EMEA, Workshop on Modelling in Paediatric Medicines
London, April 14-15, 2008

Modeling & simulation in pediatric drug development and regulation

Carl Peck, MD
UCSF Center for Drug Development Science
UC-Washington Center,Washington DC

Department of Biopharmaceutical Sciences
School of Pharmacy,
University of California San Francisco

Affiliations

- **CDDS** (**http://cdds.ucsf.edu**)
- **NDA Partners LLC (www.ndapartners.com)**
- **SimCyp (www.simcyp.com)**

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**: **P**roof of (therapeutic) **C**oncept (biomarker or clinical effect)
  - **D-E-R**: **D**ose - **E**xposure - **R**esponse
  - **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

Submitted: April 4, 2005; Accepted: April 29, 2005; Published: October 7, 2005

Venkatesh A. Bhattaram,[1] Brian P. Booth,[1] Roshni P. Ramchandani,[1] B. Nhi Beasley,[1] Yaning Wang,[1] Veneeta Tandon,[1] John Z. Duan,[1] Raman K. Baweja,[1] Patrick J. Marroum,[1] Ramana S. Uppoor,[1] Nam Atiqur Rahman,[1] Chandrahas G. Sahajwalla,[1] J. Robert Powell,[1] Mehul U. Mehta,[1] and Jogarao V. S. Gobburu[1]

[1]Food and Drug Administration, Rockville, MD 20852

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, 5 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.

Of about a total of 244 NDAs,
42 included a pharmacometrics component….

Pharmacometric analyses were pivotal in regulatory decision making in more than half of the 42 NDAs.

Of 14 reviews that were ***pivotal to approval decisions***,
… 6 ***reduced the burden*** of conducting additional trials.

Impact of Pharmacometric Reviews on New Drug Approval and Labeling Decisions—a Survey of 31 New Drug Applications Submitted Between 2005 and 2006

VA Bhattaram[1], C Bonapace[1], DM Chilukuri[1], JZ Duan[1], C Garnett[1], JVS Gobburu[1], SH Jang[1], L Kenna[1], LJ Lesko[1], R Madabushi[1], Y Men[1], JR Powell[1], W Qiu[1], RP Ramchandani[1], CW Tornoe[1], Y Wang[1] and JJ Zheng[1]

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.

PM analyses were ranked as important in regulatory decision making in over 85% of the 31 NDAs.

UCSF University of California San Francisco

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 81 NUMBER 2 | FEBRUARY 2007

C D

Applied to pediatrics

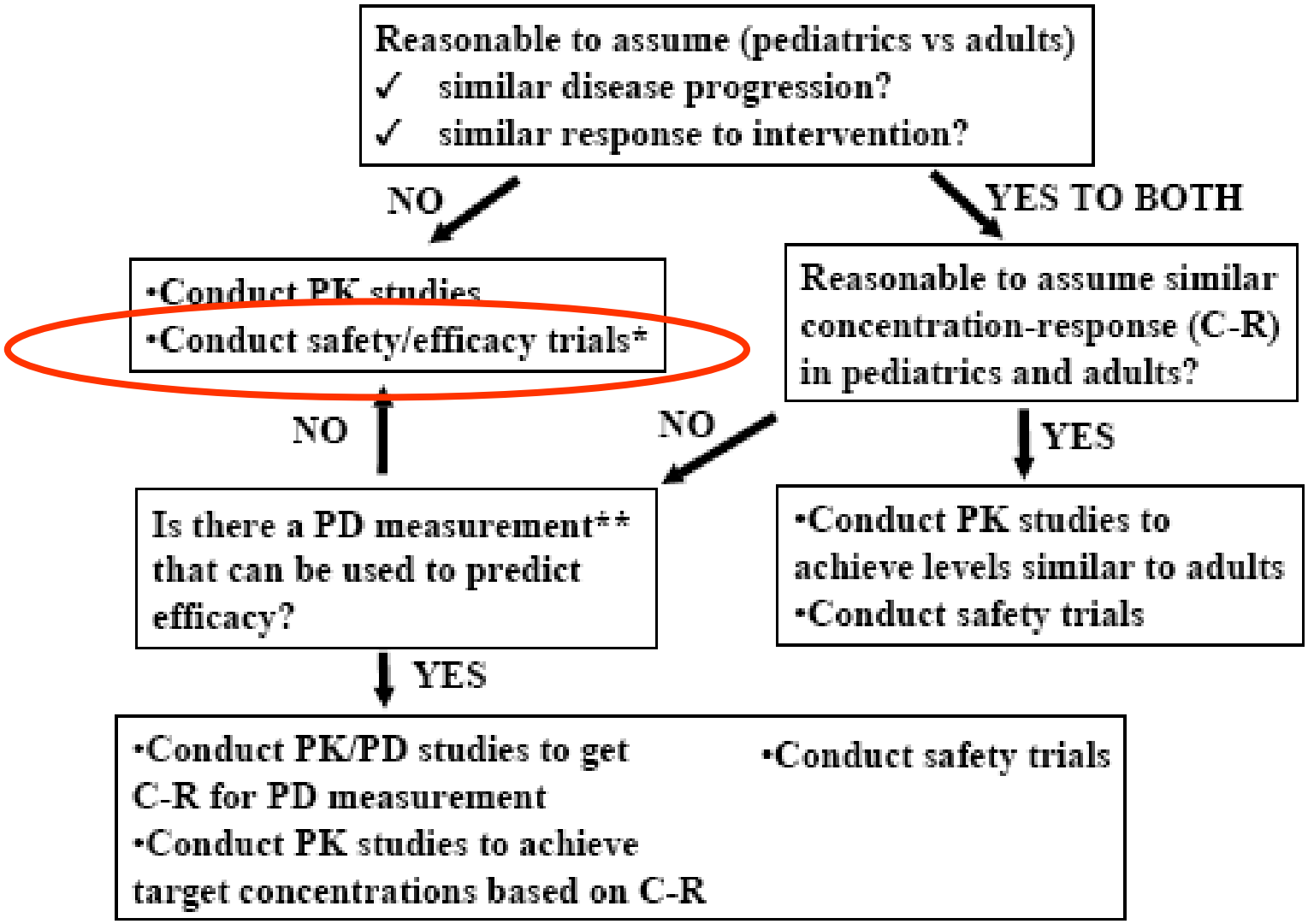
- **Principle** - Pediatric effectiveness / safety are inferred via mapping D-E-R from adults to pediatrics

- **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



http://www.fda.gov/cder/guidance/5341fnl.pdf

CLINICAL PHARMACOLOGY & THERAPEUTICS
VOLUME 73 NUMBER 6 JUNE 2003

COMMENTARY

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

Carl C. Peck, MD, Donald B. Rubin, PhD, and Lewis B. Sheiner, MD *Washington, DC, Cambridge, Mass, and San Francisco, Calif*

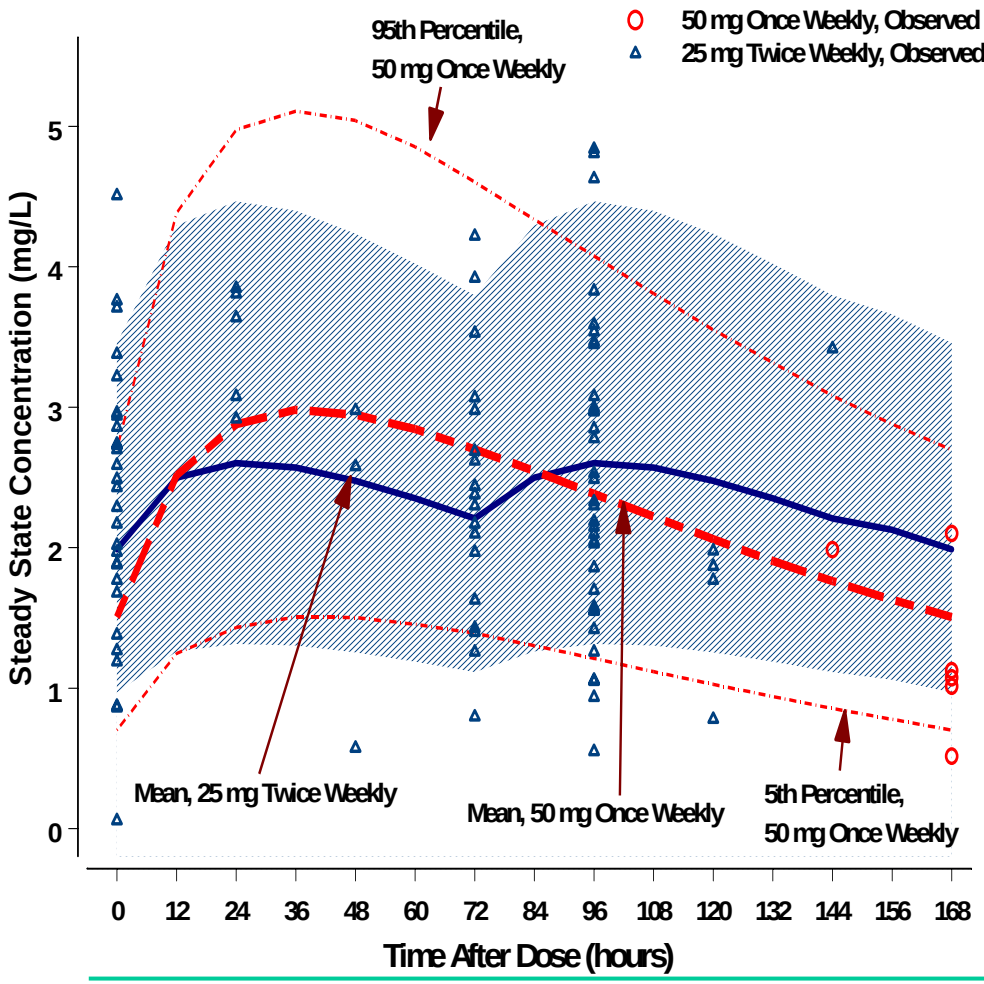
UCSF University of California San Francisco

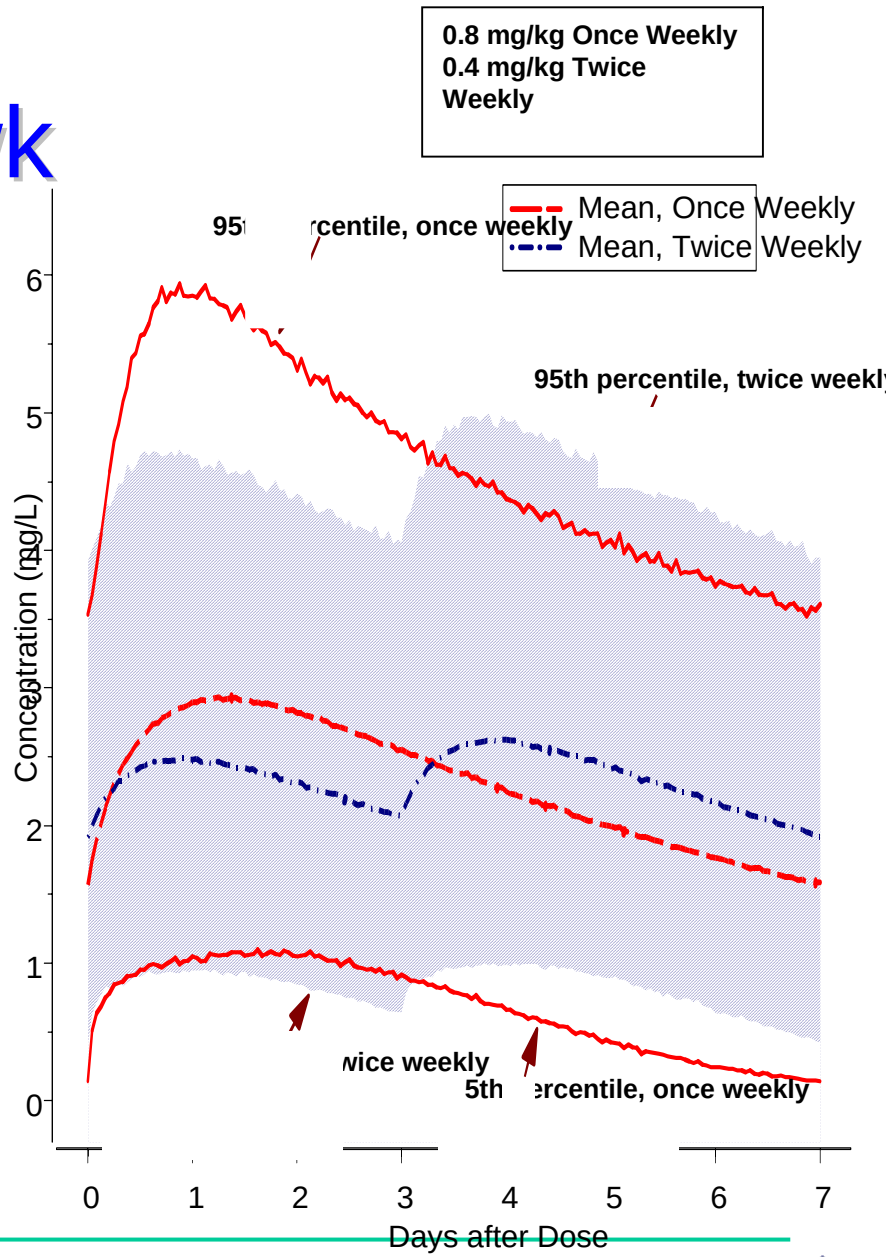
CDDS

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





University of California San Francisco

Conclusions

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

End of Presentation