ANALYSIS OF FDA SAFETY ALERTS FROM 2003 TO 2012

By

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Introduction

The Center for Drug Evaluation and Research (CDER) and the Center for Biologic Evaluation and Research (CBER) are two divisions of the FDA which regulate drugs and biologics (both brand and generic), ensuring that products are safe and effective for human use. All the drugs/biologics manufacturers who market their product in United States have to abide by the regulations (21 CFR) enforced by the FDA. Every drug/ biologic has to demonstrate to the FDA that each products' benefits should outweigh the risks associated with it use (Development and Approval Process (Drugs), 2012). Both CDER & CBER review and regulate the Drug/Biologic development process from Pre-clinical to the Post-Approval. Even though a Drug/Biologic proves its safety and effectiveness in the clinical stages, it may exhibit unknown adverse effects when used by more diverse and larger population. To understand those adverse effects manufacturer has to conduct the post marketing studies (Postmarketing Surveillance Programs, 2009). As part of its safety initiative to safeguard the public health, FDA has established the Post-Marketing Surveillance program to learn about the post marketing safety issues (Lesther, 2002). The purpose of this program is to identify, regulate and alert both the healthcare industry and consumers to adverse events which might have been identified during Post marketing surveillance or in Phase IV studies. The goal of the FDA is the continuous review of the safety of the drug/biologic products during marketing (Post marketing Surveillance Program, 2009). FAERS (FDA Adverse Event Reporting System) and MedWatch play a crucial role in collecting the post-marketing surveillance data.

FAERS (FDA Adverse Event Reporting System)

This is a centralized computer system through which consumers and/or healthcare professionals can report ‘adverse events’ and /or ‘medical error reports’ that were identified or experienced during its use or administration. The information once received is analyzed by the responsible center of FDA (CDER or CBER) and safety alerts may be issued both to the consumers and healthcare professionals (FDA Adverse Event Reporting System, 2012), thereby improving drug safety and helping to protecting the public health. Safety Alerts might include, but are not limited to, updating the labeling information, communicating new safety information to the healthcare community, product recalls, or withdrawal of approval due to severity of the adverse effects.

MEDWATCH (FDA Safety Information and Adverse Event Reporting Program)

MedWatch is a reporting system established by the FDA in 1993. MedWatch serves two main purposes. It is used to report any adverse event related to an FDA regulated product, including dietary supplements and cosmetics. Any consumer or healthcare professional may report the adverse event observed/experienced either by filling an FDA Form 3500 or online. In addition to that it provides clinical information about prescription and over the counter drugs biologics and dietary supplements (Valeri, 2007). Such adverse events reported through MedWatch will be reviewed and the necessary actions will be taken.

Purpose

The purpose of this project was to examine the trend in the number of safety alerts issued by FDA during the 10year period 2003 to 2012 and analyze the reasons for issuing safety alerts.

In addition, the following was investigated:

- Changes in the frequency of the issuance of safety alerts from 2003 to 2012?
- Possible reason behind any change in the frequency?
- The most common reasons for issuing safety alerts?

Background

Safety and efficacy of medicinal products are two crucial factors which need to be studied & evaluated before any products' release to market. An estimated 48% of Americans take at least one prescription drug during a given month. Overall 51% of approved drugs have serious adverse effects which are not detected prior to approval (Thomas et.al, 1998). It is, therefore, very important to determine the complete safety profile of any new drug to help protect the public health. According to a report by the Institute of Medicine, there are 1.5 million people are affected by adverse drug reactions every year (Valeri, 2007). As a primary governing agency for pharmaceuticals and medical devices in United States FDA has directive to investigate and make public aware of information related to adverse events once they approve for use in the market (Valeri, 2007).

IMPORTANCE OF POST MARKETING SURVEILLANCE

Every drug has its own safety profile. Some adverse events may fatal and some serious but not fatal and some non-serious. Labeling of every drug contains information about its safety profile. The safety profile at product launch are based upon observations found during the clinical studies. Upon marketing launch, however, a drug may exhibit adverse events not seen in clinical trials due its use in larger and more diverse populations.

For example, Nomifensin was used as antidepressant in Germany Since 1976, with intial labelling reflected a variety of long recognized hypersensitivity reactions, including fever, hemolytic anemia. In 1985 adverse reaction report showed serious hemolytic anemia cases which might be fatal that lead the manufacturer to voluntarily withdraw the drug in 1986. (Goldman, et al., 1996). This case exemplifies a safety profile of a drug that evolved over its lifetime.

Although CDER conducts most vigorous process before the release of the drug into the market it is not possible to detect all potential problems during premarketing clinical trials involving only several hundred to thousand patients (Post Marketing Surveillance programs, 2009). The major changes in the size and nature of the exposed patient population that occur once a medical product is available for widespread use emphasize the great importance of adverse event detection (Goldman, et al, 1996). So, post-marketing surveillance plays a major role where the drug safety issues can be monitored even after the release of the drug into the market.

Several drugs were withdrawn from the market due to the safety issues identified during post marketing. Table 1 shows 4 different drugs which were withdrawn from the market within a 12 month period of launch (Friedman, et.al, 1999).

	DRUG NAME	**YEAR OF WITHDRAWAL**	**SAFETY ISSUE**
1)	Fenfluramine and Dexfenfluramine	1997	Cardiovascular diseases
2)	Terfenadine	1998	Fatal cardiac arrhythmias
3)	Mibefradil	1998	Increased deposition of drugs which should be eliminated from the body.
4)	Bromfenac sodium	1998	Hepatotoxic effects

Table 1. Drug withdrawals due to adverse events. Data obtained from Friedman et al (1999).

When we observe all these drugs many of them did not show any of these adverse events during the premarketing studies, but several adverse events including deaths were reported after their release into the market. So, safety profile of the is very important to discover long term side effects of the drug which was done by post- marketing surveillance.

EVOLUTION OF MEDWATCH

The safety of drugs and other medical products is a key point in FDA's mission. The main aim of FDA is to protect and promote the health of the public. In early 1950s to 1970 there were two organizations collecting adverse event data. One was the American Medical Association's Committee on Adverse Events that concentrated on reports from physicians and small hospitals. The second was the FDA that collected reports from large hospitals and government agencies (Lurance, 1988). In 1970 the two groups merged and FDA took overall responsibility for collection of adverse events. In the years following several adverse events and deaths were observed only months after drug approvals. To study the adverse events that the approved novel drugs were exhibiting, FDA initiated several Post Marketing Surveillance programs. The primary aim of these programs was to protect the public from unknown serious adverse events. Such programs include Drug Safety Communication (webpages which provide the latest information on drug safety), FDA safety podcasts (provides the emerging safety information) and communications that provide ongoing safety reviews to the public. With these programs FDA has started receiving numerous adverse events from the healthcare professionals and consumers. To accommodate the increasing adverse event reports, the FDA in 1993 initiated the adverse event reporting program (AERS) called Med-Watch (Valeri, 2007). The main aim of Med-Watch was to get the safety information to the public Med-Watch was called "is an initiative designed to educate all health professionals about the critical importance of being aware of, monitoring for, and reporting adverse events and problems to FDA and/or the manufacturer and to ensure that new safety information is rapidly communicated to the medical community thereby improving patient care" (Jhon, 2000). Through Med-Watch the agency receives updates regarding serious adverse drug reactions, product problems of drugs, dietary

products, cosmetics and infant formulas from health professionals, nurses and consumers (Medwatch: Managing risks at FDA, 2011). In addition, Med-Watch encourages a sense of responsibility among physicians to report adverse events by involving them in Med-Watch program (Kessler, 1993).

According to Kessler (1993), the Med-Watch program had specific goals:

- To increase awareness of drug- and device- induced disease.
- To clarify what should (and should not) be reported to the agency.
- To make it easier to report by operating a single system for health care professionals,
- To report adverse events and product problems to the agency,
- To provide regular feedback to the health care community concerning safety issues involving medical products etc.

Med-Watch received 14,357 reports between June 1993 and July 1994 (Jhon, 2000). After evaluating these reports. FDA issued safety alerts which contain important regarding product safety (Henkel, 1988). These safety alerts issued by the FDA are called as “Med-Watch Alerts”. Every month FDA updates the new safety information on drugs, cosmetics, dietary supplements. Examples from the FDA have been provided in Tables 2 and 3..

Table 2 shows the examples of safety alerts updated by FDA in 2003 and Table 3 shows the examples of safety alerts issued in 2012.

DRUG NAME	PROBLEM	ALERT
Gynecare Intergel Adhesion prevention solution	Several serious problems including postoperative pain	Voluntarily withdrawal from the market
Risperdlal	Cerebrovascular problems	Labeling changes as not to treat for dementia.

Table 2. Examples of safety alerts from FDA in 2003. Data obtained from Medwatch Safety Alerts (2011)

DRUG NAME	PROBLEM AND ALERT
Carboplatin Injection	Recalled due to the presence of visible particles
Tylenol oral suspension for infants	Recalled due to difficulty in dosage administration

Table 3. Examples of safety alerts from FDA in 2012 (The FDA safety information and Adverse Event reporting Program, 2012)

Methodology

- All the safety alerts on the FDA website were counted from 2003 to 2012. (See Appendix)
- Changes in the safety alert frequency were calculated.
- The most common reasons behind issuing these safety alerts, such as manufacturing defects, safety issues, adverse events, unapproved drugs and more, were determined.
- The most common reasons behind issuing these safety alerts by the FDA were found. They were grouped into three different types by their commonalities.
- A regression analysis of the change in number of reports over time was calculated to determine any significant trends in the reporting rates.

Results

Table 4 shows the number of safety alerts issued by FDA each year. After evaluating the safety alerts from 2003 to 2012, several interesting results were found. Reasons for issuing safety alerts included adverse events, manufacturing defects, contamination, unapproved drug, undeclared drug ingredients, death, harm to fetus, suicidal behavior, allergic reactions, more active drug, labeling errors, and cancer. These events were divided into three clusters: Adverse events, CMC (Chemical, Manufacturing and Controls, which includes manufacturing of bulk drug substance and final drug product, setting specifications, release criteria, stability programs, and analytical methods), and Labeling. Numerous variations in the frequency of issuing safety alerts were seen. Figure 1 shows the number of safety alerts during the period of 10 years from 2002 to 2013.

YEAR	NO OF ALERTS
2003	33
2004	45
2005	107
2006	68
2007	105
2008	91
2009	84
2010	78
2011	74
2012	69

Table 4. Number of safety alerts issued from 2003 to 2012. Data obtained from Medwatch Safety Alerts for Human Medical Products (2013).

Figure 1. Number of Safety Alerts issued by Medwatch. Graphical representation of frequency of number of safety alerts from 2003 to 2012. Data obtained from Medwatch Safety Alerts for Human Medical Products (2013).

When the reasons for every safety alert in a specific year were measured, the number varied each year for the three different clusters. Tables 5 through 7 show examples of the safety alerts for each cluster. Table 5 shows safety alerts issued due to adverse events; Table 6 shows safety alerts issued due to CMC ; Table 7 shows safety alerts issued due to labeling. Figure 2 represents the changes in clusters in number of safety alerts during the 10-year period. Table 8 shows the comparison of statistics between the different clusters of safety alerts.

NAME OF DRUG	YEAR SAFETY ALERT ISSUED	REASON FOR ISSUING SAFETY ALERT
Celebrex	2005	Lack of cardiovascular safety data and serious skin reactions
Propoxyphene	2010	Risk of cardiac toxicity
Incevik	2012	Serious skin reactions
Biophosphonates	2008	Increased risk of atrial fibrillation
Crestor	2005	Serious muscle toxicity

Table 5. Examples of Safety alerts issued to different drugs due to Adverse Events. Data obtained from Medwatch Safety Alerts for Human Medical Products (2013).

NAME OF THE DRUG	YEAR SAFETY ALERT ISSUED	REASON FOR ISSUING SAFETY ALERT
Hydralazine HCL injection	2006	Contain particulates
Cleviprex	2009	Stainless steel particles
Cytarabine	2012	Lack of sterility
Dextramphetamine	2008	Presence of oversized tablets
Ibuprofen	2009	Unapproved drug

Table 6. Examples of Safety Alerts issued to different drugs due to Chemistry/Manufacturing/Controls. Data obtained from Medwatch Safety Alerts for Human Medical Product (2013).

NAME OF THE DRUG	YEAR OF SAFETY ALERT ISSUED	REASON FOR ISSUING SAFETY ALERT
Guaifensin	2010	Mislabeled (one drug with several brand names)
Albuterol sulfate inhalation	2011	Mislabeled (labeled with wrong concentration)

Table 7. Examples of Safety Alerts issued due to Labeling problems. Data obtained from Medwatch Safety Alerts for Human Medical Products (2013).

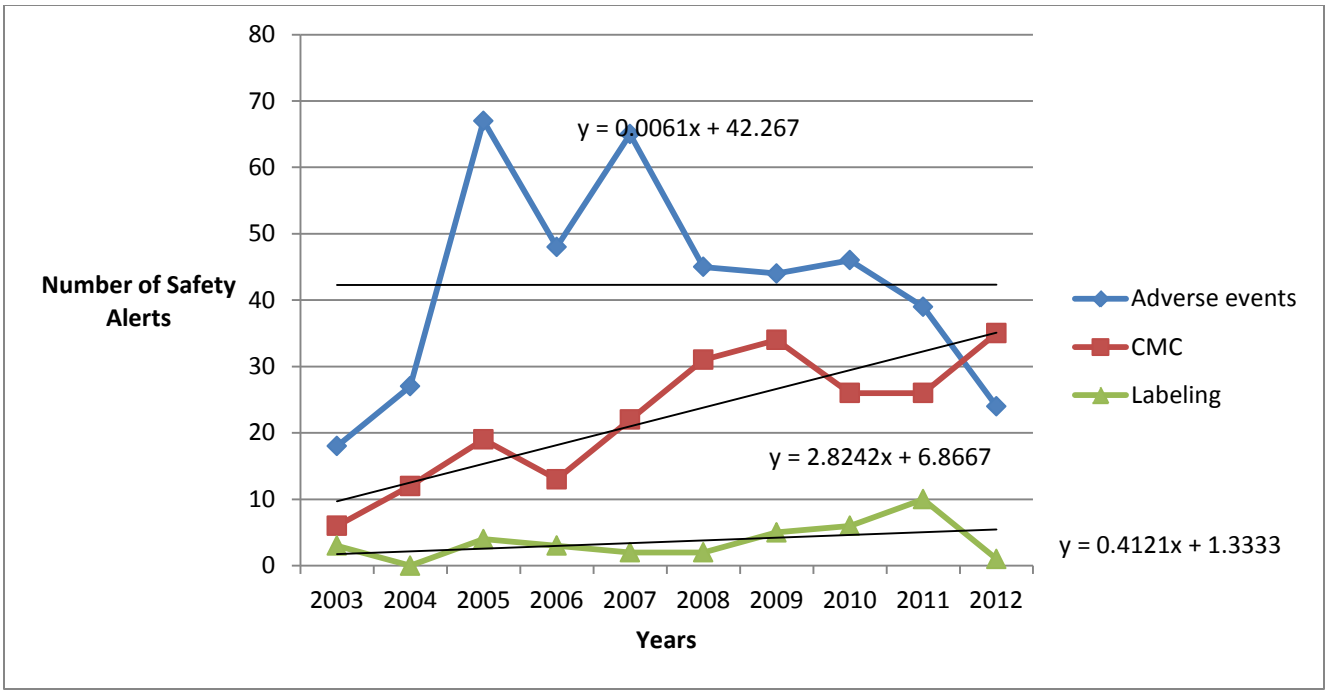

Figure 2: Incidence of Safety Alerts issued by three different clusters from 2003 to 2012. Data obtained from Medwatch Safety Alerts for Human Medical Products (2013)

CLUSTER	COEFFICIENT	R SQUARE	SIGNIFICANCE F (P-VALUE)	t-STATISTIC	F-STATISTIC
CMC	2.824242424	0.756029969	0.001080781	4.979047371	24.79091272
Adverse Events	0.006060606	1.28834E-06	0.99751708	0.003210409	1.03067E-05
Labeling	0.412121212	0.188334963	0.210170994	1.362454629	1.856282617

Table 8. Regression Analysis for three clusters showing slope, R2,P-value,t-statistic and F-statistic. Note: Coefficient is a Slope, R-Square is the amount of variance accounted for, P=0.05 (Standard p value generally used to calculate the Significance)

Discussion

Med-Watch issued safety alerts for several drugs based on the drug profile after releasing into the market. This paper mainly emphasized the analysis of safety alerts from 2003 to 2012. In a period of 10 years, there was a change in number of safety alerts issued (Figure 1). In 2003 the number was only 33, possibly due the fact that FDA was still in the process of improving their post marketing programs (2003 Safety Alerts for Human Medical Products, 2010). There are 370,898 adverse event reports to the FDA in the year 2003 (Center for Drug Evaluation and Research Update, 2007) which increased to 482,155 adverse event reports in 2007 from Med-Watch program and manufacturers (Center for Drug Evaluation and Research Update, 2007). The increase in reports paralleled the increase in safety alert reports because there were 105 safety alerts issued by CDER in 2007 (2007 Safety Alerts for human Medical Products, 2010). It appears, however, that after 2007 the numbers of alerts are reduced.

Figure 2 presents the changes throughout the 10-year period in the three different clusters of safety alerts. Adverse events account for greatest number of safety alerts. According to the P-value shown in Table 7, the slope of the change is not statistically significant.

The second cluster, CMC (Chemistry, Manufacturing and controls), is very predictive. In CMC alerts are initially far less than alerts due to adverse events concerns until 2007, but after 2007 the alerts increased and finally in 2012 the alerts due to CMC were more than alerts due to safety.

Figure 2 shows an increase in the number of alerts due to CMC from 2003 through 2012. As shown in Table 7, there is almost a 75% increase in number of alerts due to CMC from 2003 to 2012.

The increase in Safety Alerts due to CMC throughout the 10 years is statistically significant. The apparent increase of these alerts may be due to either, or both of the following:

1) Errors have increased.
2) More errors have been found due to increased inspections.

By knowing number of manufacture site inspections during these years would help to find the possible reason behind the increase. Table 9 displays the number of manufacturing inspections that occurred from October 2009 to December 2011. There were decreased manufacturing inspections from 2010 to 2011. Further data on the number of manufacturing inspections is needed to find out if the increase or decrease of inspections from 2003 to 2012 was significant. An FOI request has been made for these data for the remaining years.

YEAR	NO OF INSPECTIONS
Oct 2009	5
Nov 2009	5
Dec 2009	0
Jan 2010	2
Feb 2010	2
Mar 2010	3
Apr 2010	2
May 2010	2
Jun 2010	1
Jul 2010	0
Aug 2010	1
Sep 2010	1
Oct 2010	4
Nov 2010	3
Dec 2010	0
Jan 2011	0
Feb 2011	2
Mar 2011	1
Apr 2011	1
May 2011	4
Jun 2011	2
Jul 2011	0
Aug 2011	0
Sep 2011	0
Oct 2011	2
Nov 2011	0
Dec 2011	1

Table 9. Number of product manufacturing facilities site inspections occurred from October 2009 to December 2011.

The third cluster in Figure 2 is labeling. The Safety Alerts caused due to labeling are less common. The frequency of alerts is almost constant. It is also very clear that labeling constitutes least probable reason for issuing safety alert when compared to other two clusters.

Conclusion

Medwatch program was established by FDA to support the post-marketing surveillance program. Before the evolution of Medwatch there were no such reports from health professionals regarding adverse events. But reports from health professionals are equally important as from manufacturer. Medwatch created new era in reporting adverse events from wide population to support the drug safety. Evaluating these reports and providing 'safety alerts' is very useful for physicians and health professionals to save the public from adverse events. Evaluation of results from 2003 to 2010 led to these conclusions:

- There is no significant trend in number of safety alerts issued from 2003 to 2012
- The number of alerts due to Chemistry/Manufacturing/Controls showed a significant upward trend. Further research is needed to know the possible reasons behind these results.
- No significant trend was observed with Adverse Event or Labeling-related Safety Alerts.

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