"ARE PHARMACEUTICAL MARKET WITHDRAWALS PREVENTABLE?"

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ABSTRACT

Pharmaceutical companies may be requested by FDA to withdraw a drug from the market permanently. This request is based on fact that the risks of its usage outweigh its benefits. These requests affect the health of patients using the drugs on a regular basis, as well the pharmaceutical companies since an individual drug is the result of more than a decade of research and the use of tremendous resources. Therefore, there is a definite need in the present situation to stop these drug withdrawals by learning from the previous incidences. The first step in this approach is to find the roots of the problem. The cause of the problem can be traced to the initial approval of the drug (NDA). If these approvals are stopped at the very starting point (the point of approval) or if their fatal outcomes are predicted or foreseen then these withdrawals won't become necessary. Drugs withdrawn between 2001 and 2010 (n=15) are considered in this investigation. The primary adverse events which led to the withdrawal of these 15 drugs were compared with the data available in the original NDA medical review. From the 15 drugs considered, sufficient information for analysis was available for only 7 drugs. Among the 7 drugs analyzed, the safety data found for 2 particular drugs could have suggested or predict the future problems. Thus only 2 of the 7 NDAs analyzed offend hints of future problems. It seems that the drug withdrawal could not have been predicted for the majority of drugs removed from the market.

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INTRODUCTION

Drug development and approval is an incredibly difficult and complex process. On average it takes 10-15 years for a compound to reach patients as an approved drug. Unfortunately, some of these approved drugs are withdrawn from the market after some time. This is mainly due to the safety concerns and may also be due to the lack of efficacy.

According to Food and Drug Administration (FDA) statistics published annually on the Center for Drug Evaluation and Research (CDER) reports, on average after the introduction of Prescription Drug User Fee Act (PDUFA), the annual withdrawal of New Medical Entities (NMEs) based on safety is about 5% of the approved drugs (FDA, Center for Drug Evaluation and Research.Report to the Nation. Improving Public Health through Human Drugs, 2000). The drug withdrawal decision may be voluntary by the pharmaceutical companies or requested by the FDA based on post marketing surveillance reports.

In addition to Phase 4 trials by the respective companies, in the United States the regulating authority FDA, through its Office of Surveillance and Epidemiology (OSE) employs tools like MedWatch (for health care professionals and public) and Adverse Event Reporting Systems (AERS) for monitoring of approved drugs. Based on those monitoring reports, drugs which are thought

to have high safety concerns or efficacy concerns may be withdrawn from the market. We can see that in spite of the tremendous amount of time and energy spent on R&D by pharmaceutical companies in developing these drugs, some of these drugs end up as failures. So, there is a definite need to find a solution to prevent these withdrawals by the application of knowledge gained from past experiences.

BACKGROUND

According to the list compiled under the new statutory requirements of the Food and Drug Modernization Act (FDAMA) of 1997, there were about 60 drug products that have been withdrawn or removed from the market. (FDA, List of Drug Products That Have Been Withdrawn or Removed From the Market for Reasons of Safety or Effectiveness, 1998). According to the FDA's annual CDER reports until 2010 a total number of 33 drugs have been withdrawn from the market due to safety alone (FDA, Safety Alerts for Human Medical Products, 2011).

Shown below in the Figure1 is the history of approvals and safety-based withdrawal numbers of NMEs on 5-year time lines from 1980 to 2010 derived from CDER annual reports. This graph compares the .number of NMEs

approved in a particular 5 year cohort and the relative percentage of the safety-based NME withdrawals in the same period

Figure 1 - Safety based NME Approval and withdrawal percentages from 1980-2010

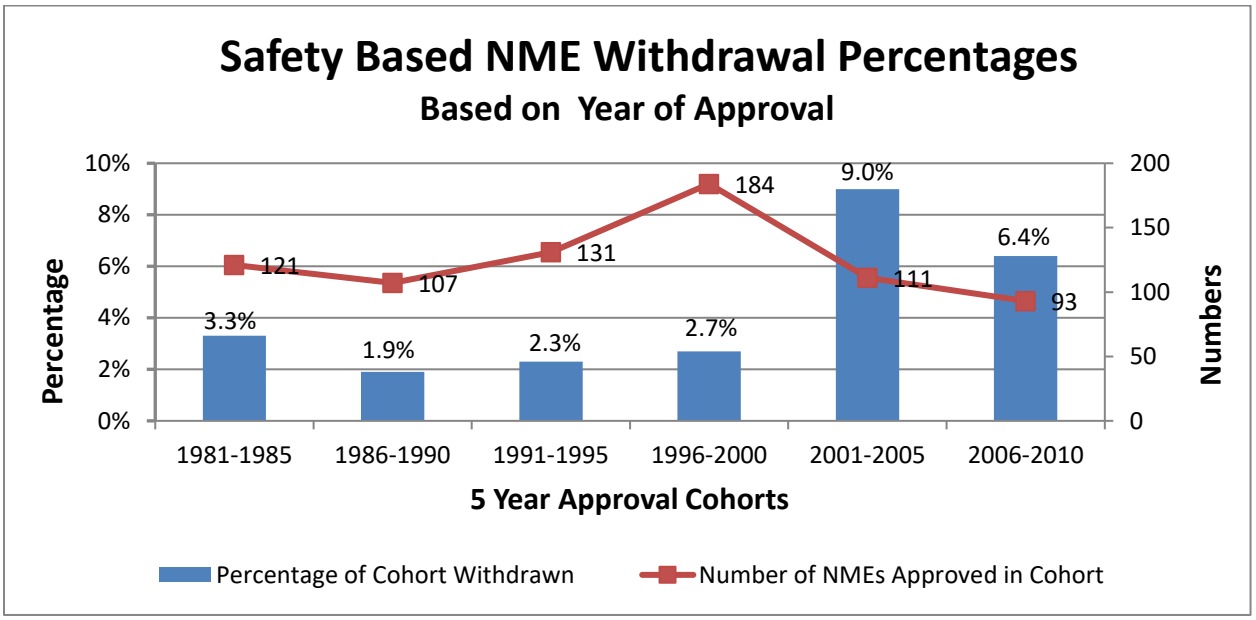

Figure 1 the data in the above table is adapted from the report "Center for Drug Evaluation and Research. Report to the Nation .Improving Public Health through Human drugs." Retrieved from http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/WhatWeDo/UCM079006.pdf.

We can see that during the pre-PDUFA period 1981-85 and 1986-90, based on the number of NMEs approved, there are 3.3% and 1.9% safety based drug withdrawals. In the PDUFA period the approval numbers from 1991-1995 reached 184 with the withdrawn percentage being 2.3. Then during the last 2 cohorts, 2001-05 and 2006-10 the safety based withdrawal reached 9% and 6.4% of the approved drugs, respectively.

PURPOSE

This proposal is to see if the market withdrawal of pharmaceutical drugs could have been predicted based on the data in the original New Drug Application (NDA).

The specific data supporting the individual drug approvals and the reasons for withdrawals will be used to determine the results.

METHODOLOGY

From the total time line of the drug approval and withdrawal in history of FDA, drugs withdrawn in the time period 2001-2010 will be considered for this research.

As per the FDA-CDER Annual reports, 15 drugs were withdrawn in this period between 2001and 2010 (FDA, Medwatch the FDA Safety Information and Adverse Event Reporting Progrm, 2011). The Table 1 below shows the drugs along with the reason for their withdrawal.

Table 1

Drug	Reason for Withdrawal
Baycol®(cerivastatin)	Rabdomylosis
Raplon®(rapicuronium)	Bronchospasm
Tegison®(etritinate)	Bone Toxicity
Orlaam®(levomethadyl)	Serious cardiac adverse events
Vioxx®(rofecoxib)	Heart attacks, heart strokes
Bextra®(valdecoxib)	Fatal cardio vascular events
Tysabri®(natalizumab),	Progressive multifocal leukoencephalopathy (PML)
Trasylol®(aprotinin)	Renal toxicity.
Permax®(pergolide)	Serious damage to patients' heart valves
Zelnorm®(tegaserod maleate)	Heart attacks ,stroke, angina
Meridia®(sibutramine	Risks for Heart disease
Raptiva®(efalizumab)	Progressive Multifocal leukoencephalopathy (PML)
Mylotarg®(gemtuzumab ozogamicin)	Death in cancer patients
Cylert®(pemoline)	life threatening hepatic failure
Neutrospec®(technitium (99m tc) fanolesomab)	Serious and life-threatening cardiopulmonary events

For these drugs, the serious side effects responsible for drug withdrawal will be determined from the FDA website and the safety data available on the drugs from the NDA approval databases (from the Medical Review) will be studied.

The goal is to observe the relationship between AEs which led to the drug withdrawal and the data (corresponding to the serious side effects responsible for withdrawal) in the NDA safety databases. Finally I will summarize the results by noting if the regulatory authorities or the pharmaceutical companies might have predicted the Adverse Events (AEs) from the clinical data available prior to approval.

RESULTS

According to the drug statistics published on Annual CDER reports, the total number of drugs withdrawn between 2001 and 2010 was 15. From those 15 drugs considered for this research, information for review of NDA data was only available for 7 of these on the FDA website. Those 7 drugs are Vioxx® (rofecoxib), Bextra® (valdecoxib), Meridia® (sibutramine), Zelnorm® (tegaserod maleate), Raplon® (rapicuronium), Mylotarg® (gemtuzumab) and Baycol® (cerivastatin), hereafter referred to by their brand names.

In the case of the 5 drugs, Baycol, Mylotarg, Zelnorm, Bextra and Vioxx, I did not find any evidence in the NDA databases that might have foreshadowed the fatal drug outcomes later seen in their post-marketing trials. Table 2 below shows those drugs along with their respective retrospection.

Table 2 - Retrospection of Drugs in relation to their Market withdrawal

Drugs	**Reasons for market withdrawal**	**Retrospective analysis of incidence of AEs in NDA safety databases**
Bextra®	Fatal cardio vascular events	No significant difference from placebo for these events
Zelnorm®	Heart attacks ,stroke, angina	No significant difference from placebo for these events
Mylotarg®	No efficacy and Death in cancer patients	Few deaths occurred in patients but not attributed to the drug
Baycol®	Rabdomylosis	No significant difference from placebo for these events
Vioxx®	Heart attacks, heart strokes	No significant difference from placebo for these events

The NDA data for Meridia and Raplon contained safety data which might have suggested the adverse drug reactions (hereafter referred to as ADRs) seen during marketing of the drug which resulted in market withdrawal.

Meridia®:

Background:

Meridia (sibutramine) is an oral anorexic agent manufactured by Abbott Laboratories. It was intended for treatment of exogenous obesity (weight loss in certain obese people with heart disease or maintenance of weight loss in the obese people). It was approved by the FDA in 1997.

Reason for withdrawal:

Due to several safety issues such as serious cardiovascular events, non-fatal heart strokes and deaths, it was removed from the U.S market in 2010 (FDA, Safety Alerts for Human Medical Products, 2011).

NDA Database Retrospection:

Placebo-controlled trials with dexfenfluramine as secondary control (FDA, Drug Approval Package, 2003) are used for the clinical research. The following issues were examined in the NDA data: premature discontinuations, dose reductions due to adverse events, cardiovascular AEs, deaths, withdrawal due to AEs, and blood pressure changes.

Permanent Dose Reductions due to AEs:

As defined in the NDA report of the drug, dose reduction was a result of an intolerable AE, or systolic blood pressure being greater than 160 mm Hg, or diastolic blood pressure being greater than 95mm Hg (FDA, CDER Drug Approval Package for Meridia, 2002). The Table 3 below show the percentage of patients who underwent dose reductions as a result of the adverse effects (FDA, CDER Drug Approval Package for Raplon, 2001).

Table 3 - No. of Permanent Dose Reductions along with Respective Drug Dose

	Placebo	1mg	5mg	10mg	15mg	20mg	30mg
	N=148	N=149	N=151	N=150	N=152	N=146	N=151
A.E	3	7	4	10	6	15	23
B.P	5	1	1	4	6	5	13
Pulse rate	1	1	2	0	4	11	4
Other	0	1	6	3	4	1	4
Unknown	0	0	1	1	0	1	1
Total	9	10	14	18	20	33	44
Percentage	6%	7%	9%	12%	13%	23%	29%

Table 3. The data is adapted from FDA. (2002, May 22). *CDER Drug Approval Package for Meridia.* Retrieved August 18, 2011, from FDA Approved Drug Products: http://www.accessdata.fda.gov/drugsatfda_docs/nda/97/020632a_apltr_thr_%20mor.pdf

The percentage reduction in subjects taking 10mg, 15mg and 20mg doses of Meridia were 12%, 13% and 23% when compared to 6% in the placebo treated subjects. Overall, the permanent dose reduction numbers found in BRI 852 are 65/899, which was about 7.2% of the study population. The common adverse

events responsible for these dose reductions were hypertension, tachycardia, chest pain, anxiety and anorexia.

Cardiovascular AEs:

Cardiovascular AEs were an important concern even before its approval. The cardiovascular AEs associated with the Meridia included arrhythmias, ventricular ectopic beats, atrial fibrillation, left bundle branch block and T-wave changes. The table below compares results in cardiovascular AEs between using Meridia and a placebo (FDA, CDER Drug Approval Package for Meridia, 2002).

Data from Table 4 below shows the comparison of cardiovascular AEs caused by Meridia and by placebo. It shows that subjects using Meridia had considerably higher incidences of cardiovascular AEs when compared to patients using the placebo. The cardiovascular AEs were the key factors responsible for withdrawal of Meridia after its release

Table 4 - Comparison of Cardiovascular AEs caused by Meridia and by Placebo

Adverse event	Meridia (N=1766)	Placebo (N=605)
Tachycardia	2.5%	0.5%
Palpitations	3.1%	1.2%
Hypertension	2.1%	0.8%

Vasodilation	2.6%	0.8%

Table 4 data adapted from FDA. (2002, May 22). *CDER Drug Approval Package for Meridia.* Retrieved August 18, 2011, from FDA Approved Drug Products: http://www.accessdata.fda.gov/drugsatfda_docs/nda/97/020632a_apltr_thr_%20mor.pdf

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Electrocardiograms (ECGs) are used to test functional activity of the heart. According to safety data in the NDA report, among the ECGs from 2473 participating subjects, 31 of them were abnormal (FDA, CDER Drug Approval Package for Meridia, 2002). Of these 31, 3 of them were seen in the placebo-treated patients, and the remaining 28 were seen in Meridia-treated subjects. Among those 28, 5 of them were considered clinically significant (FDA, CDER Drug Approval Package for Meridia, 2002).

Adverse Events:

The number of AEs that occurred in subjects in a treatment clinical trial can be directly related to the safety profile of the drug. The withdrawal of subjects from the study due to these AEs is also considered. The Table 5 below demonstrates the incidence of AEs in drug and in placebo treated patients.

Table 5 - Comparison of AEs caused by Meridia and by Placebo

Body system	Meridia (n=1766)	Placebo (n=605)
Vasodilation	2.6	0.8
Tachycardia	2.5	0.3
anorexia	14.1	4.3
constipation	11.4	6.1
Appetite increase	9.3	2.8
Insomnia	10.8	4.6
Infection	22.8	12.7

Table 5 data adapted from FDA. (2002, May 22). *CDER Drug Approval Package for Meridia.* Retrieved August 18, 2011, from FDA Approved Drug Products: http://www.accessdata.fda.gov/drugsatfda_docs/nda/97/020632a_apltr_thr_%20mor.pdf

About 9.9% of the subjects taking Meridia withdrew from the study, while 8.4% of placebo subjects withdrew. All the subjects who withdrew from the Meridia treatment were the ones who suffered from nervous system and cardiovascular AEs.

Vital Signs:

Vital signs are a direct measurement of the cardiovascular functionality in a subject. Table below shows "the mean change from baseline in systolic blood pressure and diastolic blood pressure, in uncomplicated obese patients in placebo-controlled studies by dose." (FDA, CDER Drug Approval Package for Meridia, 2002). The Table 6 below shows the comparison of mean changes from baseline in B.Ps in Meridia (different doses) and in Placebo treated subjects.

Table 6 - Comparison of mean changes from baseline in Blood Pressures (mmHg) in Meridia (different doses) and in Placebo treated subjects.

Measurement	placebo	<5mg	5-9mg	10-14mg	15-19mg	20-29mg	>_30mg	All doses
Resting SBP(mmHg)	-0.7	0.1	2	1	2.7	1.7	4	1.7
Standing SBP(mmHg)	0.9	1.2	1.1	3.1	3.3	3.5	1.2	2.3
Resting DBP(mmHg)	-0.6	-0.1	1.5	1.4	1.8	2.2	3.1	1.5
Standing DBP(mmHg)	0.5	-1.3	0.6	1.7	4	2.6	2.3	1.7

Table 6 data adapted from FDA. (2002, May 22). *CDER Drug Approval Package for Meridia.* Retrieved August 18, 2011, from FDA Approved Drug Products: http://www.accessdata.fda.gov/drugsatfda_docs/nda/97/020632a_apltr_thr_%20mor.pdf

By observing the above readings, it is quite evident that the drug might be a cause for the increase in blood pressure.

Premature Discontinuations due to Adverse Events:

Premature discontinuations due to adverse events from a clinical trial are usually a measure of drug safety and drug compliance. Table 7 below shows

the percentage of subjects discontinued without completing the study because of AEs.

Table 7 - Number of Patient discontinuations due to AEs

Type of patients	Normal Obese (N=2319)	Obese Hypertensive (N=126)	Obese Diabetic (N=96)
Placebo	8.4%	2.7%	4%
Meridia	10.2%	4.2%	6.8%

Table 7 adapted from FDA. (2002, May 22). *CDER Drug Approval Package for Meridia.* Retrieved August 18, 2011, from FDA Approved Drug Products: http://www.accessdata.fda.gov/drugsatfda_docs/nda/97/020632a_apltr_thr_%20mor.pdf

The percentage of discontinuations was higher in subjects receiving Meridia when compared to the placebo.

Meridia labeling

The labeling insert of Meridia under the warnings section stated that:

"Elevations in the blood pressures can be caused by the usage of this drug and monitoring of the vital signs for the treated patients should be done by the physicians. Meridia should not be given to the patients with uncontrollable blood pressures. Patients with Concomitant cardiovascular disease should not take Meridia as there is a possibility of elevation of disease status."(2001)

RAPLON®:

Background:

Raplon was a drug used in modern anesthesia to enable the process of endotracheal intubation. It was manufactured by Organon Company and approved by FDA in 1999.

Reason for Withdrawal:

Raplon was withdrawn from the U.S. market in 2010 because of serious side effects such as bronchospasm and unexplained fatalities.

NDA Database Retrospection:

The NDA approval of this drug was mainly based on safety data from study ORG 9487 (FDA, CDER Drug Approval Package for Raplon, 2001). Focus was primarily placed on issues related to bronchospasm, histamine levels, adverse events and the effect of concomitant medications.

The major AEs discovered during NDA submission were bronchospasm, hypotension and tachycardia.

Bronchospasm:

Bronchospasm is a high risk respiratory disorder in which a sudden constriction of the muscles in the walls of bronchioles occurs. It is mainly caused by the release of histamines. From the below table it shows that bronchospasm was one of the major AEs in NDA safety reports of Raplon. Table 8 below shows comparison of Bronchospasm occurrences in different drug treated subjects. The incidence of bronchospasm in Raplon treated subjects was clearly 4 times that of placebo treated subjects and twice that of Succinylcholine treated subjects..

Table 8 - Comparison of Bronchospasm occurrences in different drug treated subjects

Drug Name	Bronchospasm
Raplon (N=564)	4%
Succinylcholine (N=177)	2.1%
Placebo (N=84)	1.2%

Table 8 data adapted from FDA. (2001, July 2). *Drug Approval Package for Raplon.* Retrieved August 22, 2011, from FDA approved Drug Products: http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/20984_RAPLON_medr_P3.pdf

Abnormal Histamine Levels:

Abnormal levels of histamine in the body can lead to bronchospasm, hypotension and errythmetic rash (FDA, CDER Drug Approval Package for Raplon, 2001).

According to the NDA safety database, a dose-related histamine level elevation is observed in the Raplon treated patients (FDA, CDER Drug Approval Package for Raplon, 2001).

Effect of Concomitant Medications:

According to the FDA safety databases, an additional reason for the withdrawal of Raplon was a number of unexplained interactions with different drugs. In US studies, subjects taking concomitant vasoactive agents had an increased incidence of bronchospasm and hypertension compared to subjects not taking these agents (9.1% vs. 4.6% and 11.4% vs. 7.2%). In the NDA database Raplon was linked to a significant elevation of bronchospasm incidents in the case of subjects taking vasoactive agents and anti-asthmatics.

Interaction of Anesthetic Medications with Raplon:

Anesthetics like propofol, thiopental and fentanyl, when interacting with Raplon, have been shown to cause bronchospasm. When comparing patients taking anesthetics and Raplon with patients taking just anesthetics, the ratio

of bronchospasm incidents is 5.6%: 0%. In the same situation, the ratio of tachycardia incidents is 4.8%: 0% (FDA, CDER Drug Approval Package for Raplon, 2001).

Adverse Events:

As discussed earlier, one of the most common AEs observed (and of high concern) is bronchospasm. The Table 9 below provides study data comparing the incidence of common AEs caused by Raplon and by succinylcholine. The Table 10 shows the frequency of occurance of various AEs in Raplon treated subjects.

Table 9 - Comparison of incidence of Hypotension and Bronchospasm in different age group subjects (treated with Raplon or Succinylcholine)

Treatment group	Common AE	Age			
		18-30 N(%)	31-40 N(%)	41-50 N(%)	51-64 N(%)
Raplon		N=130	N= 161	N=129	N=144
n=564	Hypotension	3(2.3)	5(3.1)	7(5.4)	28(19.4)
	Bronchospasm	11(8.5)	9(5.6)	3(2.3)	2(1.4)
		N=46	N= 54	N=45	N=32
Succinylcholine					
N=177	Hypotension	1(2.2)	4(7.4)	5(11.1)	8(25)
	Bronchospasm	0.0	0.0	1(2.2)	1(3.1)

Table 9 data adapted from FDA. (2001, July 2). *Drug Approval Package for Raplon.* Retrieved August 22, 2011, from FDA approved Drug Products: http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/20984_RAPLON_medr_P3.p

Table10 - Frequency of occurance of various AEs in Raplon treated subjects.

System Organ class AE	Adults & geriatrics N =596	Children N=17	Infants N=72
Gastrointestinal	5.7%	5.9%	2.8%
Heart Rate and Rhythm	5.7%	11.8%	1.4%
Tachycardia	3.7%	11.8%	
Respiratory	15.8%	17.6%	11.1%
Bronchospasm	10.9%	5.9%	4.2%
general	0.8%	5.9%	5.6%
Application site reaction	0.7%	35.3%	29%

Table 10 data adapted from FDA. (2001, July 2). *Drug Approval Package for Raplon.* Retrieved August 22, 2011, from FDA approved Drug Products: http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/20984_RAPLON_medr_P3.p

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Raplon Labeling

The labeling insert of Raplon under the warnings section stated that:

"The usage of Raplon may sometimes result in Hypersentivity reactions and anaphylactic reactions."Clear instructions about the drug interactions incase of concomitant drug usage. Bronchospasm was described as one of very low frequency AE.

DISCUSSION

Meridia®: Based on the above observations, the key events in Meridia's withdrawal from the market were existent even before its NDA approval. At the initial NDA submission the reviewing Medical officer had recommended against the approval of Meridia as it had an unsatisfactory risk-benefit ratio (clinically significant rise of the blood pressure). Therefore Knoll laboratories was advised by FDA to provide additional information regarding the issues related to increase in blood pressure and its maintenance, change of initial treatment dosage and development of patient information insert on blood pressure and other related issues. In response to FDA advice, Knoll provided additional clinical data which showed clinically meaningful weight loss (satisfying FDA weight loss criteria).The risk vs. benefit ratio of Meridia was explained as:

"Obesity has mortality of 1168 per million per year. If these patients are treated Sibutramine treatment, adjusted for lack of lowering of blood pressure will save

235 lives per million per year while sibutramine risk related to an increase in mean blood pressure of 2mm hg is estimated to be 32 per million per year. The net benefit of treatment, 203 lives is a 9% reduction in mortality. Risk may be lowered and benefits enhanced by clinical monitoring and treatment only of responders."

Knoll Changed the initial treatment dose to 5mg (which was 15mg before initial NDA submission). The labeling insert of Meridia clearly mentioned the risk of increase in blood pressure (associated cardiovascular disease), its non-use in the patients with concomitant cardiovascular disease and uncontrollable blood pressures. The labeling insert also advised close monitoring of blood pressure by physicians. Thus FDA approved the drug on grounds that the benefit of its usage outweighed its risk and under the condition that the company must conduct Phase 4 trials for testing long term effects of its usage. The withdrawal of Meridia was mainly based on data from clinical studies observing long-term effects. Findings from these studies showed that cardiovascular risks outweighed the minimal benefits. The data from the original NDA clearly showed potential risk of long-term use. When combined with the minimal reduction in weight, it is likely that the risks were significant even at time of approval. In my opinion, the NDA should not have been approved.

Raplon®: Bronchospasm was a known AE even before the drug's approval. According to the label published at NDA approval time, there was no mention of any potential occurrences of bronchospasm connected to the use of Raplon,

which was a known AE and was a main reason for its withdrawal. If labeling had contained warnings of bronchospasm, perhaps the incidence of fatalities might have been reduced. However, given the modest benefit and high risk seen in the NDA database, Raplon likely should not have been approved.

If a researcher looks closely at the NDA safety databases he/she can detect indications for probable future withdrawals of drugs in 2 out of 7 drugs analyzed. Thus for less than 30% of drugs for which data was available, there was some indications of possible future withdrawal. If this ratio is consistent, perhaps 4 of the 15 drug withdrawals might have been stopped.

Fifteen drugs were withdrawn in the time period 2001-2010 while the number of drugs approved in the same period was 200. The rate of withdrawal was therefore 7.5%. During the pre-marketing trails drugs are tested on thousands of people (both patients and healthy volunteers) while in the post marketing stage the number of people taking these drugs is may be hundreds of times the NDA population size. Drugs act differently on different people. Results of usage depend on several factors like genetics, age, sex, race and physiological status of the person's body. The results of the clinical trials in pre-marketing stage cannot always assure a positive risk-benefit ratio once the drug reaches the market place. That is the reason why pharmaceutical companies conduct post marketing trails (along with FDA employed monitoring or surveillance activities) by which new or additional data on the effects of the marketed drugs can be better understood.

But FDA needs to be very careful while approving the drugs (not to miss or overlook any evidences of future predictability) as sometimes the usage of these drugs might cost the health and life of the patients.

If these estimates can be extrapolated to the universe of drug approvals, of the total percentage of drugs that are withdrawn from the market place, perhaps less than 30% could have been prevented with a more conservative review, although the remaining nearly 70% could not have predicted from the NDA databases.

CONCLUSION

Based on the analysis of the withdrawn drugs-during the period 2001-2010, the majority of events which lead to market withdrawal were not predictable from the NDA databases.

While a small number of withdrawals might have been predicted based on a retrospective analysis of NDA databases, the vast majority of the drug withdrawals could not have been prevented.

REFERENCES

i. FDA. (2003). *MedWatch The FDA Safety Information and Adverse Event Reporting Program* . Retrieved August 20, 2011, from FDA: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm153189.htm

ii. FDA. (2005). *MedWatch The FDA Safety Information and Adverse Event Reporting Program* . Retrieved August 2011, from FDA: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm151239.htm

iii. FDA. (2006). *MedWatch The FDA Safety Information and Adverse Event Reporting Program* . Retrieved August 2011, from FDA: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm150332.htm

iv. FDA. (2001). *MedWatch The FDA Safety Information and Adverse Event Reporting Program.* Retrieved August 2011, from FDA: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm172216.htm

v. FDA. (2002). *MedWatch The FDA Safety Information and Adverse Event Reporting Program.* Retrieved August 2011, from FDA: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm154450.htm

vi. FDA. (2004). *MedWatch The FDA Safety Information and Adverse Event Reporting Program.* Retrieved August 2011, from FDA: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm152982.htm

vii. FDA. (2007). *MedWatch The FDA Safety Information and Adverse Event Reporting Program.* Retrieved August 2011, from FDA: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm150441.htm

viii. FDA. (2008). *MedWatch The FDA Safety Information and Adverse Event Reporting Program.* Retrieved August 2011, from FDA: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm064952.htm

ix. FDA. (2009). *MedWatch The FDA Safety Information and Adverse Event Reporting Program.* Retrieved August 2011, from FDA: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm091428.htm

x. FDA. (2010). *MedWatch The FDA Safety Information and Adverse Event Reporting Program.* Retrieved August 2011, from FDA: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm196258.htm

xi. FDA. (2011, September 10). *Prescription Drug User Fee Act (PDUFA).* Retrieved Septmeber 14, 2011, from FDA: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm

xii. FDA. (2010, March 2). *CDER Drug Approval Package for Baycol.* Retrieved August 25, 2011, from Drug Approvals and Databases: http://www.accessdata.fda.gov/drugsatfda_docs/nda/97/020740_baycol_toc.cfm

xiii. FDA. (2002, May 30). *CDER Drug Approval Package for Bextra.* Retrieved August 28, 2011, from Drug Approvals and Databases: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2001/21-341_Bextra.cfm

xiv. FDA. (2002, May 22). *CDER Drug Approval Package for Meridia.* Retrieved August 18, 2011, from FDA Approved Drug Products: http://www.accessdata.fda.gov/drugsatfda_docs/nda/97/020632a_apltr_thr_%20mor.pdf

xv. FDA. (2001, June 18). *CDER Drug Approval Package for Mylotarg.* Retrieved September 4, 2011, from Drug Approvals and Databases: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/21174_Mylotorg.cfm

xvi. FDA. (2001, July 2). *CDER Drug Approval Package for Raplon.* Retrieved August 22, 2011, from FDA approved Drug Products: http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/20984_RAPLON_medr_P3.pdf

xvii. FDA. (2002, October 23). *CDER Drug Approval Package for Zelnorm.* Retrieved September 7, 2011, from Drug Approvals and Databases: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/21-200_Zelnorm.cfm

xviii. FDA. (2006, January 18). *CDER Drug Aprroval Package for Vioxx.* Retrieved September 2, 2011, from Drug Approvals and Databases: http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/021042_52_Vioxx.cfm

xix. FDA. (2000). *Center for Drug Evaluation and Research.Report to the Nation. Improving Public Health through Human Drugs.*

xx. FDA. (2003, May 22). *Drug Approval Package.* Retrieved August 18, 2011, from FDA Approved Drug Products: http://www.accessdata.fda.gov/drugsatfda_docs/nda/97/20632_meridia.cfm

xxi. FDA. (1998, October 8). *List of Drug Products That Have Been Withdrawn or Removed From the Market for Reasons of Safety or Effectiveness.* Retrieved August 21, 2011, from Federal Register:

https://docs.google.com/document/d/1ELc_v5v0FqjLH-G7JbaHC2utrbwDcsDK70F8dfDuVSw/edit?hl=en_US&pli=1

xxii. FDA. (2011). *Medwatch the FDA Safety Information and Adverse Event Reporting Progrm.* Retrieved August 19, 2011, from Food and Drug Adminstration: http://www.fda.gov/Safety/MedWatch/SafetyInformation/default.htm

xxiii. FDA. (2011, September 4). *NME Drug and New Biologic Approvals.* Retrieved September 14, 2011, from How Drugs are Developed and Approved: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/ucm121136.htm

xxiv. FDA. (2002). *Report to the Nation.Improving Public Health Human Drugs.* Retrieved September 2, 2011, from Center for Drug Evalation and Research: http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/WhatWeDo/UCM078985.pdf

xxv. FDA. (2000). *Report to the Nation.Improving Public Health Through Human Drugs.* Retrieved August 28, 2011, from Center for Drug Evaluation and Research: http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/WhatWeDo/UCM079006.pdf

xxvi. FDA. (2001). *Report to the Nation.Improving Public Health Through Human Drugs.* Retrieved September 1, 2011, from Center for Drug Evaluation and Research: http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/WhatWeDo/UCM078997.pdf

xxvii. FDA. (2003). *Report to the Nation.Improving Public Health Through human Drugs.* Retrieved September 5, 2011, from Center for Drug Evaluation and Research: http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/WhatWeDo/UCM078975.pdf

xxviii. FDA. (2004). *Report to the Nation.Improving Public Health Through Human Drugs.* Retrieved September 6, 2011, from Center for Drug Evaluation and Reasearch: http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/WhatWeDo/UCM078941.pdf

xxix. FDA. (2005). *Report to the nation.Improving Public Health Through Human Drugs.* Retrieved september 6, 2011, from Center for Drug Evaluation and Research: http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/WhatWeDo/UCM078935.pdf

xxx. FDA. (2007). *Report to the nation.Improving Public Health Through Human Drugs.* Retrieved September 7, 2011, from Center for Drug Evaluation

and Research: http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/WhatWeDo/UCM121704.pdf

xxxi. FDA. (2011). *Safety Alerts for Human Medical Products.* Retrieved August 18, 2011, from Food and Drug Adminstration: http://www.fda.gov/Safety/MedWatch/SafetyInformation/default.htm

xxxii. PhRMA. (2007, February). *Drug Discovery and Development.Understanding the R& D Process.* Retrieved September 7, 2011, from Innovation.org: http://www.phrma.org/sites/default/files/159/rd_brochure_022307.pdf