Principles of Clinical Pharmacology
NIH, April 26, 2012

FDA Guidance,
Clinical Pharmacology,
and
“Regulatory Science”

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

UCSF-CDDS 2012
Acknowledgements & Affiliations

- Contributors to ideas presented today
  - All of our colleagues in FDA & IMI/PharmaTrain

- Disclosures
  - CDDS (http://cdds.ucsf.edu)
  - NDA Partners LLC (www.ndapartners.com)

UCSF-CDDS 2012
Why FDA?

What does FDA* do, When & How?

Clinical Pharmacology at FDA*

“Regulatory Science” and Training

* Focus: CDER, CBER
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, Politicization, and Transparency

- Evolution of Drug Regulation (R. Temple)

\[
\text{SAFETY} \rightarrow \text{EFFECTIVENESS} \rightarrow \text{INDIVIDUALIZATION} \\
\text{.....} \rightarrow \text{PERSONALIZATION} \rightarrow \text{SAFETY} \rightarrow \text{??????}
\]
What does FDA do: provision of standards & 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
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)
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
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) & hepatic dysfunction (03)
- Pediatric Pharmacokinetic Studies for Drugs (98), pregnancy (04), lactation (05)
- Population Pharmacokinetics ( 99)
- Exposure-Response (03)
- Exploratory IND Studies (05)
When does FDA engage?

Figure 7: Industry - FDA Interactions During Drug Development

- Basic Research
- Prototype Design or Discovery
- Preclinical Development
- Clinical Development

IND Review Phase

- Pre-IND Meeting
- Initial IND Submissions
- End of Phase 2 Meeting
- Pre-BLA or NDA Meeting
- Market Application Submission
- End of Phase 3 Meeting
- Safety Update

Application Review Phase

FDA Filings, Approval & Launch Preparation

FDA Initiative: Innovation vs Stagnation - Challenge & Opportunity on the Critical Path to New Medical Products, March 2004
FDA “Question-based Review Template”*

- Exposure-response for safety & efficacy?

- Drug-drug interaction questions
  - CYP substrate, inhibitor, inducer?
    - Genetic influences?
    - P-glycoprotein substrate and/or an inhibitor?
    - Other metabolic/transporter pathways?
    - Pharmacodynamic drug interactions?
    - Active metabolites, protein binding?
    - PKPD modeling?

*Question Based Review
*Extracted from FDA MAPP 4000.4 (4/27/04)
When does FDA engage?

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 Filings, 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
- Ongoing Submission
- Pre-BLA or NDA Meeting

FDA Initiative: Innovation vs Stagnation - Challenge & Opportunity on the Critical Path to New Medical Products, March 2004
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
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)
**Mapping S&E Adult Dosage to Children**

- **Principle** - Pediatric effectiveness / safety are inferred via mapping D-E-R from adults to pediatrics

- **Requires**
  - Adult Dose-Exposure-Response relationship (PK & ER)
  - Pediatric Dose-Exposure relationship (PK)
  - **Confirmatory clinical trial if substantiation is required**
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
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
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
U.S. FDA Perspective: Impact Of Modeling & Simulation on Regulatory Decision Making *
C. Garnett, J. Gobburu

PM Reviews of 198 IND/NDA/BLA (‘00-’08)
- Trial designs, QT, EOP2a
- popPK, E-R, Peds (38)
- Impacted >60% APP, labeling
- Evidence of effectiveness (9) & APP unstudied doses (21)

Research & Policy
- TQT design & E-R analyses
- Disease models (2+5)
SAFETY & 2007 FDAAAA

- 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
Advancing Regulatory Science for Public Health
“Regulatory Science”
FDA’s Definition

“Regulatory science is the science of developing new tools, standards and approaches to assess the safety, efficacy, quality and performance of FDA-regulated products.” ¹

¹Advancing Regulatory Science for Public Health – A Framework for FDA’s Regulatory Science Initiative, October 2010
FDA’s Regulatory Science Priorities

- Modernizing *Toxicology*
- Crafting New Tools for *Personalized Medicine*
- Supporting New & Improved *Manufacturing Technologies*
- Readiness to *Evaluate Innovative Technologies*
- Expanding FDA’s Information Technology Infrastructure
- Implementing Prevention-focused Food Safety
- Speeding Development of *Medical Countermeasures*
- Developing Communications Strategies to help FDA Adapt to new Information Sharing Technologies
NIH & FDA

- 2-24-10 NIH and FDA Announce Collaborative Initiative to Fast-track Innovations to the Public: Joint NIH-FDA Leadership Council "for Translational + Regulatory Science

- 2-26-10 NIH Grants: Advancing Regulatory Science through Novel Research and Science-Based Technologies (U01): “…study applicability of novel technologies … towards the development and regulatory review of medical products …“

- 7-15-11 FDA Collaborating Centers of Excellence in Regulatory Science and Innovation
FDA Regulatory Science Initiative

IOM – FDA Workshops


- 3-29-11: “Advancing Regulatory Science for Medical Countermeasure Development “

- 9-20-11: Strengthening a Workforce for Innovative Regulatory Science in Therapeutics Development
Training in Drug Development & Regulation

- European Course in Pharmaceutical Medicine (ECPM) – 1991 to present
- Drug Development & Regulatory Science (CDDS, ACDRS)
American Course on Drug Development & Regulatory Science (ACDRS)

- Conceived 2006, launched 2007 - UCSF
- Evolved from (ECPM), CDDS @ Georgetown University, FDA staff college
- Emphases –
  - **Principles**
  - Quantitative/ learn – confirm approach to improving drug development process and efficiency
  - Best practices integration of *principles of efficient medical product development and regulatory science*
  - Highly experienced, currently active drug development scientists, regulators, selected academics
  - Participants committed to a career in DD&RS

Cantilena 2012

UCSF-CDDS 2012
Principles of Drug Development Science *

- Identifying an Unmet Medical Need
- Product Readiness
- Value-Driven Program Management / Execution
- “Learning and Confirming”
- Regulatory Collaborations

* www.NDAPartners.com
Principles of Regulatory Science

- **Protection**
  - Harmful effects, misinformation

- **Assurance**
  - Quality, effectiveness, valid scientific information

- **Enforcement**
  - Standards, regulations

- **Access & Facilitation**
  - **Effective** medicines, information
    - Patients, caregivers, manufacturers, public
ACDRS Session Themes

Session 1: The Pharmaceutical Development Enterprise: Current and Future Perspectives

Session 2: Learning Trials: From Discovery to First in Humans

Session 3: Learning and Confirming Trials: Finding and Confirming the Right Dose

Session 4: Confirmatory Trials: Methodology and Biostatistics

Session 5: Global Registration and Approval Process

Session 6: Integrated Product Development
Future Offerings:

- Masters in Drug Development/Regulatory Sciences
  - Drug Safety/Pharmacovigilance Track
  - Drug Safety/Pharmacovigilance Specialist Certificate

- Masters in Drug Development/Regulatory Sciences: Drug Safety/Pharmacovigilance Track

- Masters in Drug Development/Regulatory Sciences: Drug Safety/Pharmacovigilance Specialist

- Masters in Drug Development/Regulatory Sciences: Drug Safety/Pharmacovigilance Clinical Toxicology Track

- Masters in Translational Medicine: Joint UCSF (CTSI/BTS) and UCB Degree

Other Offerings:

- Drug Development/Regulatory Sciences Certificate
- Pharmacometrics/Systems Pharmacology Specialist
- ACDRS Certificate
- Intro to Biostats Certificate
- PK for Pharmaceutical Scientists Certificate
- Clinical Toxicology Certificate
- UCSF SOP/BTS Online & Blended Program Offerings

UCSF SOP/BTS

University of California
San Francisco
Innovative Medicines Initiative

IMI is the European Innovative Medicines Initiative

Unique and large-scale top-level public-private partnership (academia and industry etc.) between the European Union (EU) and the European Federation of Pharmaceutical Industries and Associations (EFPIA) – to speed up research in discovery and development of safer and more effective medicines.
IMI Education and Training Projects

EMTRAIN
European Medicines Research Training Network

Eu2P
EUROPEAN PROGRAMME IN PHARMACOVIGILANCE AND PHARMACOEPIDEMIOLOGY

PharmaTrain
MASTERING MEDICINES DEVELOPMENT

EUPATI
European Patients Academy on Therapeutic Innovation

SafeSciMET
European Modular Education and Training Programme in Safety Sciences for Medicines

imi.europa.eu
PharmaTrain Objectives

- To provide a Europe-wide comprehensive solution to training needs of integrated drug development (sciences) for all professionals involved, incl. physicians, pharmacists, pharmaceutical scientists, biologists, biometricians, health economists, safety & regulatory scientists from universities, regulatory agencies, all industry as well as research ethics committees & investigators.

- To create (new) multi-modular programmes of advanced studies in pharmaceutical medicine / drug development sciences leading to a postgraduate Master Sc / Specialist qualification and accreditation, and based on the Bologna credit and title system with 60+ ECTS credits.

*as defined in the Expression of Interest and Full Project Proposal (Annex I to Grant Agreement)*
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