Modeling & simulation in pediatric drug development and regulation

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Today

- Learn-confirm and model-based drug development - *applied to pediatrics*

- Example - Enbrel / pediatric juvenile RA
“Learn-Confirm”

Efficient scientific drug development:

- **Learn** (early): mechanistic (causal) understanding of dose-exposure-response relationships
  - Clinical pharmacology intensive
- **Confirm**: mechanism, therapeutic concept, safety & effectiveness

• **Purpose:**
  - **Inform Decisions**: provides product knowledge essential for commercial success and regulatory approval
Practice of the Learn-Confirm’ Paradigm*

• Learn-Confirm Cycles
  • POM: Proof of Mechanism (drug hits target biological effect)
  • POC: Proof of (therapeutic) Concept (biomarker or clinical effect)
  • D-E-R: Dose - Exposure - Response
  • Effectiveness / Safety (phase 3)

• Drug development data are created to inform and test mechanistic (causal) hypotheses or models - “model-based”

• Models and knowledge are extracted from data using “Pharmacometric analysis”

• Learning’s are used to inform key decisions

* Sheiner LB. Clin Pharmacol Ther 1997
Model-based drug development

An integrative framework for design, analysis & interpretation of drug development data

- **Model**: integration of dose-exposure-response knowledge in a mathematical, statistical form
  - Disease progress (untreated with new drug)
  - Dose-exposure-response
  - Pharmacokinetic - Pharmacodynamics

- **Pharmacometric**: advanced pharmaco-statistical analysis

- **Inform**:
  - Product specifications
  - Subsequent investigations
  - Key go/no-go (investment) decisions
  - Regulatory decisions
Impact of Pharmacometrics on Drug Approval and Labeling Decisions: A Survey of 42 New Drug Applications

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The value of quantitative thinking in drug development and regulatory review is increasingly being appreciated. Modeling and simulation of data pertaining to pharmacokinetic, pharmacodynamic, and disease progression is often referred to as the pharmacometrics analyses. The objective of the current report is to assess the role of pharmacometrics at the US Food and Drug Administration (FDA) in making drug approval and labeling decisions. The New Drug Applications (NDAs) submitted between 2000 and 2004 to the Cardio-renal, Oncology, and Neuropharmacology drug products divisions were surveyed. For those NDA reviews that included a pharmacometrics consultation, the clinical pharmacology scientists ranked the impact on the regulatory decision(s). Of about a total of 244 NDAs, 42 included a pharmacometrics component. Review of NDAs involved independent, quantitative evaluation by FDA pharmacometricians, even when such analysis was not conducted by the sponsor. Pharmacometric analyses were pivotal in regulatory decision making in more than half of the 42 NDAs. Of the 14 reviews that were pivotal to approval related decisions, 6 identified the need for additional trials, whereas 6 reduced the burden of conducting additional trials. Collaboration among the FDA clinical pharmacology, medical, and statistical reviewers and effective communication with the sponsors was critical for the impact to occur. The survey and the case studies emphasize the need for early interaction between the FDA and sponsors to plan the development more efficiently by appreciating the regulatory expectations better.

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Exploratory analyses of data pertaining to pharmacokinetic, pharmacodynamic, and disease progression are often referred to as the pharmacometrics (PM) analyses. The objective of the current report is to assess the role of PM, at the Food and Drug Administration (FDA), in drug approval and labeling decisions. We surveyed the impact of PM analyses on New Drug Applications (NDAs) reviewed over 15 months in 2005-2006. The survey focused on both the approval and labeling decisions through four perspectives: clinical pharmacology primary reviewer, their team leader, the clinical team member, and the PM reviewer. A total of 31 NDAs included a PM review component. Review of NDAs involved independent quantitative evaluation by FDA pharmacometricians. PM analyses were ranked as important in regulatory decision making in over 85% of the 31 NDAs. Case studies are presented to demonstrate the applications of PM analysis.
Principle - Pediatric effectiveness / safety are inferred via mapping D-E-R from adults to pediatrics

- **Learn-Confirm Cycle(s)**
  - Pediatric Dose-Exposure relationship
  - Pediatric Exposure-Response relationship
  - **Confirmatory clinical trial if substantiation is required**

- **Requires**
  - Knowledge in adults of POM, POC, D-E-R, Efficacy / Safety
  - *Pharmacometric “model-based” learning* pediatric PK, and *confirming* D-E-R

- Learning’s are used to inform pediatric labeling
**Pediatric Study Decision Tree**

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

**NO**

- Conduct PK studies
- Conduct safety/efficacy trials*

**NO**

Is there a PD measurement** that can be used to predict efficacy?

**YES**

- Conduct PK/PD studies to get C-R for PD measurement
- Conduct PK studies to achieve target concentrations based on C-R

**YES**

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

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

Hypothesis: A single clinical trial plus causal evidence of effectiveness is sufficient for drug approval

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Example - Enbrel (etanercept)

- Adult RA approved 1998 - 2x/wk dosing
  - 3 RCT’s
- Juvenile RA approved 1999 - 2x/wk dosing
  - Population PK + randomized withdrawal clinical trial
- Adult RA 1/wk dosing approved 2003
  - Population PK + safety RCT
- Juvenile RA 1/wk dosing approved 2003
  - Population PK + simulation
- Adult ankylosing spondylitis, psoriatic arthritis also approved 2003 - M&S only
Adult vs Juvenile RA
Enbrel PK, 1X & 2X/wk

- 50 mg Once Weekly, Observed
- 25 mg Twice Weekly, Observed

Steady State Concentration (mg/L)

Time After Dose (hours)

Days after Dose

Mean, Once Weekly
Mean, Twice Weekly
95th percentile, once weekly
5th percentile, twice weekly
95th percentile, twice weekly

0.8 mg/kg Once Weekly
0.4 mg/kg Twice Weekly
Conclusions

- Learn-confirm paradigm + model-based drug development practices enable efficient development and regulation of pediatric medications
- Safety and effectiveness can be confirmed using efficient trial designs
End of Presentation