

Principles of Clinical Pharmacology
NIH, April 23, 2009

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

~ 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

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 populationOther 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

Copy of a cover of scientific journal that reads as follows:

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

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. Bhattaram¹ 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.

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

VA Bhattaram¹ et al.

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

Clinical Pharmacology & Therapeutics | Volume 81 Number 2 | February 2007

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)

Critical Path Initiative (2004)

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)

**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

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

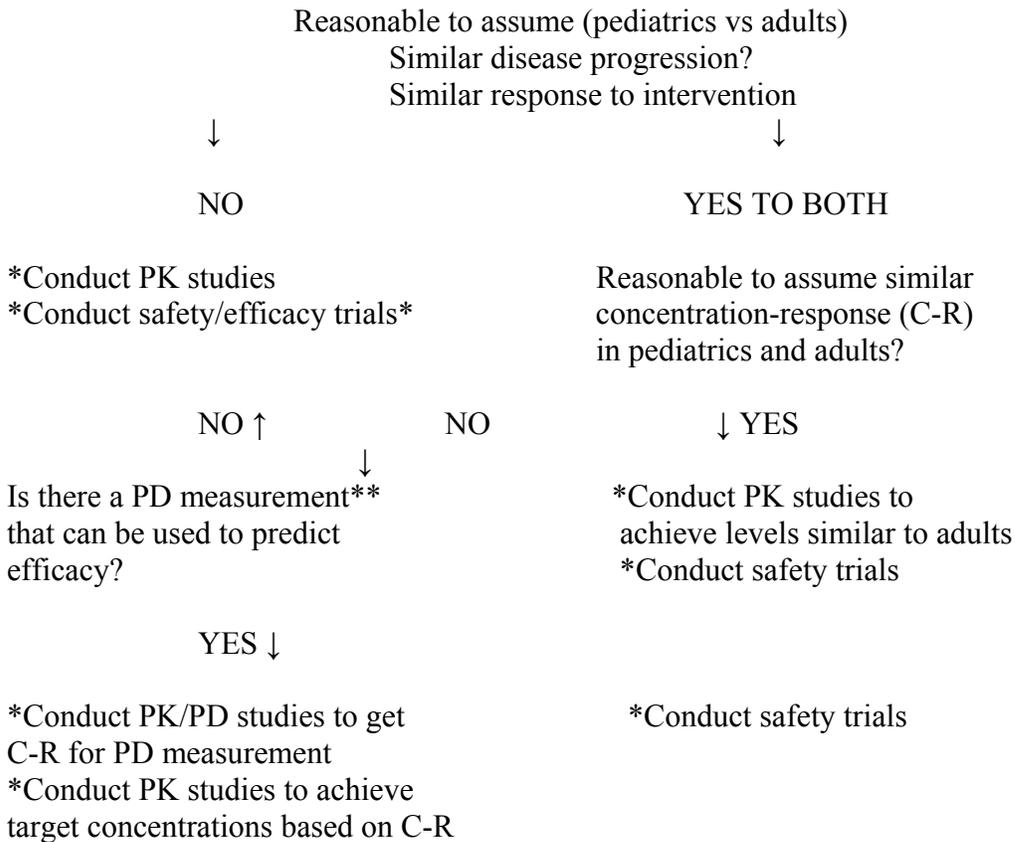
Requires

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



<http://www.fda.gov/cder/guidance/5341f1.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

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