Regulatory Standards and Guidances
DAIP/OAP/CDER/FDA

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CTTI Statistical Issues Think Tank II
19 November 2014

Statutory Standards

- Approved drugs must meet the statutory standards for effectiveness of the FD&C Act
  - Section 505(d)(1): substantial evidence as "evidence consisting of adequate and well-controlled investigations, including clinical investigations,…"
  - 21 CFR 314.126(b): Adequate and well-controlled studies
    - Placebo-control; dose-comparison control; no treatment control; active-treatment control; historical (external) control
  - Section 115(a) of the Modernization Act: allowed for data from one adequate and well controlled clinical investigation and confirmatory evidence to establish effectiveness

Statutory Standards

- There is flexibility within the statutory standards
  - Guidance for Industry, *Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products*
    - Evidence of effectiveness from a single study
  - 21 CFR 312.80, subpart E: "Drugs Intended to Treat Life-Threatening and Severely-Debilitating Illnesses"
    - "the recognition that physicians and patients are generally willing to accept greater risks or side effects from drugs that treat life-threatening and severely-debilitating illnesses, than they would accept from drugs that treat less serious illnesses"
    - "the recognition that the benefits of the drug need to be evaluated in light of the severity of the disease being treated"

http://www.fda.gov/downloads/Drugs/.../Guidances/ucm078749.pdf

Guidance for Industry

GUIDANCE	STATUS	ISSUE DATE
Neglected Tropical Diseases	Final	July 2014
Uncomplicated Gonorrhea	Draft – review of docket comments	June 2014
Hospital-Acquired and Ventilator-Associated Bacterial Pneumonia	Draft – review of docket comments	May 2014
Community-Acquired Bacterial Pneumonia	Draft – review of docket comments	January 2014
Pulmonary Tuberculosis	Draft – review of docket comments	November 2013
Acute Bacterial Skin and Skin Structure	Final	October 2013
Antibacterial Drugs for Unmet Medical Need	Draft – conversion to final	July 2013
Complicated Intra-Abdominal Infection	Draft – review of docket comments	September 2012
Acute Bacterial Otitis Media	Final	October 2012
Acute Bacterial Sinusitis	Final	October 2012
Acute Bacterial Exacerbation of Chronic Bronchitis in Patients with COPD	Final	September 2012
Complicated Urinary Tract Infection	Draft – review of docket comments	February 2012

Guidance in Antibacterial Drugs General Considerations

- Non-Inferiority trial design
  - Appendix: justification for NI margin
  - Indications for which a margin cannot be identified
    - "milder" infections ABS, ABOM, ABECB-COPD
- Clarity in the analysis populations
  - "micro-ITT" population
- Examples of sample size estimates

Guidance in Antibacterial Drugs General Considerations

- Improving trial feasibility
  - Allowing for some use of prior effective antibacterials
  - Primary Analysis Populations: ITT population acceptable for some indications such as CABP
  - Noninferiority margin: for some indications, e.g. CABP allowing for a 12.5% NI margin
  - Allowed use of comparator drug without a labeled indication for HABP/VABP, if used as standard of care
  - Allowed for inclusion of intubated HABP patients in VABP trials

Guidance in Antibacterial Drugs General Considerations

- Improving trial feasibility
  - An adequate data package could include one trial in each of the two different indications, for example
    - cUTI plus cIAI
    - CABP plus ABSSSI
    - cIAI and HABP/VABP

Regulatory Standards and Guidances: Summary

- Flexibility within the statutory standards
  - Treatment of serious and life-threatening infections
- Updated guidances
  - maintain scientific rigor to establish safety and effectiveness
  - Account for trial feasibility issues