Reflections on Existing Paradigms for Antibacterial Drug Development

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Disclosures

- Within the past 36 months: Board compensation and/or consultancy fees from Actelion, Basilea, Cempra, Cerexa, Durata, Cubist-Calixa, Fab Pharma, J&J, Kalidex, Meiji, Merada, Merck, Nabriva, Wyeth/Pfizer (DSMB).
- Equity: Durata, Calixa, Cerexa, Kalidex, Nabriva
- Member, IDSA Antimicrobial Availability Task Force
- Co-Chair FNIH Project Team, *Addressing Endpoints for Clinical Trials of Drugs for the Treatment of CABP and ABSSSI*
- Today: Representing Talbot Advisors LLC

Topics

- The influence of regulatory science on antibacterial drug development
- The role of – and our responsibility to - NI trial designs in antibacterial drug development
- Most pressing unmet clinical needs
  - Where Guidance is needed
- Activities to support antibacterial drug development

Theses

- Regulatory Science should always be in evolution
  - Science advances…..Stasis can be detrimental
  - Evolution occurs in fits and starts… incrementally
  - Periods of rapid evolution bring uncertainty and are stressful
  - Ideally, evolutionary dead ends may occur, but this should be outweighed by many more opportunities for progress
- Evolution should be encouraged, but not at the cost of paralysis in new drug development
  - Goal: pragmatic solutions that facilitate approval of safe and efficacious new drugs… due to, or despite, evolution in regulatory science
- Evolution should be managed to result in a "Win-Win" for all stakeholders: Patients, physicians, industry and regulators

Dealing with Evolution in Regulatory Science

- Regulatory decisions should be communicated broadly and in a timely, transparent manner
- Stakeholders should be open-minded until success or failure of new approaches can be judged based on accruing evidence
- Selection of the appropriate *fora* for discussion is critical
  - Global harmonization essential
  - Inclusive of varying viewpoints
  - All stakeholder groups represented
  - Non-politicized
  - Opportunity for continuing, iterative interactions
  - Ability to compromise when necessary to move forward

The Risk of Stasis Mandates New Approaches

- Drafting and issuing Guidance Documents has been laborious and time-consuming for FDA
- Workshops and advisory committees appear to have often been an inefficient way to obtain the expert input on which FDA can then base new Guidances
- Delay, uncertainty…no *New Drugs* despite more *Bad Bugs*
- New models needed to ensure timely progress on issues of regulatory science and to avoid stasis
  - Brookings Institute
  - FNIH
  - Transparent interactions with other regulators
  - Other?

NI Trials in Antibacterial Drug Development

- The bread and butter of antibacterial drug development
  - Won't change…shouldn't except in specific situations
- Hypotheses should be informed in a "Bayesian" manner by robust, highly predictive preclinical data
- But, we shouldn't pick and choose *which* preclinical data sets to accept based on purely pragmatic considerations
  - Example: prior antibiotic therapy, which could affect baseline bacterial burden and therefore confound assessment of treatment effect
- If we want to use NI trial design, we must conform to the requisite principles, and/or provide an opportunity for data accrual during future registrational studies
  - Example: major abscess in ABSSSI
  - We can't have our cake and eat it too

Most Pressing Unmet Needs/ Questions for Which Guidance is Needed

- Approval pathways for (currently) uncommon, emerging MDR pathogens
- Hospital-acquired Bacterial Pneumonia/ Ventilator-Associated Pneumonia
- Evidence-based Guidance for allowable use (or not) of prior antibiotics
- Integration of rapid diagnostics into clinical trial design to enrich study populations and avoid dilution in NI trials

Potential Future Activities to Support Antibacterial Drug Development

- Rapid issuance of new/ revised Guidances
  - CABP
  - ABSSSI
  - cIAI
  - MDR pathogens
- External review of Guidances that address Pressing Unmet Clinical Needs
  - MDR pathogen development pathways
  - HABP/VABP development
  - Approach to prior antibacterial therapy in NI trials

Thank you