

Pre-marketing Assessment of Drug Safety

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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”



Goals of NDA Safety Review

- To critically examine the sponsor's contention that their drug is safe for its intended use
 - To assess the adequacy of the testing for safety
 - To identify any safety issues that impact the approvability of the drug
 - To describe the safety issues that should be included in product labeling should the drug be approved



Recent approaches to standardizing the safety review

- “Reviewer Guidance: Conducting a clinical safety review of a new product application and preparing a report on the review”
 - Finalized February 2005

<http://www.fda.gov/cder/guidance/3580fn1.pdf>

- Clinical reviewer’s template (based in part on above guidance)
 - Evolving since 2001; formal version available since July 2004



Approach to review of NDA safety

- What are the data resources?
 - Randomized controlled trials
 - Open label trials
 - Postmarketing experience
 - Medical literature
 - Safety profile of other drugs in the class



Approach to review of NDA safety (2)

- Characterize exposure database
 - How many? At what dose? Who?
- Identify drug-related adverse events (AEs)
 - Estimate risk (or rate) of those AEs
 - Identify risk factors for those AEs
- Assess the adequacy of the search for AEs



Exposure

- What does the ICH recommend?
 - If chronically administered
 - 300-600 people for 6 months
 - 100 people for one year
 - 1500 people total
- 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?



Which events are we most interested in?

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



Other important parts of the safety review

- Common adverse events
- Laboratory data
- Vital signs data
- ECG data
- Phase 1 safety
- Exposure in pregnant women
- Overdose experience
- Assessment for withdrawal symptoms



What do you get from an NDA safety review?

Probably

Common adverse event profile

Common drug-related changes in labs, VS, ECGs

Evidence of dose-dependency for common AEs if fixed dose studies were conducted

Possibly

Evidence of drug-drug, drug-disease, and drug-demographic interactions

Evidence of causality for serious rare AE (e.g., hepatic failure, rhabdomyolysis)

Unlikely

Evidence of causality for serious AEs that occur commonly in the background (e.g., acute MI, appendicitis, mortality in an elderly population)



Impediments to a full understanding of a drug's safety profile at the NDA stage

- Limited exposure

- Observing no serious AEs should not be interpreted as “no risk”
- Can cap the risk of a finding of no cases of a rare event in an NDA database using the “Rule of 3”
 - Estimate the upper bound of 95% CI when no cases occur in sample of N; Upper CL $\sim 3/N$
 - For example, in a population of 3000, the “Rule of 3” estimates the upper 95% CL as $3/3000$ or $1/1000$
 - If an AE occurs less frequently than $1/1000$, it likely will not be detected in that development program



Impediments to a full understanding of a drug's safety profile at the NDA stage (2)

- Suboptimal case description/source data availability
 - Narrative summaries for AEs often lack important details
 - Laboratory data
 - Radiology, biopsy, and autopsy reports
 - Outcomes
- Adverse events may not be recorded as such because they are presumed to be attributable to the underlying disease
 - Particularly an issue for sick patients in intensive care settings



Impediments to a full understanding of a drug's safety profile at the NDA stage (3)

- Coding of adverse events may influence the understanding of a serious AE
 - Verbatim term “facial edema” coded to the preferred term “edema”
 - Verbatim term “fell and fractured wrist” coded to the preferred term “accidental injury”
- Syndromes require creation of a case definition to aid identification of potential cases



– Serotonin syndrome, parkinsonism

Impediments to a full understanding of a drug's safety profile at the NDA stage (4)

- Safety analyses are mainly post hoc based on data from studies designed to assess efficacy
 - Studies are rarely done in the pre-market period to address a specific safety issue that has been identified during development
 - Exceptions: bupropion, omipatrilat



Areas for improvement

- Better source documentation (medical records, etc) by sponsors for deaths, serious AEs, discontinuations due to AEs
- Consider adding reviewer positions within OND reviewing divisions specifically for premarket safety
 - Especially for priority drugs and drugs with large safety databases
 - One model: more safety teams at division or office level



Considerations in benefit and risk assessment

- Evidence of efficacy
 - Meets pre-specified endpoints
- Safety profile
 - Seriousness
 - Evidence for drug-relatedness
 - Preventability
- Indication
 - Life threatening vs. symptomatic illness
 - Are there other drugs available for the indication?



Can a safety reviewer assess the benefit and risk balance of a new drug product?

- Understanding the benefit and risk requires having reviewed both of them
- By definition, a safety reviewer only considers the risks
- In our model, the clinical team leader considers the findings of the efficacy and safety reviews and makes a recommendation about approvability, which is further discussed with the primary reviewers, the Division Director and the Office Director



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Example of narrative problems – discontinuation due to adverse event

Preferred Term	Start Date	Stop Date	Severity	Relationship to Study Drug
Vascular disorder	06/23/95	06/26/95	Moderate	Probable (Investigator's judgment)

- **Narrative accompanying the above line listing for Patient X**
"Patient X, a 43 year old female diagnosed with indication Z, received open-label study drug for 3 days from June 21, 1995 to June 23, 1995. The patient experienced a moderate vascular disorder which was considered probably related to study drug and led to discontinuation of the patient from the study."

