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)

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 (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 *<u>one</u>* 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

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 an 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:

- **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

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[1] et al.

[1]Food 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 Bhattaram[1] 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 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 conversions:

Header of Review

Table of Contents

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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Department of Biopharmaceutical Sciences
School of Pharmacy,
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The logo for UCSF is shown and the words, University of California San Francisco.

The logo for the UCSF Center for Drug Development Science is also shown.

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

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

NO ↑ NO ↓ YES

↓

Is there a PD measurement** that can be used to predict efficacy?

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

YES ↓

*Conduct PK/PD studies to get C-R for PD measurement
*Conduct PK studies to achieve target concentrations based on C-R

*Conduct safety trials

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

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

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“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/

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