Pre-marketing Assessment of Drug Safety in CAP

*Tatiana Oussova, MD, MPH*

*Medical Officer, Division of Anti-Infective and Ophthalmology Drug Products*

Center for Drug Evaluation and Research, FDA

January 17-18th, 2008
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