

# FDA Post-Approval Risk Assessment

*Based on work at FDA's Office of Drug Safety*

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# Outline

- Post-approval safety work ups
  - Sources of safety signals within CDER
  - Approaches based on
    - Cases of adverse events
    - Drug utilization
    - Defined populations and exposures
- Opportunities for improvement
  - Short, intermediate, and long-term

# Post-Approval Safety Work Up: Sources of Safety Signals

- Pre- and post-approval
  - Controlled safety data (e.g. toxicology, clinical pharmacology)
  - Review of serious, unexpected adverse events
- New clinical studies by industry, NIH, or others
- Published literature of cases or population studies
- Periodic reviews of aggregate safety experience
- International regulatory bodies
- Scheduled reviews triggered by BPCA
- Media, Congressional interest

# Post-Approval Safety Work Up: Case-Based Methods

- Case series to examine
  - Strength of drug/AE relationship
  - Risk factors
  - Accumulation of events over time
- Comparisons within context of drug exposures
  - To background rate in general or diseased population
  - To other products in therapeutic class or used in the same disease state
  - Considering time on market and typical duration of patient exposures

# Post-Approval Safety Work Up: Approaches Using Drug Use Data

- Monitor identified 'high risk' conditions
  - Refills where none are allowed (e.g. isotretinoin)
  - Concomitant prescribing with interacting drugs
  - 1<sup>st</sup> line use where risks warrant 2<sup>nd</sup> line use
- Study medication adherence in order to model risks over time
- Examine where drug use occurs (inpatient, outpatient, LTC, etc) to target population studies
- Prescription sequence symmetry analysis: not done at FDA, looks at drugs used in treatment of AEs as a surrogate for AE occurrence

# Post-Approval Safety Work Up: Population-Based

- For common outcomes (MI, psychiatric comorbidities)
  - Re-analysis of RCT data already submitted to FDA
  - Request Phase 4 studies of companies
    - RCT or observational
  - Occasionally, FDA-led studies
    - Laboratory studies of chemistry, toxicology
    - Population databases, in-house or contracted

# Post-Approval Safety Work Up: Population-Based, FDA-Led

- Validate/quantify safety signals or explore them in different populations
- Historically, ODS-initiated
  - Small network of 3-5 cooperative grantees until 2005
  - In-depth studies: 1-2 ongoing annually
  - Feasibility studies: 5 – 7 annually to assess numbers of exposures, outcomes, power
  - Process-related SOPs developed

# Post-Approval Safety Work Up: Population-Based, FDA-Led

- In-house access to UK General Practice Research Database (began Fall 2004)
- Multiple task order contracts to 4 sites (began Fall 2005)
  - Staff model HMO for large, diverse state with linkages to vital records and cancer registries
  - 1 consortium of 2 state Medicaid populations linked to vital records
  - 2 large health care networks with diversity in geography and drug use
  - Collaborations across all 4 sites possible

# Post-Approval Safety Work Up: Population-Based, FDA-Led

- CMS Part D benefit (began Summer 2005)
  - Pilot exploration using Part B-reimbursed drugs
  - Collaboration with CMS, AHRQ ongoing

# Post-Approval Safety Work Up: Population-Based, FDA-Led

## Challenges

- Observational data limitations
- Lengthy, complicated, technically difficult to conduct studies
  - 2-3 years for cooperative agreement studies
  - 16 months for first analysis of complex GPRD
- IT and analysis capacity of FDA: hardware, programmers
- Limited availability of internal analytic staff

# Opportunities for Improvement: Short Term

## *Strengthen existing capabilities*

- Develop systematic approach to choice and design of population studies, intramural and extramural by FDA and industry
- Further refine standards for population-based research
  - Prospective definition of protocols, endpoints, QC, and QA
  - Independent review of data
- Expand review and QC of increasing volume of post-marketing case reports
- Expand dedicated staff for risk management review and evaluation
- Improve completion of Phase 4 safety studies

Will require resources to hire additional staff, expand IT infrastructure

# Opportunities for Improvement: Intermediate Term

## *Expand risk assessment capabilities*

- Explore alternatives to case reports
  - Active surveillance: selected medical settings, drug-related diseases, drug products
  - “Automatic” reporting in electronic medical care environment
- Assess predictive value and best approaches among alternative surveillance systems

## Opportunities for Improvement: Intermediate Term

### *Expand risk and benefit comparisons*

- Explore processes and methods for more explicit, systematized, and quantitative risk/benefit decision-making
- Seek mechanisms and funding for systematic studies of relative safety/effectiveness of important classes of drugs
  - NSAIDs, antidepressants, etc.
  - NIH or other Federally-directed efforts

# Opportunities for Improvement: Long Term

*Advance the science of drug safety to predict safety problems*

- Subgroups or individuals at high risk of drug AEs
  - Polymorphisms and TdP, beta 2 agonist receptor sensitivity
- Subgroups or individuals most likely to benefit
  - Severe IBS and alosetron
- Establish baseline risks of AEs in highly prevalent disease states (DM, COPD, depression)

# Summary of Opportunities for Improvement

## Short-term

- Strengthen existing capabilities with additional resources and methods development

## Intermediate-term

- Expand available data resources for risk assessment
- Expand processes, methods of risk/benefit comparison

## Long-term

- Advance the science of safety to identify and predict problems before they occur