

## Role of FDA in Guiding Drug Development

**Carl Peck, MD**

UCSF Center for Drug Development Science  
Washington DC and San Francisco

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



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## Acknowledgements & Affiliations

- **Contributors to ideas presented today**
  - All of my colleagues in FDA
- **Disclosures**
  - *CDDDS* (<http://cdds.ucsf.edu>)
  - NDA Partners LLC ([www.ndapartners.com](http://www.ndapartners.com))
  - SimCyp SAB



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**Why FDA ?**

**What comprises FDA guidance ?**

**How does FDA guide drug development?**

**When does FDA get involved ?**

**What's new at FDA ?**



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## 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*



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## 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



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## 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](http://www.fda.gov)



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## 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](http://www.fda.gov/cder/guidance.htm)



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## Clinical Pharmacology Guidances

- Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies In Vitro (97); In Vivo (99)
- Pharmacokinetics in Patients w/renal & impaired hepatic function: study design, data analysis, dosing/labeling
- Pediatric Pharmacokinetic Studies for Drugs Biological
- Population Pharmacokinetics (99)
- Exposure-Response (02)
- Exploratory IND Studies (April 2005)



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*Contains Nonbinding Recommendations*

## Guidance for Industry, Investigators, and Reviewers

### Exploratory IND Studies

Office of Training and Communications  
Division of Drug Information, HFD-240  
Center for Drug Evaluation and Research  
Food and Drug Administration  
14015 Pines Blvd  
Rockville, MD 20850  
(301) 351-4373  
<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



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## Clinical/Medical Guidances

- Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs (93)
- Study of Drugs ... used in the Elderly (89)
- Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors: Exception from Informed Consent Requirements for Emergency Research
- Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (98)



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## 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



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## 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)



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## 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..”



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## 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



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## 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



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# 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*



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## 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



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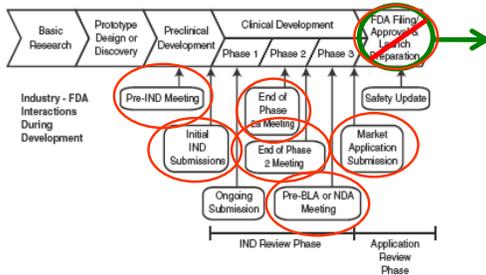
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Figure 7: Industry - FDA Interactions During Drug Development



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



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# 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

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## End of Phase 2a Meetings

- **Purpose:** ↓ Late phase clinical trial (2b, 3) unnecessary failure
- **Format:** non-binding scientific interchange.
- **Deliverables:**
  - Perform modeling (relevant phase 1/2a data) & simulation of next trial design employing
    - Mechanistic or empirical drug-disease model/Placebo effect (magnitude & time-course)
    - Rates for dropout and compliance. (prior FDA experience)
  - 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

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### 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,<sup>1</sup> Brian P. Booth,<sup>1</sup> Roshni P. Ramchandani,<sup>1</sup> B. Nhi Beasley,<sup>1</sup> Yaning Wang,<sup>1</sup> Veneceta Tandon,<sup>1</sup> John Z. Duan,<sup>1</sup> Raman K. Bawcja,<sup>1</sup> Patrick J. Marroum,<sup>1</sup> Ramana S. Uppoor,<sup>1</sup> Nam Atiqur Rahman,<sup>1</sup> Chandras G. Sahajwalla,<sup>1</sup> J. Robert Powell,<sup>1</sup> Mehul U. Mehta,<sup>1</sup> and Jogarao V. S. Gobburu<sup>1</sup>

<sup>1</sup>Food and Drug Administration, Rockville, MD 20852

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)

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## 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)



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EMA, 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



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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



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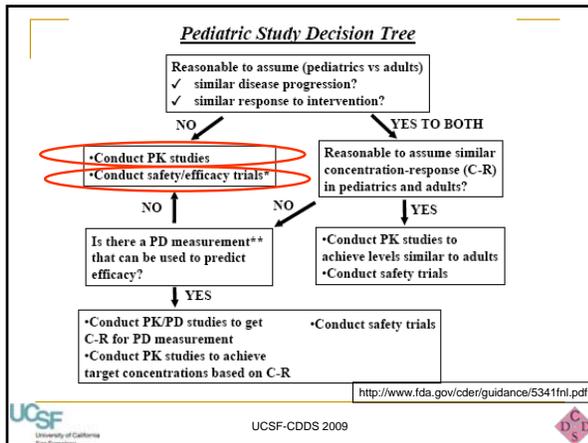
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- ### Example - Enbrel (etanercept)
- Adult RA approved 1998 - 2x/wk dosing
    - 3 RCT's
  - Juvenile RA approved 1999 - 2x/wk dosing
    - Population PK + randomized withdrawal clinical trial
  - Adult RA 1/wk dosing approved 2003
    - Population PK + safety RCT
  - Juvenile RA 1/wk dosing approved 2003
    - Population PK + simulation
  - Adult ankylosing spondylitis, psoriatic arthritis also approved 2003 - M&S only
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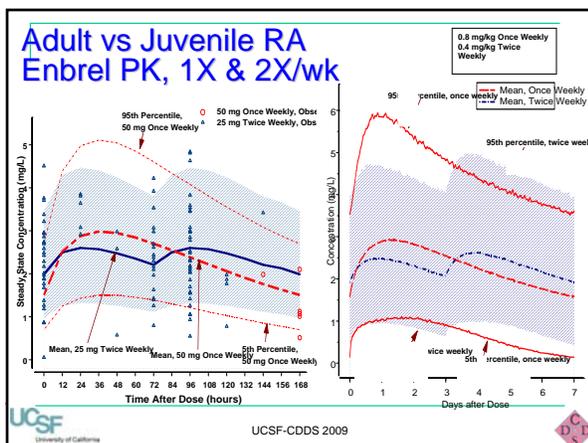
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*Innovation*  
Stagnation

**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

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**Stagnation** → **Innovation**

Basic Research → Prototype Design or Discovery → Preclinical Development → Clinical Development → FDA Filing/ Approval & Launch

Market Application | Approval

**CRITICAL PATH**

Adapted from S. Buckman: "Biomarkers 101", RAPS, 2006

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**Guiding Principles of Critical Path Initiative**

- Coordinate collaborative efforts
- "toolkits" for better product development
- Encourage academic interest
- Opportunities to share existing knowledge & databases
- Develop enabling standards

Adapted from S. Murphy: "FDA Update on Critical Path Initiative", RAPS 2006, & FDA Critical Path Initiative 2004

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## Key FDA Critical Path Activities Under Way in 2007

**U.S. Department of Health and Human Services**  
**Food and Drug Administration**  
**June 2008**

In March 2007, HHS published the second of two reports on the Critical Path to medical product development. The Critical Path Opportunities Report and List. The Opportunities Report and List presented 70 specific scientific opportunities that, if undertaken, would help modernize the Critical Path sciences. The opportunities were identified through extensive outreach with patient groups, the pharmaceutical industry, academia, other federal agencies, and other health-related organizations.

FDA also promised in that report to announce the specific activities it was undertaking in support of its Critical Path Initiative. As promised, the following pages list more than 40 Critical Path collaborations and research activities that currently are underway with FDA participation. The activities are organized according to the priority topics discussed in the Opportunities Report and List, also available on the Critical Path Web page. Where appropriate, an activity is designated as directly linked to one of the 70 specific scientific opportunities, or priority topics, in the Opportunities Report and List. The priority topics include the following:

- Better Evaluation Tools
- Streamlining Clinical Trials
- Harnessing Bioinformatics
- Moving Manufacturing into the 21st Century
- Developing Products to Address Urgent Public Health Needs
- Specific At-Risk Populations — Pediatrics

<http://www.fda.gov/oc/initiatives/criticalpath/opportunities06.html>

## 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**



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## 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 !



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## End of Presentation



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