Enterprising Breakthroughs and Catalyzing Collaboration in the Pursuit of Life-transforming Rare Disease Treatments

Innovation Keynote Panel

Moderator:
Wayne Pines, President, Regulatory Services and Healthcare, APCO Worldwide

Panelists:
David Scheer, MS, President, Scheer & Company, Inc.
Stephanie Okey, Senior Vice President and General Manager, Genzyme, a Sanofi Company
James Greenwood, President and Chief Executive Officer, BIO
Gigi Hirsch, MD, Center for Biomedical Innovation, MIT
Enterprising Breakthroughs and Catalyzing Collaborations in the Pursuit of Life-Transforming Rare Disease Treatments
NORD Summit ❖ Washington DC ❖ October 21, 2014

NEWDIGS: New Drug Development ParadIGms

Gigi Hirsch, MD
Executive Director
MIT Center for Biomedical Innovation
“Who” is NEWDIGS?

**NEWDIGS**

“Think & Do Tank”

Mission: Reliably and sustainably deliver new, better, affordable therapeutics to the right patients faster

**Payers/HTA**
Aetna  
EUnetHTA  
HAS  
INESSS  
NICE  
ZINL

**Regulators**
EMA  
FDA  
Health Canada  
HSA (Singapore)  
MHRA (UK)  
MPA (Sweden)

**Patients/Providers**
ASCO  
Friends of Cancer Research  
Genetics Alliance  
NORD

**Academia**
MIT  
Harvard Medical School  
Sloan Kettering  
National U. of Singapore

**Pharma**
BMS  
GSK  
J&J  
Novartis  
Pfizer  
Quintiles  
Sanofi

MIT Center for Biomedical Innovation = convener & neutral intermediary
What drives NEWDIGS (1)?

R&D Expenditure per employee 2000-2007 – Industry comparison

- Biopharmaceuticals: $105,428
- Communications equipment: $62,995
- Semiconductors: $40,341
- Computers and electronics: $37,980
- Chemicals: $34,978
- Navigational, measuring ....: $22,262
- Aerospace products: $22,162
- Motor vehicles, trailers, parts: $15,704
- Transportation equipment: $15,963
- Petroleum, coal: $13,319
- All Manufacturing: $9,956
- Electrical equipment, appliances: $6,411
- Machinery: $5,663
- Paper, Printing: $2,238

Adapted from: www.manhattan-institute.org : Project FDA Report # 5 – March 2012
What drives NEWDIGS (2)?
The evolution of knowledge and its consequences

*modified from Eichler, HG, NEWDIGS workshop presentation, 2011
What drives NEWDIGS (3) ?
The effort of developing and assessing safe & effective medicines

• Phase 3 trials can absorb as much as 90% of the entire development budget; they are getting more complex, longer and more patients are included\(^1\)
  » Late stage attrition remains unacceptably high
  » Limitations of randomized controlled clinical trials

• Increasing evidence requirements: cost vs. value?
  » International Conference for Harmonisation (ICH) E14 guideline – thorough QT/QTc (TQT) studies for all drugs: Cost: $3 million / sudden cardiac death prevented or $240,000 / Quality-adjusted life year (QALY) gained\(^2\)
  » Evolving requirements for Kalydeco coverage by Arkansas Medicaid\(^6,\,7\)
  » Evidence vs. access: finding the “sweet spot”\(^3\)

• Existing statutory flexibilities available to regulators and HTAs/payers are applied…..
  » In limited, inconsistent, and unpredictable ways \(^4,\,5\)
  » Lack coordination & alignment

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\(^1\) = [www.manhattan-institute.org](http://www.manhattan-institute.org); Project FDA Report # 5, March 2012


\(^3\) = Eichler H-G et al. The Risks of Risk Aversion. [http://www.nature.com/nrd/journal/v12/n12/full/nrd4129.html](http://www.nature.com/nrd/journal/v12/n12/full/nrd4129.html)

\(^4\) = Sasinowski FJ, Quantum of Effectiveness Evidence in FDA’s Approval of Orphan Drugs, NORD Report, 2011.


Medco Study Finds Many Patients on Newer Oncology Treatments Are at Risk for Drug Interactions
Oral Cancer Drugs Need Added Monitoring to Prevent Safety Risks, Impaired Effectiveness
Mar 16, 2012

WASHINGTON, March 16, 2012 /PRNewswire/ -- Oral cancer drugs that target key enzymes in tumor cells have made significant contributions to oncology care, freeing many patients from spending long hours at infusion centers to receive their chemotherapy treatments. But new research shows that many patients using these oral medications are also on other drugs that may prevent patients from getting the full benefit from their cancer treatment, or increase the risk of side effects.

(Logo: http://photos.prnewswire.com/prnh/20100509/MEDCOLOGO)

The study by the Medco Research Institute presented today at the 2012 American Society of Clinical Oncology (ASCO) Annual Meeting in Chicago provides evidence that 23-74 percent of patients taking one of nine oral oncology medications were also on a drug that had the potential to reduce the effectiveness of the cancer treatment or increase its toxicity.

“The research found that 23-74 percent of patients taking one of nine oral oncology medications were also on a drug that had the potential to reduce the effectiveness of the cancer treatment or increase its toxicity.”

Source: Medco March 16, 2012
A joint effort is needed to advance
NEWDIGS: Channeling Multi-stakeholder Collaborative Innovation to Drive Real World Impact

March 2012: Multi-Stakeholder Thought Leadership

Adaptive Licensing: Taking the Next Step in the Evolution of Drug Approval

H-G Eichler1,2, K Oye3,4, LG Baird2, E Abadie5, J Brown6, CL Drum2, J Ferguson7, S Garau7, L Hamilton6, P Honig8, M Hukkelhoven9, JCM Lim10, R Lim11, MM Lumpkin12, G Neil13, B O'Rourke13, D Shoda14, V Seyfert-Margolis14, EV Sigal19, J Sobotka20, D Tan12, TF Unger18 and G Hirsh17

Traditional drug licensing approaches are based on binary decisions. At the moment of licensing, an experimental therapy is presumptively transformed into a fully vetted, safe, efficacious therapy. By contrast, adaptive licensing approaches are based on stepwise learning under conditions of acknowledged uncertainty, with iterative gathering and regulatory evaluation. This approach allows approval to align more closely with patient needs for access to new technologies and for data to inform medical decisions. The concept of AL embraces a range of models and some see AL as an evolutionary step, extending elements that are now in place. Others envision a transformed framework that may require legislative action before implementation. This article summarizes recent AL discussions how proposals might be translated into practice, with illustrations in different therapeutic areas.

See COMMENTARY page 378

European Medicines Agency launches adaptive licensing pilot project

19/03/2014

European Medicines Agency launches adaptive licensing pilot project

Improving timely access for patients to new medicines: pilot explores adaptive licensing approach with real medicines in development

The European Medicines Agency (EMA) is inviting companies to participate in its adaptive licensing pilot project. Companies who are interested in participating in the pilot are requested to submit ongoing medicine development programmes for consideration as prospective pilot cases.

A framework to guide discussions of individual pilot studies has been published.

The adaptive licensing approach, sometimes called staggered approval or progressive licensing, is a part of the Agency’s efforts to improve timely access for patients to new medicines. It is a prospectively planned process, starting with the early authorisation of a medicine in a restricted patient population, followed by iterative phases of evidence gathering and adaptations of the marketing authorisation to expand access to the medicine to broader patient populations.

Clinical Pharmacology & Therapeutics (2012); 91 3, 426–437. doi:10.1038/clpt.2011.345

March 2014: EMA Pilot Program
Scenario Design Methodology – 13 potential medicines evaluated

Call for Assets

Asset Nominations

Asset Selection

Scenario Design Session

- Synthesize learnings
- Assess feasibility to advance to pilot project

Regulators, payers/HTAs review

Consensus feedback to sponsor

Adaptive Licensing

What is it?

• AL is a prospectively planned, adaptive approach to regulation of drugs.

• Through iterative phases of evidence gathering followed by regulatory evaluation and license adaptation, AL seeks to balance timely access for patients with the need to provide adequate evolving information on benefits and harms.

• AL builds on existing regulatory processes, including Accelerated Approval/Conditional Authorization and REMS/RMPs.

• To achieve the full potential of AL for public health and drug development, licensing decisions should be aligned with payer, prescriber, and patient decisions.

Modified from: Eichler H-G et al., Adaptive Licensing: Taking the Next Step in the Evolution of Drug Approval, Clinical Pharmacology & Therapeutics (2011); 91 3
Adaptive Licensing is not another new regulatory or reimbursement pathway, but rather a process to facilitate broader and more coordinated application of existing flexibilities.
### Adaptive Licensing
Policy vs. process innovation?

**Transition from ...**

<table>
<thead>
<tr>
<th>Magic Moments</th>
<th>Life-span Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prediction</td>
<td>Monitoring</td>
</tr>
<tr>
<td>RCT Only</td>
<td>Toolkit for Evidence Generation</td>
</tr>
<tr>
<td>Total Population at Once</td>
<td>Highest Benefit Population Early</td>
</tr>
<tr>
<td>Focus on Licensing</td>
<td>Focus on Patient Access</td>
</tr>
<tr>
<td>Open Utilization</td>
<td>Managed Utilization</td>
</tr>
</tbody>
</table>

Modified from Hans-Georg Eichler, DIA 2014
Current NEWDIGS Activities Focus on Enabling the Implementation of Adaptive Licensing

MIT NEWDIGS Adaptive Licensing Initiative

Design Phase

Global Regulatory System Innovation (Adaptive licensing)

Phase concluded with the initiation of the EMA pilot program

Implementation Phase

Janus Initiative (Modeling and Simulation)

Stakeholder engagement and semi-quantitative simulation toolset to support pilots

Data Initiative (Data and Data Systems Readiness)

Assess and enhance data system “readiness” to support pilots
Back Up
## Comparison of Traditional and Adaptive Licensing Paradigms

<table>
<thead>
<tr>
<th>Traditional</th>
<th>Adaptive Licensing</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Opportunistic” development plan</td>
<td>Prospectively planned and coordinated development</td>
</tr>
<tr>
<td>Phase 1, 2, and 3 studies, ≈ 8-12 yrs and many highly selected patients</td>
<td>Phase 1, 2 and registration study(s), ≈ 4-8 years with fewer less selected patients</td>
</tr>
<tr>
<td>Trial patients may differ significantly from treated population after approval</td>
<td>“Real world” safety and effectiveness data collected early in lifecycle</td>
</tr>
<tr>
<td>Ad hoc process for review of post-marketing data and regulatory action</td>
<td>Planned cycles of data gathering and review and regulatory action to relax or tighten access</td>
</tr>
<tr>
<td>Off-label use common</td>
<td>Monitoring and controls restrict off-label use</td>
</tr>
<tr>
<td>Uncertainties around risks and benefits may not be well understood by patients and providers</td>
<td>Risks and benefits actively communicated to patients and providers</td>
</tr>
<tr>
<td>Payer data may not support reimbursement at time of licensure</td>
<td>Generation of payer data assured and controlled</td>
</tr>
</tbody>
</table>
## Scenario Design: Characterization of Assets

<table>
<thead>
<tr>
<th>Therapeutic Area/Indication</th>
<th>Development Phase</th>
<th>Number of Sessions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic for drug resistant bacteria</td>
<td>Phase 2</td>
<td>3</td>
</tr>
<tr>
<td>Multi-drug regimen for drug resistant TB</td>
<td>Phase 1</td>
<td>4</td>
</tr>
<tr>
<td>Dyslipidemia therapeutic</td>
<td>Phase 2</td>
<td>2</td>
</tr>
<tr>
<td>Polycystic kidney disease</td>
<td>Phase 2</td>
<td>1</td>
</tr>
<tr>
<td>MAb to treat PML</td>
<td>Preclinical</td>
<td>1</td>
</tr>
<tr>
<td>Anti-bacterial vaccine</td>
<td>Phase 1</td>
<td>1</td>
</tr>
<tr>
<td>Novel-novel oncology therapeutic for rare cancers</td>
<td>Phase 2</td>
<td>1</td>
</tr>
<tr>
<td>Therapeutic Area/Indication</td>
<td>Development Phase</td>
<td>Number of Sessions</td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>-------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>ATTR therapeutic</td>
<td>Phase 2</td>
<td>2</td>
</tr>
<tr>
<td>Therapeutic vaccine for B-cell lymphoma</td>
<td>Preclinical</td>
<td>2</td>
</tr>
<tr>
<td>Anti-inflammatory for the treatment of ACS</td>
<td>Pre- Phase 3</td>
<td>1</td>
</tr>
<tr>
<td>Oncology therapeutic with companion diagnostic</td>
<td>Phase 1</td>
<td>1</td>
</tr>
<tr>
<td>Pan-amyloidosis therapeutic</td>
<td>Phase 1</td>
<td>3</td>
</tr>
<tr>
<td>Pain therapeutic</td>
<td>Phase 2</td>
<td>1</td>
</tr>
</tbody>
</table>
### Adaptive Design Features Proposed

<table>
<thead>
<tr>
<th>Design Feature</th>
<th>Number Used/Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous learning due to multiple collections and analyses of data</td>
<td>13/13</td>
</tr>
<tr>
<td>Early access to patients with highest unmet medical need with or without staged expansion</td>
<td>6/13</td>
</tr>
<tr>
<td>Early access to defined population with staged expansion</td>
<td>7/13</td>
</tr>
<tr>
<td>Early access or initial trials in region with highest need</td>
<td>3/13</td>
</tr>
<tr>
<td>Initial authorization based on surrogate endpoints followed by clinical confirmation</td>
<td>8/13</td>
</tr>
<tr>
<td>Confirmatory studies in distinct form of the condition</td>
<td>6/13</td>
</tr>
<tr>
<td>Registry or observational study to collect real world data</td>
<td>11/13</td>
</tr>
<tr>
<td>Post-authorization access restricted to qualified providers/facilities</td>
<td>7/13</td>
</tr>
<tr>
<td>Post-authorization access restricted based on lab test results</td>
<td>5/13</td>
</tr>
</tbody>
</table>
Thank you!

Gigi Hirsch, MD
Executive Director
MIT Center for Biomedical Innovation
ghirsch@mit.edu