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”

# Guidance for Industry

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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