Update on the Critical Path and Personalized Medicine Initiative Implementation

R&D Leaders Forum Spring 2007

Philadelphia, PA
March 5, 2007

Felix W. Frueh, PhD
Office of Clinical Pharmacology
CDER/FDA

What I want to talk about

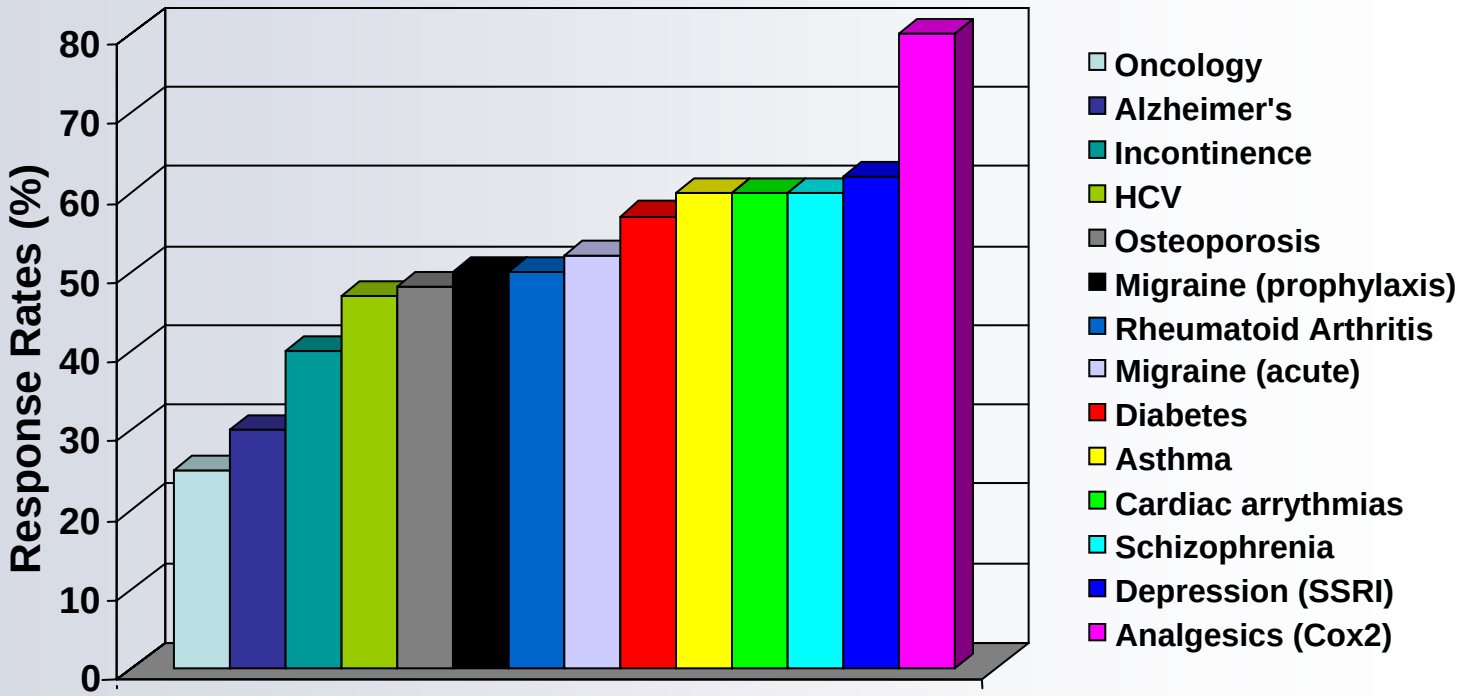
- Personalized Medicine and the Critical Path
  - Drivers for change
- Biomarkers – their use and issues around their use in:
  - New drug development
  - Label updates
  - Clinical trials
- New ways to collaborate – the role of consortia
  - Example: Predictive Safety Testing Consortium
  - Impact of this effort on infrastructure development at the FDA
- Conclusions

Personalized Medicine and the Critical Path

- Personalized Medicine is more than a buzz-word – it is a clinical, scientific, business, and regulatory opportunity:
  - Physicians are practicing personalized medicine today (ask them!) what *we* call Personalized Medicine will help doctors and patients to make better informed drug therapy decisions
  - New tools allow us to do it – today
  - Drugs can be developed more efficiently and successfully, perhaps even cheaper
  - Regulators will be able to make better decisions
- The Critical Path is the period of first-in-man to drug launch: this is precisely the period during which medicines can be "personalized"
- There are many good reasons why it is a good idea to do this

Public Health and the Critical Path to Personalized Medicine

1. The **response rate** to current medicines is often unacceptably low:



After *Spear et al. TRENDS in Molecular Medicine Vol.7 No.5 May 2001*

Public Health and the Critical Path to Personalized Medicine

2. Staggering number of **adverse events** and increasing associated health costs

- ADRs are the 4th to 6th leading cause of death in the United States with >2 mio. cases annually, 100,000 of them fatal
- Overall incidence of drug-related ADRs is 7%
  Lazarou et al, JAMA, 279, 1200, 1998
- 28% of hospitalized patients have drug-related ADRs
  Miller al, Am. J. Hosp. Pharm 30, 584, 1973
- Cost of drug-related morbidity and mortality is $177 billion
  Ernst et al, J. Am. Pharm. Assoc., 41, 192, 2001

- Identifying who will benefit from a specific drug treatment and who might be at risk is the obvious thing to do
- Health care won't get cheaper because of Critical Path and Personalized Medicine, but it provides an opportunity to shift costs to more productive efforts, such as prevention and adequate therapies

Public Health and the Critical Path to Personalized Medicine

3. **Unmet medical needs**
   - There are about 6,000 orphan diseases (NIH data)
   - Recent estimates put the number of potential drug targets at around 3.5% of the human genome (~1050 genes), yet
   - > 50% of all drugs target only 4 key gene families:
     - Class I GCPR
     - Nuclear receptors
     - Ligand-gated ion channels
     - Voltage-gated ion channels
- This relates to reason 1. “response rate”: we don’t understand in many cases why patients respond/ do not respond
  - Once we do, many diseases might in fact be orphan, i.e. they are subcategories of a broader phenotype
- And then, there was the Human Genome Project:

The Human Genome Project – Identification of New Drug Targets

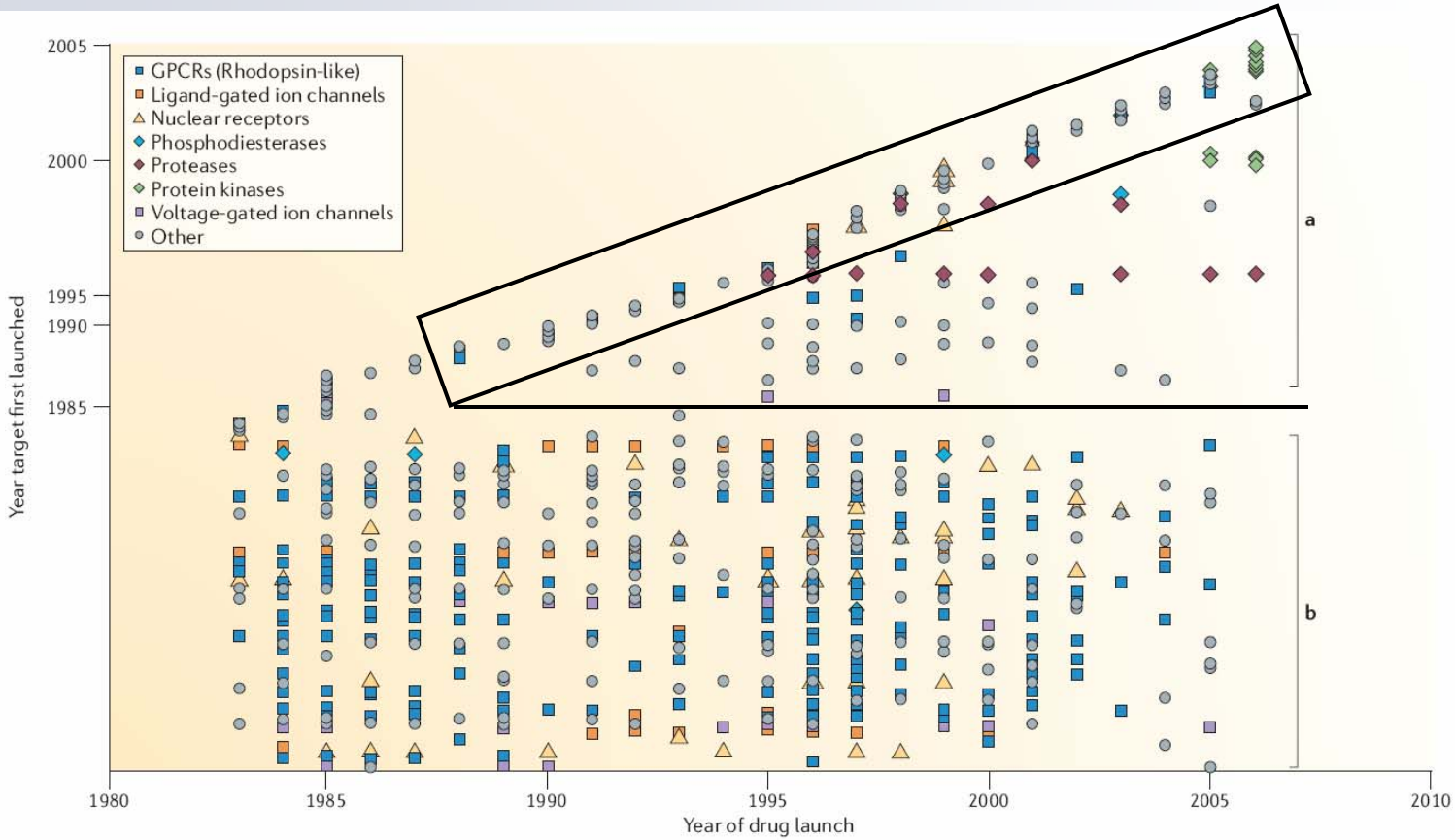
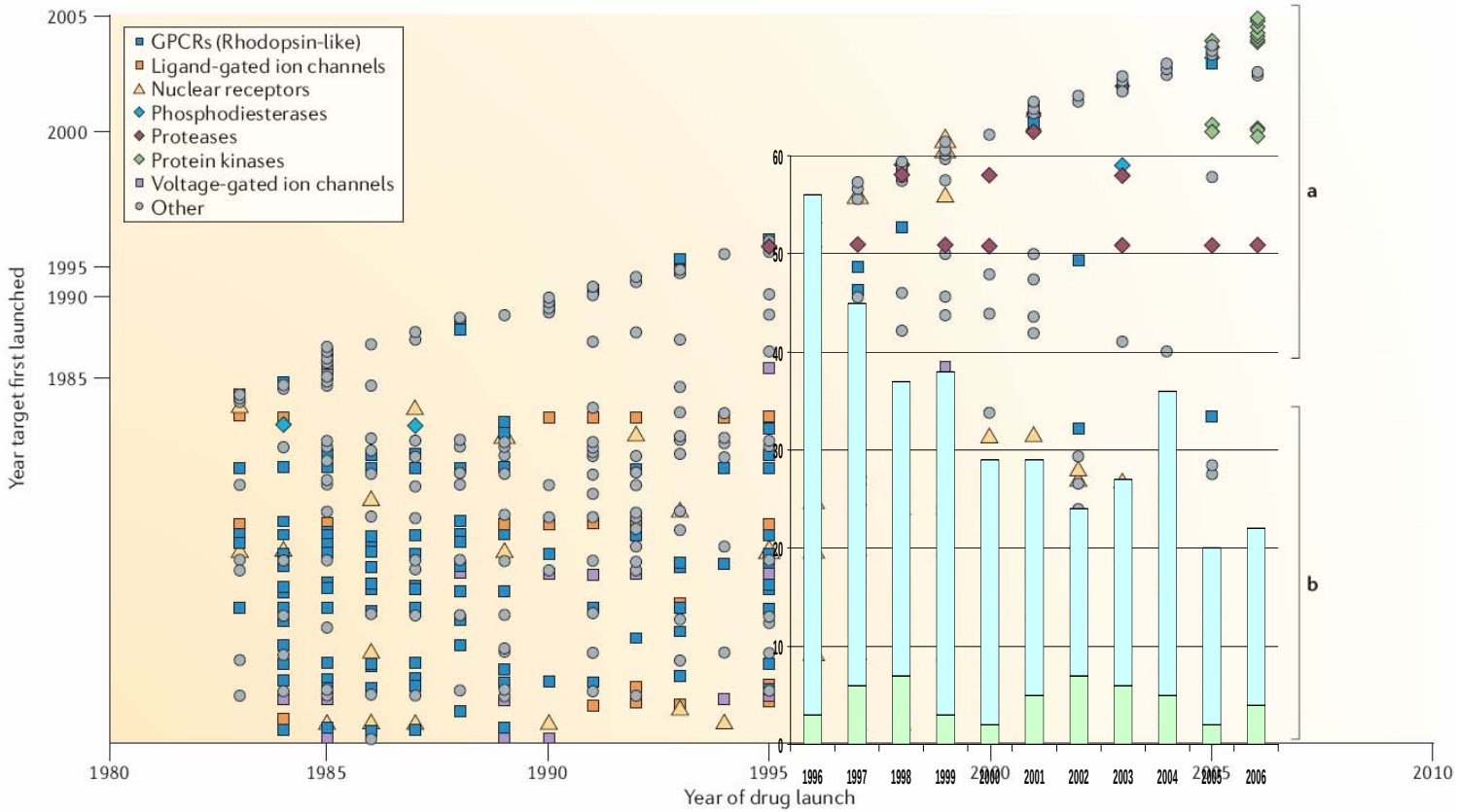


Figure 3 | **Rate of target innovation.** The y-axis represents the year of first drug launch against each target, and the x-axis is the year of each subsequent drug release, with the plot ordered so that more recently 'drugged' targets are shown at a higher y ordinate. Region **a** reflects periods of high target innovation (after 1982) while region **b** is predominantly the re-use of established mechanisms. The rate of new protein families per year is 1.9.

John P. Overington, Bissan Al-Lazikani and Andrew L. Hopkins, Nature Drug Discovery Reviews, Vol. 5, Dec 2006

… but it does not translate into an increase in new products



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As a Result, the Gap between Bench and Bedside Continues to Grow *(… but this does not mean we've made no progress!)*

- There is no shortage on new science, but it remains underutilized in drug discovery and development (the missing link is effective translational medicine)
- Impetus on public health and personalized medicine:

  We continue to use drugs with not enough understanding of the molecular mechanisms, which:

  1. Determine who responds to a specific drug
  2. Determine who is at risk for experiencing an adverse event
  3. Cause disease

- The question is, how do we effectively use our new knowledge in drug development, and how is this risk rewarded
- However, drug development has traditionally been a pragmatic process:

Nobel Prize 1988 for *"discoveries of the important principles of drug treatment"* – not so Critical Path-ish

The Nobel Chronicles

Three scientists jointly received the 1988 Nobel Prize in Physiology or Medicine, "for their discoveries of the important principles of drug treatment".

Born in Uddingston, Scotland, James Black (figure, left) studied medicine at the University of St Andrews. In 1958, he joined the Pharmaceutical Division of Imperial Che… Industries.

In 1948, American sci… Reymond Alquist had proposed… two sets of receptors were pres… α and β—that might explain… paraoxical actions of epinephrin… norepinephrine on the cardiac m… Black and his colleagues atter… to characterise these receptors. … isproterenol, an analogue of n… nephrine, they synthe… propranolol—a β-receptor antag… which became invaluable in the … ment coronary-artery diseases.

Black moved to Smith, Kline… French Company (now Smith…

Beecham) in 1964 and pursued antihistamine research. Since the antihistamines available then could inhibit nasal secretions, but not gastric-acid secretions, Black proposed the existence of a different receptor (H2), akin to the β receptor. Using a

1988: James Whyte Black, (b 1924), Gertrude Elion (1918–99), and George H Hitchings (1905–98)

carded the old "magic bullet" method and applied the basic principles of biochemistry and physiology. Having found that bacteria needed folic acid and purines for DNA synthesis, they were able to develop 6-mercaptopurine (6 MP), an effective chemother…ent against leukaemia.

…the same principles that …6 MP, Elion and Hitchings …in producing a series of … 1950, they developed …amine; then came trimetho… …thioprine, and allopurinol; … 1975, they synthesised …a powerful antiviral agent …herpes virus. Elion and … pioneering principles in …logy were also instrumental …velopment of 5-fluorouracil, …and adenine arabinosides, … recently, azadiothymidine …e, AZT).

> "The most fruitful basis for the discovery of a new drug is to start with an old drug"
>
> *- James Black*

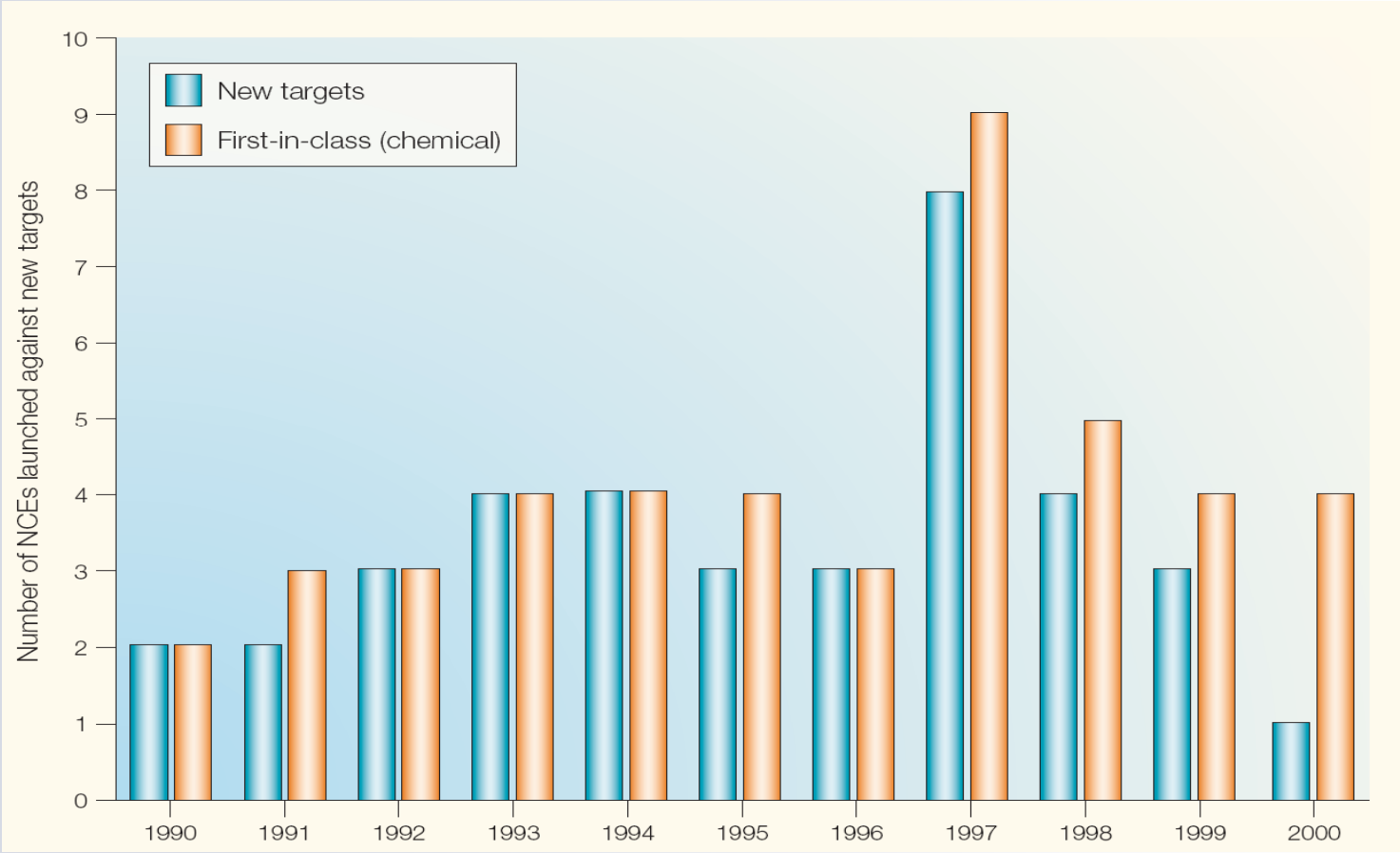
… of her sex, Elion faced numerous obstacles in her career. A compassionate, inspiring, and industrious scientist—she never stopped working until her sudden death in February, 1999—Elion once said, "The Nobel Prize is fine, but the drugs I have developed are rewards in themselves."

Tonse N K Raju
University of Illinois, Chicago, IL, USA

The Nobel Foundation

THE LANCET • Vol 355 • March 18, 2000

Since a decade, most NCEs are directed against old targets



Andrew L. Hopkins and Colin R. Groom, Nature Review Drug Discovery, Vol. 1, Sept 2002

What Has Gone Wrong ?

- Translation of new, cutting-edge science into successful drug development program happens more slowly than anticipated (e.g. “genome hype”)
- Lack of a predictable regulatory environment (e.g. the first final PGx-related guidance issued only in 2005, many more clarifications are needed)
- Industry, until recently, unwilling to change business model: the use of a biomarker-driven development plans was feared to lead to market segmentation and competitive disadvantage
- Dialogue between pharmaceutical and device companies has not happened; products have very different life-cycles making alignment of the two development processes difficult
- Many of these aspects have been realized and are being addressed in the “Critical Path” Initiative

From Stagnation to Innovation: FDA's Critical Path Initiative

- "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."

- 2006 – Critical Path Opportunity List – 76 opportunities characterized in six broad topics:
    1. Biomarker development
    2. Streamlining clinical trials
    3. Bioinformatics
    4. Manufacturing
    5. Combat emerging infections and bioterrorism
    6. Developing therapies for children and adolescents

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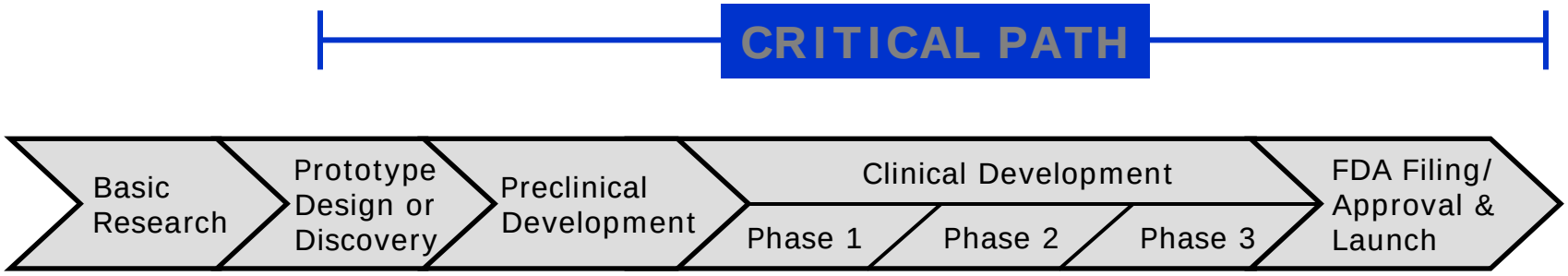
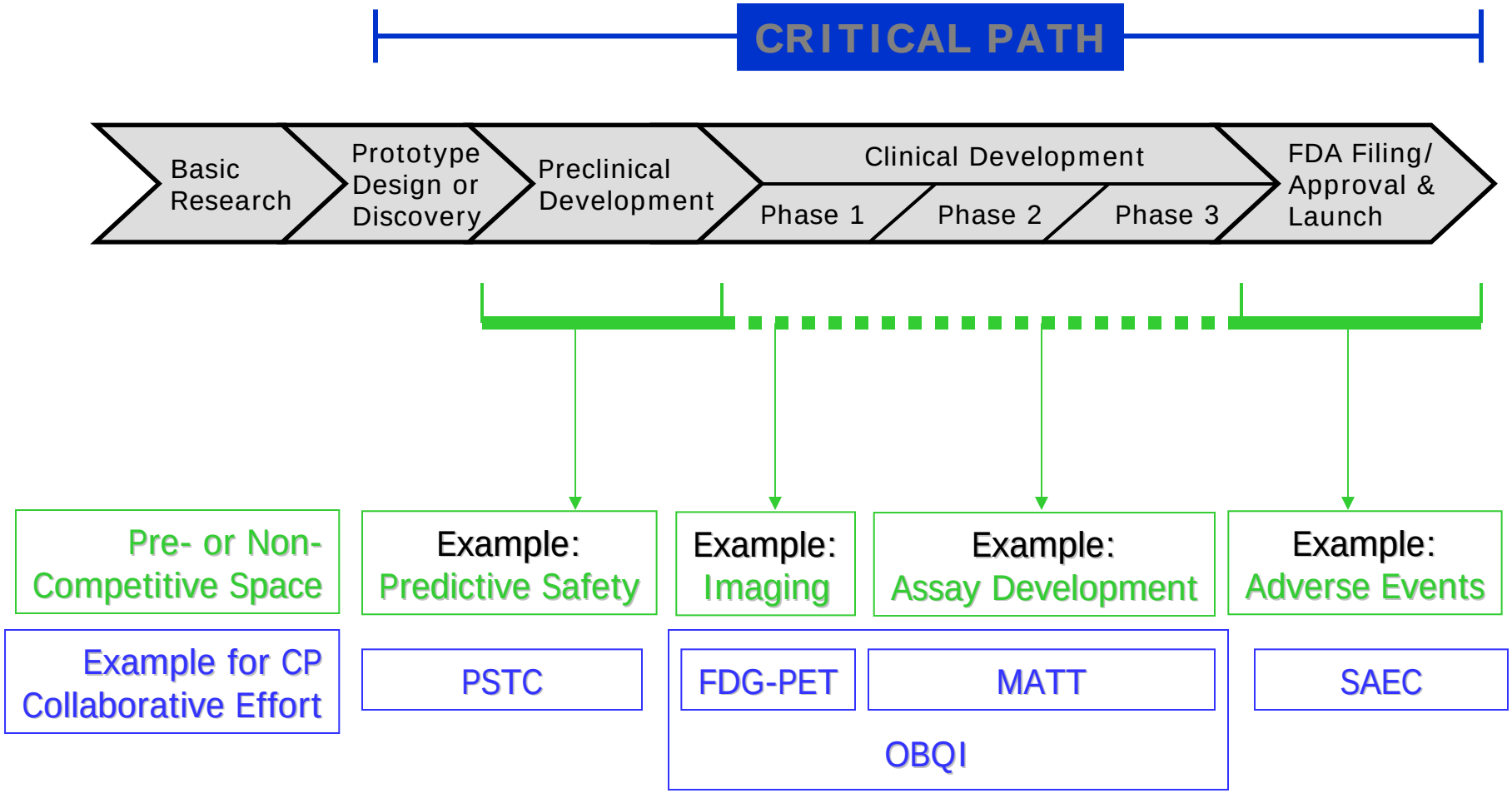
Is This Drug For You ?
Biomarkers Connect Critical Path Science to Personalized Medicine

Critical Path and Biomarker Development



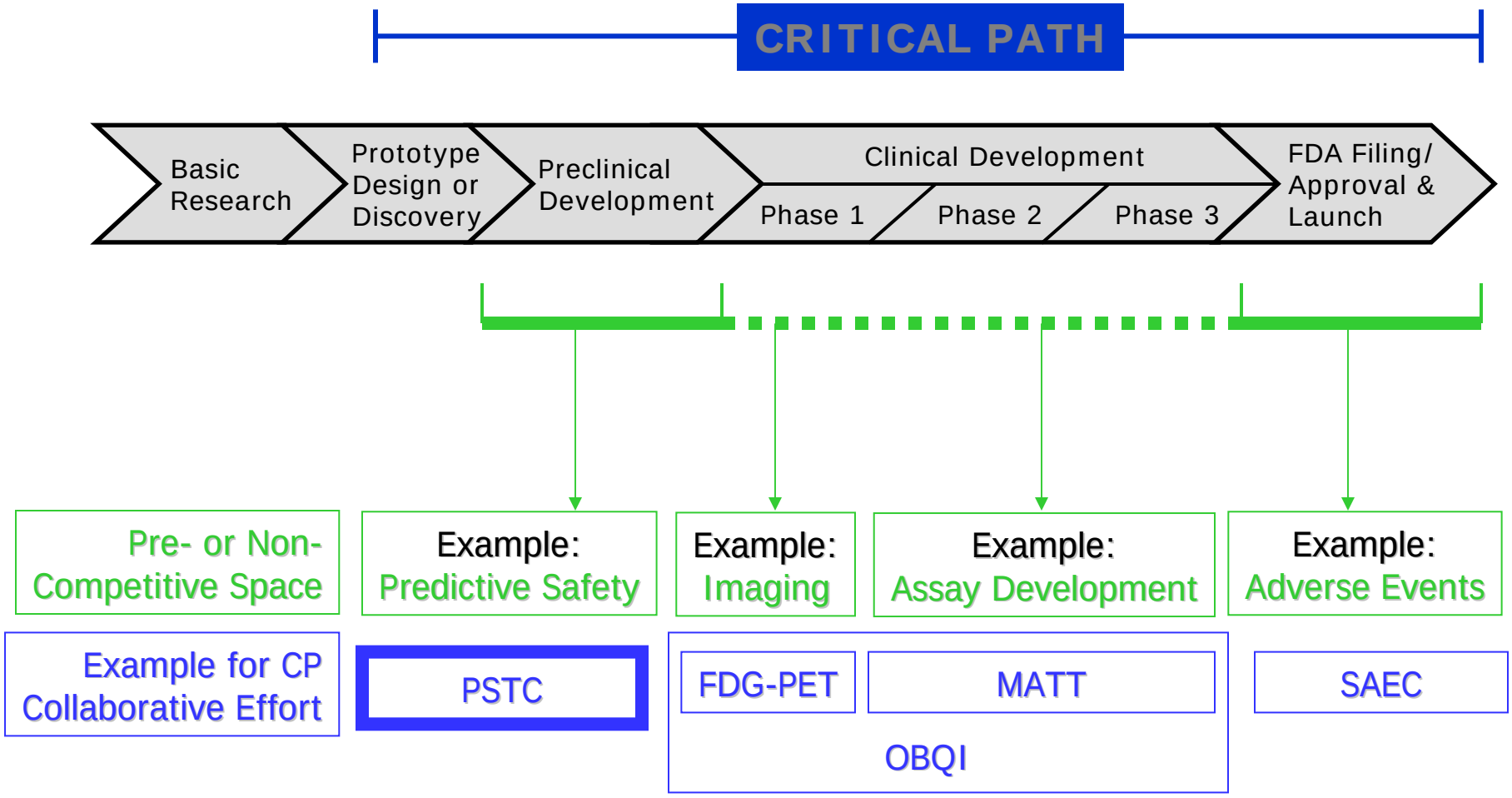
How can the Critical Path Initiative foster biomarker development and use?

Pre- or Non-Competitive Space



> 35 Critical Path projects initiated so far, will continue to unfold

Pre- or Non-Competitive Space



Predictive Safety Testing Consortium

U.S. Food and Drug Administration

U.S. Department of Health and Human Services

FDA Home Page | Search FDA Site | FDA A-Z Index | Contact FDA | FDA Centennial

FDA News

FOR IMMEDIATE RELEASE
P06-40
March 16, 2006

Media Inquiries:
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888-INFO-FDA

FDA and the Critical Path Institute Announce Predictive Safety Testing Consortium

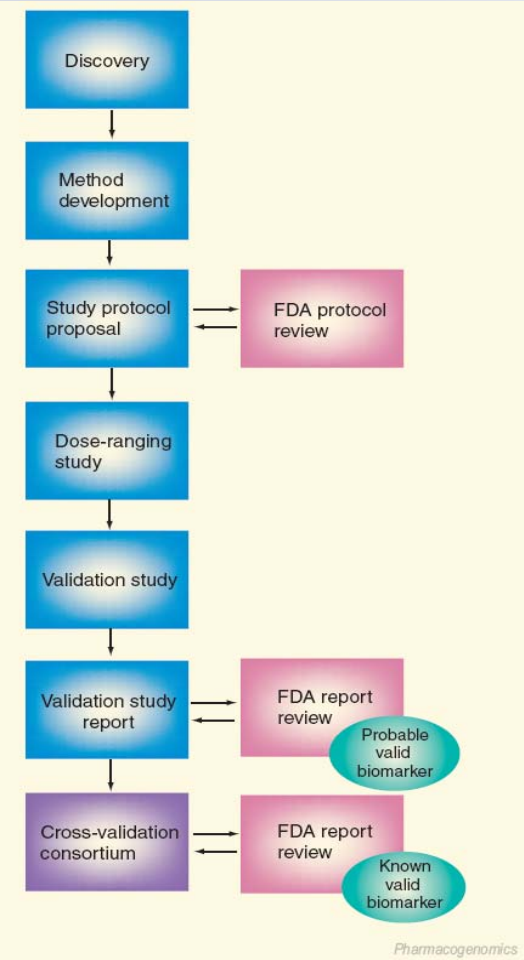
Consortium Will Share Tests to Understand Safety of Potential New Drugs Earlier

The Food and Drug Administration (FDA) and The Critical Path Institute (C-Path) today announced the formation of the Predictive Safety Testing Consortium between C-Path and five of America's largest pharmaceutical companies to share internally developed laboratory methods to predict the safety of new treatments before they are tested in humans. The FDA, while not a member of the Partnership, will assist it in an advisory capacity. This unprecedented sharing of potential early indicators of clinical safety may streamline the cost and time of preclinical drug safety evaluation and better inform the use of "personalized medicine". The Consortium was announced today at a press conference detailing the release of the Critical Path Opportunities List – 76 initial research priorities that, if accomplished, will modernize the drug development process by 2010 and help get new medical discoveries to Americans faster and at a lower cost.

- Initial discussions started 3/05 between OCP Genomics Group and Industry
- Structural framework proposal by C-Path in July 2005
- Legal framework completed in March 2006
- Six working groups:

  Nephrotoxicity, Hepatotoxicity, Vasculitis, Genotoxic and Non-Genotoxic Carcinogenicity, Muscle Toxicity and Clinical
- Current membership: 17 large pharma companies

Qualification of Pre-Clinical Biomarkers of Drug Safety



Goodsaid & Frueh, Pharmacogenomics 7(5):773

- Goal: Identify process to qualify preclinical biomarkers
  - Process that can be generalized
  - Solid science
  - Regulatory buy-in
- Requires interaction between industry stakeholders and FDA
- Preclinical safety testing consortium (led by C-Path Institute)
- Internal pilot process being developed to review qualification data – ensure that all stakeholders are involved

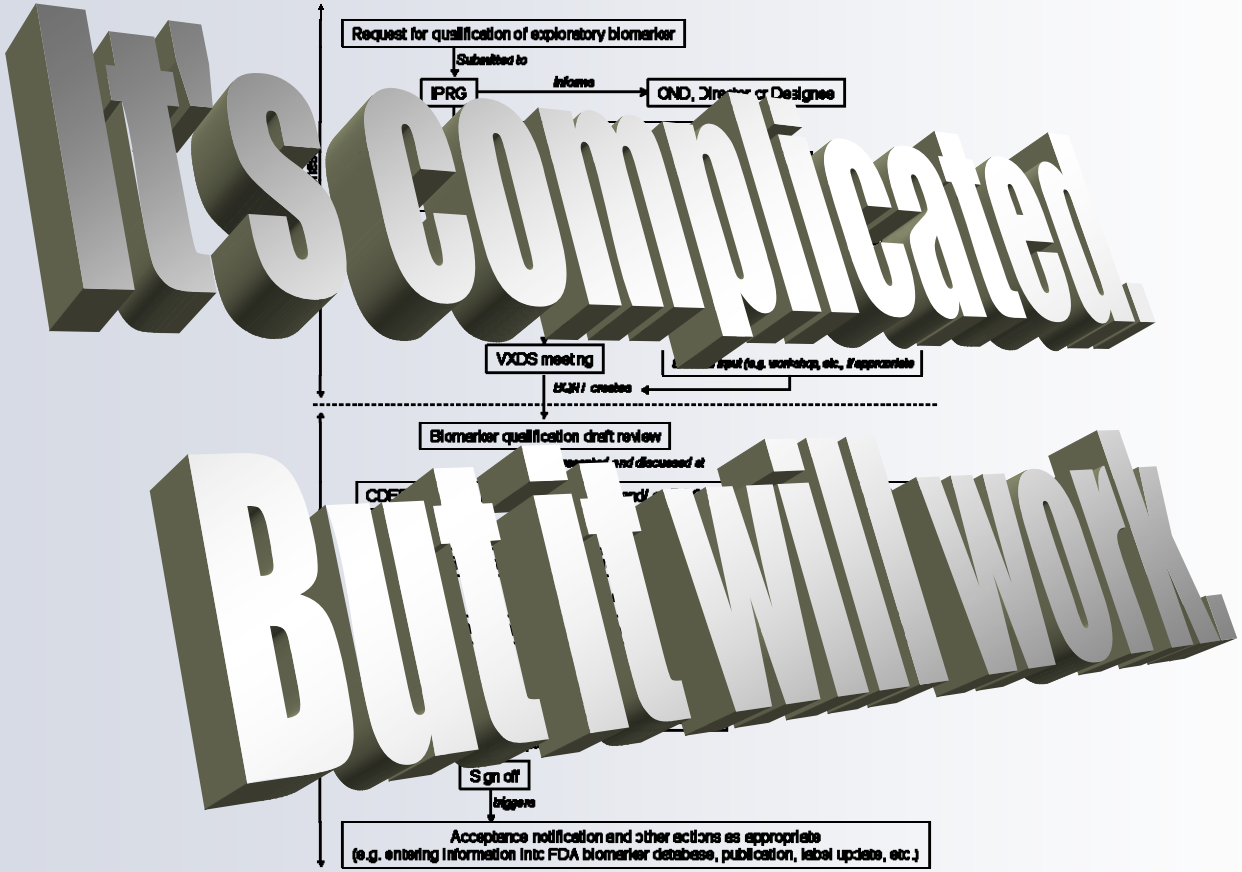
Connecting the VXDS Pathway to Biomarker Qualification

- Voluntary submission pathway:
  - Created to establish a platform for “informal” interaction between sponsors and FDA
  - 2½ years old, 30 submissions
  - VGDS expanded to VXDS (X = exploratory) program
  - True cross-Center review collaborations: IPRG
  - Significant impact on science, new policy development
- Used strategically to talk about use of novel biomarkers in drug development programs
- Will be piloted as initial step for qualification of biomarkers for pre-clinical drug safety (PSTC):
  - Nephrotoxicity VXDS planned for July 2007 as FDA/EMEA bilateral event

International Interest in PGx and Use of Biomarkers in Drug Development

- **VXDS program** has stirred interest in Europe and Japan
  - 2 bilateral VGDS meetings held with EMEA
- In 2006, formal **ICH** expert group on PGx formed (E-15)
  - Draft guidance "E15 Terminology in Pharmacogenomics" published in December 2006 (www.fda.gov/cder/guidance/7619dft.pdf)
  - Guidance is first step to harmonize on issues such as biomarker qualification, what type of data needs to be submitted, etc.
- Council for International Organizations of Medical Sciences (**CIOMS**) – Book on "Pharmacogenetics – towards improving treatment with medicines" published in 2005
- **OECD** Working Party on Biotechnology: Pharmacogenetics Policy Report (to be published)

Creating New Regulatory Review Processes Ain't Easy



Status Quo: Genomic Biomarker Information in Current Drug Labels

- How many and which genomic biomarker are mentioned in currently marketed drugs?
- How can we capture and present this information?

- What does the label say?
  - Do we “require” or “recommend” the measurement of the biomarker?
  - How does the knowledge of the biomarker affect a treatment decision?

Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels

Pharmacogenomic information is contained in about ten percent of labels for drugs approved by the FDA. A significant increase of labels containing such information has been observed over the last decade. In order to provide a reference for genomic biomarkers in labels of FDA-approved drug products, we created the table shown below. Genomic biomarkers can play an important role in identifying responders and non-responders, avoiding toxicity and adjusting the dosage of drugs to optimize their efficacy and safety. In the context of drug labels, these genomic biomarkers can be classified on the basis of their specific use, for example:

- Clinical response and differentiation,
- Risk identification,
- Dose selection guidance,
- Susceptibility, resistance and differential disease diagnosis,
- Polymorphic drug targets.

The table portrays a view on valid genomic biomarkers in the context of FDA-approved drug labels. It provides a comprehensive li… …rmacogenomic data, taking into account multiple regulatory contexts in which these biomarkers were approved. Most drug labels in this table provid… …ut no immediate recommendation for a specific action (i.e. genetic testing); however a few labels recommend or require genetic testing thereby specif… …reaching a therapeutic decision.

The table includes:

- Context-specific biomarker (column 1)
- Reference drug label information about the bio… …ug was approved (column 2 subsection 1)
- Test criteria (column 2 subsection 2)
- Prototypic drug associat… …the biomarker context (column 2 subsection 3)
- Other drugs in…
- Pa…

…ntext of a specific biomarker in their labels have had their pharmacogenomic information extracted into this table. This information can be accessed by placing the mouse over t… …under the right side of the drug name. All approved drugs in this table are linked to labels at Drugs@FDA which can be accessed by clicking over symbols under the left side of the drug name. The table will be updated on a quarterly basis.

The information provided in "label context" is taken from different sections of the actual drug labels.

The term "valid" biomarker has been defined in the "Guidance for Industry: Pharmacogenomic Data Submissions". Therein, a valid biomarker is described as a "biomarker that is measured in an analytical test system with well established performance characteristics and for which there is an established scientific framework or body of evidence that elucidates the physiologic, toxicologic, pharmacologic, or clinical significance of the test results." The classification of biomarkers is context specific.

A critical aspect of many of these drugs is the role they play in drug-drug interactions. This list does not address drug-drug interactions. More information on drug-drug interactions, please see Drug Development and Drug Interactions.

Reference is made to the requirement of testing for the biomarker:
1 = test required;
2 = test recommended;
3 = information only

Biomarker	Label Context	Examples of other	References

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Biomarker	Label Context			Examples of other Drugs Associated with this Biomarker	References (PubMed ID)
	Representative Label	**Test**	**Drug**		
C-KIT expression	**Gastrointestinal stromal tumor *c-Kit* expression** "*In vitro*, imatinib inhibits proliferation and induces apoptosis in gastro-intestinal stromal tumor (GIST) cells, which express an activating c-kit mutation." "Gleevec is also indicated for the treatment of patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST)."	**3**	Imatinib mesylate		12851888 16226710 16294026
CYP2C19 Variants	**CYP2C19 Variants (Poor Metabolizers-PM and Extensive Metabolizers-EM) with genetic defect leads to change in drug exposure**. "*In vivo* studies indicated that CYP2C19 is significantly involved in the metabolism of voriconazole. This enzyme exhibits genetic polymorphism. For example, 15-20% of Asian populations may be expected to be poor metabolizers. For Caucasians and Blacks, the prevalence of poor metabolizers is 3-5%. Studies conducted in Caucasian and Japanese healthy subjects have shown that poor metabolizers have, on average, 4-fold higher voriconazole exposure (AUCτ) than their homozygous extensive metabolizer counterparts. Subjects who are heterozygous extensive metabolizers have, on average, 2-fold higher voriconazole exposure than their homozygous extensive metabolizer counterparts."	**3**	Voriconazole	Omeprazole[m1] Pantoprazole [m2] Esomeprazole[m3] diazepam[m4] Nelfinavir[m5] Rabeprazole[m6]	12867215 11866669
CYP2C9 Variants	**CYP2C9 Variants PM and EM genotypes and drug exposure**; "Patients who are known or suspected to be P450 2C9 poor metabolizers based on a previous history should be administered celecoxib with caution as they may have abnormally high plasma levels due to reduced metabolic clearance."	**3**	Celecoxib	Warfarin[m7]	16118328 15637526 15714076 15037866 14558433
CYP2D6 Variants	**CYP2D6 Variants** "Atomoxetine is metabolized primarily through the CYP2D6 enzymatic pathway. People with reduced activity in this pathway (PMs) have higher plasma concentrations of atomoxetine compared with people with normal activity (EMs)."	**3**	Atomoxetine	Venlafaxine;[m8] Risperidone;[m9] Tiotropium bromide inhalation;[m10] Tamoxifen;[m11] Timolol Maleate;[m12]	
CYP2D6 with alternate Context	**CYP2D6 PM and EM Variants and drug exposure and risk**- "population, who are known to have a genetic defect leading to reduced levels of activity of P450 2D6. Fluoxetine, like other agents that are metabolized by P450IID6, inhibits the activity of this isoenzyme, and thus may make normal metabolizers resemble "poor metabolizers." Therapy with medications that are predominantly metabolized by the P450IID6 system and that have a relatively narrow therapeutic index should be initiated at the low end of the dose range if a patient is receiving fluoxetine concurrently or has taken it in the previous 5 weeks."	**3**	Fluoxetine HCL	Fluoxetine HCL and Olanzapine;[m13] Cevimeline hydrochloride[m14] Tolterodine;[m15] Terbinafine;[m16] Tramadol + Acetamophen [m17] Clozapine[m18] Aripiprazole;[m19] Metoprolol;[m20]	16472103 16384813; 15063083; 16271013 16236141 15828850 15492763 15037866 14639062 10431214 1302039

Not all of these drug labels had genomic biomarker information in "version 1" – the importance of label updates for Pers. Medicine

Example: Irinotecan

- Irinotecan is a topoisomerase 1 inhibitor used to treat colon cancer
- 1994: introduced in U.S. market (accelerated FDA approval)
- 1997: severe toxicity observed in 2 patients with Gilbert's syndrome
- 1998: role of UGT1A1 in the metabolism of the active metabolite of irinotecan, SN-38, described
- 2004: FDA advisory committee recommends label update to inform that patients with UGT1A1 deficiency may need a lower dose
- 2005: Irinotecan label was updated with recommendation to lower dose by 1 step if patient carries UGT1A1*28 allele
- 2005: First UGT1A1 genetic test (Invader Assay) was FDA-approved

The way to Personalized Medicine for irinotecan was paved – BUT:

Although the Critical Path to Personalized Medicine does not stop once a drug is on the market, retrofitting a label is complicated

Example: Irinotecan

- Lack of conclusive, statistically sound prospective studies demonstrating a reduction of toxicity
- Lack of studies demonstrating equal benefit of drug when dose is reduced in patients with UGT1A1*28 allele
  - This maybe unrealistic for small populations
  - We measure blood levels as “surrogate for efficacy”
    - We do this for BE and DDI studies, but somehow acceptance doesn’t seem to have transpired to genetics...
- Test has only 50% percent sensitivity (95% specificity)

- Biggest problem – changing medical practice:
  - Once drug is on the market, medical practice takes shape
  - Physicians “know” how to use the drug
  - Inherently problematic in oncology (toxicity used as measure of efficacy)
- Generally, no incentive for, and little interest from, sponsors to change label

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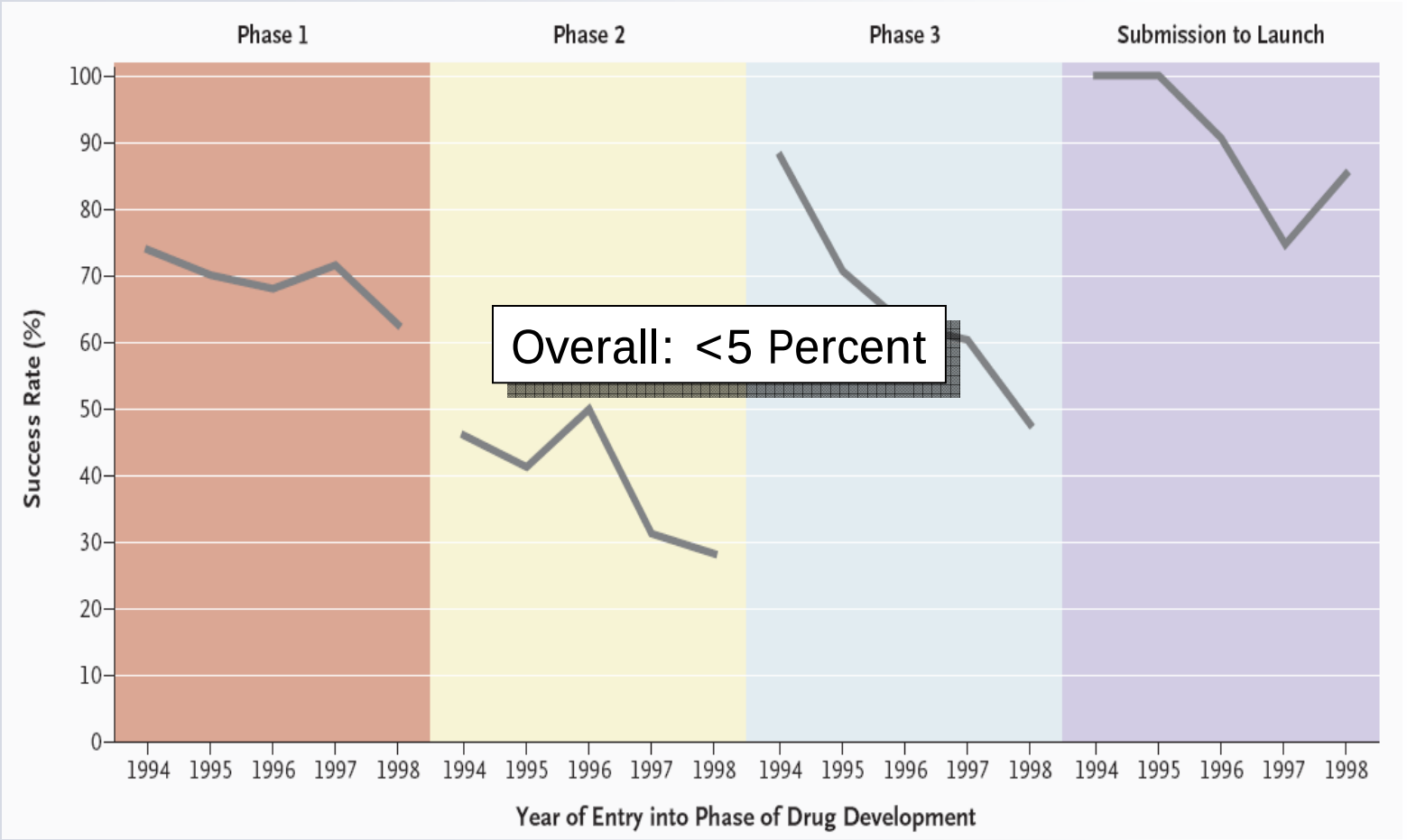
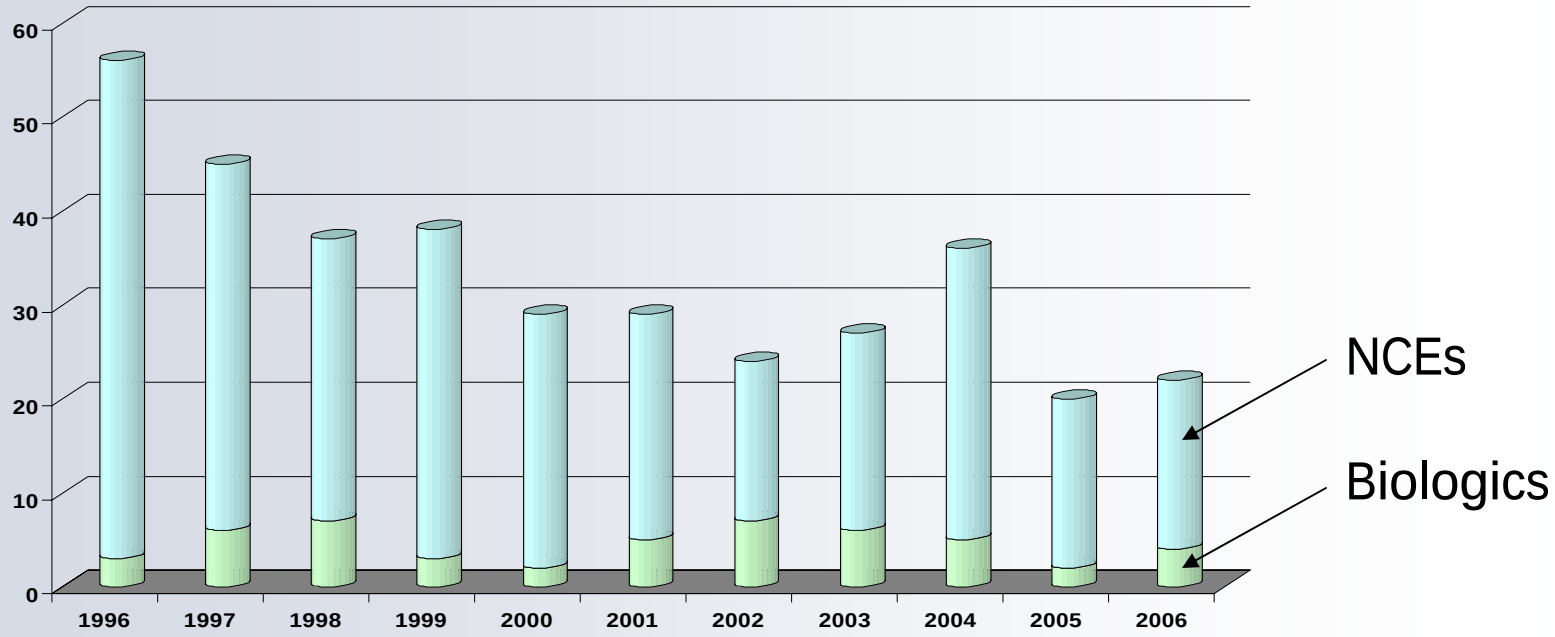
Low Success Rate in All Phases of Drug Development



Alastair J.J. Wood, N Engl J Med 355;6 – August 10, 2006

Result: Decrease in Approval of New Chemical Entities and Biologics

- 2006: the number of new CEs and biologics remains low,



- while R&D expenditures rise to US$55.3 billion, up $3.4 billion (7%) from the last record in 2005.

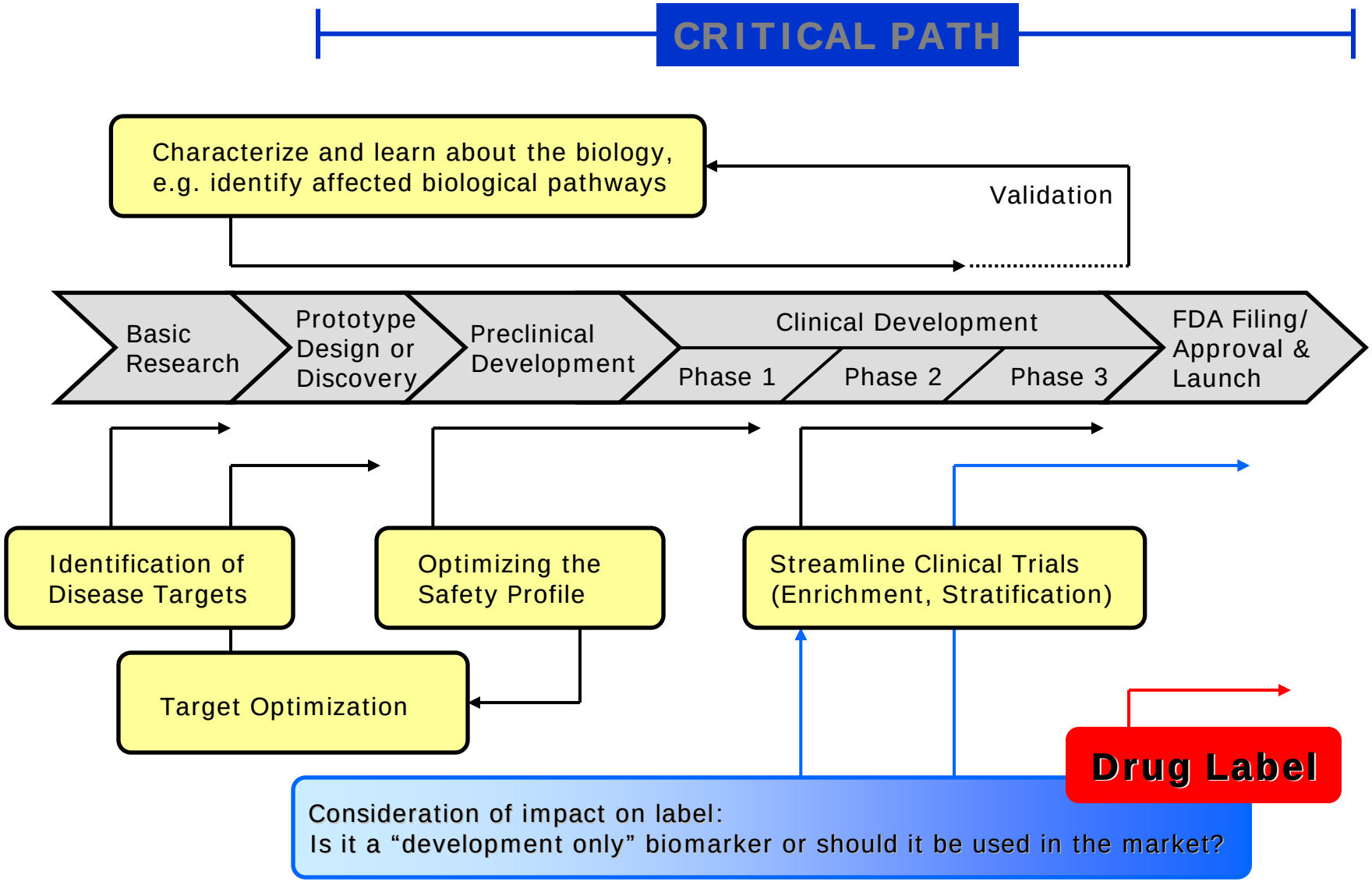
New Clinical Trial Designs

- There are many reasons for the decline in new drug approvals, but the inability to demonstrate efficacy is one key reason
- Traditional trial designs are not adequate to address complex questions that arise with the use of new biomarker strategies
- We hope that the use of biomarkers can increase trial success rate, but we have little experience with true enrichment or stratification designs
  - For example: new “hybrid”-designs are being proposed (e.g. Simon’s 0.4/0.1 design), but are untested so far
- Even when new designs are used, other issues remain open:
  - Seamless integration of development phases
  - Retrospective data analysis (fishing for new biomarkers)
  - Drug-test co-development, alignment of drug and device development
  - Conditional approval (surrogates?)

Streamlining Clinical Trials

- Area of high interest and intense debate
  - How best to do it – pertinent questions:
    - Enrichment, stratification, and adaptive trial designs
    - Late stage “learn-confirm”: introduction and qualification of new biomarkers in late phase drug development
    - Data in “off-group”: how much data is needed
- FDA plans to issue new guidances on
  - Multiple Endpoints
  - Enrichment Designs
  - Non-inferiority Designs
  - Adaptive Designs
  - Missing Data
  - End of Phase 2A

Putting it all together: Biomarker Strategy and Drug Label



More about this in the afternoon workshop on …

Clarifying the Current Regulatory Position on the Validation and Standardization of Biomarkers for Approval and Ongoing Patient Care

Workshop:

Developing Robust Decision Criteria for the Development and Use of Biomarkers – Learning from Regulatory and Industry Experience To Date

R&D Leaders Forum Spring 2007

Philadelphia, PA
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Office of Clinical Pharmacology
CDER/FDA

Conclusions

- Drug therapy is characterized by low response rates, occurrence of adverse events and unmet medical needs – in part, this is due to the old “one-size-fits-all” model of drug development and use
- At the same time, industry is spending more and getting less from current drug development efforts
- Several Critical Path projects poised to change the old drug development model are underway
- The qualification and intelligent use of biomarkers in novel clinical trial designs will streamline these trials – they will become an integral part of Personalized Medicine – globally
- Implementing Personalized Medicine is best done from the start (nobody questioned the use of a Her2/neu test for Herceptin) – retrofitting old labels is important, but also difficult and the acceptance in clinical practice is slow

www.fda.gov/cder/genomics

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