Can we reduce complexity and safety data collection to improve the quality of the data and inferences we make?

November 12, 2013

Charles Knirsch MD, MPH
Frightening Patient Vignettes: serial surgery for resistant organisms
NIH Outbreak and Hospital Deaths
John Rex: The pipeline is “very very thin” “drought”
Accountable entity (s) to address this public health crisis?

www.ctti-clinicaltrials.org
What can we do today?

Pre-Antibiotic Era: Explosive Spread of NDM-1: multi-species and pan-resistant plasmid

Red stars indicate origin in India, Pakistan, or Bangladesh; green stars indicate origin in the Balkans or Middle East (adapted from Nordmann, *EID* 2011). Recent reports describe additional cases in Turkey, Croatia, Spain, Czech Republic, Ireland, Belgium, and Algeria.
We need many (? > 50) small entities/companies at IND stage and 5 Manufacturers at P2

We are interlinked
A comprehensive regulatory framework to address the unmet need for new antibacterial treatments

John H Rex, Barry I Eisenstein, Jeff Alder, Mark Goldberger, Robert Meyer, Aaron Dane, Ian Friedland, Charles Knirsch, Wendy R Sanhai, John Tomayko, Cindy Lancaster, Jennifer Jackson

A tiered approach: Aligning feasibility and the quantity of clinical data with the unmet medical need

The need for a tiered approach is real – there are real products at each tier that need a path forward

Determination of the appropriate tier should be based on context:
- Feasibility
- Unmet medical need
- Strength of the preclinical data
- By utilizing the totality of data, existing regulatory requirements can be met at each tier

Increased degree of and decreased ability to test unmet medical need

Eisenstein - Tier B-C overview, EMA workshop 25-26 Oct 2012
Expedited Pathway to Address Projected Resistance Patterns: Efficacy in P2, Safety Continuous

- Staged approval
  - Conditional approval with PK/PD, limited clinical data, and use and promotion
  - Additional data in a post-approval commitment depending on epidemiology could lead to enhanced label

- Advantage
  - Brings much needed medicine to patients in a timely manner
  - Incentive to Discovery, Early Development
  - Benefit-Risk Evolves

Alemayehu D, Quinn J, Cook J, Kunkel M, Knirsch C et al CID 2012
Simple Substantive Steps Now
Knirsch CTTI 2012 Workshop Summary

• Increased Funding for basic bacterial laboratory work

• Infrastructure and network for clinical trial excellence particularly learn phase development at leading academic medical centers

• Enhance GAIN or other mechanisms (Foundations, NGO’s) for discovery and early development incentives

• Continue and commit to the progressive Regulatory stance we have heard at this meeting and comments in other fora eg PCAST

• Not relaxed standards but efficient development to bring much needed medicines to the clinic faster with robust pharmaco-vigilance and stewardship
  • Use of existing expedited Regulatory Pathways (Sub-part H and PV Guidance)
  • Progressive value models eg LSE report from the Swedish Presidency

Summary Knirsch April CTTI 2013 Workshop: Protocol Level Simple Substantive Steps Now

- QbD Approach to write the Tier B Phase 3 protocol and get agreement that the primary endpoint, key secondary endpoints and safety as designed are the “playing field for debate”

- Agree on Transformative QbD Safety Collection: to benefit patients, investigators and sponsors

- Consider seriously the Tier C program and agree that sub-part H applies

- Agree on FDA AC Conduct Rules with Professional Moderators
THANK YOU