New Paradigms for Drug Development – A Regulatory Perspective

Baltimore, MD

July 31, 2007

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Outline

- Personalized Medicine – why it is a good idea
  - Drivers for change
  - What happened to new drug targets?
- New Tools for Better Decision-making
  - Biomarkers
  - Modeling and Simulation
- Got to market. Done?
  - Pharmacogenomic information in drug labels – and updating it
  - Idiosyncratic adverse events – can we study them? A proposal.
- Conclusions

The (Ultimate?) Evidence Standard

*"Drug companies like to say that their most expensive products are fully worth their breathtaking prices. Now one company is putting its money where its mouth is — by offering a **money-back guarantee**.*

*Johnson & Johnson has proposed that **Britain's national health service pay for the cancer drug Velcade, but only for people who benefit** from the medicine, which can cost $48,000 a patient. The company would refund any money spent on patients whose tumors do not shrink sufficiently after a trial treatment."*

Pricing Pills by the Results - Andrew Pollack, The New York Times, July 14, 2007

Flipside

"I and others suggested a money-back guarantee on a cancer drug looked silly," said Dr. Tunis, who is now director of the nonprofit Center for Medical Technology Policy. " 'Oh, I'm sorry your grandma died. Here's your money back.' "

Pricing Pills by the Results - Andrew Pollack, The New York Times, July 14, 2007

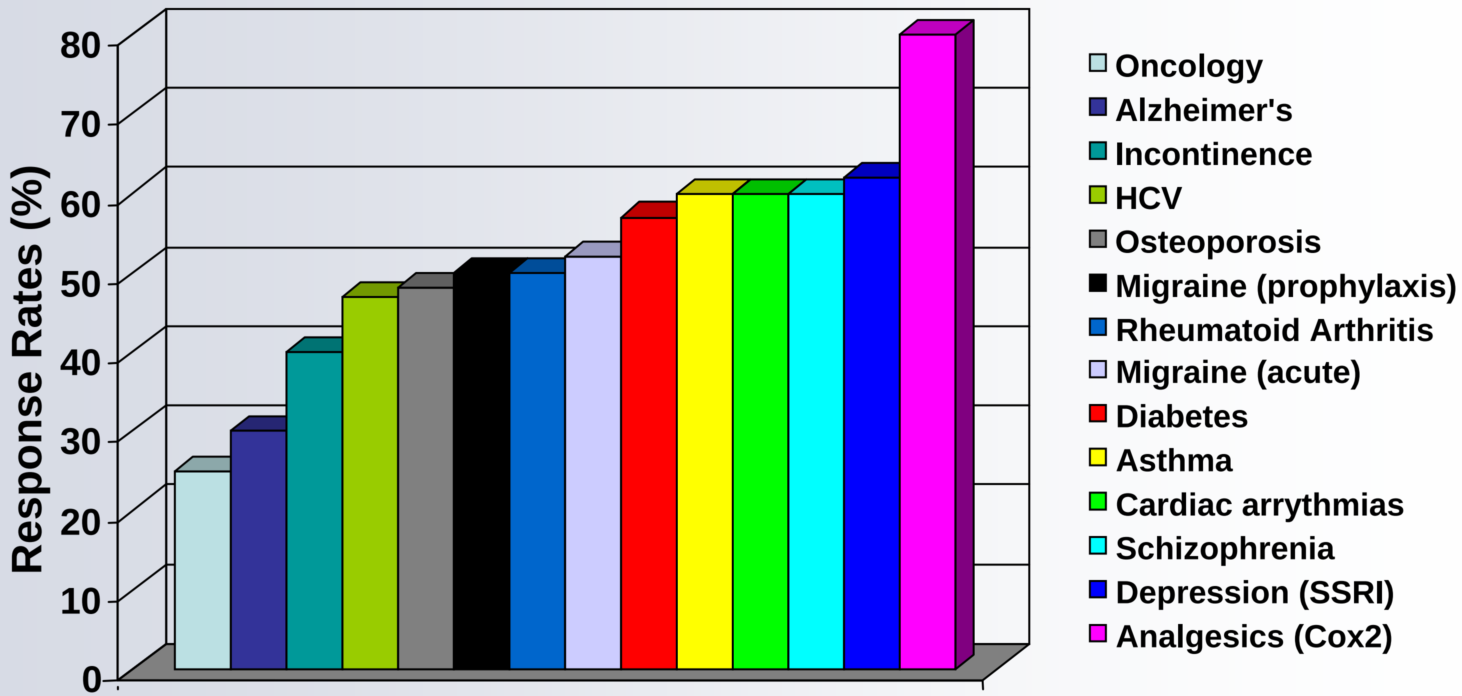
- This may be a (necessary?) paradigm shift – driven by economics.
- **But what if we could predicted whether or not a patient will experience a true response, based on the use of new biomarkers?**

Personalized Medicine

- Personalized Medicine is a clinical, scientific, business, and regulatory opportunity:
  - **New Paradigm:** Shift drug development and from a population-based to a patient-centric approach
  - **Reality:** 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
  - **How-to:** Use of new (biomarker-driven) tools for decision-making to address safety and efficacy – we can do it today
  - **Opportunity:** Drugs can be developed more efficiently and successfully, perhaps even cheaper
  - **Impact:** All stakeholders (incl. regulators!) will be able to make better decisions for development, approval, and use of drug
- There are many good reasons why it is a good idea to shift the paradigm:

Drivers to Change the Paradigm: Example 1: Improving Response Rate

Response rate to current medicines is often unacceptably low:



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

Drivers to Change the Paradigm: Example 2: Avoiding Adverse Events

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 likely won't get cheaper because of Personalized Medicine, but it provides an opportunity to shift costs to more productive efforts, such as prevention and adequate therapies

Drivers to Change the Paradigm: Example 3: Addressing Unmet Medical Needs

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

Identification of New Drug Targets ...

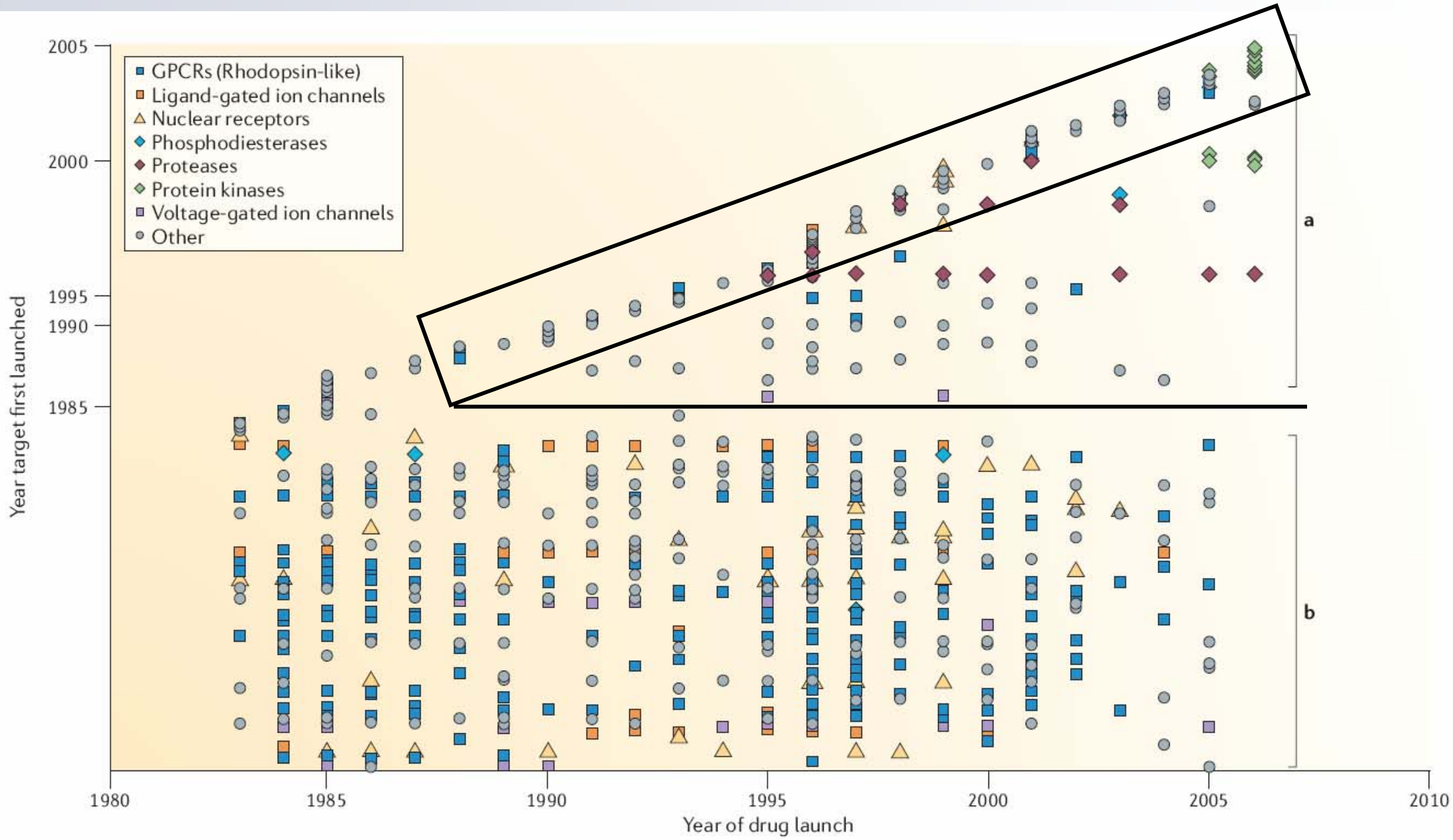
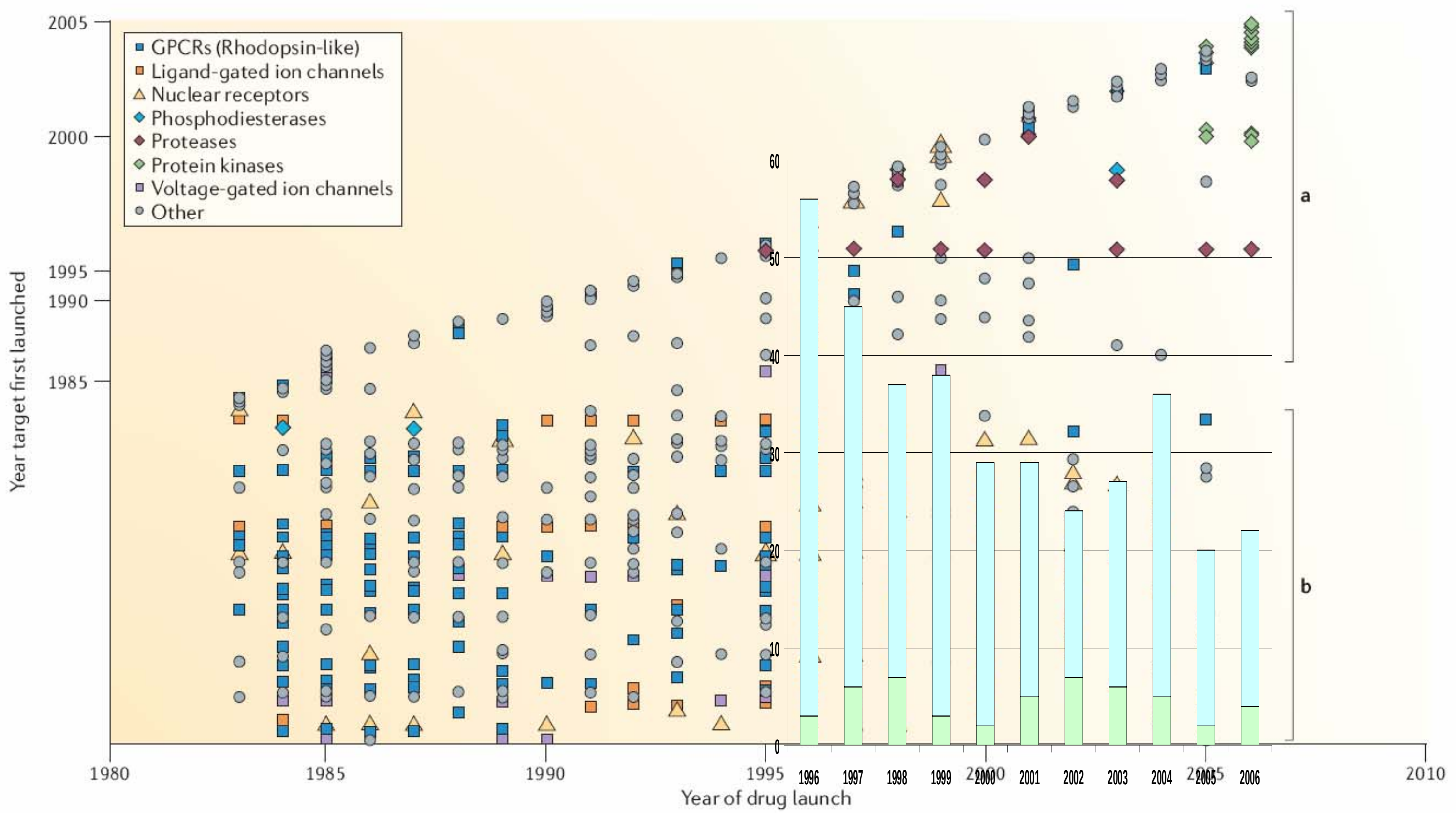


Figure 3 | **Rate of target innovation.** The *y*-axis represents the year of first drug launch against each target, and the *x*-axis is the year of each subsequent drug release, with the plot ordered so that more recently 'drugged' targets are shown at a higher *y* ordinate. Region **a** reflects periods 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

... did not translate into an increase in new drug products



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As a Result, the Gap between Bench and Bedside Continues to Grow

- 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"*

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 Chemical Industries.

In 1948, American scientist Reymond Alquist had proposed that two sets of receptors were present—α and β—that might explain the paraoxical actions of epinephrine and norepinephrine on the cardiac muscles. Black and his colleagues attempted to characterise these receptors. Using isproterenol, an analogue of norepinephrine, they synthesised propranolol—a β-receptor antagonist, which became invaluable in the treatment coronary-artery diseases.

Black moved to Smith, Kline and French Company (now Smithkline 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 series of histamine analogues, Black and co-workers developed several H2 blockers; many of them were ineffective and toxic. By 1976, Black developed cimetidine, a powerful H2 blocker useful in the treatment of gastric and peptic ulcers. Black had said that "the most fruitful basis for the discovery of a new drug is to start with an old drug".

Born in Hoquiam, Washington, USA, Hitchings (figure, right) studied biochemistry at Harvard University, and in 1942, joined the Burroughs Wellcome (BW) company. In 1944, Gertrude Belle Elion (figure, middle), a New Yorker, with a master's degree in chemistry from the New York University, joined Hitchings and remained with him as collaborator for the rest of her career.

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

Elion and Hitchings' approach in pharmacological research was revolutionary. They discarded 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 chemotherapeutic agent against leukaemia.

Applying the same principles that led them to 6 MP, Elion and Hitchings succeeded in producing a series of drugs. In 1950, they developed pyromethamine; then came trimethoprim, azathioprine, and allopurinol; and in 1975, they synthesised acyclovir, a powerful antiviral agent against herpes virus. Elion and Hitchings' pioneering principles in pharmacology were also instrumental in the development of 5-fluorouracil, cytosine, and adenine arabinosides, and more recently, azadiothymidine (zidovudine, AZT).

Because 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."

The Nobel Foundation

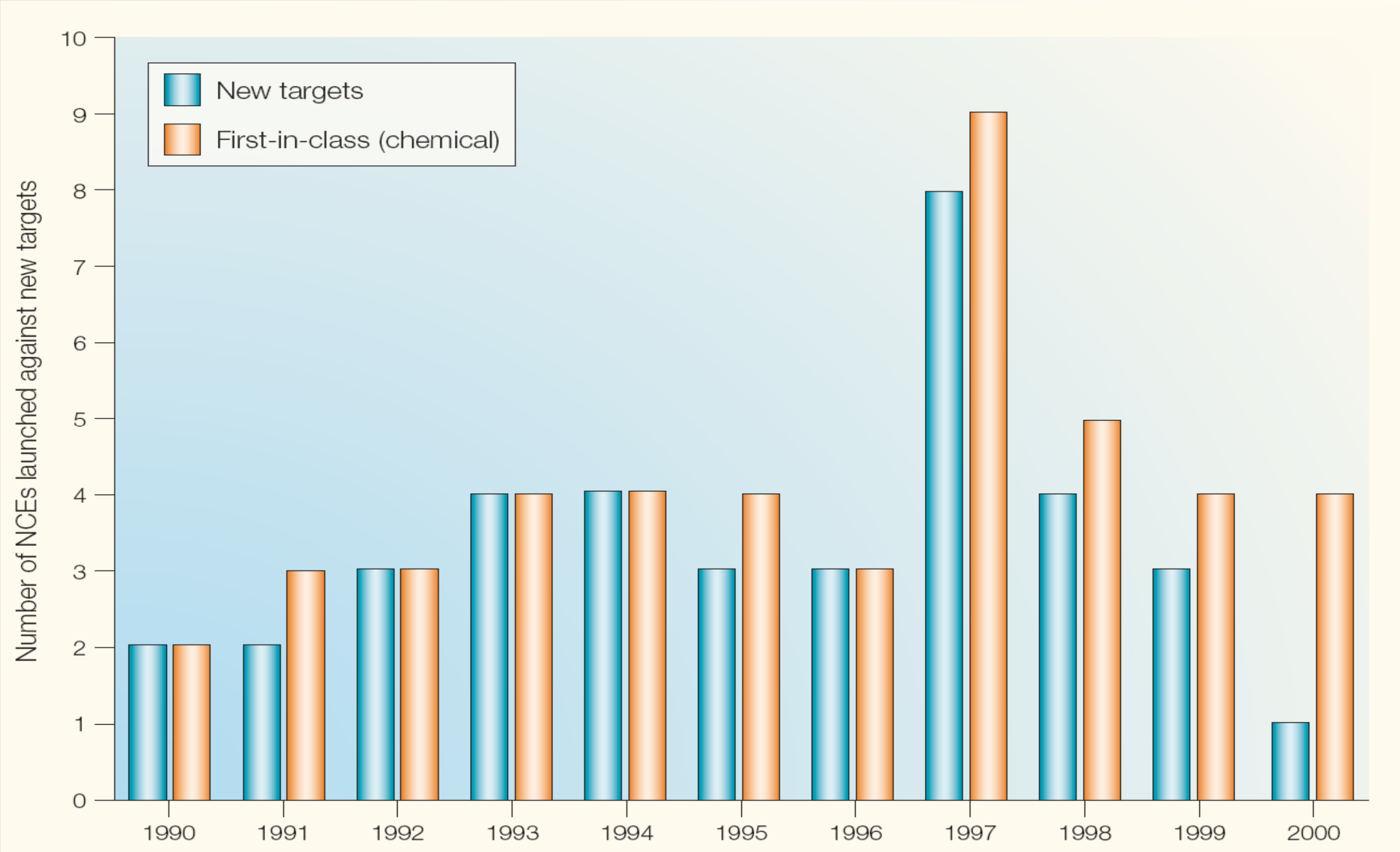
Tonse N K Raju
University of Illinois, Chicago, IL, USA

"The most fruitful basis for the discovery of a new drug is to start with an old drug"

- James Black

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 ?

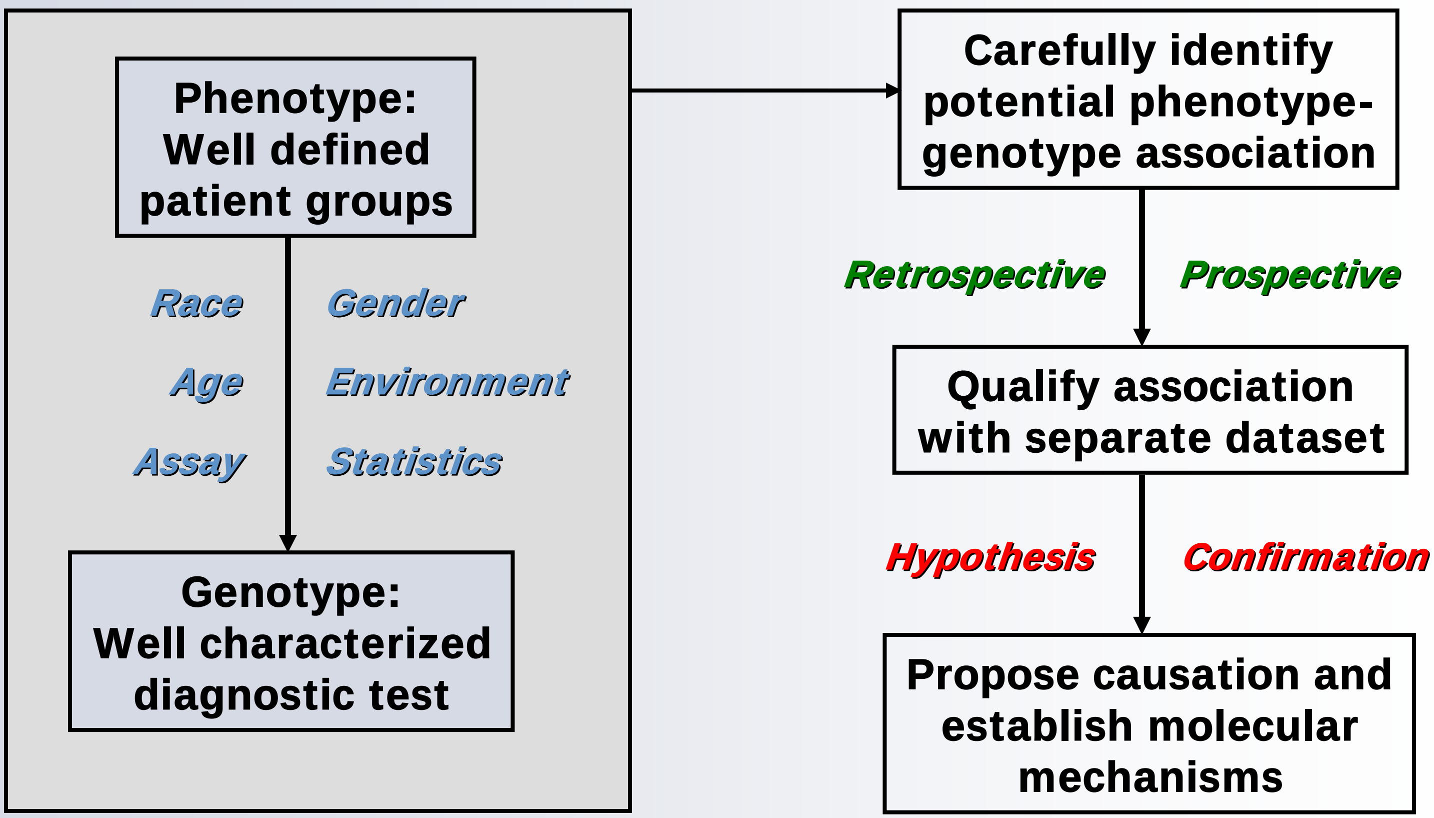
- Reluctant use of new biomarker technologies
  - Translation of new, cutting-edge science into successful drug development program happens more slowly than anticipated (e.g. “genome hype”)
  - Lack of a predictable regulatory environment (e.g. the first final PGx-related guidance issued only in 2005, many more clarifications are needed)
- Sticking to old paradigms, novel approaches such as modeling and simulation have been neglected
- 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

From *Stagnation to Innovation*: Change in Paradigm, fueled by FDA's Critical Path Initiative

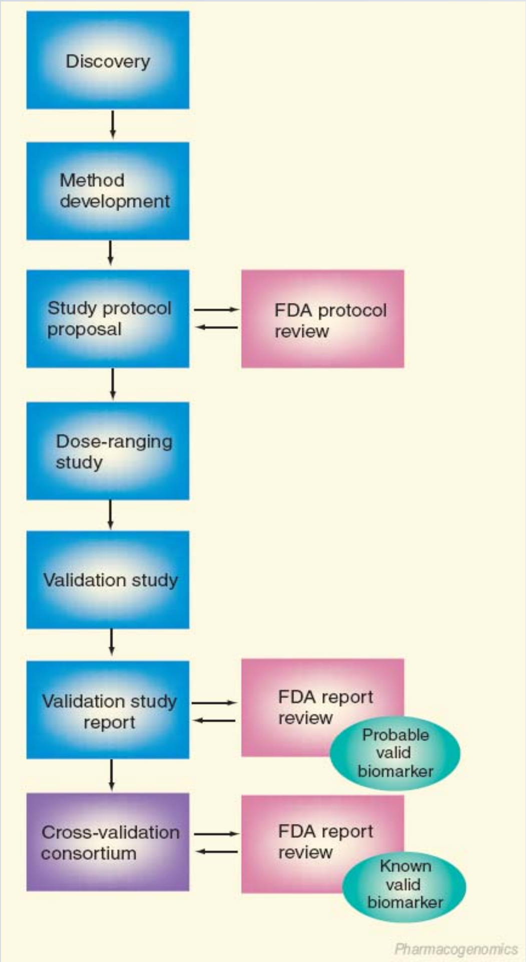
- "The Critical Path Initiative is FDA's effort to stimulate and facilitate a national effort to modernize the scientific process through which a potential human drug, biological product, or medical device is transformed from a discovery or "proof of concept" into a medical product."

- 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

New Molecular Biomarkers: How Can We Be Sure They're Meaningful ?



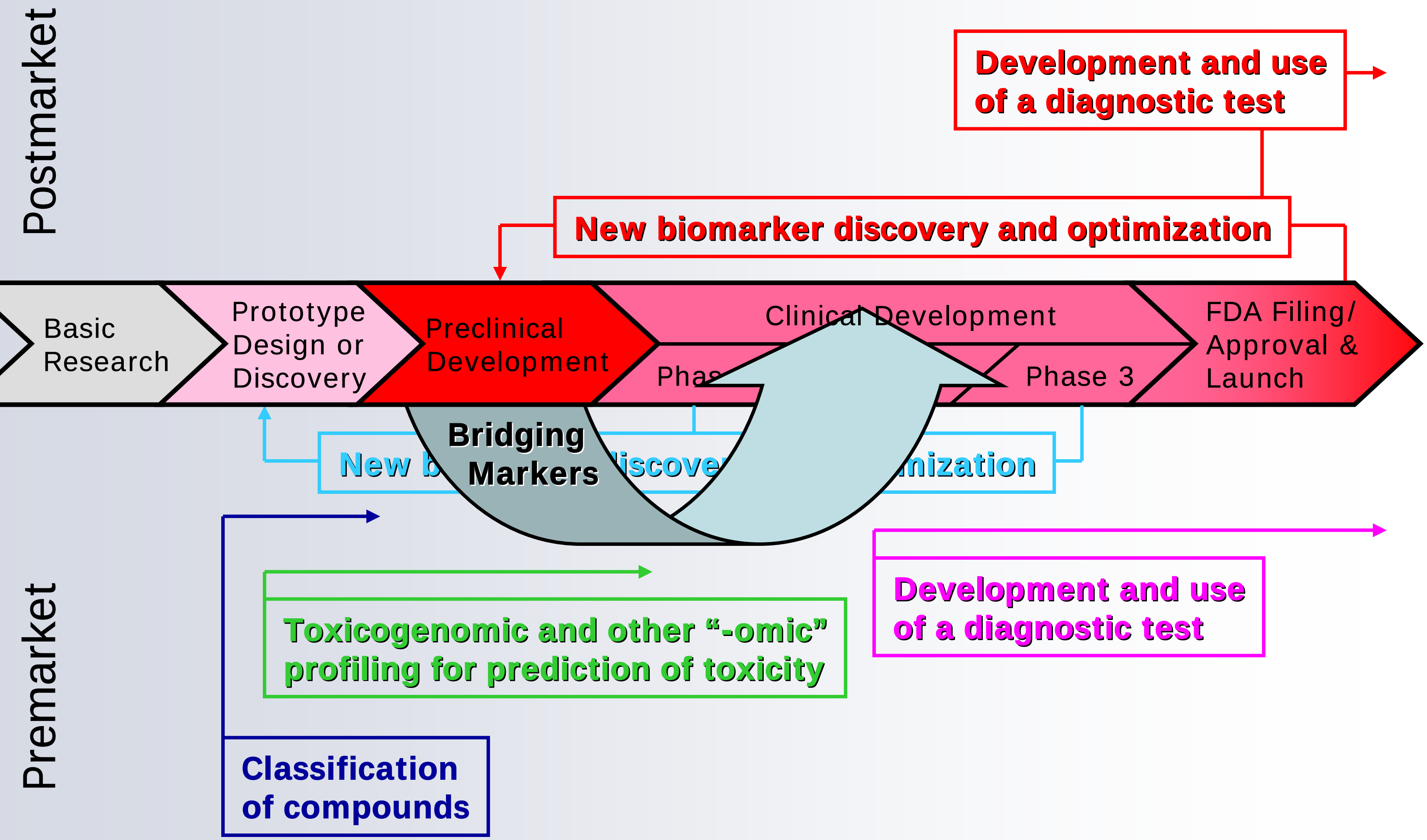
Qualification of Novel Biomarkers



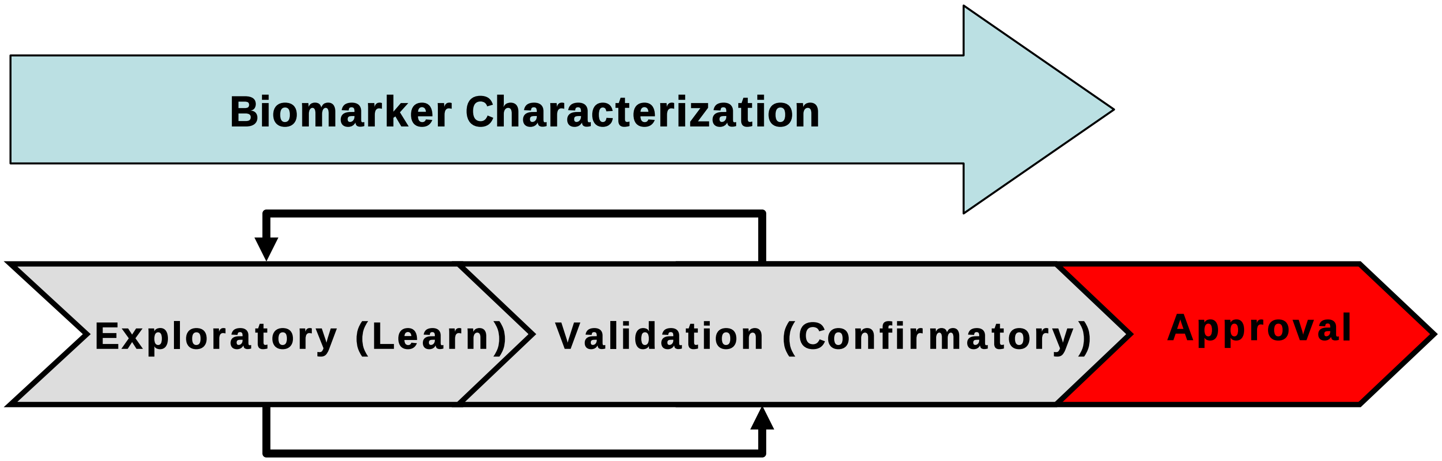
Goodsaid & Frueh, Pharmacogenomics 7(5):773

- Goal: Identify process to qualify preclinical biomarkers
  - Process that can be generalized
  - Solid science
  - Regulatory buy-in
- Requires interaction between industry stakeholders and FDA
- Predictive Safety Testing Consortium (PSTC), led by C-Path Institute in Arizona
- Internal pilot process being developed to review qualification data – ensure that all stakeholders are involved
- July 10, 2007: First joint meeting between PSTC and regulators – FDA, EMEA, PMDA to discuss submission on novel biomarkers to assess nephrotoxicity

Use of Biomarkers in Safety and Efficacy Assessment of (New) Drugs



Integration of Biomarker Information into Drug Development



Learn – Confirm Example for Discovery of Novel Biomarkers for Drug Safety

The Pharmacogenomics Journal (2007), 1–10
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ORIGINAL ARTICLE

Genome-wide pharmacogenetic investigation of a hepatic adverse event without clinical signs of immunopathology suggests an underlying immune pathogenesis

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One of the major goals of pharmacogenetics is to elucidate mechanisms and identify patients at increased risk of adverse events (AEs). To date, however, there have been only a few successful examples of this type of approach. In this paper, we describe a retrospective case–control pharmacogenetic study of an AE of unknown mechanism, characterized by elevated levels of serum alanine aminotransferase (ALAT) during long-term treatment with the oral direct thrombin inhibitor ximelagatran. The study was based on 74 cases and 130 treated controls and included both a genome-wide tag single nucleotide polymorphism and large-scale candidate gene analysis. A strong genetic association between elevated ALAT and the MHC alleles DRB1*07 and DQA1*02 was discovered and replicated, suggesting a possible immune pathogenesis. Consistent with this hypothesis, immunological studies suggest that ximelagatran may have the ability to act as a contact sensitizer, and hence be able to stimulate an adaptive immune response.
The Pharmacogenomics Journal advance online publication, 15 May 2007; doi:10.1038/sj.tpj.6500458

Keywords: pharmacogenetics; pharmacogenomics; adverse event; immune system; liver injury

Introduction

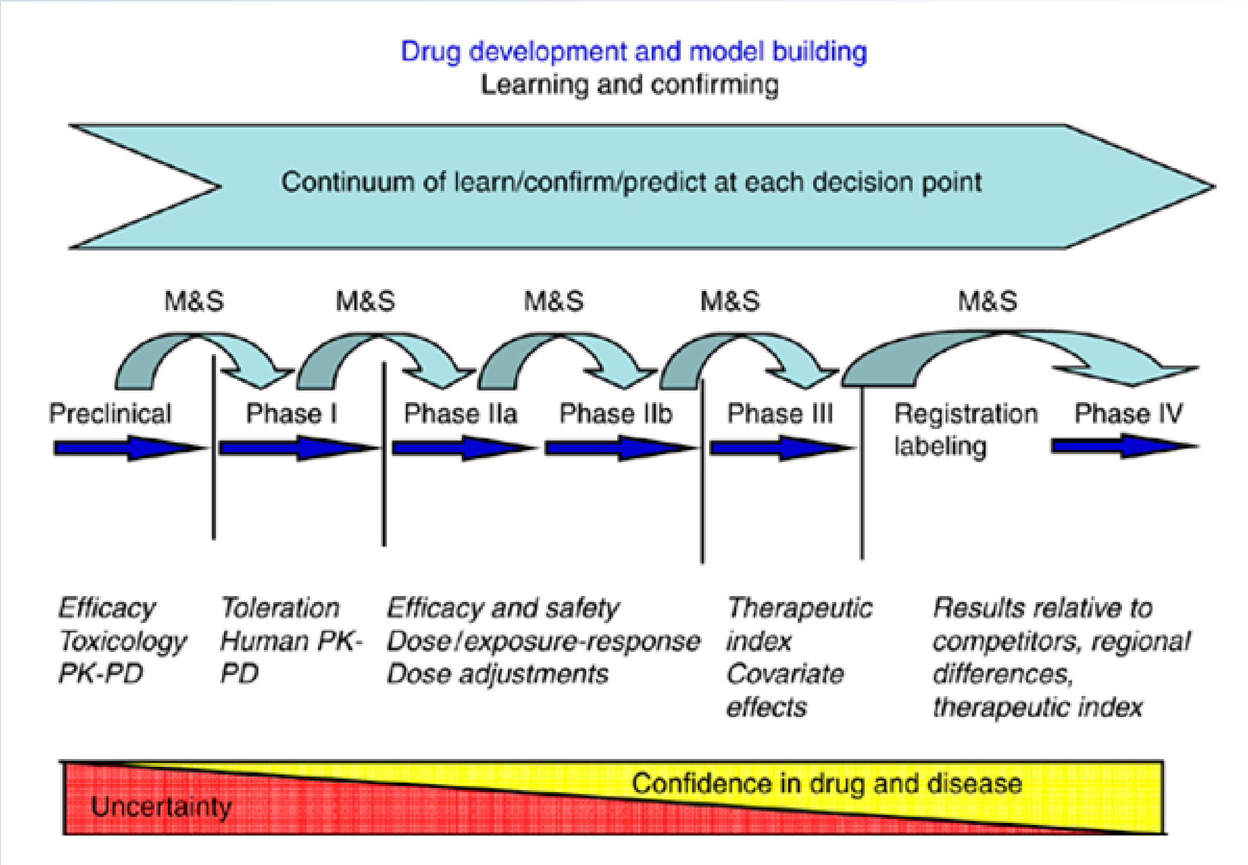
Ximelagatran, marketed as Exanta, was developed for the prevention and treatment of thromboembolism. In patients treated with ximelagatran for more than 35 days, transient elevated levels of serum alanine aminotransferase (ALAT)

"Our data further suggest that a biomarker test based on DRB1*07 would have been able to detect patients at risk of the AE with sensitivity of 47% and specificity of 83%."

What does FDA think?

If at-risk patients can be excluded, a suspected hepatotoxic drug would be potentially approvable, in the context of the overall risk/benefit analysis for the drug.

Improving Decision Making: Modeling and Simulation



RL Lalonde et al. Clin Pharm Therap 82(1):21-32

FD&C: "Confirmatory Evidence" – Opening for Modeling and Simulation Approaches

- Food and Drug Administration Modernization Act of 1997 – Section 115:

  "the term 'substantial evidence' means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts..., on the basis of which it could fairly and responsibly be concluded...that the drug will have the effect it purports or is represented to have...IF THE SECRETARY DETERMINES, BASED ON RELEVANT SCIENCE, THAT **DATA FROM ONE ADEQUATE AND WELL-CONTROLLED CLINCIAL INVESTIGATION AND CONFIRMATORY EVIDENCE** (OBTAINED PRIOR TO OR AFTER SUCH INVESTIGATION) ARE SUFFICIENT TO ESTABLISH EFFECTIVENESS, THE SECRETARY MAY CONSIDER SUCH DATA AND EVIDENCE TO CONSTITUTE SUBSTANTIAL EVIDENCE..."

Case Study: How Modeling and Simulation alleviated need for a new trial

- Background
  - Two registration trials in patients with a debilitating neurological disorder without approved treatments
    - The first study met its primary end point; patients were withdrawn from treatment after the end of the study.
    - The second study did not meet the primary end point owing to a potential protocol violation pertaining to start time of withdrawal.
  - Withdrawal effect in patients previously stabilized on this drug was compared with those continuing on treatment. Patients enrolled in both studies were started on the drug following the withdrawal phases in an open-label fashion
- Regulatory question
  - Is there adequate evidence of effectiveness in the current clinical trial database?

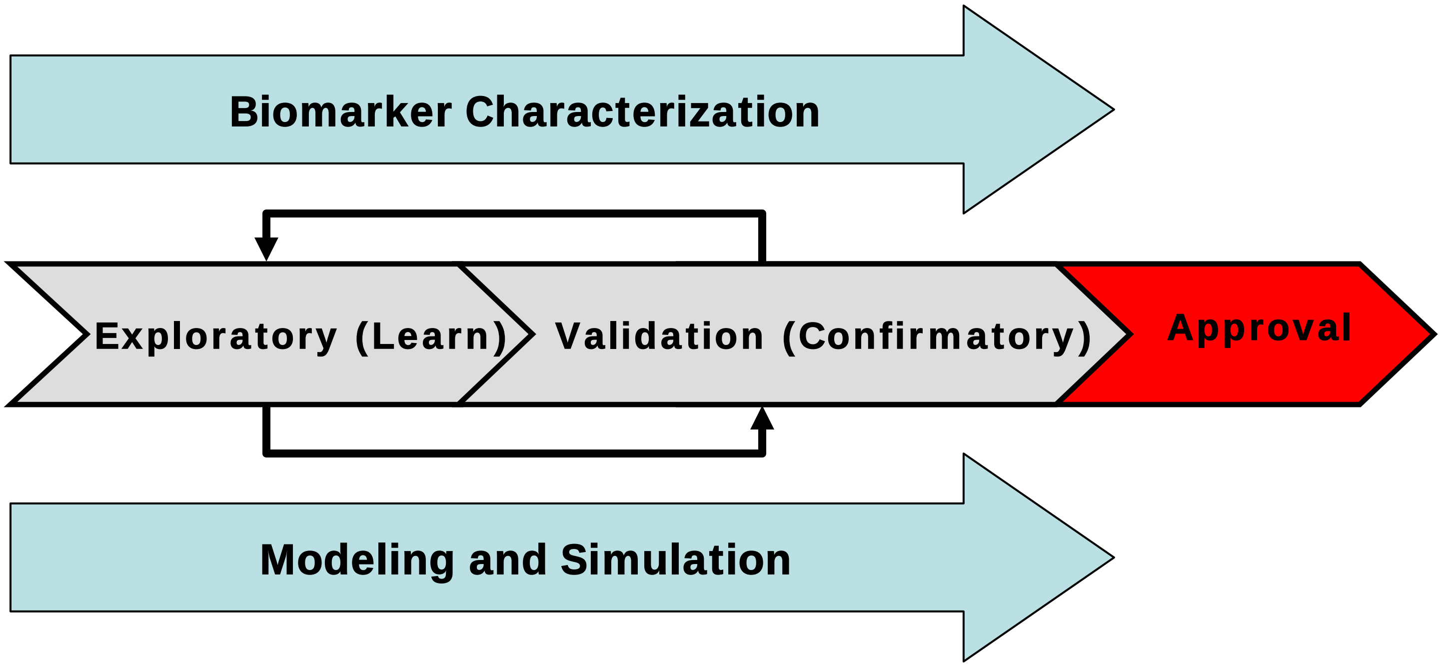
VA Bhattharam et al. Clin Pharmacol Ther. 2007 Feb;81(2):213-21.

Case Study: How Modeling and Simulation alleviated need for a new trial, cont'd

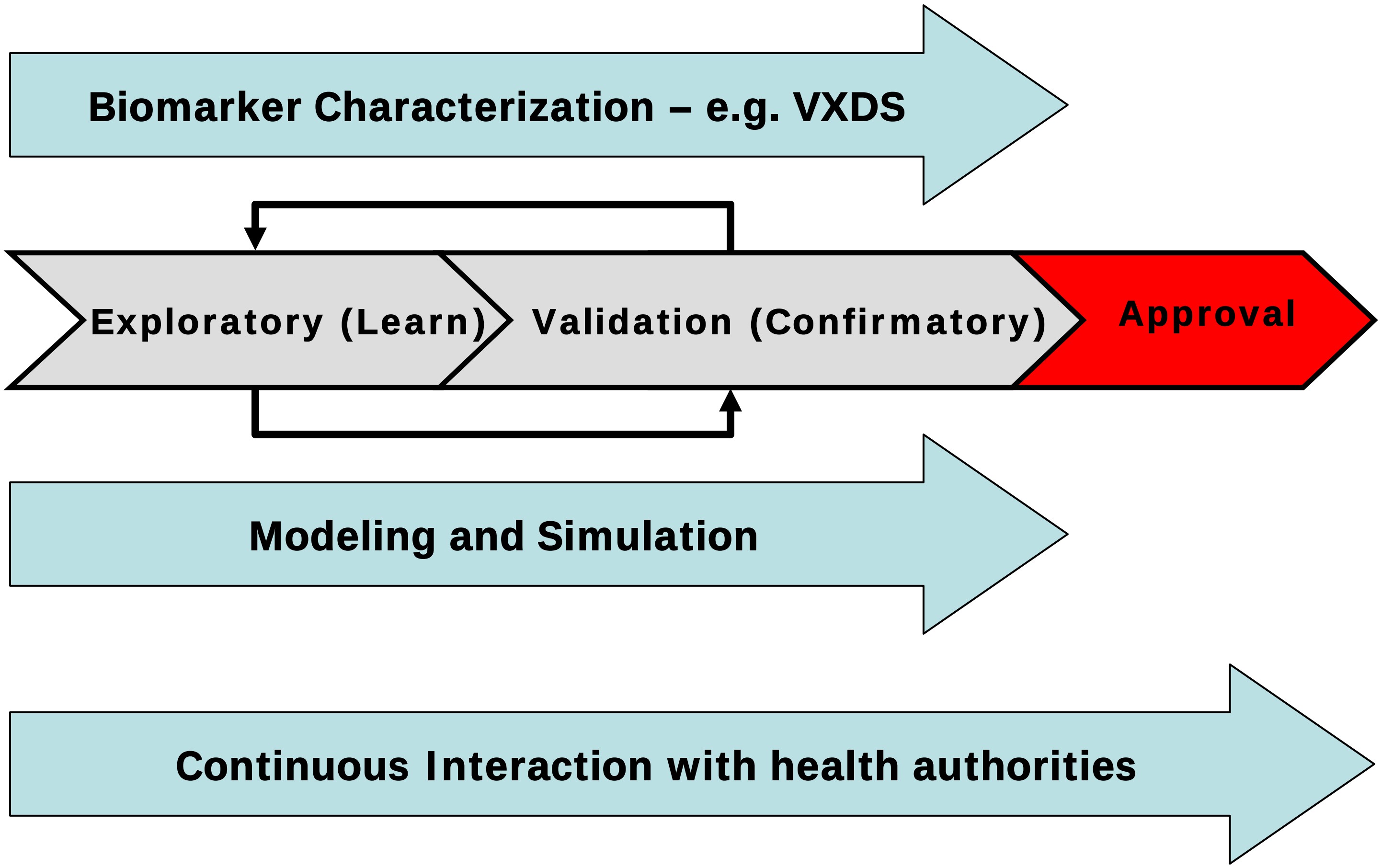
- Pharmacometrics review
  - Data across all the studies were analyzed to investigate whether there was a consistent effectiveness signal.
  - The withdrawal effects across the studies were significant and consistent
  - Patients who received active treatment in the open-label phase had significantly lower symptoms
- **Regulatory action**
  - Based on the above results and the need to supply treatment for this disease, the FDA decided that there was an adequate evidence of effectiveness. The need for additional clinical trials to establish effectiveness was alleviated.

VA Bhattharam et al. Clin Pharmacol Ther. 2007 Feb;81(2):213-21.

Integration of Biomarker and Modeling and Simulation Information into Drug Development



Interaction between Industry and Regulators



Optimizing Success of Clinical Trials by Integration of Novel Biomarkers

- Traditional trial designs are not adequate to address complex questions that arise with the use of new biomarker strategies
  - Need for novel adaptive trial designs → should use more!
- 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

Further Clarification Needed

- Areas of high interest and intense debate
  - 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

Trials Are Done. But What Goes In the Label ?

- 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 - Microsoft Internet Explorer

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Address http://www.fda.gov/cder/genomics/genomic_biomarkers_table.htm Go Links

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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… pharmacogenomic data, taking into account multiple regulatory contexts in which these biomarkers were approved. Most drug labels in this table provid… with no immediate recommendation for a specific action (i.e. genetic testing); however a few labels recommend or require genetic testing thereby speci… reaching a therapeutic decision.

The table includes:

- Context-specific biomarker (column 1)
- Reference drug label information about the bio… drug was approved (column 2 subsection 1)
- Test criteria (column 2 subsection 2)
- Prototypic drug associa… the biomarker context (column 2 subsection 3)
- Other drugs i…
- P…

…ontext 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

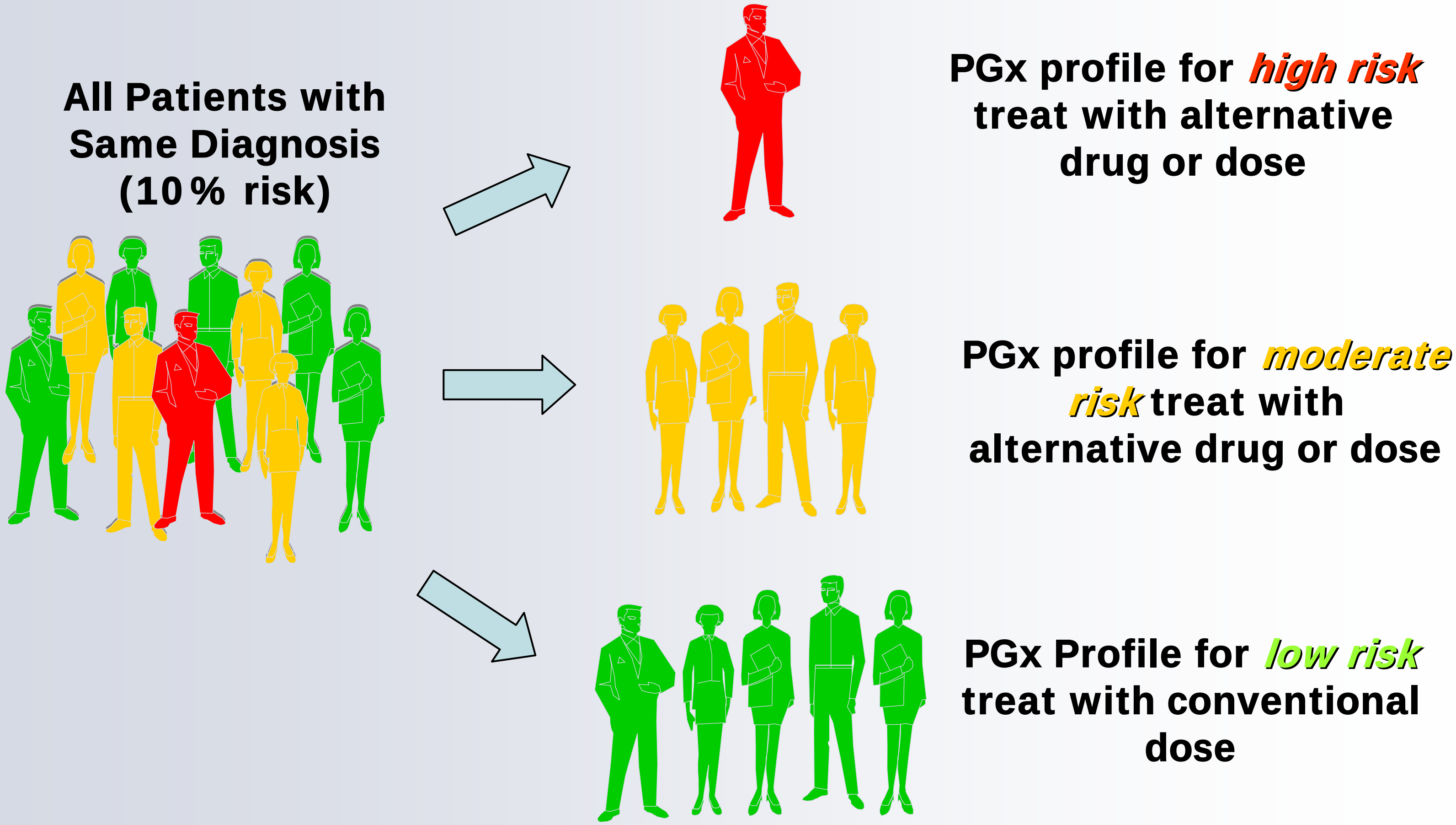
Biomarker	Label Context	Examples of other	References

Local intranet

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

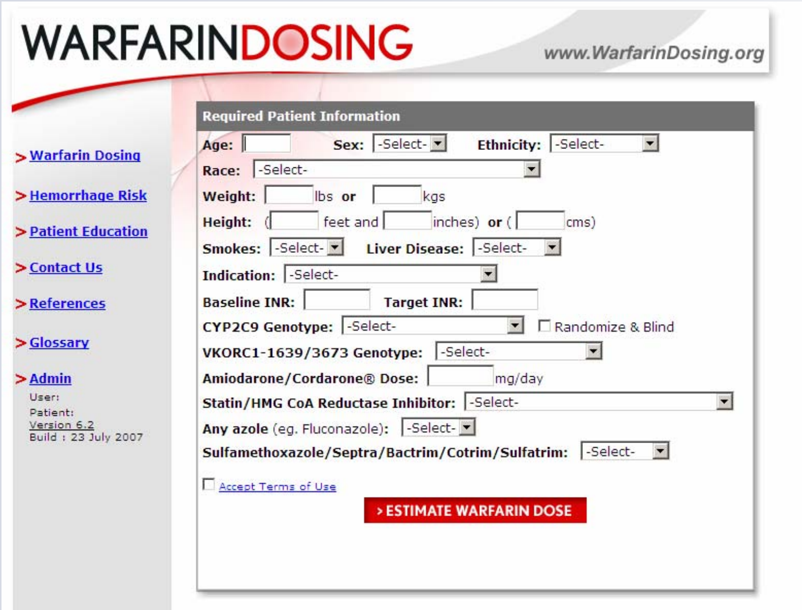
Biomarker	**Label Context**			**Examples of other Drugs Associated with this Biomarker**	**References (PubMed ID)**
	Representative Label	**Test**	**Drug**		
C-KIT expression	**Gastrointestinal stromal tumor *c-Kit* expression** "*In vitro*, imatinib inhibits proliferation and induces apoptosis in gastro-intestinal 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 ($AUC\tau$) 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] [m21]	16472103 16384813; 15063083; 16271013 16236141 15828850 15492763 15037866 14639062 10431214 1302039

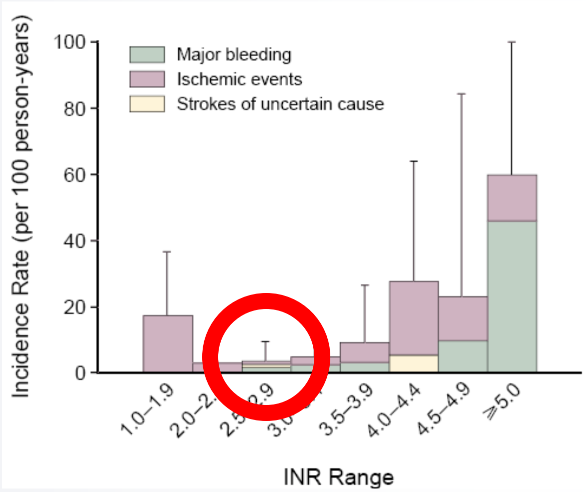
Example 1: Irinotecan UGT1A1 Testing – Making a better informed treatment decision



Example 2: Warfarin CYP2C9 and VKORC1 Testing – Better Estimation of Starting Dose

Genetics and other clinical factors can help to assess approx. 60 percent of the variability in warfarin dose





N Engl J Med 1995; 333: 5-10

Increased Focus on Safety: Serious Adverse Events of Marketed Drugs

- Adverse events can be idiosyncratic, i.e. events that are random, unexpected, often dose-independent
  - Caused likely by a combination of the properties of the drug in combination a (genetic?) predisposition of the patient

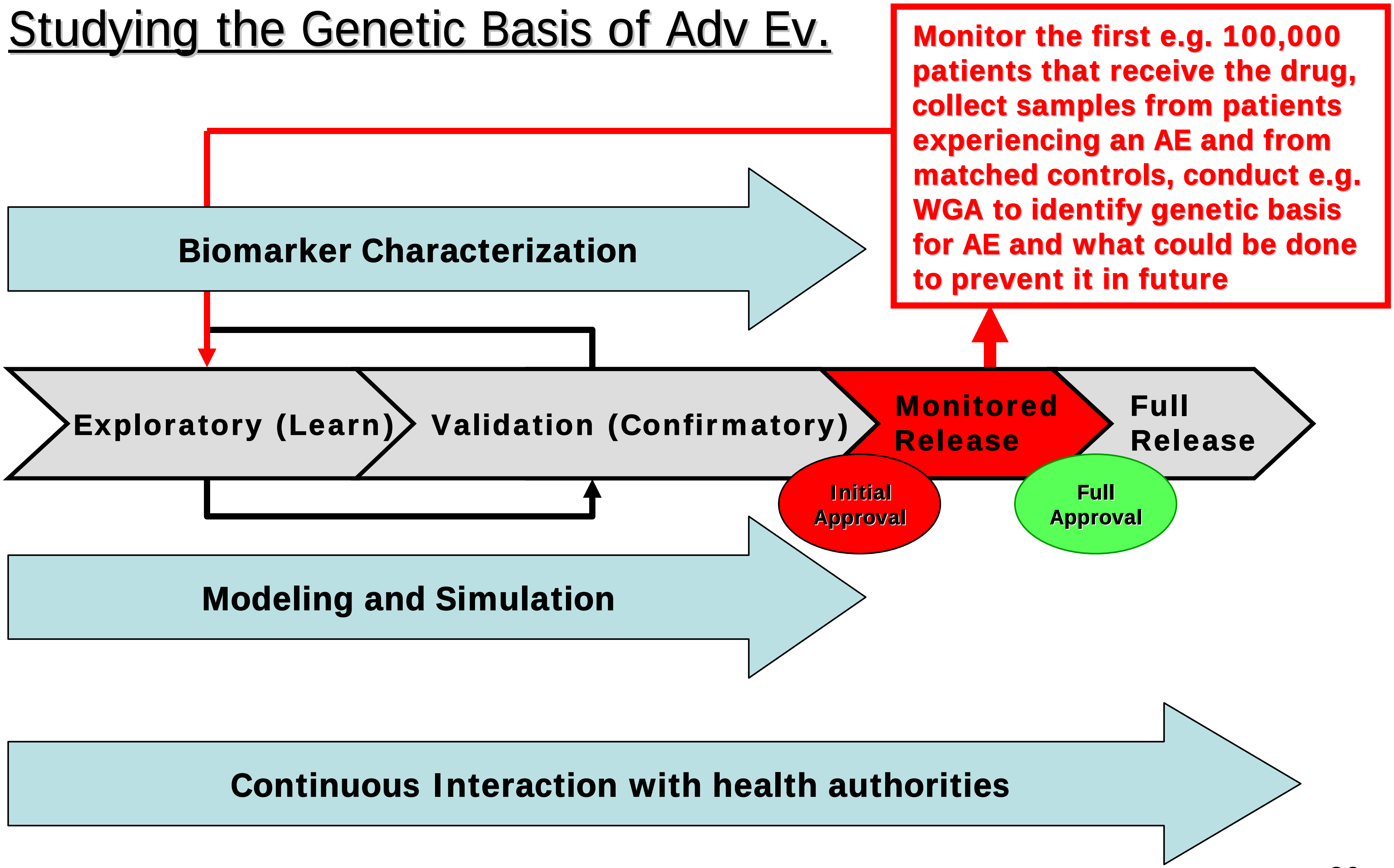
- Drugs withdrawn from the market due to rare serious adverse events
  - Should not have been on the market in the first place so that the patients harmed could have been spared from harm
  - Pose a problem for (the many more) patients that are not at risk and benefit from treatment
  - Negatively affect the companies that make the drugs

- So what can we do?
  - Develop processes and invest in research that lead to a reduction in adverse events (serious and non serious)

The Problem: Small Size of Safety Database at Time of Approval

- Typical size of clinical trials:
  - Phase 1: tens
  - Phase 2: tens – hundreds
  - Phase 3: hundreds – thousands
- What happens if an adverse event occurs 1:5,000 ?
  - We are likely to miss it because the size of the safety database is too small.
- How can we create a larger safety database before a drug is fully launched?
  - We create a system that looks something like this:

A Proposal to Significantly and Effectively Increase the Size of Drug Safety Databases and to Enable Studying the Genetic Basis of Adv Ev.



Conclusions

- Drug therapy can be improved by:
  - Increasing response rates
  - Avoiding of adverse events
  - Addressing unmet medical needs
- The qualification and intelligent use of novel biomarkers will help to move drug development and drug therapy from a population-based to a patient-centric paradigm
- Changes in clinical practice will follow innovative thinking by industry and regulators

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