Overview of Risk-Benefit within Antibacterial Drug Development

Changing the Paradigm

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Antibacterial Drug Development

- The choices we have before us
- What the impact of these choices might be
- Appropriate balance of risk and benefit and how this may impact antibacterial drug development
- Ultimately how this will impact patients and public health

Antibacterial drug development programs 1960s, 1970s and 1980s. Generally…

- Trials enrolled patients with infections at any of variety of tissue sites in a trial often with an active comparator
- Goal of showing comparable point estimates for clinical cure
- Indications were based on the subsets of tissue sites from within the trials
- In vitro data (e.g., serum from patients receiving the test drug) also evaluated
- Indications were less specific than current day (e.g., respiratory tract infection, lower respiratory tract infection, upper respiratory tract infection)

Antibacterial drug development programs 1990s. Generally…

- 1990's move towards more tissue site specific trials
  - Rationale
    - Natural history of the diseases may differ
    - Endpoints & treatment durations may differ
- Move towards tissue site specific trials reflected in
  - 1992 IDSA/FDA Guidelines
  - 1992 FDA Points to Consider document – Clinical Development and Labeling of Anti-Infective Drug Products*
  - 1998 FDA Guidance documents**

* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070975.pdf

** http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064980.htm

Antibacterial drug development programs 2000s. Generally…

- 2000 Greater emphasis on the evidence base for non-inferiority trials
  - Public concern about the scientific validity of antibacterial drug trials
  - This has generally led to larger trials
  - Continued trend towards more specific Indications
- Present – Updating Guidance documents
  - 12 antibacterial drug-related guidances in draft or final**

Antibacterial Drugs Current State - 1

- Decline in activity in the development of new antibacterial drugs
- Mature field w/ approx. 50 to 60 different active ingredients
  - Some no longer marketed
  - Some had postmarket safety problems
  - Some may not have had characteristics that would lead to their continued availability
  - Resistance has impacted upon utility of some

Antibacterial Drugs Current State - 2

- Is the current level and are the types of antibacterial drugs that are being developed meeting patient and public health needs?
  - Currently we are seeing areas of unmet need
  - Resistance continues to erode our therapeutic armamentarium
  - Importance of
    - Development of new safe & effective antibacterial drugs
    - Antimicrobial stewardship – prudent use
    - Infection control

Antibacterial Drugs Current State - 3

- Advances in clinical trials intended to improve the science of clinical trials
  - Comments on lack of feasibility
  - Economic issues in antibacterial drug development
- Pipeline of new antibacterial drugs not robust and focused on a limited disease spectrum
  - Some for skin infections, little for CIAI, CUTI, very little for CABP & HABP / VABP
- Some antibacterial drug development in important bacterial diseases reportedly going ex-U.S.

Addressing Patient and Public Health Needs

- How do we address patient and public health needs for antibacterial drug to treat patients' infections?
- What are some of the choices and/or trade-offs?
- How should these be addressed?

Goals – Theory and Practice

- Most would want
  - A robust pipeline of new antibacterial drugs – especially drugs with new mechanisms of action
  - Precise characterization of safety and efficacy & little uncertainty
  - Agents already available that are active against new resistance mechanisms that will emerge in the future
- All of these goals may not be achievable
  - economic, scientific, regulatory, practical issues/challenges
- Development of a new drug can take 5-10 years
  - Difficult to react in a timely fashion
  - Some development programs not successful
  - Ideally have options to choose from in advance of the need
- Lack of development is not standing still, resistance will move us backwards over time

Questions on the Issues and Challenges we Currently Face

- Are there ways that we can do a better, more efficient job with clinical trials?
- If a greater tolerance for risk and uncertainty is appropriate, in what areas?
  - areas of unmet need?
  - indications where development is sparse?
  - other indications?
- Why might one consider a greater tolerance for risk and uncertainty?
  - Unmet need? Lack of satisfactory options? Feasibility? Characteristics of the product (e.g., new mechanism of action of inhibitor that preserves activity)?
- If accepting greater uncertainty is appropriate, we may learn important information about a product in the postmarketing setting (e.g., new safety findings, settings where efficacy may be relatively less (or greater) than other products); will that be acceptable?

A Somewhat Paradoxical Situation

- Achieving precise characterization of efficacy and safety for traditional antibacterial drug development may lead to less antibacterial drug development and generate unmet need
- Once there is unmet need, greater risk and uncertainty may be accepted for the unmet need population
- It is somewhat paradoxical that the avoidance of uncertainty for traditional development programs is generating the situation that leads one to be willing to accept uncertainty for the unmet need scenario

A Somewhat Paradoxical Situation

- Generating unmet need also means that there is a period of time when we lack satisfactory treatment options for patients
- Addressing unmet need, while a critical thing to do once it has developed, is a situation of trying to catch up with what has already happened (resistance)
- Ideally new agents would already be available and we could avoid the unmet need scenario

Theoretical Scenarios on Drug Development – Precision and Uncertainty

- High levels of precision (lower uncertainty) may lead to few new antibacterial drugs developed for a limited range of indications that are very well characterized
  - unmet need may persist
- Lower levels of precision (higher uncertainty) may lead to more antibacterial drugs developed for more indications, but they will be less well characterized –
  - could possibly avoid an unmet need scenario(s)
  - may learn important information on a drug postmarketing
- There are many points in between these two poles and what is appropriate likely varies by indication / degree of unmet need
- Some of the new drugs that are developed may add significantly to the therapeutic armamentarium, others may not add much
- Important to articulate judgments and trade-offs in an open and transparent manner

Points for Discussion

- Unmet need – current situations
- Smaller development program targeting areas of unmet need
- Possible approaches – clinical trial design and statistical
- Potential solutions
- We welcome a discussion on the issue of appropriate balance of risks, benefits, and uncertainty in order to best meet patient and public health needs.

Thank you