Role of FDA in Guiding Drug Development

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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**

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)
- 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)
Guidance for Industry, Investigators, and Reviewers

Exploratory IND Studies

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

UCSF-CDDS 2009
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”

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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
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
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

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¹Food and Drug Administration, Rockville, MD 20852

The value of quantitative thinking in drug development and regulatory review is increasingly being appreciated. Modeling and simulation of data pertaining to pharmacokinetic, pharmacodynamic, and disease progression is often referred to as the pharmacometrics analyses. The objective of the current report is to assess the role of pharmacometrics at the US Food and Drug Administration (FDA) in making drug approval and labeling decisions. The New Drug Applications (NDAs) submitted between 2000 and 2004 to the Cardio-renal, Oncology, and Neuropharmacology drug products divisions were surveyed. For those NDA reviews that included a pharmacometrics consultation, the clinical pharmacology scientists ranked the impact on the regulatory decision(s). Of about a total of 244 NDAs, 42 included a pharmacometrics component. Review of NDAs involved independent, quantitative evaluation by FDA pharmacometricians, even when such analyses were not conducted by the sponsor. 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 identified the need for additional trials, whereas 6 reduced the burden of conducting additional trials. Collaboration among the FDA clinical pharmacology, medical, and statistical reviewers and effective communication with the sponsors was critical for the impact to occur. The survey and the case studies emphasize the need for early interaction between the FDA and sponsors to plan the development more efficiently by appreciating the regulatory expectations better.

VA Bhattaram¹, C Bonapace¹, DM Chilukuri¹, JZ Duan¹, C Garnett¹, JVS Gobburu¹, SH Jang¹, L Kenna¹, LJ Lesko¹, R Madabushi¹, Y Men¹, JR Powell¹, W Qiu¹, RP Ramchandani¹, CW Tornoe¹, Y Wang¹ and JJ Zheng¹

Exploratory analyses of data pertaining to pharmacokinetic, pharmacodynamic, and disease progression are often referred to as the pharmacometrics (PM) analyses. The objective of the current report is to assess the role of PM, at the Food and Drug Administration (FDA), in drug approval and labeling decisions. We surveyed the impact of PM analyses on New Drug Applications (NDAs) reviewed over 15 months in 2005-2006. The survey focused on both the approval and labeling decisions through four perspectives: clinical pharmacology primary reviewer, their team leader, the clinical team member, and the PM reviewer. A total of 31 NDAs included a PM review component. Review of NDAs involved independent quantitative evaluation by FDA pharmacometricians. PM analyses were ranked as important in regulatory decision making in over 85% of the 31 NDAs. Case studies are presented to demonstrate the applications of PM analysis.

**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)
    - **Critical Path Initiative (2004)**
      - *End-of-Phase 2a (EOP2a) meeting (04)*
      - *Model-based Drug Development (05)*
      - *Critical Path Opportunities List (06)*
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

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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
**Pediatric Study Decision Tree**

- Reasonable to assume (pediatrics vs adults)
  - **✓** similar disease progression?
  - **✓** similar response to intervention?

  **NO**  
  - *Conduct PK studies*
  - *Conduct safety/efficacy trials*

  **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*
    - **NO**  
      - *Conduct PK studies to achieve levels similar to adults*
      - *Conduct safety trials*

  **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

- Adult vs Juvenile RA
- Enbrel PK, 1X & 2X/wk

- 50 mg Once Weekly, Obs
- 25 mg Twice Weekly, Obs

- 0 12 24 36 48 60 72 84 96 108 120 132 144 156 168
  - Time After Dose (hours)

- 0 1 2 3 4 5 6
  - Days after Dose

- Mean, 25 mg Twice Weekly
- Mean, 50 mg Once Weekly
- 5th Percentile, 50 mg Once Weekly
- 95th Percentile, once weekly
- 95th percentile, twice weekly

- 0.8 mg/kg Once Weekly
- 0.4 mg/kg Twice Weekly

- UCSF-CDDS 2009
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

UCSF-CDDS 2009
CRITICAL PATH

Adapted from S. Buckman: “Biomarkers 101”, RAPS, 2006
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
The Critical Path to New Medical Products

Success Stories
- Vaccine Manufacturing
- West Nile Virus
- Digital Mammography

Conferences and Events
- Rapid Diagnostics Development and Infectious Disease Treatment, Nov. 6-7, 2006
- AAMC-FDA Conference on Drug Development Science, Jan. 13-14, 2005
- Medical Imaging As A Drug Development Tool: An FDA/DIA Workshop

What's New
- Opportunities-Press Release
- Report
- Opportunities List
- Questions and Answers
- Critical Path Fact Sheet
- Predictive Safety Testing Consortium-Press Release
- Predictive Safety Testing Consortium-Fact Sheet
- Quotes

Projects Underway
- Voluntary Genomics Data Submissions
- Predictive Safety Testing Consortium-Fact Sheet
- Request for Application: Cardiovascular Drug Safety and Biomarker Research

Contact Us

http://www.fda.gov/oc/initiatives/criticalpath/

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Innovation

Stagnation

Critical Path
Opportunities List

U.S. Department of Health and Human Services
Food and Drug Administration
March 2006

UCSF-CDDS 2009
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**
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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 2006, FDA published the second of two reports on the Critical Path to medical product development, Critical Path Opportunities Report and List. The Opportunities Report and List presented 76 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 76 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**
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