THE USE OF ANTIBACTERIAL DRUGS DEVELOPED VIA STREAMLINED APPROACHES FOR SERIOUS INFECTIONS WHERE THERE IS UNMET NEED

Understanding Patient and Physician Perspectives and Considerations to Take Forward

Summary of the Multi-Stakeholder Expert Meeting

held March 1, 2016

Sheraton Silver Spring Hotel
Silver Spring, MD

CTTI MISSION: To develop and drive adoption of practices that will increase the quality and efficiency of clinical trials

Meeting materials, including agenda, participant list, and presentations, are available on the Clinical Trials Transformation Initiative (CTTI) website at: https://www.ctti-clinicaltrials.org/briefing-room/meetings/use-antibacterial-drugs-developed-streamlined-approaches-serious-infections

Publication Date: September 12, 2016

MEETING BACKGROUND

Antibacterial drugs have saved millions of lives since sulfa drugs and penicillin were first developed. However, many strains of bacteria have become resistant to one or more antibacterial drugs. According to the Centers for Disease Control and Prevention (CDC), every year at least 2 million people in the US will become infected with drug-resistant bacteria and at least 23,000 of them will die as a result.[1]

From the perspective of drug manufacturers, many economic and regulatory disincentives to the development of new antibacterials exist.[2] The process of developing new antibacterials is long and costly. Clinical trials involving new antibacterials are difficult to enroll, complete, and analyze because there is often diagnostic uncertainty when patients first present with signs and symptoms of an infection, patients receive empirical antibacterial drugs promptly in settings of diagnostic uncertainty, patients may have received effective empirical antibacterial drugs before a diagnosis is established, and analysis by bacterial pathogens occurs post-randomization once culture results are obtained. Furthermore, the return on investment is low, because antibacterials are typically only prescribed for short periods of time, and physicians often hold new antibacterials in reserve for only the worst cases, due to fear of creating more drug resistance. This environment creates an urgent need to develop more treatment options for patients with unmet need[3] (e.g., those who have multi-drug resistant bacterial infections, and those who have limited or no options for treatment) and to understand the perspectives of providers and patients[4] regarding the crisis of an increase in multi-drug resistant bacteria and limited available treatment options.

In July 2012, Congress passed the Food and Drug Administration Safety and Innovation Act (FDASIA). FDASIA includes Title VIII Generating Antibiotic Incentives Now ("GAIN") and section 806 requires FDA to draft guidance in order to facilitate the development of antibacterial drugs for serious or life-threatening bacterial infections, particularly in areas of unmet need.[5,6]

In response to GAIN, FDA released a draft Guidance for Industry in July 2013: Antibacterial Therapies for Patients with Unmet Medical Need for the Treatment of Serious Bacterial Diseases which discussed streamlined approaches that could be used in drug development.[7]

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[1]Centers for Disease Control and Prevention. Antibiotic/Antimicrobial Resistance. Available at http://www.cdc.gov/drugresistance/. Accessed March 29, 2016.
[2]Spellberg, B. (2012). New Antibiotic Development: Barriers and Opportunities in 2012. Confronting Today's Crisis in Antibiotic Development. Alliance for the Prudent Use of Antibiotics (APUA) Clinical Newsletter 30(1):8-10. Accessed at http://www.tufts.edu/med/apua/news/newsletter_22_2401405063.pdf.
[3] Modernizing Antibacterial Drug Development and Promoting Stewardship Meeting Summary. Engelberg Center for Health Care Reform at Brookings. (2014). Accessed at http://www.brookings.edu/~/media/events/2014/2/07-modernizing-antibacterial-drug-development/07-antibacterial-expert-workshop-meeting-summary.pdf
[4] *Payer perspective was taken out due to complexity of determination and appropriate application into the hospital formulary.
[5]http://www.fda.gov/RegulatoryInformation/Legislation/SignificantAmendmentstotheFDCAct/FDASIA/ucm20027187.htm (see full text of FDASIA law,Title VIII).
[6]http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf
[7]http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm359184.pdf

Subsequently, FDA asked the Clinical Trials Transformation Initiative to undertake the "Unmet Need in Antibacterial Drug Development (ABDD)" project which would employ qualitative research methodology to gauge stakeholder concerns regarding acceptance of antibacterial drugs developed using streamlined approaches where the safety experience may be less than what has been seen in traditional FDA drug approvals. The objective was to obtain a better understanding of patient, caregiver, and provider risk/benefit concerns regarding use of such antibacterial drugs. The results could inform efforts in labeling and risk communication and identify potential antibacterial drug stewardship issues.

After collecting data from focus groups and interviews with patients, caregivers and providers, a multi-stakeholder expert meeting was convened to discuss the findings and any impact they might have on risk communication, labeling and stewardship efforts.

MEETING OBJECTIVES

- Present perspectives from patients, caregivers and physicians on antibacterial drugs developed using streamlined approaches.
- Identify focus group themes and discuss topics which should be further explored or where draft recommendations could be made.
- Obtain feedback to improve risk communication, public understanding and stewardship.

MEETING EXECUTIVE SUMMARY

This Expert Meeting was convened to explore data collected by the CTTI Unmet Need in Antibacterial Drug Development Project Team. This project was dedicated to characterizing the public's risk/benefit perspectives on the use of streamlined development approaches of antibacterials for unmet need and approval of such therapies when there may be greater uncertainty and lower levels of precision due to limited data in order to facilitate public discussion regarding the use of such approaches.

Recurring themes, gathered from the perspectives shared by providers who are most likely to use these antibacterials, as well as patients who had either gone through or cared for an individual undergoing treatment for a serious infection, were presented to a multi-stakeholder group including patient advocates, academic and community infectious disease specialists, pharmacists, bioethicists, hospitalists, intensivists, regulators, drug sponsors, and individuals with experience in designing and/or conducting antibacterial trials.

Highlights of the meeting include points that may serve as a framework for

1) Improving stakeholder awareness of streamlined development approaches;
2) Educating providers about the data used to support submission and approval of antibacterial therapies developed using streamlined approaches;
3) The need for obtaining and timely sharing of "real-world use" data about these therapies in the post-marketing period; and

4) Issues related to antibacterial stewardship[8] efforts.

Session I was devoted to describing the current landscape of antibacterial drug development (ABDD) and the pipeline for such therapies. Vance Fowler (Duke University) explained the magnitude of the crisis and the scientific, economic, and regulatory challenges that have presented barriers to the development of effective new therapies and the mass exodus of research sponsors from the field of ABDD.[9] Joseph Toerner (FDA) provided an overview of the regulatory structures surrounding streamlined development approaches in the context of serious unmet need, as defined in 21 CFR 312.80 Subpart E.[10] The subsequent open discussion highlighted

1) The need to not just increase the number of antibacterial drugs available but to increase the viable options available when treating serious infections and the need to assess patient and provider needs;
2) The need to understand the level and quality of data on which FDA approval is based when streamlined development approaches are used;
3) How superiority or non-inferiority methodologies might be applied; and
4) How better diagnostics will aid developers.

Session II was dedicated to a detailed description of the evidence gathered by the CTTI project (see Meeting Presentations for more information), including focus groups with patients (healthy, at risk and recovered from severe infections) and caregivers, and investigators/providers.

The ensuing open discussions focused on:

1) The need to clarify the difference between "limited options" and "no options" for patients with resistant infections recognizing that there may be a varied spectrum of resistance with some bacteria being resistant to one drug, other bacteria may be resistant to several drugs ("multidrug-resistant") and some bacteria may even be resistant to all drugs ("pan-resistant").
2) What patients may want and need to know about preclinical testing, pharmacokinetic and pharmacodynamic (PK/PD) studies, and
3) The issues of off-label use of products.

There was also discussion of the following issues:

1) The need to better understand the interplay of human biology/immunology with antibacterial treatments for multi-drug resistant (MDR) bacteria.
2) The desire of providers for access to more detailed outcomes data, including
    a. Sufficient readily available data about safety and efficacy profiles for various therapies;

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[8]According to the Association for Professionals in Infection Control and Epidemiology (APIC): Antibacterial stewardship is "*a coordinated program that promotes the appropriate use of antimicrobials (including antibiotics), improves patient outcomes, reduces microbial resistance, and decreases the spread of infections caused by multidrug-resistant organisms.*" Source: http://www.apic.org/Professional-Practice/Practice-Resources/Antimicrobial-Stewardship

[9]Coukell A. To fight antimicrobial resistance, allow FDA to approve new drugs for limited populations. Health Affairs Blog. Available at: http://healthaffairs.org/blog/2016/04/05/to-fight-antimicrobial-resistance-allow-fda-to-approve-new-drugs-for-limited-populations/. Accessed April 27, 2016.

[10]21 CFR 312.80. Subpart E – Drugs intended to treat life-threatening and severely-debilitating illnesses. Available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=312&showFR=1&subpartNode=21:5.0.1.1.3.5. Accessed March 28, 2016.

    b. Rapid diagnostics to guide treatment; and
    c. Clear guidance about when to use a specific therapy in a given clinical context.
3) The inclusion of Infectious Disease (ID) and intensive care unit (ICU) pharmacists in discussions to ensure appropriate use of these drugs and stewardship of antibacterials, especially when it is necessary to fill the prescriber education gap left when pharmaceutical detailing was prohibited.
4) The goals of prudent stewardship (to maximize treatment for current patients, not for hypothetical future patients) was emphasized, as was the need to understand perceptions about the "financial toxicities" of various therapies.

Session III was focused on a distillation of focus group/interview themes that emerged across both the physician and patient/caregiver groups, noting key areas of convergence and divergence. Participants were invited to consider gaps and challenges, implications for all stakeholders, and solutions to problems in preparation for the breakout sessions.

Seven specific issues were brought up for discussion:
1) The crisis in ABDD
2) Patient understanding (or lack thereof) of unmet need
3) Limiting misuse of streamlined development approaches
4) Decision-making and risks involving both medical and legal issues
5) Antibacterial stewardship
6) Real-time data collection/sharing and sharing/publication of treatment guidelines
7) Risk communication

Session IV was dedicated to breakout sessions. Three breakout groups met separately to discuss assigned topics: 1) Risk Communication with Public and Providers, 2) Real-Time Clinical Data Use Registry, and 3) Stewardship Issues. Breakout groups summarized the discussion for all participants and reported back to the plenary group.

Group 1: Risk Communication with Public & Providers
The breakout group discussed what information providers and the public need to know about the use of antibacterial drugs developed using streamlined approaches. Key points were:
- Terms, such as "unmet need," "risk," "limited options," "no options," "resistant," and "MDR" should be well-defined in plain language.
- Descriptions of the current landscape of resistant infections should include clear explanations that help resolve common misconceptions, such as the use of antibacterial soap, concepts of individual resistance vs. bacterial resistance in laboratories, and the interaction of specialists who treat infections.
- The importance of focusing communications to patients (and their family members) who are most at risk for developing these types of infections. This includes the development of key criteria to find these patients, and pilot testing messages.
    - The need for information tailored with varying levels of detail and scope, to improve provider access to information considered critical for each discipline or specialty.

Group 2: Real-Time Clinical Data Use Registry

The breakout group discussed whether a real-time clinical data use registry/repository for drugs developed through streamlined approaches was necessary and/or feasible. If such a repository should and could be done, the group explored what it would look like.

- A registry/repository could focus on specific organisms or types of infections. The quality of the data (i.e., quality analysis of that data done in a timely manner, with adequate comparator data) are more important than access to real-time data.
- Establishing a network of sites and having scheduled reporting and analysis were identified as key components to sustaining such a registry/repository.
- Funding for such a registry would require the input of multiple stakeholders.

Group 3: Stewardship Issues
This breakout group discussed whether antibiotics developed through streamlined development programs need a distinct level of stewardship, and if so, what would this different level of stewardship look like.

- Stewardship programs seemed to be a luxury of high-resource settings. In general, the group felt all antibiotics should have the same level of stewardship, not only to ensure appropriate use, but also to preserve their effectiveness.
- However, antibiotics approved through a streamlined development process would likely be more restricted and receive greater vigilance and better stewardship.
- There is not a one-size-fits-all approach to stewardship.

Participants noted that education, rather than restriction, is key to effective stewardship. The more a therapy is restricted, the less likely physicians are to know about it. Stewardship is most often needed when providers lacking ID expertise encounter a potential infection and are unsure of how best to treat it. In addition to being well-informed about the safety and efficacy of antibiotics, a general level of education about the importance of stewardship must be shared by all members of the healthcare team in order to ensure its success.

Session V highlighted remaining gaps and challenges ahead, including the need for rapid diagnostics to address the inability to detect MDR pathogens earlier, the wide variability of stewardship philosophies and the need to include stewardship specialists and ICU/ID pharmacists in the discussion of how to use these therapies, and the need for more robust data collection systems that capture post-approval knowledge and costs vs. benefits. Challenges include the need to develop systematic approaches to risk communication about these products and a frame of reference around drugs developed through streamlined approaches that is tailored to specific audiences and tied to stewardship.

MEETING SUMMARY

Welcoming Remarks

Introduction to the Clinical Trials Transformation Initiative (CTTI)

Pamela Tenaerts, Clinical Trials Transformation Initiative (CTTI)

CTTI Executive Director Pamela Tenaerts welcomed the meeting participants and provided a brief overview of CTTI, including the key elements of the group's approach. CTTI projects[11] are focused on creating actionable, evidence-based, consensus-driven recommendations that are designed to improve the conduct of clinical trials by accelerating trial startup activities, leveraging new technologies for improved efficiency, enhancing trial quality without adding undue burdens, and identifying streamlined strategies for meeting regulatory requirements.

CTTI's Evidence-Based Approach

CTTI projects employ both quantitative and qualitative methods (including interviews, focus groups, surveys, systematic literature reviews, and expert meetings) according to how well-suited they are for a given project's objectives. The essential aims are to:

- Identify or describe a phenomenon to gain a better understanding of it; and
- Move beyond individual views and opinions to a more complete, objective understanding of the incentives and disincentives for change.

Once data have been gathered and analyzed, CTTI project groups challenge assumptions, identify barriers, and develop recommendations and tools designed to change the ways people think about and conduct clinical research.

Background of the Antibacterial Drug Development (ABDD) Unmet Needs Program

The incidence of antibacterial resistance, including multidrug-resistant (MDR) infections, is a large and growing threat to public health. MDR infections are responsible for 1.1% of all bacterial infections and they lead to tens of thousands of deaths in the United States each year,[12] as well as causing significant illness and injury (morbidity) and incurring substantial costs. At the same time, despite a pressing need for new therapies capable of effectively combatting this health threat, there is a serious shortfall in the drug development pipeline. In 2012 the US Food and Drug Administration (FDA) convened a task force[13] to confront these issues; the task force in turn engaged with a number of organizations (including CTTI). Dr. Tenaerts concluded with an introduction of the ABDD[14] Project members and thanked the team for their work.

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[11] Clinical Trials Transformation Initiative website. Mission statement. Available at: http://www.ctti-clinicaltrials.org/who-we-are/mission. Accessed March 28, 2016.

[12] Centers for Disease Control and Prevention. Antibiotic/antimicrobial resistance. Available at: http://www.cdc.gov/drugresistance/. Accessed March 29, 2016.

[13] US Food and Drug Administration. Antibacterial drug development task force. Available at: http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/ucm317207.htm. Accessed March 28, 2016.

[14] Clinical Trials Transformation Initiative. Unmet Need in Antibiotic Development. Project summary. Available at: http://www.ctti-clinicaltrials.org/what-we-do/ctti-projects/unmet-need. Accessed March 28, 2016.

Antibacterial Drug Development Unmet Needs Project Plan: Overview & Scope

Jamie Roberts, CTTI

Jamie Roberts provided an overview of the Antibacterial Drug Development Unmet Needs project, including the specific project objectives and overall goals. Ms. Roberts also reviewed the issues that led to the need for the project, the project plan, the evidence-gathering methodologies used, and the anticipated impact of the project.

Project Objectives

- Present perspectives from patients, caregivers and physicians regarding antibacterial drugs developed using streamlined approaches;
- Identify focus group themes and discuss topics which should be further explored or where draft recommendations could be made; and
- Obtain feedback to improve labeling, risk communication, public understanding and antibacterial drug stewardship.

Specific Issues in Antibacterial Drug Development for Unmet Need[15]

There are significant economic and regulatory disincentives affecting antibiotic drug development:

- The development process is long and costly;
- Trials are difficult to conduct and analyze; and
- Return on investment is low due in part to such drugs being used, for limited time intervals for diseases that are not chronic.

At the same time, the need for new therapies continues to grow, as well as the need for adequate data about the balance of risks and benefits to guide treatment decisions. For this reason, it is important to explore the perspectives of patients and providers regarding the use of antibacterial drugs, particularly newer therapeutics developed through streamlined approaches[16] in which the safety data that are used to support approval may be less than what is seen in traditional drug development programs.

Methodology

CTTI conducted a series of focus groups and semi-structured interviews designed to elicit opinions on the use of antibacterial therapies developed using streamlined approaches among patients, healthy persons, and caregivers, as well as among physicians representing specialties involved in the treatment of antibacterial infections. The objectives of these focus groups and interviews were to:

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[15]See definition of “unmet medical need” in FDA Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf

[16]The terms “streamlined approaches” and “streamlined development programs” are discussed in reference to drugs that are intended to treat serious bacterial infections where there is unmet need. : See July 2013 *FDA Draft Guidance for Industry: Antibacterial Therapies for Patients with Unmet Medical Need for the Treatment of Serious Bacterial Diseases.* http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm359184.pdf.

- Characterize patient and provider opinions regarding the tradeoffs between precision and uncertainty in the context of non-traditional pathways to antibiotic development; and
- Identify the specific needs for patient and provider education and clarifications to improve patient understanding of the need to expedite the availability of antibiotics to a limited patient population without full knowledge of the risk (safety information).

Anticipated Impact

The anticipated impact of this project is threefold:

- Patient and providers will have an improved understanding about the precision and uncertainty that affect development, approval, and use of antibacterial drugs to treat serious infections where there is unmet need and which were developed using streamlined approaches;
- There will be increased awareness among patients and providers of the need for expedited development processes in this therapeutic area; and
- There will be improvements in the appropriate use of antibacterial therapies developed using streamlined approaches.

Session I: Current Landscape of Antibacterial Drug Development for Serious and Unmet Medical Need

Deborah Collyar, Facilitator, Patient Advocates in Research (PAIR)

Session I Objectives:

- Describe the current landscape and pipeline of antibacterial drug development
- Describe streamlined development approaches

Current Landscape and Pipeline of Antibacterial Drug (ABD) Products

Vance Fowler, Duke University School of Medicine

For details of Dr. Fowler's presentation, please see the slide set available at https://www.ctti-clinicaltrials.org/files/3-unmetneed-currentlandscape.pdf.

There are currently ~2 million serious MDR infections each year in the United States; these infections are implicated in 23,000 (1.1%) deaths.[17] The US Centers for Disease Control and Prevention (CDC) estimates that preventing MDR infections and improving antibiotic prescribing practices could potentially save 37,000 lives over 5 years.[18]

However, despite the need for new ABDs to meet this threat, a series of scientific, economic, and regulatory challenges have presented barriers to the development of effective new therapies. The expected net present value (ENPV) is negative across much of

[17]Centers for Disease Control and Prevention. Antibiotic/antimicrobial resistance. Available at: http://www.cdc.gov/drugresistance/. Accessed March 29, 2016.

[18]Centers for Disease Control and Prevention. Vital Signs. Making health care safer – stop spread of antibiotic resistance. Available at: http://www.cdc.gov/vitalsigns/stop-spread/. Accessed April 27, 2016.

the ABD portfolio,[19] the result of which has been a mass exodus from the field of ABD development.[20]
The current pipeline of antibacterial drugs in development shows some with activity against new ESKAPE[21] and urgent-threat pathogens. The pipeline shows a variety of targets, including a large number (n=16) in acute bacterial skin and skin structure infections (ABSSSI). In contrast, the number of therapies currently in development for bacteremia and joint infection shows a decrease.

Summary

The development pipeline for antibacterial therapies remains challenging:

- Limited number of agents overall
- Gaps for *Acinetobacter*, metallo-beta-lactamase producers, antipseudomonal agents, and oral formulations of antibiotics
- Very limited variety of mechanisms

Streamlined Development Approaches

Joseph Toerner, Food and Drug Administration, CDER
For details of Dr. Toerner's presentation, please see the slide set available at https://www.ctti-clinicaltrials.org/files/4-unmetneed-streamlineddevelopmentapproaches.pdf.
Joseph Toerner provided an overview of the regulatory structures surrounding streamlined development approaches in the context of serious unmet need, as defined in 21 CFR 312.80 Subpart E[22]Ref 22.

Current Landscape

- Antibiotic resistance is continuing to create areas of unmet need, while patients are left with limited or no therapeutic options:
    - Multi-drug resistant(MDR) Gram-negative rods[23]
    - MDR *Neisseria gonorrhea*[24]
- ABD development needs to keep pace with growth of new mechanisms for resistance.

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[19]Engelberg Center for Health Care Reform at Brookings. Incentive for change: Addressing the challenges in antibacterial drug development. Meeting summary (February 27, 2013). Available at: http://www.brookings.edu/~/media/events/2013/2/27-bcadd-meeting/meeting-summary-20130925-final.pdf. Accessed June 15, 2016.
[20]Coukell A. To fight antimicrobial resistance, allow FDA to approve new drugs for limited populations. Health Affairs Blog. Available at: http://healthaffairs.org/blog/2016/04/05/to-fight-antimicrobial-resistance-allow-fda-to-approve-new-drugs-for-limited-populations/. Accessed April 27, 2016.
[21]ESKAPE: acronym denoting bacterial species responsible for most hospital-acquired infections: *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aureginosa,* and various species of *Enterobacter*
[22]21 CFR 312.80. Subpart E – Drugs intended to treat life-threatening and severely-debilitating illnesses. Available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=312&showFR=1&subpartNode=21:5.0.1.1.3.5. Accessed March 28, 2016.
[23]For additional information, please see http://www.cdc.gov/std/gonorrhea/arg/ and https://www.niaid.nih.gov/topics/antimicrobialresistance/examples/neisseria/Pages/default.aspx
[24]For additional information, please see http://www.cdc.gov/std/gonorrhea/arg/ and https://www.niaid.nih.gov/topics/antimicrobialresistance/examples/neisseria/Pages/default.aspx

- Development of a new ABD can take the sponsor 5-10 years to complete a New Drug Application (NDA):
    - Difficult to react in a timely fashion once resistance emerges;
    - Some development programs are not ultimately successful; and
    - Diversity in approaches is required.

Unmet Need

In July 2013 the FDA issued a draft guidance for Industry[7] regarding antibacterial therapies for patients with unmet medical needs; the Agency is still working on finalizing the guidance. Overall themes are:

- FDA is willing to accept a smaller data package with greater uncertainty about the risk/benefit ratio.
- Infections at different body sites can be pooled for efficacy analysis.
- Greater uncertainty could be acceptable in patient populations with serious disease for whom there are no other options (21 CFR 312.80 subpart E).
- The healthcare community should be aware that streamlined development results in a smaller data package.
- Product labeling should accurately communicate the balance of risk and benefit.

Everything contained by the guidance fits within existing statutory standards that govern NDAs: An agent being evaluated for an NDA must show substantial evidence derived from adequate, well-controlled studies; one such trial is sufficient to establish efficacy. A 1998 guidance[25] describes FDA evidence standards for making determinations, including trial designs that constitute “adequate, well-controlled trials”:

- Noninferiority
- Superiority
    - Active control
    - External control
    - Add on: test drug plus standard-of-care vs standard-of-care plus placebo
- Nested noninferiority-superiority

GAIN

The Generating Antibiotic Incentives Now (GAIN) Act was implemented as part of the 2012 Food and Drug Administration Safety and Innovation Act (FDASIA). GAIN provides incentives for developing antibacterial/antifungal drugs designated as qualified infectious disease products (QIDP). QIDP therapies receive an additional 5 years of marketing exclusivity (if approved), priority review, and/or fast track review (a written request must be submitted).

[25]US Food and Drug Administration. Guidance for Industry. Providing clinical evidence of effectiveness for human drug and biological products. May 1998. Available at: http://www.fda.gov/downloads/Drugs/GuidanceCompliance%20RegulatoryInformation/Guidances/UCM078749.pdf+Providing+clinical+evidence+of+effectiveness+for+human+and+bio&client=FDAgov&site=FDAgov&lr=&proxystylesheet=FDAgov&output=xml_no_dtd&ie=UTF-8&access=p&oe=UTF-8. Accessed March 29, 2016.

Expedited Programs[5]

- Final FDA guidance on Expedited Programs for Serious Conditions – Drugs and Biologics was issued in May of 2014. [26]
- **Fast Track** (FDAMA 1997): granted for drug in development intended to treat serious unmet need; opportunities for frequent interactions with review team.
- **Priority Review** (PDUFA 1992): Both this and above overlap with GAIN act.
- **Breakthrough Therapy** (FDASIA 2012) allows expedited review under NDA/BLA.
- **Accelerated Approval** – for serious and life-threatening conditions where reporting on outcomes may be years away.

The language contained in 21 CFR 312.08 allows FDA to exercise the broadest flexibility in applying the statutory standards. The Agency feels that it is operating in concert with statutory standards in accepting smaller data sets. With regard to what CTTI can do to help, FDA believes it is important to underscore patient/provider willingness to accept drugs approved with smaller datasets to support an NDA.

Discussion

Discussion ensued on applying the described approaches and how development using these approaches compares to a more traditional development program. Participants noted that the end goal should not be to just increase the number of antibacterial drugs available, but to increase the viable options available when treating serious or life-threatening infections. Given past examples of FDA-approved antibacterial drugs having serious risks identified after approval (e.g. kidney failure; death), questions were raised with respect to the level and quality of data FDA would use to base approval on one or more streamlined approaches, or even on traditional approval paths. Participants also gave examples where action was needed to reinvigorate development, including a healthy debate on when to apply superiority or non-inferiority methodologies. The need for more assessment of patient and providers needs was also expressed. Diagnostics were mentioned as another tool that could aid drug developers and clinicians in targeting therapy and assuring appropriate use. Further discussion on diagnostics with all relevant stakeholders and regulatory centers should be explored.

Session II: CTTI ABDD Unmet Need Project & Presentation of Findings Perspectives of Patients, Caregivers, and Healthy People

Diane Bloom, InFocus Research

For details of Dr. Bloom's presentation, please see the slide set available at https://www.ctti-clinicaltrials.org/files/5-unmetneed-interviewfindings.pdf.

Diane Bloom presented an overview of findings from focus groups conducted with patients, healthy individuals, and patient caregivers to explore their perceptions and attitudes toward the use of antibacterial drugs developed through streamlined processes. Focus groups were conducted using semi-structured questions. Open-ended, exploratory, iterative questioning was performed until the desired information was elicited. Participants comprised a total of 11 focus groups (N=62). Three groups consisted of healthy participants; two of patients who

[26]US Food and Drug Administration website. Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review. Available at: http://www.fda.gov/ForPatients/Approvals/Fast/default.htm. Accessed March 28, 2016.

had recovered from serious infections; two of persons at risk for hospitalization and infection; and four of caregivers of recovered and at-risk patients.

Research Goals

The primary research goals were to 1) understand public perceptions and beliefs about infections and antibiotics; 2) assess reaction to the FDA's streamlined development processes for bringing new ABDs to market more quickly; and 3) gain insight into public levels of comfort for taking ABDs developed through streamlined approaches.

Primary Findings

- Most respondents preferred not to take prescription medications unless necessary, citing concerns about side effects and negative media reports. All agreed that if they were very ill and needed a particular medication, they would be grateful to have access.
- Patients at risk for recurrent infections were more positive about use of medications and were more concerned about dying from an infection than from chronic illness.
- Respondents typically viewed antibiotics as safer than many other prescription drugs due to relatively short-term regimens and positive experiences. Most expressed the belief that newer ABDs were not necessarily better.
- Respondents tended to believe that antibiotic overuse has led to "superbugs" that reduce the drugs' effectiveness. They also believed that antibiotic resistance is a serious problem, but were unsure regarding the mechanisms of resistance. At-risk patients may mistakenly defer taking life-saving ABDs (or take them in a manner other than prescribed), believing that they are preserving future treatment options.
- All believed new ABDs were urgently needed, but were surprised at the scope of the crisis.
- All knew that FDA review processes could be protracted, but were surprised at the actual potential length of drug development and review processes.
- All reacted positively to the description of the streamlined development program and saw its advantages, but also expressed concerns about limited data and potential misuse of the program by the pharmaceutical industry.
- Participants said they would be willing to use a streamlined therapy but also desired information about effectiveness and safety and input from multiple experts to guide use.

Discussion

Discussion centered on whether focus group responses pointed to a need to clarify the concepts of "limited options" vs. "no option" for patients being treated for resistant infections. It was noted that identifying the "better" therapy is not always straightforward: although some marketed drugs have well-established safety profiles, efficacy profiles may be less clear. Patients need and want to understand more about preclinical testing (including what is known from animal models), pharmacokinetic/pharmacodynamic studies, how off-label use works, etc. Education should emphasize what sort of things can be learned in the

course of a streamlined development process. A conjoined analysis might lead to a better understanding of what, specifically, patients find acceptable. Physicians would also benefit from better access to detailed outcomes data, including information on symptom control. Several other issues and questions were raised, including:

- Given disincentives for studying sicker populations, is it possible to parlay post-market knowledge into the premarket process?
- In many cases in the clinical setting, Infectious Disease (ID) consults are not called as part of treatment decisions.
- Scrutiny has been focused on antibacterial drug development, but there has been less discussion of some aspects of individual human biology, including immunology.

Findings: Perspectives of Providers and Investigators

Thomas Holland, Duke University School of Medicine
For details of Dr. Holland's presentation, please see the slide set available at https://www.ctti-clinicaltrials.org/files/6-unmetneed-interviewfinding-holland.pdf.
Dr. Holland presented findings from 23 semi-structured interviews conducted with academic and community-practice physicians who treat resistant infections. Specialties included internal medicine, critical care, infectious diseases (ID), pulmonology, hospitalists, and Pharmacy and Therapeutics (P&T) committee members, with some overlap among categories. The main objectives were to: 1) understand physician perspectives regarding risk and uncertainty of ABD therapies; 2) explore physician perspectives and attitudes about using ABDs developed through streamlined programs; and 3) develop a better understanding of how physicians make treatment decisions for patients with complicated or resistant infections.

- Participants identified as the greatest challenges in treating complicated patients: 1) choosing the most appropriate therapy before definitive pathogen identification via culture; 2) treating patients requiring close monitoring whose ability to tolerate ABDs with significant toxicities is unknown.
- All physicians interviewed believed that there is a crisis in resistant infections and that a streamlined approach to ABD development and review is appropriate.
- None thought that "streamlined" ABDs should be first-line therapies; instead, they should be used only for patients lacking viable options. Tolerance for uncertainty about risk/benefit balance increases along with severity of illness and dwindling options.
- Most participants were not concerned about use of new ABDs developed through streamlined processes given that they would be approved by the FDA and vetted through hospital P&T committees, although some expressed concerns about lack of efficacy and side-effect data (especially regarding renal effects) in critically ill patients.
- Some physicians wanted ongoing updates on safety, efficacy, and toxicity profiles of streamlined drugs in clinical settings and suggested that FDA require continuous submission of such data as part of the approval process, partnering with a trusted neutral third party.

- All thought use of new streamlined ABDs should be accompanied by a mandatory consult with ID specialists serving on the hospital antibiotic stewardship committee and/or certified experts in treating MDR infections, but that larger multidisciplinary teams or "advanced directives" were not needed.
- Most said they would be comfortable using the combination drug ceftazidime-avibactam (Avycaz®), which was developed through a streamlined approach,[27] but not as a front-line therapy if alternatives were available; some had reservations about its use in fragile patients.

Discussion

Discussion centered on the availability of data and the need for education. Participants noted that many physicians lack: 1) access to sufficient, readily available data about safety and efficacy profiles for various therapies; 2) rapid diagnostics that can provide reliable information to guide practice; and 3) clear guidance about when to use a given therapy in a particular clinical context. Physicians need access to information about "bug"-specific and population-specific use of drugs and clear practice guidelines, possibly developed in conjunction with the both the FDA and CDC, that include guidance on appropriate stewardship.

Another key theme that emerged during discussion was the importance of pharmacists and ICU pharmacists in ensuring appropriate use and stewardship of ABDs, and it was suggested that developing stewardship programs that encourage prudent use might be useful. In addition, the nature of stewardship itself might need to be clarified. The goal of stewardship should be to maximize treatment for that patient, not for hypothetical future patients.

Finally, the issue of costs affecting choice of ABD therapy was raised, possibly pointing to a disconnect between physician and patient perceptions: some noted that the cost of ABD therapies was a minor proportion of overall treatment costs in the intensive care setting, and others reporting that patient perceptions or worries about "financial toxicities" might raise substantial concerns.

Session III: Presentation of Focus Group Themes and Considerations

Rose Tiernan; FDA, CDER & Stephen Mikita, Patient Advocate

Stephen Mikita presented a distillation of focus group/interview themes that emerged across both the physician and patient/caregiver groups, noting key areas of convergence and divergence. The group was invited to consider gaps and challenges, implications for all stakeholders, and solutions to problems.

Key Issue 1: The Crisis in Antibacterial Drug Development (ABDD)

- Both patients and physicians recognize the crisis in ABDD and jointly acknowledge a need for streamlined development programs and other steps to effectively combat multidrug resistant infections, especially in hospital and long-term care settings.

[27]US Food and Drug Administration website. FDA approves new antibacterial drug Avycaz. February 26, 2015. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm435629.htm. Accessed March 28, 2016.

- Both groups also believe that government (regulators) share responsibility for developing streamlined programs and should work with drug developers and the medical community.

Key Issue 2: Patient Understanding of Unmet Need

- Patients need further clarity on the definition of unmet need in the context of ABDD. Patient advocacy groups have various understandings of limited vs. no options, and clinicians need to spend more time explaining the distinction.

Key Issue 3: Limiting Misuse of Streamlined Approaches

- Patients and providers agree streamlined drug development approaches are needed.
- Safeguards are needed to prevent misuse of these approaches by industry.
- Providers believe development incentives should be commensurate with severity of need.
- Regulators should maintain adequate oversight.

Key Issue 4: Decision-Making and Medico-legal Risk

- Patients desire a multidisciplinary "A-Team" to oversee decisions when to prescribe and treat them with new antibacterial drugs developed using streamlined approaches. The group's discussion revolved around the best use of existing ID consult services and staff hospital pharmacists on-call to satisfy this particular patient concern.
- Providers desire assurances that using drugs developed through streamlined approaches will not expose them to additional medico-legal risk.

Key Issue 5: Stewardship

- Providers believe that drugs developed through streamlined approaches should be reserved until culture results are known, unless there are extenuating circumstances. There was discussion to the effect that this may not be practical, in light of the critical nature of a patient's infectious disease necessitating the need for early broad spectrum treatment prior to the availability of culture results which often necessitates use of a combination antibacterial drug regimen.
- Patients feel there may be a need to increase public awareness of how decisions are made regarding treatment, determination of unmet need, and the limits of diagnostic technologies.

Key Issue 6: Real-Time Data Collection/Sharing and Publication of Treatment Guidelines

- Patients and providers both desire current safety and effectiveness information about ongoing clinical use of ABDs developed using streamlined approaches to be collected and made publicly available on a timely and ongoing basis.
- Providers also believe that in addition to conducting post-marketing studies, a registry to gather post marketing experience on drugs developed using for streamlined approaches might be useful.

Key Issue 7: Risk Communication

- Providers believe that standardized information about risks and benefits should be available to prescribing physicians. The group discussed the need for training for providers regarding the type of data that supported FDA approval of these products.
- Providers also believe that the following information should be available to physicians with hospital-prescribing privileges:
    - Is the drug on formulary?
    - Are there prescribing restrictions?
    - What does the drug cost?
    - What data in critically ill patients are available?
    - What are the renal and other side effects?

Session IV: Breakout Sessions

Three breakout groups met separately to discuss assigned topics: 1) Risk Communication with Public and Providers, 2) Real-Time Clinical Data Use Registry, and 3) Stewardship Issues. Breakout groups summarized the discussion for all participants and reported back to the plenary group.

Group 1: Risk Communication with Public & Providers

The breakout group discussed what information providers and the public need to know about the use of antibacterial drugs developed using streamlined approaches. Key points were:

- Terms, such as “unmet need,” “risk,” “limited options,” “no options,” “resistant,” and “MDR” should be well-defined in plain language.
- Likewise, it is important to describe the current landscape of resistant infections, and the fact that resistance to one ABD does not mean the bug is resistant to all current ABDs.
- Considering the limited resources for communication outreach that may be available, it may be important to focus communications to patients (and their family members) who are most at risk for developing these types of infections.
- Having tailored information, with varying levels of detail and scope, available for providers would improve access to information considered critical for each discipline or specialty. For example, providers most likely to treat patients with these serious or life-threatening infections would find information gained from the clinical trial experience critical to determining appropriate use of these new drugs. The broader group of professional organizations and societies, including those whose constituents and patients are considered at risk, were identified as potential recipients for targeted outreach about antibacterial drugs to treat serious infections developed using streamlined approaches. Information should also be made available to at-risk patients.

Group 2: Real-Time Clinical Data Use Registry

The breakout group discussed whether a real-time clinical data use registry/repository for drugs developed through streamlined approaches was necessary and/or feasible. If such a repository should and could be done, the group explored what it would look like.

- A list of current reporting options was compiled; for example, MedWatch and industry-funded post-market studies, including those that leverage existing research networks such as the Acute Respiratory Distress Syndrome (ARDS) Network.
- A registry/repository could focus on specific organisms or types of infections and would benefit all antibiotics, not just those developed using streamlined approaches or targeting disease with unmet medical need.
- The quality of the data, quality analysis of that data being done in a timely manner, and having adequate comparator data available were felt to be more important than the ability to access data in real-time.
- Establishing a network of sites and having scheduled reporting and analysis were identified as key components to sustaining such a registry/repository.
- Funding for such a registry would require the input of multiple stakeholders.

Group 3: Stewardship Issues

This breakout group discussed whether antibiotics developed through streamlined development programs need a distinct level of stewardship, and if so, what would this different level of stewardship look like.

- Stewardship programs seemed to be a luxury of high-resource settings. In general, the group felt all antibiotics should have the same level of stewardship: not only to ensure appropriate use, but also to preserve their effectiveness.
- However, antibiotics approved through a streamlined development process would likely be more restricted and receive greater vigilance and better stewardship.
- There is not a one-size-fits-all approach to stewardship.

After each breakout group presented their findings to the assembled meeting, participants noted that education, rather than restriction, is key to effective stewardship. The more a therapy is restricted, the less likely physicians are to know about it. There is a void created by the lack of direct education of physicians formerly provided by industry “detailers.” Stewardship is most often needed when providers lacking ID expertise encounter a potential infection and are unsure of how best to treat it. Some participants noted how off-label use presents challenges to stewardship, including the issue of where data could come from to help guide stewardship when antibiotics are used off-label, and emphasized how regulatory data helps in supporting institutional decisions regarding stewardship. This latter point is especially challenging when handling stewardship for new agents in low-resource settings. In addition to being well-informed about the safety and efficacy of antibiotics, a general level of education about the importance of stewardship must be shared by all members of the healthcare team in order to ensure its success.

Session V: Highlights, Gaps, Challenges & Next Steps

Jamie Roberts, CTTI; Pamela Tenaerts, CTTI; Rose Tiernan, FDA

Gaps

- The key to stewardship is rapid, and better, diagnostics to address the inability to detect MDR pathogens early to allow us to do the trials in the people who need them.
- Stewardship philosophies are widely variable.
- We must engage both infectious disease and ICU pharmacists in the discussion of use and stewardship.
- Missing knowledge:
    - There is a need for more robust data collection systems that capture new knowledge about products developed using streamlined approaches.
- We must leverage the knowledge of ID specialists about the various different products themselves.
- We must explore the costs vs. benefits of antibacterials.

Challenges and Changes Ahead

- Risk communication:
    - Gaps in information exists.
    - There is a need for a frame of reference around drugs developed through streamlined development approaches and tailored to patients (ICU setting) and providers (tiered forms of information based on specialty), and conveyed in accessible plain language. This applies to all ABDs no matter how they were developed.
    - Should be tied to stewardship.
- Consensus exists for the need to collect data (diagnosis and/or pathogen-specific).
    - ALL antibiotic therapies.
    - Independent of drug companies, and overseen by independent steering committee.
    - Funding to be provided through public-private partnership (CDC, FDA, BARDA, NIH, the pharmaceuticals industry).
        - Networks for data collection?
- Clarification of what “real-time” reporting means.
    - Timely, high-quality data and analysis against comparator.
- Stewardship:
    - Need to fill the void left when the pharmaceutical industry stopped educating providers in use of therapies in clinical practice (detailing).
    - Need a best-practice or “how-to” for multidisciplinary stewardship for antibiotic stewardship programs and P&T committees.
    - Partnership between higher- & lower-resource settings (e.g., academic medical centers partnering with community hospitals).

Considerations for the Future and Next Steps

- There is a call to act and innovate: We are facing a crisis in antibacterial drug development for serious infections where there is unmet need. Now is the time for action and innovation, including streamlined development approaches.
- Post-meeting electronic survey.
- Meeting summary and slides:
    - Consider recommendations for the future.
    - Definitely a manuscript.
- Follow-up with participants for additional feedback as needed:
  Are there still gaps this team/project should address?

Concluding Remarks

Meeting attendees and participants were very supportive of the need for (and use of) streamlined approaches to develop antibacterial drugs that treat patients with serious infection where there is unmet medical need. Other key takeaways included the need to: 1) fill the education gap for providers regarding the data that supported approval of these products, 2) improve communication to patients and providers regarding the risks and benefits of using antibacterial drugs approved with smaller data sets, 3) determine the best way to collect, analyze and share with providers the real-world clinical use data with these products, and 4) continue discussion of appropriate stewardship activities.

FUNDING STATEMENT

Funding for this manuscript was made possible, in part, by the Food and Drug Administration through grant R18FD005292 and cooperative agreement U19FD003800. Views expressed in written materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services, nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government. Partial funding was also provided by pooled membership fees from CTTI's member organizations.

R18FD005292 refers to grant work 09/01/2014 – 08/31/2019

U19FD003800 refers to grant work 09/20/2009 – 08/31/2014

ABOUT CTTI

The Clinical Trials Transformation Initiative (CTTI) is a public-private partnership to develop and drive adoption of practices that will increase the quality and efficiency of clinical trials. The CTTI vision is a high quality clinical trial system that is patient-centered and efficient, enabling reliable and timely access to evidence-based prevention and treatment options.

Appendix A. Meeting Agenda

TUESDAY, MARCH 1, 2016

7:15	**Breakfast** *(Provided)*
8:00	**Welcoming Remarks**
	Introduction to the Clinical Trials Transformation Initiative and the ABDD Program *Pamela Tenaerts, Clinical Trials Transformation Initiative (CTTI)*
8:15	Project Overview and Scope *Jamie Roberts, CTTI*
8:30-9:15	**Session I: Current Landscape of Antibacterial Drug Development for Serious and Unmet Medical Need**
	Session I Facilitator: Deborah Collyar, Patient Advocates in Research (PAIR) *Session I Objectives*: ► Current landscape and pipeline ► Streamlined development approaches
8:30	Current Landscape and Pipeline of Antibacterial Products *Vance Fowler, Duke University School of Medicine* Q & A
8:45	Streamlined Development Approaches *Joseph Toerner, Food and Drug Administration, CDER* Q & A
9:05	Open Discussion
9:15	**Break**
9:30–11:30	**Session II: CTTI ABDD Unmet Need Project & Presentation of Findings**
	Session II Facilitator: Jamie Roberts, CTTI *Session II Objectives*: ► Background and current status of project ► Findings from focus groups and interviews
9:30	Findings: Perspectives of Patients, Caregivers and Healthy People *Diane Bloom, InFocus Research*
9:55	Open Discussion
10:15	Findings: Perspectives of Providers and Investigators *Thomas Holland, Duke University School of Medicine*
10:45	Open Discussion
11:30	**Working Lunch** *(Provided)*

TUESDAY, MARCH 1, 2016 *(Continued)*

12:00-1:00 Session III: Presentation of Focus Group Themes and Considerations

Session III Facilitators: Rosemary Tiernan, FDA, CDER; Stephen Mikita, Patient Representative

Session III Objectives:

- Review draft themes, considerations and questions for discussion
- Identify gaps and challenges
- Discuss implications for stakeholders

12:00 Focus Group Themes and Questions for Consideration
Stephen Mikita

12:20 Open Discussion
Facilitator: Rosemary Tiernan

12:45 Introduction and Instructions for Breakouts
Jamie Roberts

1:00-2:00 Session IV: Breakout Sessions

- **Breakout 1: Risk communication with the Public & Providers**
  Facilitators: Deborah Collyar, PAIR & Amy Corneli, Duke
- **Breakout 2: Real-time Clinical Data Use Collection**
  Facilitators: Pamela Tenaerts, CTTI & Jeff Loutit, The Medicines Company
- **Breakout 3: Stewardship Issues**
  Facilitators: Thomas Holland & Diane Bloom

2:00 Break

2:15-2:45 Session V: Breakout Sessions Report Outs

2:15 Breakout 1: Speakers: *TBD by Breakout Group*
- *Open Discussion*

2:30 Breakout 2: Speakers: *TBD by Breakout Group*
- *Open Discussion*

2:45 Breakout 3: Speakers: *TBD by Breakout Group*
- *Open Discussion*

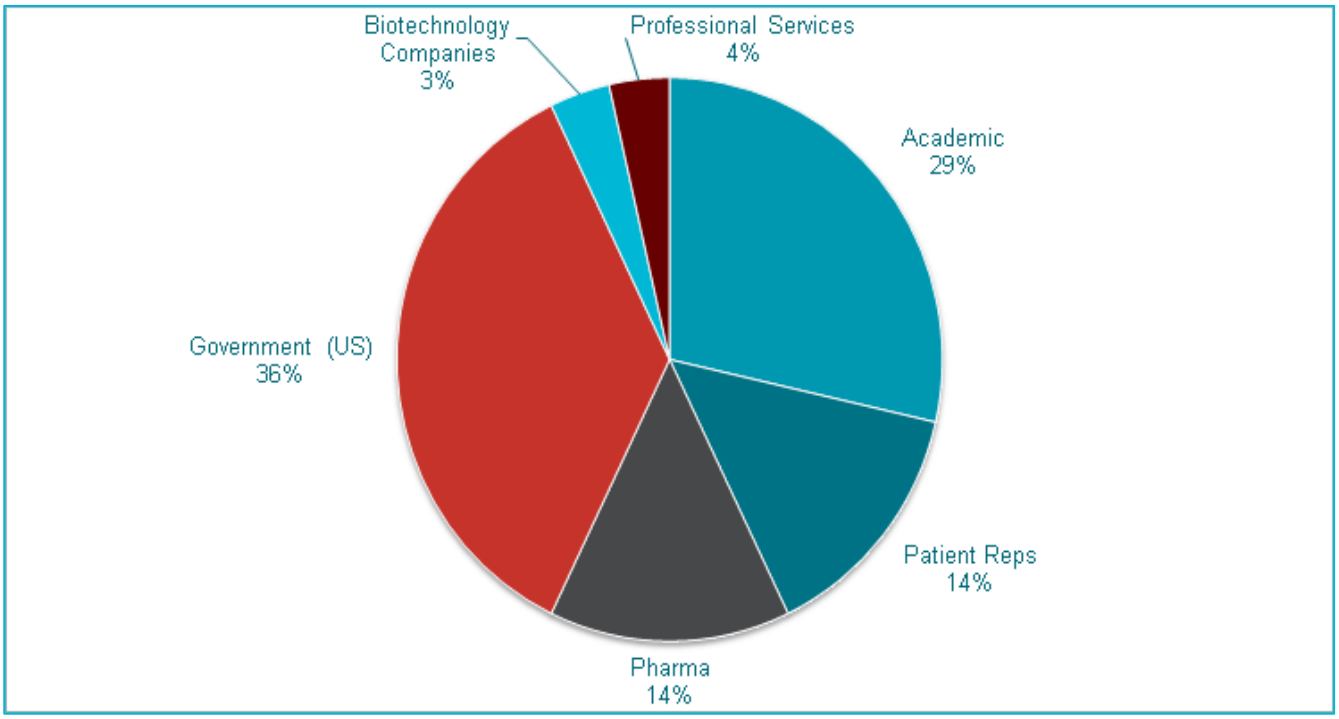
3:00 Highlights, Wrap-Up & Next Steps
Speakers: Pamela Tenaerts, Rosemary Tiernan, Jamie Roberts

3:15 Adjourn

Appendix B. Multi-Stakeholder Expert Meeting Participants

Our meeting participants included representatives from a broad cross-section of the clinical trial enterprise including regulators, government sponsors of clinical research, academia, industry, patient advocates, clinical investigators, and other interested parties.

STAKEHOLDERS REPRESENTED



MULTI-STAKEHOLDER EXPERT MEETING ATTENDEES

Diane Bloom	InFocus Research
Luke Chen	Duke University of Medicine
Laura Cleveland	Patient Advocates In Research (PAIR)
Deborah Collyar	Patient Advocates In Research (PAIR)
Adelaide Doussau	National Institutes of Health
Vance Fowler	Duke University of Medicine
Ian Friedland	Achaogen
David Friedland	Wockhardt Inc.
Ahimsa Govender	Duke-Margolis Center for Health Policy
Lauri Hicks	Centers for Disease Control and Prevention
Thomas Holland	Duke University of Medicine
Christopher Houchens	BARDA
Sara Hull	National Institutes of Health
Sarah Ikenberry	Food and Drug Administration
Sylvia Lee	Food and Drug Administration, CDER
Jeff Loutit	The Medicines Company
Steve Mikita	Patient Advocate
Linda Park	Food and Drug Administration, CDER
Jason Pogue	Detroit Medical Center
John Powers	George Washington University School of Medicine
Scott Proestel	Food and Drug Administration, CDER
Keith Rodvold	University of Illinois at Chicago
Vijay Tammara	Wockhardt Inc.
Jeanine Thomas	MRSA Survivors Network
Rose Tiernan	Food and Drug Administration, CDER
Joseph Toerner	Food and Drug Administration, CDER
John Tomayko	Spero Therapeutics
Richard Wunderink	Northwestern University Feinberg School of Medicine

CTTI TEAM & PROJECT STAFF ATTENDEES

Sara Calvert	Clinical Trials Transformation Initiative
Amy Corneli	Clinical Trials Transformation Initiative
Jennifer Goldsack	Clinical Trials Transformation Initiative
Gerrit Hamre	Clinical Trials Transformation Initiative
Jonathan McCall	Duke Clinical Research Institute
Jamie Roberts	Clinical Trials Transformation Initiative
Kimberley Smith	Clinical Trials Transformation Initiative
Pamela Tenaerts	Clinical Trials Transformation Initiative

For more information, contact the Unmet Need in ABDD Project Manager, Jamie Roberts, at Jamie.Roberts@duke.edu or visit http://www.ctti-clinicaltrials.org.