Antimicrobial development: Overview and Update

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- *The views expressed are those of the author and do not necessarily represent the views of the U.S. Food and Drug Administration*
Outline

• Antibacterial drug development
  – Overall development
  – Challenges
  – Lessons learned
  – Recent approvals
  – Safety considerations
  – Safety resources

• What’s in the pipeline
Drug Development

- Identification of potential compounds
- Animal toxicology studies
- Phase I trials
- Phase II trials
- Phase III trials
- Adverse Event Reporting
- Data mining
Antibacterial Drug Development

- Urgent need for new therapies as armamentarium is limited
  - Emergence of resistance
  - Emerging pathogens
  - Better safety profiles

- Development in the field of antibacterials is fairly limited
  - Questions raised about the scientific basis of antibacterial clinical trials
  - Waning commercial interest in antibacterial drug development
Challenges with Antibacterials

- Placebo-controlled trials not an option for most acute bacterial infections
- Since advent of antibiotics in 1930s and 1940s, significant reduction in mortality from infectious diseases
- Mortality not a feasible endpoint for most infectious diseases; clinical endpoint most relevant
- Generally noninferiority trials; reliance on historical data from pre/early antibiotic era to estimate treatment effect
- Superiority trials generally not feasible
  - some indications-impetigo, acute bacterial sinusitis
Antibacterial Drug Development

• Nonclinical
  – Animal models of infection such as neutropenic murine thigh, rat pneumonia, rabbit endocarditis
    • Pharmacokinetic/pharmacodynamic parameters identified which correlate with efficacy
      – Area Under the Curve (AUC): Minimum Inhibitory Concentration (MIC) ratio; Cmax:MIC ratio, T>MIC

• Tissue penetration
  • Epithelial lining fluid concentrations
  • CSF penetration
  • Urinary concentrations/excretion
Antibacterial Drug Development

- In vitro microbiology
  - Time-kill studies
  - Surveillance data on MIC distribution
  - Tentative breakpoints for susceptibility
  - Mechanism of action
  - Resistance mechanisms
  - Testing methods, including quality control parameters
Antibacterial Drug Development

- Phase 3 trials—typically two adequate and well-controlled trials in each indication
- Since the 1990’s, indications have been based on body site of infection such as urinary tract infections or intra-abdominal infections
  - Recognition of differing clinical course, microbial pathogens, dosing regimens, and factors at different tissue sites of infection (e.g., drug penetration) that may impact outcomes
- More recently discussions on how trials in different indications can support each other
  - November 2011 Advisory Committee Meeting
    [Link](http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/ucm242307.htm)
Current discussions

- New endpoints
- Earlier assessment of clinical response
- Limiting prior antibacterial therapies
- Need for microbiologic documentation
- Focus on patient reported outcomes
Lessons learned

• Failed phase 3 trial of daptomycin
  – Animal models
  – Effect of prior effective antibacterials
• Timing of endpoint
  – Community acquired pneumonia
• New information from postmarketing trials
  – Increased risk of mortality in doripenem treated patients in a recently terminated clinical trial in ventilator associated pneumonia
  – Increased risk of death with tigecycline compared to other antibiotics used to treat similar infections
Daptomycin

- Daptomycin is a lipoglycopeptide antibacterial active against gram positive pathogens including MRSA
- Approved for treatment of complicated skin and skin structure infections and *S. aureus* bacteremia (including right-sided infective endocarditis)
- Two Phase 3 noninferiority trials compared daptomycin to ceftriaxone for the treatment of community acquired pneumonia
- Second trial terminated as first trial failed to show noninferiority
- Pre-specified noninferiority margin was 10%
- Clinical Cure in pooled ITT population: 70.9% in the daptomycin arm and 77.4% in comparator arm; treatment difference was -6.5% (95% CI 12.4, -0.6)

Differential Effect by Body Site

Inhibition of Daptomycin by Pulmonary Surfactant: In Vitro Modeling and Clinical Impact

Jared A. Silverman, Lawrence I. Mortin, Andrew D. G. VanPraagh, Tongchuan Li, and Jeff Alder
Cubist Pharmaceuticals, Lexington, Massachusetts

The Journal of Infectious Diseases 2005;191:2149–52
Daptomycin Animal Models

- In a mouse model of broncho-alveolar pneumonia, daptomycin not as effective as ceftriaxone
  - No detectable reduction in bacterial burden observed at 24 h after infection, even at 100 mg/kg, (drug exposure significantly greater than that produced in clinical settings)

- Daptomycin more effective than nafcillin or vancomycin in a model of hematogenous pneumonia (mimic infections that develop secondary to bacteremia)

Silverman et al
Daptomycin Animal Models

<table>
<thead>
<tr>
<th>Model</th>
<th>Organism</th>
<th>Dose, mg/kg</th>
<th>Log reduction</th>
<th>Comparator Drug (dose, mg/kg)</th>
<th>Log reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse BAP</td>
<td><em>S. pneumoniae</em></td>
<td>100</td>
<td>0.1 ± 0.13</td>
<td>Ceftriaxone (50)</td>
<td>4.5 ± 0.28</td>
</tr>
<tr>
<td>Mouse BAP</td>
<td>MRSA</td>
<td>100</td>
<td>0 ± 0.4</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Rat HP</td>
<td>MRSA</td>
<td>50</td>
<td>2.1 ± 0.56</td>
<td>Vancomycin (100)</td>
<td>1.3 ± 1.19</td>
</tr>
<tr>
<td>Rat HP</td>
<td><em>S. aureus</em></td>
<td>75</td>
<td>2.2 ± 1.0</td>
<td>Nafcillin (150)</td>
<td>1.5 ± 0.62</td>
</tr>
</tbody>
</table>

Modified from Table 1, Silverman et al
Daptomycin Animal Models

• Daptomycin demonstrated efficacy against both *S. aureus* and *S. pneumoniae* in other models of infections including skin and soft tissue (thigh) infections, meningitis, and endocarditis

• In vitro studies showed that the binding of daptomycin with surfactant inhibits its antibacterial activity

Silverman et al
Effect of Prior Therapy

- Post hoc subgroup analyses based on aggregate data from these two trials performed
  - Prior effective antibacterial therapy: Antibacterials with greater potency and longer half-lives (levofloxacin, ceftriaxone, azithromycin, clarithromycin)
  - No prior effective antibacterial therapy: Antibacterials with lesser potency/shorter half-lives (penicillins, tetracyclines, or trimethoprim-sulfamethoxazole)
- Prior effective antibacterials had a greater impact on the cure rates in the daptomycin arm compared to the ceftriaxone arm
## Prior Antibacterial Therapy

<table>
<thead>
<tr>
<th>Prior antibacterial therapy</th>
<th>Treatment difference (95% CI)</th>
<th>No Prior antibacterial therapy</th>
<th>Treatment difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daptomycin N=97 n (%)</td>
<td></td>
<td>Daptomycin N=272 n (%)</td>
<td>Ceftriaxone N=279 n (%)</td>
</tr>
<tr>
<td>88 (90.7)</td>
<td>2.7 (-6.1%, 11.4%)</td>
<td>205 (75.4)</td>
<td>245 (87.8)</td>
</tr>
<tr>
<td>Ceftriaxone N=92 n (%)</td>
<td></td>
<td></td>
<td>-12.4 % (-18.8%, -6.0)</td>
</tr>
</tbody>
</table>
Endpoints: Community Acquired Bacterial Pneumonia

• Clinical Cure: Clinical resolution of signs and symptoms at test of cure about 7-14 days after completion of treatment
• Best evidence for treatment effect from historical studies for a mortality endpoint
  – Mortality rate not very high except for certain subgroups
• Although clinical response is clinically meaningful, it is not as well characterized historically
Clinical Response in CABP: Historical evidence*

*Adapted from Bullowa (1937); Meakins and Hanson (1939); Flippin, et al. (1939)
Interim Endpoint

- Symptom improvement at days 3-5
- Absence of elevated body temperature and improvement in important measures of physiological clinical stability not included in the proposed symptom-based endpoint
- Need for later assessment - end of therapy and at an off-therapy time point

Post-marketing trials: Doripenem

- Carbapenem antibacterial approved in 2007
  - complicated intra-abdominal infections
  - complicated urinary tract infections
- Was evaluated for hospital acquired/ventilator-associated pneumonia in two phase 3 trials
- Presented at AIDAC in July 2008
  - Concern raised related to the higher mortality noted in one trial at the end of IV therapy
- Not approved for HAP/VAP in the US
Doripenem

- Ongoing trial in ventilator-associated pneumonia halted early due to higher mortality and lower clinical cure rates in the doripenem arm

<table>
<thead>
<tr>
<th>Analysis Population</th>
<th>Doripenem Group %</th>
<th>Imipenem Group %</th>
<th>Difference %</th>
<th>2-sided 95% CI %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Cure Rates</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MITT</td>
<td>45.6</td>
<td>56.8</td>
<td>-11.2</td>
<td>-26.3 to 3.8</td>
</tr>
<tr>
<td>ME</td>
<td>49.1</td>
<td>66.1</td>
<td>-17</td>
<td>-34.7 to 0.8</td>
</tr>
<tr>
<td>All Cause 28-day Mortality Rate (MITT)</td>
<td>21.5</td>
<td>14.8</td>
<td>6.7</td>
<td>-5.0 to 18.5</td>
</tr>
</tbody>
</table>

Post marketing trials: Tigecycline

- Glycylcycline antibacterial approved in 2005
  - complicated intra-abdominal infections, complicated urinary tract infections, complicated skin and skin structure infections, and community acquired pneumonia
- At the time of approval, more deaths noted in tigecycline-treated patients compared to comparators
- Trial in HAP/VAP showed lower cure rates in the tigecycline arm and higher mortality in the VAP subgroup
- Meta-analysis of the Phase 3 and 4 trials showed statistically significantly increased risk for mortality; higher risk seen for every infection type; largest difference in VAP
- Labeling updated to reflect these results
<table>
<thead>
<tr>
<th>Infection Type</th>
<th>Tygacil deaths/total patients (%)</th>
<th>Comparator Antibiotics deaths/total patients (%)</th>
<th>Risk Difference* (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>cSSSI</td>
<td>12/834 (1.4%)</td>
<td>6/813 (0.7%)</td>
<td>0.7 (-0.3, 1.7)</td>
</tr>
<tr>
<td>cIAI</td>
<td>42/1382 (3.0%)</td>
<td>31/1393 (2.2%)</td>
<td>0.8 (-0.4, 2.0)</td>
</tr>
<tr>
<td>CAP</td>
<td>12/424 (2.8%)</td>
<td>11/422 (2.6%)</td>
<td>0.2 (-2.0, 2.4)</td>
</tr>
<tr>
<td>HAP</td>
<td>66/467 (14.1%)</td>
<td>57/467 (12.2%)</td>
<td>1.9 (-2.4, 6.3)</td>
</tr>
<tr>
<td>Non-VAP†</td>
<td>41/336 (12.2%)</td>
<td>42/345 (12.2%)</td>
<td>0.0 (-4.9, 4.9)</td>
</tr>
<tr>
<td>VAP†</td>
<td>25/131 (19.1%)</td>
<td>15/122 (12.3%)</td>
<td>6.8 (-2.1, 15.7)</td>
</tr>
<tr>
<td>RP</td>
<td>11/128 (8.6%)</td>
<td>2/43 (4.7%)</td>
<td>3.9 (-4.0, 11.9)</td>
</tr>
<tr>
<td>DFI</td>
<td>7/553 (1.3%)</td>
<td>3/508 (0.6%)</td>
<td>0.7 (-0.5, 1.8)</td>
</tr>
<tr>
<td><strong>Overall Adjusted</strong></td>
<td><strong>150/3788 (4.0%)</strong></td>
<td><strong>110/3646 (3.0%)</strong></td>
<td><strong>0.6 (0.1, 1.2)</strong></td>
</tr>
</tbody>
</table>

† Subgroups of the HAP population
** Overall adjusted (random effects model by trial weight) risk difference estimate

Safety Resources

• Drug Safety Communications:

• Potential Signals of Serious Risks/New Safety Information Identified from the FDA Adverse Event Reporting System.

• Summary information about ongoing and completed postmarketing safety evaluations of adverse experience reports made to FDA for New Drug Applications (NDAs) and Biologic License Applications (BLAs) approved since September 27, 2007.
  – [http://www.fda.gov/drugs/guidancecomplianceandregulatoryinformation/surveillance/ucm204091.htm](http://www.fda.gov/drugs/guidancecomplianceandregulatoryinformation/surveillance/ucm204091.htm)

• MedWatch: The FDA Safety Information and Adverse Event Reporting Program
MedWatch Online Voluntary Reporting Form (3500)

Click the BEGIN button to report serious adverse events for human medical products, including potential and actual product use errors and product quality problems associated with the use of:

- FDA-regulated drugs,
- biologics (including human cells, tissues, and cellular and tissue-based products)
- medical devices (including in vitro diagnostics)
- special nutritional products and cosmetics

A Message about Privacy
You can continue to make adverse event reports under the Health Insurance Portability and Accountability
Some Recent approvals

- Doripenem (Doribax; 2007)
- Telavancin (Vibativ; 2009)
- Ceftaroline (Teflaro; 2010)
- Inhaled aztreonam (Cayston; 2010)
- Fidaxomicin (Dificid; 2011)
Ceftaroline

- Ceftaroline is a cephalosporin with activity against MRSA. Antibacterial activity is mediated through binding to penicillin-binding proteins (PBPs).
  - Ceftaroline is bactericidal against *S. aureus* due to its affinity for PBP2a and against *Streptococcus pneumoniae* due to its affinity for PBP2x.
- Approved for treatment of community acquired bacterial pneumonia and acute bacterial skin and skin structure infections
- Product labeling describes outcomes based on both early and late endpoints

http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/200327s008lbl.pdf
Fidaxomicin

• A macrolide antibacterial drug indicated in adults (≥18 years of age) for treatment of *Clostridium difficile*-associated diarrhea

• Evaluated in two Phase 3 trials compared to vancomycin. Shown to be non-inferior to vancomycin at the end of therapy and superior to vancomycin for a sustained clinical response endpoint 25 days after end of treatment

• The most common adverse reactions seen were nausea (11%), vomiting (7%), abdominal pain (6%), gastrointestinal hemorrhage (4%), anemia (2%), and neutropenia (2%)

http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/201699s000lbl.pdf
Telavancin

- Lipoglycopeptide antibacterial with activity against MRSA. Indicated for the treatment of adult patients with complicated skin and skin structure infections
- Boxed warning regarding adverse developmental outcomes in animals and need for serum pregnancy test prior to administration in women of child-bearing age
- Warning regarding risk of nephrotoxicity and need to monitor renal function
- Warning regarding decreased efficacy with moderate/severe baseline renal impairment (CrCl ≤50 mL/min)

http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022110s000lbl.pdf
### Approval History

**NDA 206327**

*Note: Not all reviews are available in electronic format from FDA. Older labels are for historical information only, and should not be used for clinical purposes. Approval dates can only be verified from 1984 to the present.*

Click on a column header to re-sort the table:

<table>
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<tr>
<th>Action Date</th>
<th>Supplement Number</th>
<th>Approval Type</th>
<th>Letters, Reviews, Labels, Patient Package Insert</th>
<th>Note</th>
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<td>Labeling Revision</td>
<td>Label (PDF) Letter (PDF)</td>
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<tr>
<td>05/22/2012</td>
<td>005</td>
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<td>Label (PDF) Letter (PDF) Review Summary Review (PDF)</td>
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Note: If you need help accessing information in different file formats, see *Instructions for Downloading Viewers and Players*.

*There are no Therapeutic Equivalents*

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist
Drug Approval Package

Teflaro (ceftaroline fosamil) Injection
Company: Cerexa, Inc.
Application No.: 200327
Approval Date: 10/29/2010

Persons with disabilities having problems accessing the PDF files below may call (301) 796-3634 for assistance.

- Approval Letter(s) (PDF)
- Summary Review (PDF)
- Officer/Employee List (PDF)
- Office Director Memo (PDF)
- Cross Discipline Team Leader Review (PDF)
- Printed Labeling (PDF)
- Medical Review(s) (PDF)
- Chemistry Review(s) (PDF)
- Pharmacology Review(s) (PDF)
- Statistical Review(s) (PDF)
- Microbiology Review(s) (PDF)
- Clinical Pharmacology Biopharmaceutics Review(s) (PDF)
- Proprietary Name Review(s) (PDF)
- Other Review(s) (PDF)
- Administrative Document(s) & Correspondence (PDF)
Examples of Drugs in the Pipeline

- Aminoglycosides: Plazomicin
- Cephalosporins: Ceftobiprole
- Beta-lactam, beta-lactamase inhibitor combinations
  - Ceftaroline or ceftazidime in combination with avibactam
  - Imipenem in combination with MK-7655
- Macrolides: Cethromycin, Solithromycin
- Oxazolidinones: Tadezolid, Radezolid
- Quinolones: Delafloxacin, JNJ-Q2
- Tetracycline: Omadacycline, TP-434

Examples of Drugs in the Pipeline

Table 1

<table>
<thead>
<tr>
<th>Classes of antibacterial agents approved for clinical use.</th>
<th>Original member of the class or subclass</th>
<th>Date of original class identification</th>
<th>Recent compounds in development post-2000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycoside</td>
<td>Streptomycin</td>
<td>1943</td>
<td>Plazomicin</td>
</tr>
<tr>
<td>β-Lactam</td>
<td>Benzy1penicillin (Penicillin G)</td>
<td>1928</td>
<td>None</td>
</tr>
<tr>
<td>Penicillin</td>
<td>Cephalosporin (Cephalosporin C)</td>
<td>(1948)</td>
<td>Ceftobiprole, ceftaroline(^a), ceftolozane</td>
</tr>
<tr>
<td>Cephalothin</td>
<td>Imipenem</td>
<td>1976</td>
<td>Doripenem(^b)</td>
</tr>
<tr>
<td>Carbapenem</td>
<td>Azeotrenam</td>
<td>1981</td>
<td>BAL30072, MC-1</td>
</tr>
<tr>
<td>Monobactam</td>
<td>Clavulanic acid</td>
<td>1976</td>
<td>Non-β-lactams: avibactam, MK-7655</td>
</tr>
<tr>
<td>β-Lactamase inhibitor (clavam)</td>
<td>Vancomycin</td>
<td>1952</td>
<td>Dalbavancin, oritavancin, telavancin(^a)</td>
</tr>
<tr>
<td>Glycopeptide</td>
<td>Daptomycin</td>
<td>1985</td>
<td>None</td>
</tr>
<tr>
<td>Lipopeptide</td>
<td>Erythromycin</td>
<td>1949</td>
<td>None</td>
</tr>
<tr>
<td>Macrolide</td>
<td>Telithromycin</td>
<td>1997</td>
<td>Cethromycin, solithromycin</td>
</tr>
<tr>
<td>Oxazolidinone</td>
<td>Linezolid</td>
<td>1995</td>
<td>Radezolid, tedizolid</td>
</tr>
<tr>
<td>Quinolone</td>
<td>Fluoroquinolone</td>
<td>1962</td>
<td>Delafloxacin, JNJ-Q2, nemonoxacin TP-434</td>
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<tr>
<td>Tetracycline</td>
<td>Nalidixic acid</td>
<td>1945</td>
<td>Omadacycline</td>
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<tr>
<td>Glycycycline</td>
<td>Chlortetacycline</td>
<td>1945</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tigecycline</td>
<td>1998</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Approved by the FDA.

\(^b\) Approved by the FDA and EMA.

Aminoglycosides

• Plazomicin: Active against multidrug resistant Gram-negative bacteria including carbapenem-resistant Enterobacteriaceae; not active against NDM producing organisms

• Activity against *P. aeruginosa* and Acinetobacter spp. lower

• Phase 2 trial in complicated urinary tract infection/acute pyelonephritis completed


Beta-lactam, beta lactamase inhibitor combinations

• Ceftazidime-Avibactam
  - Compared to Doripenem Followed by Oral Therapy for Hospitalized Adults With Complicated UTIs
  - Compared to Meropenem for treating hospitalized patients with complicated intra-abdominal infections

• Ceftolozane-Tazobactam (CXA-201)
  - Compared to Intravenous Levofloxacin in Complicated Urinary Tract Infection, Including Pyelonephritis
  - Compared to Intravenous Levofloxacin in Complicated Urinary Tract Infection, Including Pyelonephritis

http://www.clinicaltrials.gov/ct2/show/NCT01499290?term=avibactam&rank=8
Anti-TB:

• **Bedaquiline**: Developed for treatment of patients with multi-drug resistant pulmonary tuberculosis.
  - Meeting materials will be available at [http://www.fda.gov/AdvisoryCommittees/default.htm](http://www.fda.gov/AdvisoryCommittees/default.htm)

• **Delamanid (OPC-67683)**, a nitro-dihydro-imidazooxazole derivative, was studied in a randomized, placebo-controlled, multinational clinical trial, with pulmonary multidrug-resistant tuberculosis for 2 months in combination with a background drug regimen.
  - Delamanid was associated with an increase in sputum-culture conversion at 2 months among patients with multidrug-resistant tuberculosis. (N Engl J Med 2012; 366:2151-2160)
New Provisions

• Generating Antibiotic Incentives Now (GAIN): Incentives to develop new antibacterials and antifungals for the treatment of serious or life-threatening infectious diseases including those caused by drug resistant pathogens e.g. MRSA, VRE, multi-drug resistant gram negative bacteria, *C. difficile* and MDRTB.  

• Limited Population Antibacterial Drug (LPAD) Approval Mechanism, proposed by the Infectious Diseases Society of America
http://www.idsociety.org/2012_LPAD_Proposal_Backing/

• Tropical Diseases Priority Review Vouchers: Granted to Sponsors of certain tropical disease product applications that meet the criteria specified by the Act. May be used by the sponsor who obtains it or another sponsor to obtain a priority review for a different application.
Summary

• Provided an overview of antibacterial development, outlined some challenges and lessons learned from previous trials

• Drug information resources
  – Reviews, labeling, safety communications, safety reporting

• Discussed some recent approvals and drugs in development