Exposure-Response Analysis
– Regulatory perspectives

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Agenda

• What does Exposure-Response Analysis Provide?
  • Knowledge of relationship between exposure and favorable and unfavorable effects
    • Exposure: Dose, AUC, $C_{\text{max}}$, $C_{\text{min}}$, 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

![Diagram showing therapeutic window, exposure-response relationship, and toxicity]

Therapeutic Window
Effect
Toxicity
Exposure
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
Several Guidances Emphasize the Need

ICH E4 Dose-Response Guidance

- 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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Slide no 6
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)
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)
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”
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

<table>
<thead>
<tr>
<th>Clinical Development</th>
<th>Thorough QT Study</th>
<th>Labeling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waive TQT study for drug that prolongs QTc</td>
<td>Support the primary endpoint (E14)</td>
<td>Write informative label for drug that prolongs QTc</td>
</tr>
<tr>
<td>Assess drug effect on QTc when TQT study cannot be conducted</td>
<td>Predict QTc risk at different dose levels</td>
<td>Adjust doses for drug-interactions, special populations, poor CYP metabolizers</td>
</tr>
<tr>
<td>Select doses based on Benefit-Risk assessment</td>
<td>Evaluate assay sensitivity</td>
<td></td>
</tr>
</tbody>
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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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**Pediatric Study Decision Tree**

1. **Reasonable to assume (pediatrics vs adults)**
   - **similar disease progression**?
   - **similar response to intervention**?

   - **NO**
     - Conduct PK studies
     - Conduct safety/efficacy trials

   - **YES TO BOTH**

2. **Reasonable to assume similar concentration-response (C-R)** in pediatrics and adults?

   - **YES**
     - Conduct PK studies to achieve levels similar to adults
     - Conduct safety trials

   - **NO**
     - Conduct PK/PD studies to get C-R for PD measurement
     - Conduct PK studies to achieve target concentrations based on C-R

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*PD measurement** that can be used to predict efficacy?
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**.
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/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

Pre-clinical Information Supports Approach

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

Estimated Treatment Effect of 37% (95%CI -6;80%) for Fluoroquinolones in CAP against *S. Pneumoniae*
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
Case Study 2

NDA 22406 Rivaroxaban, VTE Prophylaxis

Special populations

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

Dose (mg)

Proportion of Patients with DVT, PE, or Death (%)

25% 15% 11% 9% 14% 6%

0 10 20 30 40

*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

- **Is there Evidence of Dose/Exposure-Response for Effectiveness and Safety?**
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Case Study 3

Argatroban Injection in pediatrics (birth to 16 yrs)

Match PD

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

**Models**
- PK/PD
- Demographics
- Baseline aPTT

**Dosing**
- 0.25-10 ug/kg/min in increments of 0.25 ug/kg/min

**Starting Dose Simulations**
- Generate conc. & aPTT data in 10,000 peds at each dose

**Titration Scheme Simulations**
- Patients < Target at each dose are given the next higher dose

**Analysis**
- Count % patients: Below Target, Achieving Target, Exceeding Target
1. Establish PK/PD Relationship
Concentration-aPTT relationship is similar between adults (healthy) and pediatrics (patients)
2. Explore Optimal Pediatric Starting Dose

**Models**
PK/PD
Demographics
Baseline aPTT

**Dosing**
0.25-10 ug/kg/min in increments of 0.25 ug/kg/min

**Starting Dose Simulations**
Generate conc. & aPTT data in 10,000 peds at each dose

**Analysis**
Count % patients:
Below Target
Achieving Target
Exceeding Target

**Titration Scheme Simulations**
Patients < Target at each dose are given the next higher 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

- Pediatric
- Adult

% Reaching target aPTT vs. Dose, ug/kg/min

% Exceeding target aPTT vs. Dose, ug/kg/min

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3. Select Incremental Pediatric Dose

**Models**
PKPD
Demographics
Baseline aPTT

**Dosing**
0.25-10 ug/kg/min
in increments of 0.25 ug/kg/min

**Starting Dose Simulations**
Generate conc. & aPTT data in 10,000 peds at each dose

**Titration Scheme Simulations**
Patients < Target at each dose are given the next higher dose

**Analysis**
Count % patients:
- Below Target
- Achieving Target
- Exceeding Target

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)

20 of the 39/100 non-responders at 0.75 ug/kg/min respond when titrated to 1.0 ug/kg/min.
Summary

• **What does Exposure-Response Analysis Provide?**
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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