A New Paradigm for Drug Safety

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“Drug Safety”: Two Meanings

- First: Positive benefit/risk assessment for an individual drug when used as directed for specific indications
  - This is drug safety as reflected in a drug package insert
- Second: Population-based adverse outcomes from the use of medicine
  - For a particular drug
  - For all drugs

“Drug Safety”

- FDA regulation has historically focused on the first definition
- Increasingly, since early 1990’s, responding to second definition as well
  - Concern about failure to monitor (clozapine, thalidomide etc)
  - Concern about safety consequences of off-label use
  - Concern about abuse potential
  - Concern about medication mixups
  - Concern about uninformed patients (Medguides)

Understanding Drug Safety

- Urgent need to understand and quantify overall adverse (and beneficial) consequences of drug use by patients and consumers, as well as understanding harm from abuse
- Need to sort out inherent drug risks (i.e, side effects) from preventable harm:
  - From informational/conceptual errors on the part of prescribers and consumers
  - From process errors
  - From drug quality problems

New Paradigm for Drug Safety

- Explicit focus on real-world outcomes of drug use
- Apply best scientific expertise in all phases of regulation, including communication science
- Use risk-based approach to prioritize efforts
- Much greater emphasis on postmarket phase
- Safe Use Initiative: doing in partnerships what can’t be accomplished through regulatory efforts

CDER's Core Businesses

- Oversight of
  - Drug Development
  - Postmarketing Safety, Compliance and Promotion
  - Drug Quality
- Everything someone in CDER does is linked to one of these activities
- Majority of activities relate to drug safety

The Safety First Initiative

WHAT IS SAFETY FIRST?

- Safety First is a major CDER initiative to ensure safety throughout the drug product lifecycle by:
  - Integrating drug safety activities across the center
  - Strengthening CDER safety-related policies and procedures
- Safety First imposes new requirements on OND, OSE, OC, and OGD
  - Cross-office collaboration for all significant new safety issues
  - Changes in internal practices
  - New MAPPs; new technology

Drug Development Oversight

Changes Impacting on Safety

New Regulatory Authority

- FDAAA Section 901 gave FDA new authorities to:
  - Require postmarketing studies and clinical trials
  - Require sponsors to make safety related labeling changes
  - Require sponsors to develop and comply with risk evaluation and mitigation strategies (REMS)
- Many of these authorities impact the new drug review process

REMS Statistics

- 63 new REMS approved since March 25, 2009
- 47 of 63 Medication Guide only REMS
- 10 REMS with stand alone communication plans
- 6 new REMS with elements to assure safe use

REMS Are Not New

- 16 drugs were approved with restrictive risk management programs before FDAAA (e.g., isotretinoin, thalidomide, mifepristone)
- REMS built on previous experience with risk management programs
- FDAAA clarified FDA's authority to require risk management programs that are enforceable

Medication Guides as REMS Elements

- Medication Guide (if meets 21 CFR 208)
- 47 of 63 REMS were Medication Guide only REMS
- Medication Guides were previously considered only part of labeling
- Will be part of REMS if necessary for safe use of the drug
- If previously approved Medication Guide needs to be changed to reflect a serious risk based on new safety information, revised Medication Guide will become part of a REMS

Communication Plans

- Communication plan
  - 10 new REMS included a stand alone communication plan
  - Plan may include: letters to healthcare providers, disseminating info about the REMS to encourage implementation; disseminating information through professional societies about any serious risks of the drug and any protocol to assure safe use
  - Generics not required to have communication plans

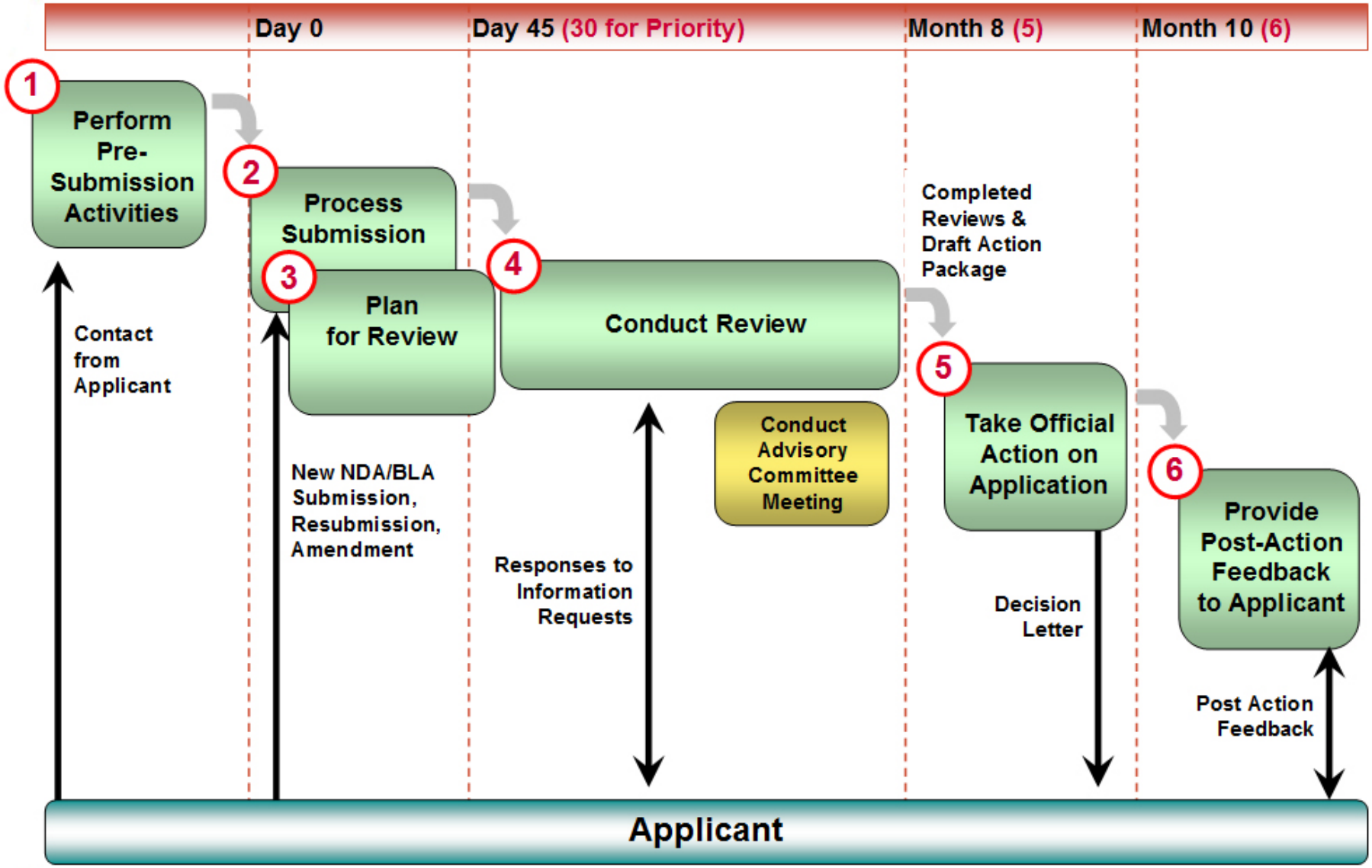
Elements to Assure Safe Use

- 6 REMS had elements to assure safe use
- Elements to assure safe use may include:
  - Healthcare providers who prescribe the drug have particular training or experience or special certifications
  - Pharmacies, practitioners, or healthcare settings that dispense the drug are specially certified
  - The drug may be dispensed only in certain healthcare settings
  - The drug may be dispensed to patients with evidence of safe-use conditions
  - Each patient must be subject to monitoring
  - Patients must be enrolled in a registry

21st CENTURY REVIEW: Managing an Increasingly Complex Review Process

- Targets:
  - 2008 pilot program 1 application per OND division (17)
  - 2009 all NMEs and new BLAs (~30)
  - 2010 all NMEs and new BLAs plus certain efficacy supplements (>130)
- Incorporate 21st Century Review in CDER-wide training
- Assessment and Audit
- Continue refinement of tools/processes

21st Century Schedule Allocates 4-6.5 Months to Conduct Review



PDUFA IV Goals Will Expand Number of Applications for 21st C Review Process

Unit	Sample period: 7/1/2008- 6/30/2009
Drugs/Biologic INDs with activity	5,728
IND Special Protocol Assessments	342
IND/NDA Meeting Requests	1,977
Original NDA/NME and BLAs	**40**
Original NDA/BLAs	**138**
Efficacy Supplements	**135**
Manufacturing Supplements	1,887
NDA/BLA Labeling Supplements	1,167
NDA/BLA Annual Reports	2,669

PDUFA IV Commitment: 21st C Review Applies to All NMEs & some ES in FY 2010 (~130)

PDUFA IV Commitment: 21st C Review Expands to All Original NDA/BLAs in FY 2011

PDUFA IV Commitment: 21st C Review Expands to All Efficacy Supplements in FY 2012

Basic Goals of New Drug Review

- We review information contained in the NDA to determine:
  - Whether the drug is safe and effective in its proposed use(s), and whether the benefits of the drug outweigh the risks.
  - Whether the drug's proposed labeling (package insert) is appropriate, and what it should contain.
  - Whether the methods used in manufacturing the drug and the controls used to maintain the drug's quality are adequate to preserve the drug's identity, strength, quality, and purity.

NDA Review Task is Further Defined by Some Additional Parameters

- NDA/BLAs submitted in most recent year had an average size of 10 gigabytes
  - FDA has 60 days to determine whether the application is complete enough to file and be reviewed.
- Once the application is filed, the review schedule begins
  - FDA expects to review and act on at least 90 percent of NDAs for standard* drugs no later than 10 months after the applications are filed.
  - The review goal is 6 months for priority* drugs and biologics.

* PDUFA (Prescription Drug User Fee Act) workload year 7/1/2007- 6/30/2008

Applications for drugs similar to those already marketed are designated as "standard," while "priority" applications represent drugs offering significant advances over existing treatments.

Standards for Clinical Safety Review

- Deaths
  - Overall mortality
  - Cause specific
  - Expected vs unexpected
  - Dose response
  - Time to death analysis
  - Subgroup analysis
  - Interaction analysis
- SAEs
  - Overall rates
  - Rates by event
  - Dose response
  - By duration of exposure
  - By person-time exposure as denominator
  - Assessment according to alternative explanation
  - Assessment of interaction by subgroup
- Dropouts and other SAEs
  - Overall rates
  - Profile of dropouts (by reason)
  - AEs associated with Dropouts
  - Exposure response
  - Time dependency
- Other significant AEs as defined by ICH
  - Marked lab abnormalities
  - Any AE leading to dropout or intervention
  - Potentially important abnormalities not meeting above definition
- Construct of algorithms of combo's of clinical findings
  - Identify possible combinations of clinical findings that may be a marker for a particular toxicity
- Identify possible consequences of a safety signal from any source
- Common AEs
  - Incidence for subsets -controlled studies
  - LLT's should be compared to mapped PT's
  - Assess for causality
  - Comparison of severity between treatment arms
- Dose dependency for AEs
  - Titration studies
- Time to onset for AEs
  - Particularly for events that occur commonly
- AE incidence by interaction
  - demographic
    - race, gender, age
  - Drug-drug interaction
  - Underlying medical problems such as DM or renal disease
  - Dose response
    - body weight-adjustted dose
    - cumulative dose
    - Body surface area-adjusted dose
    - dosing schedule
  - Exposure adjusted event rates "person-time approach"
    - When hazard rate is constant over time
    - Break observation period into intervals
  - Relative risks and attributable risks for subgroup differences
  - Life table/ time-to-event analyses/ cumulative incidence anlayses
  - Hazard rates – risk over time estimation

Standards for Clinical Safety Review (Cont. 2)

- Less common AEs
  - Identify and group by body system for rates
- Laboratories
  - Overview of testing methodology
  - Analysis of measures of central tendency
  - Analysis of outliers or shifts to abnormal
  - Marked outliters and dropouts due to lab abn
  - Dose dependency
  - Time dependency
  - Demographic interactions
  - Drug-drug interactions
  - Underlying medical condition interactions
  - Special section on Liver laboratory abn
  - Shift tables
  - Scatter plots
  - Box plots
  - Cumulative distribution displays
  - Tables of deviation in >1 parameter
- Vital signs
  - Overview of testing
  - Analysis of measures of central tendency
  - Analysis of outliers or shifts to abnormal
  - Marked outliters and dropouts due to lab abn
- ECG's
  - Describe baseline and number of on-study ECGs
  - Analysis of measures of central tendency
  - Analysis of outliers or shifts to abnormal
  - Marked outliters and dropouts due to lab abn
- Immunogenicity
  - Summarize and assess available data
- Carcinogenicity
  - Summarize and assess
- Special Safety Studies
  - Summarize any such studies
  - Similar to other drugs in pharmacological class?
  - Studies on cumulative irritancy, sensitizing potential
  - Photosensitivity, photoallergenicity
  - Special Thorough QT study
    - To be done on all NMEs
  - Studies to demonstrate a safety advantage over existing therapeutics
- Withdrawal phenomenon or Abuse potential
  - Reivew/summary of relevant studies
  - Scheduling recommendations
- Human Repro and Pregnancy data
- Assessment of Effect on Growth
- Overdose Experience
- Post-marketing experience
- Causality determination
- Adequacy of patient exposure and Safety assessments
  - Refer to ICH
  - Adequate numbers of various demogrpahic subsets
  - Doses and durations of exposrue were adequate to assess safety for intended use
  - Were study designs adequate to answer critical questions
  - Were potential class effects evaluated
  - Did patient exclusions from studies limit relevance of satey assessments
- Review of secondary clinical data sources
  - IND data
  - Post-marketing data
    - Literature reports

Standards for Clinical Safety Review (Cont. 3)

- Additional Clinical Issues
  - Level of confidence for dose/regimen
  - Dose-toxicity and dose response relationships
  - Dose modification for special populations
- General assessment of adequacy of Special Animal and/or In Vitro testing
  - Pre-clinical animal models
  - QT studies
- Adequacy of routine clinical testing
  - Labs, vital signs, ECGs, assessment of certain events
- Adequacy of metabolic, clearance, and interaction workup
  - P450 and p-glycoprotien pathways
  - Other drug-drug interaction studies
  - Specify potential safety consequences
- Adequacy of evaluation for potentially problematic AEs that might be expected for a new drug
  - Assess adequacy and note pertinant negative findings (absences of findings)
- Assessment of Quality and completeness of data
  - Generall overall assessment of the quality an dcompleteness of data with a description of the basis for this assessment
- Additional submissions, including safety update
  - Particularly those submission whose data were not incorporated into the rest of the review
- Summary assessment of important identified adverse events
  - Not important limitations of data and make conclusions
- General Methodology
  - Discussion of general methodological issues
- Pooled data vs. individual study data
- Causality determination
- Exploration of predictive factors
  - Plasma levels, duration of treatment, concom meds, concom illnesses, age, sex, race
- Special populations
- Pediatrics
- AC meeting
- Literature review
- Post-marketing Risk management plan
- Other relevant materials
  - Result of consultations with DDMAC, ODS reviews, actual use and labeling comprehension studies, marketing studies
- Overall assessment
  - Conclusions
  - Recommendation (regulatory)
  - Recommendations on post-marketing actions
- Risk management activity
  - Include all such recommended activity with rationale
- Required phase 4 commitments
  - Include the agreed upon studies, the timeline for submission, and basis for each phase 4 commitment
- Labeling review

When Reviewing Premarket Data We Are Also Thinking About Postmarket

- Review considerations pre-FDAAA now expanded by new requirements of Title IX
- Better determination of post-market safety, and design and impact of REMS, requires better ability to link:
  - Data related to B-R of drug in clinical development with data related to B-R of drug in clinical practice/healthcare delivery
  - However, Clinical Research and Clinical Healthcare have some very different data needs.

Clinical Research
Focus on Patient Groups
Build datasets
Batch processes
Blinding / Randomization
Protocol context
Structured assessment
Clinical data only

Clinical Healthcare
Focus on Individuals
Continuity of care
Real-time processes
Open / Non-random
Care context
Personal assessment
Financial, billing info

FDAAA Tile IX Has Added Requirements Within Existing Review Timeframes

Important Examples:

- Section 505 (o)(3) Postmarket Studies may be required at the time of approval
  - Requirement must be based on scientific data, in order to assess know serious risk, signals of serious risk or identify unexpected serious risk
  - Level of study requirement must be based on FDA findings related to sufficiency of potential source/method
- Section 505-1 Risk Evaluation and Mitigation Strategies (REMS) may be determined necessary to ensure benefits outweigh risks pre-approval, inform sponsor and require sponsor to submit a REMS
  - REMS elements: MedGuides and PPI, Communication Plan, Elements To Assure Safe Use, Implementation System, Timeline for Assessments
  - Determination of most appropriate and effective elements => more analysis during NDA review

How to Accomplish Thorough New Drug Review in Timely Manner?

- CDER still missing user fee goals—hope that new staff hired and new procedures will improve performance
- Urgent need to improve review efficiency
- Electronic review still not a reality
- Need to think through FDAAA requirements still adding time to review
- Continue to deal with new science—pharmacogenomics; trial designs

CDER COMPUTATIONAL SCIENCE CENTER (CSC)

- Outreach - CSC Website (internal) launched July 17th
- Skills - Hiring plan for:
  - Data managers, Project management support, Data and technical architects, Medical/Statistical programmers
- Resources
  - Contracts are underway to support:
    - Data standards training (CDISC)
    - Legacy data transformation/harmonization
    - Analytical tools development and pilot implementation in selected review areas
  - Actively collaborating with NCI/CaBIG (Cancer Bioinfromatics Grid) on clinical study data warehouse and data standards efforts

INFORMATION TECHNOLOGY

- Replacement of “COMIS”
- DARRTS v3.0 Roll Out in July 2009
  - The scope of DARRTS 3.0 Release is most significant FDA IT effort in over 20 years
    - 17 Systems/subsystems consolidated into DARRTS
    - Over 23 M records migrated with only minor issues
    - Over a million lines of code

BIORESEARCH MONITORING/ HUMAN SUBJECT PROTECTION

- Risk-based site selection model
  - Developing a tool to support prioritization of clinical trial sites for inspection

- FDA-European Medicines Agency GCP initiative
  - Leveraging resources due the increased number of foreign sites
  - Periodic exchanges on good clinical practice information
  - Streamlining sharing of GCP inspection planning information
  - Communicating more effectively and in a more timely manner on inspection outcomes

CDER BIOMARKER QUALIFICATION PROGRAM: Improving the Science of Safety

- Internal document describing the goals and process for the Biomarker Qualification Program developed and discussed with representatives of the CDER SMT
- 7 biomarker submissions under review/evaluation
- Biomarker Qualification management team established
- Biomarker Qualification review teams established (multidisciplinary representation)
- Working group developing a guidance detailing the administrative process for qualification (submission/review/evaluation)
- Working group developing a guidance on use of histopathology in biomarker qualification
- Plans for training potential biomarker qualification review team members underway

Drug Quality Initiatives Impacting on Safety

Drug Quality Initiatives

- Electronic Drug Registration and Listing
  - eDRLS became a reality in June
  - Thanks to registrants!
  - A reliable database will help us prevent unsafe/unapproved drugs from being marketed
- Quality by Design
  - Building quality into the product from the start
  - Pilot programs in new drug quality, generics, and biological therapeutics

Globalization of Drug Supply and Drug Safety

- Increase in numbers of investigators doing out of US inspections
- Increased collaboration with other regulatory authorities
- A central message for pharmaceuticals: manufacturers must ensure quality of supply chain

Generic Drug Review

- Expect to approve about 600 generics this year
- Expect to receive about 800 applications
- This situation has be ongoing for a number of years
- Safety: we continue to investigate concerns that, for a small number of patients, innovator-generic switches or generic-generic switches result in problems. Goal: studies

Oversight of Postmarket Safety, Compliance and Promotion

UNAPPROVED DRUGS INITIATIVE

- Compliance Policy Guide, Issued June 2006
- Priorities include:
  - safety, effectiveness
  - fraudulent drugs
  - drugs directly competing with an approved drug
  - drugs with formulation changes intended to avoid enforcement
  - drugs otherwise violative
- Over 200 firms and over 500 products affected
- Enforcement Actions
  - Seizure: 1 firm; $24.2 million dollars of unapproved drugs
  - Consent decrees/injunctions: 8 firms
  - Class actions: 12 class actions

SAFETY RELATED DRUG ACTIONS: Products not Approved by FDA

- Zicam
  - Public health announcement instructing consumers to stop using three OTC Zicam intranasal zinc products marketed as cold remedies -- associated with the loss of sense of smell
- Body Building Products with Steroids
  - PHA warning consumers to stop using body building products represented as containing steroids or steroid-like substances due to reports of serious adverse events

FDAAA Drug Safety Actions

- From March 25, 2008 to June 1, 2009, CDER
  - Sent 14 letter requiring clinical studies or clinical trials for already approved drugs with new safety information
  - Issued 18 Safety Labeling Notification letters
    - Some for drug classes

Regulation of Drug Advertising and Promotion

- Huge area for CDER
- More research needed on impacts
- Additional appropriation this year
- We are discussing additional initiatives in this area

Expanding Office of Surveillance and Epidemiology

- Hired about 60 people this year
- As part of 2008 appropriation, received increased funding for database access for surveillance
- Implementing procedures and processes around safety, developing guidances and regulations, improving the science, and working on improved informatics support

OSE Regulatory agenda

- Regulations under development
  - Safety Reporting Rule (formerly SADR rule, “The Tome”)
    - Comment being reviewed
  - Postmarketing Safety Reports for Human Drug and Biological Products: Electronic Submission Requirements
    - Proposed rule announced August 2009
- Guidances (various stages of development or planning)
  - Contents of a complete submission for a proposed proprietary drug/biologic name
  - Best test practices for evaluation of proprietary names
  - Good naming, labeling, and packaging of drugs/biologics to reduce medication error
  - Best practices for conducting pharmacoepidemiologic studies using electronic healthcare data
  - Others related to FDAAA – REMS, PMRs/PMCs, safety-related labeling changes

OSE Science Activities

- Pharmacovigilance
  - 18-month/10,000 patient review
    - Preceded by NME pilot program
  - Bi-weekly screening of AERS
  - Best Practices for AERS reviews
  - Improve signal detection
  - New FAERS system
- Pharmacoepidemiology
  - Developing guidance
    - Observational studies of large healthcare databases for drug safety (guidance)
  - Expanding external epidemiological data resources
  - Expanding federal collaborations
    - VA, DoD, CMS, AHRQ
  - Expanded epidemiology training

OSE Science Activities

- Medication Error Prevention
  - OSE has “taken the lead” on proprietary name review
  - Need for more evidence-based methods for proprietary name review, carton/container review, and labeling review
  - Pilot program for industry to assess proprietary names, and FDA to review these assessments
- Risk Management
  - Developing and refining approaches to risk management
    - FDAAA REMS framework
  - REMS assessments
- Other initiatives
  - Pharmacogenomics
  - Risk-benefit decision analysis

Other CDER Safety Initiatives

Prescription Drug Information for Patients: Public Meeting Last Week

- Patient-directed labeling
  - Medication Guides
  - Patient Package
  - Now can be part of a Risk Evaluation and mitigation Strategy (REMS)
- Consumer Medication Information
  - Not produced by manufacturer
  - Not regulated by FDA
  - Results of recent study show not meeting standards
  - Future efforts subject of meeting

Sentinel Initiative: "Mini-Launch" this Year

- Develop distributed network of health care data
- Safety issues identified & evaluated in near real-time
  - Early detection of emerging safety problems
  - Allows for conduct of more rigorous analysis
- Expanded capacity for evaluating safety issues
  - Improved access to subgroups, special populations
  - Improved precision of risk estimates
  - Evaluation in the context of measurable denominators and background rates
  - Identification of increased risk of common adverse events (e.g., MI, fracture)
  - Continuous monitoring and evaluation of risk

Safe Use Initiative

- Vast majority of harm from approved drugs comes from misuse, inappropriate use, medical mixups, etc.—called “medication errors” and from abuse
- Hundreds of thousands of injuries and deaths
- Results from interaction of inherent properties of drug with characteristics of our healthcare system
- FDA does not control the healthcare system

Safe Use Initiative

- REMS and other regulatory tools act on pharmaceutical manufacturers
- FDA also must collaborate with healthcare system to develop effective interventions
- Interventions will be on drug or drug class basis—not wholesale
- Coordinate with regulatory and private sector interventions to develop synergistic result
- Measure effectiveness

Summary

- Drug safety is a foundation of drug regulation
- Complex efforts span drug review process, drug quality regulation, monitoring of promotion and advertising, compliance activities, and postmarket safety surveillance
- FDA is strengthening each of these components
- Safe Use initiative enlist help beyond FDA