FDA Guidance, Clinical Pharmacology, And “Regulatory Science”

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Affiliations

CDDS (http://cdds.ucsf.edu)

NDA Partners LLC (www.ndapartners.com)
Why FDA?

What does FDA* do, When & How?

Clinical Pharmacology at FDA*

FDAMA, FDAAA, FDASIA

Initiatives to Improve Drug Development & Regulation

*Focus: CDER, CBER

UCSF-CDDS 2013
A Horse Called “Jim”

Picture of 4 men and a horse

UCSF-CDDS 2010
“Patent Medicines” in Early 20th Century

Based on testimonials of “miracle cures”

Most were ineffective, many were dangerous

main ingredient: alcohol
Examples of Snake Oil in Early 20th Century

Peter’s Specific Blood Purifier
for all ailments: arsenic, opium, and insect parts

Curforhedake Brane-Fude
“a most wonderful, certain and harmless relief”
“no ... poisonous ingredients of any kind”
acetanilid - killed numerous people and was addictive

Microbe Killer
cure all disease: 99% water, hydrochloric acid, red wine
Articles and advertisement for Hamlin’s Wizard Oil

“There is no Sore it will Not Heal, No Pain it will not Subdue”

50% - 70% alcohol, camphor, ammonia, chloroform, sassafras, cloves, turpentine
Patent Medicine

Pictures and advertisements

Muckraker journalists and other investigators began to publicize instances of death, drug addiction, and other hazards from the compounds.
FD&C Acts and Selected Amendments

graph
FD&C Act: history and its supporters
resulted from public safety events or public health challenges
Safety
Effectiveness
Individualization
Access
Guidance, transparency, speed & efficiency
a uniquely American phenomenon
Investment in FDA
Media, Politicization, and Transparency
16 What does FDA do: provision of standards and guidance

Standards
chemistry and manufacturing controls (CMC)
preclinical animal toxicology requirements
ethics of human clinical trials
documentary requirements for INDs, & NDAs

Clinical trials
safety
effectiveness
trial design
17 How does FDA provide guidance?

**Written guidances**
- Regulations, guidelines (incl. ICH), guidances
- Literature publications
- Regulatory letters
- (Statute, Congressional Reports)

**Face-to-face & telephonic meetings**
- Pre-IND, EoP2a, EoP2, pre-NDA, others as-needed

**FDA Advisory Committee meetings**

**Podium presentations**

**Website** – [www.fda.gov](http://www.fda.gov)
18 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
19 Some 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)
20 When does FDA engage?

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 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)
26 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)
“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.”
“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
29 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 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)\n
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. 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.

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 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

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

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 Clinical Pharmacology
   2.2 Intrinsic Factors
   2.3 Extrinsic Factors
   2.4 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)
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

Modeling & simulation in pediatric drug development and regulation

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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

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.
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”.

“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