

# FDA Updates and Perspectives

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Session: Regulatory Pathways for AMR and Technology Appraisal Process



# Outline

- Unmet need programs
- Discuss some areas of ongoing development
- Pediatric antibacterial drug development
- Update on guidances
- GAIN and 21<sup>st</sup> Century Cures Act

# Antibacterial Drug Development

- Antibacterial drug development continues to be a challenging area
- Concerted efforts on many fronts by various stakeholders over the years has helped address many of the challenges
- Encouraging that we have had some recent approvals and few others in late stage development/completed clinical trials



# Antibacterial Drug Development

- **Standard Development Programs**
  - Provides foundation for evaluating safety and efficacy of a drug
  - Degree of uncertainty regarding efficacy and safety is limited
  - Feasible to study the clinical conditions
  - Other effective therapies are available
  - Most of the antibacterial drugs that we rely upon today were developed using such an approach
  - Evidence from two adequate and well-controlled trials; one per indication acceptable
- **Unmet Need Development Programs**
  - Address an existing or future unmet need
  - Smaller programs, with greater uncertainties in safety and efficacy; evidence from a single adequate and well-controlled trial
  - Reserved for use in patients with limited or no treatment options

# Approvals in last 5 years

- Bedaquiline: MDRTB, December 2012:
  - Subpart H approval
- Dalbavancin: ABSSSI, May 2014
  - Two trials in ABSSSI
- Tedizolid: ABSSSI, June 2014
  - Two trials in ABSSSI
- Oritavancin: ABSSSI, August 2014
  - Two trials in ABSSSI
- Ceftolozane-tazobactam: cUTI and cIAI, December 2014
  - One trial each in cIAI and cUTI
- Ceftazidime-avibactam: cUTI and cIAI, February 2015\*
  - Phase 2 data for initial approval; followed by one trial each in cIAI and cUTI
- Obiltoxaximab: Inhalational anthrax, March 2016
  - Animal Rule

Multidrug-resistant pulmonary tuberculosis

ABSSSI: Acute Bacterial Skin and Skin Structure Infections; cUTI: complicated urinary tract infections;  
cIAI: complicated intra-abdominal infections; \* Limited Use; subsequently revised to remove limited use labeling  
<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>

# Approvals in last 5 years (contd.)

- Bezlotoxumab: Reducing recurrence of *C. difficile* infection in patients at high-risk for CDI recurrence, October 2016
  - Two trials in patients with CDI; superiority over SOC
- Delafloxacin: ABSSSI, June 2017
  - Two ABSSSI trials
- Meropenem-vaborbactam: cUTI, August 2017
  - Single cUTI trial
- Pediatrics
  - Ceftaroline: CABP and ABSSSI (May 2016) in children  $\geq 2$  months of age
  - Daptomycin: cSSSI (March 2017) in children  $> 1$  year of age; *S. aureus* bacteremia (September 2017)
  - PK, safety studies; trials not powered for efficacy



# Antibacterial Drugs in Development\*

- Plazomicin: cUTI and BSI
- Cefiderocol: cUTI
- Fosfomicin: cUTI
- Omadacycline: ABSSSI and CABP
- Iclaprim: ABSSSI
- Eravacycline: cIAI

\*Publicly-available information

<http://investors.achaogen.com/releasedetail.cfm?releaseid=1003671>

<http://www.prnewswire.com/news-releases/shionogi-announces-positive-top-line-results-for-cefiderocol-pivotal-cuti-clinical-trial-300389912.html>

<https://globenewswire.com/news-release/2017/04/03/953801/0/en/Paratek-Announces-Positive-Phase-3-Study-of-Omadacycline-in-Community-Acquired-Bacterial-Pneumonia.html>

<http://investor.paratekpharma.com/phoenix.zhtml?c=253770&p=irol-newsArticle&ID=2286829>

<http://1v6gi215h9gy3y4dgh3it40h-wpengine.netdna-ssl.com/wp-content/uploads/2017/04/Motif-Bio-Press-release-version-Apr-18-2017-final-UK.pdf>

<http://ir.tphase.com/releasedetail.cfm?releaseid=1019756>

# Unmet Need Programs

- Recent development programs have followed the approaches outlined in the draft unmet need guidance; final guidance issued August 2017
- Smaller trials; single trial to support an indication
- Most common approach has been a single NI trial at a body site of infection
- BL-BLI combinations have used either
  - A single NI trial approach (meropenem-vaborbactam)
  - Phase 2 trial(s) in indication(s) for which the BL is approved (ceftazidime-avibactam)

BL: Beta-lactam; BLI: Beta-lactamase inhibitor

<https://www.fda.gov/downloads/Drugs/Guidances/UCM359184.pdf>





# Unmet Need Programs

- Lessons Learned
  - Need to consider attributes of the drug and suitability for streamlined development programs
  - We have seen requests for streamlined programs for small incremental benefits and not really addressing an unmet need; e.g., marginal increase in spectrum of activity/1-2 dilution difference in activity
  - Challenges in conducting a trial in patients with infections due to organisms of a specific resistance phenotype



# Unmet Need Programs

- Lessons Learned:
  - Important to evaluate pharmacokinetics of drugs in the unmet need population; often differ from that of other patients
  - Descriptive studies: Some programs included a small descriptive study in patients with infections due to organisms of a specific resistance phenotype (CRE); lack of a pre-specified analysis plan makes it difficult to analyze once study is completed and results are known



# Unmet Need Programs

- Chemistry Manufacturing and Controls (CMC)
  - Important to plan for CMC aspects of development program early on
  - With expedited clinical development programs, often CMC aspects of program lag behind
    - More recently, a number of development programs have been impacted by non-compliance with cGMPs; often involve contract manufacturers
    - We encourage early consultation with the Office of Pharmaceutical Quality, including discussions around manufacturing facilities, e.g., PIND/EOP2, pre-NDA meetings



## Some other topics

- Developing a stand-alone beta-lactamase inhibitor
- Non-traditional therapies
  - Monoclonal antibodies (therapeutic/prophylactic)
  - Immune modulators
  - Anti-virulence factors
  - Microbiome-targeted
  - Lysins
- Uncomplicated urinary tract infections (uUTI)
- Inhaled antibacterial drugs

## Some other topics

- Developing beta-lactamase inhibitor alone
  - Medication errors
  - Differences in stability of various beta-lactams
  - Potentially need for different ratios of BL-BLI
  - Different dosing regimens/need for dose adjustment for the BL and BLI
- Non-traditional therapies
  - Usually used as adjunctive treatment
  - Superiority trial of standard of care (SOC) plus adjunctive therapy vs. SOC



## Some other topics

- Inhaled antibacterial drugs
  - Non-Tuberculous Mycobacterial (NTM) infections, cystic fibrosis (CF), Non-CF bronchiectasis (NCFB), Ventilator-associated bacterial pneumonia
  - Some challenges:
    - Heterogeneous patient population
    - Defining a clinically meaningful endpoint
    - Defining optimal treatment regimen and duration of therapy

# uUTI

- Key Considerations:
  - Evidence-based treatment effect for clinical and microbiologic outcome can be established
  - NI or superiority trials are potential options
  - An NI trial is dependent on a comparator that is effective therapy; also an issue with some recent cUTI trials
  - For an NI trial, the appropriate analysis population is those with baseline isolates susceptible to comparator drug
  - High rates of fluoroquinolone resistance (30-40%) in some regions limits the use of fluoroquinolones as a comparator, especially for an NI trial

# Pediatric Drug Development

- The time lag between approval of an anti-infective drug in adults and approval in children is generally > 5 years
- Requirements and Incentives:
  - Pediatric Research Equity Act (PREA): Requires pediatric studies, unless the applicant has obtained a waiver or deferral
  - Best Pharmaceuticals Act for Children (BPCA): Provides for additional six months of marketing exclusivity
  - Food and Drug Administration Safety and Innovation Act (FDASIA): Requires pediatric plans to be submitted within 60 days of EOP2 meeting

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>  
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>





# Pediatric Drug Development

- Over the last several years, we have streamlined many aspects of pediatric antibacterial drug trials
  - Smaller programs
  - Non-sequential approach to enrolling age cohorts unless specific safety concerns
  - Including adolescents in adult trials if safety and PK acceptable
  - Broadening inclusion/exclusion criteria
  - Streamlining collection of safety data
  - Safety data from one indication can support another indication provided dose/duration of treatment are not different
  - Some consideration to collect additional safety data post-approval
- Studying neonates remains a challenge

# PREA Studies: Antibacterial Drugs



Drug	Approval Year	Pediatric Labeling
Linezolid	2000	All pediatric age groups
Ertapenem	2001	3 months and older
Daptomycin	2003	Avoid use in < 1 year old, neuromuscular effects in dogs Children > 1 year of age for cSSSI ( <b>March 2017</b> ) Children > 1 year of age for SAB ( <b>September 2017</b> )
Telithromycin	2004	Peds trials halted- hepatic adverse reactions in adults
Tigecycline	2005	Peds trials not conducted – mortality risk in adults
Doripenem	2007	S/E in pediatric patients not established
Telavancin	2009	S/E in pediatric patients not established
Ceftaroline	2010	Children ≥2 months for CABP and ABSSSI ( <b>May 2016</b> )
Fidaxomicin	2011	S/E in pediatric patients not established
Dalbavancin, Tedizolid, Oritavancin, Ceftolozane-tazobactam, Ceftazidime-avibactam	2014-15	S/E in pediatric patients not established



# Neonates

- Labeling for very few anti-infective products have information about use in neonates
- Dosing recommendations for the use of meropenem in neonates and infants < than 91 days of age with cIAI under the BPCA process
- Ongoing project under a Broad Agency Announcement to evaluate CNS penetration of drugs in infants

[http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2014/050706s035lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/050706s035lbl.pdf)

<https://www.federalregister.gov/articles/2015/05/28/2015-12848/pediatric-studies-of-meropenem-conducted-in-accordance-with-the-public-health-service-act>



# Guidances

- Issued, 2016-2017
  - Antibacterial Therapies for Patients With an Unmet Medical Need for the Treatment of Serious Bacterial Diseases, Final
  - Microbiology Data for Systemic Antibacterial Drugs — Development, Analysis, and Presentation, Final
  - Bacterial Vaginosis: Developing Drugs for Treatment, Draft
  - Vulvovaginal candidiasis: Developing Drugs for Treatment, Draft
  - Anthrax: Developing Drugs for Prophylaxis of Inhalational Anthrax, Draft
- Topics under consideration
  - Uncomplicated urinary tract infections (uUTI)
  - Antibacterial drugs that treat a single species
  - Antibacterial drugs for pediatric population



# Collaboration with other Regulatory Authorities

- We do recognize that development programs are global and it is not practical or feasible to have different programs to meet different regulatory requirements
- We have focused on providing a sound scientific basis for our recommendations; this makes it much easier to align the various requirements
- In some cases, differences remain partly due to the different statutory requirements and regulatory frameworks under which we operate
- Under existing confidentiality agreements, we have regular interactions with colleagues at the EMA

### MEETING SUMMARY

#### **Tripartite meeting held between the EMA, FDA and PMDA at EMA, London, on 1-2 September 2016 to discuss regulatory approaches for the evaluation of antibacterial agents**

The EMA, FDA and PMDA consider that a robust response to the problem of antimicrobial resistance must be multi-faceted and that the regulatory approach for the evaluation of antibacterial agents is only one element of the total response that is required to encourage accelerate new antibacterial drug development to meet patient needs.

These three regulatory agencies recognize that:

- It is appropriate to exercise flexibility with regard to the requirements for clinical development programmes for antibacterial agents, especially for new agents that be used to treat patients with limited treatment options because of antimicrobial resistance;

### MEETING SUMMARY

#### **Tripartite meeting held between the EMA, PMDA and FDA in Vienna, on 26-27 April 2017 to discuss regulatory approaches for the evaluation of antibacterial agents**

The EMA, FDA and PMDA consider that a robust response to the problem of antimicrobial resistance must be multi-faceted and that the regulatory approach for the evaluation of antibacterial agents is one element of the total response that is required to encourage and accelerate new antibacterial drug development to meet patient needs. Following on from the meeting of September 2016, representatives of the three agencies met for the second time.

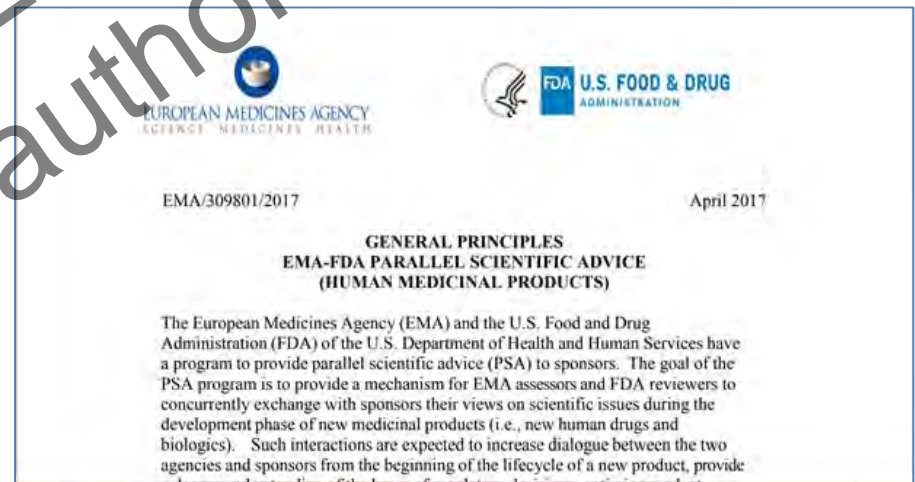
Progress was made as follows:

- EMA, PMDA, and FDA discussed in detail clinical trial recommendations for respiratory tract, urinary tract, intra-abdominal, and skin infections, as well as for drugs intended to treat patients with multi-drug resistant infections.
- A number of areas of similarity were identified with regard to clinical trial design recommendations, such as patient selection criteria, and endpoints for certain types of infections.



# Interactions with FDA and EMA

- Parallel Scientific Advice (PSA) Process
  - [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Other/2009/11/WC500014868.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/11/WC500014868.pdf)
- Consultative advice procedure allows sponsors to request scientific advice from one regulatory agency and concurrently notify the other regulatory agency of the request







# Coordinated Development

- Many challenges in making Antimicrobial Susceptibility Test (AST) available in a timely manner following approval of a new antibacterial drug
- Discussions at a public workshop held on September 29, 2016
  - Key bottlenecks and potential solutions to facilitate timely development of AST devices
  - Guidance on Coordinated Development of Antimicrobial Drugs and AST Devices
- In the last several months, CDER and CDRH have participated in joint meetings with drug/device manufacturers to discuss potential developmental approaches



# FDA Public Meetings

- July 18 and 19, 2016: Facilitating Antibacterial Drug Development for Patients with Unmet Need and Developing Antibacterial Drugs that Target a Single Species  
<http://www.fda.gov/Drugs/NewsEvents/ucm497650.htm>
- September 15, 2016: Anti-Infective Drug Development in Neonates:  
<https://www.fda.gov/Drugs/NewsEvents/ucm507958.htm>
- September 29, 2016: Coordinated Development of Antimicrobial Drugs and Antimicrobial Susceptibility Test Devices:  
<https://www.fda.gov/Drugs/NewsEvents/ucm512519.htm>
- March 1, 2017: Current state and further development of animal models of serious infections caused by *A. baumannii* and *P. aeruginosa*:  
<https://www.fda.gov/Drugs/NewsEvents/ucm534031.htm>
- April 13, 2017: Meeting of the Antimicrobial Drugs Advisory Committee  
<https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/ucm551361.htm>
- July 19, 2017: Development of New Tuberculosis Drug Regimens-Scientific and Clinical Design Considerations  
<https://www.fda.gov/Drugs/NewsEvents/ucm548365.htm>
- September 13, 2017: Antimicrobial Susceptibility and Resistance: Addressing Challenges of Diagnostic Devices  
<https://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm564756.htm>

# Research Projects

- Ongoing projects in the antibacterial space through Broad Agency Announcements
  - Development of an Automated and Sustainable Electronic Approach for Data Mining to Evaluate Clinical Outcomes of Patients with Bacterial Infections
  - Evaluation of Measurement Properties of PRO Instruments in Patients with CABP, HABP, and ABBSSI
  - Bridging Novel Laboratory Animal and Hollow Fiber Infection Models to Evaluate Central Nervous System Penetration of Drugs in Infants
- Review of the research proposals for animal model development completed; awardees to be announced shortly and can be viewed at [www.fda.gov/OAPresearch](http://www.fda.gov/OAPresearch)

# Research Activities

## About the Center for Drug Evaluation and Research

CDER Offices and Divisions

Drug Safety Oversight Board

Jobs at the Center for Drug Evaluation and Research (CDER)

Meeting Presentations (Drugs)

CDER Exclusivity Board

FAQs about CDER

Reports & Budgets (CDER) ▼

Manual of Policies & Procedures (CDER)

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## Office of Antimicrobial Products Research Activities

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### Antimicrobial Regulatory Science Research

Antibacterial drug resistance is a major threat to public health. In March 2015, The National Action Plan for Combating Antibiotic-resistant Bacteria was developed in response to Executive Order 13676: [Combating Antibiotic-Resistant Bacteria](#), which was issued on September 18, 2014. The National Action Plan outlines steps for implementing the National Strategy for Combating Antibiotic-Resistant Bacteria to address urgent and serious drug-resistant threats that affect people in the U.S. and around the world. Implementation of the National Action Plan will also support World Health Assembly resolution 67.25 (Antimicrobial Resistance), which urges countries to take urgent action at the national, regional, and local levels to combat resistance.

The FDA's roles in combatting antibacterial drug resistance include:

- Facilitating the development of new antibacterial drugs to treat patients; and
- Advancing the science of clinical trial design. The design and conduct of clinical trials to evaluate new antibacterial drugs in patients with serious bacterial infections is challenging and therefore of particular interest for FDA's regulatory science program.

### What's New

- [Fiscal Year 2017 and 2018 Office of Antimicrobial Products Research Priorities](#) (PDF - 105 KB) **NEW**
- [FY 2016 Office of Antimicrobial Products Research Contracts](#) (PDF - 90 KB) **NEW**

[www.fda.gov/OAPresearch](http://www.fda.gov/OAPresearch)

## Generating Antibiotic Incentives Now (GAIN)

- Provides incentives for the development of certain antibacterial and antifungal drug products designated as Qualifying Infectious Disease Products (QIDP)
- Can be requested at any time before submission of a marketing application
- Provides for
  - Priority review
  - Additional 5 years marketing exclusivity at the time of approval
  - Eligible for fast track designation
- So far, FDA has granted QIDP designations for 71 different antibacterial/antifungal products (136 designations)
- Eight approved antibacterial/antifungal drugs had QIDP designation

# New Legislation

- 21<sup>st</sup> Century Cures Act was signed into law on December 13, 2016
- Title III, Subtitle E – Antimicrobial Innovation and Stewardship
  - Section 3044. Susceptibility test interpretive criteria for microorganisms; antimicrobial susceptibility testing devices
  - Section 3041. Antimicrobial Resistance Monitoring
  - Section 3042. Limited Population Pathway for antibacterial and antifungal drugs (LPAD)



## Section 506(h): LPAD

- The drug is intended to treat a serious or life-threatening infection in a limited population of patients with unmet needs
- Standards for approval under 505(c) and (d) or standards for licensure under 351 of Public Health Service Act are met
- Written request from the Sponsor that the drug be approved as a limited population drug

# LPAD: Additional Requirements

- Labeling: To indicate that safety and effectiveness has only been demonstrated with respect to a limited population
  - All advertising and labeling will include “Limited Population” in a prominent manner, and
  - The prescribing information will contain the statement “This drug is indicated for use in a limited and specific population of patients”
- Promotional Materials:
  - Pre-submission of promotional materials at least 30 days prior to dissemination of such materials



## Section 511: Requirements

- FDA to establish interpretive criteria website within 1 year of enactment
- Website will include:
  1. FDA-recognized breakpoints established by standard development organizations (SDOs)
  2. Other breakpoints, where:
    - FDA does not recognize, in whole or in part, a standard
    - FDA withdraws, in whole or in part, recognition of a standard
    - FDA approves an application for a drug for which breakpoints are not included in a standard
    - FDA determines a product that contains the same active ingredients requires different breakpoints due to the characteristics of the product, and such different breakpoints are not reflected in a standard





## Section 511: Requirements (contd.)

3. Following disclaimers:
  - That the website provides information about the in vitro susceptibility of bacteria, fungi, or other microorganisms, as applicable to a certain drug (or drugs)
  - That the safety and efficacy of such drugs in treating clinical infections due to such bacteria, fungi, or other microorganisms, as applicable, may or may not have been established in adequate and well-controlled clinical trials in order for the breakpoints to be included on the website
  - The clinical significance of the breakpoints in such cases is unknown
  - That the approved product labeling for each drug provides the uses for which FDA approved the product



## Section 511: Requirements (contd.)

- Federal Register notice to be published not later than the date on which the interpretive criteria website is established
- FDA will review certain breakpoints every 6 months and update the website as appropriate
  - When updates occur, FDA will publish a notice on the website
- When a drug is approved based on breakpoints not included in or different from those recognized or otherwise listed on the website, FDA will update the website to include the breakpoints on which the approval was based
- FDA will compile all website updates and publish an annual notice in the Federal Register for public comment
  - FDA must review comments and, if appropriate, update the website in response

# Drug Labeling

- Labeling for drugs approved after establishment of website will contain reference to website in lieu of breakpoints
- An applicant can seek breakpoints that differ from those listed on the website
  - Will need to provide data to support the proposed breakpoints
- Application holders will have 1 year following establishment of website to remove breakpoints from approved drug labeling
  - replace with a reference to the website
  - can be submitted as annual reportable change



# Summary

- Progress has been made in designing feasible and scientifically sound clinical trials for antibacterial drugs; many challenges remain
- Some recent approvals and reports of successful trials
- We appreciate the efforts made by the various stakeholders to facilitate antibacterial drug development
- Ongoing work and lessons learned from recent trials will further help us to continue to refine trial recommendations and make safe and effective therapies available for patients

# Thanks!

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