Follow-on Biologics:
Getting Past The Exclusivity Debate

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The RPM Report
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Credit Where Credit is Due

- The RPM Report
  - Ramsey Baghdadi, Managing Editor
  - Kate Rawson, Senior Editor
  - Cole Werble, Editor In Chief

- FDC Windhover Biopharma Group
  - Roger Longman, Managing Partner

Material from this presentation is derived from interviews with company executives and investors, and from transaction data tracked by Windhover Information Inc., publisher of *The RPM Report*. 
Key Takeaways

- Exclusivity Dominates Legislative Debate
  - 5 Years? 14 Years?
  - It Doesn’t Matter As Much As You Think

- The New Line for Innovation
  - Me Too vs. Me Better
  - Cautionary Lessons From Waxman/Hatch

- The Business Models In Play
  - Why Big Pharma May be Biggest Player
- Legislation came close in 2007, but failed to pass
  - Biotech would have been the big winner in 2007 compromise

- Is 2009 the Big Year for FOBs?
  - Tied To Health Care Reform Proposal
  - Separate Bill, or Await Consensus?
  - Could Slip to PDUFA V
Exclusivity Dominates Debate

5?

14???
Exclusivity is a Red Herring

- Even with a “follow-on” pathway, biosimilars approved under any new regulation are not a near-term commercial option
  - FDA needs to develop regulation, and ongoing resource constraints could delay implementation
  - Long approval process for existing follow-ons (Omnitrope)
  - Spotlight on drug safety = more cautious FDA
- Clinical study requirement is expected…
  - …but FDA could waive trials if deemed unnecessary
- Therapeutic substitution is a LONG way off
  - Uptake of follow-on products will be slower than what is seen with AB-rated small molecules

“Generic Biologics” Debate is Over 10 Years Old. Will APPROVING Generic Biologics Move Faster?
### A CASE OF PRECEDENTS

**Exhibit 2:**

*Below are a number of technical follow-on biologic FDA approvals and therapeutics under development.*

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Biogeneric/peptide</th>
<th>Innovator</th>
<th>Indication</th>
<th>Regulatory Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roche</td>
<td>CERA (continuous erythropoietin receptor activator)</td>
<td>Amgen Epogen</td>
<td>Anemia</td>
<td>BLA Expected In 2006</td>
</tr>
<tr>
<td>Barr</td>
<td>Adenovirus Vaccine</td>
<td>Wyeth Adenovirus Vaccine</td>
<td>Adenovirus</td>
<td>Manufacturing Plant Complete</td>
</tr>
<tr>
<td>Unigene</td>
<td>Fortical (calcitonin)</td>
<td>Sanofi-Aventis CalciMar</td>
<td>Osteoporosis</td>
<td>Approved August 2005</td>
</tr>
<tr>
<td>Halozyme Therapeutics</td>
<td>HyleneX (hyaluronidase)</td>
<td>Wyeth Wydase</td>
<td>Diffusing Agent</td>
<td>Approved December 2005</td>
</tr>
<tr>
<td>PrimaPharm</td>
<td>Hydase (hyaluronidase)</td>
<td>Wyeth Wydase</td>
<td>Diffusing Agent</td>
<td>Approved October 2005</td>
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<tr>
<td>Ista</td>
<td>Vitrase (hyaluronidase)</td>
<td>Wyeth Wydase</td>
<td>Diffusing Agent</td>
<td>Approved May 2004</td>
</tr>
<tr>
<td>Amphastar</td>
<td>Amphadase (hyaluronidase)</td>
<td>Wyeth Wydase</td>
<td>Diffusing Agent</td>
<td>Approved October 2004</td>
</tr>
<tr>
<td>Ferring</td>
<td>ReproxeX (menotropins)</td>
<td>Serono Pergonal</td>
<td>Ovulation Induction</td>
<td>Approved January 1999</td>
</tr>
<tr>
<td>NovoNordisk</td>
<td>Glucagen (glucagon)</td>
<td>Eli Lilly Glucagon</td>
<td>Diabetes/Insulin</td>
<td>Approved June 1998</td>
</tr>
<tr>
<td>Novartis</td>
<td>Omnitrope (somatropin)</td>
<td>Pfizer Genotropin</td>
<td>Human Growth Hormone</td>
<td>Pending</td>
</tr>
</tbody>
</table>

**SOURCE:** The RPM Report
"Safety First" Implementation

Kefauver Amendments
August 1962

FDA Amendments Act,
September 2007

"We are writing the history of drug regulation with what we are doing every day in response to FDAAA."
--Office of New Drugs Director John Jenkins
FDA’s Credibility Crisis

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Restoring FDA’s Self-Confidence

- **Risk Evaluation and Mitigation Strategies**
  - Increase Ability of FDA to Control Who Gets a Drug
  - Builds in Timelines for Reassessments

- **Mandatory Post-Marketing Trials**
  - Assures Agency that Questions Will Be Answered

- **Fundamentally Changes Launch Model**
  - Era of the “Mini-buster” or “Progressive Blockbuster”
  - More *Xolairs*, *Clozarils*; Fewer *Singulairs*, *Zyprexa* — *No Vioxx*

Regulatory Model Stresses “Safety First”
The Implementers?

**Commissioner Nominee**
Margaret Hamburg

**Principle Deputy/Acting Commissioner**
Joshua Sharfstein
The New FDA: Leadership

Other Names To Know…

- Jesse Goodman
  - Former CBER Head
  - Now CMO/CSO
  - Ties To Hamburg/Sharfstein via Transition Team, Biodefense, Vaccines

- David Dorsey
  - Ex-Kennedy Staffer
  - Senior Counselor, Head of Leg. Affairs
  - REMS/FOBS Architect

- Michael Landa
  - Acting Chief Counsel
Will FOBs Hurt Innovation?

Ideas + Funding = New Medicine
The Biotech Equation

Ideas + Funding = New Medicine

FOBs?
Sources of Funding

- **Government**
  - Direct Research Investment
  - Tax Incentives
  - Purchase Agreements

- **Industry R&D Budgets**
  - Funded by Product Sales
  - Internal R&D
  - Licensing/Acquisitions

- **Wall Street**
  - Venture Capitalists
  - Private Equity
  - Institutional Investors

All Three Are Critical to Biotech…

…but not equally or at all stages
Sensitivity to FOBs

- **Government**
  - Programs Unaffected by ROI
  - Policy Priorities Drive Investment
  - More Attractive in Current Economic Climate

- **Industry R&D Budgets**
  - Direct Impact from Lost Sales
  - R&D Spending Driven by ROI
  - But, Innovation is Life

- **Wall Street**
  - Big Investors Not Tied to Industry
  - Capital Will Chase Highest Return
  - Perception IS Reality
Lower Limits on Exclusivity

Orphan Drug Act: 7 Years

Chart 1
Total Orphan Designations and Approvals

<table>
<thead>
<tr>
<th>Year</th>
<th>Designations</th>
<th>Approvals</th>
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<tr>
<td>1983</td>
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<td>1999</td>
<td>79</td>
<td>14</td>
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<tr>
<td>2000</td>
<td>68</td>
<td></td>
</tr>
</tbody>
</table>

Source: HHS IG Report, 2001
Lower Limits on Exclusivity

Hatch-Waxman: 5 Years

Source: PhRMA
The View From Wall Street

- Even With FOBs, Product Lives Will be Longer
  - Generic Cliff not as Steep

- Product Improvements (e.g., Delivery, Formulation) Can Make Big Therapeutic Differences
  - Payors Will Accept Value of Improvements

- Biotech Development is Less Risky
  - Fewer Dropouts
  - Less Costly Sales Infrastructure

It's The ECONOMY, Stupid
What if the Equation is Wrong?

Ideas + Funding = New Medicine
R&D Not Paying Off

Exhibit 2
Still Waiting for the Rebound:
Drug Approval Statistics Since 1996

More First Generics Than NMEs

Source: FDA and The RPM Report
Unintended Consequences

*Pfizer CEO Jeff Kindler*

*Merck SVP Ken Frazier*
FOBs Can Encourage Innovation

Business Plans Based on FOBs

Example 1: Getting a Head Start
Innovative Therapeutic in Oncology
Use EPO to Build Sales & Marketing
(and Fund Development)

Example 2: Saving the Pie
Oncologic to Add to Rituxan
Premium Price Only Viable if Rituxan Costs Less
FOBs Can Encourage Innovation

Vaccines
FOB-Proof Investment
Already Experiencing Significant Growth
*Prevnar, Gardisil, Etc.*

Manufacturing
Drive to Reduce Costs
Likely to Attract New Entrants
Breakthroughs Will Enhance All Biotech Production
“Evergreening”: The Myth of the Bright Line

- Innovators Will Innovate Within the System
- Incentive to do Minimum Necessary for Exclusivity

Case 1: Drug Delivery

PROCARDIA XL®

Case 2: Metabolite/Enantiomer

allegra®
fexofenadine HCl

Nexium®
esomeprazole magnesium
Two Routes for “Follow-on” Biologics

- **“Me-Too” Biologics**
  - “Generic” biologics approved under 505(b)(2); legislation pending in Congress to authorize an abbreviated pathway

- **“Me-Better” Biologics**
  - Using novel technology to tweak an existing, well-validated molecule; “Avastin with a twist”
The Downside Risks

- **Novartis’ *Omnitrope*: The Market Penetration Problem
  - Generic human growth hormone = 3.4% of market (IMS Health)
  - But...HGH is a highly saturated market; uptake trends in other treatment categories may be different

- **Roche’s *Mircera*: The Intellectual Property Problem
  - Third generation, long-acting EPO approved by FDA nearly a year ago (November 2007)
  - Amgen has been successful in keeping *Mircera* off the market through patent litigation

- **Genzyme’s *Myozyme*: The Manufacturing Problem
  - FDA refused to allow the company to sell *Myozyme* made out of a different manufacturing plant because it considers it a different product. To sell that version, Genzyme needs a new NDA.
Why Wait? Advantages of “Me-Betters”

- **Big Pharma is already “bioteching” itself**
  - Primary care, me-too, DTC-driven model is over

- **Biotech has a lower R&D risk than small molecules**
  - Biologics have a faster development time than small molecules
  - More targets from which to choose
  - Technology advancements in production and drug delivery are minimizing the disadvantages

- **Patent estates generally more robust (process, not product)**

- **Payors have demonstrated a willingness to pay for small improvements (for certain diseases)**
  - Future in high-value, more personalized medicine
  - Plenty of room for pricing discount

- **Lots of acquisition opportunities among start-up platform technology companies**
<table>
<thead>
<tr>
<th></th>
<th>Me-Too Pathway</th>
<th>Me-Better Pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical trial requirements</td>
<td>Abbreviated clinical trials; potential for FDA waiver</td>
<td>Full clinical trials—but de-risked (unless FDA/payors demand head-to-head studies.)</td>
</tr>
<tr>
<td>Capital investment</td>
<td>$30-$50 million (Cowen &amp; Co.)</td>
<td>More Than $50 Million, But Less Than $1 Billion</td>
</tr>
<tr>
<td>Therapeutic interchangeability?</td>
<td>No (at least not yet)</td>
<td>No</td>
</tr>
<tr>
<td>FDA approval timeline</td>
<td>Uncertain</td>
<td>10 months (but perhaps ~18 months is more realistic)</td>
</tr>
<tr>
<td>Exclusivity period (assuming 2007 compromise holds)</td>
<td>1 year (first follow-on gets exclusivity)</td>
<td>12 years data exclusivity</td>
</tr>
</tbody>
</table>
A Question of Capital

- Biotech Can’t Get It
  - Except From Pharma

- All eyes on generic drug industry…
  - Obvious choice given experience in small molecules
  - Slowing R&D pipeline means that the wave of blockbuster patent expirations will crest early next decade

- But Investment in FOBs May Exceed Their Grasp…

- And Legacy of Generic Drug Scandal Remains
“BioBetter” Dealmaking

- **GlaxoSmithKline’s Domantis**
  - £230 million ($454 million) in cash; December 2006

- **Bristol-Myers Squibb’s Adnexus**
  - $430 million in cash plus $75 million in three earn-out payments; September 2007

- **Wyeth’s Haptogen**
  - October 2007

- **Teva’s CoGenesys**
  - $400 million in cash; January 2008
Domantis will allow GSK to “re-do a monoclonal for everything that is on the market, from Avastin to Rituxan….We can do our own version, without infringing IP, with a product that might even have a twist.”

-- GSK’s JP Garnier

“Regardless of how the legislative or regulatory pathway may evolve” in follow-on biologics, “there is always going to be a competitive advantage in that space that will be a little bit different than in small molecules for pharmaceutical sciences and manufacturing.”

-- Pfizer’s Jeffrey Kindler
The New Pharma Model?

Carnegie

Rockefeller

Kindler

Clark
Why Big Pharma Loves Biotech

- Lifecycle Still Relatively Attractive
  - No One Talking About Substitutable Biologics
  - Generic-style Price Competition Unlikely
  - Patent Estates Generally More Robust
    - Process, Not Product

- Other Pressures on Big Pharma Model
  - Payors, Regulators Favor “Specialty” Products
  - Future in High Value, More Personalized Medicine
  - Biotech Business Model Ascendant
Why Big Pharma Loves Generics

The Generic’s Share of Prescription
Unit Volume US, 1984-2007

SOURCE: Pfizer
Questions?

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