The Post-Approval Challenges of Antimicrobial Development

Committee on the Long-Term Medical and Economic Effects of Antimicrobial Resistance
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Disclosures and Disclaimer

• Kevin Krause is the V.P. Clinical Sciences and Development Operations, and a shareholder in AN2 Therapeutics, Inc.

• He is a former employee of Achaogen, Cerexa (Forest Laboratories/Actavis, Allergan, now Abbvie) and Theravance

• He played various roles in the clinical development, approval and/or launch of Zemdri® (plazomicin), Avycaz® (ceftazidime-avibactam), Teflaro® (ceftaroline fosamil), Vibativ® (telavancin), Colobreathe® (inhaled colistin) and Quinsair® (inhaled levofloxacin)

• He has accepted consulting fees from Achaogen, Inc., Cipla USA, Spero Therapeutics, Felix Biotechnology, ID Biologics, Genentech/Roche, SMAC, and F-prime Capital

• He is an advisor to and shareholder in BioAmp Diagnostics

• The views and opinions expressed in this presentation are those of the author
Antibiotics - It’s Not About the Size of Profit but Rather the Magnitude of the Loss

• The market does not support investment in new drugs
  – Revenue is significantly less than R&D and post-launch costs
  – 7+ years before an antibiotic makes enough money to pay annual costs of keeping it on the market
  – It takes 23 years (O’Neill AMR report) for an antibiotic to break even…just as the patent is expiring

• The shrinking pipeline mostly sits with small companies that can’t absorb post-launch losses, increasing the risk that new drugs don’t survive

Clin Infect Dis, ciaa859, https://doi.org/10.1093/cid/ciaa859
Why is the Marketplace so Challenging?

• We have a basic math problem:
  – There aren’t a lot of patients and new drugs are reserved
  – New drugs cost a lot of money to keep on the market
  – The market does not accept the high prices needed to keep a rarely used drug on the market

• How drugs are developed vs. how they are used are different
  – Package insert and/or publications not always informative for formulary or treatment decisions
  – Treatment guidelines often recommend only off-label use, which the company can’t promote

• AMR is a large problem, but individual resistance types are a rare disease
  – No antibiotic is designed to address “2.8 million people [that] get an antibiotic-resistant infection”
Focus of Today’s Talk

• Required post-approval expenses are substantial - why?
  – Post-marketing regulatory commitments
  – Manufacturing expense and availability in the U.S.
  – AST development costs (see tomorrow’s agenda)
  – Global Drug Safety/Pharmacovigilance infrastructure and reporting, Medical Affairs, Sales and Marketing
  – Resources:

• Post-approval revenue is typically low - why?
  – True unmet need patients are uncommon to rare, but consequences are high
  – ~70% mortality reported for invasive Gram-negative infections when effective therapy unavailable
  – Formulary review, out of date breakpoints, stewardship, clinical data availability, etc.
  – Pricing and reimbursement challenges for the hospital
  – Resources:
    – Why are new antibacterials failing as commercial products? – by Patricia A. Bradford – REVIVE (gardp.org)
    – Why is it so hard to develop new antibiotics? | Wellcome
    – New Antibiotics Development | Newsletter by John Rex | AMR Solutions
    – Home | AMR Review (amr-review.org)
### Expected 5-Year Expenses For A New Antibiotic Are Daunting

*Not Shown: Sales, Marketing, Company Operations, and Employee Costs*

<table>
<thead>
<tr>
<th>Commitment</th>
<th>Single Indication, Minimum requirements</th>
<th>Two Indications Some safety signals</th>
<th>Several indications Expected broad use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatric PK and Safety Studies</td>
<td>$25M</td>
<td>$50M</td>
<td>$75M</td>
</tr>
<tr>
<td>Additional Phase 3 study</td>
<td>N/A</td>
<td>$50M</td>
<td>$75M</td>
</tr>
<tr>
<td>PK in Special Adult Populations</td>
<td>$2M</td>
<td>$3M</td>
<td>$5M</td>
</tr>
<tr>
<td>Surveillance</td>
<td>$3M</td>
<td>$5M</td>
<td>$5M</td>
</tr>
<tr>
<td>Pharmacovigilance</td>
<td>$5M</td>
<td>$5M</td>
<td>$5M</td>
</tr>
<tr>
<td>Medical Affairs</td>
<td>$50M</td>
<td>$50M</td>
<td>$50M</td>
</tr>
<tr>
<td>AST</td>
<td>$7M</td>
<td>$7M</td>
<td>$7M</td>
</tr>
<tr>
<td>Drug Manufacturing</td>
<td>$150M</td>
<td>$250M</td>
<td>$400M</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>$242M</strong></td>
<td><strong>$420M</strong></td>
<td><strong>$622M</strong></td>
</tr>
</tbody>
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Clinical Expenses - Meeting Requirements for an Approved Product

• Post-marketing commitments/requirements
  • NDA approval letter describe PMRs/PMCs; publicly available
  • Pediatric study(s)
  • Additional safety/PK studies
  • Sometimes P3 “do overs” (!!!)
  • Microbiological surveillance

• Pharmacovigilance
  • Systems and staff to provide support and record/track/resolve any product concerns
  • Quarterly and annual reports to FDA; Drug safety update reports; Surveillance reports

• Medical Affairs
  • Medical information receives and responds to queries from HCPs
  • Can discuss “off-label” data to help HCPs understand data published but not in Package Insert

• Susceptibility testing devices (AST)
  • Required for labs to determine antibiotic susceptibility
Manufacturing/Tech Ops Expenses
*Key Decisions To Supply The Market Are Made At Risk*

<table>
<thead>
<tr>
<th>Capacity</th>
<th>Inventory Policy</th>
<th>Oversight</th>
<th>Total Cost (over 5 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single Source</td>
<td>Low</td>
<td>Distant</td>
<td>~$150M</td>
</tr>
<tr>
<td>Mix Single &amp; Dual</td>
<td>Medium</td>
<td>Engaged</td>
<td>~$250M</td>
</tr>
<tr>
<td>Multiple Sources</td>
<td>High</td>
<td>Directive</td>
<td>~$400M</td>
</tr>
</tbody>
</table>

Potential Supply Chain Map
Few Manufacturers, Multiple Continents & Long Lead Times

Source (Lead Time: 8 mo)
- Source(s)
  - Raw Material
    - Spain
    - China
    - Switzerland

Make (Lead Time: 14 mo)
- Drug Substance (DS)
- Drug Product (DP)
- Pack & Label (FG)
- TBD Warehouse (DS)

Deliver and Return
- 3PL (FG)
- Channel Distribution
- IHP

~24 Months

Drug Batches Takes Several Years To Complete
Manufacturing Expenses Incurred Years Before Product is Sold

New Drugs Are Focused On Individual Resistance Types, Not AMR
Example - The CRE U.S. Market is <0.5% of AMR Patients

- CDC reports 13,100 CRE patients in the U.S. per year, but where are they?
- Need geographically dispersed (expensive) field teams to make sure drug gets to these patients
- Need to charge $50,000/treatment course for a drug that treats 2,500 patients per year to cover annual expenses of $100m in a no-profit scenario
Illustrative Example - >$420M cumulative shortfall vs. $20M raise

These are real numbers averaged across many products!

- Self-sustaining revenue in Year 7
- Does not mean break-even point!
- $500M - $1B invested before launch not accounted for in this math
- These costs apply to companies of any size – requirements aren’t reduced for a smaller company with fewer resources

Net Revenue = Sales – Clinical, Manufacturing, and Sales/Marketing Expenses
Profitability = Net Revenue – Company Operations (leases, salaries, finance, HR, etc.) of $40M/year

Can’t Commercial Companies Always Raise Money?

- Raising Money is challenging in the face of a declining stock price
- Small company equity raises limited to ~20% of the market cap
- Illustrative Example:

  10* antibiotic pure-play companies totaling $1.76b in market cap 
  (as of 12/31/20 close)

  $176M average; Range $7.7-$527.3M

  20% dilutive raise nets average $35.2M, $1.5 - $105M at range limits

- We are still $383M short!

*Cidara, Contrafect, Entasis, Iterum, Nabriva, Paratek, Scynexis, Summitt, Spero, Synthetic Biologics
Plus…Antibiotic Companies Stock Price Often Drops After Approval

- Positive clinical data drives up stock value pre-NDA
  - Seen as an inflection point and traditionally where M&A occurs
- Increased stock value and looming commercial investments trigger early investors to take profits
  - Broader investor base can mean more volatility
- At the same time, the company risk profile changes and increases
  - Will the drug be approved?
  - What will the final package insert say?
  - Will the launch meet expectations?
  - M&A doesn’t materialize in the face of market challenges
- Any new institutional investor will want proof of commercial success
- Leads to the “Short the Launch” scenario
  - Single product companies lose 40% of market cap on average and see increase in short position at launch

Can’t Commercial Companies Always Raise Money, Part 2?

• Investors know three things:
  – Launching a drug is incredibly expensive
  – Launches often underperform in the hospital and in the antibiotic space
  – Money invested at launch is likely to be further diluted later (i.e. first money in does not win)

• Companies may turn to debt, but it will be “expensive” at this point
  – High interest rates
  – Challenging covenants based on sales milestones

• Increasing financial strain decreases investor confidence

• Short interest begins to increase, putting further price on the stock

• Investors understand these financing challenges and will wait on the sidelines, making raising money that much tougher
Conclusions

• The cost to develop and maintain a branded antibiotic greatly outweigh the sales potential
• Economists would call working in the space an “irrational investment”
• Push incentives have saved the R&D pipeline for new drugs
• However, companies are largely in the negative once the product launches
  – Few to no financial options to maintain antibiotics on the market
  – Lack of exit options
• **Pull incentives are needed to keep these drugs on the market in even in the best-case scenario (is this enough?)**
  – DISARM Act – reimburse antibiotics outside of the bundled payment system – removes artificial cap/financial COI; should tolerate higher pricing
  – PASTEUR Act – award a bulk payment/subscription; removes pressure to push high volume
• …or we need to accept disease/orphan like prices, otherwise we will no longer have new antibiotics