Exposure-Response Analysis
– Regulatory perspectives

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changing diabetes

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Agenda

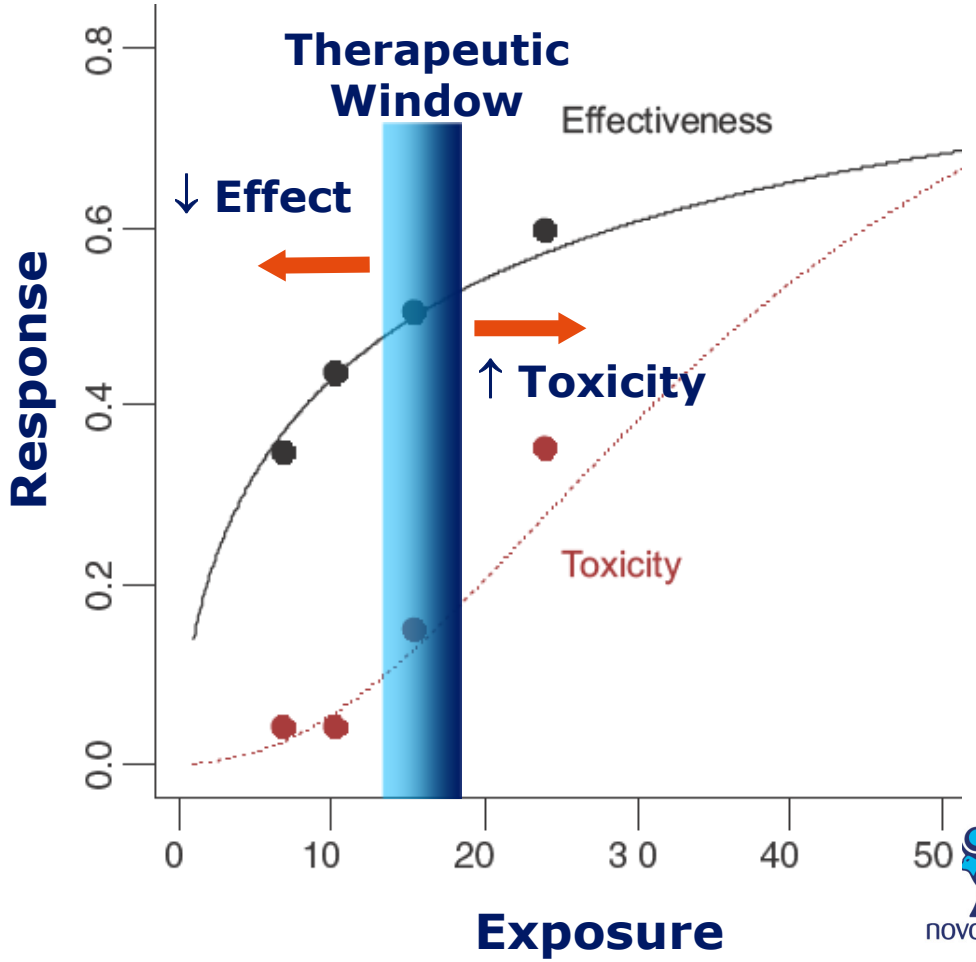
- **What does Exposure-Response Analysis Provide?**
  - Knowledge of relationship between exposure and favorable and unfavorable effects
    - Exposure: Dose, AUC, C_{max}, C_{min}, conc-time profiles
    - Response: Clinical outcome/endpoint, effects on surrogate or remote biomarker

- **What is Exposure-Response Analysis used for in Regulatory Decision-Making?**
  - Dose selection through all phases of drug development
  - Evidence of effectiveness
  - Assess impact of new formulations
  - Critical to safe & effective use of drugs (dose recommendations)
  - Dosage and administration instructions in product labeling

Rationale for Exposure-Response

- Knowledge of relationship between exposure and favourable and unfavourable effects

- Provides information about
  - Starting dose
  - Highest dose
  - Titration steps
  - Individualization
  - Dosing in special populations



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Regulatory Expectations to Exposure-Response

- 21 CFR 314.125 describes the rules for NDA refusal
  - "There is insufficient information about the drug to determine whether the **product is safe for use** under the conditions prescribed, recommended, or suggested in its proposed labeling as a **basis for refusal**"
- 21 CFR 314.126
  - Indicates that a **well-controlled dose-response study** may be one type of study that **supports efficacy**
- 21 CFR 314.50
  - Call for **integrated summaries of safety and effectiveness** that provide **evidence to support the dose** and dose interval recommended, including modifications for gender, age, and racial subgroups

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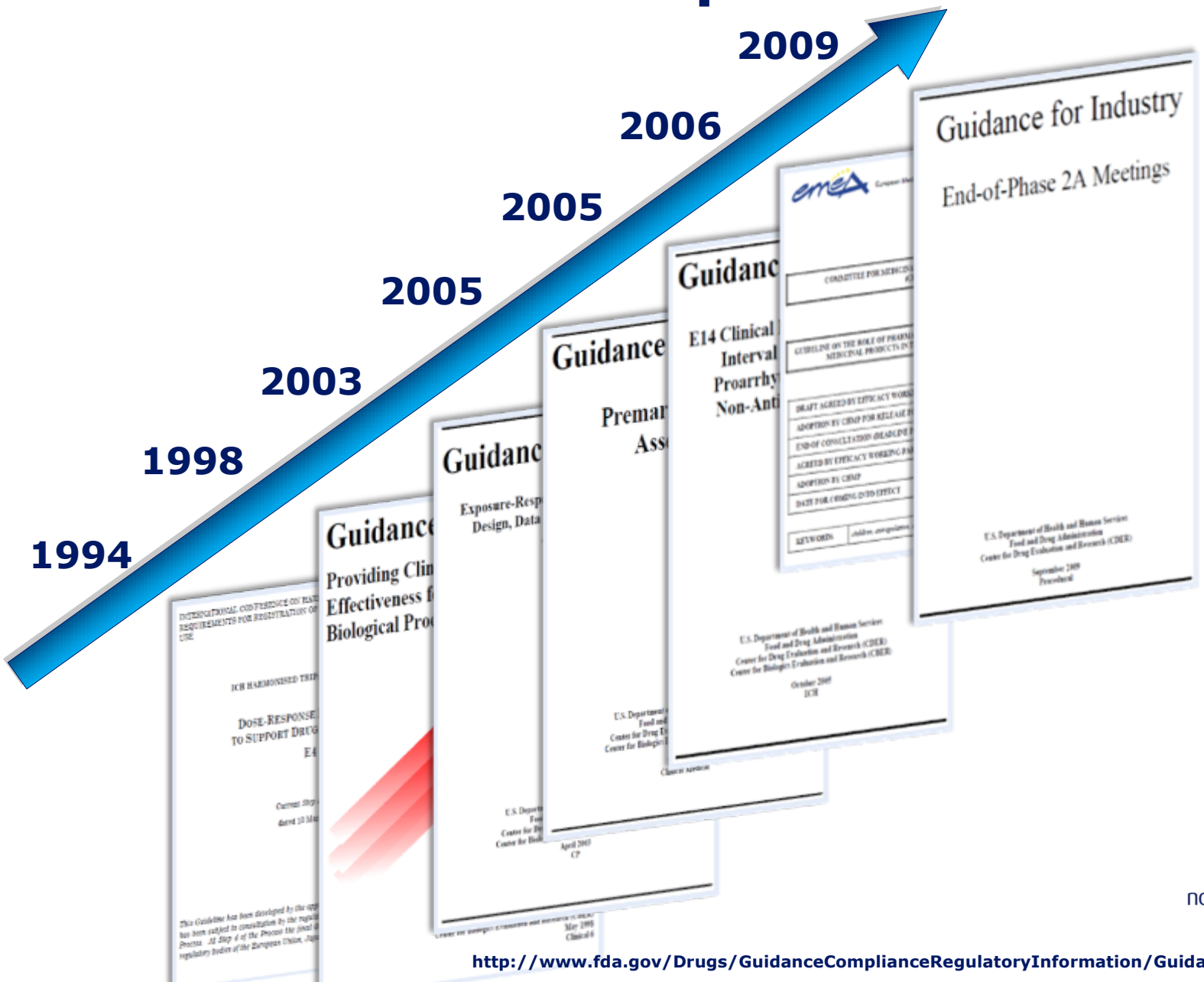
Several Guidances Emphasize the Need



http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

ICH E4 Dose-Response Guidance

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

DOSE-RESPONSE INFORMATION TO SUPPORT DRUG REGISTRATION

E4

Current Step 4 version

dated 10 March 1994

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

- Knowledge of the **relationships** among **dose, drug-concentration, and clinical response** (effectiveness and undesirable effects) is important for the **safe and effective** use of drugs in individual patients

- Information is used for:
  - Supportive evidence of effectiveness
  - Starting dose, dose adjustments
  - Prepare dosage and administration instructions in product labeling

- Ideal dose-response study should cover a range that shows a **dose with no effect** and a **dose beyond which no further effect** is seen

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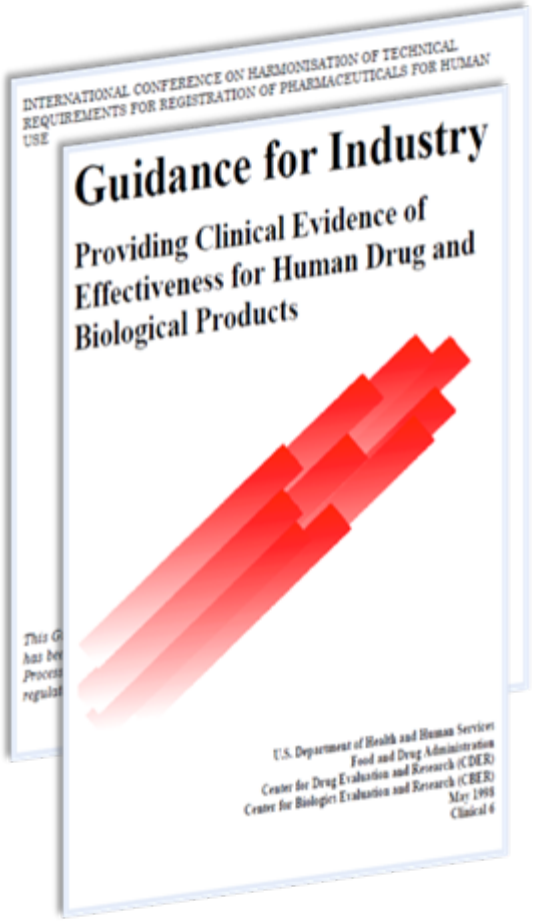
FDA Clinical Effectiveness Guidance



- Dose-response can **inform effectiveness** of doses not tested
- New dose with **similar exposure** can be concluded **effective** on the **basis of PK data alone**
- May be possible to conclude that new dose with **different exposure** is effective based on **exposure-response** relationship (and time course) **without an additional clinical efficacy trial**
- PK data, together with the well-defined PK/PD relationship, are used to **translate the controlled trial results from one dose to a new dose** (e.g. special populations)

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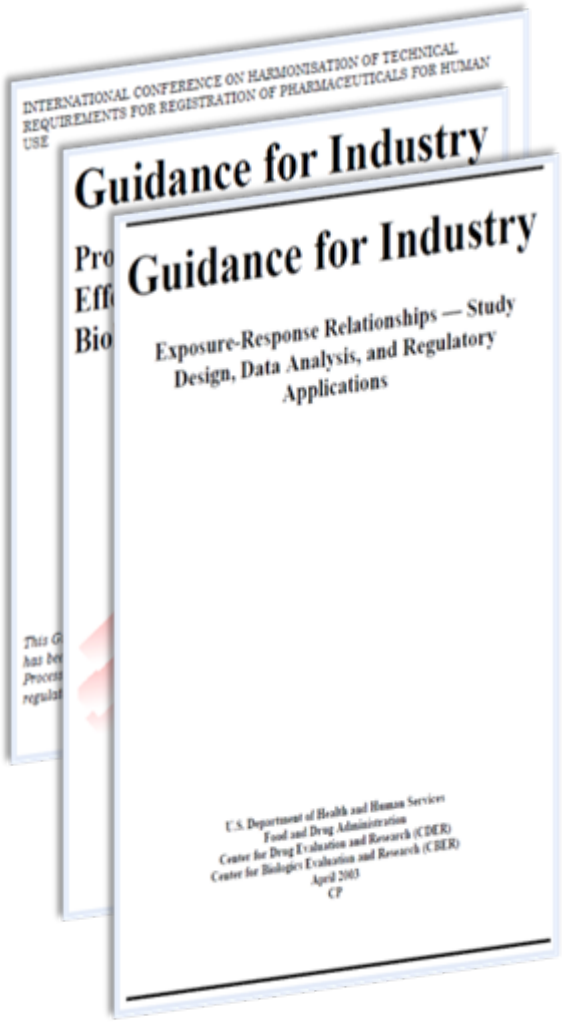
FDA Exposure-Response Guidance



- Describes the **use of exposure-response** studies in **regulatory decision-making**
- Encourages integration of assessment of exposure-response relationships into **all phases of drug development**
- Exposure-response analysis can
  - Represent a well-controlled clinical study contributing to **substantial evidence of effectiveness**
  - Add to the weight of evidence **supporting efficacy** where mechanism of action is well understood
  - **Support approval** of different doses, dosing regimens, or dosage forms, or use of a drug in different populations (e.g. pediatrics)

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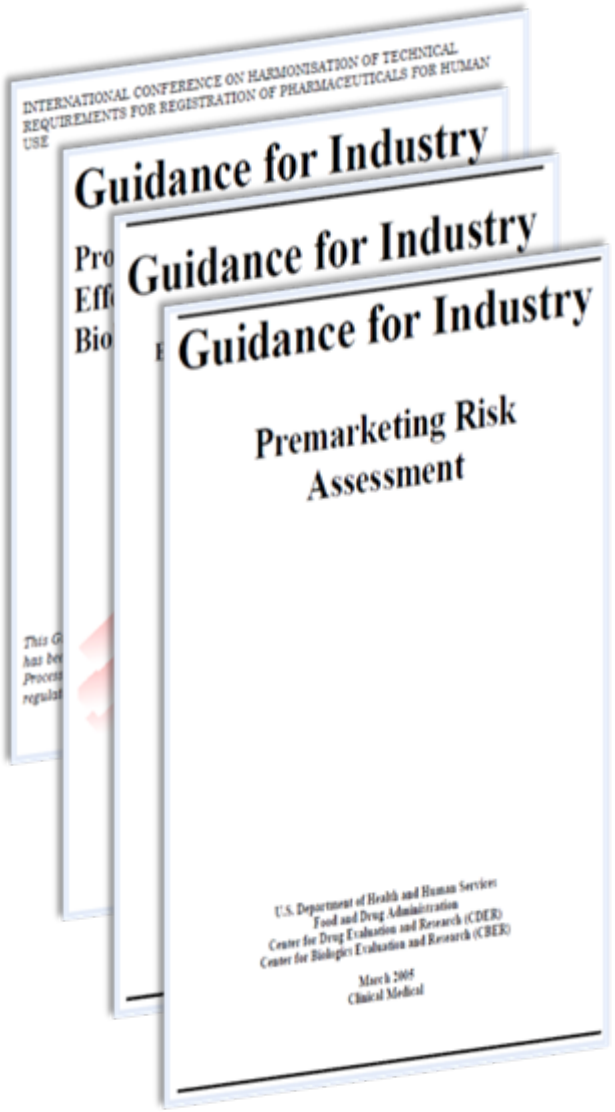
FDA Premarketing Risk Assessment Guidance



- "Although phase 3 trials do not necessarily need to examine a **range of doses**, such an examination is **highly desirable**, particularly when phase 2 studies cannot reasonably be considered to have established a single most appropriate dose"

- "When a dose is not established in phase 2, more than one dose level should be examined in phase 3 trials of fixed dose products to better **characterize the relationship between product exposure and resulting clinical benefit and risk**"

- "Dose-response data from phase 3 trials with **multiple dose levels** will help to better define the **relationship of clinical response to dose for both safety and effectiveness**"

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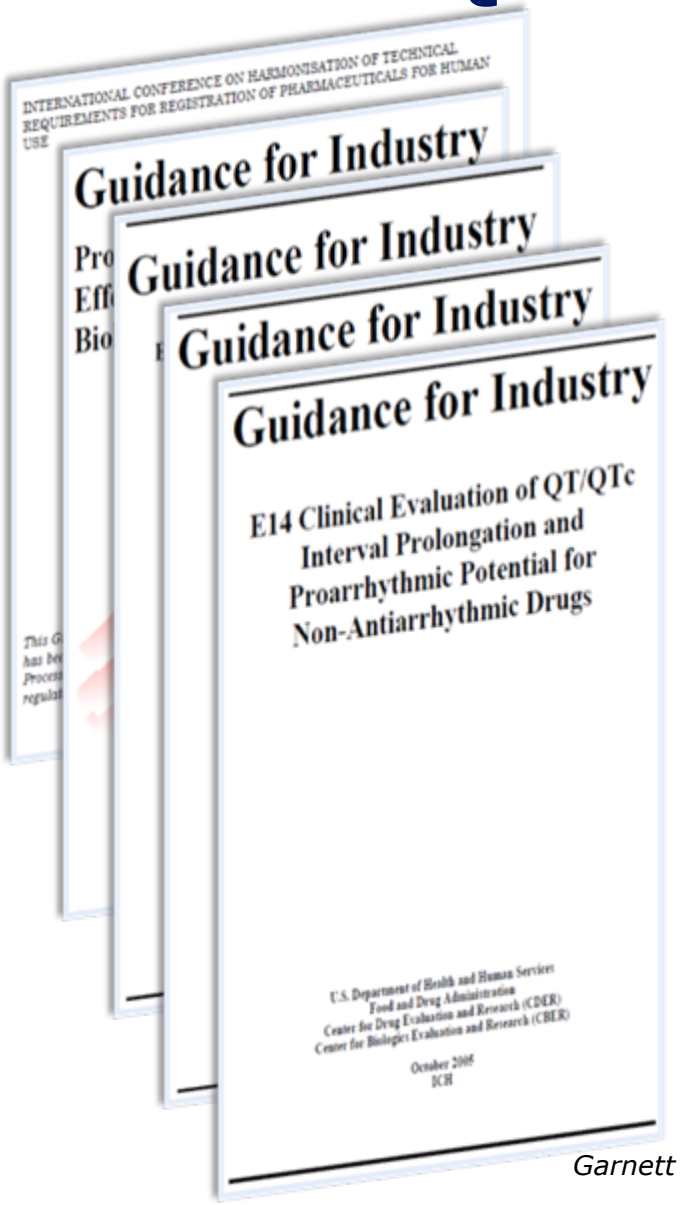
ICH E14 QT Guidance



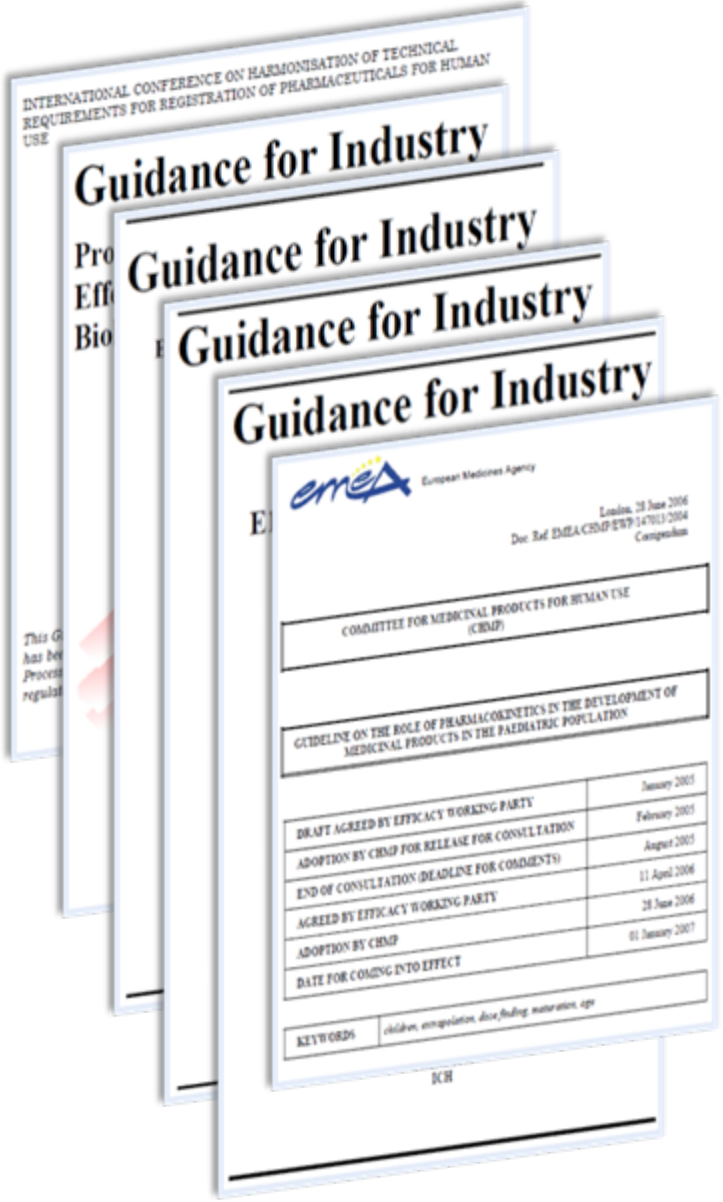
- Analysis of relationship between drug exposure and QT/QTc interval change under **near worst case clinical exposure** scenario

- **Exposure-response** analysis assists in the **planning** and **interpretation** of studies assessing cardiac repolarization

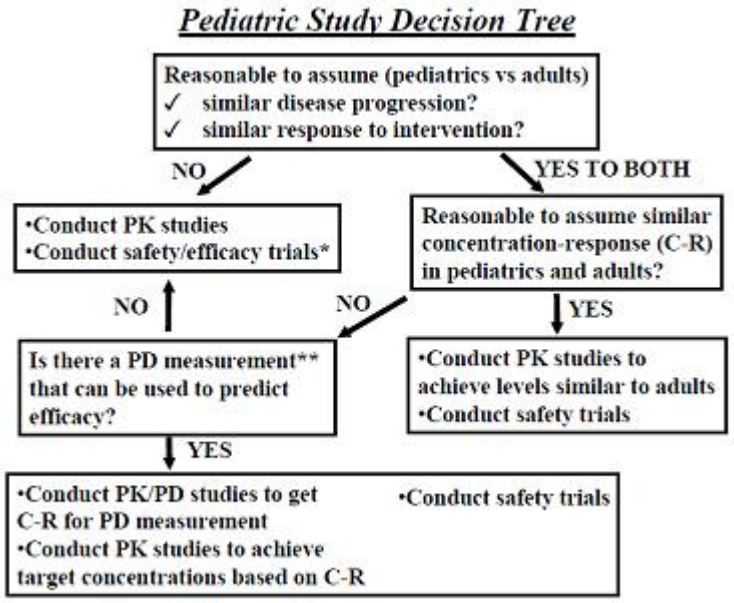
Clinical Development	Thorough QT Study	Labeling
❑ Waive TQT study for drug that prolongs QTc ❑ Assess drug effect on QTc when TQT study cannot be conducted ❑ Select doses based on Benefit-Risk assessment	❑ Support the primary endpoint (E14) ❑ Predict QTc risk at different dose levels ❑ Evaluate assay sensitivity	❑ Write informative label for drug that prolongs QTc ❑ Adjust doses for drug-interactions, special populations, poor CYP metabolizers

Garnett et al., Concentration-QT Relationship Play a Key Role in the Evaluation of Proarrhythmic Risk During Regulatory Review, JCP 48:13-18 (2008)

EMA Pediatrics Guideline



- "If similar exposure in adult and paediatric patients can be assumed to produce similar efficacy, **PK data alone** can be used to extrapolate efficacy"
- "If a similar relationship between concentration and clinical efficacy cannot be assumed **paediatric PK/PD** (biomarker) data can be used to extrapolate efficacy"



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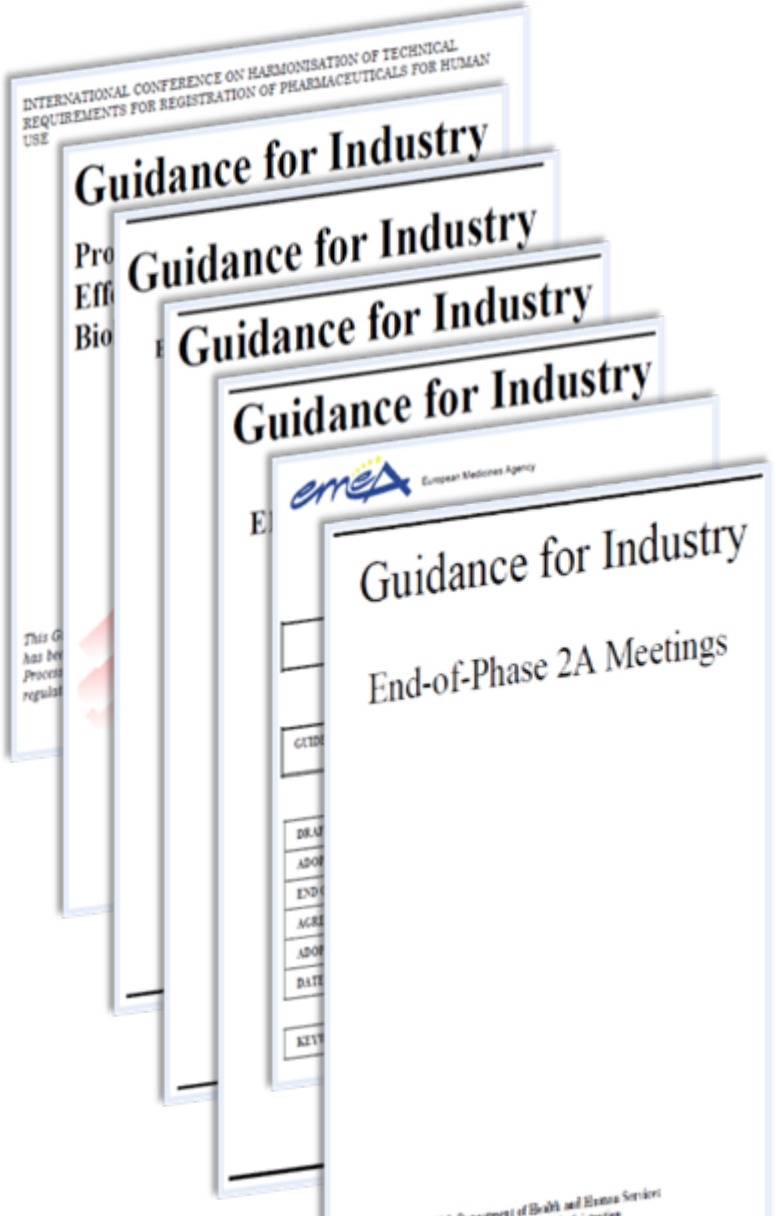
FDA EOP2A Meeting Guidance



- The overall purpose of an EOP2A meeting is to discuss options for **trial designs**, **modeling strategies**, and clinical trial simulation scenarios to improve the **quantification of the exposure-response information** from early drug development.
- The goal of these meetings is to **optimize dose selection** for subsequent trials to improve the efficiency of drug development.
- The **exposure-response data** discussed might be pertinent to evaluation of **efficacy outcomes** or **adverse outcomes**.

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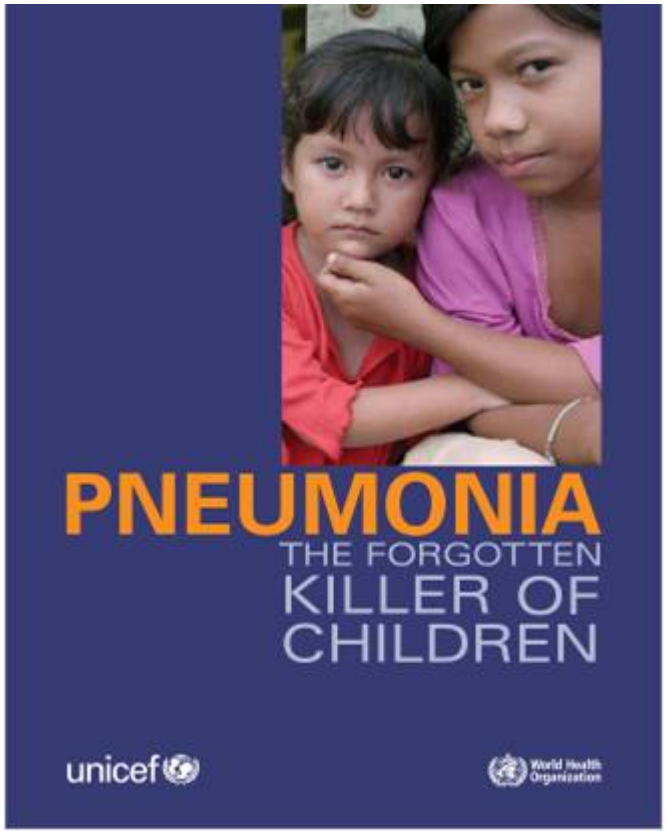
Case Studies

1. AC Meeting on Community-Acquired Pneumonia
2. AC Meeting on Rivaroxaban for VTE prophylaxis
3. Argatroban Injection in pediatrics

Case Study 1

FDA Advisory Committee on Community-Acquired Pneumonia



http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4343b1-01-FDA.pdf
http://www.fda.gov/ohrms/dockets/ac/08/slides/2008-4343s1-01-FDA-corepresentation.ppt

Background

- Community-acquired pneumonia (CAP) is a leading cause of morbidity and mortality in the world
- Recent FDA effort to justify the non-inferiority margins used in active control studies of antibacterial products
- Particular problem for diseases such as CAP where antibacterial use became the standard of care long before careful placebo-controlled or dose-response studies became accepted practice during drug development

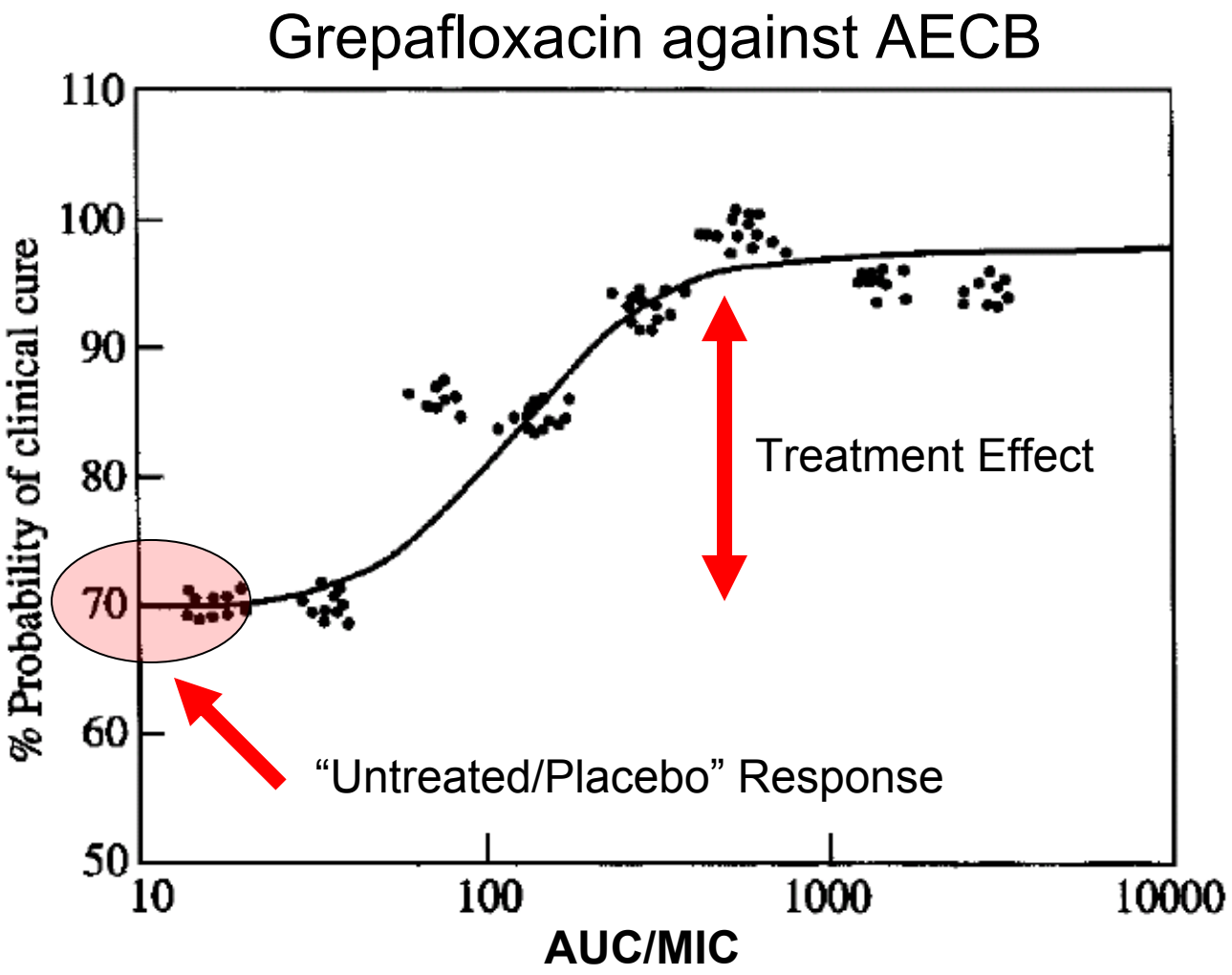
Key Question

Can exposure-response analysis contribute to the discussion of a non-inferiority margin for studies of Community-Acquired Pneumonia (CAP)?

a) What is the exposure-response derived treatment effect against *Streptococcus pneumoniae* in patients with mild-moderate CAP?

b) Can exposure-response analysis support the choice of non-inferiority margin in CAP trials?

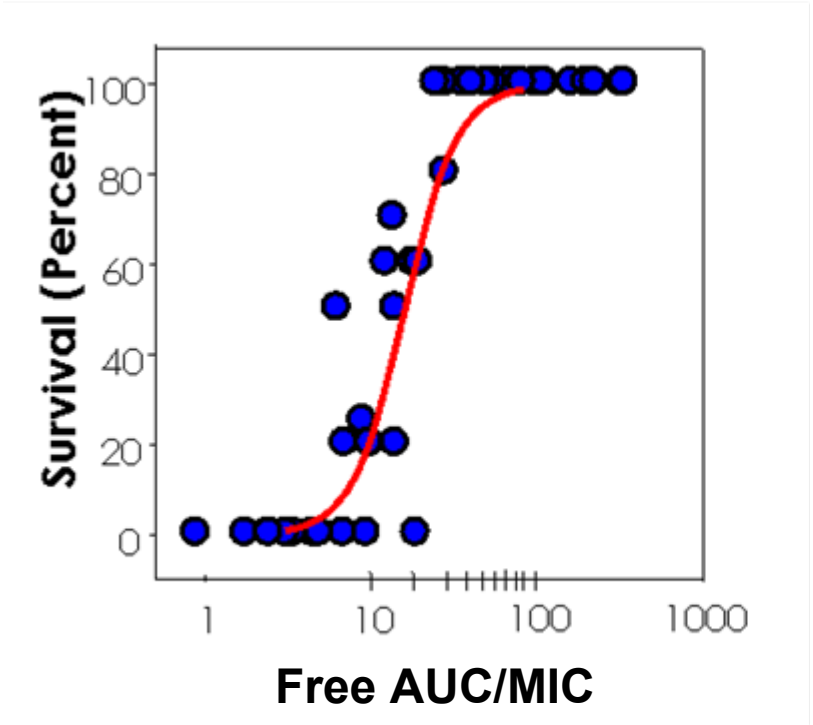
Y-intercept as "Placebo" Response Estimate

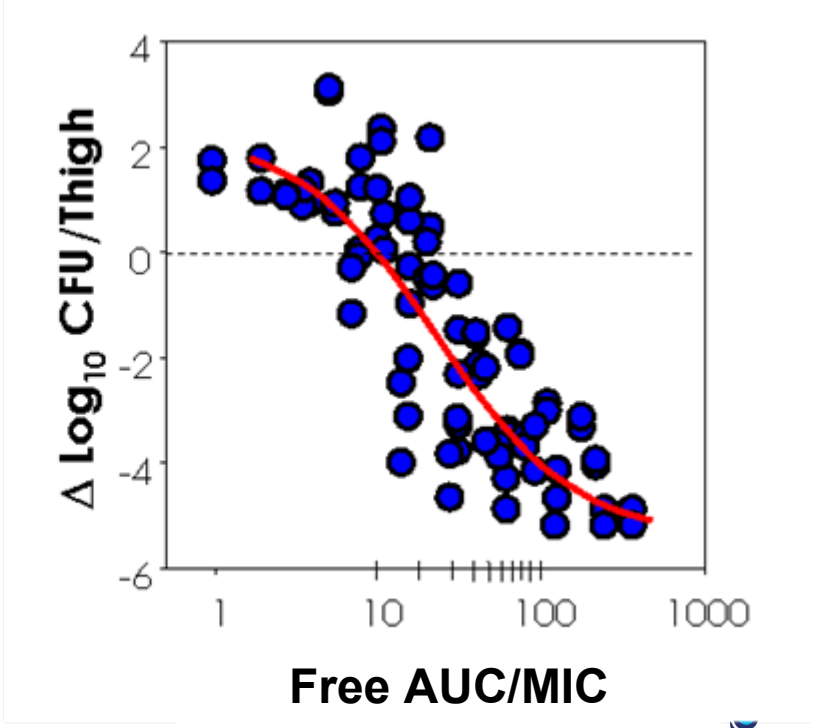


Forrest A et al. Pharmacokinetics and pharmacodynamics of oral grepafloxacin in patients with acute bacterial exacerbations of chronic bronchitis. J Antimicrob Chemother. 1997;40 Suppl A:45-57.

Pre-clinical Information Supports Approach

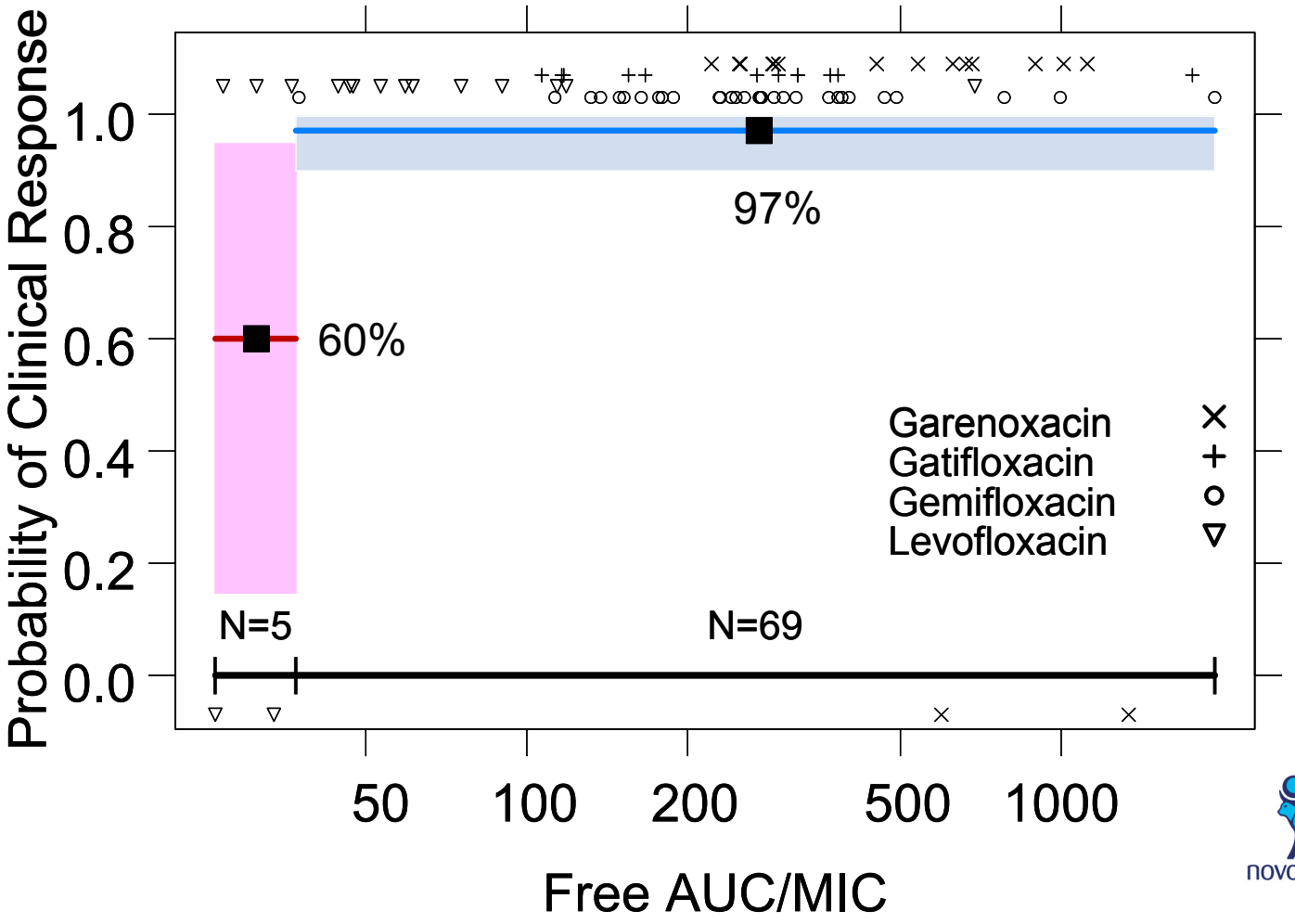
Ciprofloxacin, gatifloxacin, gemifloxacin, levofloxacin, moxifloxacin, and sitafloxacin





Craig WA, Andes DR. Correlation of the Magnitude of the AUC_{24}/MIC for 6 Fluoroquinolones against *Streptococcus pneumoniae* with survival and bactericidal activity in an animal model. In Abstracts of the 40th ICAAC, Toronto, Canada, Sept. 17-20, 2000. Abs-289.

Estimated Treatment Effect of 37% (95%CI -6;80%) for Fluoroquinolones in CAP against *S. Pneumoniae*



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Key Questions (Revisited)

- What is the exposure-response derived treatment effect against *Streptococcus pneumoniae* in patients with mild-moderate CAP?
  - 37% (95%CI -6;80%)

- Can exposure-response analysis support the choice of non-inferiority margin in CAP trials?
  - Very likely, but more data (with low free AUC/MIC ratios) are needed to precisely quantify the treatment effect

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Case Study 2

NDA 22406 Rivaroxaban, VTE Prophylaxis

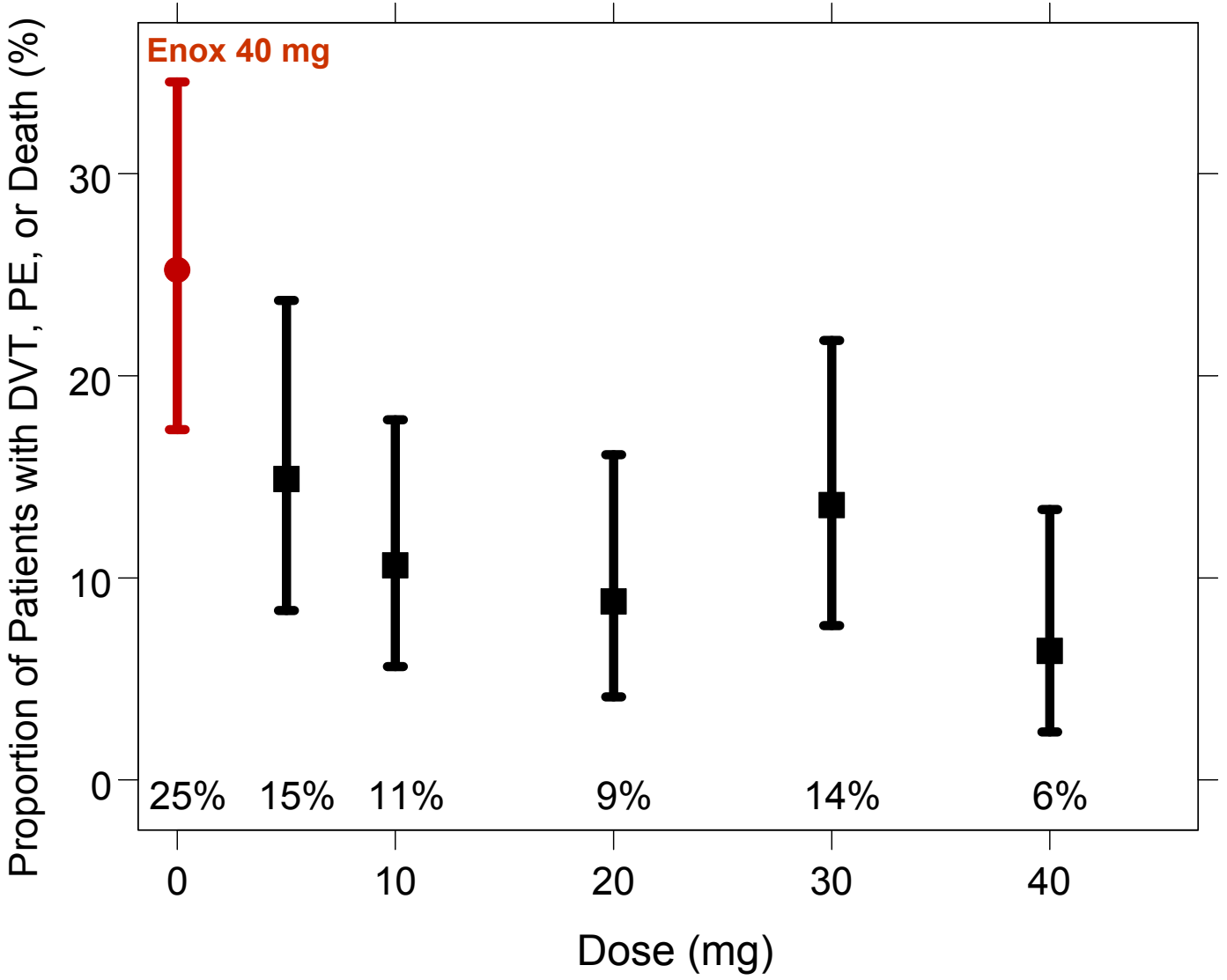
Special populations

FDA AC meeting: http://www.fda.gov/ohrms/dockets/ac/09/slides/2009-4418s1-06-FDA-Tornoe.pdf

Key Questions

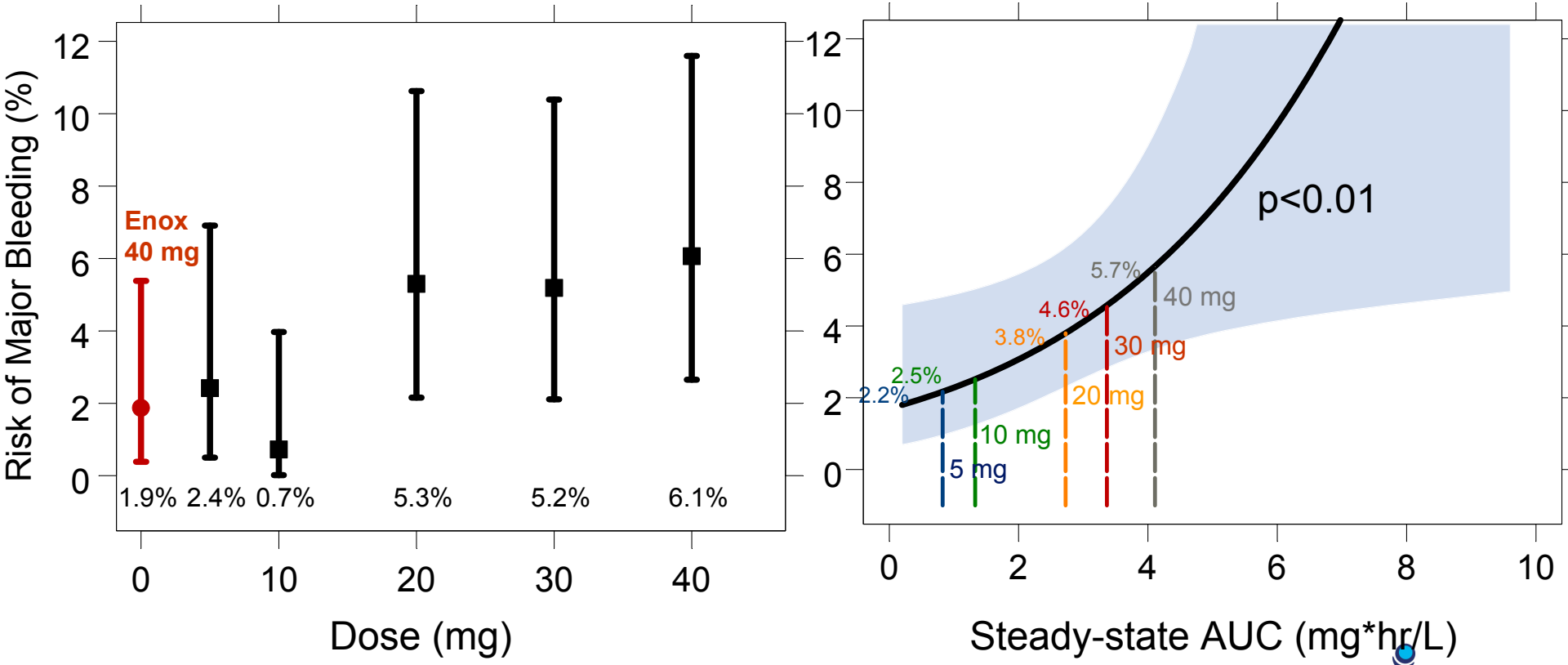
- **Is there Evidence of Dose/Exposure-Response for Effectiveness and Safety?**
  - Shallow dose-response for composite efficacy endpoint
  - The risk of major bleeding increases with increasing rivaroxaban dose/exposure
- **Which Special Populations are at Risk for Clinically Relevant Increases in Exposure?**
  - Moderate-severe hepatic patients
  - Concomitant use of strong CYP3A4/P-gp inhibitors
  - Mild-moderate renal impairment + moderate CYP3A4/P-gp inhibitors
- **What are the Strategies to Address Increased Exposure Risk of Bleeding in Special Populations?**
  - Lower dose is the best option and help larger patient population to receive this treatment

Shallow Dose-Response Relationship for Composite Efficacy Endpoint



*The error bars represent the 95% confidence interval of the mean proportions

Increasing Risk of Major Bleeding with Increasing Dose and Exposure



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Key Questions

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- **What are the Strategies to Address Increased Exposure Risk of Bleeding in Special Populations?**
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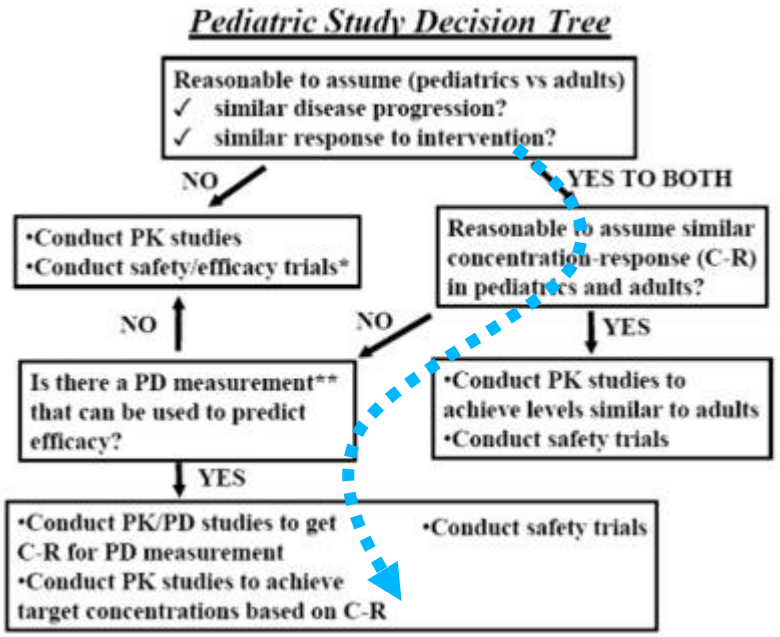
Case Study 3

Argatroban Injection in pediatrics (birth to 16 yrs)



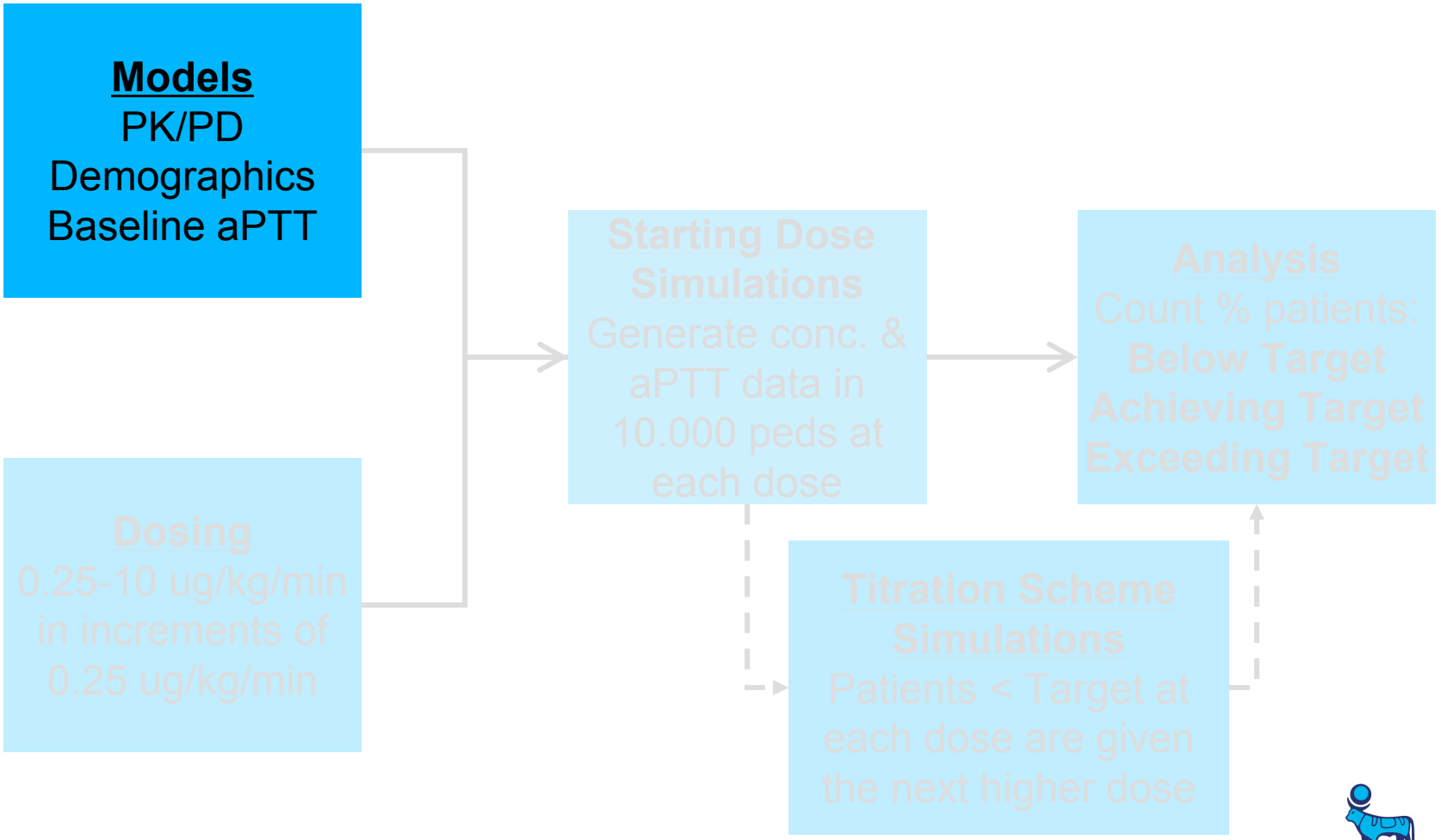
Match PD

http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm071734.pdf
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM193136.pdf

Argatroban (Anti-coagulant)

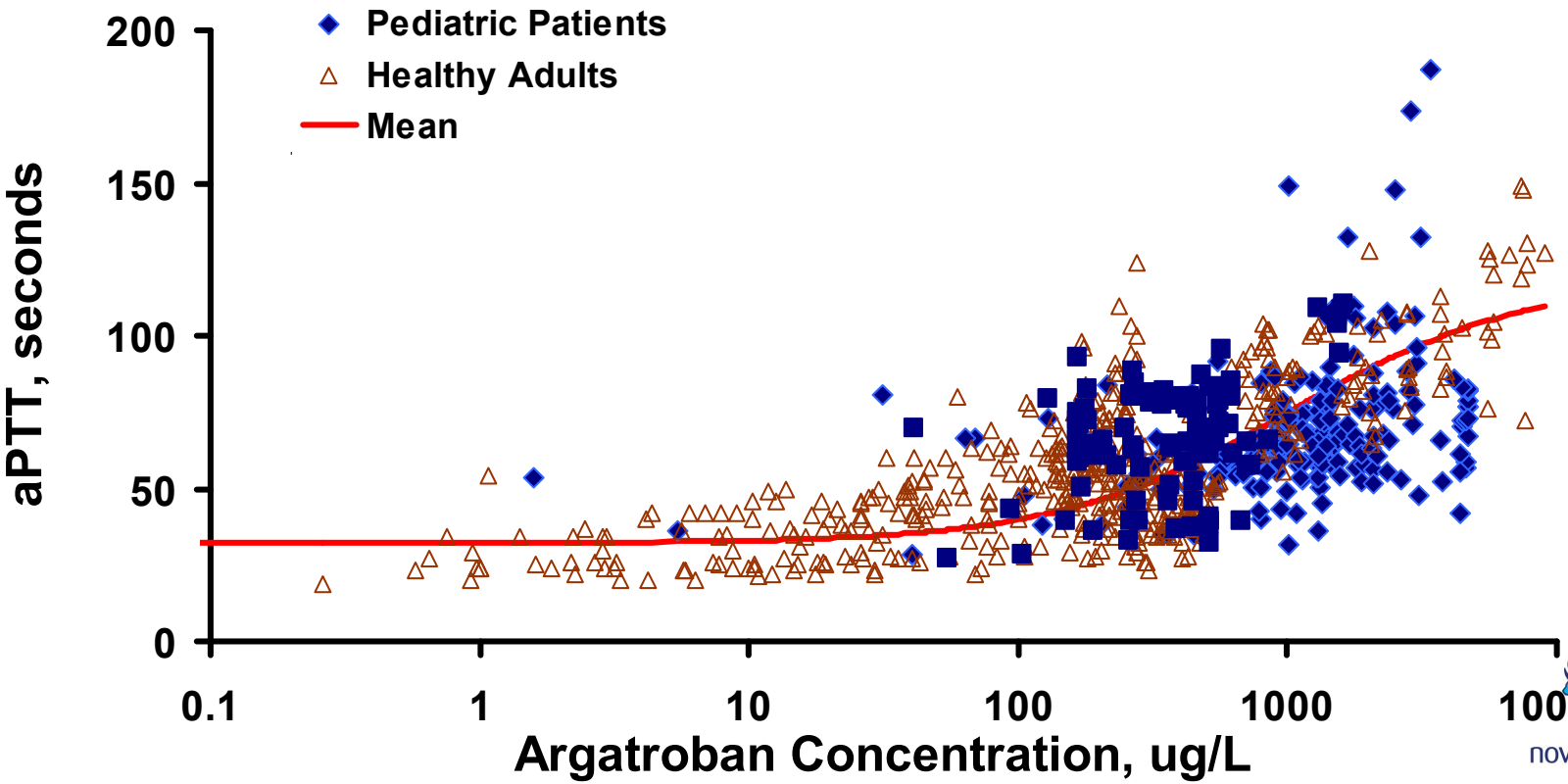
- Indications
  - Heparin-induced thrombocytopenia (HIT)
- Adult dosing
  - Start and Max dose: 2 ug/kg/min and 10 ug/kg/min
  - Titrated to 1.5 – 3 times baseline aPTT
- Pediatric dosing
  - Use concentration – aPTT relationship and PK model to explore competing dosing schemes

1. Establish PK/PD Relationship



1. Establish PK/PD Relationship

Concentration-aPTT relationship is similar between adults (healthy) and pediatrics (patients)



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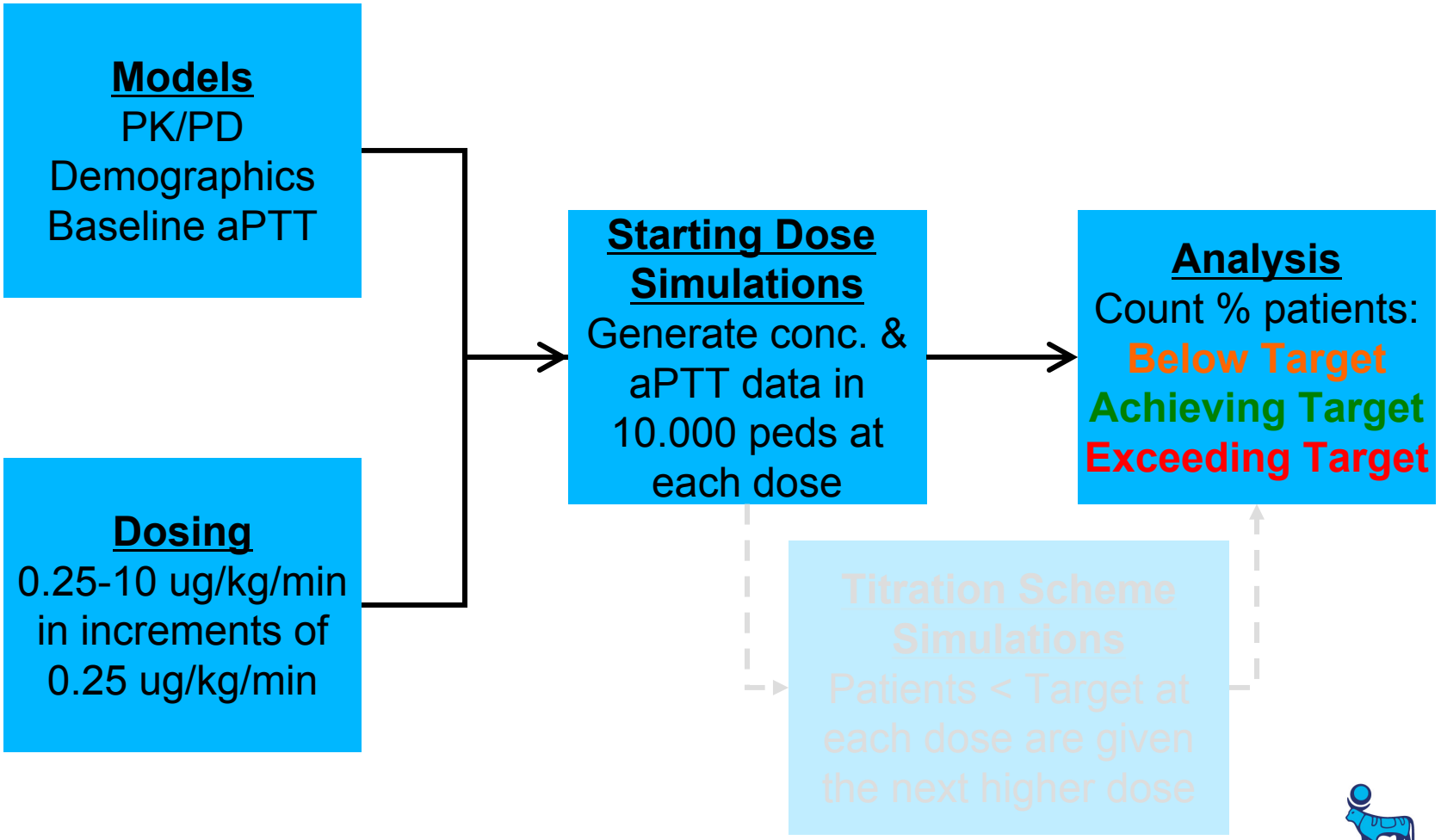
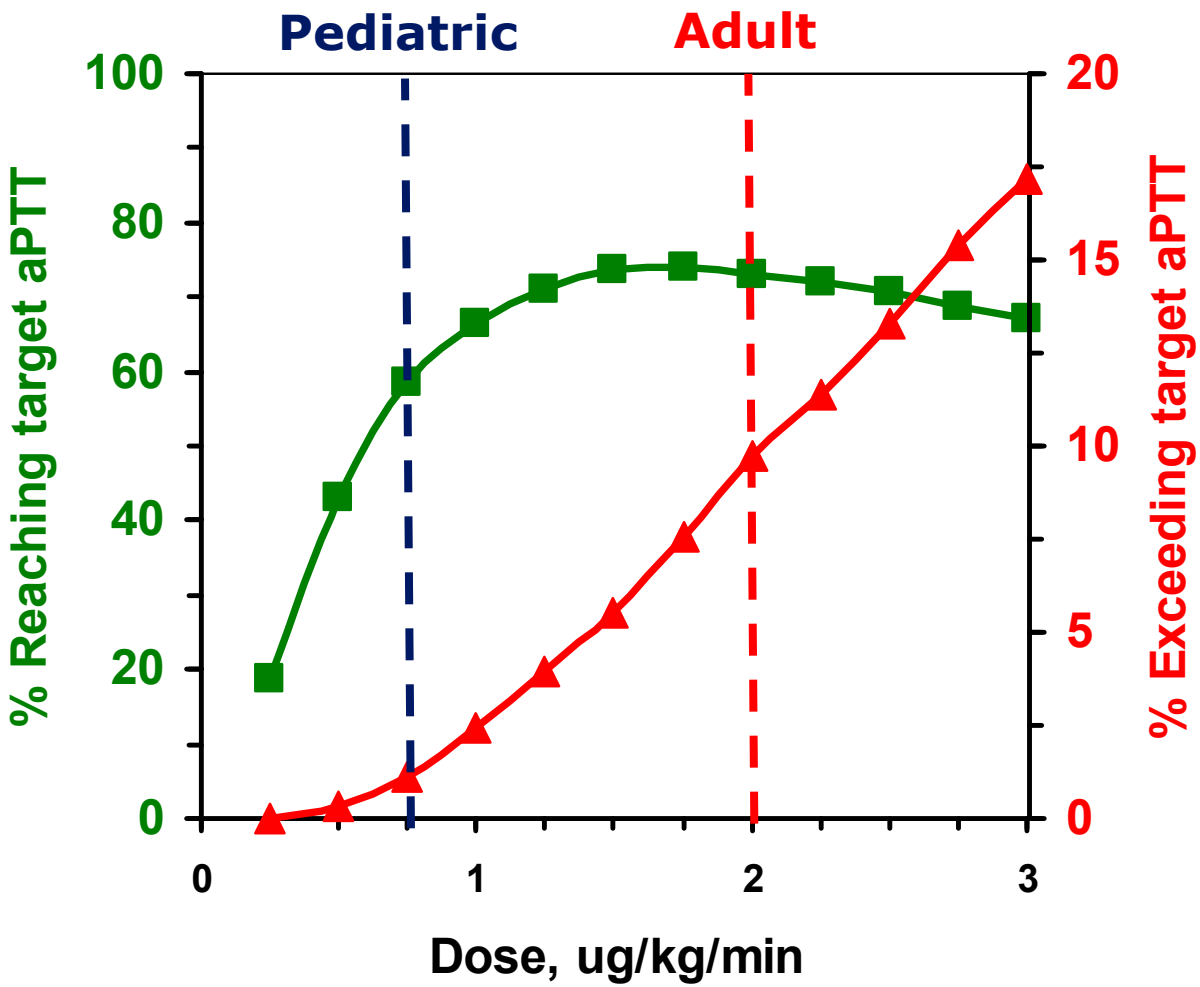
2. Explore Optimal Pediatric Starting Dose



Target: 1.5-3 times baseline aPTT and < 100 seconds.

2. Explore Optimal Pediatric Starting Dose

Adult Starting Dose of 2 ug/kg/min is Too High for Pediatrics



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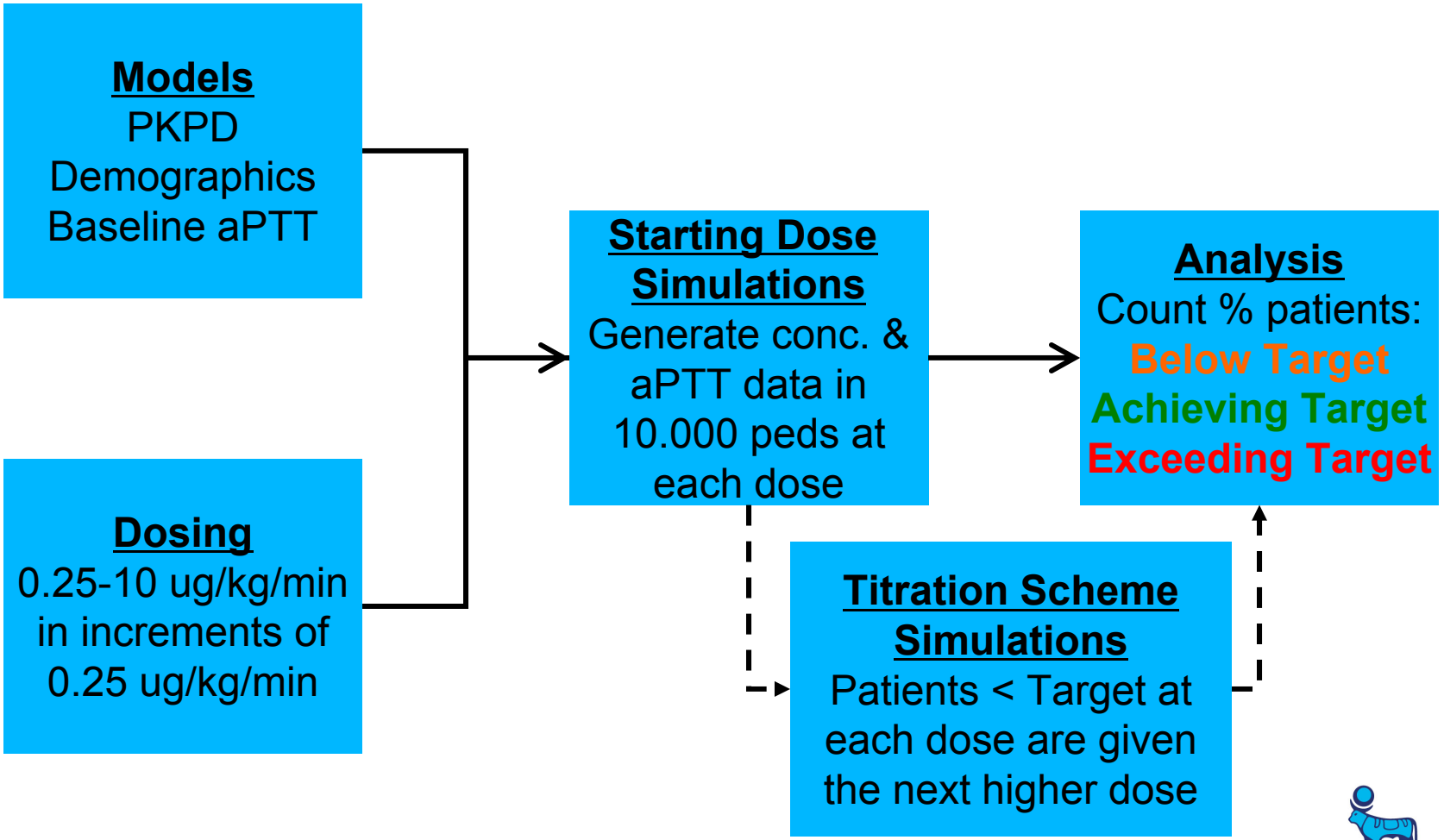
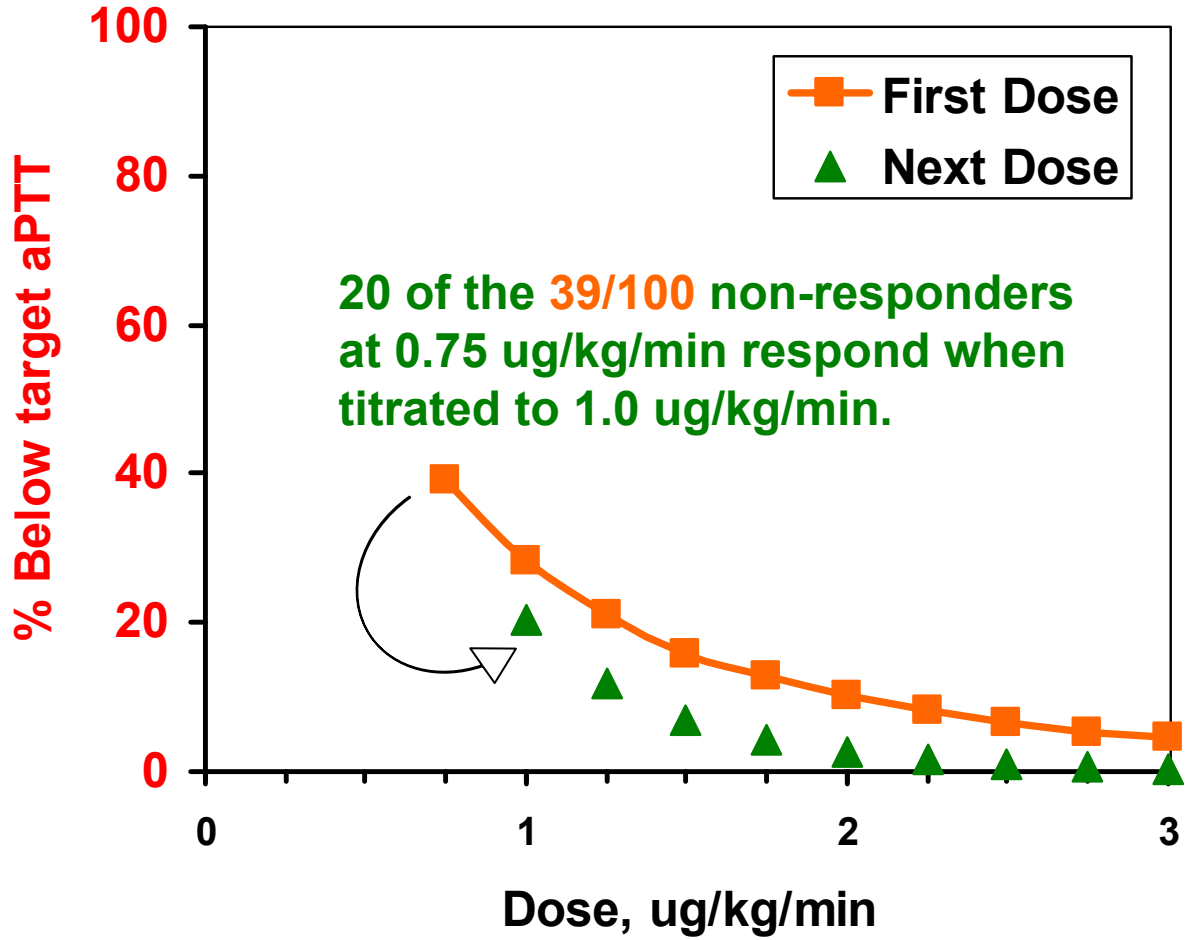
3. Select Incremental Pediatric Dose



Target: 1.5-3 times baseline aPTT and < 100 seconds.

3. Select Incremental Pediatric Dose

0.25 ug/kg/min with no additional anti-coagulation beyond 3 ug/kg/min (compared to 10 ug/kg/min for adults)



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Summary

- **What does Exposure-Response Analysis Provide?**
  - Knowledge of relationship between exposure and favorable and unfavorable effects
    - Exposure: Dose, AUC, C_{max}, C_{min}, conc-time profiles
    - Response: Clinical outcome/endpoint, effects on surrogate or remote biomarker

- **What is Exposure-Response Analysis used for in Regulatory Decision-Making?**
  - Dose selection through all phases of drug development
  - Evidence of effectiveness
  - Assess impact of new formulations
  - Critical to safe & effective use of drugs (dose recommendations)
  - Dosage and administration instructions in product labeling

Take Home Messages

- Little regulation on exposure-response but clear guidance and long history
- Exposure-response information is needed for dosing recommendations but selection is complex
- Exposure-response is the strongest form of evidence of effectiveness
- Totality of evidence is used to write informative product labelling

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