Streamlining Antibacterial Drug Development Programs To Address Unmet Medical Need: Patient And Provider Attitudes On A Modified Benefit-Risk Calculus

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Introduction/Rationale

Proliferation of resistant strains of pathogenic bacteria and a paucity of effective therapies present a public-health crisis. Considering this, sponsors have worked with FDA to streamline development programs (e.g., approving antibacterial drugs with limited safety and efficacy) when patients have serious infections, treatment options are limited/nonexistent, and likelihood of benefit is high. Streamlining may result in increased uncertainty at time of approval, and the benefit-risk calculus for patients and providers concerning use of FDA-approved products developed under a streamlined program is not well-characterized. The Clinical Trials Transformation Initiative (CTTI) sought to describe patient and provider opinions regarding tradeoffs between precision and uncertainty in the context of antibacterial therapies developed under streamlined programs.

Methods

The CTTI Antibacterial Drug Development (ABDD) Unmet Needs project conducted a series of focus groups and interviews to characterize attitudes of 2 groups:

1) Recovered patients/healthy persons/caregivers;

2) Physicians involved in caring for patients with resistant bacterial infections.

To elicit input from patients/caregivers, 11 semi-structured focus groups were conducted (N=62 individuals) among participants comprising healthy persons, caregivers, and patients who had recovered from resistant infections. A series of in-depth, semi-structured telephone interviews were also conducted with physicians (N=23) treating complex resistant antibacterial infections in community practice (n=12) and academic (n=11) settings. Participant responses were categorized according to themes that emerged during discussions.

Results

Focus group and physician interview findings are provided in **Table 1.** Both groups showed broad thematic agreement in key areas:

· Need to develop drugs to address antibiotic resistance;

· Potential for streamlining development to benefit patients with unmet needs;

· Need for continuous collection and monitoring of data on efficacy and safety;

· Need for oversight to prevent abuse of streamlining programs

Conclusions

Based on findings from these focus groups and interviews, the CTTI ABDD program distilled the following consensus points for consideration when aiming to streamline antibacterial development programs targeting unmet need:

· Unmet need in antibacterial drug development has reached a crisis point;

· Streamlined development programs are needed and should be continued;

· Medical-legal risk should be limited for FDA-approved therapies developed under streamlined programs;

· Appropriate use and stewardship should be ensured through oversight;

· Consultations with infectious disease specialists should be required when using therapies developed under streamlined programs;

· Safety and efficacy data should be collected and reported in real time, fed back to continuously updated treatment guidelines/registries, and standardized information should be provided to prescribers.

Detailed Thematic Responses to Focus Groups and Guided Interviews

PATIENT / CAREGIVER GROUP
Mindset Regarding Prescription Medications
Wary of prescription drug use*
Concerned about potential risks and side effects*
See prescription drugs in more positive light*
Theoretically prefer natural/homeopathic remedies or lifestyle changes, but also value lifesaving medications†
Underlying health conditions make them vulnerable to infection†

Perceptions of Existing and New Antibiotics
Most viewed antibiotics as safer than many other prescription drugs
Most do not believe that "newer is better"
Most adopt "wait and see" attitude toward adopting new medication
Perceptions of Antibiotic Resistance
Almost all familiar with general concept of antibiotic resistance
Many mistakenly thought overuse leads to resistance *in individuals*
All were surprised by magnitude of problem
All were surprised that "superbugs" can be transmitted from person to person
All believe new antibiotics are urgently needed
Perceptions of FDA Drug Review Process
Almost all surprised at potential length of process
Confidence in process eroded by recalls & DTC advertisement listing side effects
Perceptions of Streamlined Approaches
All reacted positively to SDP description
Saw advantage in getting new antibiotics to critically ill patients with few/no additional options
Concerned about abuse/overuse by industry
Use in Situations of Critical Need
Most would not want to rely on judgment of single doctor
Preferred interdisciplinary "A-Team" to oversee use decision
Most would find decision-making on behalf of loved one more difficult
Would like information in advance to let doctors/family know wishes†
Almost all believed that if critically ill, they would not be able to make decisions
Information Desired About Drugs Approved Using Streamlined Approaches
In how many people/what populations has drug been tested?
What are the side effects, including most common and most serious?
What drug interactions have been observed?
How effective is drug, and what else is known about the drug?
How do they know they actually have a resistant infection?
What are the odds of survival without the medication?
What would likely happen if they do not take the medication?
Who decides to offer the new antibiotic, and what are alternatives?
PHYSICIAN GROUP
Greatest Challenges in Treating Patients with Complicated Infections
Choosing appropriate treatment before definitive culture available
Treating very ill/fragile patients requiring close monitoring where tolerance and toxicity are difficult to predict
Perceptions of Streamlined Approaches
All believed there is a crisis in antibacterial-resistant infection treatment and streamlined development approaches are an appropriate measure
Use of Antibiotics Approved Using a Streamlined Approach
None believed SDP products should be frontline therapies; all would wait for culture results before using
Would use only for patient with true unmet needs who have exhausted options
Concerns Regarding SDP Program
Most were not concerned about using such drugs in critically patients with unmet needs.
Some expressed concern about lack of efficacy & safety data (esp. renal toxicity)
Before using for patients with HAP/VAP, would want to know sensitivity to pathogens and whether it had sufficient lung penetration
Confidence Regarding Use of a Drug Developed Using Streamlined Approaches
Confidence would be boosted by FDA approval via SDP and vetting by hospital P&T Committee
Restrictions on Use

Few restriction on ID/Critical Care physicians' prescribing authority
Should be mandatory consults with ID physicians on hospital stewardship committee/experts in multidrug resistant infections
Some wished to ensure that ID consults would not interfere with timely use in critical situations
Ongoing Need for Information
Some expressed desire for continuous updates on efficacy/safety
Some suggested data from use in clinical settings be continuously submitted to trusted neutral third party to inform physicians and create guidelines
Bedside Consult
All believe multidisciplinary "A-Team" was neither necessary or desirable and that a mandatory ID consult would suffice
Patient Advance Directive for SDP Therapy Use
None thought "advance directive" regarding SDP therapy use would be practicable or desirable

Abbreviations: DTC, direct-to-consumer; FDA, US Food and Drug Administration; HAP, hospital-acquired pneumonia; ID, infectious diseases; P&T, pharmaceutical and therapeutic; SDP, streamlined development program; VAP, ventilator-associated pneumonia