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**

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