

Overview of Antibacterial Drug Trials

Sumati Nambiar MD MPH

Director, Division of Anti-Infectives

Office of Infectious Diseases

Center for Drug Evaluation and Research, FDA

FDA-IDSA-NIAID-Pew Workshop

November 18, 2019

Agenda

- History: How did we get here?
- Why are we here today?
 - Criticisms and rebuttals
 - Discuss potential solutions to address the issues
- We shouldn't lose our focus on scientific principles
 - Lessons learned from trials
 - Labeling supported by data
- Summary and next steps

Antibacterial Drug Development: 1960's-1980's

- Patients with a variety of infections at different body sites were enrolled in the same trial
- Objective to demonstrate “comparable point estimates” to active control for clinical cure for each of the different infection types (no formal inference testing)
- Indications based on subsets of body sites of infection from within the trials
- Less specific indications e.g.
 - Lower respiratory tract infection (included bronchitis and pneumonia)
 - Skin infections

Antibacterial Drug Development: 1990's-2000's

- Move towards more site-specific trials
 - Natural history of the disease may differ
 - Endpoints and treatment duration may differ
 - Drug efficacy may differ at different sites of infection
 - Dosing regimen may differ for different sites as well
- 1992 IDSA Guidelines
- 1992 FDA Points to Consider document – Clinical Development and Labeling of Anti-Infective Drug Products
- Recognition of the aforementioned differences in these documents represented an advance in clinical trial design

Antibacterial Drug Development: 2000's

- ~ 2006, there was significant turmoil in the field; scientific questions raised about noninferiority (NI) trials
- Considerable effort and stakeholder participation in designing scientifically sound NI trials; evidence based NI margin justification; trials conducted for common indications, usually 2 trials/indication
- ~ 2012, focus on unmet need, particularly to treat gram-negative infections; streamlined drug development programs pursued; often single trial per indication; smaller safety database (~300-500)
- Upcoming years:
 - Continued focus on unmet need programs, including difficult to study indications
 - Development of nontraditional therapies

Recent Approvals

- Types of data packages:
 - Standard indications (cIAI, cUTI, ABSSSI, CABP): Two trials per indication or at least one trial per indication
 - Limited Use indication: A single trial with supportive evidence (phase 2 study, in vitro studies, animal models of infection)
 - LPAD Pathway: Small data packages (single trial); well-defined and limited population of patients; given unmet need, some flexibility in benefit-risk considerations

cIAI: Complicated intra-abdominal infections; cUTI: complicated urinary tract infections;

ABSSSI: Acute bacterial skin and skin structure infections; CABP: Community acquired bacterial pneumonia

LPAD: Limited Population Pathway for Antibacterial and Antifungal Drugs

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Why are we here today?

- While we have made progress, it appears that we are at a critical juncture in antibacterial drug development
- There is criticism regarding the clinical utility of some recently approved products and the registrational trials conducted to support their approval
- There is an unmet need for some difficult to study indications, e.g. osteomyelitis, prosthetic joint infections
- We need to work together to map out the needs and potential solutions
- While labeling is an important component of the discussion, addressing the scientific and feasibility issues is key

Criticisms regarding recent registrational trials (1)

- *Clinical condition studied (e.g., cUTI)*
 - Such trials are feasible and demonstrate the efficacy of the product at a body site; provides reasonable safety information in a population with fewer confounding factors; allows for a step-up to a more difficult to study condition
 - Need to balance the realities of drug development with the desire to study difficult indications/populations
 - HABP/VABP trials are difficult to enroll; often more confounding factors; from a developer's perspective, risky for a first indication

Criticisms regarding recent registrational trials (2)

- *Lack of data on patients with infections due to resistant organisms*
 - Conducting a randomized controlled trial in patients with infections due to resistant organisms can be challenging
 - Recently conducted trials in CRE infections were difficult to interpret as they were descriptive trials without any pre-specified hypothesis testing
 - As new therapies become available, the resistant phenotype of interest can change
 - Potential trial designs
 - Finding of superiority over best available therapy
 - Enrich trial population in an NI trial if appropriate comparator chosen

Criticisms regarding recent registrational trials (3)

- *Mostly noninferiority trials; new product only noninferior to existing therapies*
 - Well-conducted noninferiority trials are interpretable and provide useful information on the efficacy of a product
 - Demonstrating superiority to currently available therapies is difficult; most available therapies are effective; we really do not want to be in a situation where available therapies are so inadequate that superiority can readily be demonstrated
 - Most drugs we use today were in fact approved based on a finding of noninferiority (though superiority is of course helpful if shown)
 - Having some redundancy is helpful to address patient needs, potential shortages

Criticisms regarding recent registrational trials (4)

- *Lack of/very few patients enrolled in the US*
 - We need to better understand reasons for limited enrollment in the US
 - Review of data from recently conducted trials are reassuring in that most disease and patient characteristics from US and ex-US sites are comparable
- *Patients with comorbidities and more severe disease often excluded*
 - Assessment of PK in patients with hepatic/renal impairment earlier in drug development can help limit exclusionary criteria
 - Flexibility in inclusion/exclusion criteria, while ensuring patient safety

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Clinical Trials – Unexpected Findings (1)

- Well-designed comparative clinical trials teach us important and unexpected lessons
 - Binding of drug to surfactant; interaction identified after a failed CABP trial (daptomycin)
 - Higher mortality and lower cure rates in VABP (e.g., tigecycline, doripenem)
 - Altered pharmacokinetics in sick patients; augmented renal clearance
 - Differences in lung penetration between animals and humans
 - Importance of body site of infection; efficacy of drug seen in one indication, but not in others

Clinical Trials – Unexpected Findings (2)

Table 1. Unexpected Clinically Important Findings in Well-Controlled Clinical Trials.*

Antibacterial Drug	Findings in Clinical Trials
Daptomycin ^{5,6}	Successful trials in skin infections and <i>Staphylococcus aureus</i> bloodstream infections Daptomycin did not perform as well as the comparator in treating community-acquired pneumonia Further studies showed that daptomycin was bound by surfactant
Doripenem ^{7,8}	Successful trials in complicated UTIs and intraabdominal infections Higher mortality and lower cure rates than the comparator in VABP
Tigecycline ^{8,9,10}	Successful trials in skin infections, intraabdominal infections, and community-acquired bacterial pneumonia Higher mortality and lower cure rates than the comparator in the subgroup of patients with VABP
Ceftobiprole ^{8,11}	The cure rates were similar in the ceftobiprole group and the comparator group in the overall population of patients with hospital-acquired bacterial pneumonia and VABP, but the cure rates in the subgroup of patients with VABP were much lower in the ceftobiprole group than in the comparator group
Delafloxacin ¹²	Successful trials in skin infections Phase 3 trial in uncomplicated gonorrhea stopped on the basis of an interim review showing that the single monotherapy dose may not be sufficient to treat some patients
Solithromycin ¹³	Efficacy in patients with community-acquired pneumonia was shown in two trials, but a clinical trial in uncomplicated gonorrhea was not successful in meeting its noninferiority margin
Eravacycline ^{14,15}	Successful trials in intraabdominal infections Two trials in complicated UTIs were not successful in meeting their noninferiority margins

* UTI denotes urinary tract infection, and VABP ventilator-associated bacterial pneumonia.

Labeling

- Two key considerations:
 - Labeling regulations; ensuring consistency
 - Including information in labeling based on sound scientific evidence is helpful to all stakeholders-providers, payers, and patients

21 CFR 201.57

Prescription Drug Labeling Resources:

<https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources#Presentations%20%E2%80%93%20Sections%20of%20the%20Prescribing%20Information>

Labeling

- 21 CFR 201.57: Specific requirements on content and format of labeling for human prescription drug and biological products
- 21 CFR 201.57(c)(15), Clinical Studies Section: For drug products other than biological products, any clinical study that is discussed in prescription drug labeling that relates to an indication for or use of the drug must be adequate and well-controlled as described in 314.126(b) and must not imply or suggest indications or uses or dosing regimens not stated in the "Indications and Usage" or "Dosage and Administration" section.

Labeling

- Recent approvals:
 - Indication includes the organisms for which adequate clinical data were available in the trial(s); information regarding limited population, if applicable
 - Microbiology section provides information including in vitro activity and relevant animal models of infection; first and second list organisms
 - Clinical Studies section describes the adequate and well-controlled trial(s) that support the indication(s)

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Summary

- Over the last decade, we have made significant progress with development of antibacterial drugs; new safe and effective therapies are available to patients
- Important to learn from our experiences and continue to refine our approaches to address patient needs
- Some considerations to encourage as we move forward:
 - Need to identify the types of infections/patients in whom there is an unmet need
 - Novel study designs/endpoints that are scientifically sound
 - Improve clinical trial infrastructure in the US
 - Establish clinical trial networks
 - Need to identify barriers and stimulate investigator interest in participating and enrolling in clinical trials for anti-infective products

Thanks!

Sumathi.Nambiar@fda.hhs.gov

301-796-1400