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
Acknowledgements & Affiliations

Contributors to ideas presented today
All of my 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
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
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)

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)
Copy of the cover of an FDA Guidance for Industry, Investigators, and Reviewers entitled Exploratory IND Studies

Contains Nonbinding Recommendations

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 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)
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
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
Copy of a flow chart of “Figure 7: Industry – FDA Interactions During Drug Development”

A flow chart indicates the following sequence of events:

- Basic research
- Prototype design or discovery
- Preclinical development – Pre-IND meeting
  (Initial IND submissions)
- Clinical Development
  - Phase 1 – Ongoing submission
  - Phase 2 – End of Phase 2a Meeting
  - Phase 3 – Pre-BLA or NDA Meeting
  - Market Application submission
  - Safety Update
    - FDA filing approval & launch preparation (that line has been lined through and an arrow pointing to the right has been added).

FDA Initiative: Innovation vs Stagnation - Challenge & Opportunity on the Critical Path to New Medical Products, March 2004
Copy of a cover for a FDA Guidance for Industry that reads as follows:

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:**
- 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
Copy of an article from the AAPS Journal 2005;7 (3) Article 51 (www.aapsj.org) entitled 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

By Venkatesh A. Bhattaram et al.
1Food and Drug Administration, Rockville, MD 20852

The following specific comments from the article are shown on the slide:

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

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

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

VA Bhattaram¹ et al.

Pharmacometrics (PM) analyses were ranked as important in regulatory decision making in over 85% of the 31 NDAs.
FDA – what’s new?

Leadership
Commissioner Hemurg (Eschenbach), (Crawford), (McClellan), (Henney), (Kessler), (Young)
CDER Director (Woodcock)

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
FDA leadership to improve drug development (2003)

End-of-Phase 2a (EOP2a) meeting (04)
Model-based Drug Development (05)
Critical Path Opportunities List (06)
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)
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

UCSF
University of California, San Francisco
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

Reasonable to assume (pediatrics vs adults)
Similar disease progression?
Similar response to intervention
↓
↓
NO              YES TO BOTH

*Conduct PK studies
*Conduct safety/efficacy trials*

NO ↑              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

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

NO

↓

YES

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

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

Two plots are shown. The one on the left shows steady state concentration (mg/L) over time after dose from 0 to 168 hours for patients administered 50 mg once weekly and for patients administered 25 mg twice weekly. The second plot shows concentration (mg/L) over 0 to 7 days after dose for patients administered 0.8 mg/kg once weekly and for patients administered 0.4 mg/kg twice weekly.
Copy of the cover page of a FDA publication that reads as follows:

**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
Copy of a graphic illustration from S. Buckman: “Biomarkers 101”, RAPS, 2006 that reads as follows:

“Stagnation → Innovation”

A flow chart shows the following stages in the development of biomarkers.

- Basic research
- Prototype design or discovery
- Preclinical Development
- Clinical development followed by market application
- FDA Filing/approval and Launch followed by approval

“Critical Path”
Guiding Principles of Critical Path Initiative

Coordinate collaborative efforts

“tool kits” 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
Copy of the lead page of an FDA/DHHS article/publication entitled, “The Critical Path to New Medical Products”.

“The Critical Path initiative is FDA’s effort to stimulate and facilitate a national effort to modernize the scientific process through which a potential human drug, biological product or medical device is transformed from a discovery or “proof of concept” into a medical product”.

http://www.fda.gov/oc/initiatives/criticalpath/
Copy of the cover page of an FDA /DHHS publication entitled, “Innovation, Stagnation – Critical Path Opportunities List”
Critical Path Initiative
Six Priority Public Health Challenges

1. **Biomarker** development
2. Streamlining **clinical trials**
3. **Bioinformatics**
4. Efficient, quality **manufacturing**
5. antibiotics and countermeasures to combat emerging **infections** and **bioterrorism**
6. Developing therapies for **children and adolescents**
Copy of the index of the Critical Path publication dealing with biomarkers that lists
Topic 1: Better Evaluation tools
Continuation of the Critical Path publication index with Topic 2: Streamlining Clinical Trials, and Topic 3: Harnessing Bioinformatics
Copy of a cover page of an FDA/DHHS publication entitled, “Key FDA Critical Path Activities Under Way in 2007”.

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

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**
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