Improving Risk Management and Drug Safety

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TOPICS

• Sentinel Initiative
• Risk Evaluation and Mitigation Strategy (REMS)
• Post Market Trials
• US Market Withdrawals
• Regulatory science in the decision-making process
• Update: FDA’s implementation of previous IOM drug safety recommendations
• Develop a national electronic safety monitoring system

  – Strengthen FDA's ability to monitor postmarket performance of medical products
  – Enable FDA to access existing automated healthcare data by partnering with data holders (e.g., insurance companies with large claims databases, owners of electronic health records, others)

• Will augment, not replace, existing safety monitoring systems
Potential Capabilities of Sentinel

• Safety issues may be identified and evaluated in near real-time

• Sentinel may expand current capacity for evaluating safety issues
  – Improved access to subgroups, special populations
  – Improved access to long-term data

• Active surveillance may identify an increased risk of common AEs (e.g., MI, fracture) that health care providers may not suspect are related to medical products
A Work in Progress

- May 2008: Sentinel Initiative launched with release of initial report
- 2008 – 2009: Foundational work on privacy, governance and data models completed
- Fall 2009: Launched “Mini-sentinel”
- Ongoing: Broad stakeholder outreach
- Managing expectations - Sentinel will be implemented in stages and will necessarily evolve
Mini Sentinel
Harvard Pilgrim Healthcare

- Provide a "laboratory" for developing and evaluating scientific methodologies that might later be used in a fully-operational Sentinel Initiative.

- Offer the Agency the opportunity to evaluate safety issues in existing automated healthcare data system(s) and to learn more about some of the barriers and challenges, both internal and external.
A. Only those academic institutions with automated data will be recipients of queries.

B. No entities will have access to protected health information that they do not already hold. Instead, those whose queries are accepted by the **Mini-Sentinel Coordinating Center** for processing will receive results summaries from analyses conducted by each data holder that receives and agrees to respond to those queries. Results summaries will not include protected health information.
Federal Activities

• Collaborations with CMS, DoD, and VA
  – SafeRx project with CMS to develop near-real time active surveillance methods using Medicare data
  – Several ongoing projects within medical product Centers to evaluate potential medical product-adverse event signals and develop active surveillance and statistical methodologies

• Federal Partners Working Group
  – Share information and discuss issues related to complementary efforts being carried out by the various Agencies within the Federal government
  – Participants include FDA, ONC, NIH, CDC, CMS, DoD, VA, AHRQ, IHS, HRSA, OHRP, SAMHSA, and CPSC
Observational Medical Outcomes Partnership

http://omop.fnih.gov

- Public-Private Partnership with FNIH, FDA, and PhRMA
- Conducts experiments to assess value, feasibility, and utility of observational data to identify and evaluate the safety risks and potential benefits of prescription drugs
- Tests approaches for creating the infrastructure for accessing and managing required data
- Enables the evaluation of a possible governance model, consisting of an Executive Board, and Scientific and Technical Advisory Boards
International Discussions

Europe
- Creating a “network of excellence” of research, medical care centers, healthcare databases, electronic registries
  - Strengthen postmarket monitoring
  - Facilitate conduct of safety-related post-approval studies
- Developing tools and methods to enhance adverse event data collection, signal detection, and create standards for epidemiology studies
- Using e-healthcare records and biomedical databases for early detection of adverse drug reactions

Canada
- Linking researchers creating national agenda for research priorities

Japan
- Access to claims data to assess drug safety using a pharmacoepidemiological approach
Risk Evaluation and Mitigation Strategies (REMS)

How have REMS been used in the past and how often
Plans for using REMS in the future
REMS limitations and strengths

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REMS Are Not New

• 16 drugs were approved with restrictive risk management programs (under Subpart H regulations) 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
Drugs Deemed to Have REMS

• Section 909 states that drugs approved before FDAAA with elements to assure safe use were deemed to have REMS

• On March 27, 2008, we issued FR notice identifying 16 different drugs from 24 sponsors that were deemed to have REMS

• Proposed REMS were to be submitted by September 21, 2008, and then reviewed and approved by FDA
Implementation Progress

• Approved REMS for 146 products, with 60 unique REMS, including 9 of the most complex programs with elements to assure safe use, and 3 “deemed” REMS

• Issued 25 safety labeling change notification/order letters (each class labeling change is counted as one letter)

• Developing several FDAAA-related guidance documents (to publish soon)
  – Guidance that should reduce burdens on the healthcare system of “Medication Guide-only” REMS, while preserving use of Medication Guides to present important information to patients as part of patent labeling
  – Guidance on safety related labeling changes
  – Guidance on Postmarketing Studies and Clinical Trials
Limitations and Strengths of REMS

• REMS Authorities Are Enforceable
  – May not introduce drug into interstate commerce if in violation of provisions
  – Drug may be found to be misbranded
  – FDA can impose civil penalties for violations of the Act

• Limitations and strengths discussed at 2-day public meeting in July
  – Over 70 individual presentations to obtain stakeholder views on the REMS program
  – Issues and challenges for healthcare system associated with the development and implementation of REMS for drugs
What we heard...

• REMS are necessary to preserve access to drugs whose risks would otherwise exceed benefits

• Multiplicity of unique REMS places burdens on the healthcare system
  – Particularly, REMS with elements to assure safety use (now totaling 20 different programs: 15 new and 5 “deemed”)
  – Also, “Medication Guide-only” REMS

• Standardize REMS programs to reduce burden on the healthcare system
What we heard…

• Consult with prescribers, pharmacists, patient groups, and others to get input
  – How to design REMS so that they preserve access while effectively addressing risk

• Standardize REMs to better integrate into existing healthcare systems to reduce burden

• Use developing informatics systems (e.g., e-prescribing, e-health record, pharmacy systems) to implement REMS more efficiently and effectively
Next Steps for REMS

• Developing a framework for improving REMS

• Will be engaging in public outreach through a variety of different efforts to discuss various components of the framework

• Objective: develop standardized REMS that can be plugged into existing healthcare systems to address particular risks and categories of risk
Post-marketing Clinical Trials

Requesting versus requiring clinical trials
How often have we taken action
How much follow-up on whether trials are initiated and completed
Design of Post Market Trials

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Actions

• Since FDAAA went into effect, through September 10, 2010:
  – issued approximately 290 postmarketing requirements (i.e. postmarketing studies and clinical trials to evaluate a safety issue)
  – of these approximately 35% of PMRs were clinical trials and 30% were other studies
What are PMR/PMCs?

• Studies/clinical trials *required of* or *agreed to* by a sponsor
• May be ongoing at time of approval or conducted after FDA has approved a product for marketing
• Provide additional information about a product’s safety, efficacy, optimal use, quality, stability, or consistency in manufacturing
Section 505(o)(3) - Postmarket Studies and Surveillance

- FDA may require studies or clinical trials at the time of approval, or after approval based on new safety information.
- Requirement must be based on scientific data and is limited to certain specific purposes:
  - To assess a known serious risk related to the use of the drug involved
  - To assess signals of serious risk related to the use of the drug
  - To identify an unexpected serious risk when available data indicates the potential for a serious risk.
Pre-FDAAA: PMCs

- Most postmarketing investigations agreed upon
- Some were required
  - PREA, Animal Efficacy Rule, Accelerated Approval (subpart H/E)
- All called “PMCs”
- Tracked in “PMC Database”
- Annual reporting requirements per FDAMA
  - Applicant to FDA
  - FDA publicly, in FR and website
Post-FDAAA: PMRs and PMCs

• New 505(o) authorizes FDA to require safety-related postmarketing “studies and clinical trials”

• FDA clarified its terminology
  – All **required** investigations = “postmarketing requirements” (PMR)
    • PREA, Animal Efficacy, Accel AP, FDAAA safety
  – All **agreed upon** investigations = “postmarketing commitments” (PMC)

• Tracked in the “PMR/PMC database”

• Reporting follows FDAMA requirements for both
New Definitions

- FDAAA distinguishes “study” and “clinical trial”
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning the investigational product or other interventions to ≥ 1 human subject(s)
- Study: all investigations other than clinical trials
  - Animals, laboratory/in vitro
  - In humans, only observational/epidemiologic
Requesting vs Requiring

• Under FDAAA, FDA has authority to require postmarketing studies and clinical trials that are intended to:
  – Assess a known serious risk related to the use of a drug,
  – Assess signals of a serious risk, or
  – Identify an unexpected serious risk (when available data indicate the potential for a serious risk).

• Defined clinical trials as:
  – "any prospective investigations in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects"

• Postmarketing "studies" are defined as
  – “all other investigations, such as investigations in humans that are not clinical trials as defined above (e.g., observational epidemiologic studies), animal studies, or laboratory experiments”
Requiring

• Statute clear that FDA can require postmarketing studies or clinical trials
  – to investigate or further characterize a safety issue.

• A postmarketing clinical trial intended to evaluate efficacy cannot be required under FDAAA.*

• FDAAA specifies when clinical trials (as opposed to postmarketing studies) can be required.
  – Must be appropriate scientific data about the serious risk, and
  – FDA must find that spontaneous adverse event reporting will not be sufficient to assess the safety signal, and that a postmarketing study (e.g. observational epidemiological study) will not be sufficient to assess the safety signal.

• Generally, FDA makes all postmarketing clinical trials intended to evaluate a safety issue postmarketing requirements
  – i.e., trials are not requested from or "agreed upon" by the sponsor. Postmarketing safety clinical trials are not "postmarketing commitments."

(*Note that there are other legislation or regulations under which a postmarketing clinical trials not intended to evaluate safety can be required. For example, FDA can require postmarketing trials to confirm the efficacy of products approved under Subpart H of 21 CFR part 314.)
Schedule Milestones

• Standard:
  – Final protocol submission
    • “Final”, in order to provide feedback on acceptability
  – Study/trial completion date
    • Implies timely start date and accrual
  – Final report submission
    • What counts for fulfillment

• Should be in the Approval letter
Milestones and Tracking

• Can add other milestones, but
  – Should be well-justified (PMR/PMC development template)
  – Must be proactively tracked
  – Milestones have compliance implications
    • If missed, need to consider action
    • Does the date truly reflect PMR progress?

• We are required to publicly report based on the original schedule milestones
  – No provision in FDAAA to change the dates
New Role:
PMR/PMC Development Coordinator

• Generally, the Deputy Director for Safety in New Drug Division
  – Most postmarket investigations will be PMRs
  – Many will be safety-related

• Responsible for ensuring PMRs/PMCs are reasonable, feasible, have an appropriate schedule, and that the objective is clearly articulated for inclusion in the action package

• Ensure consistency within division and across ODEs
New Role: PMR/PMC Tracking Coordinator

• Generally, the safety Regulatory Project Manager
• Primarily post-approval role
• Ensuring PMR/PMC information has been verified and that expected PMR/PMC-related activities are completed in a timely fashion
• Responsible for corresponding with applicant re: expected PMR/PMC submissions, discrepancies in applicant reported PMR/PMC statuses post approval.
  – PMR/PMC content related communications will generally remain with the RPM
FDA Role in Design of Post Market Trials

• When notifying sponsors of a required postmarketing clinical trial, FDA describes the risk of concern, and the necessary investigation to assess that risk. As much detail as possible about the investigation is provided.
  – For example, details about the trial objective(s), design, duration, comparator group(s), and endpoint(s) may be included.

• Based on this information, sponsors submit a proposed protocol for review.
  – Protocol contains much more specific information about the investigation, and includes a proposed statistical analysis plan.
  – Agency reviews the protocols and provides feedback, as indicated.

• For required postmarketing studies and clinical trials, the FDA must agree to the study/trial design and important milestone dates.
Drugs Withdrawn from the U.S. Market

• ~37 products since 1956

• 25 drugs based on reports of Individual Cases of adverse events
  – Examples: Bextra, Baycol, Rezulin

• 4 drugs based on Epidemiological Data
  – Examples: phenformin, phenylpropanolamine (PPA)

• 8 drugs based on Clinical Trial Data
  – Examples: Vioxx, Zelnorm, Meridia
Work with CMS on drug safety issues
Launch of the SafeRx Project

• In May 2008, the Medicare Part D prescription benefit data became available for research purposes

• SafeRx evolved as a collaboration between FDA and CMS with early support from the HHS Assistant Secretary for Planning and Evaluation
  – Launched June 2008

• Expands earlier FDA-CMS collaborations
  – To develop near-real time active surveillance methods
  – To provide opportunities for more formal epidemiological studies of medical product safety issues in the Medicare and Medicaid populations
Assessing the Feasibility of Using Medicare Claims Data for Near Real-time Safety Evaluations

• If we want to use Medicare data for near real-time active surveillance, what do we need to know about the weekly (diagnoses, procedures) and monthly (prescriptions) data updates?
  – How long is the delay to claims submission?
  – What is the frequency with which clinical information changes in the database due to claims adjudication?

• Results:
  – Over 85% of health services claims were processed within 8 weeks after the date of service, and 72% of drug claims were processed within 3 months after the dispense date.
  – Clinical information changed for no more than 3% of unique claim groups in Inpatient Hospital, Outpatient Institutional, Physician’s Office, and prescription drug Medicare claim settings.

• Conclusions
  – Claims delay is consistent across time and minimal.
  – Claims adjudication does not substantially impact the content of clinical information in the Medicare claims database.
  – Medicare data is useful for near real-time drug safety surveillance

Hartzema AG, Macurdy TE, Gibbs JM, et al. Impact of Medicare Claim Resubmissions on Drug and Health Identifiers (abstract). 26th International Conference on Pharmacoepidemiology and Therapeutics, August 2010
Some Presentations from SafeRx Projects

• Active surveillance projects

• Epidemiologic studies
Evaluation of Comparative Safety

- **SafeRx epidemiologic study**
  - Retrospective new user inception cohort of rosiglitazone vs. pioglitazone to assess risk of severe cardiovascular harm
  - Medicare patients ≥65 with at least 1 year of Part A and Part B eligibility and 6 months of Part D eligibility from June 2006-June 2009
  - Cardiovascular outcomes based on ICD-9 hospital discharge codes and mortality ascertained by linkage to the Social Security Master Beneficiary Record database
  - Outcomes not validated as part of this study, but coding algorithms used to identify cardiovascular outcomes had been previously validated in earlier studies and shown to have good positive predictive value
CMS Part D data

Benefits:
• Large populations available
• Clinical data stable over time

Drawbacks
• Outcome validation difficult (i.e., medical record level verification)
• Part D data quality not thoroughly studied yet
Increasing public communication

- In January 2010, adopted a new standardized format for electronic communication about drug safety issues
  - “Drug Safety Communication” (DSC)
  - Targets both patients and providers
  - Intended to communicate new or emergency safety issues about drug products and recommended actions based on this information
- Between January and October 2010, CDER has issued 33 DSCs
Patient Medication Information (PMI)

• Current multiplicity of Medguides, voluntary “consumer medication information” and patient package inserts

• Near-consensus that US needs a “single document solution” to PMI

• FDA has held multiple meetings on this topic to get stakeholder input

• Hope to implement pilots/move towards implementation
FDAAA Section 921

“...conduct regular, bi-weekly screening of the Adverse Event Reporting System [AERS] database and post a quarterly report on the Adverse Event Reporting System Web site of any new safety information or potential signal of a serious risk identified by Adverse Event Reporting System within the last quarter…”

• list any potential signals of serious risks/new safety information identified using the AERS database during the indicated quarter

• appearance on the list does not mean FDA concluded the drug has this listed risk; rather, that FDA has identified a potential safety issue, but not a causal relationship between the drug and the listed risk.

• 10 quarters of information posted, starting in January 2008
Safe Use Initiative

• Most drug-induced harm from known side effects
• Significant amount is preventable
• Safe Use is FDA’s collaboration with other stakeholders to reduce drug-related preventable harm
• Public meeting next week—results of multiple listening sessions with various groups
• Examples:
  – Opioid misuse
  – Multi-drug therapy in elderly
  – Medication handoffs after hospital discharge
Improving the Science of Drug Safety

• Pre-market
  – Science of drug-induced liver injury
  – Predicting/assessing adverse immune responses to pharmaceuticals
  – Safety biomarker qualification
  – Computational science—electronic submission of standardized trial data for use with automated tools

• Post-market
  – FDA Science Board review of Pharmacovigilance Program
  – Scientific partnerships
Scientific partnerships to address drug safety

- Serious Adverse Event Consortium (SAEC)
  - Pharmaceutical industry/Welcome Trust
  - Genetic basis of rare serious AEs

- Predictive Safety Testing Consortium (PSTC)
  - Convened by C-Path Institute
  - Biomarkers for drug-induced organ toxicity

- The Biomarker Consortium (FNIH) addresses safety biomarkers as well as other biomarkers
Personalized Medicine

• Pediatric patients – improving dosing, addressing the safety of chronically administered drugs, and risks posed by certain drugs

• Pregnant women – improving dosing and addressing pregnancy-specific risks

• Gender differences in adverse events

• Pharmacogenomics – predicting risk of safety concerns due to genetic variations in both drug metabolism and drug target genes

• Targeted therapy—decrease exposure of patients likely to receive no benefit