Targeted Medicine: A New Paradigm for Drug Development

John J. Orloff, M.D.
Novartis Pharma AG
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Scientific and technical advances will trigger a paradigm shift in R&D and medicine

From ... 
Clinical definition of disease diagnosis

To ...
Molecular definition diagnosis and predisposition
Pharmaceutical R&D – The Old Paradigm

- Research
- Toxicology
- Phase I: Initial safety, PK
- Phase II: Efficacy, Safety
- Phase III: Approval
- Phase IV: Market

- Multi-phase
- Sequential
- Milestone-led

1 Pharmacokinetics
Pharmaceutical R&D – The New Paradigm

Target discovery and validation → PoC\(^1\) clinical trials → Clinical development

Exploratory Phase:
- Target
- Proof-of-Concept

Confirmatory Phase:
- Efficacy
- Safety
- Approval
- Market

• Adaptive
• Parallel
• Data-led

\(^1\) Proof-of-Concept
Comprehensive genome-wide science: Pathways organize our approach to discovery.
Pathways .... In Disease

- Breast cancer
- Osteoporosis/sclerosis
- Colon cancer
- Liver cancer
- Vitreoretinopathy
- Pancreatic cancer

Cytoskeletal changes due to TGFβ/BMP

- Fibrodysplasia ossificans
- Pulmonary hypertension
- Hemorrhagic telangiectasia
- Juvenile polyposis syndrome

- Tcf-4
- β-catenin
- CBP

Comprehensive genome-wide science: Pathways in human disease
mTor Inhibitors: opportunities being tested

Tuberous sclerosis

Retinitis pigmentosa

Cancer

Immune diseases, Tx rejection

Vascular proliferation after stent implant
Key Drivers to Transform Development Model

1. Biomarkers
2. Modeling and simulation
3. Rapid compound selection in man
4. Innovative clinical trial design
5. Innovative approaches to registration
6. Integrated safety assessment & risk management
7. Quality by design manufacturing
Integrating Knowledge for Model-based Drug Development

Genes … Cells … Tissues … Systems … Patients … Populations

Development time axis

Integrated approach to Modeling & Simulation:

- **Biological modeling** – model pathways of disease as targets of intervention
- **Pharmacological modeling** – determine relationships for dose, exposure, response
- **Statistical modeling** – assesses development strategies and trial designs in populations
From Target Validation to PoC\textsuperscript{1} in Humans

- **Exploratory**
  - Build model of potential safety and efficacy of drug in the disease state
    - Incorporate predictive toxicology, metabolism, kinetics
    - Qualification biomarker studies prior to confirmation
  - Simulate clinical development in target patient population
  - Enhance model with human data via early entry to man

Early collaboration with Health Authorities on acceptable models

\textsuperscript{1} Proof of Concept
Contribution of Biomarkers

- Prognostic / Diagnostic
- Disease Progression
- Pathway Elucidation
- Animal Model Validation
- Target Identification / Characterization / Prioritization

- Safety / Toxicity
- Efficacy
- Mechanism of Action

- Responder / Non-Responder
- Safety / Efficacy

- Discovery
- Pre-Clinical Development
- Clinical Development

- Product Decision
From Simulation to Confirmation

- Utilize model-based / Bayesian approach to optimize use of all available data for study design
- Implement innovative study designs to improve dose/regimen selection and confirm model (e.g. adaptive/seamless designs)
- Target patients with a high likelihood of response based on a biomarker
- In absence of short-term clinical outcome, use qualified biomarker as surrogate endpoint

Early buy-in from Health Authorities of trial design, adaptations, and outcome criteria to support marketing application
Staged Approval

Goal

Enable patients to have more rapid and controlled access to new drug therapies while enhancing learning about how best to use the medicine in the “real world”
Development of the Future

Modeling & Simulation

Exploratory

Confirmatory

Targeted Approval

Monitored Release

Full Release

Biomarkers

-------------Continuous sharing of data with Health Authority-------------
... Leading to Different Product Types Emerging Over Time

From: Pharma 2010: Threshold of Innovation; IBM Business Consulting Services
Targeted Medicine: Imitinab for CML

- Specifically designed to target the cause of CML (Bcr-Abl)
- High rates of cytogenetic and hematologic response
- Significant delay in time to disease progression
Targeted Medicine: Predictions from Pharma

Pink sheet, 25 May 2006

Pfizer Senior VP-Science & Technology Peter Corr

"Are we destroying the blockbuster model by using pharmacogenomics. . . I actually think not. . . . The big upside is in those patients in which you can define that they would respond to the drug, third-party payers would have no excuse about not paying."

Lilly CEO Sidney Taurel

"How the economic model [for personalized medicine] will be worked out nobody can tell you. On the sales side, you might argue that this will be smaller molecules in terms of sales."
‘in vitro’ Diagnostic Devices

*In vitro* diagnostic tests are considered to be medical devices for purposes of regulatory oversight and are defined as reagents, instruments and systems intended for use in the diagnosis of disease or in the determination of the state of health in order to cure, mitigate, treat or prevent disease.

Pharmacogenomic Tests

An assay intended to study interindividual variations in whole-genome or candidate gene single-nucleotide polymorphism (SNP) maps, haplotype markers, and alterations in gene expression or inactivation that may be correlated with pharmacological function and therapeutic response.

Pharmacogenetic Tests

An assay intended to study interindividual variations in DNA sequence related to drug absorption and disposition (pharmacokinetics) or drug action (pharmacodynamics) including polymorphic variation in the genes that encode the functions of transporters, metabolizing enzymes, receptors and other proteins.

*FDA Guidance for Industry, Pharmacogenomic Data Submissions*
Leaders in the Critical Path initiative: FDA/NVS Collaborations

- Help define a regulatory process by which biomarkers can be qualified
  - Public Meeting scheduled to discuss Best Practices for genetic and genomic biomarker data sharing, Q4 2006
  - Pilot biomarker review process

- Help define a regulatory process by which a diagnostic and a therapeutic can be co-developed to enable identification of patients who are most likely to benefit from therapy.
  - Process map for drug and diagnostic co development to be shared with academia and industry.
  - Assessment of key learnings.
### Purpose

<table>
<thead>
<tr>
<th>Category</th>
<th># Companies with interest*</th>
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<td><strong>Drug Discovery</strong></td>
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<td>Exclude candidates with DME-associated ADRs</td>
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<td>Genomic subpopulations</td>
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<td><strong>Drug Safety: development</strong></td>
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<td>Preclinical and early trial design/monitoring</td>
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<td><strong>Disease Stratification</strong></td>
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*Applying internally, offering services and/or offering products*
Commercial Rationale: The Value Proposition

**Personalized Medicine with linked PGx/Biomarker Diagnostic-Therapeutic (Dx-Tx)**

- Dx increases probability of success by enriching trials with responders, reducing late stage attrition, a large cost driver for drug development
- Less empiricism addresses stakeholder needs
- Removal of non-responders
  - cost avoidance (e.g. lack of efficacy)
  - avoid drug exposure in non-responders
- Greater responder rates and fewer adverse events will improve patient compliance and adherence
- Efficiency in identifying relevant patient populations
- More attractive to payers, prescribers and patients – willingness to pay for less uncertainty
- Shift in healthcare to prevention will open opportunities that did not previously exist, facilitated by PGx Dx-Tx
A Mixed Business Model: Targeted and Traditional (Blockbuster) approaches

Yes, we do prescribe individually targeted, exclusively formulated medicines - but not for indigestion.
Value Drivers for a Targeted Medicine Approach

- Unmet medical need
- Competitiveness of market environment in disease area
- Level of product differentiation
- Sensitivity / specificity / accessibility / timeliness of Dx test
- Order of market entry
- Optimized benefit / risk profile – mitigate unforeseen safety issues and reduce uncertainty of response
- “Pathways“ - opportunities across disease areas and indications
- Revised pricing/reimbursement environment to capture value creation
Who will capture the added value represented in a Dx-Tx?

"Sure the medicine cured him .... but I'm the one who guessed it!"

From MJ Finley Austin, DIA, 2006
Who captures the value?

Determinants

- Value-based or cost-based pricing reimbursement for Tx and Dx, and combinations thereof
- Flexibility of value-based pricing structures
- Characteristics of the Dx and the Tx
- Timing of introduction of Dx – at launch with Tx vs. post-launch
- IP protection – key to capture appropriate value
- Competitive market conditions
- Insurance market competitiveness
- Regulatory environment

Adapted from MJ Finley Austin and L Garrison, DIA, 2006
Incentives for targeted medicine with a linked Dx-Tx

Public Policy / Reimbursement / Patent

• Value-based pricing and reimbursement for drugs and diagnostics
• Linking pricing and reimbursement for drugs and diagnostics to value creation
• Favorable IP environment for Tx as well as Dx

Regulatory

• Additional marketing exclusivity (e.g. A. Wood – NEJM Aug 2006)
• Clearly defined regulatory pathways for co-development
Thank you !!