Role of FDA in Guiding Drug Development

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
Why FDA?

When does FDA get involved?

How does FDA guide drug development?

What comprises FDA guidance?

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
    - Politicization

- Evolution of Drug Regulation (R. Temple)

SAFETY → EFFECTIVENESS → INDIVIDUALIZATION

..... → PERSONALIZATION → SAFETY
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
Figure 7: Industry - FDA Interactions During Drug Development

- Basic Research
- Prototype Design or Discovery
- Preclinical Development
- Clinical Development
  - Phase 1
  - Phase 2
  - Phase 3
- FDA Filing/Approval & Launch Preparation

Industry - FDA Interactions During Development

- Pre-IND Meeting
- Initial IND Submissions
- End of Phase 2a Meeting
- End of Phase 2 Meeting
- Market Application Submission
- Safety Update

IND Review Phase
- Pre-BLA or NDA Meeting
- Application Review Phase

End of Phase 2a Meeting
End of Phase 2a meeting

CONCEPT PAPER

End-Of-Phase-2A Meetings With Sponsors Regarding Exposure-Response of IND and NDA Products (Draft 10/16/2003)

Two Year’s Experience Reviewed at FDA Pharmaceutical Sciences Advisory Committee Meeting, November 14, 2005

http://www.fda.gov/ohrms/dockets/ac/05/slides/2005-4194S1_Slide-Index.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

October 2003
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
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**
Of about a total of 244 NDAs, 42 included a pharmacometrics component....

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 reduced the burden of conducting additional trials.
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 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)*
Contains Nonbinding Recommendations

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) 301-597-4273
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

Copyright © Carl Peck, All Rights Reserved
Goals of the Exploratory IND

- Reduce time & resources on drugs unlikely to succeed
  - Select most likely to succeed from group of candidate drugs
  - To learn PK, biodistribution, mechanism of action
  - Reduced preclinical requirements due to less risk
Exploratory IND

- “Phase 0” studies – prior to traditional drug development Phase I trials

- Microdose, sub-pharmacologic or pharmacologic dose
  - Single dose or limited period of administration
Types of Exploratory Studies

- Single Dose
  - PK, Imaging

- Multiple Dose
  - Pharmacological, Pharmacodynamic endpoints
Requirements

- **CMC**
  - GLP (+/-)
  - Incomplete impurity profile
  - Summary report

- **Toxicology - depends upon goal**
  - Single Dose - 1/100 est. pharmacological dose or < 100 ug
    - Single species (rodent), 14 day observation
  - Multiple Dose (<1/50 NOAEL + max 1/4 of 2 wk NOAEL)
    - Two species, 14 day repeat dose
Nontraditional approaches to first-in-human studies to increase efficiency of drug development: will microdose studies make a significant impact?

RA Boyd¹ and RL Lalonde¹

In summary, several nontraditional approaches are available to obtain an early assessment of pharmacokinetics and pharmacodynamics in first-in-human studies. Under the right circumstances, these methods may help early drug development decisions to be made more efficiently. Microdose studies are one of those approaches, but they will allow only assessment of pharmacokinetic properties. Based on the data by Lappin et al., our own experience, and the current more common causes of attrition (Figure 1), microdose studies will have a very limited impact on the overall efficiency of drug development.
Clinical/Medical Guidances

- **Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products** (98)
- 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
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.”
“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
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
FDA – what’s new?

Leadership
- Commissioner Eschenbach, (Crawford), (McClellan), (Henney), (Kessler)
- Deputy Commissioner (Woodcock)

Safety
- Drug withdrawals (Vioxx et al) (04)
  - Safety Oversight Board (05)
- PDUFA renewal 2007

Initiatives
- 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)
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

Copyright © Carl Peck, All Rights Reserved
Adapted From Colin Garner: “R&D expenditure is increasing whilst Productivity is falling”
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
Organization of Critical Path Initiative within FDA

- **Commissioner’s Office: Office of Critical Path Programs**
  - Critical Path Steering Committee

- **CDER: Office of Translational Sciences**
  - Clinical Pharmacology
  - Biostatistics
  - Critical Path Initiatives
  - Intramural Research
The Critical Path to New Medical Products

Background
- Press Releases
- Speeches
- Testimony
- Presentations
- Frequently Asked Questions
- More

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 Presentations

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

Critical Path Report (March 2004)

http://www.fda.gov/oc/initiatives/criticalpath/
Critical Path Opportunities List
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**
<table>
<thead>
<tr>
<th>Topic</th>
<th>Sub-topics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>2. Standards for Microarray and Proteomics-Based Identification of Biomarkers</strong></td>
</tr>
<tr>
<td></td>
<td><strong>3. Qualifying Disease- and Disorder-Specific Biomarkers</strong></td>
</tr>
<tr>
<td></td>
<td><strong>4. Role of Beta Adrenergic Receptor Polymorphisms in Asthma Treatments</strong></td>
</tr>
<tr>
<td></td>
<td><strong>5. Pregnancy</strong></td>
</tr>
<tr>
<td></td>
<td><strong>6. Measures of Effectiveness of Fertility Treatments</strong></td>
</tr>
<tr>
<td></td>
<td><strong>7. Markers of Effectiveness of Treatment for Pre-term Labor</strong></td>
</tr>
<tr>
<td></td>
<td><strong>10. Circulating Biomarkers in Cardiovascular Diseases</strong></td>
</tr>
<tr>
<td></td>
<td><strong>11. Infectious Diseases</strong></td>
</tr>
<tr>
<td></td>
<td><strong>12. Proving the Efficacy of Preventive Vaccines</strong></td>
</tr>
<tr>
<td></td>
<td><strong>13. Markers of Disease Progression in Hepatitis C</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Cancer</strong></td>
</tr>
<tr>
<td></td>
<td><strong>11. Markers of Disease Progression in Prostate Cancer</strong></td>
</tr>
<tr>
<td></td>
<td><strong>12. Drug Targets as Critical Path Tools: Cancer Therapies</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Neuropsychiatric Diseases</strong></td>
</tr>
<tr>
<td></td>
<td><strong>13. Diagnostic Markers for Neuropsychiatric Conditions</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Presbyopia</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Autoimmune and Inflammatory Diseases</strong></td>
</tr>
<tr>
<td></td>
<td><strong>15. Markers of Disease Activity in Systemic Lupus Erythematosus, Inflammatory Bowel Disease, and Related Diseases</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Safety Biomarkers</strong></td>
</tr>
<tr>
<td></td>
<td><strong>16. Predicting Adverse Reactions to Vaccines</strong></td>
</tr>
<tr>
<td></td>
<td><strong>17. Early Indicators of Effects of Immune Responses on the Safety of Cell and Tissue Products</strong></td>
</tr>
<tr>
<td></td>
<td><strong>18. Predicting Cardiac Toxicity</strong></td>
</tr>
<tr>
<td></td>
<td><strong>19. Gene Therapy</strong></td>
</tr>
<tr>
<td></td>
<td><strong>20. Modernizing Predictive Toxology</strong></td>
</tr>
</tbody>
</table>

Copyright © Carl Peck, All Rights Reserved
### Topic 2: Streamlining Clinical Trials

<table>
<thead>
<tr>
<th>Topic</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advancing Innovative Trial Designs</td>
<td>8</td>
</tr>
<tr>
<td>34. Design of Active Controlled Trials</td>
<td>8</td>
</tr>
<tr>
<td>35. Enrichment Designs</td>
<td>8</td>
</tr>
<tr>
<td>36. Use of Prior Experience or Accumulated Information in Trial Design</td>
<td>8</td>
</tr>
<tr>
<td>38. Development of Trial Protocols for Specific Therapeutic Areas</td>
<td>9</td>
</tr>
<tr>
<td>39. Analysis of Multiple Endpoints</td>
<td>9</td>
</tr>
<tr>
<td>Improving Measurement of Patient Responses</td>
<td>10</td>
</tr>
<tr>
<td>40. Measuring Disease-Related Symptoms</td>
<td>10</td>
</tr>
<tr>
<td>41. Measuring Patient-Centered Endpoints</td>
<td>10</td>
</tr>
<tr>
<td>42. New Trial Design in Oncology</td>
<td>10</td>
</tr>
<tr>
<td>43. Improving Efficacy Endpoints for Infectious Diseases</td>
<td>10</td>
</tr>
</tbody>
</table>

**Streamlining the Clinical Trial Process**

<table>
<thead>
<tr>
<th>Topic</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>44. Development of Data Standards</td>
<td>10</td>
</tr>
<tr>
<td>45. Consensus on Standards for Case Report Forms</td>
<td>11</td>
</tr>
</tbody>
</table>

### Topic 3: Harnessing Bioinformatics

<table>
<thead>
<tr>
<th>Topic</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>46. Identification and Qualification of Safety Biomarkers</td>
<td>12</td>
</tr>
<tr>
<td>47. Virtual Control Groups in Clinical Trials</td>
<td>12</td>
</tr>
<tr>
<td>48. Adverse Event Data Mining</td>
<td>12</td>
</tr>
<tr>
<td>49. Multiple Complex Therapies</td>
<td>12</td>
</tr>
<tr>
<td>50. Modeling Device Performance</td>
<td>12</td>
</tr>
<tr>
<td>51. Clinical Trial Simulation</td>
<td>12</td>
</tr>
<tr>
<td>52. Failure Analysis</td>
<td>13</td>
</tr>
<tr>
<td>53. Natural History Databases for Rare Diseases</td>
<td>13</td>
</tr>
</tbody>
</table>
Critical Path Opportunities Initiated During 2006

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
Critical Path Collaborations with NIH

- Joint workshops with FDA
  - Genetic basis of Adverse Events – December 11 & 12, 2006
  - Imaging in Alzheimer’s Disease

- Drug development education for NIH
  - NIAID
  - National Institute on Aging
  - Individual Scientist Assistance
Public/Private Partnerships

- **Predictive Safety Testing Consortium**
  - CDER-OCP, CPath Institute, 15 pharma firms
  - Pre-clinical toxicogenomic biomarkers
    - Nephrotoxic biomarkers expected early 07

- **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 Collaboration**
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