Postapproval Safety Surveillance and Pharmacovigilance

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Lecture in Course: Clinical Trials in Biomedical Enterprise

Five Trends Are Transforming Our Industry

- Spiraling R&D costs coupled with decreased productivity
- Demand for safety and post-marketing surveillance
- Expectation of personalized medicine
- Reimbursement driven by medical and economic outcomes
- Proliferation and redistribution of healthcare outcomes information

Ted Torphy, Ph.D. (2009, 'Bridging the Valley of Death" talk)
CSO & Head
External Research & Early Development
Johnson & Johnson Pharmaceutical R&D, L.L.C.

Dr. Jacques Lelorier, a Canadian pharmacologist:

- Classification of All Substances
  - Inert compounds
  - Poisons
    - Pure poisons
    - Drugs (selective toxicity)

Definitions

- Drug Safety Surveillance/Pharmacovigilance
  - The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems.

Sample Case Histories

Refs:

Powerful Medicines, The Benefits, Risks, and Costs of Prescription Drugs, Avorn, 2007

The Future of Drug Safety, Promoting and Protecting the Health of the Public, IOM report 2007

Thalidomide

- In the late 1950's, early 1960's, it was a fairly effective sedative and antinauseant particularly popular with pregnant women overseas.
- Its approval in the US slowed by a diligent FDA medical officer named Dr. Frances Kelsy, (who was deemed to be overly conservative by some in industry) who wasn't convinced that the manufacturer had adequately demonstrated its safety.
- Reports began to appear in Europe of babies born with grotesque abnormalities of arms and legs
- Since this was an extremely rare adverse event, and was observable after a relatively short time from the drug exposure (less than 9 months), cause and effect was relatively clear (not the usual situation).
- The Kefauver Act, providing FDA with additional authority to demand that drugs be effective as well as not be poisonous, was heading for sure defeat in congress, when it was passed in 1962 without a dissenting vote.

- *"In a former British colony, most healers believed the conventional wisdom that a distillation of fluids extracted from urine of horses, if dried to a powder and fed to aging women, could act as a general tonic, preserve youth, and ward off a variety of diseases. The preparation became enormously popular throughout the culture, and was used widely by older women in all strata of society. Many years later modern scientific studies revealed that long-term ingestion of the horse-urine extract was useless for most of its intended purposes, and that it caused tumors, blood clots, heart disease, and perhaps brain damage"*

Avorn, 2007

Prempro/Premarin: Hormone Replacement Therapy (HRT) for postmenopausal women

- Used since the 1970's, thought to reduce the unwanted and uncomfortable symptoms of hot flashes, insomnia, and drying of the internal surface of the vagina (which it does do)
- Also for many years, it was thought to have "cardio-protective" properties, treat depression and incontinence associated with menopause, as well as prevent Alzheimer's disease (which as it turns out probably does the opposite)
- Logically consistent with the well known decrease of estrogen at menopause, and originally tested to determine if it could reduce the acute symptoms, obviously not tested as a lifelong 'replacement' therapy.
- Only observational studies were done up until the late 1998's (estrogen was approved for short-term use, but Dr's. could prescribe it off-label)
- By this time, it became difficult to actually start a randomized controlled clinical trial due to the potential ethical issues of withholding what was thought to be an important treatment.

Prempro/Premarin: Hormone Replacement Therapy (HRT) for postmenopausal women (con't)

- Finally, primarily due to the powerful insistence of a variety of women's groups, Wythe (the manufacturer of Premarin) agreed to do a randomize controlled trial in 1998 (published in JAMA)
- The study showed that subjects given estrogens had significantly more heart attacks, higher rates of blood clots and gallbladder disease than did women given the placebo. This in addition to higher rates of endometrial cancer formerly found.
- Then, in 1998, an additional on-going NIH Women's Health Initiative study including over 16,000 women was now troubled by the ethics of continuing the study for the opposite reason (potential risk of the treatment group).

Prempro/Premarin: Hormone Replacement Therapy (HRT) for postmenopausal women (con't)

- Through much consternation, it was decided to continue the study, but inform women participating, of what was found in the Wythe study, giving them the option of withdrawing consent to participate.
- In 2001, Amer. Heart Assoc. rewrote their guidelines on prevention and stated the estrogen should not be assumed to have protective effect on the heart
- In May, 2002, the WHI safety monitoring board reviewed outcomes to that point, and found that women in this study were developing a higher rate of heart disease, breast cancer, strokes, blood clots and gallbladder disease, but had a slight protective effect on the risk of colon cancer and a reduction in hip fractures.
- It was argued that the risks way outweighed the benefits, and stopped the study.

Redux (fenfluramine-phentermine, "fen-phen")

- Originally (1970's-1990's) fenfluramine marketed as Pondimin by the company acquired by Wyeth.
  - Studies that were done showed an unimpressive decrease of only a few pounds vs. control
  - As soon as the patient stopped taking the drug, the weight returned
  - Approved by FDA only for "short term" weight loss.
- In the 1990" a pharmacologist discovered that when combined with a second not terribly effective 2nd diet pill (phentermine), the two could act synergistically
- During later litigation, it came to light that Wyeth was not reporting the true incidence of pulmonary hypertension over the decades of fenfluramine use

Redux (fenfluramine-phentermine, “fen-phen”) con’t

- At laboratory associated with MIT, chemists had begun work on developing an isomer of fenfluaramine
  - Potential (although rarely) for the different isomer to maintain effectiveness and decrease bad side-effects
  - Additional advantage of prolonging patent coverage
  - Dexfenfluarmine was presented to FDA with the trade name Redux
- In 1994, a large pulmonary hypertension study in France was finding clear association between pulmonary hypertension and the diet pills (any of the isomers).
- Sales for the old drug Pondimin began to grow ($3.7M in 1993, to $150.1M in 1996, and thought the market for Redux would reach greater than $1B.

Redux (fenfluramine-phentermine, “fen-phen”) con’t

- In September, 1995 the FDA advisory panel voted not to approve Redux due to too many safety concerns, given the fairly modest 5-6 lbs of weight loss vs. control.
- Although quite unusual, after significant company pressure the FDA agreed to re-visit Redux in November 1995
- With no substantial additional information on the benefit/risks of the drug, it was approved by a one-vote margin to recommend that Redux be approved for unrestricted use in the U.S.
- Initially, FDA argued that there should be a “black box” warning of pulmonary hypertension, and that post-approval studies by done by the company to address these safety concerns

Redux (fenfluramine-phentermine, "fen-phen") con't

- When Redux received its final green light for marketing in early 1996, no such requirements existed
- One of the chief FDA medical reviewers that had asked for these conditions, Dr. Leo Lutwak, refused to sign the approval letter. Another FDA official had to and did sign the letter.
- About this time, based on preliminary data coming from the French study (that would be published later that year in the NEJM) the European regulatory agencies determined that the risk of pulmonary hypertension was so great, all advertising would have to include a major warning about this risk.
- Physicians started prescribing the drug for all patients, not just the "severely obese" patients it was intended for in the FDA trial

Redux (fenfluramine-phentermine, “fen-phen”) con’t

- Wyeth argued that the overall risks associated with obesity should be taken in to account when determine the overall risk/benefit of the drug
  - Since there was only an average 6 lb difference found even in a well controlled FDA trial, this argument was weakened by the fact the drug was essentially being used by patients well outside of the original study population definition
  - Although the risks of obesity are relatively well known, there was no evidence that this drug significantly impacted on that risk
- Final blow to the drug came from a North Dakota study (after an observation from one astute echo cardiology technician) made public in July of 1997 that showed increased rate of heart valve disease in otherwise healthy young women for women taking diet pills.

Redux (fenfluramine-phentermine, “fen-phen”) con’t

- To that time, this was the largest (now exceeding $21B) set of judgments class action judgments awarded against Wyteh.
- It is estimated that beyond those with pulmonary hypertension, thousands of others have damaged heart valves.
- Why was a drug, with a only modest a potential benefit (6 lbs weight loss), approved by FDA?
  - At the time, if the drug had no ‘provable’ safety issues, then FDA argued that it is up to the medical community to decide on the value of this borderline effect.
  - The safety issues, although suspected, were not well studied
  - There wasn’t complete disclosure by the company of safety issues before approval
  - FDA had no power to insist on post-approval studies short of complete withdrawal of the drug from the market.

Rezulin (troglitazone)

- First marketed in 1997 as a first in class diabetes medication
- As with viagra and minoxidil, a cousin of this class of drug was first use to determine if it could decrease cholesterol.
  - As with viagra and minoxidil, it didn't lower cholesterol very well, but what it did do was lower was blood glucose
  - The mechanism was that it apparently persuaded the liver to produce less glucose and rendered fat cells more sensitive to the effects of insulin
- In a study of about 2500 patients, it showed a decreased blood glucose vs. placebo (not other diabetes medications).
- In the FDA advisory panel of Dec. 1996, a physician representing the manufacturer (Parke-Davis) reported that the risk of liver toxicity was "comparable to placebo".

Rezulin (troglitazone) con't

- The company had accumulated other safety data from previous studies that was not presented at the advisory meeting.
  - It was stated by the company that the results of these other studies showed that the rate of liver damage was "very, very, similar" to what was reported at the meeting.
  - Parke-Davis promised to submit this additional safety data after the meeting
- Based on the data presented that day, the vote was to allow marketing of the drug to be used only as an adjunct to those taking insulin
- Parke-Davis did submit the additional safety data a week later, and it showed that the rate of liver abnormalities was in fact substantially greater.
  - However by this time, the drug was approved and little attention was paid

Rezulin (troglitazone) con't

- Just 8 months after the drug was on the market, there were already increasing reports of liver damage.
- In preparation for the FDA meeting called in Oct. 1997, a company physician apparently tightened the definition of what was an "abnormal" blood test for liver function for the treatment group, and not the placebo group.
- By fall, 1997, there were 137 cases of sever liver damage, and at least 5 of these were fatal for those who used Rezulin
- The drug was licensed to be used in Europe by Glaxo, who promptly concluded that with so many safer options for diabetes, the risk/benefit relationship became indefensible.
- Glaxo and the Japanese company (original inventors of the drug) withdrew their application for marketing in 26 additional companies

Rezulin (troglitazone) con't

- At this time, Parke-Davis was taking a completely different tact
  - They sent a "physicians letter" to all doctors to monitor liver function closely in patients taking the drug with a once a month blood test
- During this time at the end of 1997, researchers at NIH were trying to decide what to do with a $150M study they were intending to fund on Rezulin
- One of the senior diabetes researchers on the project (who was later found to have a potential conflict of interest as a paid consultant by Parke-Davis) was instrumental in deciding the study should go on, even given Glaxo's decision to withdraw the drug
- Under the cover of the new labeling (requiring a once a month blood test, which was not likely to happen) FDA continued to support marketing the drug.

Rezulin (troglitazone) con't

- In May 1998, within a month of a teacher's death due to liver failure that occurred as part of the NIH study, despite frequent liver function blood tests, the NIH study was halted. The liver toxicity occurred too quickly, even for the once a month testing.
- Finally, after further data became available, and significant political pressure was applied, the FDA voted to discontinue the drug's approval in March, 2000.
- Parke-Davis had earned over $2B in drug sales to that point, with 94 cases of acute liver failure, 66 of these were fatal.

PPA (phenylpropanolamine)

- Since early the 1900's, PPA (related to the amphetamine class of drugs) was know to reduce appetite, dried up nasal secretions, and raised blood pressure.
- By the 1950's, PPA was being used in dozens of OTC remedies in two categories, cold remedies and diet aids.
  - For colds, it was packaged as Dimetapp, Contac, Triaminic, and Coricidin.
  - For diet aids, it was packaged as Thinz and Dexatrim. Ayds, once used for weight loss significant market share in the 1980's due to the emergence of a health problem.

PPA (phenylpropanolamine) con't

- PPA was such an old product that it actually predated key FDA legislation and manufacturers were not required to prove the drug's safety and effectiveness as they would if it were introduced today
  - No formal assessment of this ubiquitous drug was to be done until the Drug Efficacy Study Implementation (DESI) program, the review of grandfathered and combination drugs the FDA began in 1962.
  - The DESI initiative focused first on prescription drugs, than 20 years later, began the focus on OTC drugs.
- By 1979, reports began to appear of patients having increase rates of strokes while taking PPA.
  - One author recommended the "withdrawal of preparations containing PPA from general use should be considered in view of their potential for adverse reactions with other commonly used drugs and their doubtful therapeutic value"
  - In 1980, a Lancet paper showed significant rise in diastolic BP in otherwise healthy patients

PPA (phenylpropanolamine) con't

- Advocacy groups such as the Center for Science in the Public Interest wrote the FDA commissioner demanding the PPA be removed from the market.
- Just as in it's sister drug amphetamine, PPA patients exhibited tachyphylaxis (bodies ability to adapt over time to the effects of the drug). This usually results in and did result in drug addiction
- By 1982, FDA began to express official concern about the possibility of blood pressure elevation and stroke, and ruled that combination of PPA with caffeine and/or ephedrine were a potential hazard
- Although there was some activity, FDA did not decide until 1985 that it was concerned about the drug's risks and refused to designate it as safe and effective (Category I status)

PPA (phenylpropanolamine) con't

- Through the late 1980's and early 1990's, congressional hearings, case reports and review articles that indicated an association between PPA and hypertension and strokes continued to appear.
- The combination of the fact that other, safer drugs started appearing, and it's continued lack of evidence for weight reduction, caused the benefit side of the risk/benefit equation to seem weak
- Finally in 1992, under significant pressure the OTC drug association decided to fund a study to clarify the situation
  - The study, a case-control design, eventually got off the ground in 1994, and took five years to complete
  - If was found that out of 2,078 patients contacted, of whom 702 had suffered stroke. The study found that PPA significantly increased the risk of stroke (3 times for all patients, and 16 times for diet patients).

PPA (phenylpropanolamine) con't

- Finally, by the end of 2000, 20 years after the initial questions arose, all products using PPA were removed from the shelves.
- The drug manufacturers quickly replace PPA with the safer pseudoephedrine (a reformulation that was available for years).

Summary of Sample Cases

- Redux, Rezulin and PPA all represented extreme examples of failures of risk assessment.
- In each case, there was willful ignoring of hazard signals as they emerged.
- THESE ARE THE EASY CASES

Summary of Sample Cases con't

- In most situations, the story is even 'greyer' and issues are usually much more complicated
- Some of these include the more recent drug safety episodes:
  - such as a Merck drug called Vioxx which is an NSAID shown to have increased risk of significant cardiovascular events
  - A Biogen drug named Tysabri which is an MS treatment with potentially increased risk of PML (progressive multifocal leukoencephalopthy), an extremely rare viral infection of the brain that could result in death
  - An Amylin drug named Byetta, another type II diabetes drug that may be associated with acute pancreatitis
  - Etc., etc.

Post-Approval Safety Surveillance

Increasing Awareness of Safety Issues

Association vs. Causality

Until recently, FDA lacked appropriate resources and statutory empowerment

Increasing priority for safety issues

- The realization that FDA approval does not mean an absolutely positive risk/benefit for the drug, only that it was likely given the available data at the time of approval
  - Statistical rules of thumb:
    - Most pre-approval studies are between 500 and 3,000 patients exposed to the drug (sample size then typically doubles this for control patients)
      - Studies of this size have the ability to detect drug effects with an incidence as low as 1 per 1000 to 6 per 1000
    - Given this, a post-approval study must then generally be greater than 10,000 patients
      - Studies of this size have the ability to detect drug effects with an incidence as low as 3 per 10,000

Increasing awareness of safety issues

- Increasing general medical community and public awareness
- An explosion in the technologies that can be used to develop new medical entities (NME's) or Class III devices
  - By definition, less is known about first-in-class drugs or new technology high risk devices
  - Animal models for safety can only take you so far
- Pressures on manufacturers to bring drugs to market sooner
- Pressures on FDA due to user fees to more quickly review new drug applications

Increasing awareness of safety issues

- Post-approval data usually:
  - Lacks a reliable control group
  - Episodic, prone to reporting bias
    - estimated that only about 1% of events are reported
    - % reported is sometimes a function of things having little to do with actual safety issues (e.g. publicity, FDA communications, etc.)
  - Actual exposure of drug/device is typically not available

- Standardized tools and processes for detection are not available or sometimes even possible
  - Tools can't make up for unreliable information

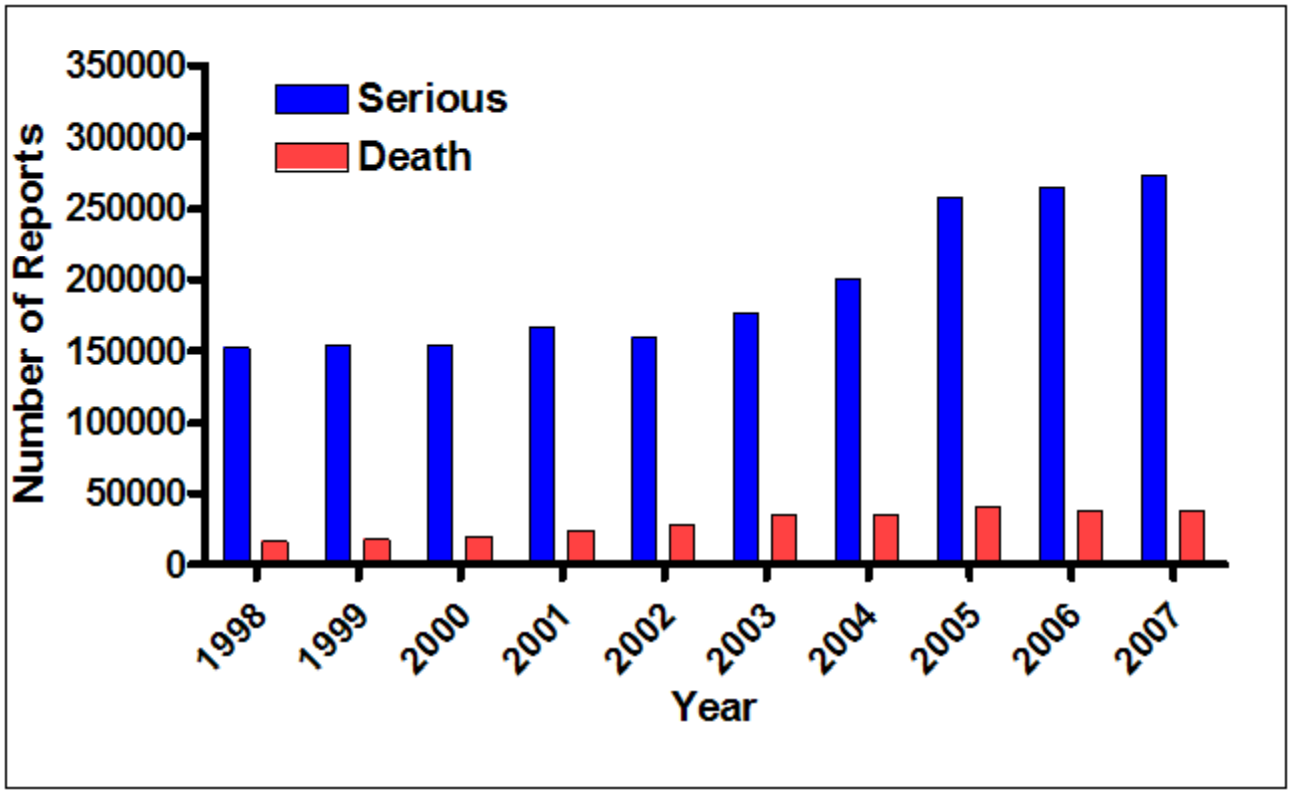
FDA Safety Surveillance

- Primary post-approval method for detecting signals of adverse drug reactions is via MedWatch forms and stored in AERS
- Reports can go (via web and by paper) to FDA directly, or the manufacturer (they have a specific short time to submit it to FDA)
- The AERS received nearly 440,000 reports in 2007
- It is well known that the system underreports AE's
  - it is estimated that they only receive <1% of AE's
  - It requires physicians to volunteer their time
  - Unclear when/what to report
  - Potential risk liability

AERS Patient Outcomes by Year
as of December 31, 2007

These data describe the outcome of the patient as defined in U.S. reporting regulations (21 CFR 310.305, 314.80, 314.98, 600.80) and Forms FDA 3500 and 3500A (the MedWatch forms). *Serious* means that one or more of the following outcomes were documented in the report: death, hospitalization, life-threatening, disability, congenital anomaly and/or other serious outcome. Documenting one or more of these outcomes in a report does not necessarily mean that the suspect product(s) named in the report was the cause of these outcomes.

This figure illustrates the patient outcome(s) for reports in AERS since the year 1998. Serious outcomes include death, hospitalization, life-threatening, disability, congenital anomaly and/or other serious outcome.



Increasing awareness of safety issues

- Each case often requires individualized assessment:
  - In following one drug or device (as our clients need to do) there is usually a small amount of growing data available (unlike data mining approaches on very large safety databases)
  - *Finding a possible association between drug and event does not mean you have found cause and effect (causality).*

Association vs. Causality

- Given the complexity of the situation, determination of the likelihood of causality, relatively senior multidisciplinary expertise is often required:
  - Epidemiology
  - Biostatistics
  - Clinical
  - Clinical trial
  - Pharmacology (Drugs), Technical (Med. Devices)
  - Database management
  - Signal Processing
  - Product liability
    - Insurance
    - Legal

Until recently, FDA lacked appropriate resources and statutory empowerment

- Until recently PDUFA/MDUFMA actually prohibited any use of these funds for post-approval safety surveillance by FDA
  - resources were extremely limited, especially relative to the funds available for pre-approval

- FDA had (until very recently) no real power to enforce post-approval commitments made by manufacturers
  - It has been estimated that over 65% of all commitments to date made by companies to perform post-approval studies were not followed

The safety surveillance services market

Manufacturer's reticence

What's changing?

Current reticence of manufacturers

- Head-in-the-sand phenomena, or resistance to look: "If you look, you will find", often potential safety signals turn out to not be safety issues at all after further study.
  - Potential for inappropriate significant negative impact on sales
    - Not an unreasonable point-of-view given complexity of the situation

- It is quite possible, given the limitations in the data and analytic tools available for both false positives and false negatives to occur.
  - Both situations can be harmful to the well being of the patients. One for inappropriately removing an efficacious drug, and the other for leaving it on the market too long.

What has to happen in order to decrease their reticence?

- Manufacturers need to feel more comfortable with the process to be assured that inappropriate actions will not be taken based on inadequate information and misinformed conclusions
  - They need to be assured that confidentiality will be maintained until the conclusions are well informed
  - They need to maintain control over the situation
- With increasing external pressures, manufacturers will be more receptive to options regarding post-approval safety surveillance services
  - FDA
  - Judicial
  - Public Relations

Changes At FDA – IOM Committee Report

- In 2006, an Institute of Medicine committee was formed to review FDA processes regarding post-approval safety. The reason for its formation was identified in the report's preface:
  - "…recent drug safety events have called in question FDA's regulatory decision-making and oversight processes, and caused the public to question its ability to accomplish a balanced evaluation of the safety and efficacy of drugs it reviews after their approval…"

- The committee made many recommendations, the most important of which includes those that recommend more resources and empowerment to FDA for post-approval safety regulatory tasks.

Changes At FDA – Increasing Resources

- Increasing powers and resources granted to FDA Under the Food and Drug Administration Amendments Act of 2007, and the specific provisions outlined in PDUFA IV, as part of this Act for post-approval safety surveillance

- Over $150M increase in funding over the next 5 years for post-approval safety surveillance
  - Increase to $29M/yr base,
  - Congressional approval to increase user fees above base
    - Rising from $25M/yr for year 1, to $65M/yr for year 5

Changes At FDA – Increasing Resources

- FDA is planning to double the number of safety officers (from 100 to 206)

- FDA now can require post-approval studies or clinical trials at the time of approval and after, instead of the requesting companies on a 'voluntary' basis to do them previously.

- As part of the IOM committee's recommendation, the creation of the new Drug Safety Oversight Board and appointment of Susan Cummins, MD, MPH as Exec. Director in 2005

Changes At FDA – Relevant Guidances

- In 2005, two new safety related guidances are published:
  - "Guidance for Industry, Development of Use of Risk Minimization Action Plans", March 2005
    - Initiating and designing plans called risk minimization action plans or RiskMAPs to minimize identified product risks
    - Selecting and developing tools to minimize those risks
    - Evaluating RiskMAPs and monitoring tools
    - Communicating with FDA about RiskMAPs
    - The recommended components of a RiskMAP submission to FDA
  - "Guidance for Industry, E2E Pharmacovigilance Planning", April 2005
    - Intended to aid in planning pharmacovigilance activities, especially in preparation for early postmarketing period of a new drug.

Changes At FDA – FDAAA and REMS

- Food and Drug Administration Amendments Act (FDAAA), March 2008, defined Risk Evaluation and Mitigation Strategy (REMS)
  - A strategy to manage a known or potential serious risk associated with a drug or biologic product
  - A REMS is necessary to "ensure that the benefits of the drug or biological product outweigh the risks of the product, and FDA notifies the sponsor", can be required pre or post-approval
  - A REMS can include:
    - A Medication Guide
    - A Patient Package Insert
    - A communication plan
    - Elements to assure safe use
    - An implementation system
    - Timetable for assessment of REMS

Changes At FDA – Sentinel Initiative

- The DHHS, with FDA playing a key role, has launched a set of initiatives. These include:
  - Expanding its current system for monitoring medical product performance and safety through its entire lifecycle
  - Exploring the possibility of building on the capabilities of multiple data systems to augment the Agency's query capability
  - Creating a public-private collaboration as a framework for such an effort
  - Leveraging increasingly available large, electronic databases run by
    - Private health plans
    - Insurance plans
    - Government agencies (including FDA, WHO)
    - Industry

Selected Automated Data Systems Available for Pharmacoepidemiological Studies

- Spontaneous Reporting
  - FDA Adverse Event Reporting System (AERS)
  - The WHO Programme for International Drug Monitoring (Uppsala Monitoring Center, UMC, covering 73 countries)
- Claims Databases
  - Group Health Cooperative (Group-Staff Model HMO's)
  - Kaiser Permenente Medical Care Program (pre-paid Group HMO)
  - The HMO Research Network (consortium of 14 health plans)
  - UnitedHealth Group (diversified health services company)
  - Medicaid/Medicare (Government payors)
  - Health Services Databases in Saskatchewan

Selected Automated Data Systems Available for Pharmacoepidemiological Studies

- Pharmacy Databases
  - Medco Database (and other online prescription services)
  - CVS Pharmacy Database
  - Automated Pharmacy Record Linkage in the Netherlands
- Socialized Medicine Databases
  - The Tayside Medicines Monitoring Unit (MEMO) (Scotland)
  - The UK General Practice Research Database

Judicial reasons for increase in potential liability exposure

- Starting around the year 2000, judges and courts have became less tolerant of the FDA approval and labeling as the sole defense in product liability claims.
  - After cases such as Rezulin, where it was deemed as an unrealistic burden to assume all physicians and patients could adhere to a once monthly blood test, the courts held the manufacturer of Rezulin culpable for the continuing safety issues.

Increased public awareness

- Over the last 5-10 years, there has been a substantial increase in public awareness of medical product safety issues
  - Increased FDA communication with the public
    - FDA web site greatly enhanced: Recalls, Market Withdrawals and Safety Alerts web page
    - FDA offers proactive sending 'alerts' as it institutes any post-market safety action including recalls.
    - Separate guidance for public communications: 'FDA Guidance: Drug Safety Information - FDA's Communication to the Public', March 2007
  - Increased media attention
  - Increased activity of special interest patient groups, web sites

FDA Website (2008)

Summary

- The overall average long term experience with drugs is decreasing with the advent of ever increasing new mechanisms to identify NME's,
- There are important safety issues that are not possible to find with standard clinical testing and evaluation pre-approval
- FDA's resources and oversight have been recently substantially increased
- There increasing liability for manufacturers related to not finding post-approval problems in an 'appropriate amount of time'
- Manufacturers will need to increase its resources substantially to identify potential issues earlier

Appendix

"Spending on Postapproval Drug Safety" Ridley, DB et. al. Health Affairs, vol 25, no. 2 (2006)

- Survey of drug manufacturers in 2003 from 25 of largest pharmaceutical manufacturers
- Respondents were assured that firm-level information will be kept confidential
- 11 companies responded (but accounted for 71%) of 2003 drug sales of top 20
- Mean pharmaceutical sales per company was $17B
- Each company marketed about 200 prescription drugs and 200 OTC drugs.

"Spending on Postapproval Drug Safety" Ridley, DB et. al. Health Affairs, vol 25, no. 2 (2006)

- Survey limited to postapproval safety activities
  - No postapproval studies exploring new indications
  - Handling of AE's, including collection, scientific analysis, data entry into database, medical review, follow-up and reporting to worldwide regulators
  - Summary report production including periodic safety update reports (PSUR's)
  - Safety department operations including QA, technology support and training
  - Safety surveillance activities including those related to postapproval risk management including safety-related product quality complaints including
    - product recall for safety reasons, responses to safety questions from regulators, literature review for AE information, and provision of information to healthcare professionals
  - Postapproval safety studies
  - Safety-focused epidemiologic activities (postapproval)
  - Activities required for safety-related labeling changes (excluding labeling changes for other reasons).

EXHIBIT 1
Descriptive Statistics At The Company Level, 2003

Variable	Number of responding companies	Mean (standard deviation)
Pharmaceutical sales (billions of dollars)	11	17.4 (10.52)
Portfolio (number of drugs)		
Prescription drugs	10	183.6 (186.78)
Over-the-counter drugs	10	197.6 (204.01)
Drugs for serious conditions	9	17.6 (15.19)
New drugs	9	8.1 (5.16)
Blockbuster drugs (2003 sales greater than $1 billion)	11	3.8 (2.89)
Drugs approved for pediatric use	9	39.6 (44.76)
Share of postapproval safety spending		
United States	10	0.6 (0.22)
Europe	10	0.2 (0.15)
Japan	10	0.1 (0.09)
Rest of world	10	0.1 (0.09)
Adverse events (thousands)		
Initial nonserious	10	27.8 (18.45)
Initial serious, expedited	10	7.4 (7.56)
Initial serious, not expedited	10	11.1 (13.59)
Follow-up nonserious	10	13.9 (14.31)
Follow-up serious, expedited	10	8.4 (13.20)
Follow-up serious, not expedited	10	13.0 (10.87)
Periodic safety update reports		
Small (fewer than 100 cases)	11	67.6 (84.26)
Medium (101 to 500 cases)	11	40.1 (58.52)
Large (more than 500 cases)	11	25.3 (23.33)
Share of costs by employee type		
Physicians	10	0.2 (0.09)
Other health staff	10	0.3 (0.20)
Scientists	10	0.1 (0.08)
Management	10	0.1 (0.05)
Other staff	10	0.3 (0.24)
Full-time-equivalents	11	298.1 (159.01)
Share of spending on postapproval safety	11	0.7 (0.11)
Share of sales for postapproval safety	9	0.003 (0.001)
Postapproval safety spending for personnel (millions of dollars)	10	38.1 (18.77)
Nonpersonnel postapproval safety spending (millions of dollars)	9	16.6 (14.85)
Postapproval safety spending (millions of dollars)[a]	9	55.72 (31.82)

SOURCE: Unweighted descriptive statistics at the company level for 2003 using survey data and company annual reports.

[a]One respondent declined to estimate nonpersonnel and total costs, so the averages for personnel and nonpersonnel do not add to the average total.

EXHIBIT 2
Correlations Between Variables Measuring Postapproval Safety Effort (Spending And Staff) And Other Variables Of Interest

Variable	Postapproval safety spending	FTEs
Postapproval safety spending	1.00	0.88***
Full-time-equivalents (FTEs)	0.88***	1.00
Pharmaceutical sales	0.93***	0.84***
Number of adverse events		
Initial nonserious	0.73**	0.77**
Initial serious, expedited	0.57	0.62
Initial serious, not expedited	0.75**	0.60
Follow-up nonserious	0.77**	0.66**
Follow-up serious, expedited	0.79**	0.65**
Follow-up serious, not expedited	0.47	0.64**
Portfolio		
Prescription drugs	0.62	0.52
Over-the-counter drugs	0.17	0.39
Drugs for serious conditions	0.36	0.39
New drugs	0.86***	0.77**
Drugs approved for pediatric use	0.47	0.48
Blockbuster drugs (2003 sales greater than $1 billion)	0.93***	0.79***

SOURCE: Authors' analysis using survey data and company annual reports.
**$p < .05$ ***$p < .01$