Design of Dose Response Clinical Trials

BASS XIII

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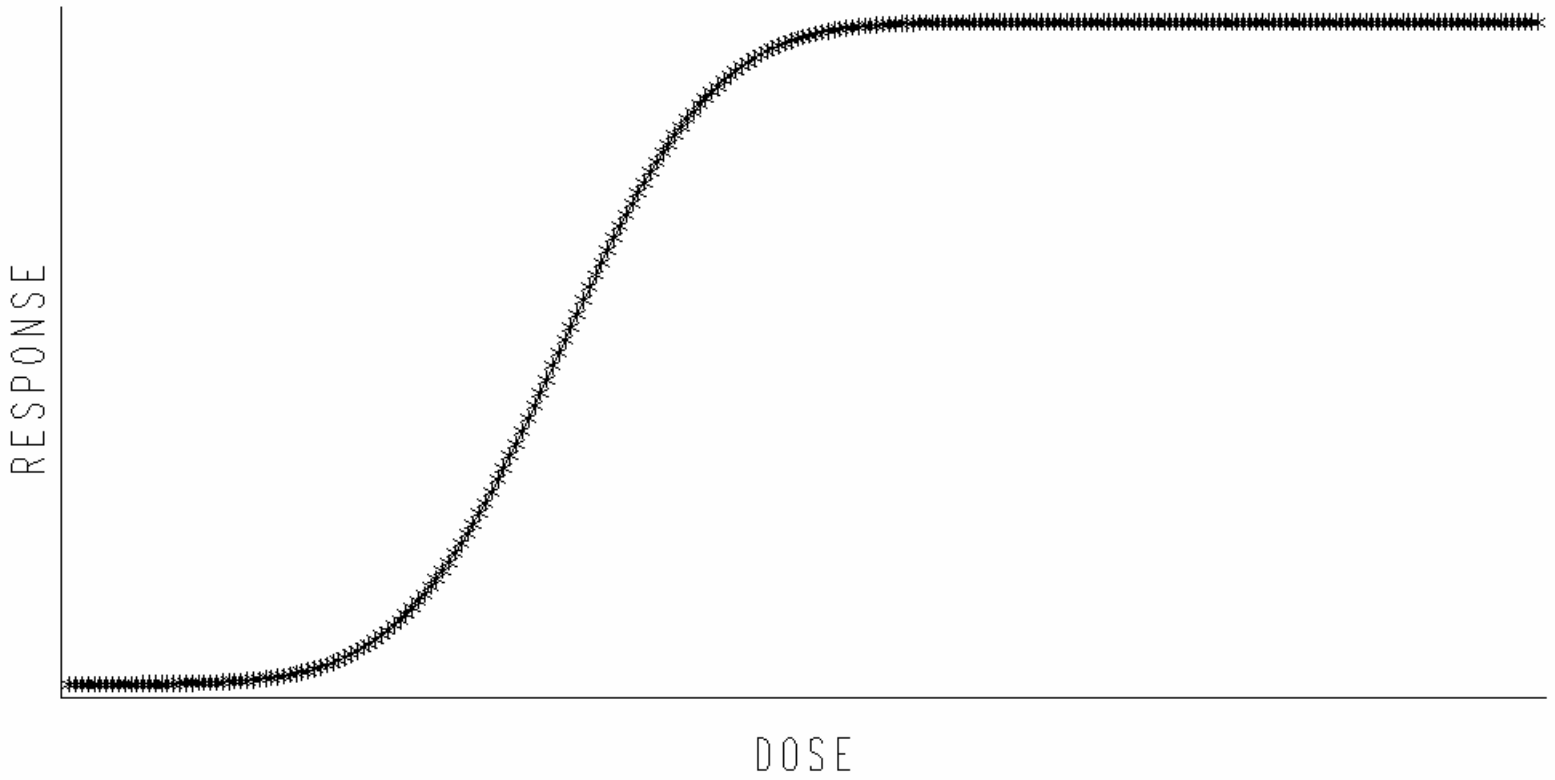
Drug Development Process

- Drug Discovery
- Non-clinical Development
- Clinical Development
  - Phase I Clinical pharmacology (PK/PD, MTD)
  - Phase II Drug efficacy/safety, dose ranging
  - Phase III Long-term, large scale, confirmatory
  - Phase IV Post-market

FIGURE 1 A THEORETICAL DOSE–RESPONSE CURVE



Phase I Studies (Drugs developed for non-life-threatening diseases)

- Healthy normal volunteers
- Single dose
- Double-blind, placebo controlled, randomized, dose escalation
- Clinical pharmacology – PK/PD, MTD
- Cross-over studies (BA, BE)
- Answer the question – how often should we dose the patient?

Phase II Studies (Non-life-threatening diseases)

- Patients with the disease under study
- Dose ranging, efficacy dose response
- Double-blind, placebo controlled, randomized, fixed doses
- Clinical efficacy and safety endpoints
- Exploratory, estimation of efficacy, dose,..
- Answer the question – how much should we dose the patient?

FIGURE 1.1 INDIVIDUAL AND AVERAGE DOSE—RESPONSE CURVES

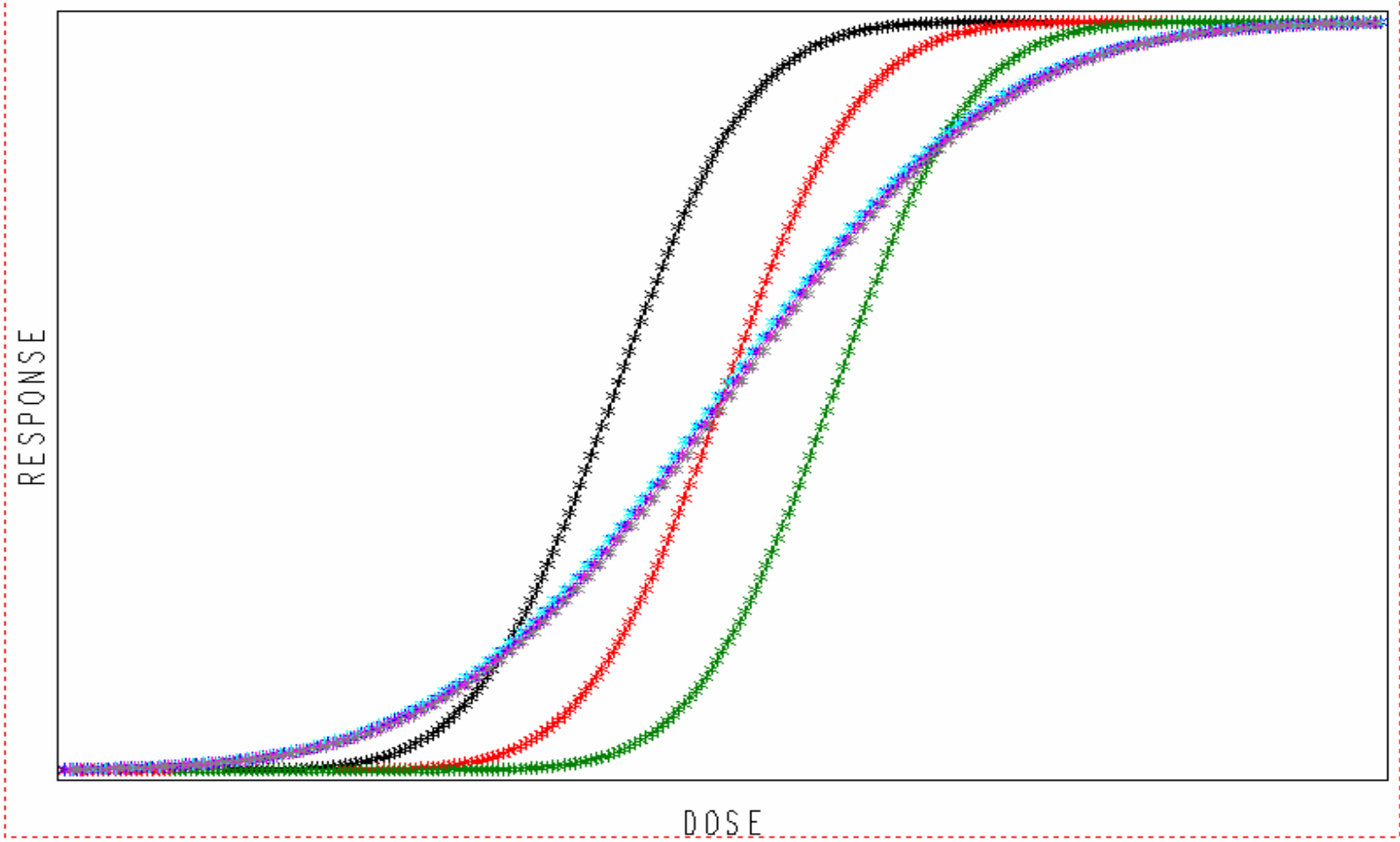
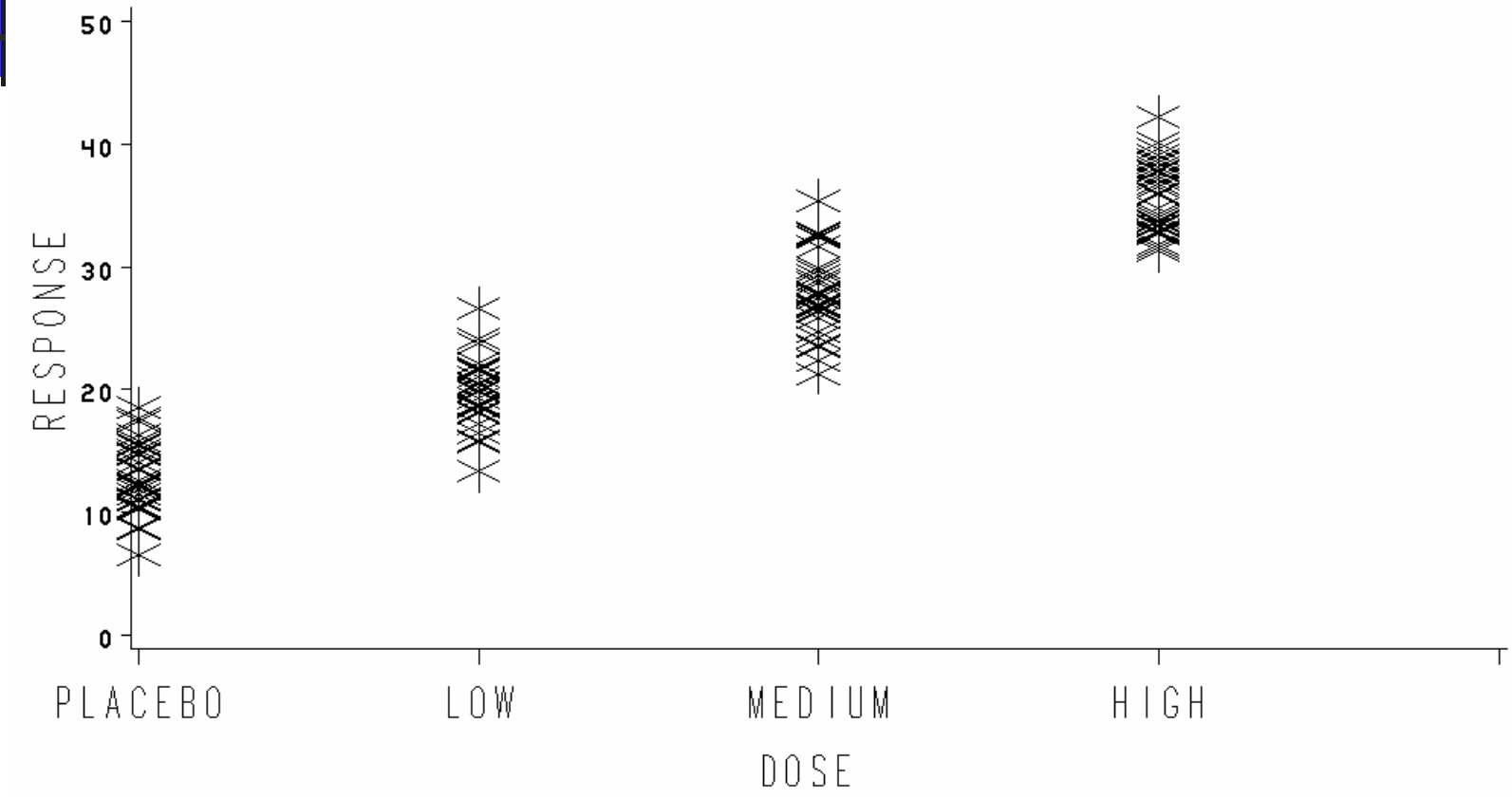


FIGURE 3 OBSERVATIONS FROM A SIMULATED DOSE RESPONSE STUDY



Phase III, IV Studies

- Phase III studies are for registration purposes
- Confirmatory, hypothesis testing
- Study for target dose(s)
- Phase IV studies are for larger scale safety surveillance, or new indication
- Change of labeled dose post market is possible

Concerns in Developing Drugs for Life-Threatening Diseases

- May not be ethical to use placebo control
- May not be ethical to recruit normal healthy volunteers
- Open label, single arm, dose titration study designs

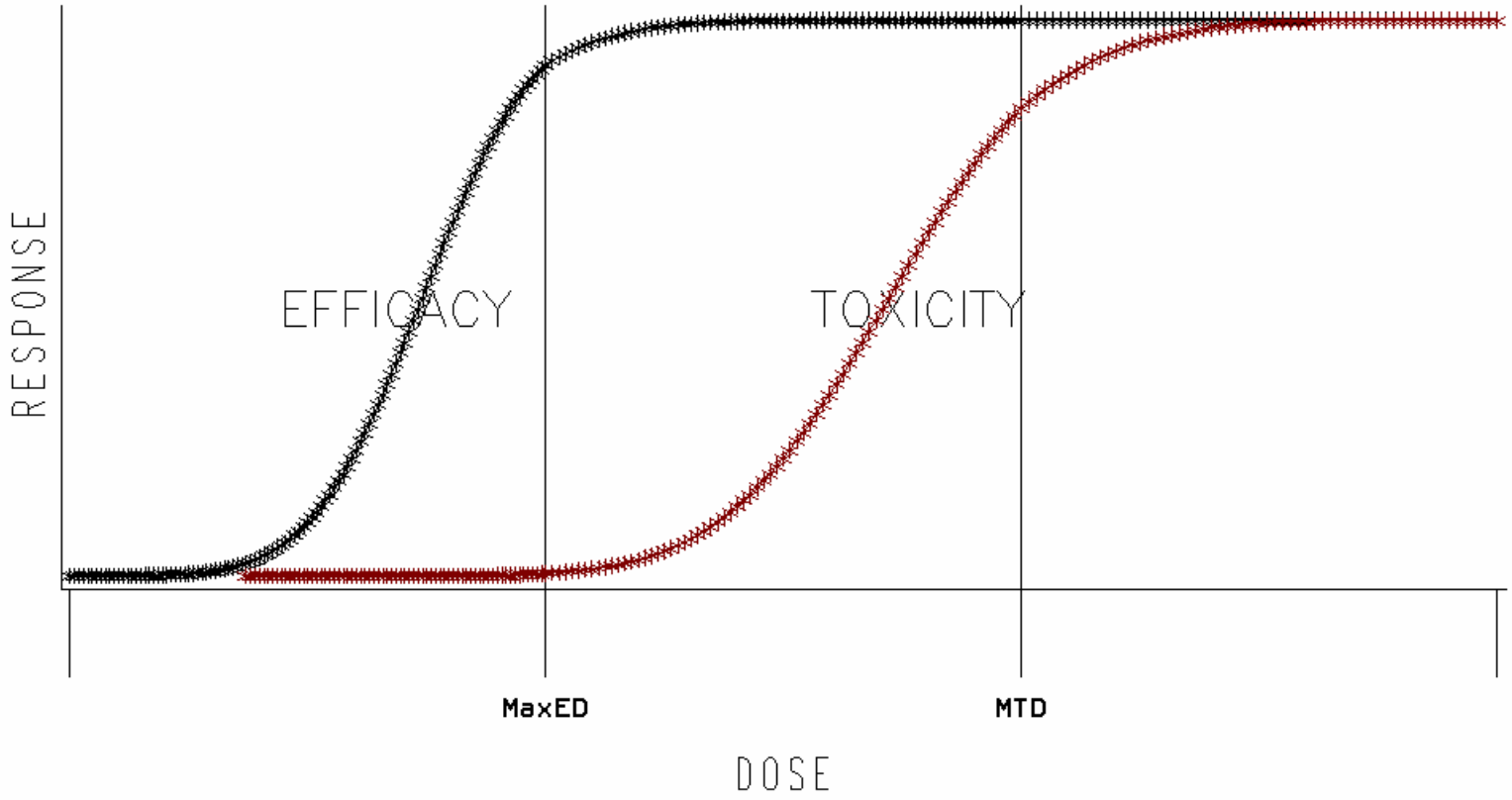
Challenges in dose selection

- Every stage of drug development – from drug discovery to post market
- What is the right range of doses
- Individual dose response curves vs population curve
- Exposure-response vs dose-response
- Other challenges (choice of primary endpoint, multiple comparison, ...)

WHAT ARE THE ISSUES IN DOSE FINDING?

- Individual versus global responses
- What are you looking for?
- What range of doses should we consider?
- How many doses to be tested?
- What are we measuring?
- The differences in exploration and confirmation

FIGURE 2 DOSE–RESPONSE FOR EFFICACY AND TOXICITY



INDIVIDUAL VERSUS GLOBAL RESPONSES

- In most of drugs, we need to recommend a few fixed doses
- For wide Therapeutic Index (TI), it is possible to use one dose
- Dose response relationship vs concentration response relationship

PHARMACOKINETICS (PK), PHARMACODYNAMICS (PD)

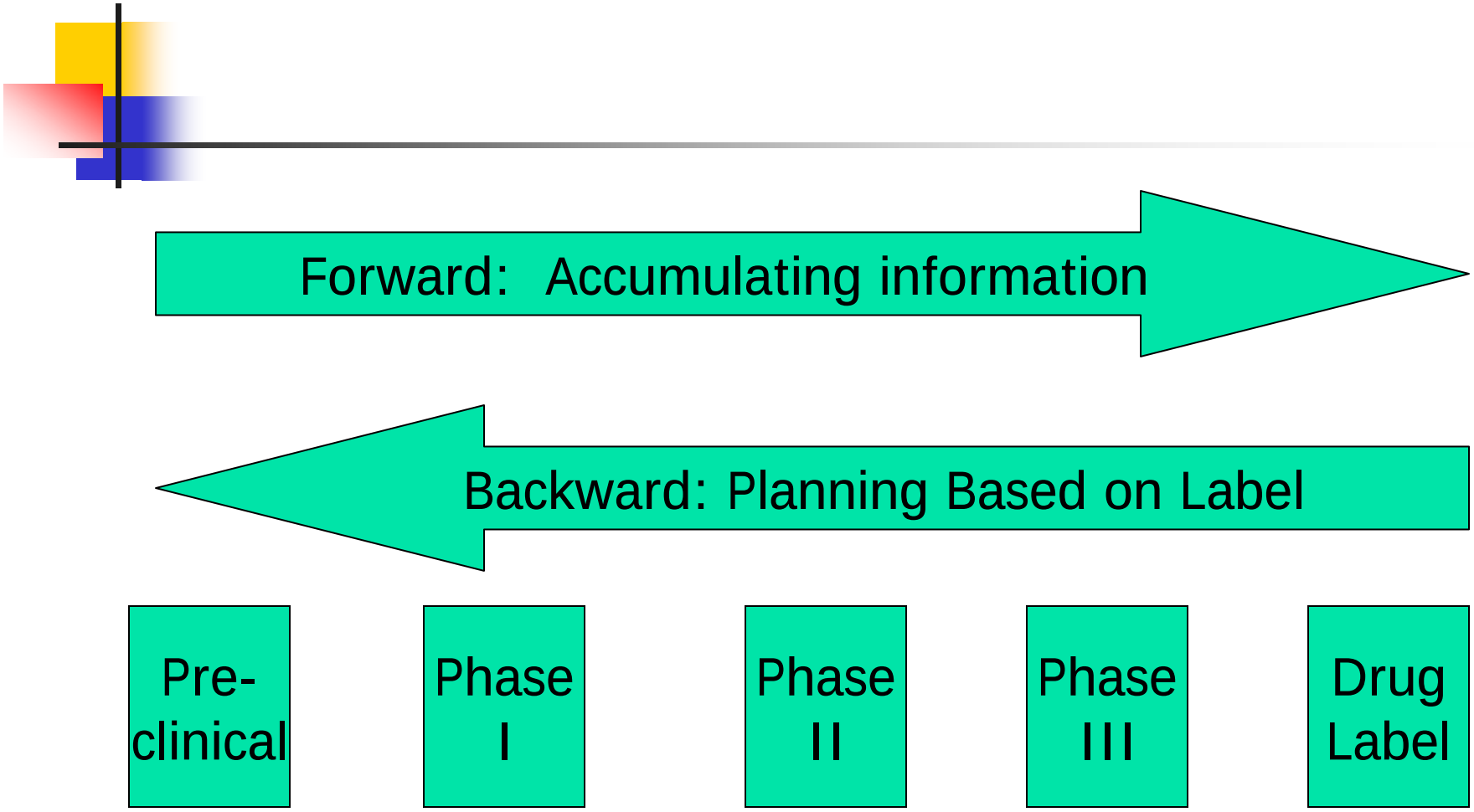
- PK, PD, PK/PD
  - PK: body act on drug
  - PD: drug act on body
- Concentration response uses PK, but should we consider PD?

WHAT ARE YOU LOOKING FOR

- A single dose or a range of doses
- Fixed dose or titration doses
- As needed or chronic treatment
- How many doses a day

DRUG LABEL (Package Insert)

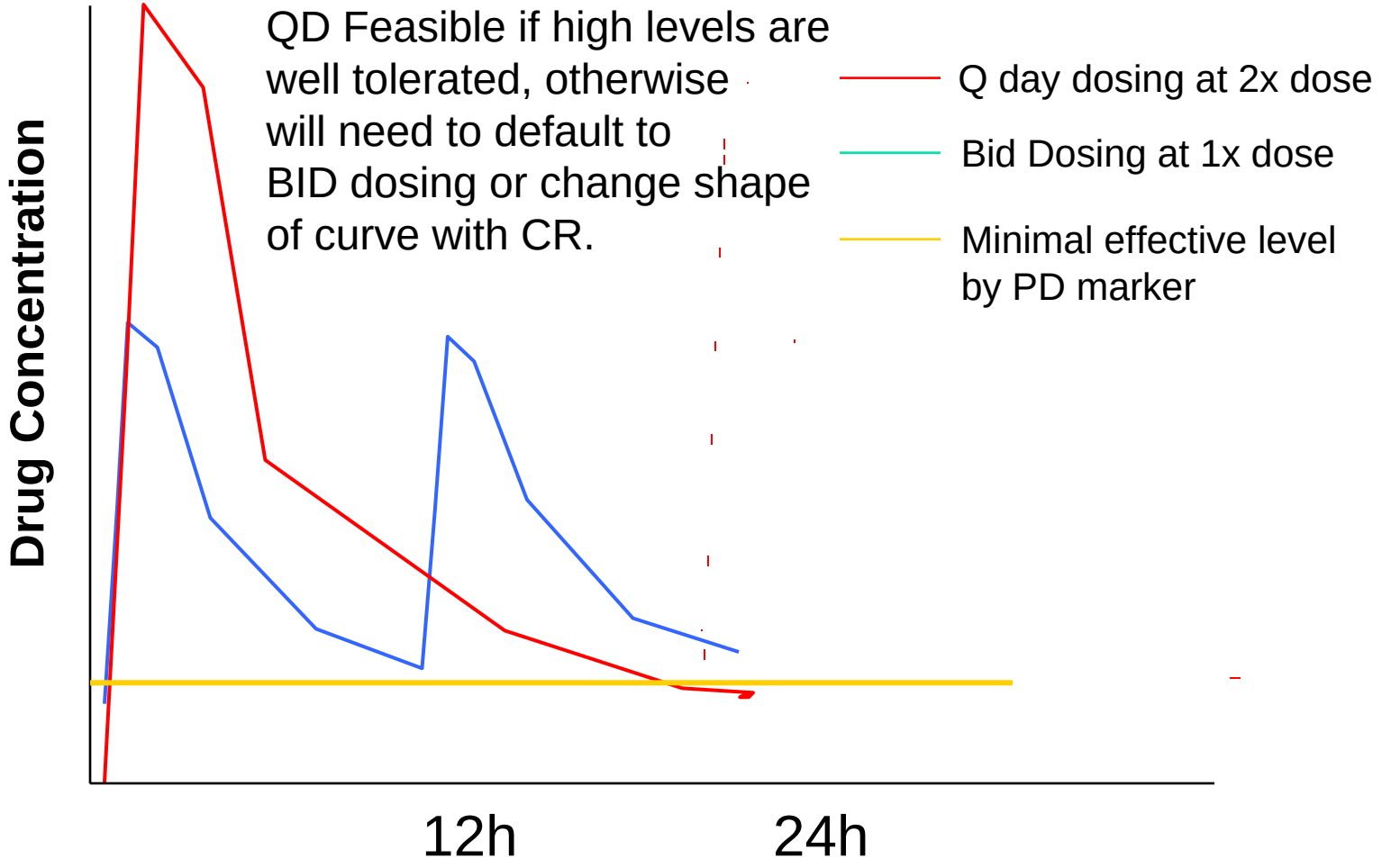
- Summary Information of the Drug
- Agreed with Regulatory Agencies
- Target Product Profile
- Competitors on Market
- Easy for Physicians to prescribe


Forward: Accumulating information
Backward: Planning Based on Label
Pre-clinical
Phase I
Phase II
Phase III
Drug Label

DETERMINING DOSING FREQUENCY

- When determining dosing frequency, the pharmacodynamics of a compound should be considered as critical as the pharmacokinetics
- In contrast to the pharmacokinetic half-life, the pharmacodynamic half-life will be dose dependent
- Will a control release formulation be needed?

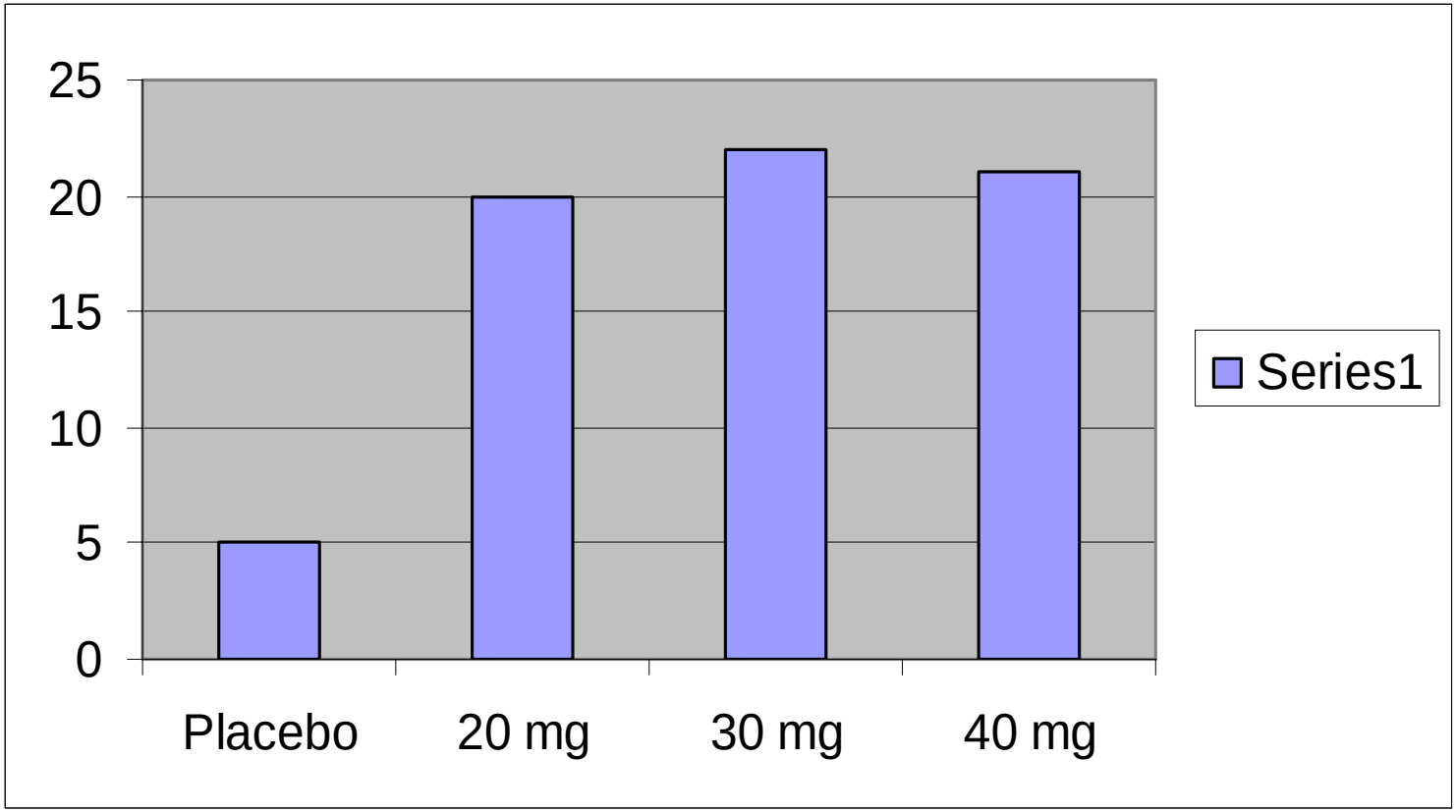
DETERMINING DOSING FREQUENCY



WHAT RANGE OF DOSES SHOULD WE CONSIDER

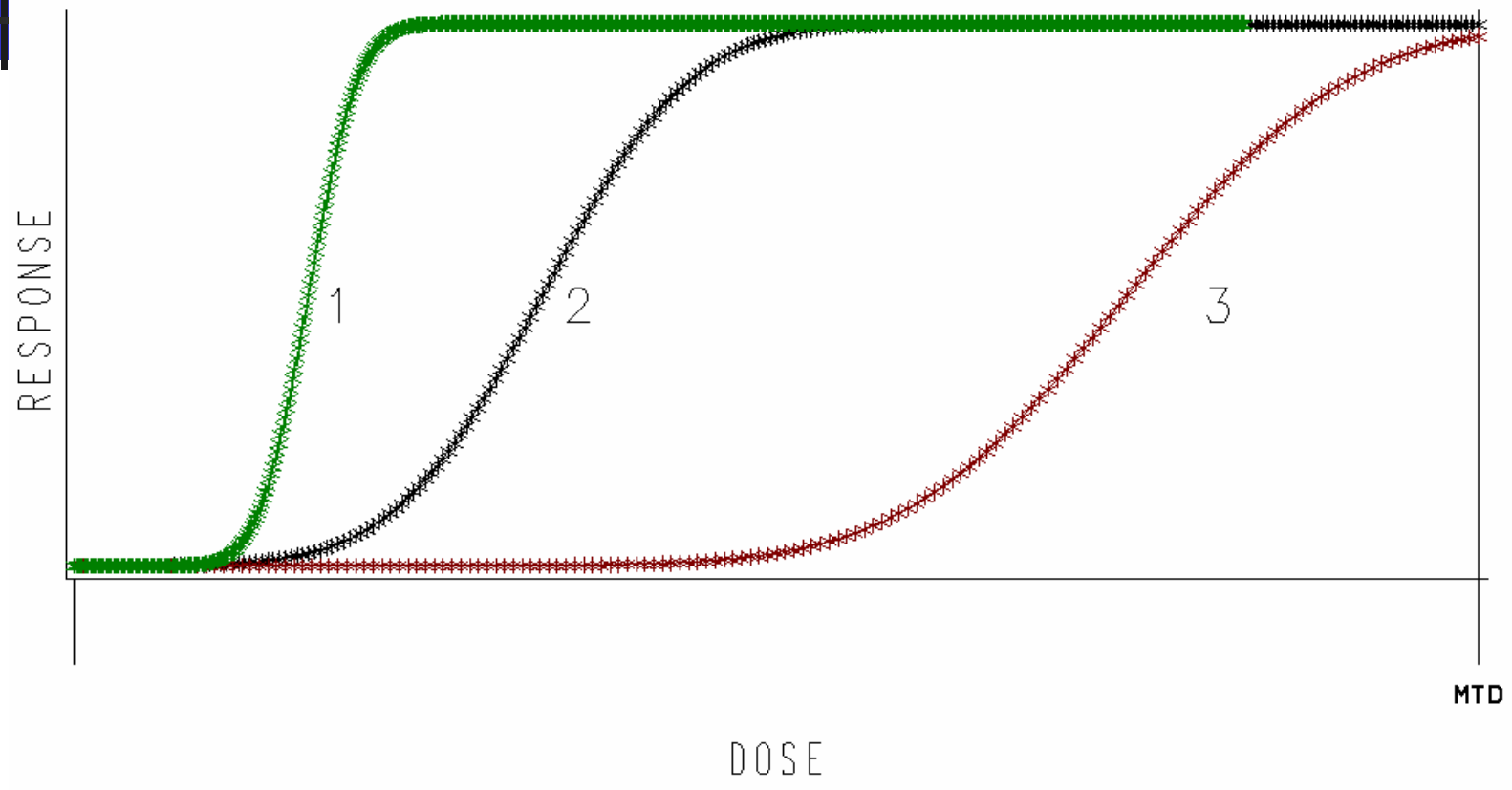
- In early Phase II, not much information available (pre-clinical, PK, MTD)
- We know 0 (Placebo), we know MTD
- Exploring an Adequate Dose Range
- Selecting Doses for Early Dose-ranging Studies

STUDY 1 - WHAT'S NEXT?



STUDY 2

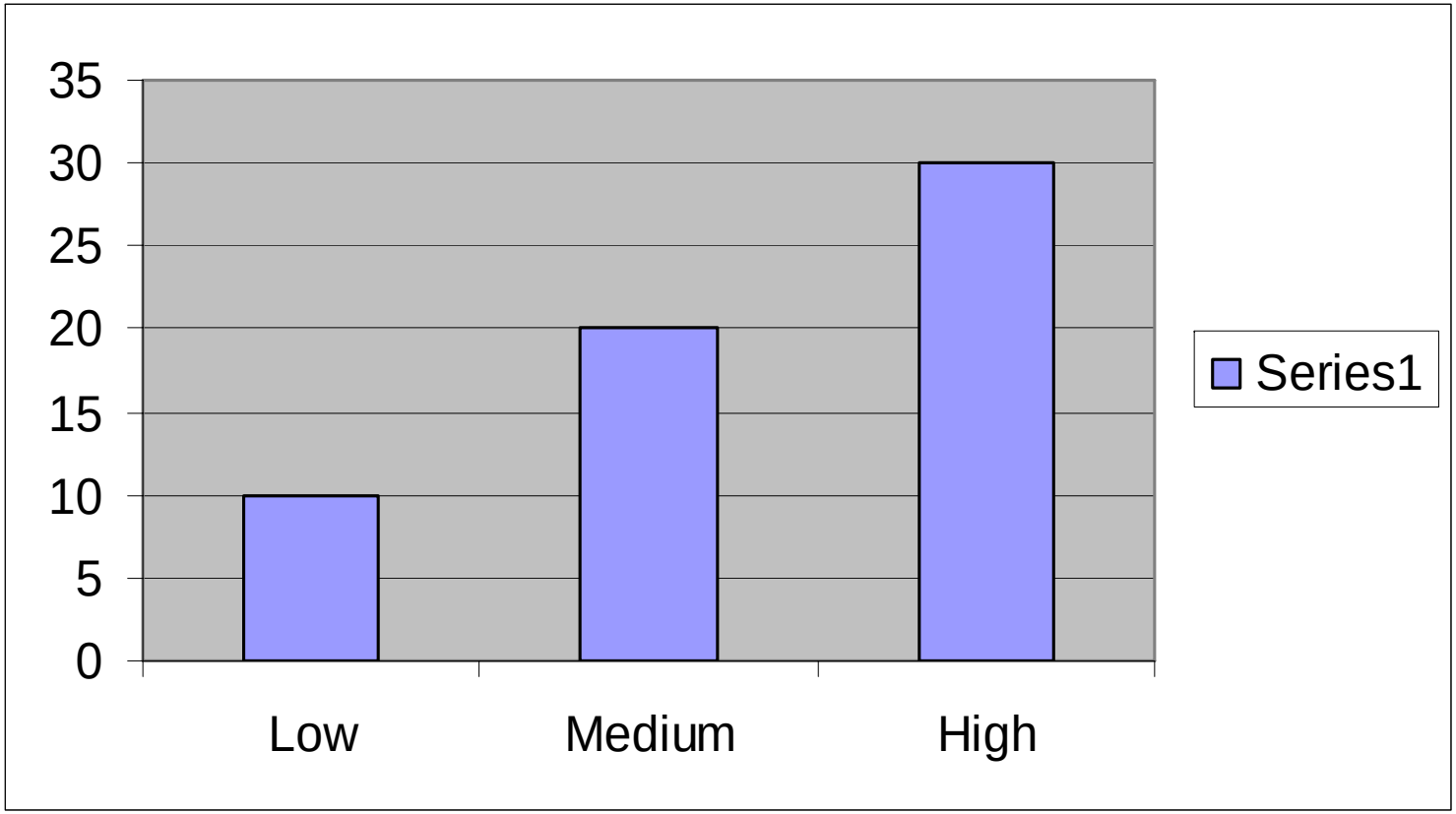
FIGURE 4 SEVERAL POSSIBLE DOSE–RESPONSE CURVES



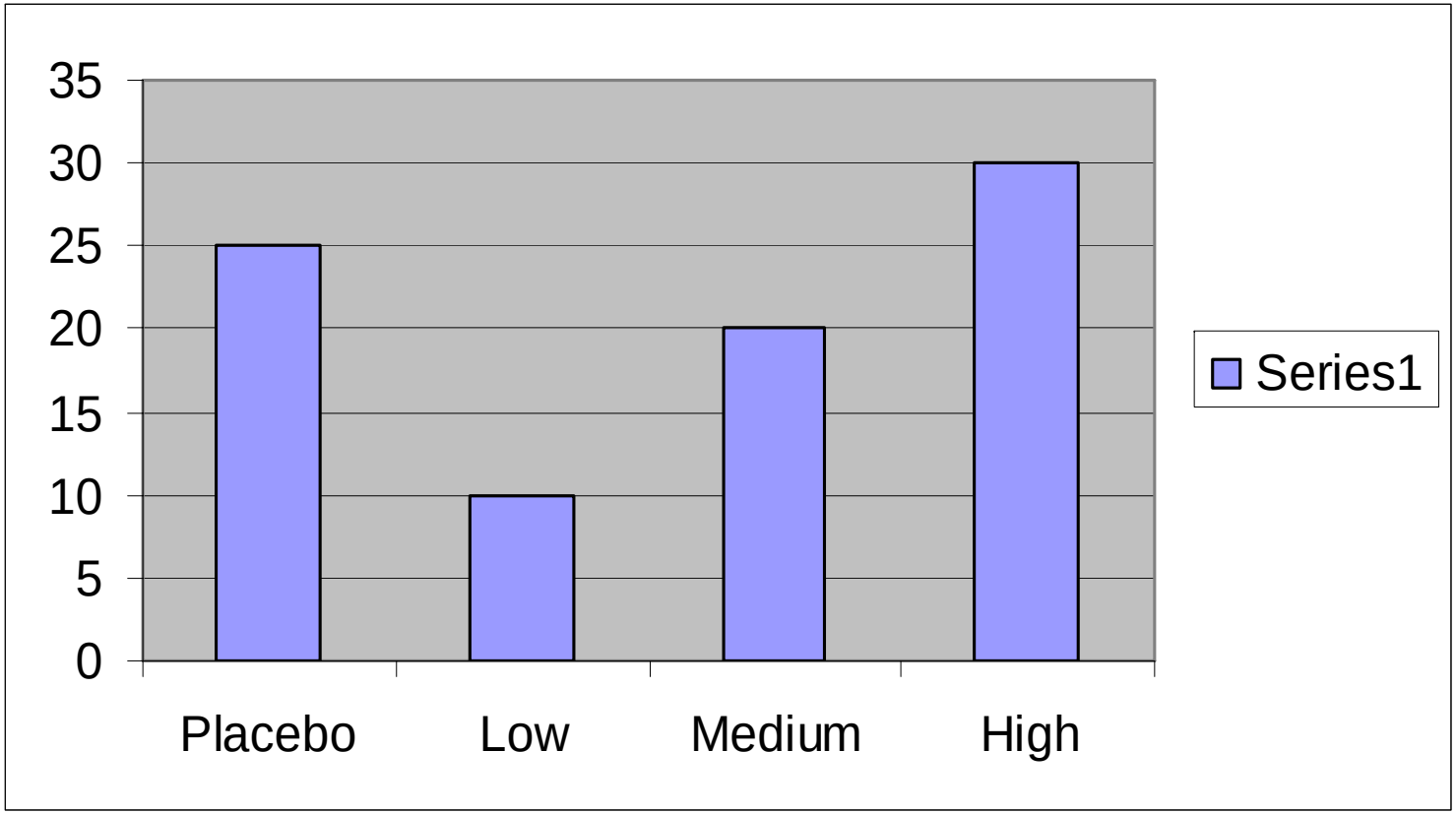
WHAT RANGE OF DOSES SHOULD WE CONSIDER

- Examine a wide dose range in early development and follow this study with a narrower dose range study
- Use pharmacological response or biological markers from animal studies and phase I studies to guide the selection in dose range for the early studies
- Although not always attainable in early studies, a goal should be to try and define the Maximally Tolerated Dose (MTD), the Maximally Effective Dose (MaxED), and the Minimum Effective Dose (MinED)

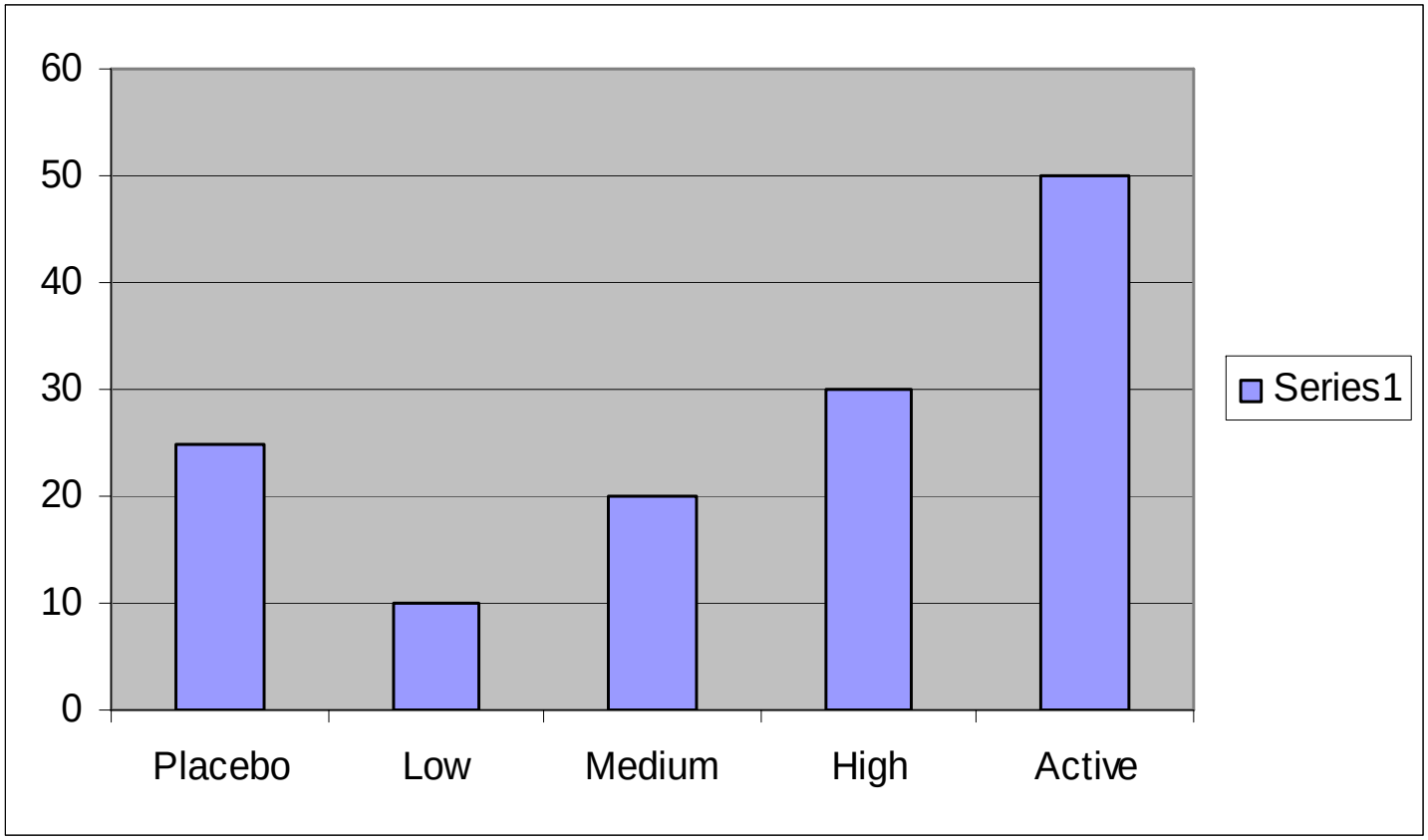
IS THERE A DOSE RESPONSE?



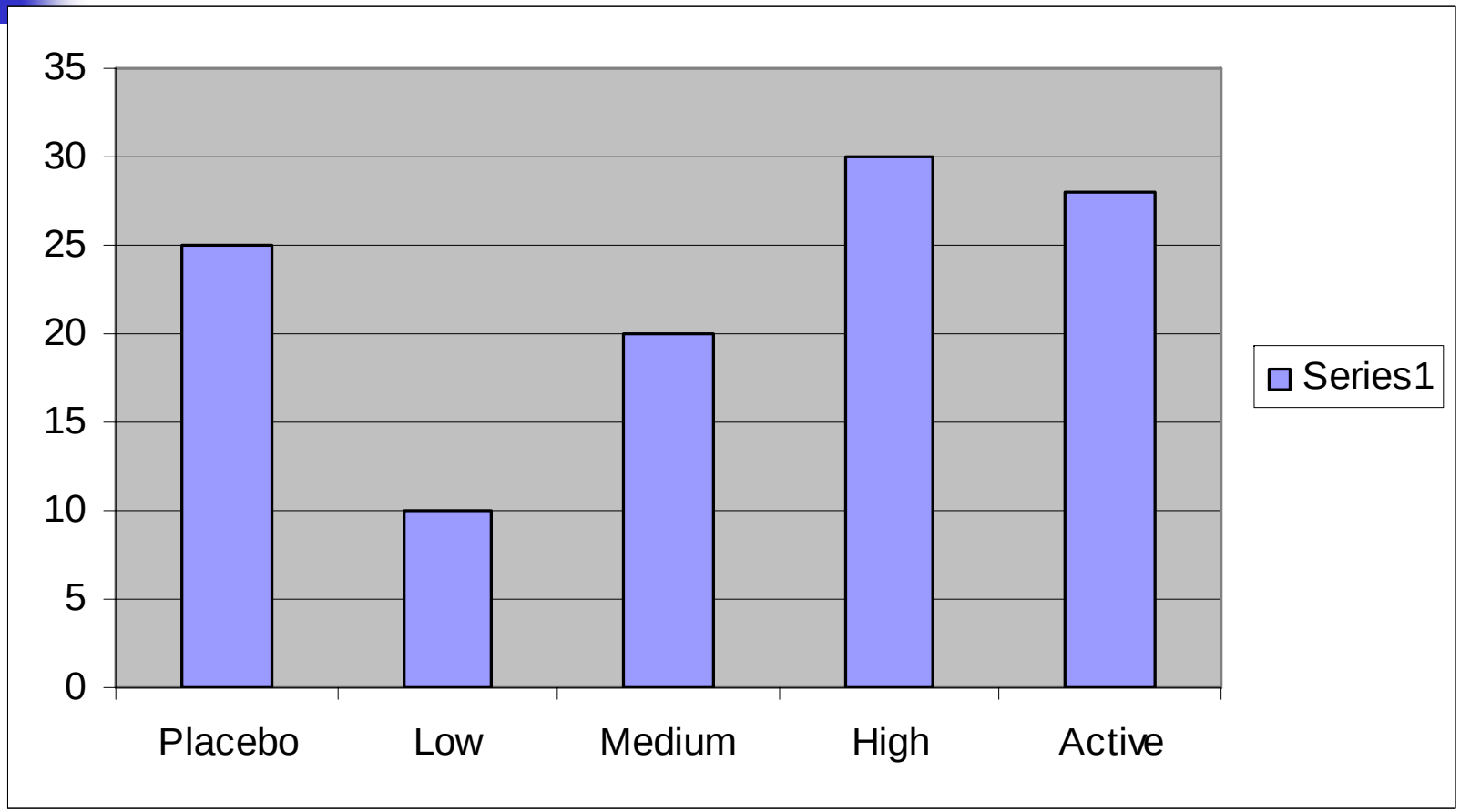
IMPORTANCE OF PLACEBO RESPONSE



ACTIVE CONTROL



ACTIVE CONTROL



ACTIVE CONTROL

- Active control is not strictly necessary
- It serves as a useful control in case the test drug “doesn’t work” or works poorly
  - Active control “worked” or not?
- An active comparator may also be critical if there is an effective competitor on the market
  - How appropriate are Phase II comparisons?
  - Statistically valid vs “looks similar”?

HOW MANY DOSES TO BE TESTED

- Can we set all possible doses to test
- Do we include control groups
- If so, which controls
- Spacing between doses

LIMITED NUMBER OF FIXED DOSES

- Multiple center designs
- Formulation considerations
- Placebo and maximally tolerable dose (MTD)
- Incorporate active control?
- Concerns in interpreting titration dose

TREATMENT BY CENTER INTERACTION

	Placebo	Low	Medium	High
Center 1	6	7	6	8
Center 2	1	1	0	1
Center 3	4	2	3	2

DOES THE DRUG WORK?

- Test hypothesis - does the drug work?
- Null hypothesis (H_0) - no difference between test drug and placebo
- Alternative hypothesis (H_a) - there is a difference

TYPES OF ERRORS

	Null True	Null False
Accept Null	OK	II
Reject Null	I	OK

If there is no true difference, but concluded there is

=> Type I error

If there is a difference, but concluded there isn't

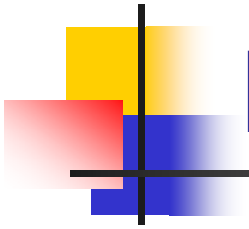
=> Type II error

TYPES OF ERRORS

- Regulatory agencies focus on the control of Type I error
- Probability of making a Type I error is not greater than α
- In general, $\alpha = 0.05$; i.e., 1 in 20
- Avoid inflation of this error
- Change method of analysis to fit data will inflate α

MULTIPLE COMPARISONS

- For 20 independent variables (clinical endpoints), one significant at random
- For 20 independent treatment comparisons, one significant at random
- For 20 small studies, one sig. At random
- Multiple comparison adjustment



MULTIPLE COMPARISONS

- Consider a dose response study with high and low dose against placebo
- 2 comparisons each dose vs placebo
- Bonferroni is to divide α by 2
- Step-down
- Special contrasts
- Fisher protected LSD

MULTIPLE COMPARISONS

- Other types of multiple comparisons
  - compare test drug with placebo and active control
- Multiple endpoints
- Subset analysis
- Various statistical methods available to handle these situations

INTERIM ANALYSIS

- Final analysis: LPV -> closed database -> break blind -> final analysis
- Any analysis before final is interim
- Objectives
  - claim efficacy
  - stop for no efficacy (for safety, ...)
  - help decision making for other studies
  - other

INTERIM ANALYSIS

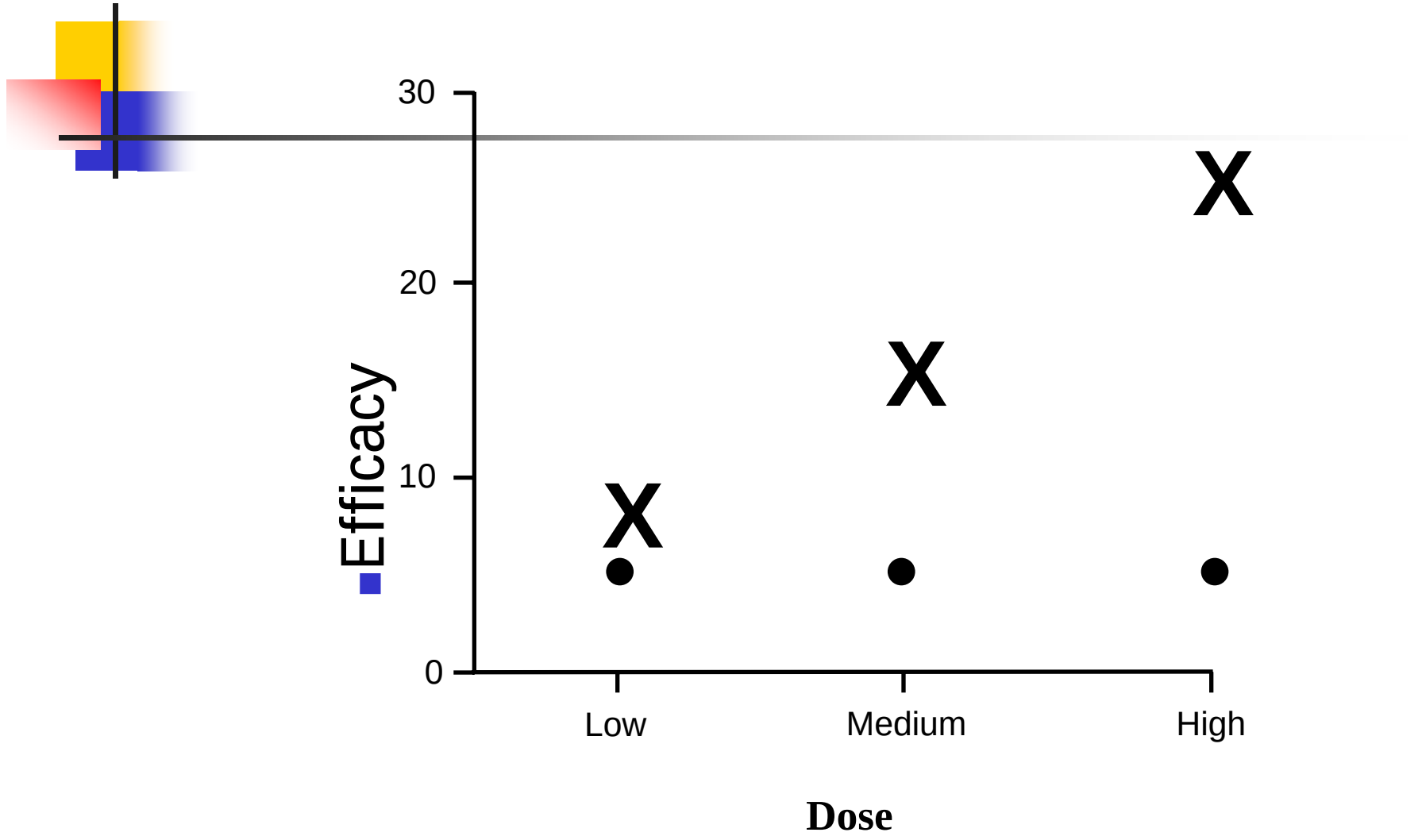
- Randomized Double-Blind study to control for bias
- Multiple look at data will inflate α
- Statistical penalty
  - inflation of α -> need adjustment
  - enough efficacy data to help decision?

CONTROL OF TYPE I ERROR

- Experiment-wise Type I error is controlled by specifying primary endpoint, primary comparison, primary time point for the primary study population
- Keep analysis method as stated in the protocol
- If interim analysis is needed, we should pre-specify, and plan for it

WHAT ARE WE MEASURING

- PD marker, clinical endpoint (hard, soft) or safety
- Efficacy can’t be observed from normal volunteer
- Early Phase or late phase
- Time after baseline (short, long)
- Multiple endpoints


30
20
10
0
Efficacy
Low
Medium
High
Dose

EXPLORATION AND CONFIRMATION

- Phase I, II, III clinical trials
- Exploratory – estimation
- Confirmatory – hypothesis testing
- Learning process

EXPLORATION AND CONFIRMATION

- Design considerations for exploratory and confirmatory are different
- Analysis method depending on objective
- For labeling, may consider the entire database to select doses