Role of FDA in guiding Drug Development

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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
    * 1902/6, 1938, 1962, 1972, 1984, 1987, 1997, 2004-2007
  - a uniquely American phenomenon
    * Investment in FDA
    * Politicization

* Evolution of Drug Regulation (R. Temple)

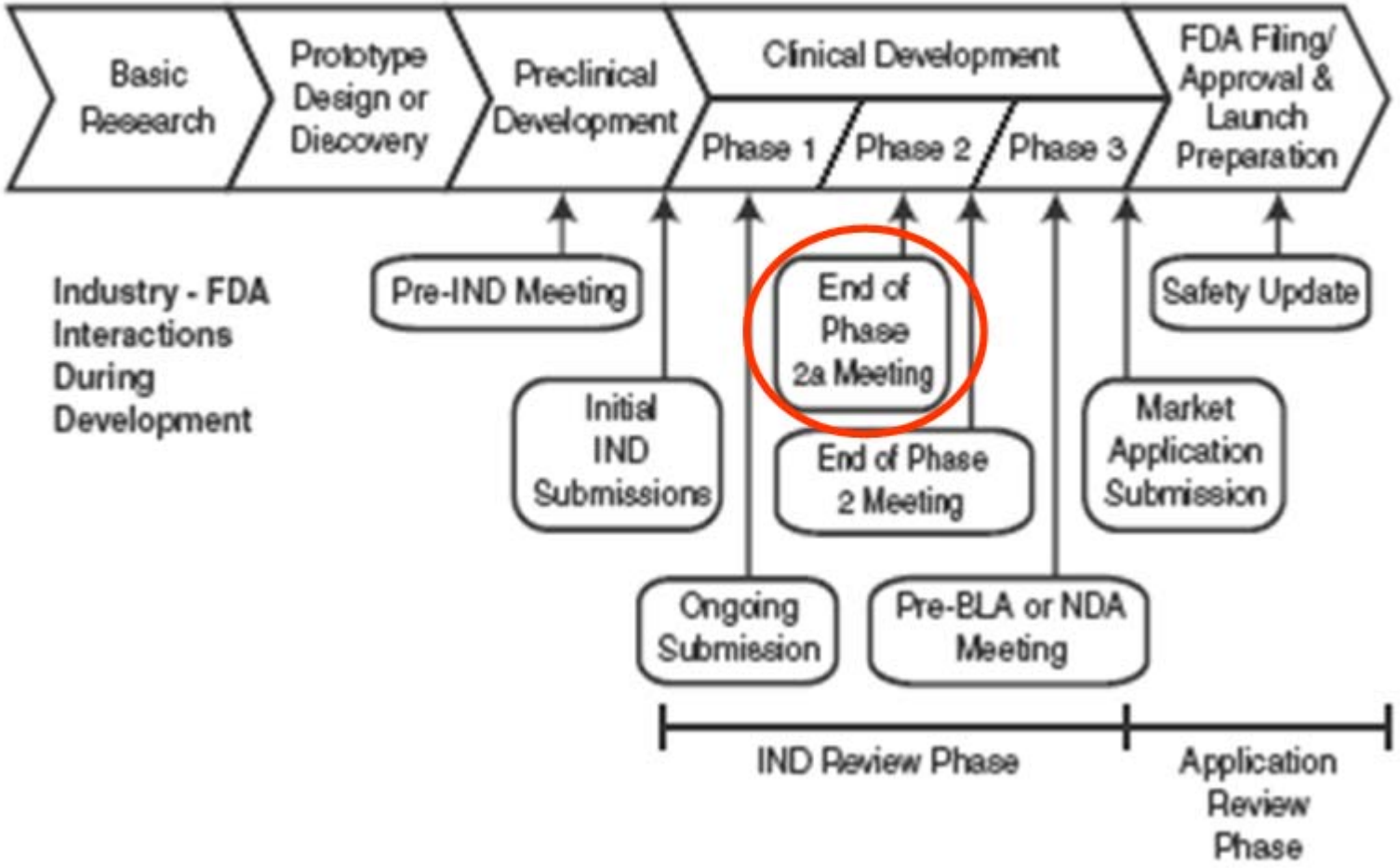
SAFETY → *EFFECTIVENESS* → *INDIVIDUALIZATION*

..... → *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



FDA Initiative: Innovation vs Stagnation - Challenge & Opportunity on the Critical Path to New Medical Products, March 2004

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 modelPlacebo 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**

Website - www.fda.gov

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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[1]Food 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 evaluatio FDA pharmacometricians, even when such ana not conducted by the sponsor. Pharmacom were pivotal in regulatory decision making in half of the 42 NDAs. Of the 14 reviews that were pivotal to approval related decisions, 5 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.

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.

AAPS Journal 2005;7 (3) Article 51 (www.aapsj.org)

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], C Bonapace[1], DM Chilukuri[1], JZ Duan[1], C Garnett[1], JVS Gobburu[1], SH Jang[1], L Kenna[1], LJ Lesko[1], R Madabushi[1], Y Men[1], JR Powell[1], W Qiu[1], RP Ramchandani[1], CW Tornoe[1], Y Wang[1] and JJ Zheng[1]

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.

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**

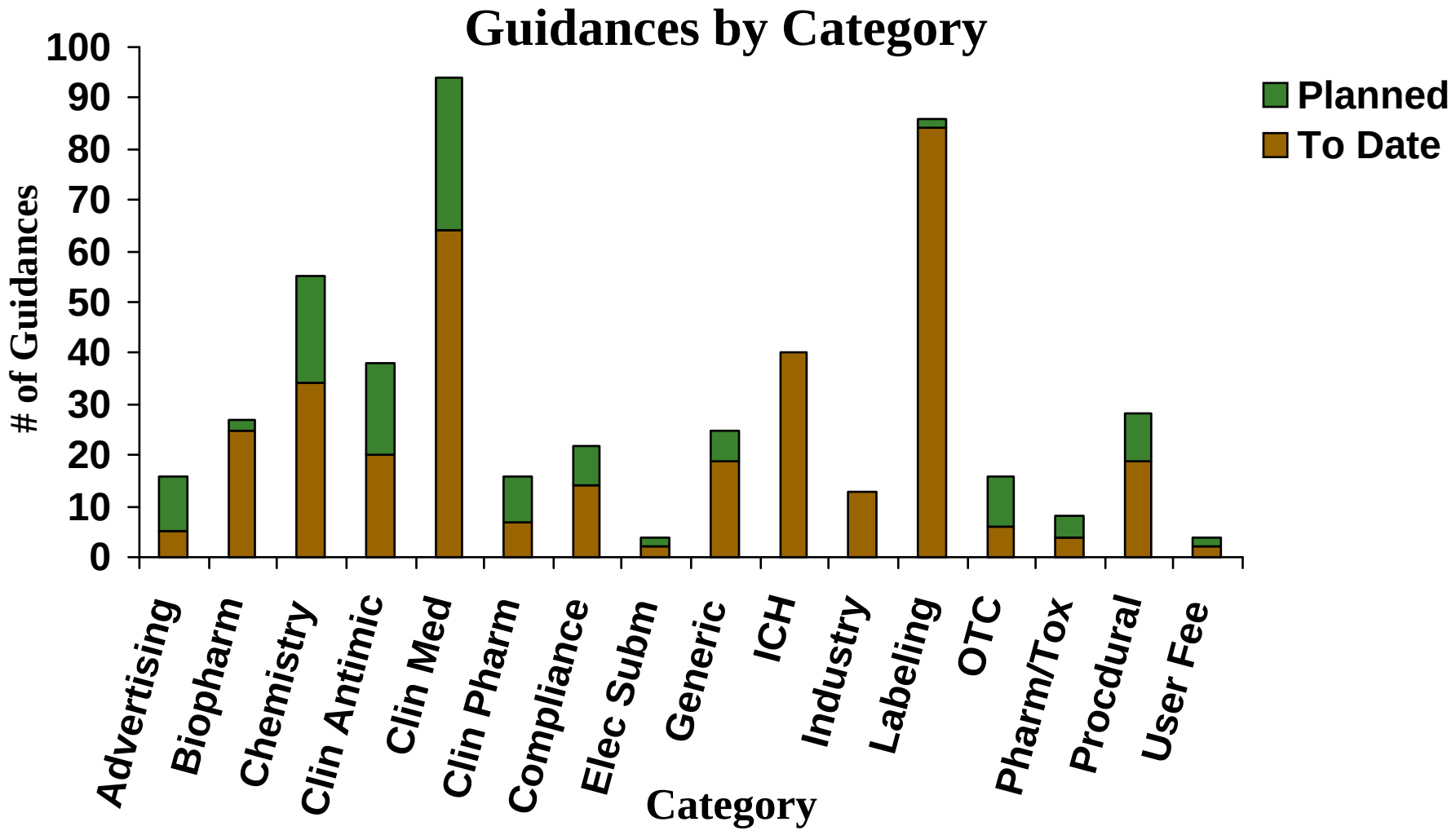
- safety
- effectiveness
- trial design

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

Planned Guidances (as of 2000)



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) 301-827-4573
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

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**

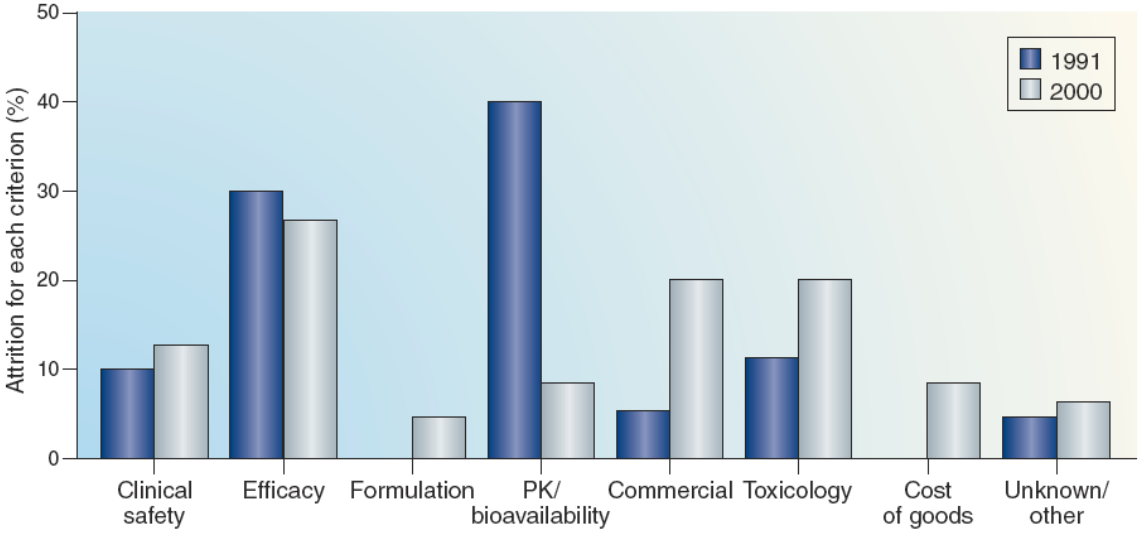
- Single Dose - 1/100 est. pharmacological dose or < 100 ug
  - * Single species (rodent), 14 day observation
- Multiple Dose (<1/50 NOAEL + max 1/4 of 2 wk NOAEL)
  - * Two species, 14 day repeat dose

PERSPECTIVES

Nontraditional approaches to first-in-human studies to increase efficiency of drug development: will microdose studies make a significant impact?

RA Boyd[1] and RL Lalonde[1]

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 81 NUMBER 1 | JANUARY 2007



Lappin, G. *et al.* Use of microdosing to predict pharmacokinetics at the therapeutic dose: experience with 5 drugs. *Clin. Pharmacol. Ther.* **80**, 203–215 (2006).

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

* **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"**

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

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*

FDA – what's new?

*** Leadership**

- **Commissioner Eschenbach, (Crawford), (McClellan), (Henney), (Kessler)**
- **CDER Director (Woodcock)**

*** Safety**

* Drug withdrawals (Vioxx et al) (04)

- 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)

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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School of Pharmacy,
University of California San Francisco

Applied to pediatrics

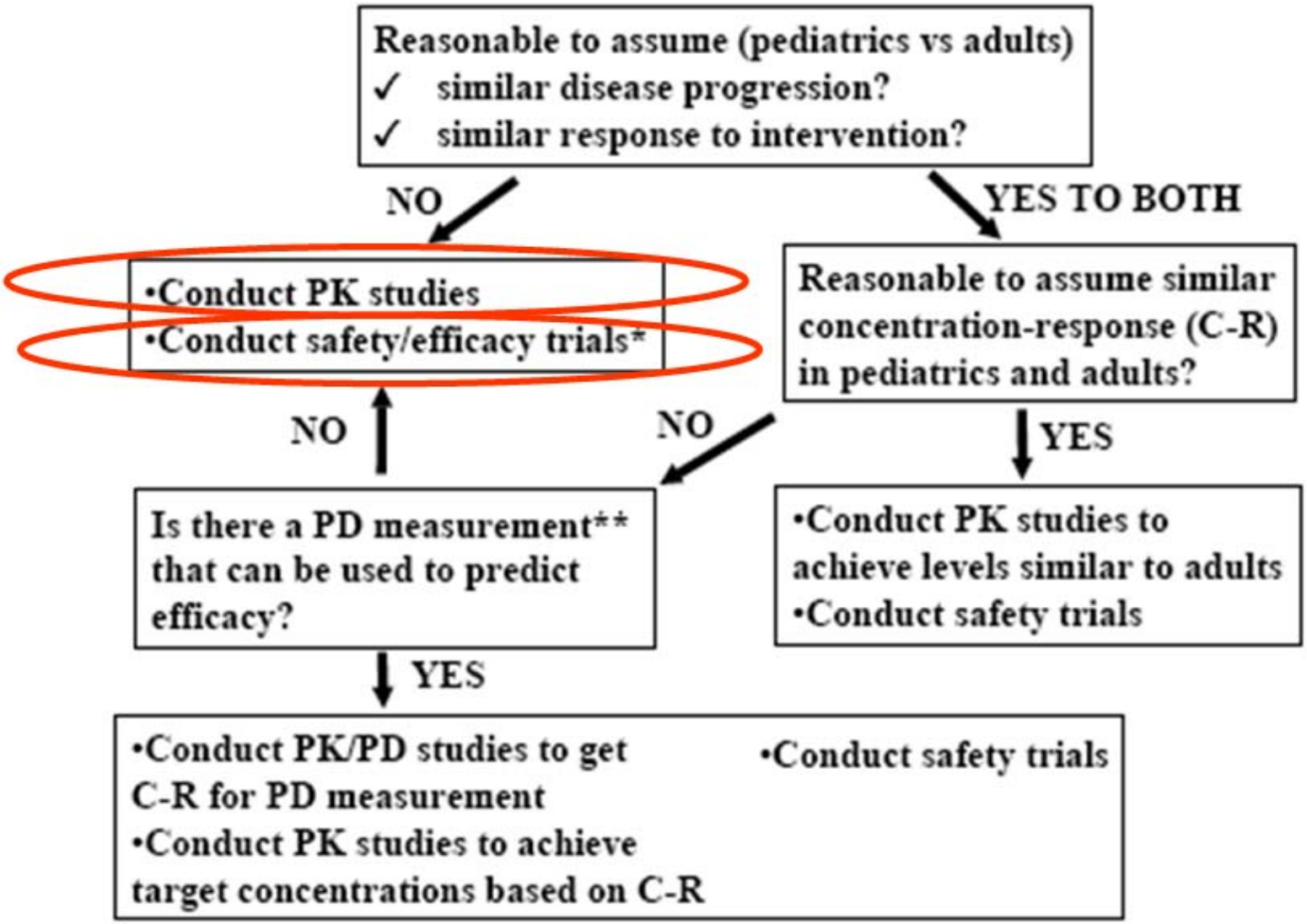
* **Principle** - Pediatric effectiveness / safety are inferred via mapping D-E-R from adults to pediatrics

* **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



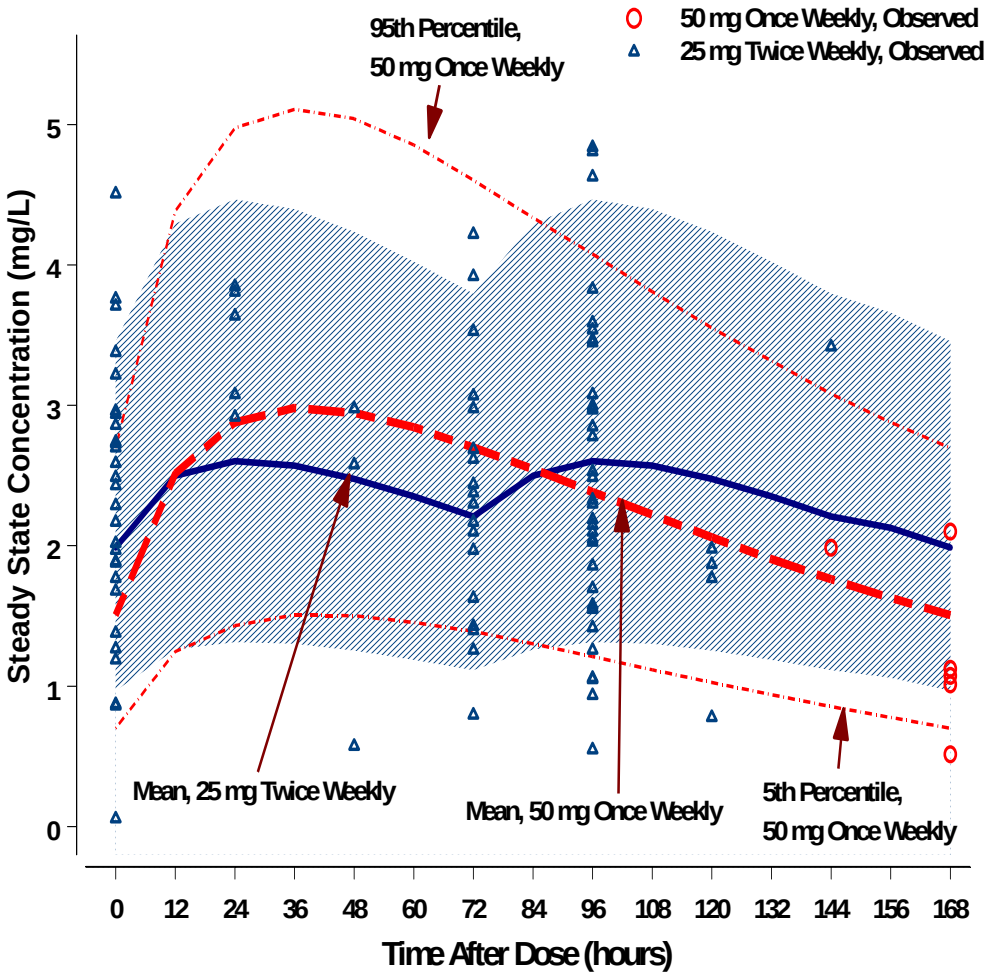
http://www.fda.gov/cder/guidance/5341fnl.pdf

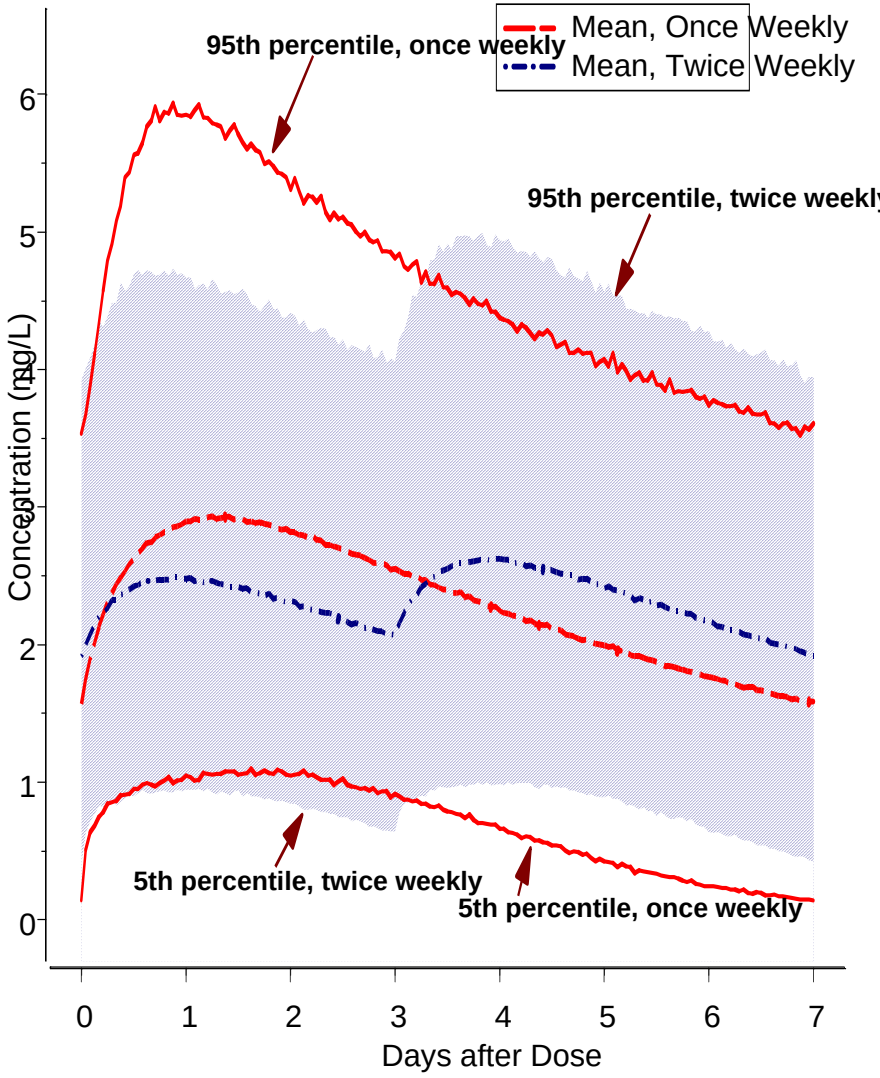
Example - Enbrel (etanercept)

* 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

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





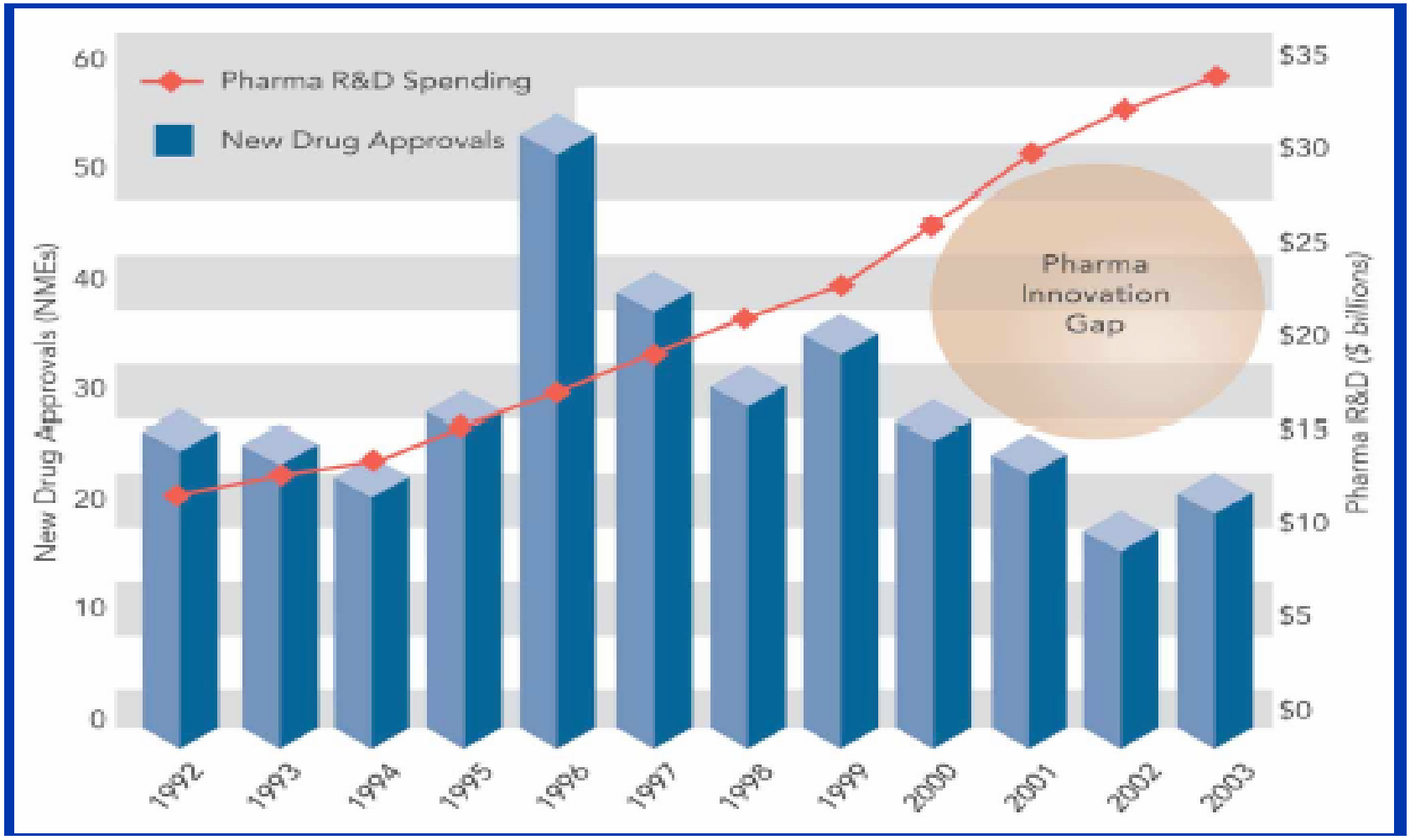
Innovation

Stagnation

Challenge and Opportunity on the Critical Path to New Medical Products

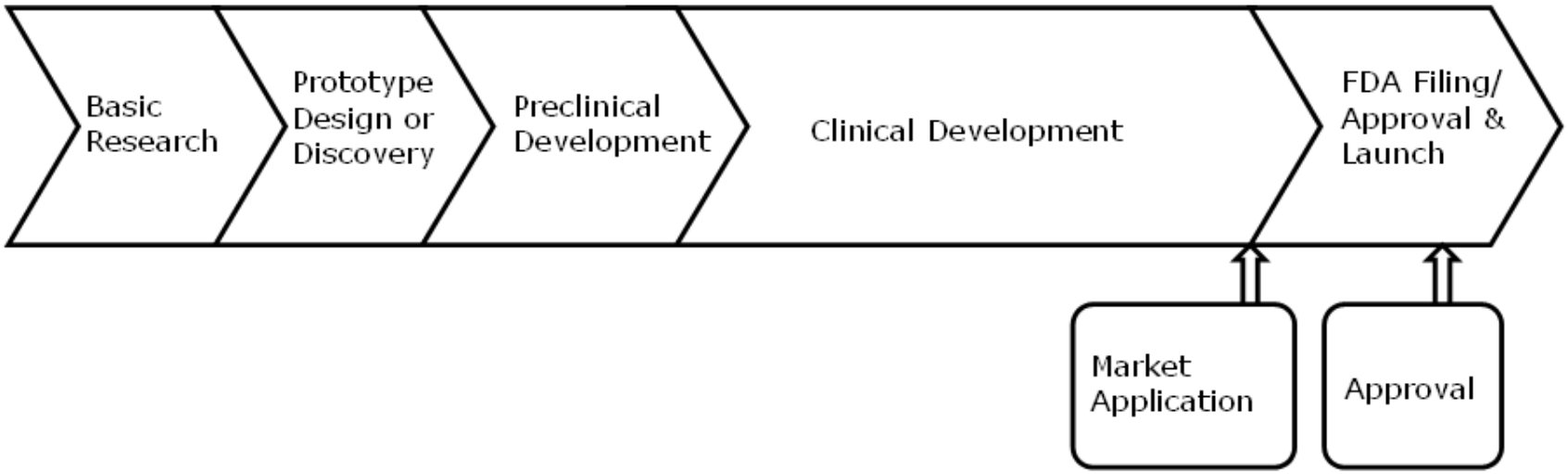
U.S. Department of Health and Human Services
Food and Drug Administration

March 2004



Adapted From Colin Garner: “R&d expenditure is increasing whilst Productivity is falling”

Stagnation → *Innovation*



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

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. More.

Background

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

Opportunities List

- Report [PDF 447 KB]
- List [PDF 486 KB]
- Press Release

Critical Path Report (March 2004)

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

Contact Us

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

Critical Path Opportunities List

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

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**

Critical Path Opportunities Initiated During 2006

Printable version of this report [436 KB]

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. 1 Where appropriate, an activity is designated as directly linked to one of the 76 specific scientific opportunities, 2 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