Pre-marketing Assessment of Drug Safety in CAP

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Disclaimer

- The opinions expressed here are those of the speaker and do not necessarily reflect the policy of the Food and Drug Administration

- Potential Financial Conflicts of Interest: None

Safety: Requirement for Approval
[Food, Drug, and Cosmetic Act (Sec. 505)]

- "include all tests reasonably applicable to show…drug is safe…under…proposed labeling"

- "results of such tests show…drug is safe under such conditions"

Safety assessment during drug development

- Safety data is continuously evaluated at all stages of drug development
- Non-clinical identify target organs of toxicity/determine safety margins for clinical trials
- Before progressing to phase 3 trials, non-clinical data and Phase 1-2 safety data are reviewed
- Predict possible AE in phase 3 trials
- Allow design safety assessment for phase 3 trials
- Rarely identify serious AEs due to limited exposure (a few hundred patients)

Goals of NDA Safety Review

- To critically examine the sponsor's contention that their drug is safe for its intended use (CAP)
  - To assess the adequacy of the testing for safety
  - To determine the significance of the adverse events and their impact on the approvability of the drug (risk/benefit analysis)

Goals of NDA Safety Review (2)

- To describe the safety issues that should be included in product labeling should the drug be approved
- To decide whether additional safety studies and /or risk-management plan is needed

What are the data sources?

- Randomized controlled trials
- Open label trials
- Postmarketing experience
- Medical literature
- Safety profile of other drugs in the class (inclusive of other indications)

Approach to review of NDA safety database

- Characterize:
  - Population (age, gender, underlying medical conditions, etc)
  - Dose
  - Magnitude of exposure
- Identify adverse events (AEs) and assess drug-event relationship
- Identify risk factors for those AEs
- For common AEs, it is helpful to look at the rates in comparator arm

Exposure

- What do we want to know about exposure?
  - Is there adequate exposure at the intended dose range?
  - If labeling will recommend a dose range, how much exposure was observed at the high end of the dose range?
  - Were any special population groups included into the study/analysis (renally/hepatically impaired)?
  - Pharmacometric analysis that links exposure with adverse events

Which events are most concerning?

- Deaths
- Serious adverse events
- Discontinuations due to adverse events

Other important parts of the safety review

- Common adverse events
- Laboratory data
- Vital signs data
- ECG data
- Safety in pregnant women and special populations (elderly, renal impairment, etc)

Specific safety issues we usually address with antibiotics

- Liver toxicity
- Renal toxicity
- Allergy-related toxicities
- QT studies/cardiac repolarization
- Not unique to CAP

Inherent limitations to what can be learned from NDA safety database

- Limited exposure (a few thousand patients)
  - Rare serious AEs are not usually captured (in order of 1/10000-1/100000)
  - Observing no serious AEs should not be interpreted as “no risk”
- Studies are not designed to address specific safety questions:
  - Powered for efficacy with no pre-specified safety end-points
- Adverse events erroneously attributed to the underlying disease
  - Particularly an issue for sick patients in intensive care settings

Approval/Non-approval

- Risk-benefit assessment
- We have an advantage of using Advisory Committee input on any concerns about risk/benefit assessment

Application of the results of pre-marketing safety evaluation

- FDA-approved professional labeling
  - includes patient education materials
- A surveillance plan to assess known serious risks and to identify unexpected serious risks

Post-approval stage

- Assessment of safety does not end after the NDA gets approved
- Continuing monitoring for AEs (PSUR, annual reports, AERS/Medwatch)
- Labeling changes/updates
  - Adverse reactions, postmarketing AE reports
  - Warnings (Boxed)
  - Medication Guide