Principles of Clinical Pharmacology
NIH, April 8, 2010

Role of FDA in Guiding Drug Development

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Acknowledgements & Affiliations

- **Contributors to ideas presented today**
  - All of our colleagues in FDA
- **Disclosures**
  - *CDDS* (http://cdds.ucsf.edu)
  - NDA Partners LLC (www.ndapartners.com)
  - SimCyp SAB

?

Why **FDA ?**

What **comprises FDA guidance ?**

How **does FDA guide drug development?**

When **does FDA get involved ?**

What's new ***at FDA ?***

Why FDA ?

- **FD&C Act: history and its supporters**
  - **resulted from public safety events or public health challenges**
    - **~ 1902/6, 1938, 1962, 1972, 1984, 1987, 1997, 2004-2007**
  - **a uniquely American phenomenon**
    - **Investment in FDA**
    - **Media and Politicization**
- **Evolution of Drug Regulation (R. Temple)**

SAFETY → EFFECTIVENESS → INDIVIDUALIZATION

….. → PERSONALIZATION → SAFETY → ?????

What comprises FDA guidance ?

- **Standards**
  - chemistry and manufacturing controls (CMC)
  - preclinical animal toxicology requirements
  - ethics of human clinical trials
  - documentary requirements for INDs, & NDAs
    - Electronic records (21 CFR part 11)
- **Clinical trials**
  - safety
  - effectiveness
  - trial design

How does FDA guide drug development ?

- **Written guidances**
  - Regulations, guidelines (incl. ICH), guidances
  - Literature publications
  - Regulatory letters
  - (Statute, Congressional Reports)
- **Face-to-face & telephonic meetings**
  - Pre-IND, EoP2, EoP2a, EoP2, pre-NDA, others as-needed
- **FDA Advisory Committee meetings**
- **Podium presentations**

Website - www.fda.gov

How many guidances and are they binding ?

- **GUIDANCES**
  - > *500* guidances (final/draft, FDA/ICH)
- **Guidance documents:**
  - Cannot legally bind FDA or the public
  - Recognizes value of consistency & predictability
  - Because companies want assurance
  - So staff will apply statute & regulations consistently

www.fda.gov/cder/guidance.htm

Clinical Pharmacology Guidances

- Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies In Vitro (97); In Vivo (99, 06)
- Pharmacokinetics in Patients w/renal (10) & impaired hepatic function (03)
- Pediatric Pharmacokinetic Studies for Drugs (98), pregnancy (04), lactation (05)
- Population Pharmacokinetics (99)
- Exposure-Response (03)
- Exploratory IND Studies (05)

Contains Nonbinding Recommendations

Guidance for Industry, Investigators, and Reviewers

Exploratory IND Studies

Office of Training and Communication
Division of Drug Information, HFD-240
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4573
http://www.fda.gov/cder/guidance/index.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

January 2006
Pharmacology/Toxicology

Clinical/Medical Guidances

- **Study and Evaluation of Gender Differences (93)**
- **Study of Drugs ... used in the Elderly (89)**
- **Guidance for IRB's, PI's, Mfgr's: Informed Consent Exception: Emergency Research**
- **Foreign data (01), Unmet Medical Needs (04)**
- **Adaptive Trial Designs (10), Cancer Trial Endpoints (07)**
- ***Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (98)**

Statutory Guidance: *FDA Modernization Act of 1997 - "FDAMA"*

- Sec. 111. ***Pediatric*** studies of drugs
  - **PK bridging studies**
- Sec. 115a. Clinical investigations
  - **support of *one* adequate and well-controlled clinical investigation by *"confirmatory evidence"* comprising PK or PK/PD**

Pediatric Labeling Regulations

"FDA may approve a drug for pediatric use based on ... studies in adults, with other information supporting pediatric use…. additional information supporting pediatric use must ordinarily include data on the *pharmacokinetics* of the drug in the pediatric population ….Other information, such as data on ***pharmacodynamic* studies**….."

(21 CFR 201.56)

FDAMA, Sec. 115a
Clinical investigations

"If the Secretary determines, based on relevant science, that data from *one* adequate and well-controlled clinical investigation and *confirmatory evidence* …. are sufficient to establish effectiveness, the Secretary may consider such data and evidence to constitute substantial evidence.."

FDAMA, Sec. 115a
CONGRESSIONAL COMMITTEE REPORTS

- ***"confirmatory evidence"* = "scientifically sound data from any investigation in the NDA that provides substantiation as to the safety and effectiveness of the new drug"**
- **confirmatory evidence = "consisting of earlier clinical trials, *pharmacokinetic* data, or other appropriate scientific studies"**

1 House Commerce Committee, 10/7/97, and Committee of Conference on Disagreeing votes of the two Houses, 11/9/97

New Formulations and Doses of Already Approved Drugs

- Where ***blood levels ... are not very different***, it may be possible to conclude ... is effective on the basis of **pharmacokinetic data alone**.
- Even ***if blood levels are quite different***, if there is **a well-understood relationship between blood concentration and response**, ..., it may be possible to conclude ... is effective on the basis of **pharmacokinetic data *without*** an additional clinical efficacy trial.

Guidance for Industry "Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products", May 1998

CLINICAL PHARMACOLOGY & THERAPEUTICS
VOLUME 73 NUMBER 6 JUNE 2003

COMMENTARY

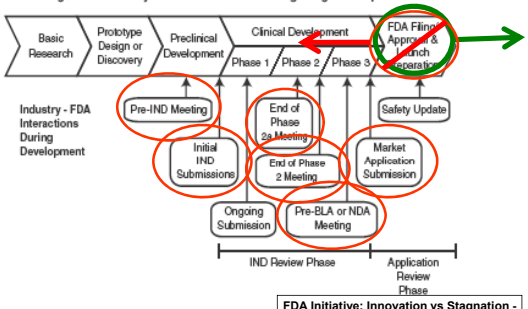
Hypothesis: A single clinical trial plus causal evidence of effectiveness is sufficient for drug approval

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

When does FDA get involved ?

- **Preclinical (on request) phase**
  - IND requirements for CMC, animal testing, design of Phase 1 clinical studies
- **IND phase**
  - Type A, B, C meetings
- **NDA review phase**
  - Meetings + many communications
- **Marketing phase**
  - ADR surveillance
  - new uses, product changes, withdrawals

Figure 7: Industry - FDA Interactions During Drug Development



FDA Initiative: Innovation vs Stagnation - Challenge & Opportunity on the Critical Path to New Medical Products, March 2004

Guidance for Industry
End-of-Phase 2A Meetings

DRAFT GUIDANCE

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

September 2008
Procedural

End of Phase 2a Meetings

- **Purpose**: ↓ Late phase clinical trial (2b, 3) unnecessary failure
- **Format**: non-binding scientific interchange.
- **Deliverables**:
  - Modeling (relevant phase 1/2a data) & simulation of next trial design employing
    - Mechanistic or empirical drug-disease model ("Placebo effect")
    - Rates for dropout and non-compliance
  - Recommendation on sponsors trial design + alternative including patient selection, dosage regimen,…
  - Answers to other questions from the clinical and clinical pharmacology development plan
- **Time-course**: ~ 6 weeks
- **Key sponsor & FDA participants**: physician, biostatistician, clinical pharmacology (pharmacometrics), project management

Adapted from R. Powell, FDA

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 analyses were not conducted by the sponsor. Pharmacometrics 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.

AAPS Journal 2005;7 (3) Article 51 (www.aapsj.org)

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.

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FDA – what's new?

- **Leadership**
  - **Commissioner Hamburg, (Eschenbach), (Crawford), (McClellan), (Henney), (Kessler), (Young)**
  - **Division of Pharmacometrics – Joga Gobburu**
- **Safety**
  - Drug withdrawals (Vioxx et al, 04; Raptiva 4-8-09/
    - Safety Oversight Board (05)
  - ***PDUFA renewal 2007 -- FDAAA***
- **Initiatives**
  - **Pediatric Initiatives (USA & Europe)**
  - **Improving drug development**
    - ***Critical Path Initiative (2004)***
    - ***End-of-Phase 2a (EOP2a) meeting (04)***
    - ***Model-based Drug Development (05) (PBPK – 09)***
    - ***Critical Path Opportunities List (06)***
  - ~~***Clinical Pharmacology Question-based Review Template (QBR)***~~

GENERAL CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

All CPB reviews should contain the following sections organized as shown below. If necessary because of a specific NDA or sNDA, reviewers should feel free to organize subsections under these main headings, as needed, using standard outline conventions.

Header of Review

Table of Contents

1 *Executive Summary*

1.1 *Recommendations*

1.2 *Phase 4 Commitments*

1.3 *Summary of Important Clinical Pharmacology and Biopharmaceutics Findings*

2 *Question Based Review*

2.1 *General Attributes of the Drug*

2.2 *General Clinical Pharmacology*

2.3 *Intrinsic Factors*

2.4 *Extrinsic Factors*

2.5 *General Biopharmaceutics*

2.6 *Analytical Section*

3 *Detailed Labeling Recommendations*

FDA "QBR" *

- Drug-drug interaction questions
  - In vitro metabolism & transporter studies ?
  - CYP substrate, inhibitor, inducer ?
  - Pharmacogentic influences ?
  - P-glycoprotein substrate and/or an inhibitor ?
  - Other metabolic/transporter pathways ?
  - Co-administered of active ingredient ?
  - Co-medications ?
  - Altered exposure and/or exposure-responses Pharmacodynamic drug interactions ?
  - Active metabolites, protein binding ?
  - PKPD modeling ?

•**Question Based Review**
•**Extracted from FDA MAPP 4000.4 (4/27/04)**

FDAAA

- **Motivated by prominent market W/D's due to unexpected lack of safety**
- **New Authorities**
  - Public listing of all clinical trials & results
  - Post-approval trials and surveillance
  - Safety labeling
  - REMS (Risk Evaluation & Mitigation Strategy)
  - Pre-approval of Direct to Consumer Ads
  - Penalties
  - Advisory Committees
    - Risk Communication
    - COI

Pediatric Initiatives in US and Europe

- **US**
  - **Pediatric Exclusivity - 1997**
  - **Pediatric Research Equity Act - 1998**
  - **Best Pharmaceuticals for Children Act - 2002**
- **Europe**
  - **Better Medicines for Children - 2007**
    - **Pediatric Investigations Plans (PIPs)**
    - **Pediatric Marketing Use Authorization (PUMAs)**

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

Modeling & simulation in pediatric drug development and regulation

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Applied to pediatrics

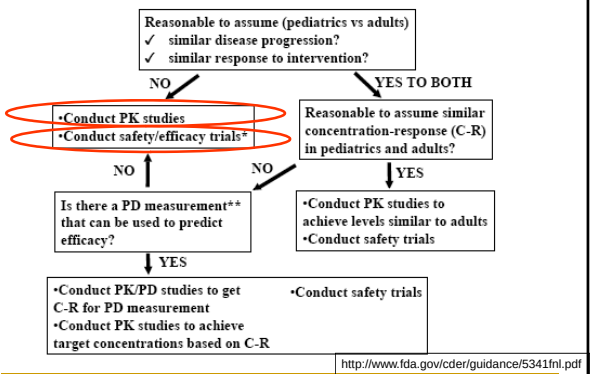
- **Principle** - Pediatric effectiveness / safety are inferred via mapping D-E-R from adults to pediatrics

- **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

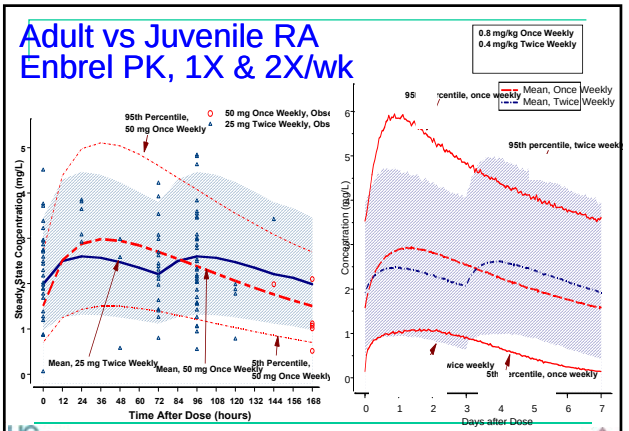


http://www.fda.gov/cder/guidance/5341fnl.pdf

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



Innovation

Stagnation

Challenge and Opportunity on the Critical Path to New Medical Products

FDA

U.S. Department of Health and Human Services
Food and Drug Administration
March 2004

Critical Path Initiative
Six Priority Public Health Challenges

- **Biomarker** development
- Streamlining **clinical trials**
- **Bioinformatics**
- Efficient, quality **manufacturing**
- antibiotics and countermeasures to combat emerging **infections** and **bioterrorism**
- Developing therapies for **children and adolescents**

Public/Private Partnerships

- **Predictive Safety Testing Consortium**
  - CDER-OCP, CPath Institute, 15 pharma firms
  - Pre-clinical toxicogenomic biomarkers
    - Nephrotoxic biomarkers report expected 09
- **Biomarker Consortium**
  - NIH/ PhRMA/ FDA/CMS
  - regulatory pathway for biomarker validation
    - FDG-PET in NHL
- **Oncology Biomarker Qualification Initiative**
  - FDA, NCI and CMS
- **Microarray Quality Consortium**
- **Duke/FDA ECG & Clinical Trial Transformation Collaborations**

Some Final Observations

- **FDA regulation is science-based**
  - Advances innovation
  - Facilitates needed drugs for patients
- **FDA clinical guidances are increasingly based on *principles of clinical pharmacology***
- **Social value: "guidance" versus "regulation"**
- **FDA guidance**
  - national "treasure" versus "national nuisance"
  - a bargain !

End of Presentation