The Post-Approval Challenges of Antimicrobial Development

COMMITTEE ON THE LONG-TERM MEDICAL AND ECONOMIC EFFECTS OF ANTIMICROBIAL RESISTANCE
NATIONAL ACADEMY OF SCIENCE, MEDICINE AND ENGINEERING

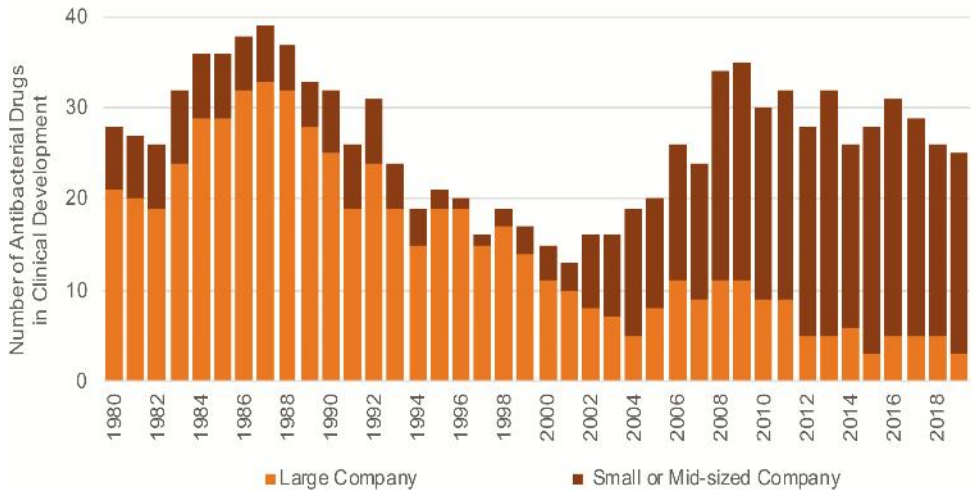
January 5, 2021

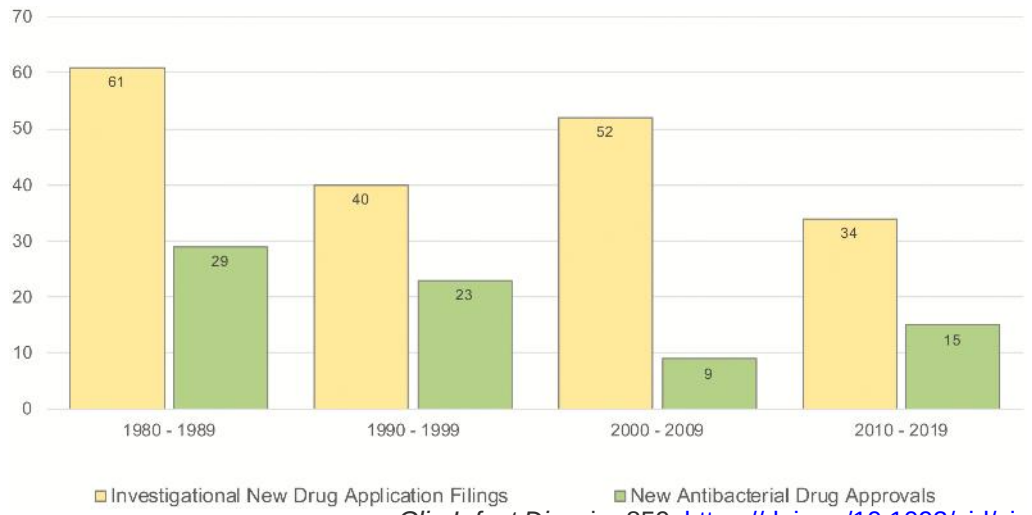
Disclosures and Disclaimer

- 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

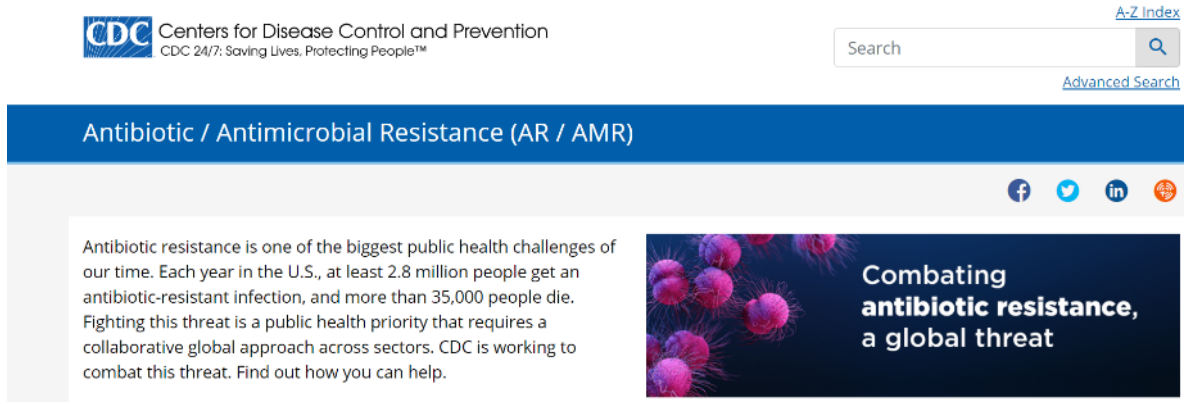




Clin Infect Dis, ciaa859, https://doi.org/10.1093/cid/ciaa859

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:
    - Bootcamp: Post-Approval Economics for New Antibiotics (ASM/ESCMID 2019) – REVIVE (gardp.org)
- 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

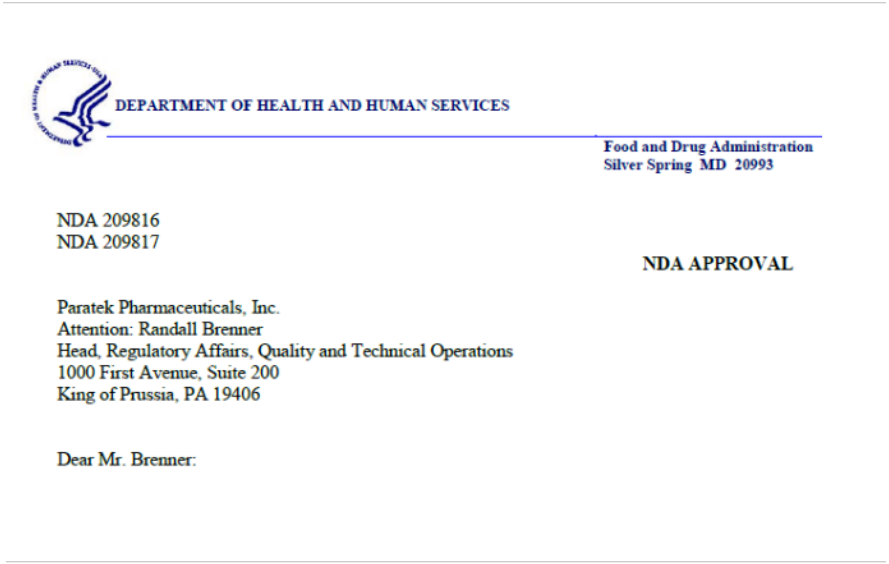
Not Shown: Sales, Marketing, Company Operations, and Employee Costs

Commitment	Single Indication, Minimum requirements	Two Indications Some safety signals	Several indications Expected broad use
Pediatric PK and Safety Studies	$25M	$50M	$75M
Additional Phase 3 study	N/A	$50M	$75M
PK in Special Adult Populations	$2M	$3M	$5M
Surveillance	$3M	$5M	$5M
Pharmacovigilance	$5M	$5M	$5M
Medical Affairs	$50M	$50M	$50M
AST	$7M	$7M	$7M
Drug Manufacturing	$150M	$250M	$400M
Total	**$242M**	**$420M**	**$622M**

From: Bootcamp: Post-Approval Economics for New Antibiotics (ASM/ESCMID 2019) – REVIVE (gardp.org)

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



DEPARTMENT OF HEALTH AND HUMAN SERVICES

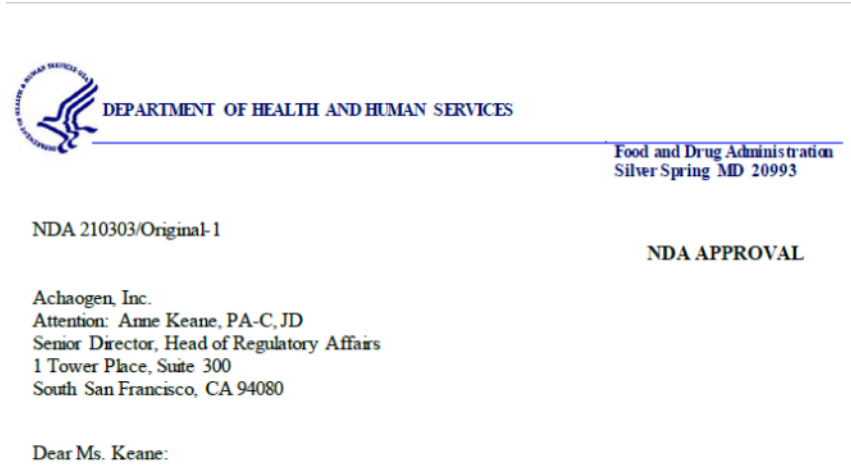
Food and Drug Administration
Silver Spring MD 20993

NDA 209816
NDA 209817

NDA APPROVAL

Paratek Pharmaceuticals, Inc.
Attention: Randall Brenner
Head, Regulatory Affairs, Quality and Technical Operations
1000 First Avenue, Suite 200
King of Prussia, PA 19406

Dear Mr. Brenner:



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

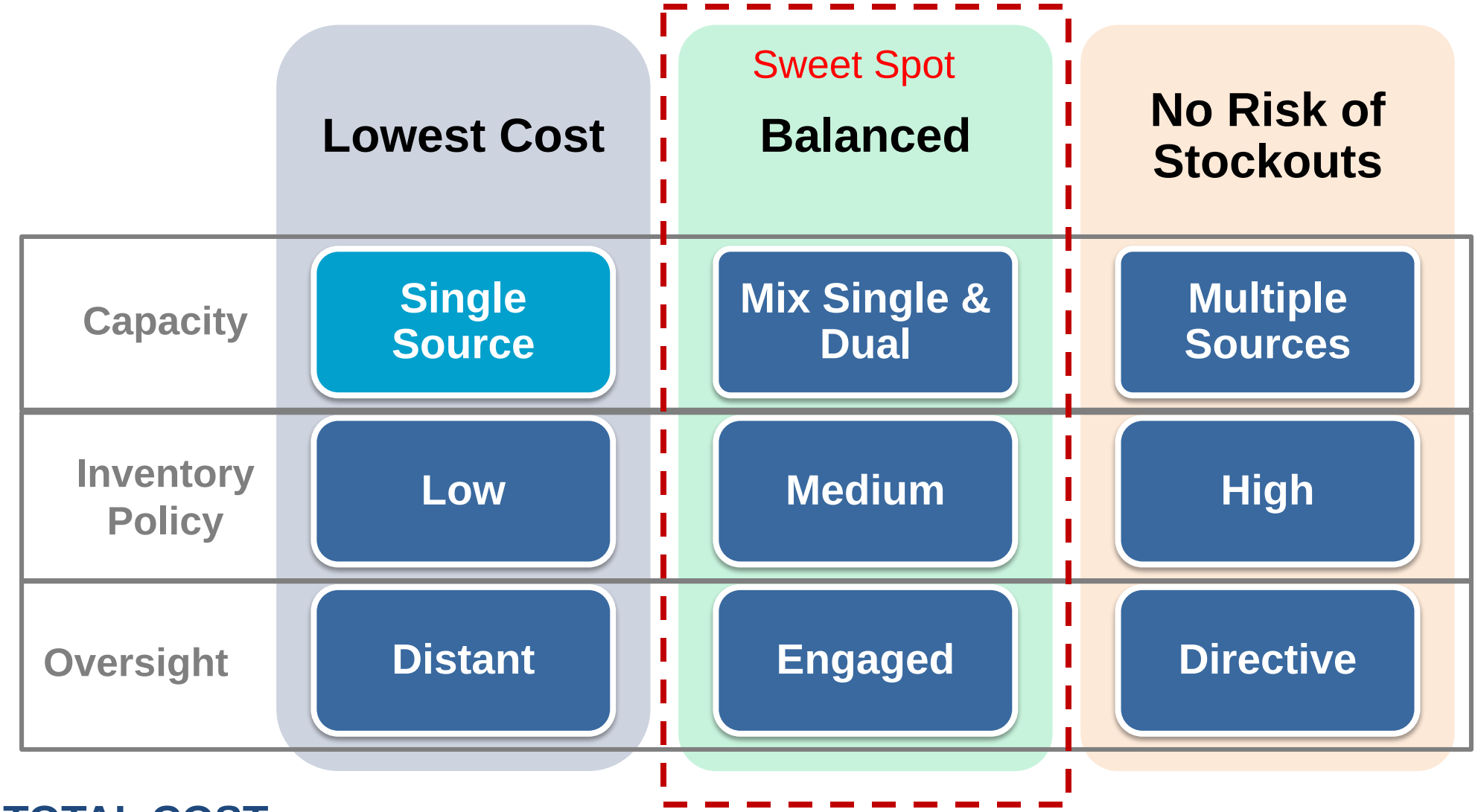
NDA 210303/Original-1

NDA APPROVAL

Achaogen, Inc.
Attention: Anne Keane, PA-C, JD
Senior Director, Head of Regulatory Affairs
1 Tower Place, Suite 300
South San Francisco, CA 94080

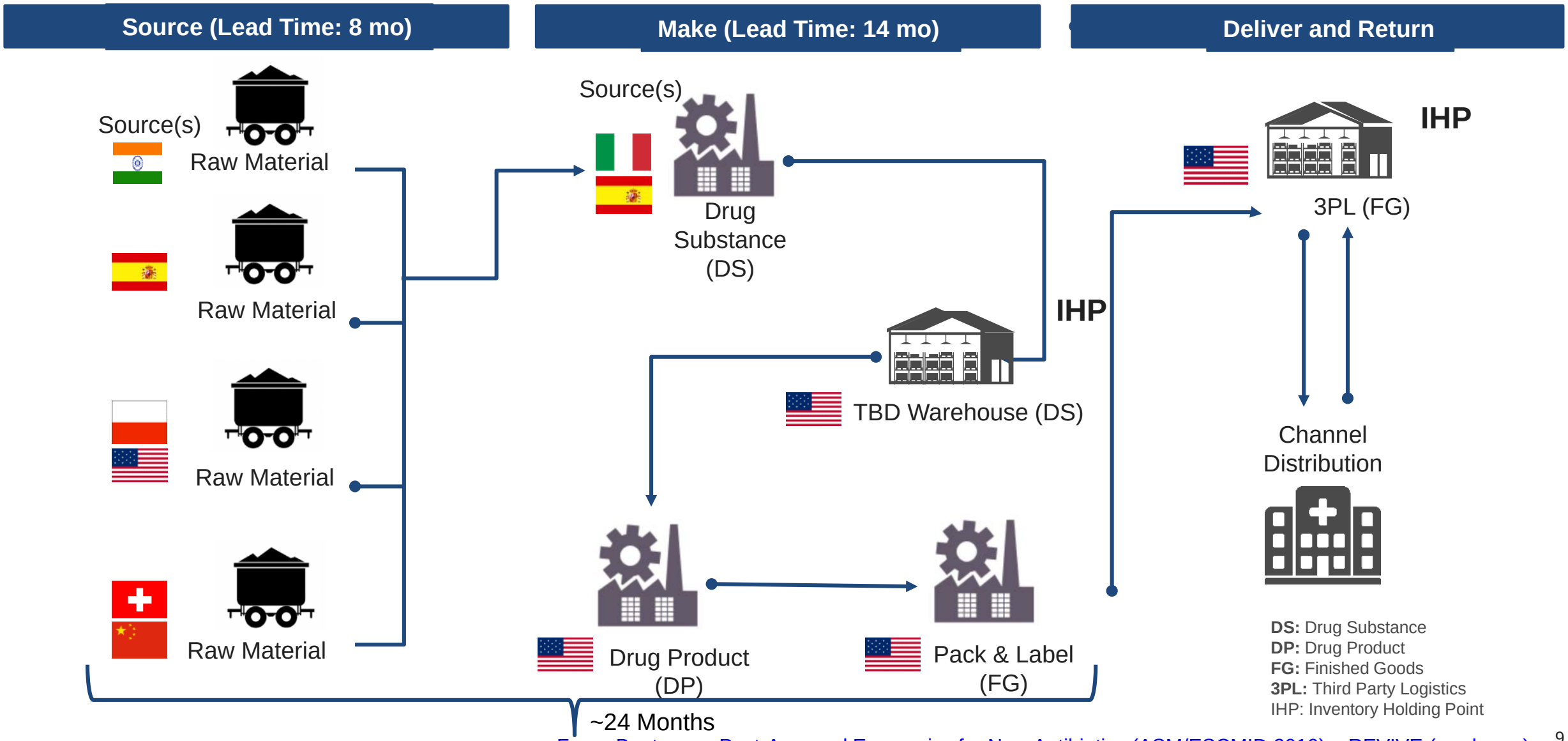
Dear Ms. Keane:

Manufacturing/Tech Ops Expenses
Key Decisions To Supply The Market Are Made At Risk



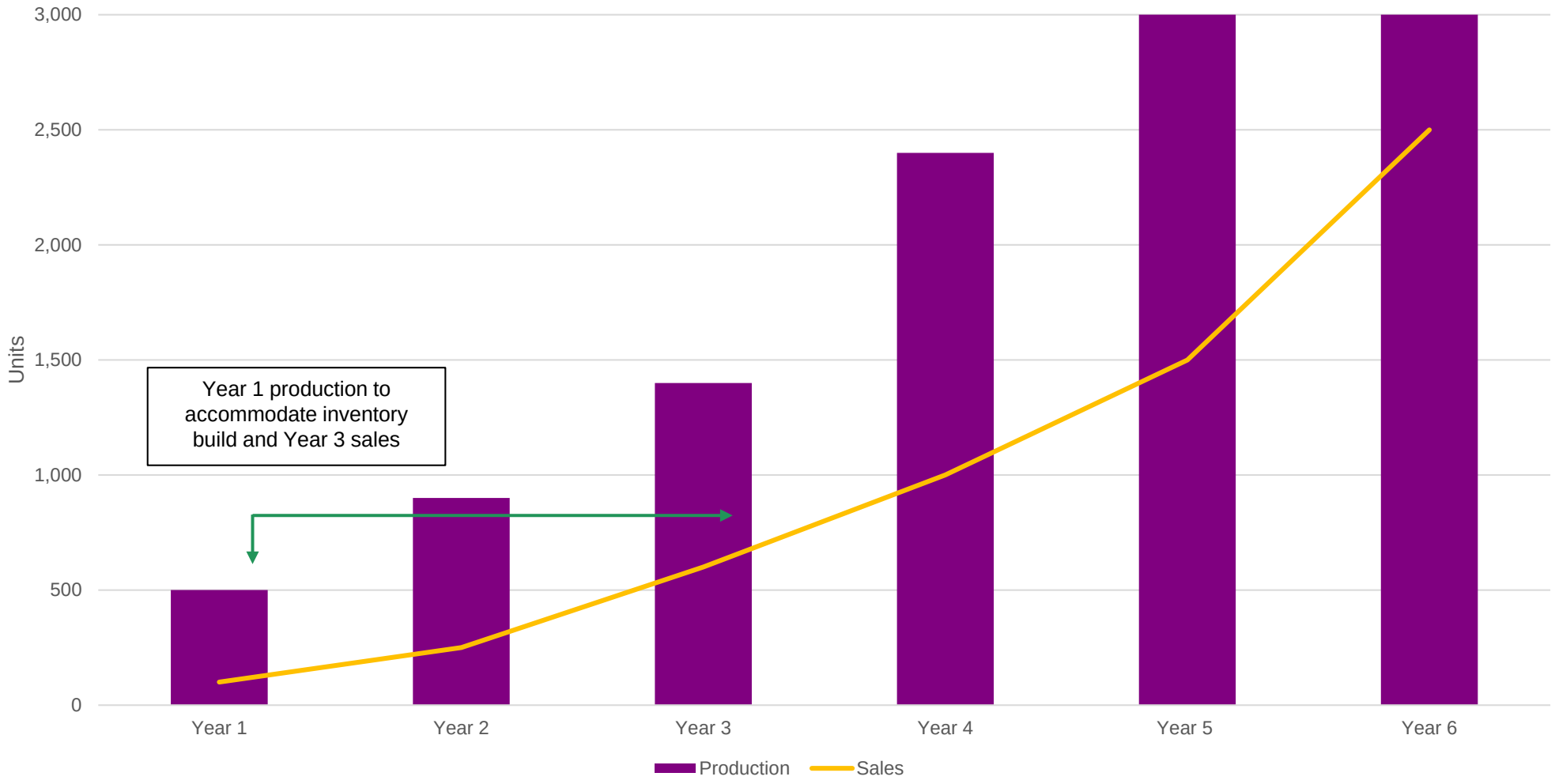
From: Bootcamp: Post-Approval Economics for New Antibiotics (ASM/ESCMID 2019) – REVIVE (gardp.org)

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



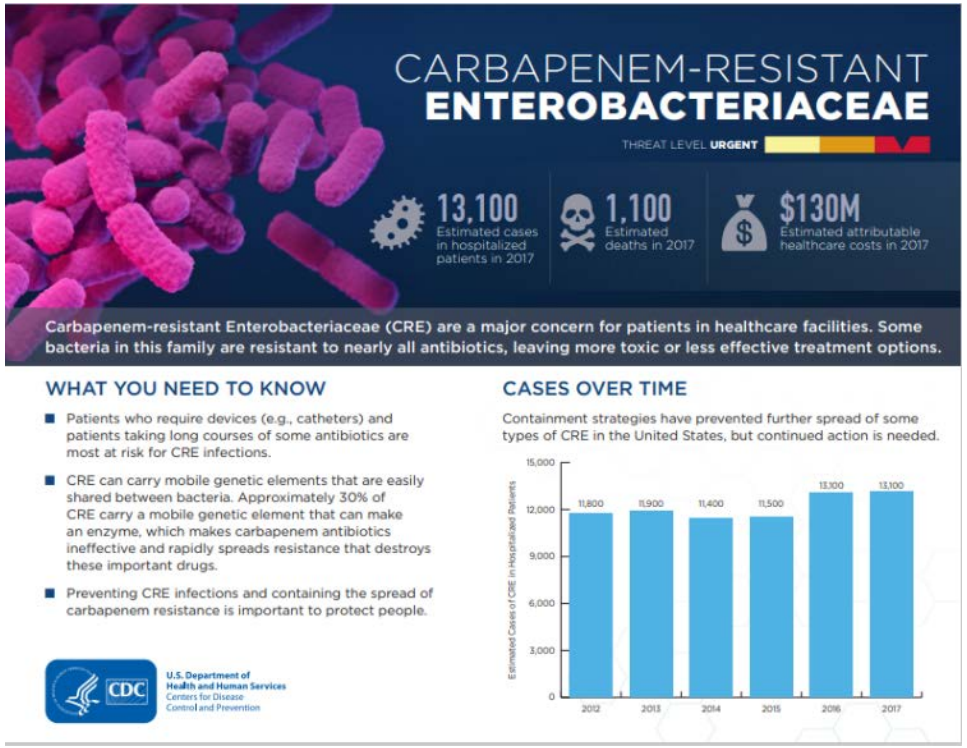
From: Bootcamp: Post-Approval Economics for New Antibiotics (ASM/ESCMID 2019) – REVIVE (gardp.org)

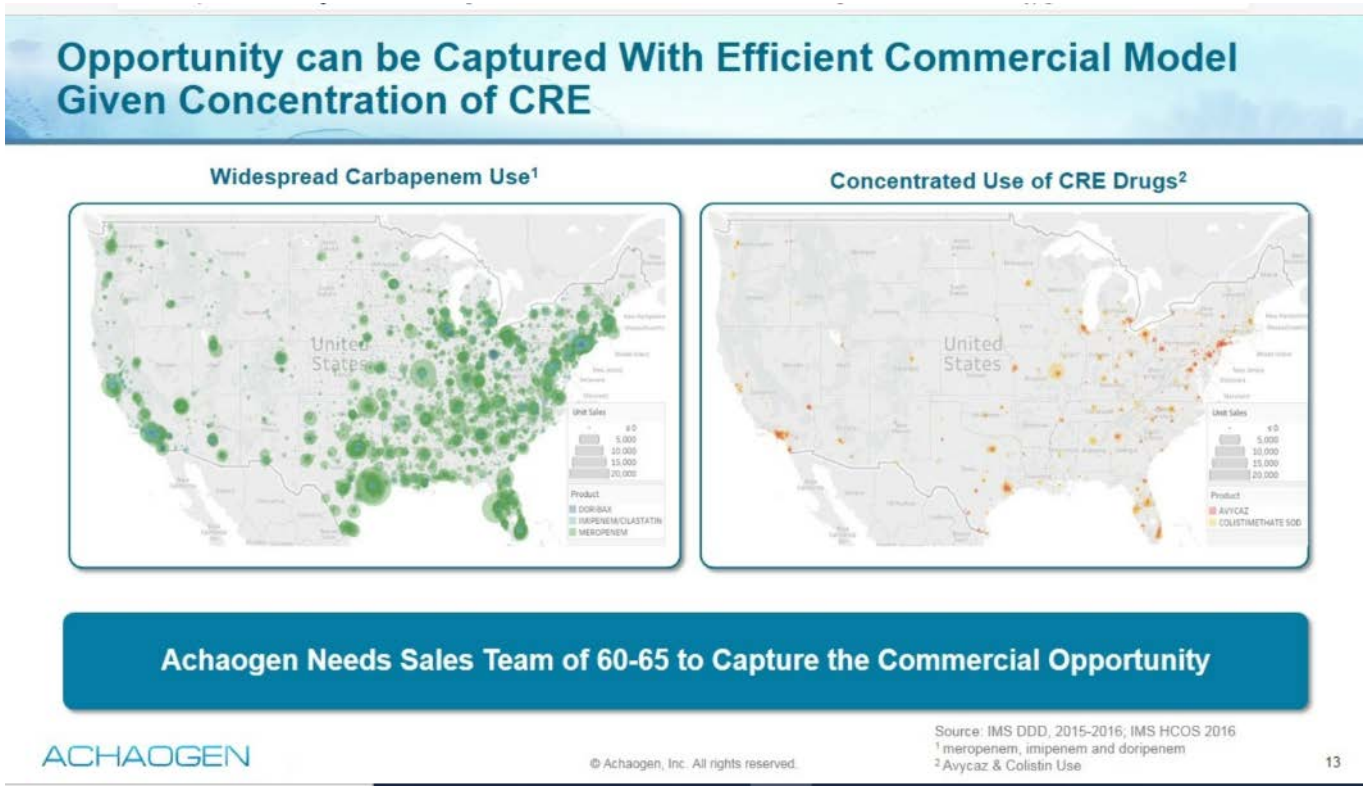
Drug Batches Takes Several Years To Complete
Manufacturing Expenses Incurred Years Before Product is Sold



From: Bootcamp: Post-Approval Economics for New Antibiotics (ASM/ESCMID 2019) – REVIVE (gardp.org)

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

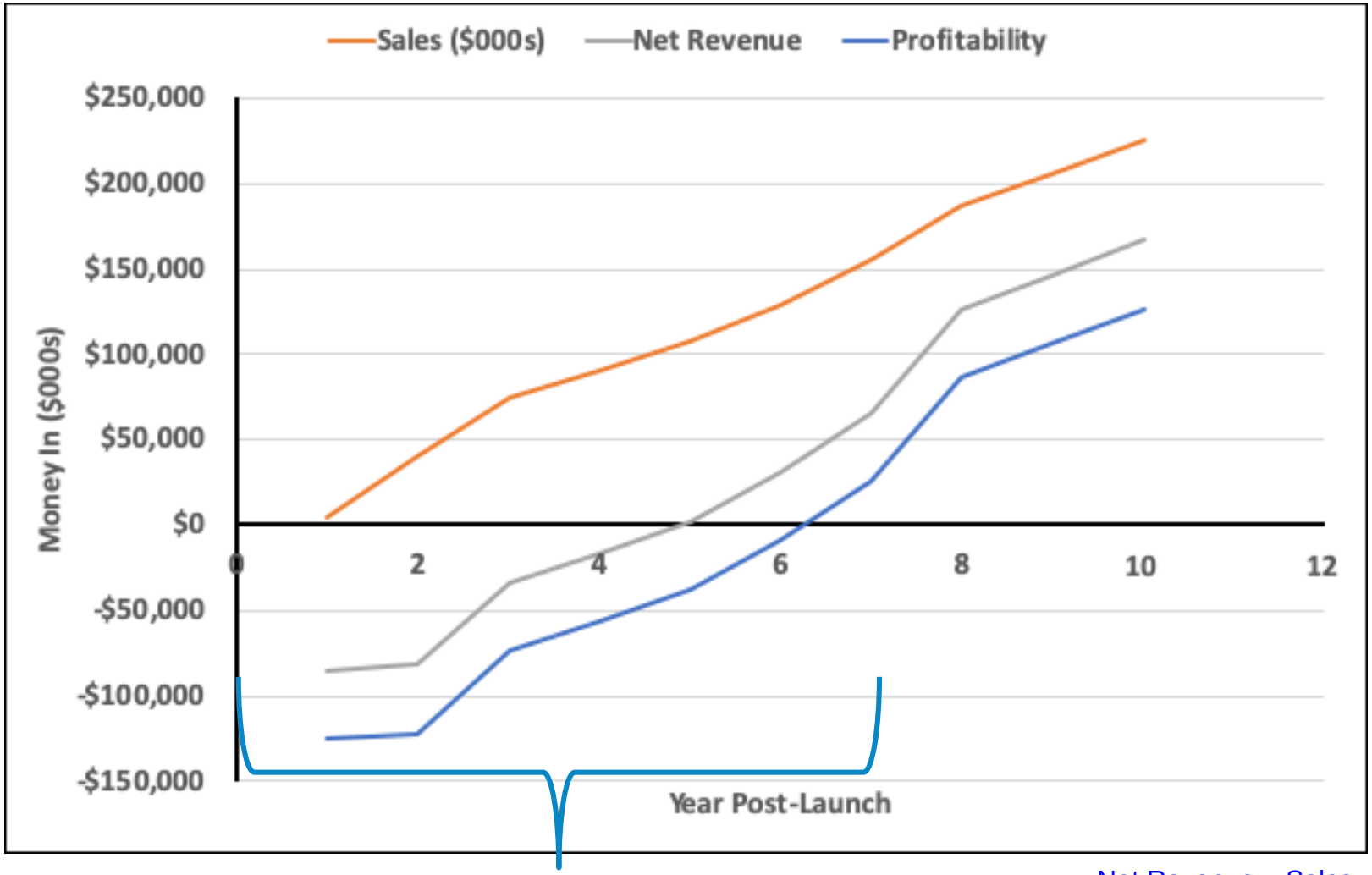




Downloaded from: galflwebcwnd000013.jpg (1280×720) (sec.gov)

- 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
From: Bootcamp: Post-Approval Economics for New Antibiotics (ASM/ESCMID 2019) – REVIVE (gardp.org)

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

From: Bootcamp: Post-Approval Economics for New Antibiotics (ASM/ESCMID 2019) – REVIVE (gardp.org)

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**