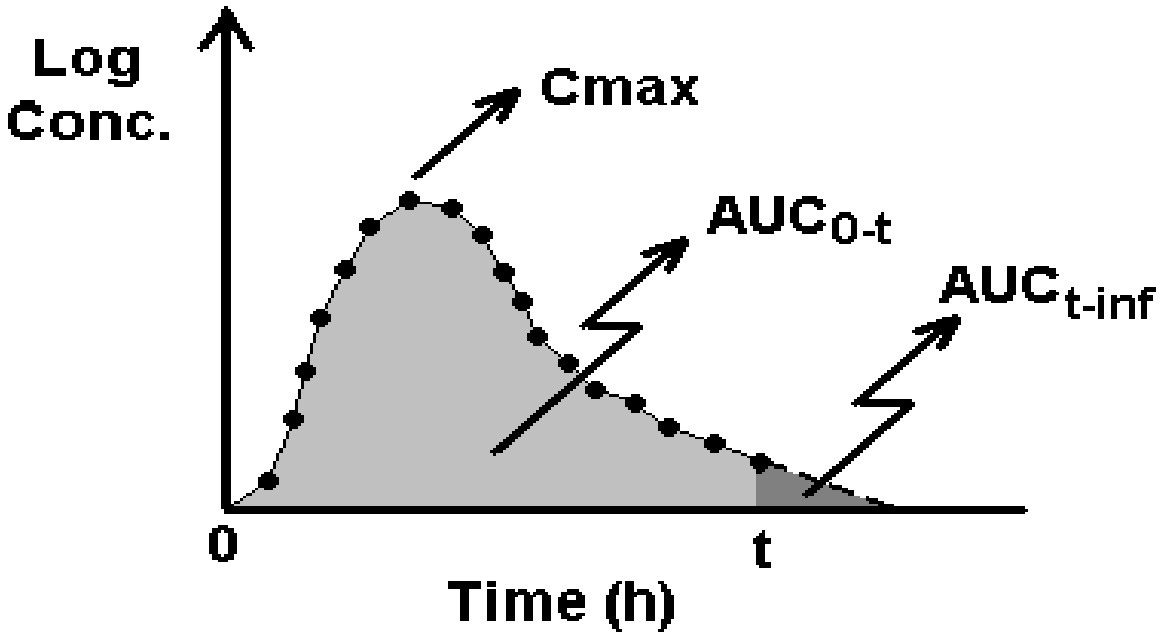
# A Short Lesson in Pharmacokinetics

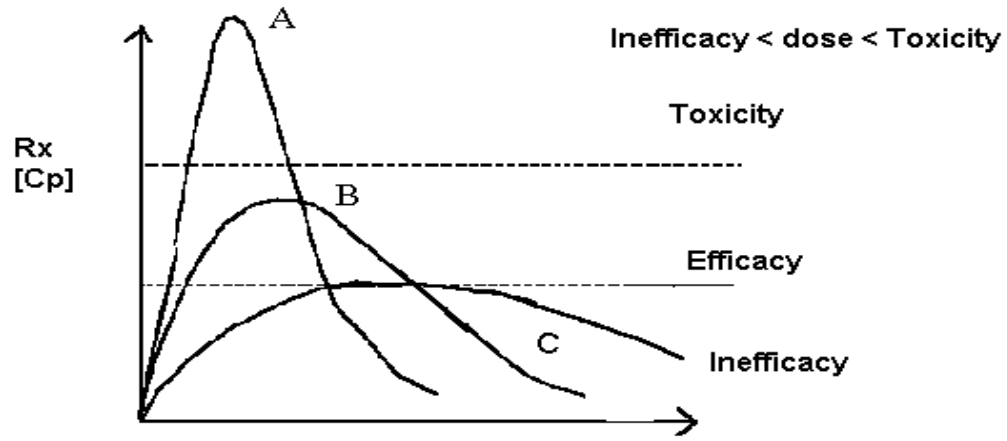
2 essential measures of pharmacokinetics:

- Rate of bioavailability (**Cmax** – maximum concentration)
- Total exposure of bioavailability (**AUC** – area under the curve)

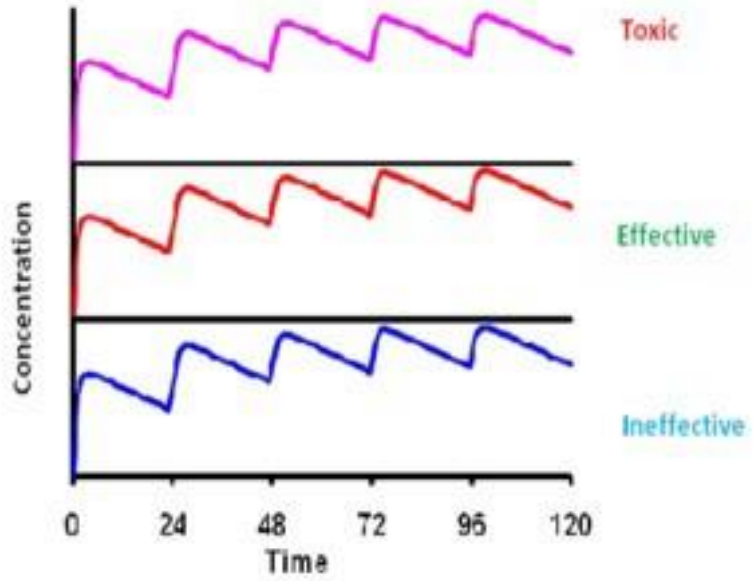


# PK/PD Fundamentals: Therapeutic Range

Single Dose




Multiple Dose

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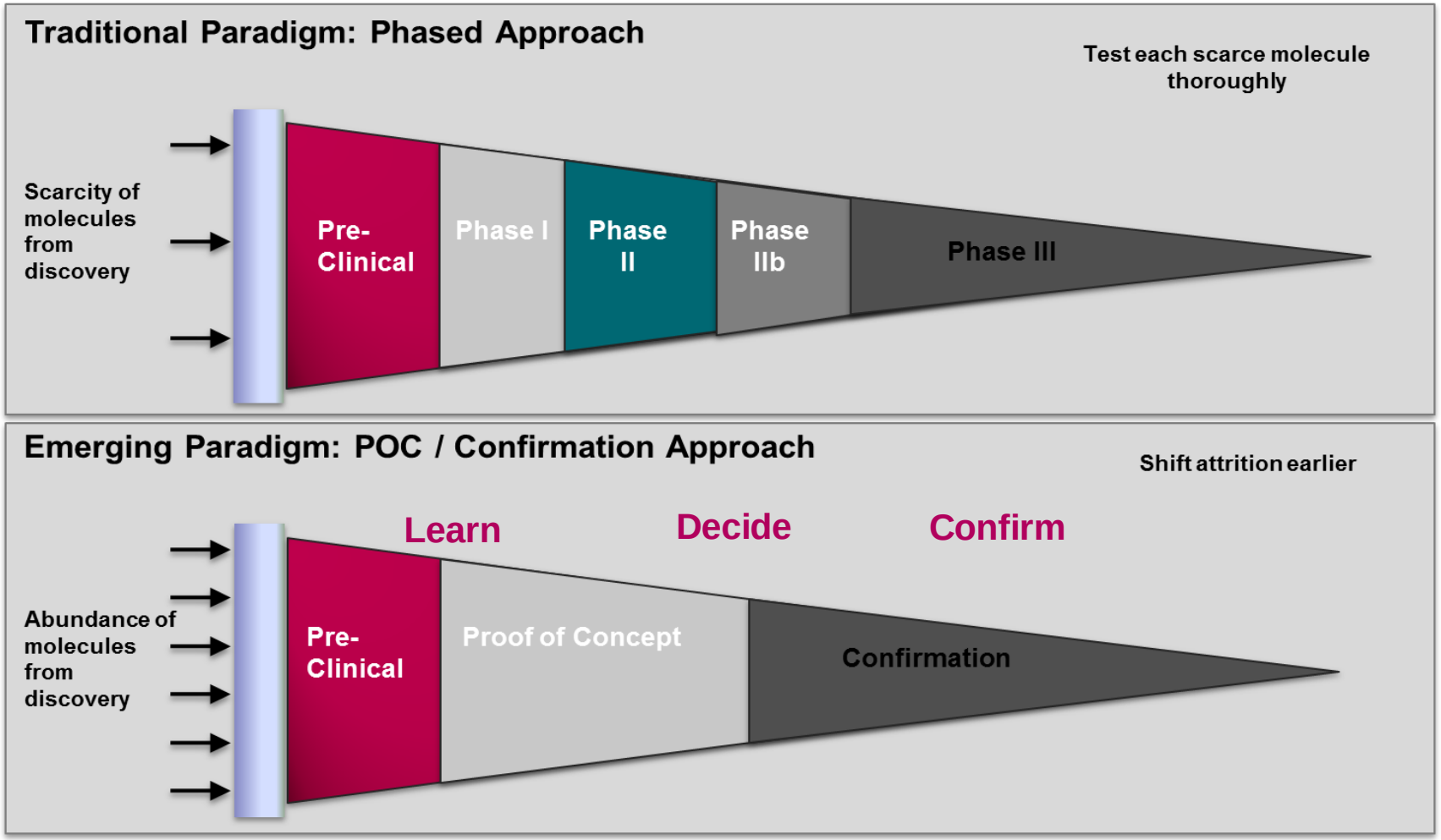
# Changing Paradigm




Source: William Blair & Company, (Bain and Company) Covance Investors Overview June 16, 2010

# Definition of Adaptive Designs

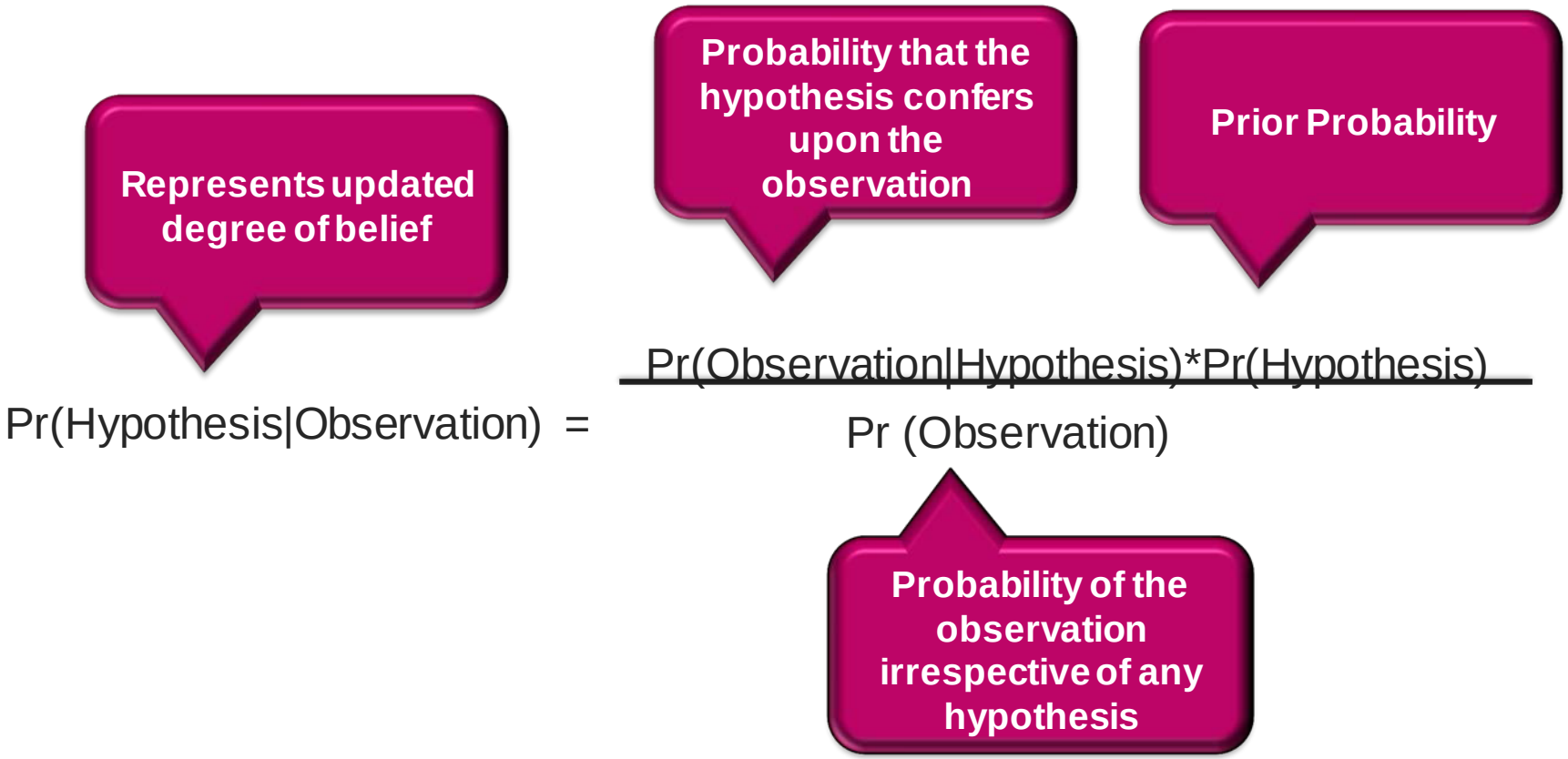
- A clinical trial design that uses accumulating data to decide how to modify aspects of the study as it continues, without undermining the validity and integrity of the trial.[1]

- "…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

# Bayes Theorem



# 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 Adequate & Well-Controlled studies and play an important informative role.

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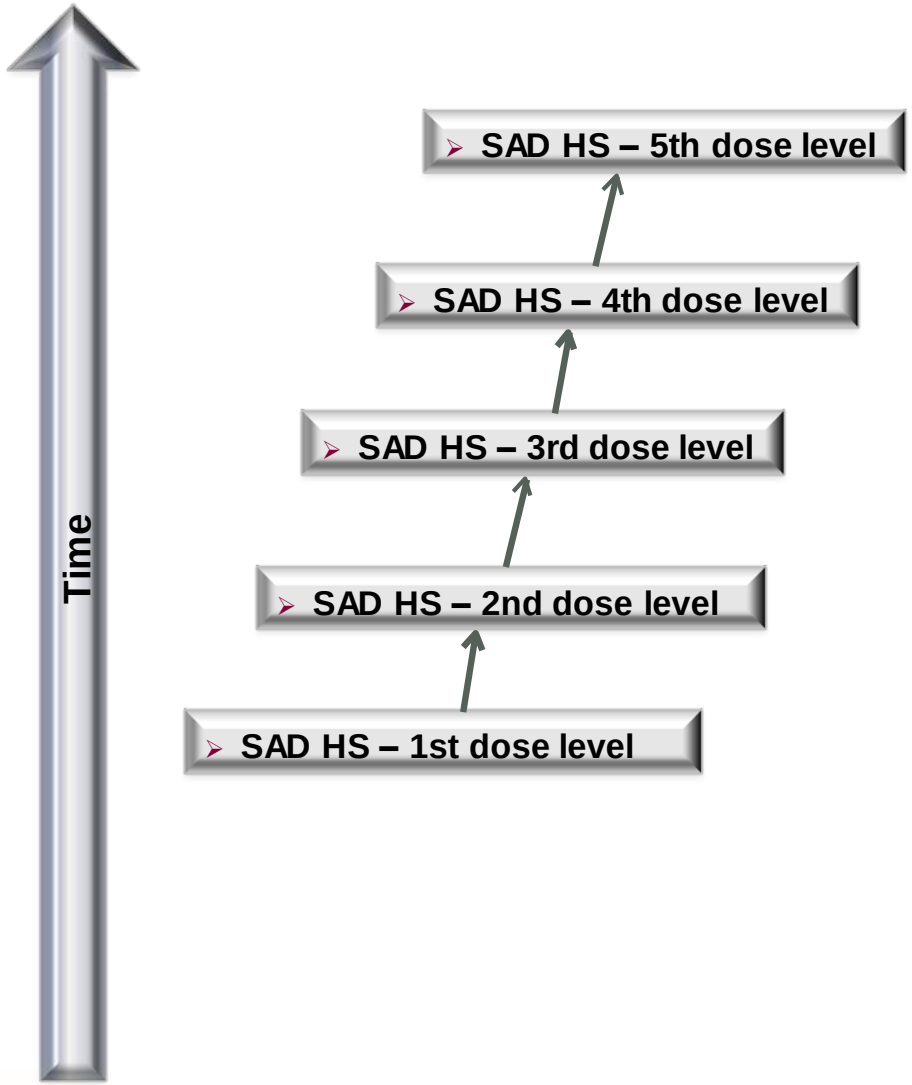
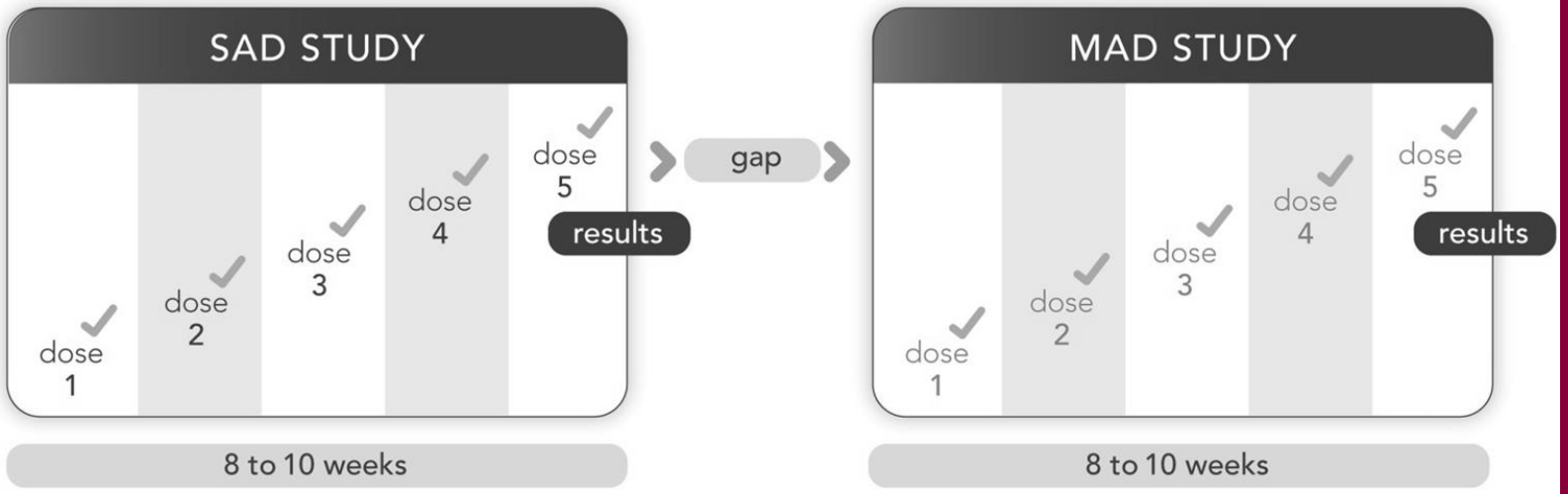
# Traditional Single Ascending Dose Study

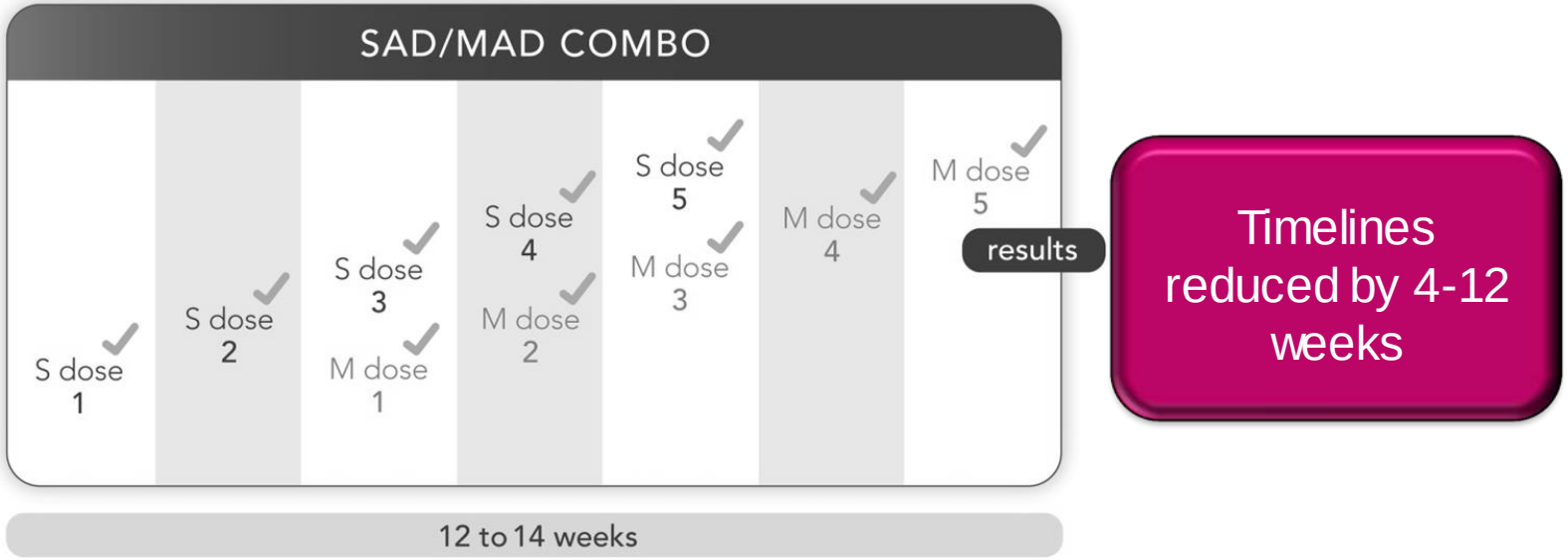



- Assess safety
- Assess PK?
- Progress through pre-planned dose levels
- Arrive at Maximum Tolerated Dose

SAD HS = Single Ascending Dose – Healthy Subjects

# Single Ascending Dose (SAD)/Multiple Ascending Dose (MAD) Combination Studies




Timelines reduced by 4-12 weeks

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# Discrete SAD & MAD Protocols with Pause Between Phases

## Pros

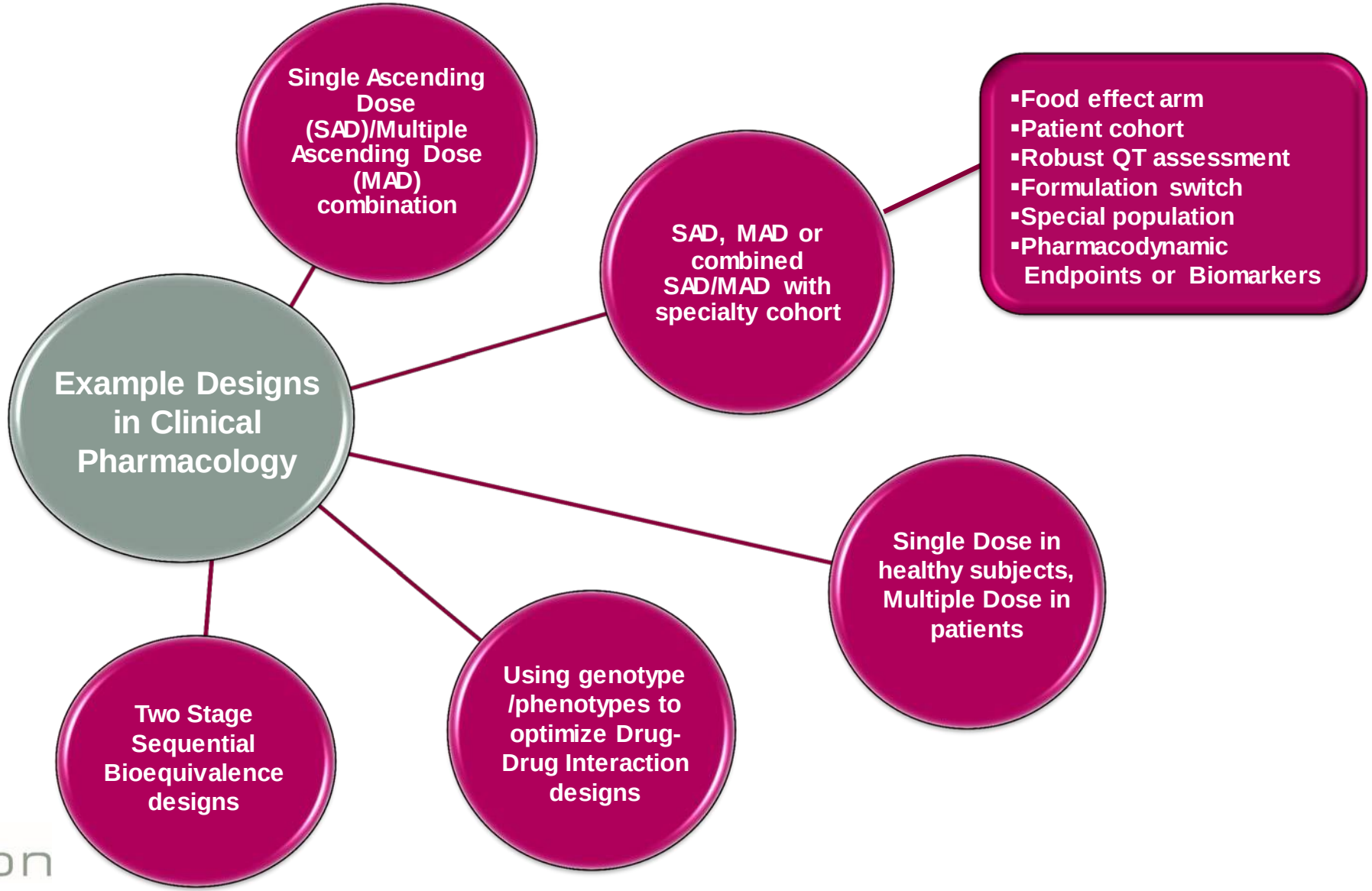
- Low risk
- Allows for full evaluation of SAD Safety and Exposure prior to designing the MAD

## Cons

- Longer duration due to not starting MAD until SAD complete
- Potentially higher cost associated with multiple protocols, CSRs, study start-up, IRB approval

**CSR:** Clinical study report
**IRB:** Institutional review (ethics) board

# Adaptive Study Designs in Early Clinical Research

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# Case Study 1

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

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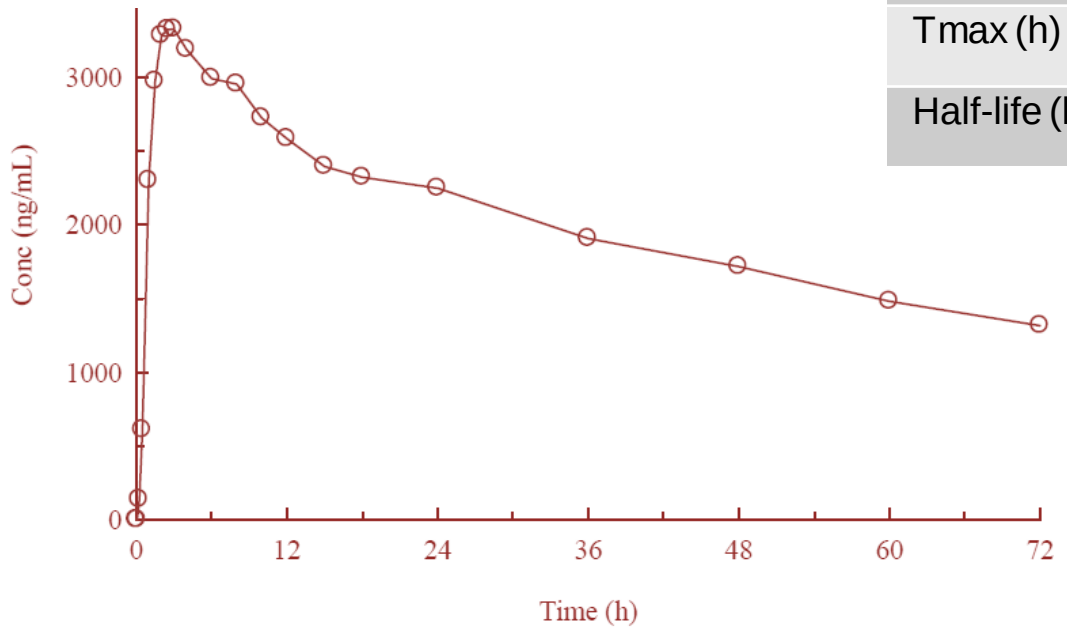
# Cohort I

| 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 |




**PK:** Pharmacokinetics

# Cohort I

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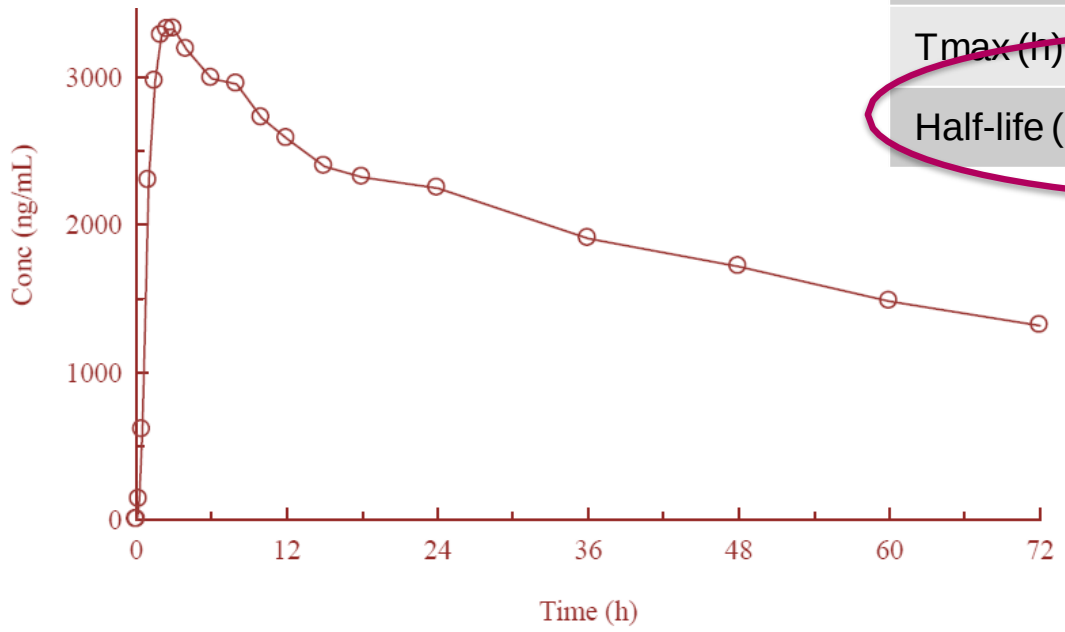
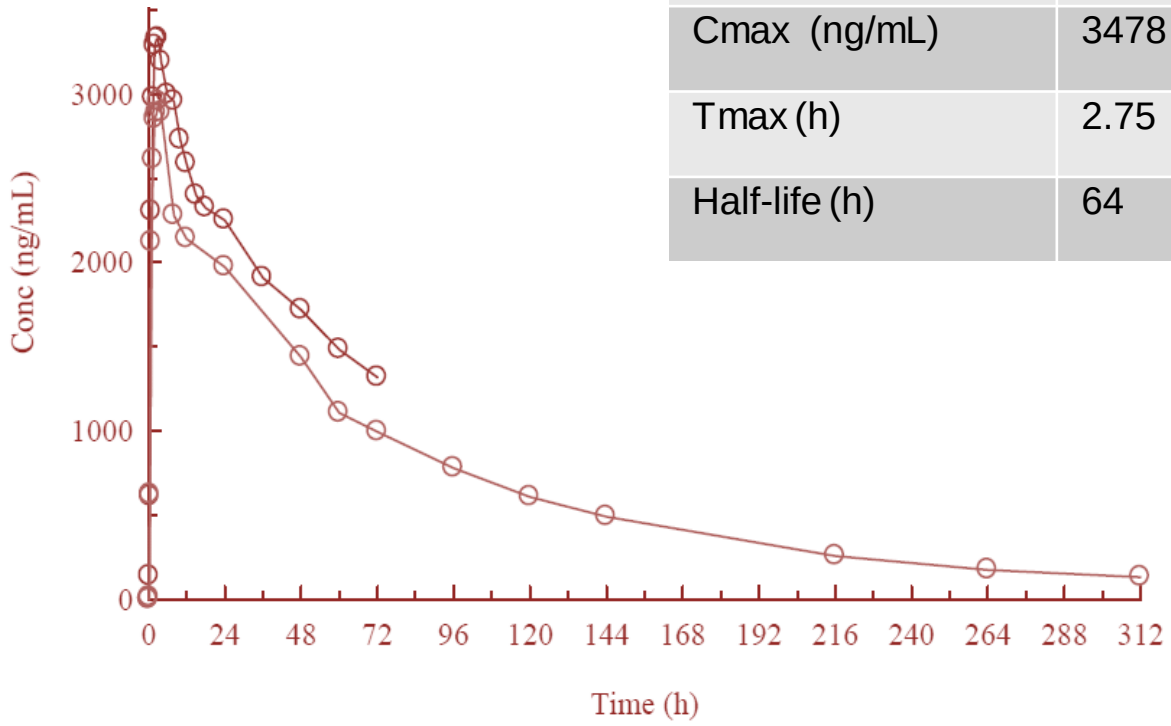



**PK:** Pharmacokinetics

# Cohort 2

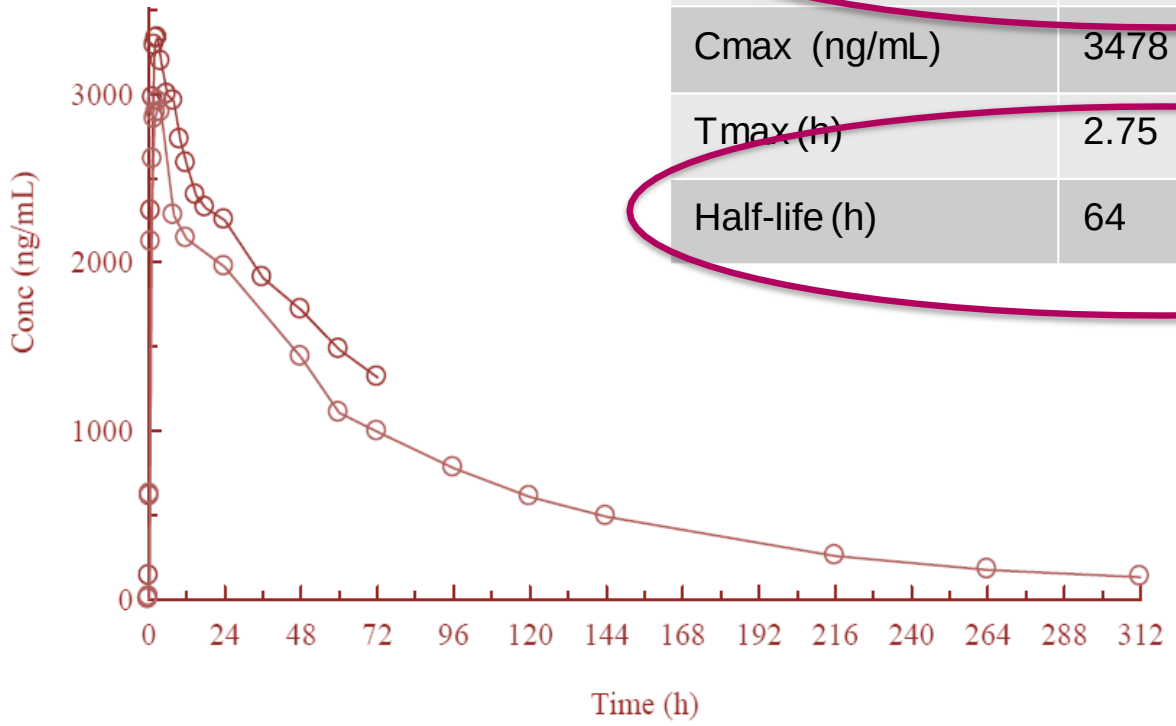
| PK parameter | Cohort I | Cohort 2 |
|---|---|---|
| AUC0-t (ng/mL●h) | 133407 | 217344 |
| AUCinf (ng/mL●h) | 270000 | 233302 |
| Cmax (ng/mL) | 3478 | 3035 |
| Tmax (h) | 2.75 | 3 |
| Half-life (h) | 64 | 80 |




**PK:** Pharmacokinetics

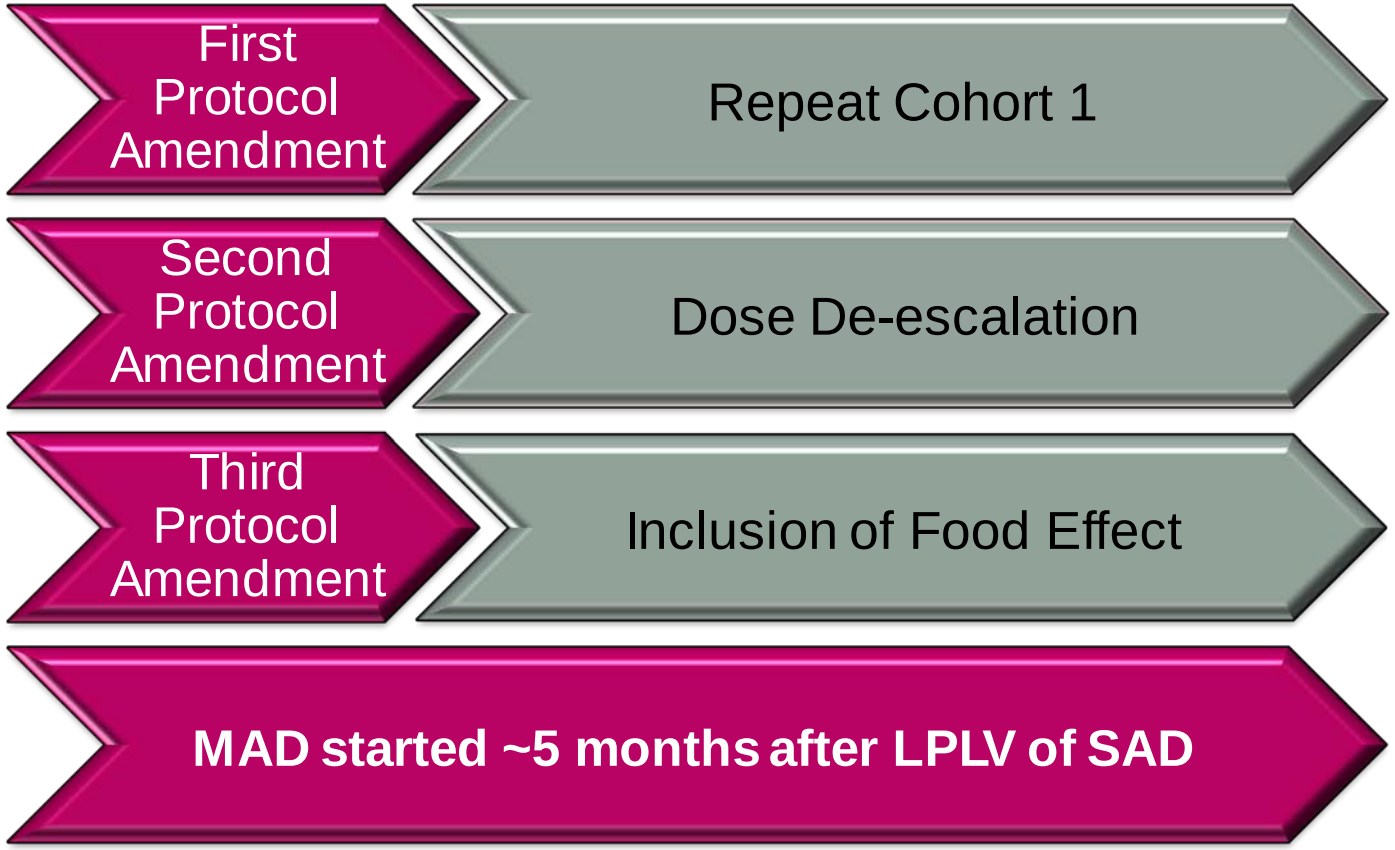
# Cohort 2

| 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 |



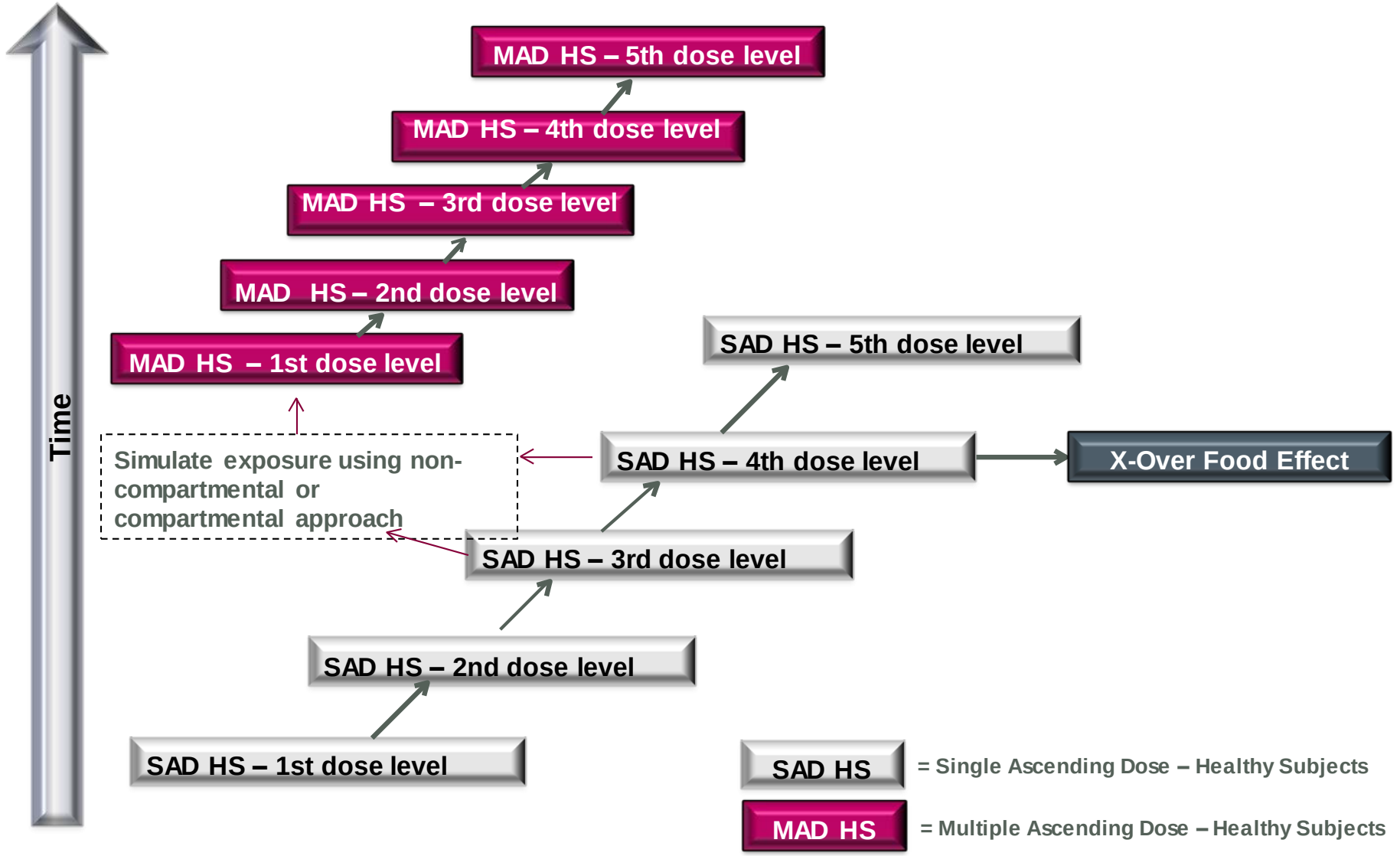

**PK:** Pharmacokinetics

# Case Study I Continued




**LPLV:** Last Patient, Last Visit
**SAD:** Single Ascending Dose

# Case Study 1 Redesigned

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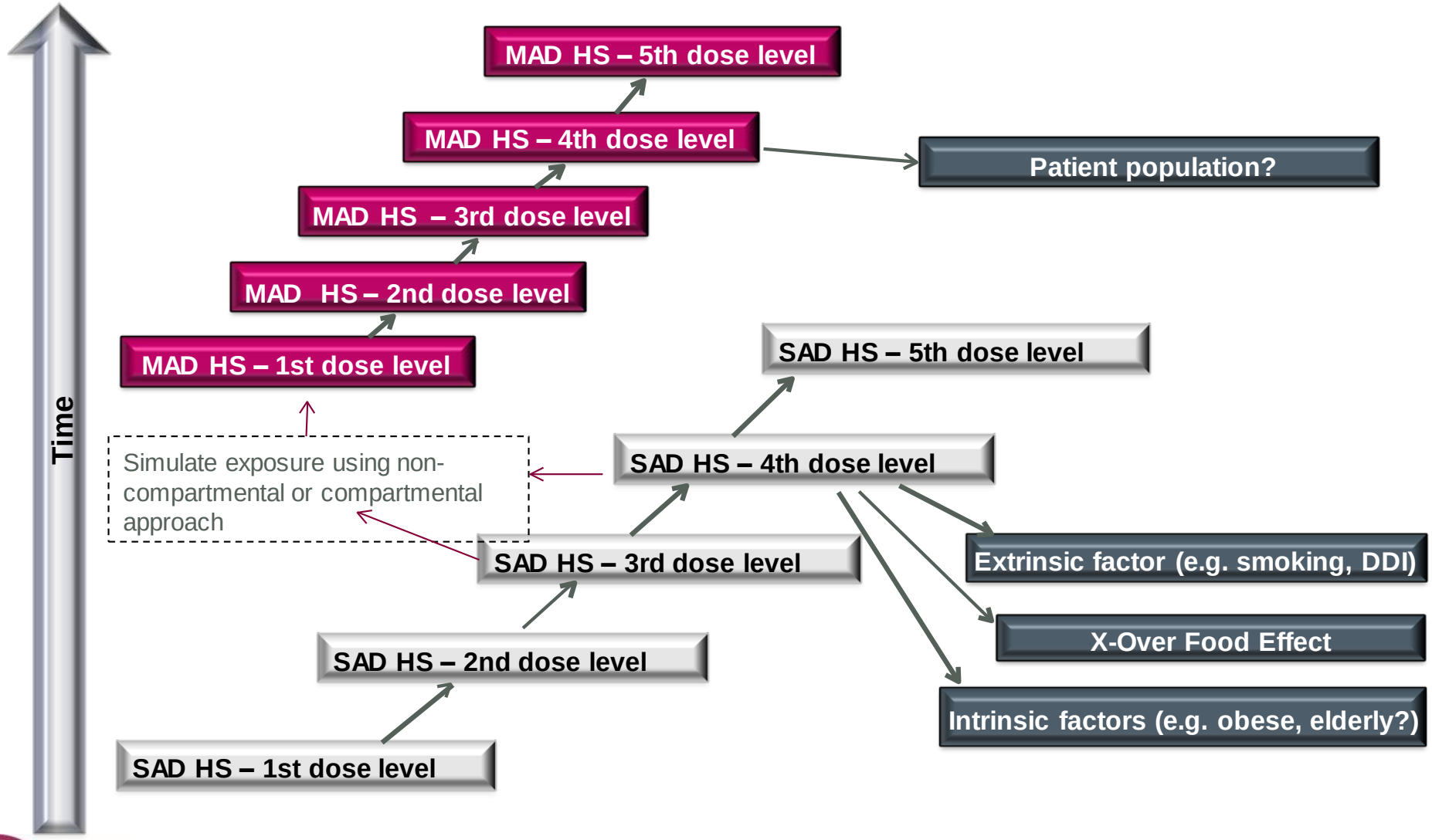
# Optional Modifications (drug/therapeutic area specific)




**DDI:** Drug-Drug Interaction

# Case Study 2

| | |
|---|---|
| Requested Design | Combined SAD/MAD |
| | |
| Therapeutic Area | Endocrinology |
| | |
| Study Population | SAD: Normal Healthy<br>MAD: Target Population |

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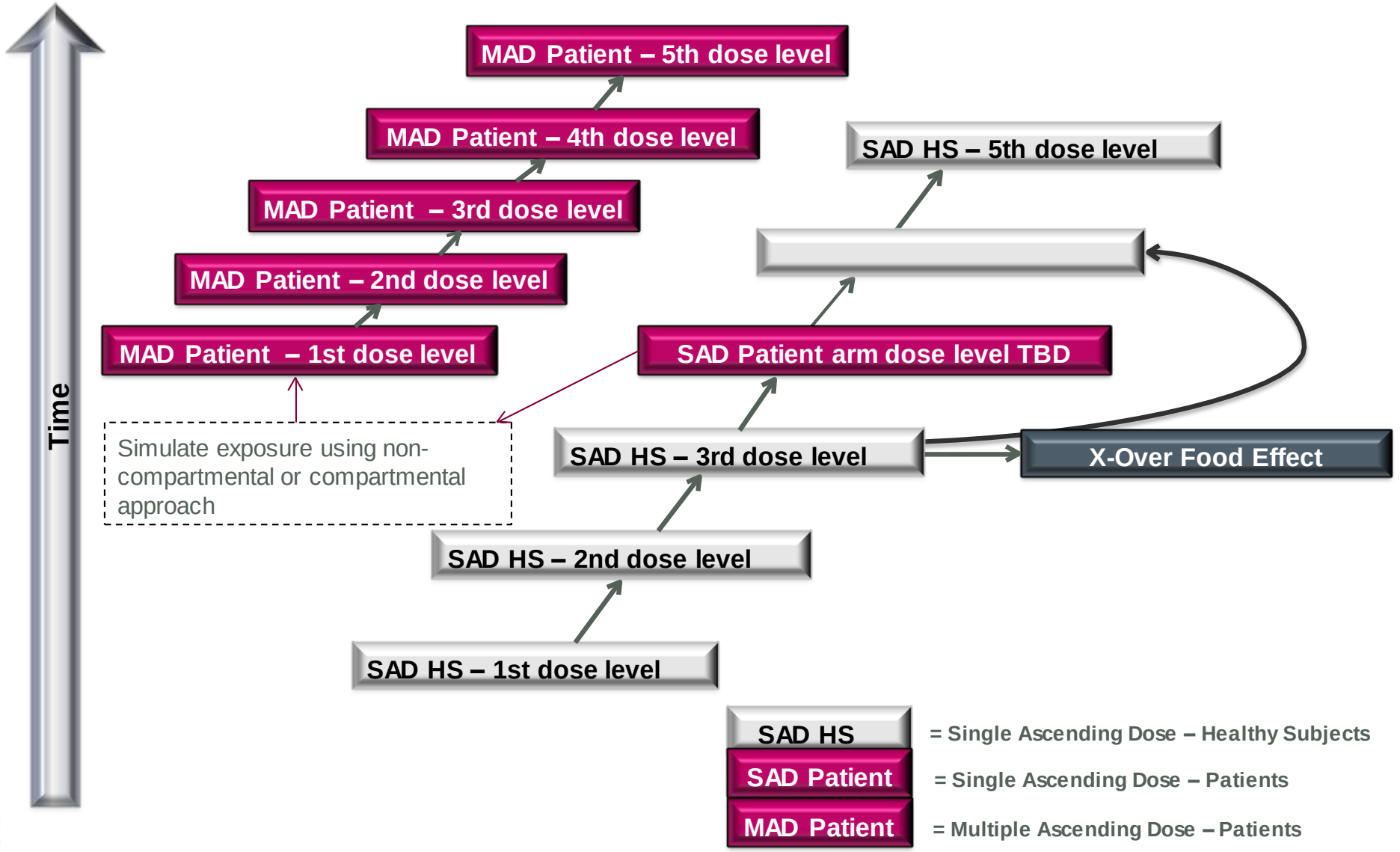
# Case Study 2


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

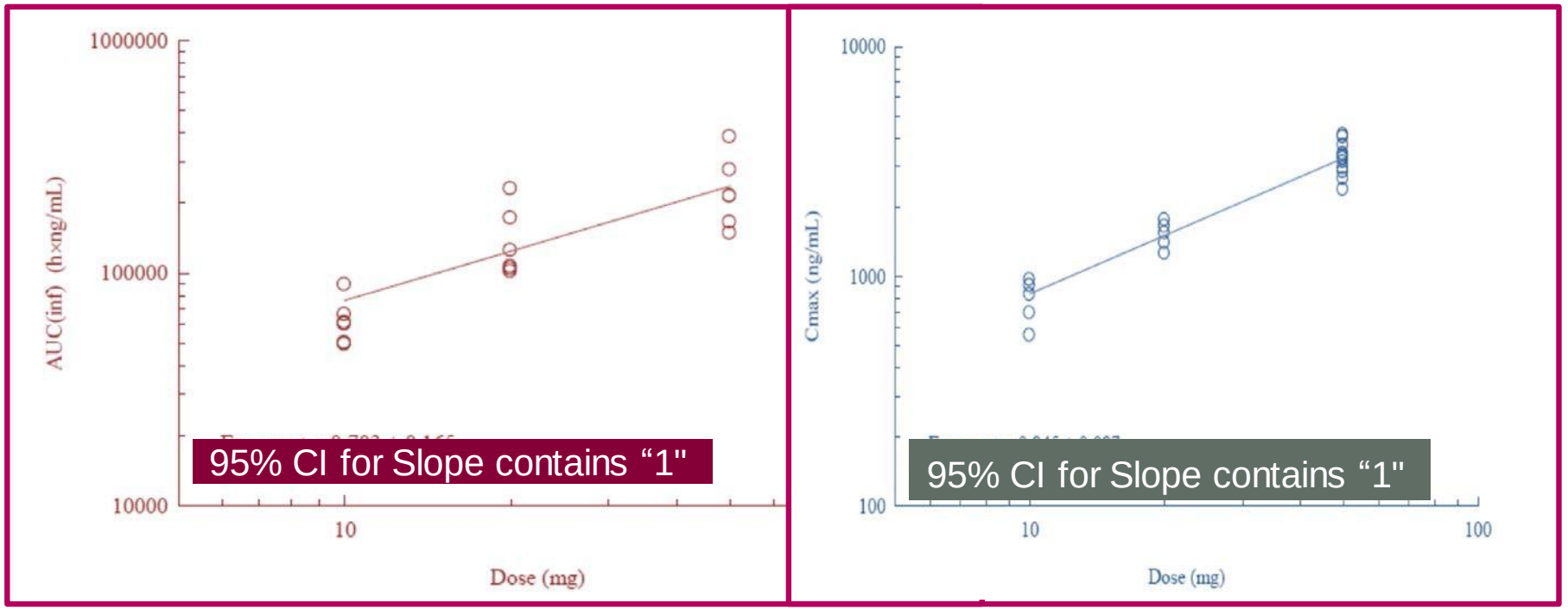
# Adapting MAD Starting Point Based on Modeling Approaches

- Selecting MAD starting dose can be challenging
- Traditional approach has been to “ballpark” the MAD starting point well before any data is collected or once SAD data is 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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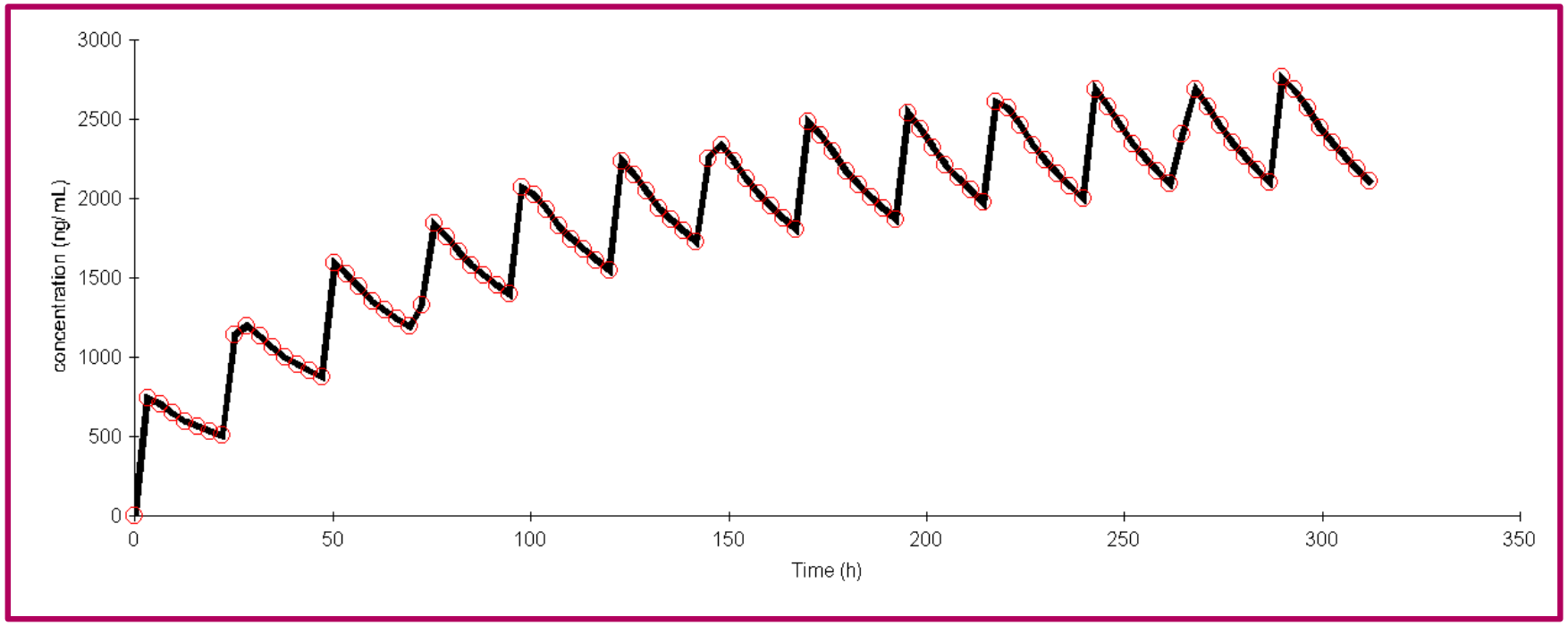
# Simulating Using Non-Parametric Superposition: Rise to Steady-State

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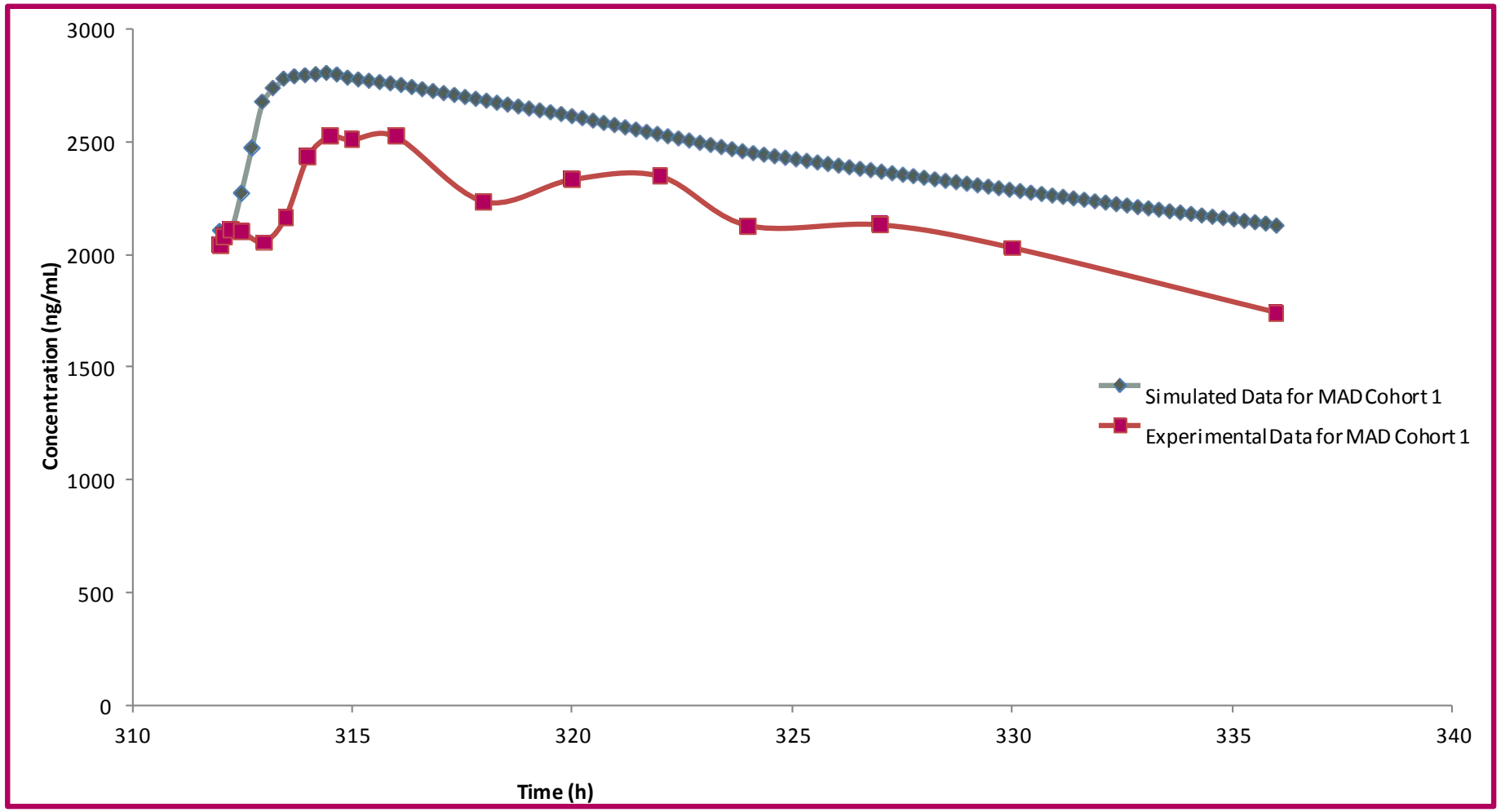
# Non-Compartmental Simulated vs. Experimental Data

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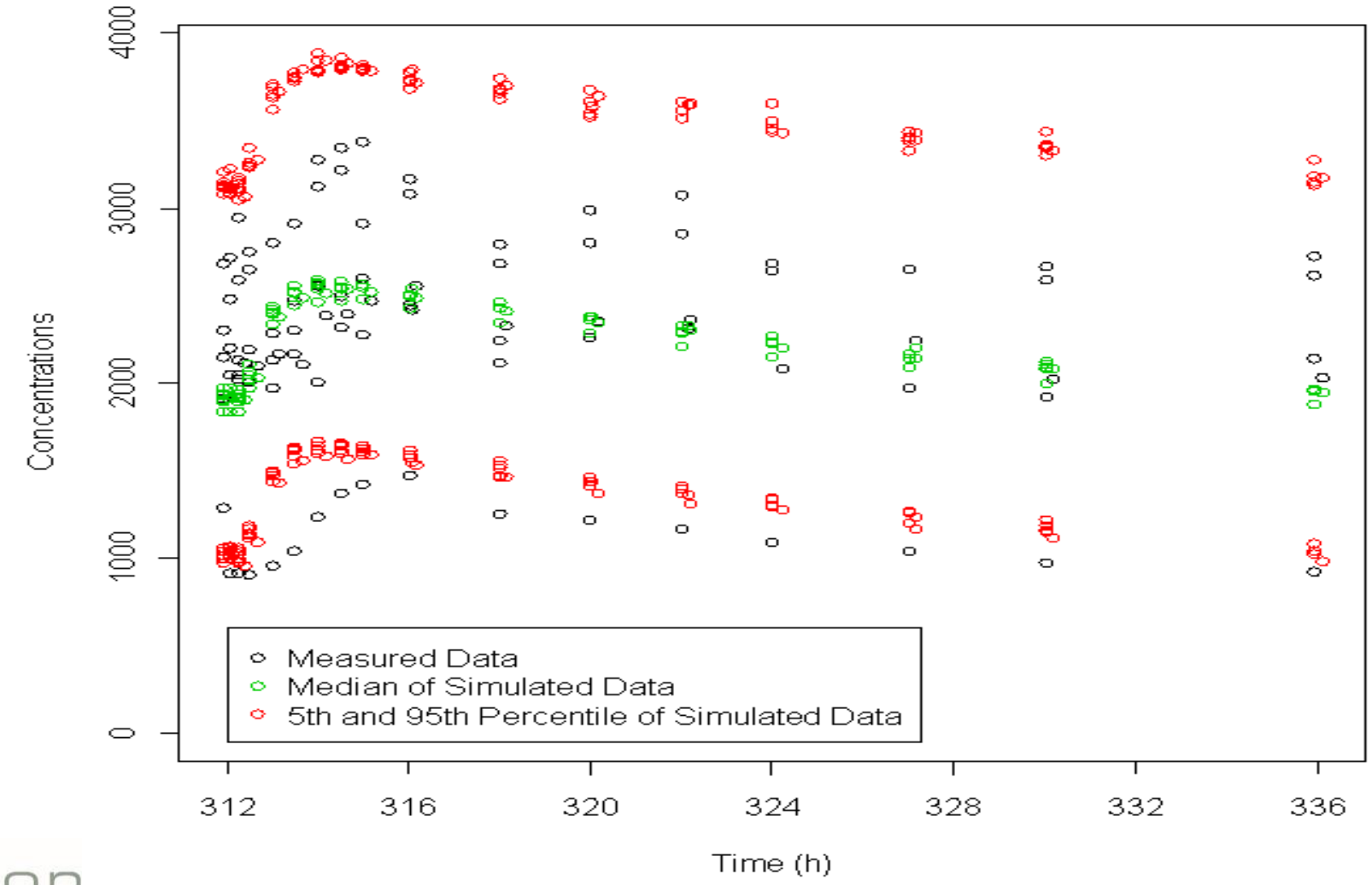
# Mixed-Effect Modeling and SAD/MAD Studies


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

**PK/PD:** Pharmacokinetics / Pharmacodynamics

# Simulated Multiple-Dose Curve from SAD Data

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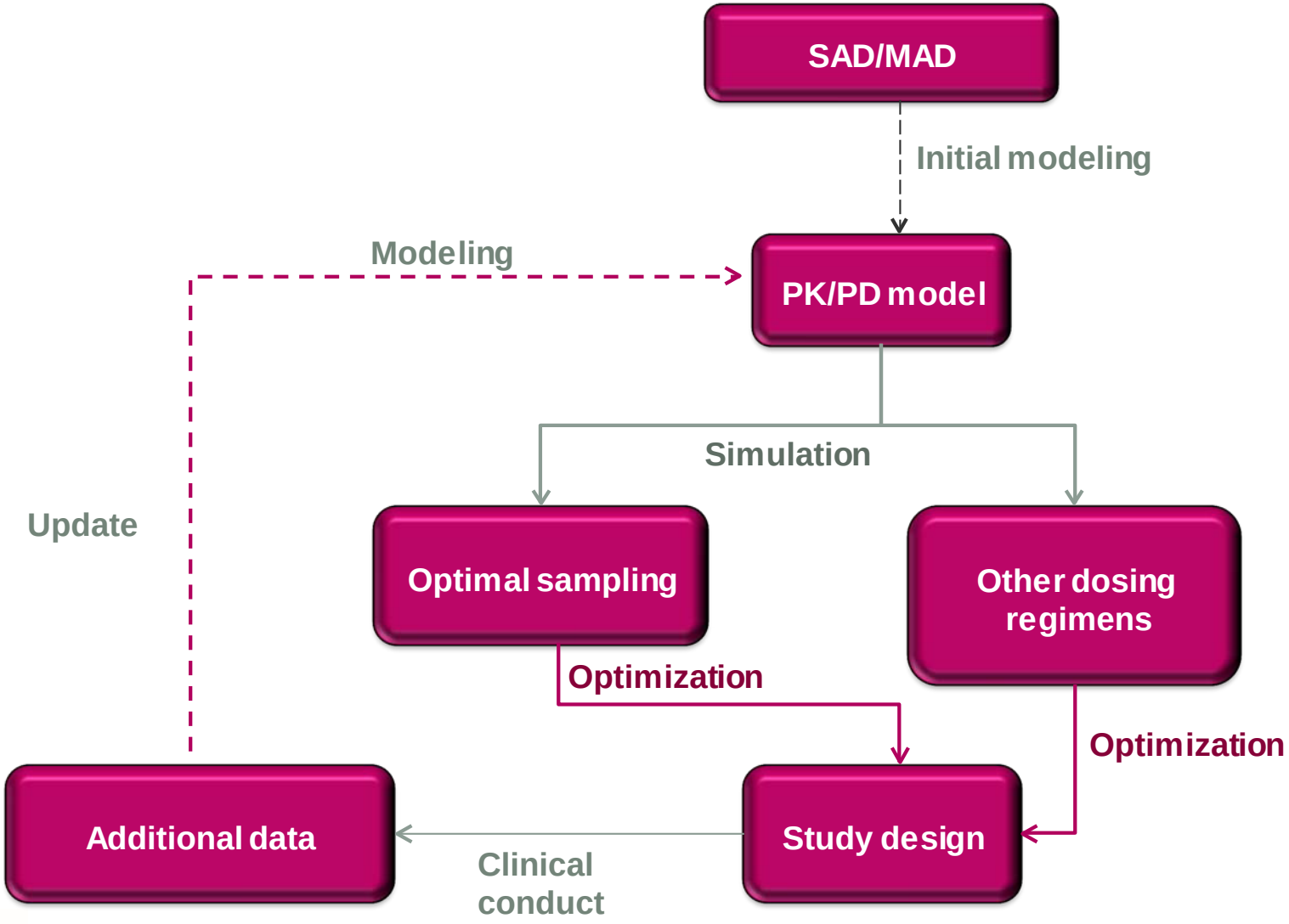
# Benefits of Mixed-Effect Modeling Beyond SAD/MAD: “Learn & Confirm”

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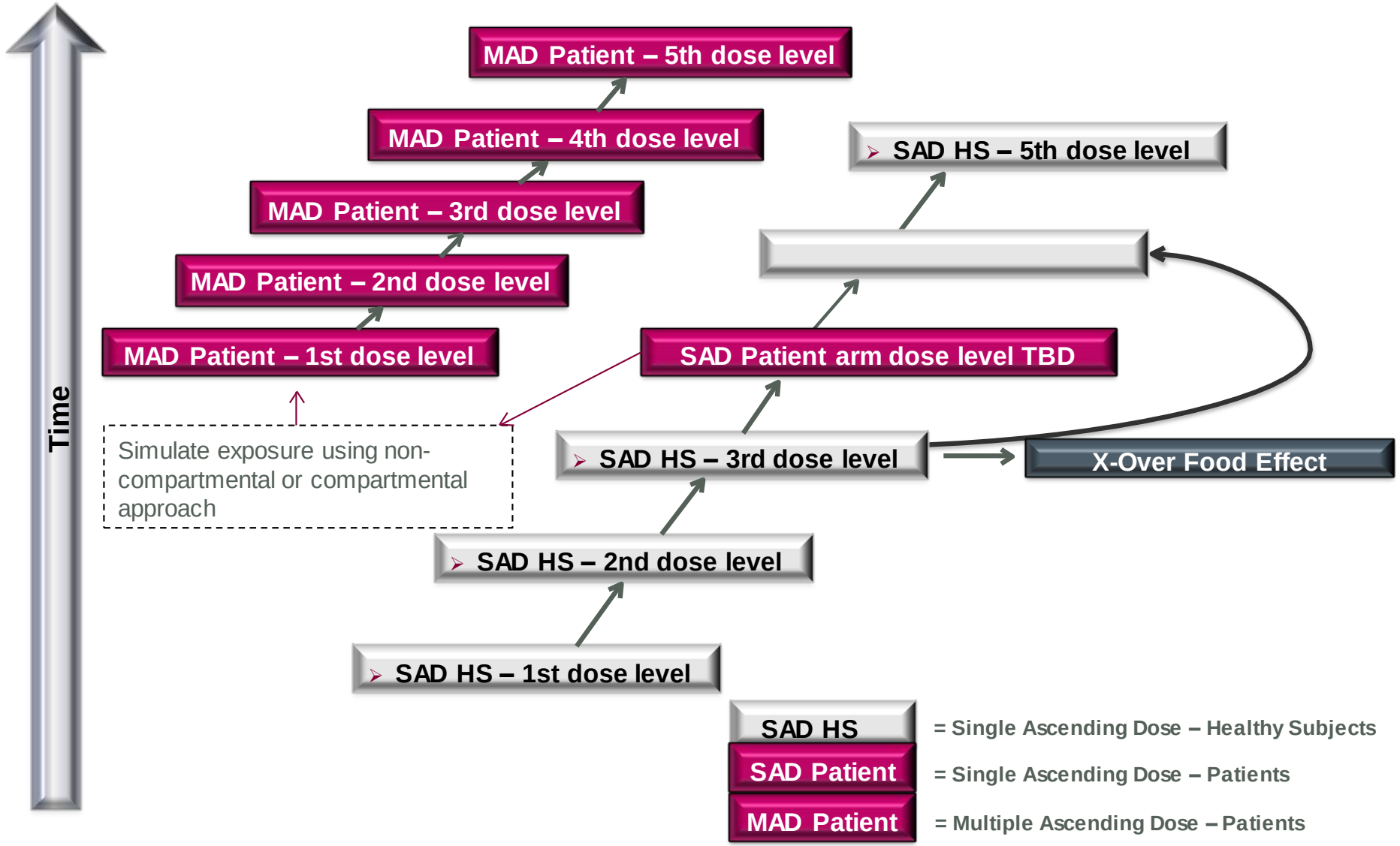
# Case Study 2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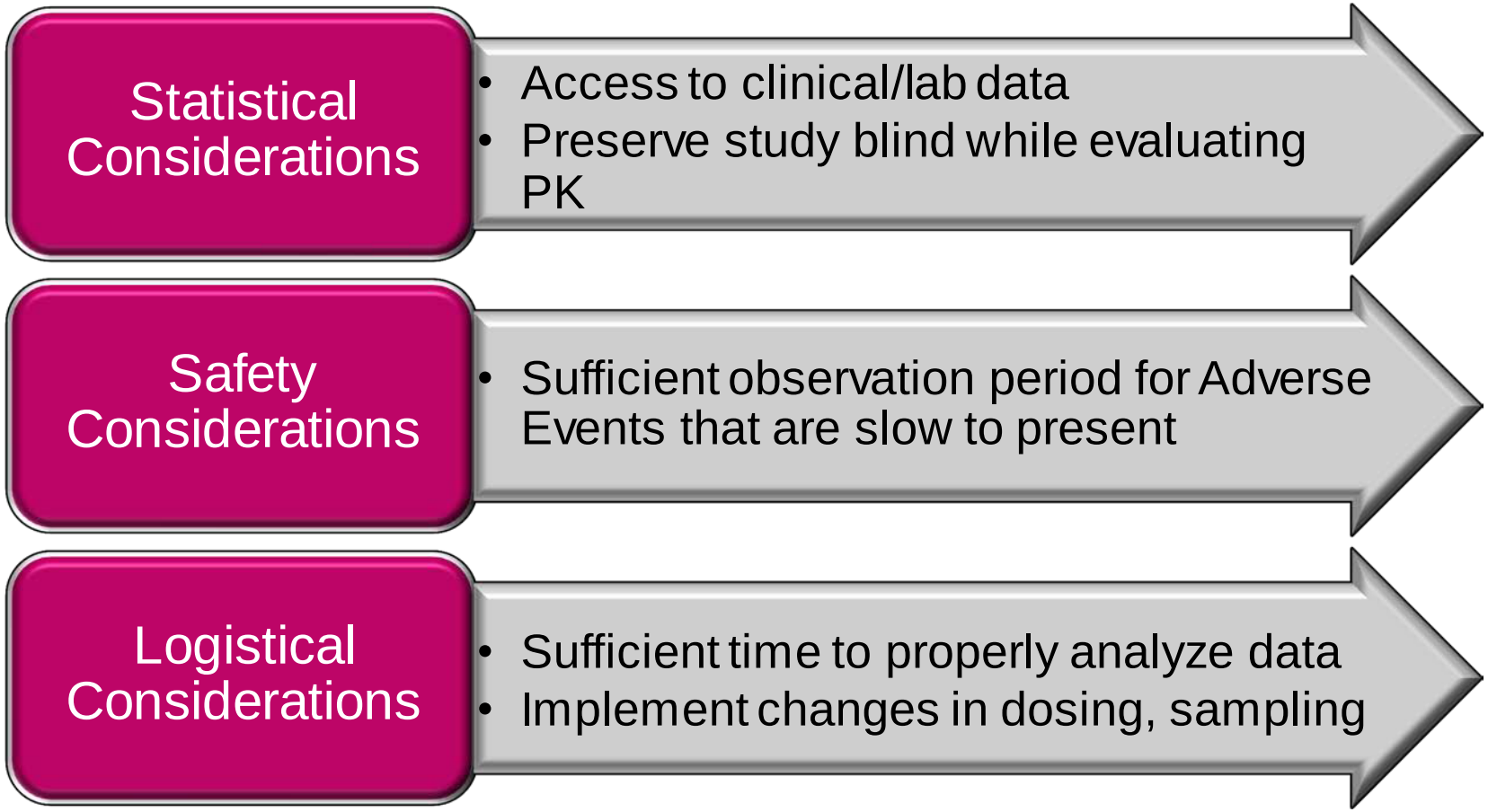
# Practical Considerations



# Lessons Learned: Combined SAD/MAD

- Combining is lowest risk when more is known about the NCE
  - PK/exposure well understood & consistent across species
    - If not, definitely recommend interim PK between SAD cohort or at least one pause prior to MAD
- Failure to write protocols adaptively/flexibly results in multiple amendments & additional IRB review
    - Delay in data delivery
    - Additional costs
- Failure to confirm PK prior to MAD
    - More cohorts dosed than necessary
    - Longer duration to POC than necessary
- Desire to combine too many unrelated objectives can delay important milestones and adds risk (e.g. addition of a DDI arm adds risk to a combined SAD/MAD when PK in absence of DDI unknown and safety issues arise)



**NCE:** New Chemical Entity

# Thank You!