A Case Study of Vioxx using STAMP

By

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Abstract

The goal of this thesis is to investigate and demonstrate the application of a systems approach to drug safety. The recall of the prescription drug Vioxx (Rofecoxib) was used as a test case to study whether STAMP (Systems Theoretic Accident Model and Processes) could be used to outline the interactions between the different pharmaceutical system components, identify the safety control structure in place and understand how this control structure failed to prevent the marketing of an unsafe drug which killed an estimated 27,000 people in the United States.

To supplement this static analysis, System Dynamics models were used to analyze the social and organizational dynamics that underline the US healthcare system and to understand how the system moved from a safe to an unsafe state which allowed a dangerous drug to be left on the market for over five years.

The recall of Vioxx was followed by a number of legislative changes, in particular the Food and Drug Administration Amendment Act of 2007. Those changes were mapped on the safety control structure and again System Dynamics models were used to understand the systemic implications of the policy changes. The models suggested that further changes might be necessary to protect the American public and so, based on the results of the STAMP analysis, a new set of systemic recommendations was proposed.

Thesis Supervisor: **Professor Nancy Leveson**
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Introduction

In this research, a systems engineering approach was applied to pharmaceutical safety and focused on the system as a whole, not on the individual specialized system components. The objective was to integrate the subsystems into the most effective system possible to achieve the overall objectives, given a prioritized set of system design criteria. Optimizing the system design often requires making tradeoff between these design criteria (*system goals*).

A systems engineering approach to safety and risk management starts from the basic assumption that some properties of systems (often called *emergent properties*), such as safety, can only be treated adequately in their entirety, taking into account all variables and relating the social to the technical aspects. These properties derive from the relationships among the parts of the system, i.e., how they interact and fit together.

A basic assumption of systems engineering is that optimization of individual components or subsystems will not in general lead to a system optimum; in fact, improvement of a particular subsystem may actually worsen the overall system performance because of complex, non-linear interactions among the components. Similarly, individual component behavior (including events or actions) cannot be understood without considering the components' role and interaction within the system as a whole. This basic principle of system engineering is often stated as the system being more than the sum of its parts.

Attempts to improve long-term safety in complex systems by analyzing and changing individual components (such as the pharmaceutical companies alone or the regulatory agencies alone) have proven in other industries to be unsuccessful over the long term. Changing only local features of a system or individual component behavior often is compensated for by people or other system components simply adapting to the change in unpredicted ways that negate the intended effect.

In a systems approach to safety, the focus is on eliminating or mitigating hazards through appropriate system design and operations. Rather than focusing on adverse events after they occur, emphasis is instead placed on system modeling and analysis and building safety into the system design. While a systems approach to safety does include investigating accidents (adverse events) when they occur, hazard analysis is used to investigate an accident or adverse event before it happens. The results of the modeling and analysis are used to proactively identify causal factors and take steps to eliminate or control them. Such modeling and analysis must include identifying the unintended consequences of system designs.

Because of the complexity of healthcare systems, standard systems engineering approaches that focus on individual component failure as the cause of accidents or losses are not easily applicable. A new approach to safety engineering is therefore necessary. Here safety is treated instead as a dynamic control problem that considers the entire socio-technical system as well as the social dynamics under which it operates. This new model of accident causality, called STAMP (System-Theoretical Accident Model and Process), is capable of handling much more complex systems than traditional safety engineering methods based on simpler, more limited assumptions about causality. Another unique feature of this approach is that systems are

expected to be dynamic and constantly changing. Systems and organizations migrate toward accidents (states of high risk) under cost and productivity pressures in an aggressive, competitive environment. In order to understand and design safer systems, these pressures need to be identified and included in the models and analyses.

This thesis intends to demonstrate and experimentally validate the practicality of this new approach to modeling and designing improved pharmaceutical safety which entails determining whether it is possible to model and analyze the organizational and social dynamics behind a major failure of the system. Vioxx was chosen as the example not only because of the severity of the problems but also because this case included a large number of the factors involved in such losses.

The thesis starts with an introduction to the drug Vioxx, including a short timeline of the development of the drug. Section 1 is a rapid introduction to the basic technical vocabulary and required to understand this thesis, followed by an overview of the accident model used. Section 2 represents the core of the STAMP analysis with an analysis of the safety control structure and a detailed analysis of the different components of the system. Section 3 is an introduction to System Dynamics and the Causal Loop diagrams used in this analysis. Finally Section 4 covers the main reports that followed the Vioxx recall and includes an analysis of the relevant legislative changes while Section 5 outlines a new set of policy recommendations.

Background information on Vioxx

Vioxx (Rofecoxib) was a prescription COX-2 inhibitor manufactured by Merck & Co., Inc. that was approved by the Food and Drug Administration (FDA) in May 1999. It was widely used for pain management and was primarily prescribed for patients suffering from osteoarthritis. Vioxx was one of the major sources of revenue for Merck while on the market. It is estimated that in 2003 it represented 11% of Merck's sales – US$2.5 Billion (Fielder, 2008). In September 2004, Merck voluntarily withdrew the drug from the market because of safety concerns: The drug was suspected to increase the risk of cardiovascular events for the patients taking it. According to an epidemiological study done by an FDA scientist, Vioxx has been associated with more than 27,000 heart attacks or deaths: "[Vioxx] may be the single greatest drug safety catastrophe in the history of this country or the history of the world" (Graham, 2004).

A Vioxx timeline

A short timeline of the events relevant to Vioxx's discovery, marketing and recall is included below. Refer to Appendix A for a more detailed timeline.

Date	Event
1994	Vioxx molecule discovered.
Nov. 1998	Merck Seeks FDA approval.
Jan. 1999	Vioxx Gastrointestinal Outcomes Research (VIGOR) trial begins. The study was designed to compare the efficacy and adverse effect profiles of rofecoxib and naproxen.
May 1999	FDA approves Vioxx for the relief of osteoarthritis symptoms and management of acute pain.
Dec. 1999	Vioxx has more than 40% of new prescriptions in its class
Feb. 2000	Adenomatous Polyp Prevention on Vioxx (APPROVe) trial begins. The study was designed to determine the drug's effect on benign sporadic colonic adenomas.
Nov. 2000	The NEJM publishes the results from the VIGOR study.
Aug. 2001	A meta-analysis is published in JAMA casting serious doubts on the safety of Vioxx. The authors found that the myocardial infarction rates for Vioxx were significantly higher than that in the placebo group.
Apr. 2002	FDA approves changes to Vioxx label which include cardiovascular risks, gastrointestinal benefits and a new use to treat rheumatoid arthritis.
Sep. 2004	● APPROVe shows that the drug raises the risk of heart attacks after 18 months. ● Merck announces withdrawal of Vioxx.
Oct. 2004	Merck receives conditional approval for Arcoxia, Vioxx's replacement.

Adapted from (Martin, 2006; Reuters, 2005)

Table 1 – Short Vioxx Timeline

Section 1: Introduction to System Safety Engineering

This section is an introduction to system safety engineering. First the vocabulary required to understand this paper is defined followed by a description of the model used for the analysis. The following definitions are adapted from (Leveson, 2003).

Safety vocabulary

Safety: Safety is defined as the absence of loss due to an undesirable event (accident).

Accidents: An accident is defined as "an undesired and unplanned event that results in a loss (including loss of human life or injury, property damage, environmental pollution, etc)".

Incidents: Incidents are defined as events not leading to an unacceptable loss but that could have under other circumstances ("near-miss").

Hazards: Hazards are defined as "a system state or set of conditions that, together with a particular set of worst-case environment conditions, will lead to an accident (loss)".

Safety Control Structure: The control structure is the web of individuals and organizations (government agencies, companies, individuals ...) whose purpose is to enforce safety related constraints. This control structure is typically embedded in an adaptive socio-technical system.

Controllers: The controllers are all the agents that are part of the control structure and who "control" the safety of the system through their actions.

STAMP: As discussed in the introduction, STAMP (System-Theoretical Accident Model and Process) is a model of accident causality based on systems theory and systems thinking and is capable of handling complex systems problems. In STAMP, safety is treated as an emergent property that results from the enforcement (through system design and operation) of safety-related constraints on the behavior of the system components. Accidents or losses result from unsafe interactions among humans, machines or physical devices, and the environment. Losses are the result of complex processes, including indirect and feedback relationships, rather than simply chains of directly-related failure events (the typical model used to understand causality).

STAMP Framework

Now that the reader is familiar with the basic safety vocabulary required to understand this thesis, the STAMP framework is described using a 6 steps model. This introduction is followed by a detailed description of two keys elements of the analysis: the control structure and the analysis of the controllers. Section 3 presents the third major element of the model, System Dynamics.

STAMP Steps

The STAMP based risk analysis process used in this thesis can be defined in six steps:

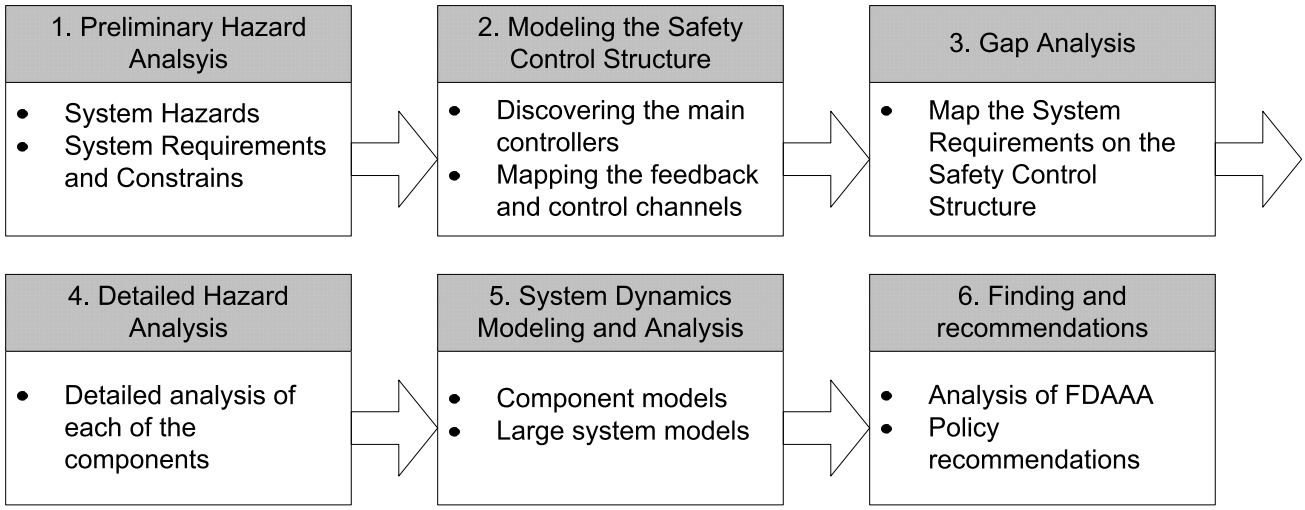


Figure 1 – The STAMP-Based risk analysis process (adapted from (Leveson, 2005))

In Step 1, the system hazards, requirements and constraints that are relevant for the system studied are defined. They represent the broad overarching goals the system is supposed to achieve and enforce. Step 2 involves outlining who (or what) is in charge of enforcing the safety requirements for this systems and how they interact with each other (feedback and control channels). In Step 3 the requirements defined in Step 1 are mapped to the control structure outlined in Step 2 and each responsibility is assigned to one or several components. In Step 4 involves a detailed analysis of the context, responsibilities, mental models and control actions of each of the controllers. In Step 5 the components and the system as a whole are modeled using System Dynamics methods. Finally, in Step 6 the previously proposed safety recommendations are analyzed and using what was learned from the system a new set of recommendations is proposed. Note that even though the technique is represented as a linear process it is in practice highly iterative and later steps often offer insights into the previous steps, forcing the person doing the analysis to go back and rework previous sections.

Section 2 of this thesis covers Steps 1 through 4. The control structure is outlined including the relationships between the different actors and then each of the components is analyzed. Section 3

covers Step 5: The System Dynamics models are used to create dynamic models of the safety structure. Step 6 encompasses Section 4 which is the analysis of the changes embodied in the Food and Drug Administration Amendments Act (FDAAA) of 2007 and Section 5, which includes the new set of recommendations.

Two of the more complicated steps of the analysis will now be described: the Safety Control Structure and the Detailed Hazard Analysis.

Safety Control Structure

The hierarchical safety control structure is the core of the STAMP accident causality model (Leveson, 2003, 2004). In the STAMP framework, understanding why an accident happens first means understanding why the safety control structure was ineffective at preventing the accident: Were some control structures missing in the original design? Did the system evolve over time, migrate towards the boundaries of acceptable performance and eventually stepped over one of those boundaries (Rasmussen, 1997) ? Figure 2 shows a generic example of a hierarchical safety control structure.

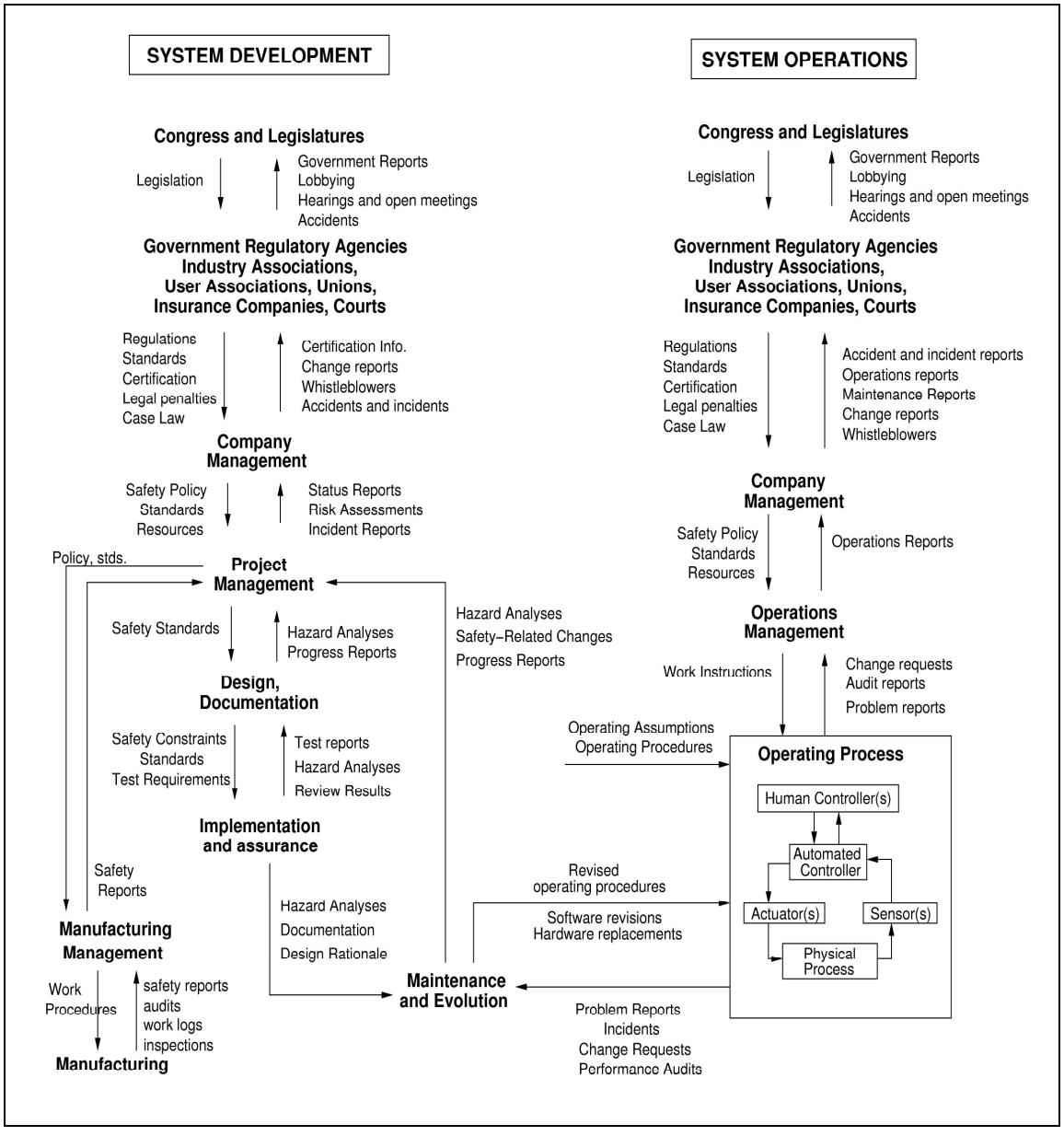


Figure 2 – General Socio-Technical Safety Control Structure (Leveson, 2003)

This model includes two basic hierarchical control structures, one illustrating the system development process (on the left) while the other represents the system operations (on the right), with the two structures interacting at the lowest level. Between each hierarchical level there is a downward control channel and an upward feedback channel: The control channels represent the ability of one controller to assert its authority and influence over another controller; the feedback channels update the controller's model of the process it is controlling. Every controller contains a model of the state of the process it is controlling and assumptions about how the controlled process behaves. For human controllers, this is referred to as a mental model.

Detailed Hazard Analysis

Once the overall control structure of the system has been defined, each component is studied individually to understand its role in the system as a whole and the part it played in the accident. In STAMP, accidents are considered to be complex processes (rather than simply a sequence of events) and the goal of the accident analysis is to understand how each component contributed to the overall accident process. The ultimate objective is not to assign blame—blame is the enemy of safety (Dekker, 2007; Leveson, 2010)—but to understand why well-meaning people acted the way they did so that changes can be made to the system to reduce unsafe behavior in the future. The hazard analysis has four main parts:

1. *Safety Requirements:* A controller has specific responsibilities regarding the safety of the system and has to operate within certain safety boundaries. Those responsibilities can either be explicitly defined or can be implied. For example, the FDA is mandated to only approve drugs that are safe and efficacious. When a loss occurs, either the assignment of responsibilities is flawed or the responsibilities were not adequately carried out.

2. *Context in Which Decisions Were Made:* Decisions and behavior are always influenced by the context in which they occur. Understanding why decisions are made, or people behave the way they do, requires understanding this context. Examples include financial pressures, time pressures or the information available (or not available) to the controller at the time.

3. *Process or Mental Model:* Control decisions are only as good as the assumptions and information on which they are based. If the controller's model of the state of the process is flawed, control decisions are likely to be flawed. As an example, if a doctor believes that a drug is safer than it really is, he might prescribe it more aggressively. This part of the description includes the information the controller needs in order to make safe decisions. When modeling an accident, it includes any information that might have contributed to any unsafe control decision provided by this system component.

4. *Inadequate Control Actions:* Here the first three steps come together to explain the accident. The inadequate control actions are the different actions the controller took that led to the unsafe state. Those actions can be broadly classified in one of the following four categories (Leveson, 2003):

1. A required control action is not provided or is inadequately executed
2. An incorrect or unsafe action is provided
3. A potentially correct or adequate control action is provided at the wrong time
4. A correct control action is provided at the right time but then is stopped too soon or continued too long

Both the vocabulary needed to understand this thesis and the modeling approach have now been introduced. The rest of the thesis will be an application of this technique to the Vioxx case.

Section 2: Drug Safety Using a System Safety Engineering Approach

This section starts with the definition of accidents, incidents and hazards in the context of healthcare in the United States and the Vioxx case specifically. Those definitions are followed by a list of requirements that need to be fulfilled for the system to be considered safe and an outline of the safety control structure that was supposed to prevent large-scale drug related accidents. Once the requirements have been outlined a gap analysis maps the safety requirements to the system controllers the controllers are described individually.

Goal, Accidents, Incidents and Hazards within the context of Vioxx

Defining what are considered the goals of any system studied is critical to understand its purpose, and to evaluate how well it fulfills its objective. In the case of healthcare, the system goal can be defined as:

> **System goal**: *To provide safe and effective pharmaceuticals and biological products to enhance the long-term health of the American people.*

Note that the focus of this thesis was limited to the United States for practical reasons. First of all, the needs between developed and developing countries are very different and therefore would require a significantly different analysis. Second, even if other developed countries have similar pharmaceutical safety problems, there are also important differences in particular in the safety control structure.

Accidents[1] or Losses and Incidents

A clear definition of what is consider accidents and incidents is key to any STAMP analysis since preventing or mitigating them is the ultimate goal of the analysis. In the healthcare system there are two sources of accidents:

1. *Patients get a drug treatment that negatively impacts their health*

A patient's health can be negatively impacted by a drug treatment for a variety of reasons: Medication is not properly prescribed, drug treatments are taken without proper medical supervision or the drug is not properly manufactured.

2. *Patients do not get the treatment they need*

Here again, there are a variety of reasons why patients do not get the treatment they need: they cannot afford the treatment, they do not have access to medical professionals who can prescribe it or no treatment has been developed for their condition.

[1] The term "accident" used in engineering is awkward in this context so instead use the term "loss" was used. Accidents are defined in engineering as "unacceptable losses" so it is an easy substitution.

For Vioxx, losses are defined as serious adverse events resulting from the use of the drug, in particular fatal cardiovascular (CV) events such as heart attacks and strokes while incidents are defined as non-fatal CV events related to the use of Vioxx.

Hazards

In the healthcare field, as in most other domains, it is impossible to reach a totally "safe" state. The goal then is to reduce hazards, which are the events and states that can lead to an accident. In medicine "safe" can be interpreted as having an acceptable risk/benefit profile for a drug with respect to a specific population. In this analysis, three hazards were identified. These are not specific to Vioxx but are common to all pharmaceutical products.

System Hazards:

H1: The public is exposed to an unsafe drug

1. The drugs are released with a label that does not correctly specify the conditions for safe use of the drug
2. Approved drug are found to be unsafe and appropriate responses are not taken (warnings, withdrawals from market, etc.)
3. Patients are subjected to unacceptable risk during clinical trials

H2: Drugs are taken unsafely

1. The wrong drug for the indication is prescribed
2. The pharmacist provides incorrect medication
3. The drugs are taken in an unsafe combination
4. The drugs are not taken according to directions (dosage, timing)

H3: Patients do not get an effective treatment they require

1. Safe and effective drugs are not developed or are not approved for use
2. Safe and effective drugs are not affordable for those who need them
3. Unnecessary delays are introduced into development and marketing
4. Physicians do not prescribe needed drugs or patients have no access to those who could provide the drugs to them
5. Patients stop taking a prescribed drug due to perceived ineffectiveness or intolerable side effects

The effects of public exposure to an unsafe drug (*Hazard 1*) are magnified in the case of popular drugs like Vioxx where a large part of the population is treated with the drug and therefore potentially exposed to its negative side effects. As stated during Congressional hearings on Vioxx, "[w]hen exposure to a drug is so widespread, even a small safety problem can have major public health consequences" (Waxman, 2005b). At the same time, if many people will benefit from the drug and there is no existing safe alternative, approving the drug quickly becomes key for a large part of the population (limits *Hazard 3*).

Pharmaceutical System Safety Requirements and Constraints

From this list of goals and hazards, a set of system requirements can be derived. In systems engineering, the requirements may not be totally achievable in any practical design. For one thing, they may be conflicting among themselves or with other system (non-safety) goals or constraints. The goal is to design a system (or to evaluate and improve an existing system) that satisfies the requirements as much as possible today and to continually improve the design over time using feedback and new scientific and engineering advances. Tradeoffs that must be made in the design process are carefully evaluated and revisited when necessary.

Four main requirements emerged the goals and hazards outlined above. The requirements are deemed necessary to ensure patient safety during the development and subsequent distribution of pharmaceuticals.

1. Pharmaceutical products are developed to enhance long-term health
    a. Continuous appropriate incentives exist to develop and market needed drugs
    b. New scientific knowledge and technology is developed to create new drugs
    c. New drugs are developed and manufactured when the scientific and technical knowledge is available

2. Drugs on the market are adequately safe and effective
    a. Drugs are subjected to effective and timely safety testing
    b. New drugs are approved by the FDA based upon a validated and reproducible decision-making process
    c. Drug approval is not unnecessarily delayed
    d. The labels attached to drugs provide correct information about safety and efficacy
    e. Drugs are manufactured according to Good Manufacturing Practices
    f. Marketed drugs are monitored for known and unknown adverse events, side effects, and potential negative interactions
    g. Long term studies are conducted, even after the drug as been approved, to validate the FDA's approval decision (e.g., Phase IV studies) both on the long term and for subpopulations
    h. New information about potential safety risks is reviewed by an independent advisory board
    i. Marketed drugs found to be unsafe after they are approved are removed, recalled, restricted, or appropriate risk/benefit information is provided

3. Patients get and use the drugs they need for good health
    a. Drugs are obtainable by patients[2]
    b. Accurate information is available to support decision-making about risks and benefits
    c. Patients get the best intervention reasonable for their health needs
    d. Patients get drugs with the required dosage and purity

[2] Implies that the FDA approves, physicians prescribe, and payers provide access.

4. Patients take the drugs in a safe and effective manner
    a. Patients get correct instructions about dosage and follow them
    b. Patients do not take unsafe combinations of drugs
    c. Patients are properly followed by a physician while they are being treated
    d. Patients are not subjected to unacceptable risk during clinical trials

Hierarchical Safety Control Structure

Now that the system goals, accidents and the requirements have been defined, it is important to study the system itself, identify the different controllers who have a role to play regarding safety and specify how they interact with each other. The first step in studying the system is to identify the hierarchical safety control structure relevant for this system.

United States Pharmaceutical Products Control Structure

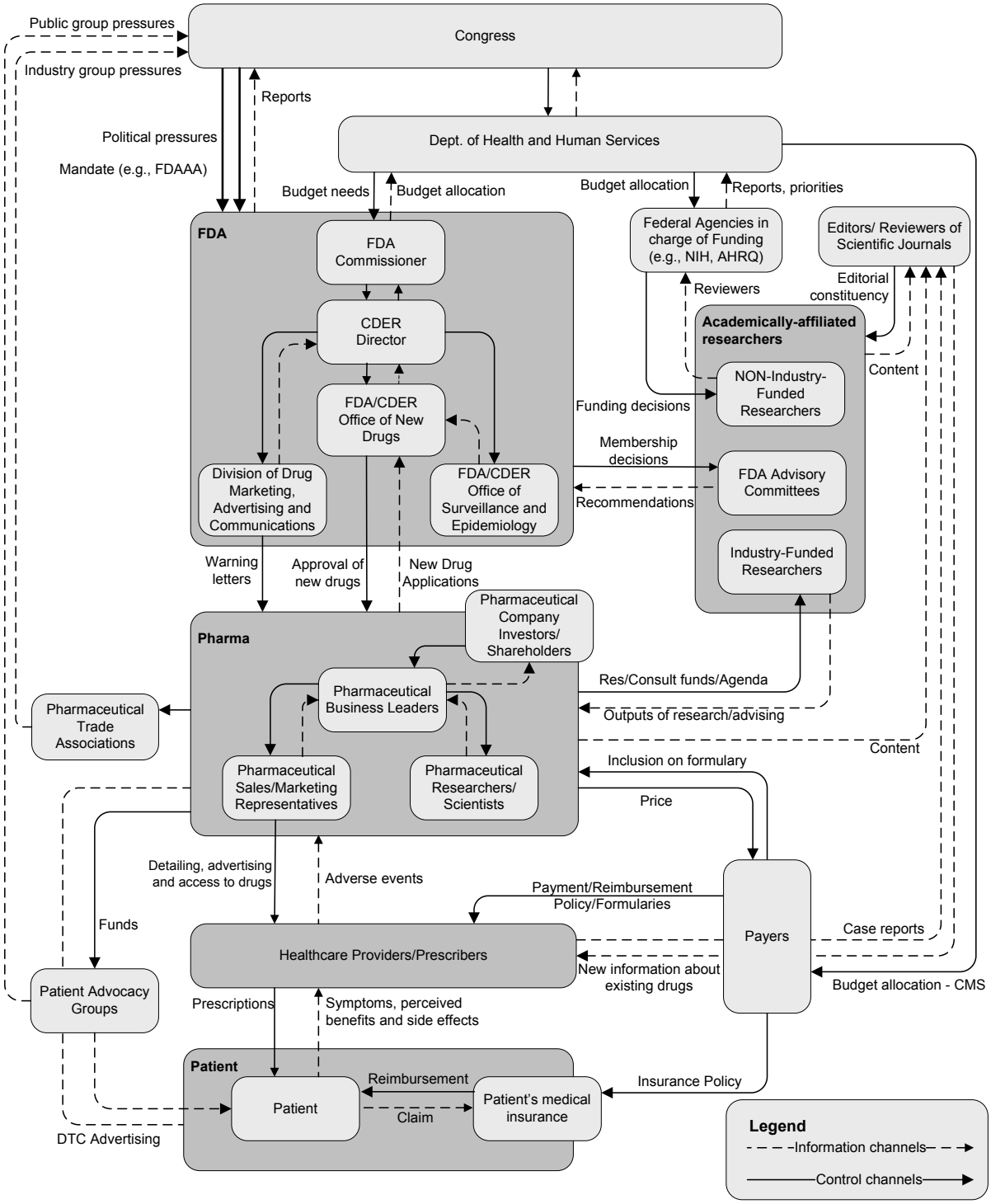


Figure 3 – Hierarchical Safety Control Structure3

[3] Dr. Meghan Dierks provided critical input and advice in creating and developing this control structure.

This control structure shows that the post-approval safety is enforced by a very complex and interconnected system. Five main groups (the FDA, Pharmaceutical companies, Patients, Academically-affiliated researchers and the Healthcare providers) compose the core of the system and a variety of smaller controllers play a peripheral role in drug safety (Congress, Journal editors, Patient groups…).

Those groups are interrelated and their interactions are of two types: control and information. The control channels allow one group to impose safety requirements on another. For example, healthcare providers control patient's access to drugs through prescription channel. The information channel serves as feedback mechanism: in this case, patients can report the side effects they notice when taking the drug.

The control decisions are based on the feedback information sent by the group being controlled but also based on the controls imposed on the controller. For example, the healthcare providers make decisions based on patients' symptoms (feedback information), but also based on drug companies' advertising, their knowledge of relevant medical research, insurance reimbursement practices and so forth. They receive feedback from their patients on the efficacy of the drugs, but this information can be misleading (especially in cases like Vioxx where the side effects are long term).

Now that the safety control structure has been established, the next step is to map the safety requirements defined earlier on this control structure and see what controllers have which responsibilities. This step is useful for three distinct reasons:

1. To check that at least one controller in charge of enforcing each of the safety requirements
2. To check whether there is more than one controller in charge of a safety requirement, which is important since too often accidents happen when responsibilities overlap
3. To study each of the controllers independently to verify whether they are capable of enforcing the controls assigned to them

Gap Analysis

Thanks to the safety control structure it is possible to map the requirements to the different controller(s) in charge of enforcing them and narrow the general system requirements to the responsibilities specific to each of the controllers. A detailed assignment of responsibilities is a good way to see how effective the control structure is at enforcing the safety requirements. Table 2 shows the results of this analysis. For a more detailed table see Appendix B.

#	Safety Requirements and Constraints	Controller
1	***Pharmaceutical products are developed to enhance long-term health***	
1.a.	Continuous appropriate incentives exist to develop and market needed drugs	Government
		Market
1.b.	New scientific knowledge and technology is developed to create new drugs	Pharmaceutical companies
		NIH/NAS
1.c.	New drugs are developed and manufactured when the scientific and technical knowledge is available	Pharmaceutical companies
2	***Drugs on the market are adequately safe and effective***	
2.a.	Drugs are subjected to effective and timely safety testing	Pharmaceutical companies
		FDA - OND
2.b.	New drugs are approved by the FDA based upon a validated and reproducible decision-making process	FDA - OND
		Pharmaceutical companies
2.c.	Drugs are not unnecessarily delayed	FDA - OND
2.d.	The labels attached to drugs provide correct information about safety and efficacy	Pharmaceutical companies
		FDA - OND
		FDA - OSE
2.e.	Drugs are manufactured according to Good Manufacturing Practices	Pharmaceutical companies
		FDA
2.f.	Marketed drugs are monitored for known and unknown adverse events, side effects, and potential negative interactions	FDA - OSE
		Physicians
		Pharmaceutical companies
2.g.	Long term studies are conducted, even after the drug as been approved, to validate the FDA's approval decision (e.g., Phase IV studies) both on the long term and for subpopulations	Pharmaceutical companies
		FDA - OND
		Researchers
2.h.	New information about potential safety risks is reviewed by an independent advisory board	FDA - Commissioner
		FDA Advisory Board
		Researchers
2.i.	Marketed drugs found to be unsafe after they are approved are removed, recalled, restricted, or appropriate risk/benefit information is provided	Pharmaceutical companies
		FDA - OSE
3	***Patients get and use the drugs they need for good health***	
3.a.	Drugs are obtainable by patients	Payers
3.b.	Accurate information is available to support decision-making about risks and benefits	Pharmaceutical companies
		FDA - DDMAC
		Journals
		AHRQ
3.c.	Patients get the best intervention reasonable for their health needs	Physicians
3.d.	Patients get drugs with the required dosage and purity	Physicians

4	***Patients take the drugs in a safe and effective manner***	
4.a.	Patients get correct instructions about dosage and follow them	Patients
		Physicians
4.b.	Patients do not take unsafe combinations of drugs	Patients
		Physicians
4.c.	Patients are properly followed by a physician while they are being treated	Physicians
4.d.	Patients are not subjected to unacceptable risk during clinical trials	Pharmaceutical companies
		FDA - OND
5	**The necessary legislative and judiciary infrastructure exists to ensure that the public is protected**	Congress

Table 2 – Gap Analysis

In this analysis no obvious gaps in the safety control structure were found. Each of the safety requirements is enforced by at least one controller. The problem here is that multiple controllers are often in charge of enforcing the same safety requirement. For example, the FDA, the pharmaceutical companies and physicians are all in charge of monitoring drugs for adverse events. Having multiple controllers in charge of a single requirement is not an issue if the controllers work together and share the information they have. However, if each of the controllers relies on the others to monitor the drug safety issues can go unmonitored. In addition, the assignment of responsibilities does not mean that they are effectively carried out. Part of the analysis of an accident is determining whether responsibilities were fulfilled and, if not, why not.

Once the responsibilities for each of the controllers has been identified, the controllers can be analyzed independently to see whether the context they work in allows them to properly fulfill their safety responsibilities and if they have the resources and information they need to enforce the safety constraints they have been assigned.

Analysis of the Hierarchical Safety Control System Components

In this section, each component of the pharmaceutical safety control structure is analyzed to see the role it played in the Vioxx loss. Note however that some of the responsibilities of the controllers have changed since the accident; for example, the Food and Drug Administration Amendments Act of 2007 (FDAAA) increased the responsibilities of the FDA and provided it with new authority (Congress, 2007). Those changes are studied later to evaluate how effective they might be in preventing future losses.

Patients

General Information

The patients were the ones most directly affected by the risks and benefits of the drug: they benefited from the pain relief provided by Vioxx but might also have suffered from a cardiovascular (CV) event related to the use of the drug. It has been estimated that over 106.7 million prescriptions were given to patients in the United States (BBC, 2005).

A patient is considered to be anyone who was treated with Vioxx either as prescribed by their doctors or during clinical trials. However, patients who were prescribed the drug and did not take it, or patients who should have been prescribed the drug but were not are not included because only the population who was actively taking the drug was at an increased risk.

Summary of Accident Causal Factors

Safety Requirements:

1. Accept limited responsibility for their own health and treatment (limited by what is practical)
2. Follow their physicians instructions and take drugs as prescribed
3. Accede to doctor's superior knowledge when appropriate
4. Patients must go through a doctor to get a prescription for drugs like Vioxx

Context in Which Decisions Were Made:

1. Patients had limited information about the safety and effectiveness of Vioxx. Most of the information they had came from Direct-To-Consumer (DTC) advertising which provided a rosy picture of the efficacy of the drug along with glamorous and respected spokespersons (e.g., Dorothy Hamill)
2. Patients have limited medical knowledge about both their disease and the medication they are taking
3. Vioxx was approved by the FDA which provided a "guarantee" of safety

Mental Models:

1. Patients believed that the drug was safer than it really was
2. Patients believe that newer, more expensive drugs are better than older, alternative treatments.

Inadequate Control Actions:

1. Some patients pressured their doctor into prescribing Vioxx even if it was not necessarily the most appropriate treatment for their specific needs

Safety Requirements

Patients are expected to take care of their own health, which entails seeing a doctor when they feel ill and maintain a healthy lifestyle. Similarly, when patient are prescribed a treatment they are expected to follow their physicians' instructions and take drugs as prescribed. In some cases, patient access to a drug is limited and the drug has to be prescribed by a doctor (which was the case for Vioxx).

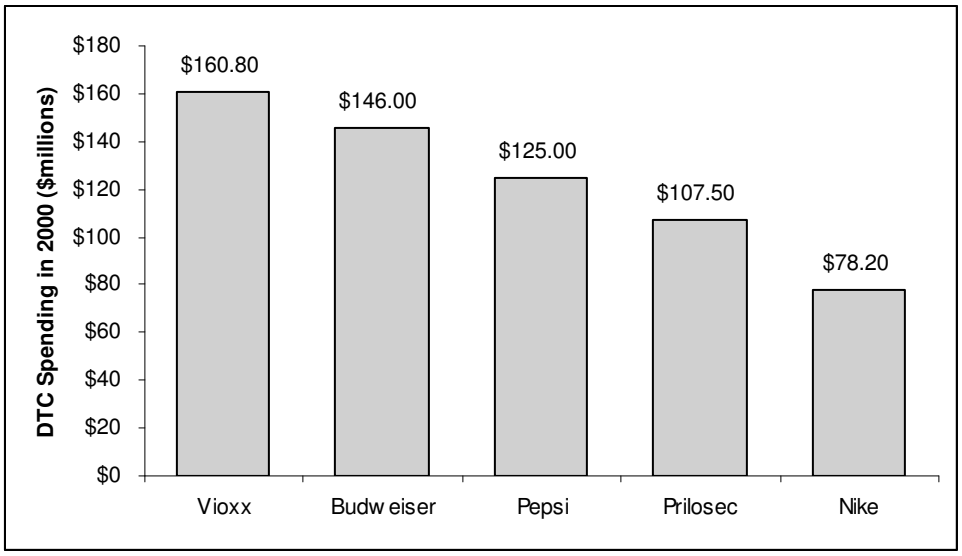
Context in Which Decisions Were Made

Vioxx was approved by the FDA in May 1999 to relieve osteoarthritis symptoms and for the management of acute pain. In April 2002, the FDA approved a label change and a new use of the drug for the treatment of rheumatoid arthritis. The fact that the drug had been repeatedly approved by the FDA created the illusion that the drug was safe.

This impression was reinforced by the few information sources patients had access to: at the time the main source of information was Direct-To-Consumer (DTC) advertising which provided only a rosy picture of the efficacy of the drug along with glamorous and respected spokespersons (e.g., Dorothy Hamill). For Vioxx alone, Merck spent $160.8 million in DTC advertising in 2000, which was the highest DTC advertising budget that year of all drugs. For comparison, Proctor & Gamble spent $107.5 million on Prilosec, the second most advertised drug that year, while Budweiser, Pepsi and Nike respectively spent $146 million, $125 million and $78.2 million on advertising (Debabrata & Eric, 2003).

Rank	Name	Type of Drug	DTC Spending in 2000 ($millions)
1	Vioxx	Antiarthritic	$160.80
2	Prilosec	Antiulcerant	$107.50
3	Claritin	Oral Antihistamine	$97.00
4	Paxil	Antidepressant	$91.80
5	Zocor	Cholesterol Reducer	$91.20
6	Viagra	Sex Function Disorder	$89.50
7	Celebrex	Antiarthritic	$78.30
8	Flonase	Respiratory Steroids (Inhaled)	$73.50
9	Allegra	Oral Antihistamine	$67.00
10	Meridia	Antiobesity	$65.00

Adapted from (Debabrata & Eric, 2003)



Adapted from (Debabrata & Eric, 2003)

Figure 4 – Relative DTC spending in 2000

This problem is compounded by the fact that patients have limited medical knowledge about both their disease and the medication they are taking. In the case of Vioxx, patients could not be expected to have enough medical knowledge to fully understand their disease, the way Vioxx worked, or all the potential side effects and consequences and most patients had to rely on their doctor's opinion and advice. Even when more information is available, for example on the Internet, many patients do not have the background knowledge to thoroughly understand this information.

Mental Models

Even though the FDA approved the drug, approval is not an absolute guarantee that the drug is safe, a fact often overlooked and misunderstood by patients. Drugs are approved based on the best information available at the time but this information is often incomplete and needs to be supplemented after the drug has been approved (Baciu, Stratton, & Burke, 2007). For example, in 2000, the FDA recommended that Merck conduct an animal study to evaluate CV safety after a potential risk was suggested by new studies.

The belief that a drug, like Vioxx, is safe and an improvement over the existing treatments is reinforced by the fact that the drug is approved by the FDA, apparently endorsed by the scientific community in medical journals and tacitly endorsed by the insurance companies, which are willing to reimburse the patients for the new treatments (G. M. Anderson, Juurlink, & Detsky, 2008).

Similarly consumers have a natural tendency to believe that price is associated with quality and recency with progress and since the new drugs are typically much more expensive than the traditional treatments (usually because the older drugs have generic formulations), consumers are led to believe that the new treatments are better than the older alternatives (G. M. Anderson, et al., 2008). This belief is reinforced by pharmaceutical companies in their DTC advertising in particular when the older drug is going off-patent and the company hopes to avoid the loss associated with generics coming on the market by making patients switch from the old drugs to the new ones that are still under patent.

Inadequate Control Actions

As was seen from the context describe above, patients typically believe that new drugs are safer than they really are which helps explain why they often request the new drugs even if they are not necessarily the best option for their condition.

No studies have been done to quantify this particular problem for Vioxx but more general studies (Finkelstein & Temin, 2008) have show this to be a real problem. Doctors reported that they felt increased pressures from patients to prescribe new drugs (e.g., Vioxx instead of the traditional pain killers) and studies show that 15% of patients would "consider switching doctors if they didn't get a drug they specifically asked for" (Finkelstein & Temin, 2008). A study of British General Practitioners suggests that in 22% of new prescription cases, a patient request for the drug was an influencing factor: "I prescribed it on one occasion only after much pressure from patients. I don't like it, I don't like prescribing it, but after much pressure I prescribed it" (Prosser, Almond, & Walley, 2003). Typical reasons given by the doctors when they conceded to patients' pressures include time constraints on the part of the doctor, patients being poorly managed on current therapy, trying to maintain a good doctor–patient relationship, avoiding conflict, and acknowledging the patient's right to be involved in decision making about their health. A similar study ran in US and Canada found that patients who requested drugs seen in advertisements were much more likely to receive one or more new prescriptions than those who did not request advertised drugs (Mintzes, et al., 2003).

It is clear, as will be discuss later, that a large number of patients taking Vioxx should not have been taking the drug because they had very low risk of gastrointestinal problems and therefore should have been prescribed non-steroidal anti-inflammatory drugs (NSAIDs). Further research is required to know how many of those patients were taking the drug because they had requested it from their doctors and not because their doctors thought it was the best treatment for them. By pressuring doctors into prescribing drugs that were not optimal for their condition, patients eroded the safety constraint supposed to ensure their safety.

Physicians

General Information

This category covers general practitioners who prescribed Vioxx to their patients but does not include doctors/researchers involved in clinical trials or new research (see later section on Research Scientists/Centers).

Summary of Accident Causal Factors

Safety Requirements:

1. Make treatment decisions based on the best interests of their patients
2. Weigh the risks of treatment and non-treatment
3. Prescribe drugs according to the limitations on the label
4. Maintain an up-to-date mental model of the risk/benefit profile of the drugs they are prescribing
5. Monitor symptoms of their patients under treatment for adverse events and negative interactions
6. Report adverse events potentially linked to the use of the drugs being prescribed

Context in Which Decisions Were Made:

1. Doctors mostly learn about new products from the drug companies themselves (sales force, CME presentations and advertisement in trade journals)
2. Doctors are notoriously busy and their time is limited
3. Doctors have limited access to unbiased information
4. Studies of new drugs are typically done against placebos
5. Doctors are part of the service industry and do not want to alienate their patients by not prescribing the drugs they request
6. Vioxx label did not mention CV risks

Mental Models:

1. Belief that new drugs are better than existing treatments
2. Belief that information from pharmaceutical companies is accurate
3. Physicians did not understand the risk/benefit tradeoffs of Vioxx. In particular, they did not know about potential cardiovascular risks associated with the long-term use of the drug
4. Doctors believed that patients might go to another practitioner if Vioxx was not prescribed

Inadequate Control Actions:

1. Doctors prescribed Vioxx, both on and off label, for patients for whom it was not indicated

Safety Requirements

Our society has high expectations for physicians. It is believed that they will make the best treatment decisions based on the best interests of their patients, that they will weigh the risks of treatment and non-treatment and prescribe drugs according to the limitations on the label. They are expected to keep their medical knowledge up-to-date, both regarding the way diseases spread and behave but also how drugs work and what treatments are available. Finally physicians are expected to monitor the long term health of their patients and report potential adverse events or negative interactions to the drug manufacturers.

Context in Which Decisions Were Made

As mentioned above, doctors are expected to keep informed about new treatments, a process which often involves drug company's representatives who visit doctors' offices and update them on new products. Senator Waxman has had access to a large body of documents concerning Vioxx while he was on the Committee on Oversight and Government Reform and in particular, he studied the role the sales force played in this case; he found that Merck assigned over 3,000 company representatives to "engage in face-to-face discussions with physicians about Vioxx" (Waxman, 2005b).

The role of pharmaceutical companies in doctors' education is justified, according to the Pharmaceutical Research and Manufactures Association of America (PhRMA), an industry trade group, because pharmaceutical representatives are "essential for physicians, allowing physicians to have sufficient information about new drugs so they can prescribe them appropriately" and "many physicians learn about new drugs—indeed, about ongoing research in their areas of specialization—largely through information provided by the companies that market new products" (Waxman, 2005b), which of course influences doctors' opinions of the new products.

Furthermore, physician education is now largely paid for and influenced by the pharmaceutical companies. These companies play a large role in doctors' continuing medical education (CME) programs, which they often subsidize and help organize. The pharmaceutical companies decide which speakers present and in some cases write the presentations, often without disclosing their involvement. These practices can been seen as a conflict of interest because the primary goal of the pharmaceutical companies is to promote their own drugs whereas a CME presentation should be unbiased and balanced (Wazana, 2000). For an interesting discussion of this problem see "Separating Continuing Medical Education From Pharmaceutical Marketing" (Relman, 2001) or "Doctors' education: the invisible influence of drug company sponsorship" for a discussion of the same problem in Australia (Moynihan, 2008).

The problem is compounded by limited number of sources of unbiased information available to doctors and by the fact that doctors are notoriously busy and do not necessarily read medical journals on a regular basis or keep up with the latest treatments, who they are indicated for and what are the associated risks. Furthermore, even when research is available on a specific drug, the studies are usually done against a placebo—very few studies compare drugs to one another and even when those studies are conducted, they are criticized by other experts (Pollack, 2008).

Doctors are left with a number of treatment choices for their patients but without the information needed to decide which is most appropriate for a specific patient.

Doctors' busy schedules also affect their patients in other ways: They have little time to spend with their patient and rarely have the time to thoroughly discuss the benefits and risks of a treatment. This time pressure is particularly important when a patient comes in with a request for a specific drug: a doctor who does not want to lose a patient is likely to simply prescribe the requested drug instead of spending time arguing why it is not the optimal treatment (Mintzes, et al., 2003).

Finally, the FDA label did not include any warnings of potential CV adverse events linked to the use of Vioxx. The label was only changed in August 2001 to include a tepid note in the precaution section which concluded that "[t]he significance of the cardiovascular findings from these 3 studies (VIGOR and 2 placebo-controlled studies) is unknown. Prospective studies specifically designed to compare the incidence of serious CV events in patients taking VIOXX versus NSAID comparators or placebo have not been performed" (Merck, 2002).

Mental Models

Like patients, doctors often believe that new drugs are better than alternative treatments: In the case of Vioxx, doctors believed that it was an improvement over the traditional nonselective non-steroidal anti-inflammatory drugs (NSAIDs). High prices, endorsement by the scientific community through publications and the tacit endorsement of the third-party payers all feed into the perception that a new drug is a better drug (G. M. Anderson, et al., 2008).

Doctors also typically believe that information provided to them by pharmaceutical companies is accurate. Wazana reviewed the existing studies on the topic and found that residents and physicians believe that representatives provide accurate information about their drugs. At the same time, in an apparent contradiction, doctors believe that representatives prioritize product promotion above patients' welfare and are likely to use unethical practices (Wazana, 2000).

In the case of Vioxx, physicians did not know about potential cardiovascular risks associated with the long-term use of the drug. The long term risk/benefit profile of Vioxx was poorly understood by most doctors as very little was published on potential long-term risks: Some studies showed ambiguous results (e.g., the Vigor study) but most publications and promotional material showed the drug to be safe, which goes a long way to explain why doctors had little reluctance to prescribe the drug, even if it might not have been the optimal treatment for the patients.

As was hinted at in the previous section, doctors are part of the service sector and depend on "customers" coming back. Doctors believed, possibly accurately, that patients might see another practitioner if they did not prescribe Vioxx when the drug was requested (which the patients might have seen in DTC advertisements). Of course the patients could not force the doctors to prescribe the drug for them, but in a competitive environment, where doctors have to fight to

keep their clientele, it is easy to imagine how doctors might cave under the pressure and prescribe a potentially less than optimal drug for their patients.

Inadequate Control Actions

Vioxx was first approved as an alternative treatment to generic pain killers for people at high gastrointestinal risk, for whom the traditional drugs posed a risk. However, "by the time of rofecoxib's withdrawal from the market […], more than 100 million prescriptions had been filled in the United States. *Tens of millions of these prescriptions were written for persons who had a low or very low risk of gastrointestinal problems*" (Waxman, 2005a). Clearly, doctors prescribed Vioxx for patients for whom it was not indicated, typically either because the patients pressured them to do so as discussed previously or because they did not realize that the drug was not indicated for their patient.

As discussed in the context and mental model sections, doctors are part of the service industry and rely on repeat customers. They must please their clients and it is likely that if a patient requests a drug, doctors will prescribe it especially if they have a limited amount of time to discuss treatment options and the existing literature gives them no reason not to prescribe the drug.

Physicians also prescribed Vioxx in situations where it was not indicated because they had the wrong mental model of the risk/benefit profile of the drug. Pharmaceutical firms have a strong financial interest to convince doctors to prescribe their drug as much as possible, even in cases where it is not necessarily in the best interest of the patients. For that purpose, pharmaceutical companies maintain a large sale force with the goal of promoting the different products made by the firm. In 2003, the year before Vioxx was removed from the market, pharmaceutical companies spent $5.7 billion on marketing drugs to physicians (Waxman, 2005b). There is no direct data available that shows how effective the Merck sales force was in promoting Vioxx, but the 3,000 sales representatives (Waxman, 2005b) were evidently very well trained to influence doctors. For a description of the training techniques used by Merck, please refer to Senator's Waxman memorandum to the Committee on Government Reform (Waxman, 2005b).

Prosser's study of British general practitioners is used to quantify to some extent the effect of sales representatives (Prosser, et al., 2003). The study found that 39% of new drug uptake was influenced by pharmaceutical companies, with another 4% of cases due to ads and mailings (note that prescribing decisions were often influenced by more than one factor). These are probably conservative numbers if they are applied to the United States since pharmaceutical sales forces have even more presence here than in Great Britain.

To conclude, doctors did not have accurate information about the risk-to-benefit profile of the drug and were led to believe by the Merck sales force that the drug was safe and that it posed no cardiovascular (CV) risk to the patients. In general, the drug's risk-to-benefit profile was misrepresented in the literature for reasons discussed in the Merck section.

Merck

General Information

Merck is a fortune 500 pharmaceutical company with headquarters in the United States. The company was established in the United States in 1891, originally as a fine chemical supplier (Merck, 2008b). The current Chairman, President and CEO is Richard T. Clark and the company currently has 59,800 employees worldwide (Merck, 2008a). In 2007, the company had sales of $24.2 billion and a net income of $3.3 billion. At the time of the events, the CEO was Raymond Gilmartin. See appendix B for a detailed structure of the senior management at Merck between 1994 and 2004.

Summary of Accident Causal Factors

Safety Requirements:

1. Ensure that patients are protected from avoidable risks
    a. Provide safe and effective drugs
    b. Test drugs for effectiveness
    c. Properly label the drugs
    d. Protect patients during clinical trials by properly monitoring the trial
    e. Do not promote unsafe use of the drugs
    f. Remove a drug from the market if it is no longer considered safe
    g. Manufacture the drugs according to Good Manufacturing Practices

2. Monitor drugs for safety
    a. Run long-term post-approval studies as required by the FDA
    b. Run new trials to test for potential safety hazards
    c. Provide, maintain, and incentivize adverse-event reporting channels

3. Give accurate and up-to-date information to doctors and the FDA about drug safety
    a. Educate doctors
    b. Provide all available information about the safety of the drug to the FDA
    c. Inform the FDA of potential new safety issues in a timely manner

4. Conduct or sponsor research that can be useful for the development of new drugs and treatments

Context in Which Decisions Were Made:

1. Merck has a fiduciary duty to shareholders to provide a return on their investment and stakeholders demand a high return. Furthermore, drug company executives are partly paid in stock options
2. Most clinical research on drugs is sponsored by companies that make them. Drug companies now have more control than in past on the way the research is carried out and reported
3. Merck had a reputation to maintain. Withdrawing Vioxx from the market and acknowledging CV events would have hurt their reputation
4. As a blockbuster drug, Vioxx was extremely profitable and a major source of Merck's revenue
5. The drug pipeline was dwindling and older drugs were going off patent protection. Merck was about to lose five of its most profitable patents
6. Drug companies have no incentive to do Phase IV safety testing, even if it is required by the FDA. Similarly, they have no incentives to publish negative internal studies
7. Merck was facing fierce competition from a rival drug, Celebrex, which had been approved by the FDA earlier than Vioxx
8. Primary results could be interpreted as a protective action from naproxen (Aleve) or as negative side effects from Vioxx

Mental Models:

1. Merck believed it could convince doctors to prescribe the drug despite the potential CV risks
2. Satisfactory financial results depended on Vioxx being a blockbuster
    a. Merck had to aggressively promote the drug to be competitive with Celebrex which had a first mover advantage
    b. Merck could not allow negative study results to impact sales
3. Comparative studies suggested that Vioxx had a higher number of CV events than naproxen. Merck assumed that difference came not from Vioxx having any negative side effects bur rather because naproxen protected patient's hearts.
4. Merck apparently believed that it could protect its reputation by hiding negative results

Inadequate Control Actions:

1. Merck did not run studies that might have found negative CV results. Company executives rejected doing a study of Vioxx's CV risks
2. Merck's studies, and the results the firm published, did inadequately represented the risk/benefit profile of the drug
    a. The studies were motivated by marketing goals
    b. If the results were published, they were typically released very late or only partially released
    c. The results were biased to appear better than they were
    d. Some of the studies that were run did not have an active Data and Safety Monitoring Board (DSMB) to monitor the clinical trials and protect the patients. The safety of the patients was solely in the hands of the Merck investigators
3. Merck published and disseminated misleading information about the safety profile of Vioxx
    a. Merck aggressively promoted drug usage with a task force trained to avoid CV questions
    b. Merck used promotional activities and materials that were false, lacking in fair balance or otherwise misleading. The company continued to minimize unfavorable findings up to a month before withdrawing Vioxx
    c. Merck published or promoted publication using guest authorship or ghostwriting; Merck employees' involvement in the writing process was often not mentioned and the financial ties of the main authors were not always disclosed
    d. Merck created journals made to look like independent peer-reviewed journals. These journals were actually marketing compilations of articles promoting Vioxx and another drug made by Merck

Safety Requirements

The safety requirements and constraints imposed on Merck extend from the pre-approval phase, where the company is expected to be researching new drugs, to post-approval requirements such as conducting Phase IV studies to look for long-term side effects. Those safety requirements and constraints are organized in four major sections believed to cover the major safety requirements imposed on Merck.

1. Ensure that patients are protected from avoidable risks

Manufactures are expected to provide safe and effective drugs, especially when, like Merck, the company states that **"**[its] business is preserving and improving human life" (Merck, 2008c). They are also expected to test their drugs for effectiveness, a process which typically involves three or four phases of clinical trials. Phase I is done to test the toxicity of the drug while phases II, III and IV are designed to test the drug's effectiveness by running studies on an increasing number of patients and for an increasing period of time (FDA, 2002). During those trials, patients are exposed to drugs that are at the time untested. The pharmaceutical company is expected to set up an institutional review board (IRB) and a data and safety monitoring board (DSMB) to ensure the safety of the patients and avoid their exposure to unnecessary and preventable risk.

Once drugs have been approved they need to be manufactured according to Good Manufacturing Practices (GMPs). GMPs are guidelines that outline how products, in this case drugs, need to be manufactured to ensure that they are safe and meet a set of minimum requirements. In the United States GMPs are enforced by the FDA, which is authorized to conduct unannounced inspections of manufacturing plants. In a more global economy, with plants all across the globe, enforcement is becoming more difficult (Harris, 2008; Harris & Bogdanich, 2008).

Manufactures are also expected to properly label their drugs with FDA-approved labels. These labels consist of the "official description of a drug product, which includes indication (what the drug is used for); who should take it; adverse events (side effects); instructions for uses in pregnancy, children, and other populations; and safety information for the patient" (FDA, 2004). It is expected that pharmaceutical companies will accurately label their drugs, reflecting all the information they have about the safety of the medication. When new risks are discovered the drug label needs to be updated and if the risks are significant, manufacturers are expected to recall the drug.

2. Monitor drugs for safety

After a drug is on the market, pharmaceutical companies are expected to keep on monitoring it for long term side effects. For example, the FDA can require a pharmaceutical company to do a postmarketing study (also known as a Phase IV study) to gather more information about a "product's safety, efficacy or optimal use" (FDA, 2002). These studies are requested by the FDA when a drug has been approved using the priority process. It is the responsibility of the drug companies to run the studies in a timely manner and report to the FDA annually on the progress of their postmarketing commitment (FDA, 2003a).

As mentioned above, the general public expects that when a pharmaceutical company becomes aware of a new potential health hazard, the company will try to investigate that risk and conduct new studies to test the hypothesis, even if it is expensive for the firm. Such new risks are often detected thanks to adverse event reporting channels provided and maintained by the pharmaceutical companies. According to Title 21, *Code of Federal Regulations* section 314.80, drug manufacturers have the obligation to "promptly review all adverse drug experience information" and report those events to the FDA within 15 days (FDA, 2009a). Those adverse events reports represent approximately 90 percent of the reports received by the FDA (Woodcock, 2000). Similarly, if new risks are discovered during studies run by the pharmaceutical companies, it is expected that they will share this information with the FDA, even if the results are negative. The disclosure of negative results goes against the company's business interest but it would be considered unethical for a company to conceal health risks associated with a drug.

3. Give accurate and up-to-date information to doctors

Pharmaceutical companies help keep doctors up-to-date with the latest treatments by sponsoring the doctors' Continuing Medical Education (CME) events and by sending sales representatives to doctors' offices and to educate them about new available treatments. Note that it has been argued that it should not be the responsibility of the pharmaceutical companies to sponsor doctors' CME programs.

4. Conduct or sponsor research that can be useful for the development of new drugs and treatments

Pharmaceutical companies are constantly innovating, finding treatments for new diseases or improving on the existing treatments to limit their side effects. The breakthroughs are either the result of in-house research or collaboration with universities, often sponsored by federal grants.

Context in Which Decisions Were Made

Merck has a fiduciary duty to shareholders to provide a return on their investment and stakeholders demand a high return. Furthermore, drug company executives are partly paid in stock options and therefore have strong incentives to return a high profit. This requirement is embedded in the company's mission statement: "The mission of Merck is to provide society with superior products and services by developing innovations and solutions that improve the quality of life and satisfy customer needs, and to provide employees with meaningful work and advancement opportunities, and *investors with a superior rate of return* [emphasis added] "(Merck, 2008c).

To reach this goal, drug companies have to continuously develop new products and keep costs down. Nowadays, the survival of large pharmaceutical companies often depends on them developing blockbuster drugs (drugs that generate revenue of more than $1 billion per year). In 1999, Merck was about to lose five of its most profitable patents (Vasotec, Prinivil, Mevacor, Pepsid, and Prilosec), accounting for 25 percent of the company's US sales (Shook, 2000). The

success of Vioxx was therefore crucial for the financial future of the company, to the point that drug industry analysts at the investment bank Raymond James & Associates called Vioxx "Merck's savior" (Berenson, Harris, Meier, & Pollack, 2004). The drug proved to be the blockbuster the company needed "generating US$2.5 billion in 2003, 11% of Merck's sales" (Fielder, 2008).

The success of Vioxx was somewhat surprising because the drug faced fierce competition from Celebrex, which had been approved by the FDA in 1998, 5 months before it approved Vioxx. This competition might have fueled the escalation in advertising expenses.

The problem with the blockbuster model is that the fate of the company depends on a few products. As Fielder puts in, "blockbusters […] create huge amounts of financial inertia: they are so profitable it is difficult to shut off the money machine when problems arise''(Fielder, 2008). Massive drug sales can lead companies to turn a blind eye to negative results or at least try to cast them in a more positive light. In the case of Vioxx, ambiguous preliminary results were interpreted as a protective action from naproxen (Aleve) instead of as negative side effects from Vioxx. The VIGOR (Vioxx GI Outcomes Research) study, conducted by Bombardier, at al. and published in November 2000 in the New England Journal of Medicine (Bombardier, et al., 2000) showed that the overall mortality rate and the rate of death from cardiovascular causes were similar in the two groups—however, there was a 4-fold increase in the risk of acute myocardial infraction. Merck scientists interpreted this difference as a protective action from naproxen rather than a negative side effect from Vioxx: "[Merck] claims that the difference in myocardial infarctions between the two groups is primarily due to the antiplatelet effects of naproxen" (Targum, 2001).

Another problem is that pharmaceutical companies have no incentives to do Phase IV studies because there is no benefit for the firm to do such a study. Negative results can force the company to change the drug's label or recall the drug. According to an article published in 2005 by Okie in the New England Journal of Medicine, "[o]f more than 1300 post-marketing studies to which drug companies have committed themselves, 65 percent have not been started" (Okie, 2005). Similarly, the companies have no incentive to publish negative results from internal studies.

One way pharmaceutical companies gained greater control over publication is buy shifting their clinical research from academic medical centers to Contract Research Organizations (CROs), which boast they can do clinical trials faster and cheaper while giving more control to the research sponsors who hire them (ACRO, 2007).

Finally, "Merck [had] an excellent reputation within the drug industry and supports many products, such as vaccines, that are medically essential but not very profitable" (Waxman, 2005a) but this reputation ended-up hurting the firm since once the drug had been marketed, recalling it and acknowledging the related accidents would have been a blow to the firm's image.

Mental Models

As mentioned above, Merck originally believed that Vioxx did not cause any CV events but rather than naproxen protected patients' hearts. The company also believed that Vioxx had the potential to become a blockbuster drug and significant source of revenue if only Merck could effectively limit the publication of negative results and convince doctors to prescribe the drug despite potential CV risks.

Inadequate Control Actions

Merck's inadequate control actions can be broken down into three main themes and studied within this framework: 1) Merck avoided running studies with potential negative results; 2) For the studies that were run, the results were biased and 3) Merck published and disseminated misleading information about the safety profile of Vioxx.

1. Merck did not run studies that might have found negative CV results

As mentioned in the previous section, Merck had no financial incentives, at least in the short term, to run studies that might find its products to be dangerous. Such studies are costly, hard to organize, might send the wrong message to the public and the scientific community and can find devastating evidence against blockbuster drugs which would force a market recall. "[Merck] executives rejected pursuing a study focused on Vioxx's cardiovascular risks. According to company documents, Merck's scientists wondered if such a study, which might require as many as 50,000 patients, was even possible. Merck's marketers, meanwhile, apparently feared it could send the wrong signal about the company's confidence in Vioxx, which already faced fierce competition from a rival drug, Celebrex. 'At present, there is no compelling marketing need for such a study,' said a slide prepared for the meeting. 'Data would not be available during the critical period. The implied message is not favorable' " (Berenson, et al., 2004).

Of course, Merck is not the only company to avoid running potentially negative studies. Recent litigation uncovered a memorandum from a Bayer company executive arguing that: "If the F.D.A. asks for bad news, we have to give it, but if we don't have it, then we can't give it to them" (Avorn, 2006).

2. Merck's studies, and the results the firm published, did not appropriately represent the risk/benefit profile of the drug

For studies that Merck did run: a) the studies were motivated by marketing goals; b) if the results were published, they were typically released very late, were only partially released c) or were biased to appear better than they were and d) the patients were not always protected by a Data Safety Monitoring Board

Point a: The studies were motivated by marketing goals.

It has been argued that the 1999 ADVANTAGE study organized by Merck was primarily a marketing tool: “Merck conducted a seeding trial to promote the prescription of Vioxx. The trial coincided with the FDA's approval and the availability of the product on the market in 1999. Although billed as a gastrointestinal safety study, ADVANTAGE was actually a sophisticated marketing tool designed to allow optimal seeding of positive experiences with Vioxx among customers—primary care physicians—before its approval” (Hill, Ross, Egilman, & Krumholz, 2008).

Hill and colleagues support their view by quoting several internal Merck documents that were made public during litigation. For example, they quote a memorandum from Charlotte McKines, Executive Director of Marketing Communications at Merck, and Lou Sherwood, Senior Vice President for Medical and Scientific Affairs, to Merck Marketing that illustrates the role of the marketing department in the development of the study: “The design was the result of a close collaboration between CDP [Clinical Development Program] and Marketing. […] The sales force nominated potential investigators and completed intake forms, allowing a very large number of sites to be evaluated and enrolled and ensuring equal distribution of investigators across the business groups.’ [...] Feedback from the field has been overwhelmingly positive about their ability to access key customers and the influence that being involved in the trial has had on their perceptions of VIOXX and Merck” (Hill, et al., 2008).

Similarly, they are quoted in another memo where they describe their goal for the ADVANTAGE study: “The objectives were to provide [a] product trial among a key physician group to accelerate uptake of VIOXX as the second entrant in a highly competitive new class and gather data important to this customer group” (Hill, et al., 2008). The fact that ADVANTAGE was a seeding study seemed to have been commonly accepted in the marketing division of Merck: “Rebecca Higbee, an employee in the Merck marketing division, attempted to convince others to avoid using this term in describing ADVANTAGE: ‘It may be a seeding study, but let's not call it that in our internal documents’ ”(Hill, et al., 2008).

Point b: If the results were published, they were typically released very late or only partially released.

Psaty and Kronmal point out in a paper published in JAMA that an intention-to-treat analysis of protocols 091 and 078 that was conducted by Merck in 2001 was not submitted to the FDA until 2003 (Psaty & Kronmal, 2008). Similarly, Angell claims that “Merck had misled the FDA by not supplying it with an internal analysis the company had done of Vioxx's risks” (Angell, 2006).

Note that this behavior happens throughout the industry and seems to be a fairly frequent phenomenon: “A few years ago, it was discovered that some companies had funded multiple clinical trials of their selective serotonin-reuptake inhibitor antidepressants but reported the results of only the favorable trials—distorting the evidence-base physicians use in choosing drugs. But the issue is thornier for epidemiologic analyses. Companies can conduct them secretly, even in-house, with the use of a purchased proprietary database, making the results even easier to conceal” (Avorn, 2006).

Point c: The published results were biased to appear better than they were.

In the case of analysis of protocol 091 and 078, Merck biased the results from the studies and hide the CV risks associated with Vioxx by publishing "on-treatment rather than intention-to-treat analyses, an approach that minimized the appearance of the mortality risk" (Psaty & Kronmal, 2008). Similarly, Congressman Waxman argues that the results from the VIGOR trial were skewed in favor of Vioxx; the actual data showed Vioxx to be more dangerous than naproxen: "According to Merck's press release, the patients receiving Vioxx had fewer gastrointestinal problems, while the patients receiving naproxen suffered fewer heart attacks and strokes. The actual data from the study showed that patients in the VIGOR study on Vioxx were five times more likely to suffer a heart attack than those on naproxen" (Waxman, 2005b).

By conducting studies motivated by marketing interests, the company did not fulfill its responsibility to properly monitor the drug for potential safety problems. At the same, time, by misrepresenting the data from its studies, Merck violated the company's safety requirements that states that the company has to keep the doctors and the FDA informed about the potential risks associated with the use of Vioxx.

Point d: A few of studies did not have an active Data and Safety Monitoring Board (DSMB) to monitor the clinical trials and protect the patients. Safety was solely in the hands of the Merck investigators.

Here again, the article published by Psaty and Kronmal in JAMA are referred to for support: "In the letter of December 5, 2001, the FDA had also assumed that protocol 078 had an active data and safety monitoring board (DSMB). But the 078 study, which had IRB approval, did not have a DSMB. The only human-subjects protections available to the study participants were those provided by the investigators who were blind not only to the treatment allocation but also to the findings for study wide adverse events, and by the unblinded Merck investigators, who did not discern a safety issue" (Psaty & Kronmal, 2008).

Pharmaceutical companies have little incentive to find safety issues when running trials, a conflict of interest that can put the trial patients at risk. As discussed earlier in the requirements section, pharmaceutical companies need to make a profit and generate revenues for their stakeholders, and therefore they have no incentive to interrupt a trial, which could jeopardize the approval of a drug. This conflict of interest should disqualify sponsors from important safety duties including those normally accorded to a data safety monitoring board (DSMB) and institutional review boards (IRBs). By not having an active DSMB, Merck not only put the patients from its clinical trials at risk but also limited its capability to monitor the drug for potential safety problems.

3. Merck published and disseminated misleading information about the safety profile of Vioxx

Merck aggressively promoted Vioxx to physicians and trained its sales representatives to avoid CV questions. This topic has been thoroughly documented by Representative Waxman in his report for the Committee on Government Reform where he extensively quotes internal memoranda and training documents that show that the marketing department was actively trying to avoid the topic. See Figure 5 for an extract of the report.

- **After Merck's VIGOR study reported increased heart attack risks, Merck directed its sales force to show physicians a "Cardiovascular Card" that made it appear that Vioxx could be 8 to 11 times safer than other anti-inflammatory drugs.** This card omitted any reference to the VIGOR findings and was based on data FDA considered to be inappropriate for a safety analysis.

- **After the FDA advisory committee voted that physicians should be informed about the risks found in the VIGOR study, Merck sent a bulletin to its sales force that advised: "DO NOT INITIATE DISCUSSIONS ON THE FDA ARTHRITIS COMMITTEE … OR THE RESULTS OF THE … VIGOR STUDY."** If physicians asked about the VIGOR study, Merck representatives were directed to respond, "I cannot discuss the study with you."

- **After the *New York Times* reported on the cardiovascular dangers of Vioxx, Merck instructed its field staff to tell physicians that patients on other anti-inflammatory medications were eight times more likely to die from cardiovascular causes than patients on Vioxx.** The Merck bulletin told its sales force to show physicians the Cardiovascular Card and state: "Doctor, As you can see, Cardiovascular Mortality as reported in over 6,000 patients was Vioxx .1 vs. NSAIDS .8 vs. Placebo 0."

Source: (Waxman, 2005b)

Figure 5 – Quotes on the marketing of Vioxx

Waxman believes that this promotional effort can explain, at least to some extent, why the sales of Vioxx remained strong even as the evidence against the drug started to accumulate. When aggressively promoting Vioxx, Merck distorted the information given to the doctors and did not inform them about all the potential risks.

The company continued to minimize unfavorable findings up to a month before withdrawing Vioxx. The FDA's Division of Drug Marketing, Advertising and Communications sent a warning letter to Merck in September 2001, where they denounced the use of "promotional activities and materials [that were] false, lacking in fair balance, or otherwise misleading in violation of the Federal Food, Drug, and Cosmetic Act" (Abramas, 2001). However, little was done to correct the situation and Merck continued to hide unfavorable findings until the drug was recalled (Waxman, 2005b).

Other deceptive practices from Merck included the promotion of ghostwritten or guest-authored publications: Guest authorship is defined by Ross as "the designation of an individual who does not meet authorship criteria as an author"(Ross, Hill, Egilman, & Krumholz, 2008). Ghostwriting is "defined [as] the failure to designate an individual (as an author) who has made a substantial contribution to the research or writing of a manuscript" (Ross, et al., 2008).

In his paper, Ross describes the systematic strategy used by Merck to facilitate the publication of ghostwritten articles. He also gives examples of papers that had been written by Merck employees and subsequently published under a different author, typically an academically

affiliated investigator: “Articles related to rofecoxib were frequently authored by Merck employees but attributed first authorship to external, academically affiliated investigators who did not always disclose financial support from Merck, although financial support of the study was nearly always provided” (Ross, et al., 2008).

Ross also quotes an article from the New York Times (Berenson, 2005) where Lisse, the first author for the ADVANTAGE study describes the involvement of Merck in the trial: “Merck designed the trial, paid for the trial, ran the trial […] Merck came to me after the study was completed and said, ‘We want your help to work on the paper.’ The initial paper was written at Merck, and then was sent to me for editing” (Ross, et al., 2008). Here again, by using guest authorship and ghostwriting Merck distorted the information available to the doctors to make the drug appear safer than it really was.

Finally, the Australian Class Action suit against Merck showed that the pharmaceutical giant commissioned “journals” made to look like independent peer-reviewed journals that were actually marketing compilations of articles promoting Vioxx and another drug (Fosamax) made by Merck. This “journal” (the Australasian Journal of Bone and Joint Medicine) was published twice a year, from 2002 to 2005, by the largest medical publisher in the world (Elsevier), which also prints journals such as The Lancet and The American Journal of Medicine. A company spokesman for Elsevier said that one of the issues of this “journal” was distributed to 20,000 doctors in Australian while other issues typically were distributed to about 10,000 doctors (Garfield, 2009; Singer, 2009).

FDA/CDER

General Information

The U.S. Food and Drug Administration (FDA) was established in 1906 by the Federal Food and Drugs Act as an extension to the Bureau of Chemistry. It is a scientific, regulatory, and public health agency in charge of most food products (other than meat and poultry), human and animal drugs, therapeutic agents of biological origin, medical devices, radiation-emitting products for consumer, medical, and occupational use, cosmetics, and animal feed (Swann, 2009). It currently employs over 9,000 employees (FDA, 2009e) and requested a budget of $2.4 billion for the fiscal year 2009 (FDA, 2009j).

The section within the FDA responsible for human drugs is called the Center for Drug Evaluation and Research (CDER) and was established at the same time as the FDA in 1906. Its role was expanded in 1938 by the Food and Drug Cosmetic Act, largely in response to the Elixir Sulfanilamide scandal which killed 107 people (FDA, 2009f). It is responsible for "ensuring that prescription, generic, and over-the-counter (OTC) drug products are adequately available to the public and are safe and effective. The program is also responsible for monitoring marketed drug products for unexpected health risks, and for monitoring and enforcing the quality of marketed drug products" (FDA, 2008). It represents $738 million of the 2008 $2.4 billion FDA budget (FDA, 2008).

Within CDER, the Office of New Drugs (OND) is in charge of approving new drugs, setting drug labels and, when required, recalling drugs. The Office of Surveillance and Epidemiology (OSE) focuses on identifying adverse events that were not detected during the approval of drugs and can recommend actions, such as label changes or recalls, to OND (FDA, 2009i).

See Appendix D for a detailed structure of the FDA and CDER as of 2008.

Summary of Accident Causal Factors

Safety Requirements:

Committee Staff

1. Select competent advisory committee members and establish and enforce conflict of interest rules
2. Provide researchers access to accurate and useful adverse events reports

OND

3. Oversee all U.S. human trials and development programs for investigational medical products to ensure safety of participants in clinical trials. Provide oversight of IRBs that perform these functions for the FDA
4. Set the requirements and process for the approval of new drugs
5. Critically examine a sponsor's claim that a drug is safe for intended use (New Drug Application Safety Review). Impartially evaluate new drugs for safety and efficacy and approve them for sale if deemed appropriate
6. Upon approval set the label for the drug
7. Do not unnecessarily delay drugs that may have a beneficial effect
8. Require phase IV safety testing if there is a potential long-term safety risk
9. Remove a drug from the market if new evidence shows that the risks outweigh the benefits
10. Update the label information when new information about drug safety is discovered

DDMAC

11. Monitor the marketing and promotion of drugs. Review advertisements for accuracy and balance

OSE

12. Conduct on-going reviews of product safety, efficacy, and quality. Perform statistical analysis on adverse event data received to determine whether there is a safety problem
13. Re-assess risks based on new data learned after a drug is marketed and recommend ways to manage risk
14. Serve as consultants to OND with regards to drug safety issues
15. Recommend that a drug be removed from the market if new evidence shows significant risks

Context in Which Decisions Were Made:

Agency Wide

1. Lack of strong leadership at the head of the FDA, high turnover and unfilled positions
2. Tensions between the Office of New Drugs (OND) and the Office of Surveillance and Epidemiology (OSE). OND was much larger than OSE and had more resources. When OSE proposes to recall a drug, it is perceived as a failure of OND
3. PDUFA: The FDA is partly sponsored by the pharmaceutical companies it is supposed to monitor and regulate. This leads to (a) pressure to reduce approval time and (b) comparatively less staff in safety monitoring and marketing oversight than in approval
4. Limited resources in personnel and budget
5. Many of the experts who are asked to be on an advisory panel work with the pharmaceutical companies. It is difficult to find experts who do not have such ties
6. Political and congressional pressures (e.g., anti-regulatory climate, special interests)

OND

7. For pre-market review, the FDA only has information provided by the company with no other independent research data
8. Legislation inhibits full disclosure of information: Clinical information is kept secret and the FDA cannot share proprietary data for independent analysis
9. The FDA is unable to keep track of ongoing clinical trials
10. Legislation makes it difficult for the FDA to require label changes
11. A very high certainty that the drug is dangerous is required before the drug is recalled
12. OND is in charge of both approving and recalling drugs
13. PDUFA fees represent more than 50% of ODN's budget; The FDA depends on PDUFA funding which affects the decision making process

OSE

14. No independent decision-making responsibility
15. High turnover of OSE directors
16. No control over selective publication (companies are not required to publish results from clinical trials or even the fact that clinical trials were being conducted)
17. No legal authority to require additional safety studies once a drug is approved. Post-marketing safety requirements are rarely enforced
18. Adverse event reporting is limited: reporting voluntary, no certainty the event was actually due to the product, reports often not detailed enough for use. Researchers do not know how many people are taking the medication so cannot use the Adverse Event Reporting System' (AERS) data to calculate incidence in the population
19. Very limited sources of information about adverse events

Inadequate Control Actions:

Agency Wide

1. Allowed waivers of conflict of interest rules for advisory panel members
2. Pressured an FDA employee to change conclusions and recommendations on a study of Vioxx and prevented publication of the results
3. Was not able to provide quality adverse event reports for researchers to use

OND

4. Gave expedited review and approval to Vioxx even though the drug did not meet the criteria for expedited review
5. Did not check whether clinical trial safety requirements were being enforced (e.g., that protocol 078 had an active DSMB)
6. Approved Vioxx without requiring a Phase IV study even though the long term risks were unclear
7. Did not update the Vioxx label in a timely fashion
8. Delayed the recall of Vioxx. Did not act fast or effectively enough

DDMAC

9. Original warning letter was not followed by subsequent warnings; false and misleading promotional material went un-reviewed

OSE

10. Did not properly monitor the drug for long-term risks. Could not differentiate normal adverse events from the ones due to the drug within the population affected
11. Did not insist that Merck launch a large-scale clinical trial when suspicions first arose
12. Did not require a recall of the drug

Safety Requirements

Since the FDA is a complex organization, this section focuses on to the Center for Drug Evaluation and Research and breaks down the analysis according to the functional divisions that exist within the center.

Agency wide

The FDA is served by a number of committees that help with different functions by providing their expert opinion. The FDA Committee staff is in charge of selecting the committee members and make sure that they do not have any conflicts of interest that would forbid them from sitting on the committees (FDA, 2009c; Suydam, 2000).

The FDA is also expected to provide adverse event reports to external researchers for analysis. This information is currently collected through the Adverse Events Reporting System.

OND

OND is in charge of overseeing all U.S. human trials and development programs for investigational medical products to ensure safety of participants in clinical trials. OND also provides oversight of the Institutional Review Board to "ensure the protection of the rights, welfare, and safety of human subjects and the quality and integrity of data submitted to the Agency" (FDA, 2006).

OND sets the requirements for all New Drug Applications (NDA) and defines the approval process for new drugs. Those standards were first established in 1938 and every drug since has been the subject of an NDA before U.S. commercialization. The FDA provides guidance documents for different types of NDAs on its website (FDA, 2009h).

Once an application has been submitted to the FDA, it is OND's responsibility to critically examine the sponsor's claim that a drug is safe for intended use (conduct an NDA Safety Review) and to impartially evaluate the new drug for safety and efficacy and approve it for sale if deemed appropriate. OND does not run the clinical trials but sets the standards for the evidence required for a drug's approval, monitors the research and reviews the results from the company's data. If OND considers that the drug is effective and its health benefits outweigh the risks, the drug is approved. In 2007, CDER approved 88 new products (FDA, 2008). As part of the approval process the FDA is also responsible for approving a specific treatment and dosage.

If OND decides to approve a drug, it must then decide what will be on the drug's label. Labels typically include indication (what the drug is used for), dosage information, target population and relevant safety information (FDA, 2009d). Discussions between the FDA and the drug manufacturer on what should be on the label are usually part of the drug approval process. Note that when Vioxx was on the market, regulations stated that the label could only be changed with the approval of the drug manufacturer.

Another important requirement for drug approval is that it be done in a timely fashion; By delaying potential life saving drugs, the FDA puts people's lives at risk (Conko, 2008; Sofer, 2008). CDER therefore gives priority status to products for diseases such as cancer and AIDS and assesses them using an accelerated evaluation process (FDA, 2008). However, allowing an accelerated process means that some drugs are approved based on very limited information and the FDA recognizes that pre-marketing trials are often too short and too small to learn everything about a drug. OND can therefore require the pharmaceutical company to run a post-approval study (phase IV) to try to gather more data about the drug's safety.

The FDA also collects notices of adverse events in its Adverse Event Reporting System (AERS) and analyzes this data to monitor for new potential risks. OND has the power, and the responsibility, to remove a drug from the market if it discovers new information about the safety and effectiveness profile of the drug that may put the public at risk (FDA, 2009i). Note, however, that in the case of Vioxx, the product was recalled by Merck and not by the FDA. An alternative to drug recalls is to update the label information when new information about drug safety is discovered. For example, Vioxx's label was updated after the FDA negotiated with Merck to add a warning that "patients with a history of heart disease should use the drug with caution" (Berenson, et al., 2004).

DDMAC

The FDA's Division of Drug Marketing, Advertising, and Communications (DDMAC) is responsible for overseeing the promotion of prescription drugs and ensures that promotional materials are not misleading or false. In particular, the FDA prohibits pharmaceutical companies from promoting drugs for uses inconsistent with the drug label (off-label uses) (GAO, 2008).

DDMAC has to review all the written material submitted by drug companies and identify potential violations such as off-label promotion or advertisements minimizing the risks of a drug and overstating a drug's safety and effectiveness. It is also responsible for monitoring other promotional activities such as information booths and literature distributed at medical conferences (GAO, 2008).

DDMAC intervened in September 2001 against Vioxx by sending Merck a warning letter stating that "Merck's promotional campaign for Vioxx 'minimizes the potentially serious cardiovascular findings' in Vigor. The agency required Merck to send letters to physicians across the country 'to correct false or misleading impressions and information' " (Berenson, et al., 2004). The July 2008 GAO report: "Prescription Drugs: FDA's Oversight of the Promotion of Drugs for Off-Label Uses" provides more information about the monitoring process and its difficulty.

OSE

The FDA's Office of Surveillance and Epidemiology is in charge of postmarketing surveillance and risk assessment programs to identify adverse events that were not detected during the initial drug approval process (FDA, 2009i). OSE is in charge of providing more information to the community and can recommend the implementation of a risk management program if deemed necessary (FDA, 2009i). OSE staff also serves as consultants to OND regarding safety issues.

OSE typically takes a population-based perspective, conducts an analysis and sends its results to OND for regulatory action (recall, warning, label change…). Even though OSE does not have the authority to recall a drug, it is expected that in its role of surveillance it will do everything in its power to make sure OND recalls a drug that is dangerous for the general public.

Context in Which Decisions Were Made

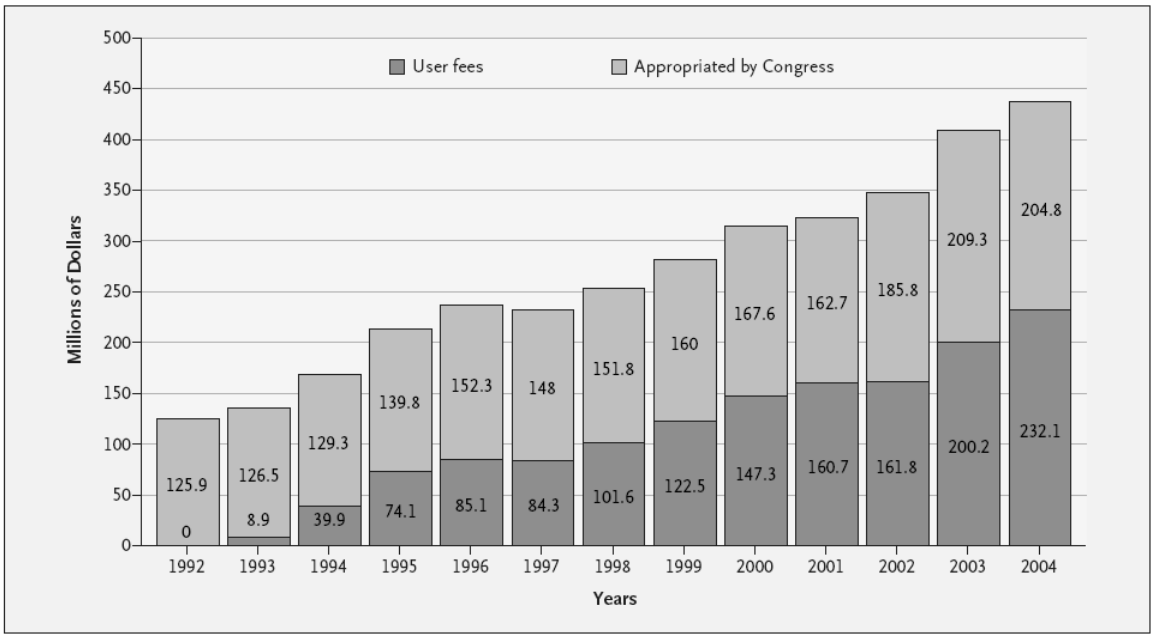
Here again, the context is broken down into different sections based on the functional divisions of the agency.

Agency Wide

In a 2005 perspective article published in the New England Journal of Medicine, Okie explains that one of the problems of the FDA is "the lack of strong and independent leadership, which has contributed to an atmosphere that stifles debate and discourages some employees from expressing scientific concerns about drugs" (Okie, 2005). She goes on to explain that several of the leadership positions had been left unassigned during most of President's Bush first administration. For example the FDA commissioner, Mark McClellan, was only confirmed in November 2002 and left in March 2004. Similarly, several other high level positions were held by acting officers, instead of appointees: "Over the past 10 years, no commissioner has served more than two years, though the term is open-ended" (Harris, 2006).

One of the effects of this power vacuum was that there was nobody to help resolve the tension between the Office of New Drugs (OND) and the Office of Surveillance and Epidemiology (OSE). The two offices are part of CDER but have conflicting objectives: OND is in charge of approving drugs will OSE tries to identify drugs that need to be recalled. The work of OSE can be seen as "double-checking" the work of OND to make sure that they made no mistakes when approving a drug. Every time OSE proposes to recall a drug, it is perceived as a failure of OND, which should not have approved the drug in the first place. This tension was accentuated by the Prescription Drug Use Fee Act (PDUFA), which significantly inflated OND's budget and created a resource gap between the two offices.

PDUFA was passed by Congress in 1992 and was subsequently reauthorized in 1997, 2002 and 2007. This law allows the FDA to collect fees from the pharmaceutical companies for approval of new drugs. In return, the FDA agrees to meet drug-review performance goals (FDA, 2003b). The main goal of PDUFA is to accelerate the drug review process by allowing the pharmaceutical companies to sponsor the FDA. Originally, the user fees were only to be used for activities related to the drug approval process. According to the 2009 FDA budget report, the user fees amounted to $327 million in 2008 and are expected to represent $350 million in 2009 (FDA, 2008). "Between 1993 and 2002, user fees allowed the FDA to increase by 77 percent the number of personnel assigned to review applications. User fees from pharmaceutical companies now account for more than half the money the FDA spends on the review process" (Okie, 2005). In 2004, more than half of the funding for the CDER was coming from user fees (see Figure 6).



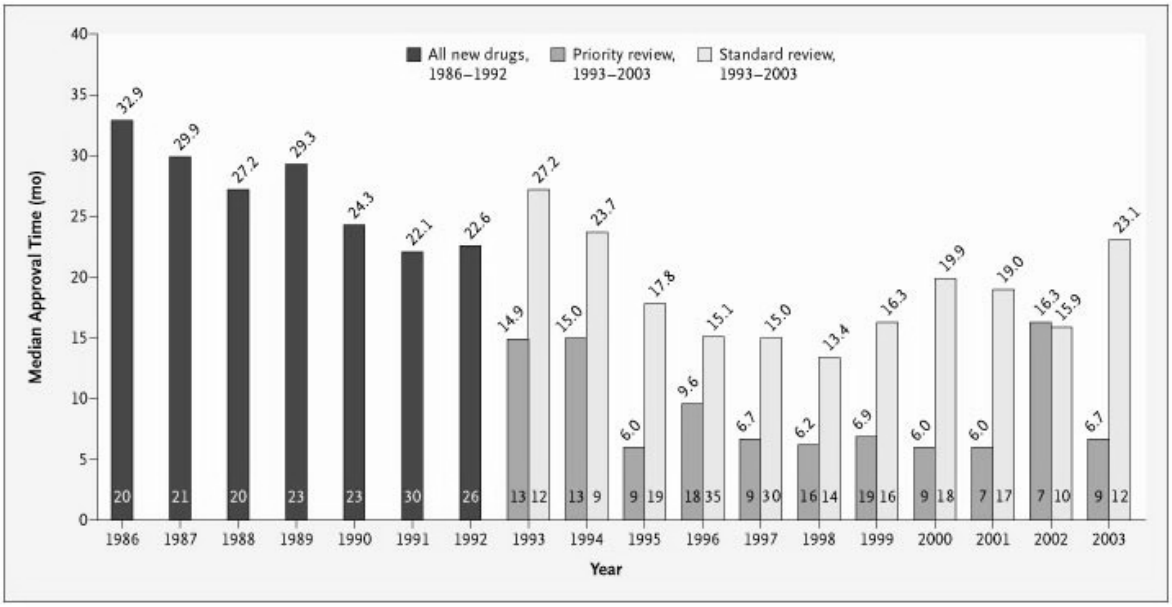
Funding for the FDA's Center for Drug Evaluation and Research.
Data are from the FDA.

Source: (Avorn, 2007)

Figure 6 – Funding for the FDA's CDER

A growing group of scientists and regulators (Angell, 2006; Avorn, 2007; Okie, 2005) are afraid that by allowing the FDA to be sponsored by the pharmaceutical companies, the FDA shifted its priorities to satisfying the pharmaceutical companies, its "client", instead of protecting the public: "[A] scientist, who has worked at the FDA for about 15 years, said in an interview that PDUFA produced a 'sea change' in the priorities set by agency managers. 'When I joined, there was an absolute emphasis on safety; he said. 'It is very, very clear that the emphasis now is getting drugs approved' " (Okie, 2005).

At the same time, thanks to PDUFA, drugs have been approved and marketed faster (see Figure 7): "the increase in resources has resulted in important public health benefits, including a reduction in drug review time estimated to have saved 180,000 to 310,000 lives" (McClellan, 2007).



Source: (Okie, 2005)

Figure 7 – Median Total Time to FDA Approval for NDAs, 1986–2003.

PDUFA is an important source of funds for OND but the rest of the agency is still very much underfunded. A 2007 IOM report notes that "[t]here is little dispute that FDA in general is, and the Center for Drug Evaluation and Research (CDER) specifically remains, severely underfunded. […] There is widespread agreement that resources for postmarketing drug safety work are especially inadequate and that resource limitations have hobbled the agency's ability to improve and expand this essential component of its mission" (Institute of Medicine, Baciu, Stratton, & Burke, 2007).

Finally, the agency is subject to external pressures. Many of the experts who are asked to be on an advisory panel work with the pharmaceutical companies—it is hard to find experts who do not have such ties. According to an article published in the New York Times "ten of the 32 government drug advisers who […] endorsed continued marketing of the huge-selling pain pills Celebrex, Bextra and Vioxx have consulted in recent years for the drugs' makers […]. If the 10 advisers had not cast their votes, the committee would have voted […] 14 to 8 that Vioxx should not return to the market. The 10 advisers with company ties voted […] 9 to 1 for Vioxx's return" (Harris & Berenson, 2005). Similarly, OND is subject to political congressional pressures and, as discussed later, the Pharmaceutical lobby is one of the most powerful in Washington.

OND

As mentioned previously, clinical trials and other drug tests are done by the pharmaceutical company manufacturing the drug, there is no independent external group that tests the drug and the only information available to the FDA at the time of approval is the information in the New Drug Application, all of which is provided by the drug manufacturer.

However, this information cannot be published by the FDA as it is considered confidential. The agency must request the permission of the sponsor to make a study public and, of course, drug companies will only allow the most favorable results to be published. This lack of transparency hinders the work of the FDA and puts the public at risk by hiding potentially important safety information: "By allowing less favorable results to remain buried, the agency puts proprietary interests ahead of the public interest, and doctors and the public come to believe prescription drugs are better than they are" (Angell, 2006).

Similarly, legislation makes it difficult for the FDA to require label changes since OND cannot change a drug label once it has been approved without having the manufacturer agree to the change: "FDA cannot unilaterally compel label changes, addition of boxed warnings, or fulfillment of postmarketing study commitments" (Institute of Medicine, et al., 2007).

Another problem is that the OND is unable to keep track of ongoing clinical trials. In 2007, the Office of the Inspector General (OIG) at the Department of Health and Human Services published a report on the FDA's oversight of clinical trials. It found that:

> "Because FDA does not maintain a clinical trial registry, it is unable to identify all ongoing clinical trials and their associated trial sites. Further, because FDA does not maintain an IRB registry, it is unable to identify all IRBs. Even though FDA maintains six databases to track BiMo [Bioresearch Monitoring] inspections, none includes complete information needed to track all such inspections" (Levinson, 2007).

In the same report the OIG estimated that in the fiscal year 2000-2005 periods, the FDA inspected only one percent of clinical trial sites and 75 percent of those inspections were surveillance inspections focusing on the quality of clinical trial data instead of IRB inspections, which focus on the oversight of human subject protections.

There are also some important issues with the way OND handles drug recalls. In a testimony given to the Senate Financial Committee, David J. Graham explains that the requirements to recall a drug are very high, typically equivalent to the ones necessary for a drug to be approved: "a drug is safe until you can show with 95% or greater certainty that it is not safe. This is an incredibly high, almost insurmountable barrier to overcome. […] In order to demonstrate a safety problem with 95% certainty, extremely large studies are often needed. And [those] large studies can't be done" (Graham, 2004). Furthermore, OND is both in charge of approving and recalling drugs which creates a disincentive to recall a drug: a recall could be interpreted as an admission that the approval process failed to detect the problem and that the office has put patients at risk.

Finally, it is important to point out that the PDUFA fees which started in 1992 to help accelerate the approval of drugs represented in 2005 more than 50% of the Office of New Drugs expenditures (GAO, 2006). The office therefore now relies on PDUFA as a source of funding creating a situation where the regulator is dependent on the industry it is in charge of regulating.

OSE

According to the 2006 GAO report on drug safety, there has been a high turnover of OSE directors in the past 10 years, with eight different directors of the office. The turnover has a negative effect on the work and morale of the staff and it means that there is little consistency in leadership and that the OSE leaders have little knowledge of the ongoing issues (GAO, 2006).

Also, as mentioned above, OSE has very limited powers. OSE is only a research and advising branch of CDER and has no authority to recall a drug or change a label. Recalling a drug has to always be done through OND which may or may not follow the advice and recommendations of OSE (GAO, 2006). Similarly, OSE has no legal authority to require additional safety studies after the approval of the drug by OND. However, it can ask a manufacturer to include safety measures in follow-up trials to confirm efficacy or to support new uses and label changes. Note that the FDA has never withdrawn a drug because of a manufacture's reluctance to conduct post-approval studies, yet 65 percent of post-marketing studies have not been started (Okie, 2005).

Finally OSE has access to very limited sources of information. The Adverse Event Reporting System (AERS) is a useful tool for the FDA and helps identify new risks associated with marketed drugs, but it also has important limitations: 1) there is no way to verify whether a reported event is actually due to the product; 2) reporting is voluntary, fairly limited and most reports do not have enough details to evaluate an event; 3) since all events are not reported, there is no way to calculate the incidence of an adverse event in the U.S. population (FDA, 2009b). Another problem is that the FDA cannot force pharmaceutical companies to publish negative results from internal or even external studies and, as mentioned above, the FDA did not have the infrastructure to keep track of clinical studies and therefore had no way of knowing that some results were not being published.

Inadequate Control Actions

Agency Wide

The FDA is responsible for approving new drugs and in some cases deciding whether to remove a drug from the market or not. For these decisions, the FDA convenes an advisory committee of experts and typically follows the recommendations of the panel. The problem is that many of the experts have financial ties with pharmaceutical companies, either as primary investigators or as paid consultants. The FDA typically has to grant waivers for several committee members.

For example, in the 1999 advisory committee meeting that led to the approval of Vioxx: "four of the six members, including the chairman, needed waivers because they had a 'potential for a conflict of interest' "(Angell, 2005). As mentioned in the context section, similar problems were obvious when the FDA had to decide if it wanted to keep COX-2 on the market (Harris & Berenson, 2005).

Furthermore, advisory panels dealing with product recalls sometimes allow testimonials from patients who have been taking the drug. The problem is that these testimonials are unreliable for demonstrating a drug's effectiveness and they represent a biased sample of the population: only

patients invited by the pharmaceutical companies, and therefore favoring the drug, present their points of view and opinions (Angell, 2006).

Finally, pressures to find favorable results exist within the agency. David Graham, a scientist working for the FDA, was pressured to change the conclusions of a study he conducted that found high-doses of Vioxx significantly increased the risk of heath attacks and sudden death. According to his testimony to the Senate Financial Committee, he was forbidden to attend a conference to present his research if he did not change his results beforehand because the recommendations in that study contradicted OND's official position (Graham, 2004).

OND

As mentioned above, there exists an accelerated approval process that is typically reserved for potential life saving medications, especially for treatments against cancer and AIDS. The problem is that this procedure is abused and used for medications that would not typically be considered life saving. Vioxx, for example, was given a six-month priority review "because the drug potentially provided a significant therapeutic advantage over existing approved drugs due to fewer gastrointestinal side effects, including bleeding" (Kweder, 2004). It is dubious that this accelerated process was warranted for Vioxx, especially because there was already a similar drug on the market (Celebrex). It is more likely that Merck wanted the priority review so that Vioxx could be on the market earlier, to compete with Celebrex.

The problem is that the FDA is now focused on fast approval of drugs, which can be in part seen as the consequence of PDUFA. The FDA yields to pressure from the pharmaceutical companies to process drug approvals rapidly and not necessarily with enough evidence:

> "In a survey of CDER scientists conducted in 2002 by the Office of Inspector General of the Department of Health and Human Services, 18 percent of the respondents said that they had 'been pressured to approve or recommend approval' of a drug despite having reservations about its safety, efficacy, or quality. For drugs assigned to priority review, 58 percent of the respondents said that reviewers were not given enough time 'to conduct an in-depth, science-based review' " (Okie, 2005).

Those pressures affect the way OND operates and could help explain some of the lapses that occurred with Vioxx. For example, OND did not check whether clinical trial safety requirements were being enforced (e.g., check that protocol 078 had an active DSMB). As a result, there was no was external review board capable of assessing the risks the patients were exposed to. Merck argued that no safety issue had been identified, and therefore it did not need to alert the IRBs. Similarly, OND approved Vioxx without requiring a Phase IV study even though the long term risks were unclear and the drug had been approved through the expedited review process. Another example of the pressures on OND and why it is important that the OND be given authority to change labels can be seen in the extended fight over Vioxx's label change: It took nearly two years for the label of Vioxx to be updated after the VIGOR study and Merck resisted for close to six months the FDA's proposals, which led to an "extended series of conference calls to negotiate differences. […] Eventually, it appears that FDA officials conceded on several key points of dispute" (Waxman, 2005b).

Finally, as mentioned in the context section, the FDA requirements for a drug approval are extremely demanding and OND only approves a drug if the FDA scientists believe with a 95% or higher probability that the drug works, which reflects the FDA's responsibility to only approve drugs that are safe and effective. The problem is that a similar paradigm is also applied to drug recalls: A drug is recalled only if it is proven, with 95% certainty or higher, that the drug is unsafe. This burden of proof is very high and difficult to meet for a drug recall (Graham, 2004). The problem with these criteria was made clear in the Vioxx case: Even though the evidence was mounting against Vioxx and both internal (Graham, et al., 2005) and external analyses of the drug (Jüni, et al., 2004; Mukherjee, Nissen, & Topol, 2001) showed it to be dangerous, the FDA was reluctant to recall the drug.

One example of such results was the epidemiological study conducted by FDA scientist David Graham, who having doubts about the safety profile of Vioxx, ran a nested case control study using data from Kaiser Permanente in California. He and his colleagues found that Rofecoxib (Vioxx) increased the risk of serious coronary heart disease and disproved the hypothesis that Naproxen protects the heart. Yet, in a Senate committee testimony, Graham explained that his supervisor pressured him to change his conclusions and recommendations, under the threat of not being allowed to publish and present his results otherwise. Similarly, senior managers in the Office of Drug Safety (now OSE) prevented him from publishing his results, even though his research had been accepted in a prestigious peer-reviewed journal. He goes on to explain that "CDER and the Office of New Drugs have repeatedly expressed the view that ODS [now called OSE] should not reach any conclusion or make any recommendations that would contradict what the Office of New Drugs wants to do or is doing" (Graham, 2004). From this testimony, it is possible to suppose that the FDA was aware of the issues surrounding Vioxx, but refused to act upon them.

The FDA's resistance to the negative news above Vioxx can in part be explained by the fact that the FDA, and in particular OND, is responsible (both in and out of the agency) for the drugs it has approved. A market recall is interpreted as a failure instead of what it really is: a post-marketing safety success.

DDMAC

The FDA does not have the resources to properly monitor all promotional material. The GAO report on the *FDA's Oversight of the Promotion of Drugs for Off-Label Uses* gives an unflattering account of the FDA's capacity to review all materials submitted by the pharmaceutical companies:

> FDA also acknowledges that it cannot review all submissions because of the volume of materials it receives and that only a small portion of the required submissions of final promotional materials are examined for potential violations. Although the agency conducts additional monitoring and surveillance to detect violations that could not be identified through a review of submitted materials, the extent and variety of promotional activities make it difficult for FDA to monitor these in a comprehensive manner (GAO, 2008).

In the same report, the issue of in-office promotion of drugs is discussed. Such promotion is very difficult for the FDA to monitor, and DDMAC has to rely on voluntary complaints from physicians to identify illegal promotion of drugs (GAO, 2008), which explains why abuses by the Merck sales team such as the Cardiovascular Card documented in Congressman Waxman's report (Waxman, 2005b) or the "Dodge Ball" marketing technique described in Merck's training presentation (Merck, 2001) were left uncontrolled.

OSE

FDA's reliance on AERS for post-approval surveillance of drugs meant that OSE could not properly monitor Vioxx for long term risks. Indeed AERS has many weaknesses—reporting of events is voluntary, the reports are not always detailed enough for use and the AERS data cannot be used to calculate the incidence of an adverse event in the U.S. population. Furthermore, the FDA does not keep track of all the ongoing clinical trials and therefore does not know about negative results if the pharmaceutical companies fail to disclose them, a situation which further hinders the FDA's capability to properly monitor drugs.

If the FDA had suspected that the drug was dangerous, it would have had to rely on Phase IV trials because the FDA, at the time of Vioxx, lacked the authority to require companies to conduct follow-up studies on suspected safety problems, although it could ask the "manufacturer to include safety measures in any further trials that are done to confirm efficacy or support a new indication" (Okie, 2005). Even if the FDA had required a Phase IV study commitment at the time of approval, it is unlikely that Merck would have actually run the study: Out of more than 1300 post-marketing studies to which the companies had committed themselves, only 35% had been started (Okie, 2005).

In the case of Vioxx, the FDA did not require Merck to launch a large scale clinical trial to study the CV risks associated with the medication, even after signs of potential problems appeared. Even if the FDA did not have the legal authority to require such a trial, Angell argues that the FDA could have threatened to remove the drug from the market, which would have forced Merck to organize a trial (Angell, 2006).

It could be argued that the lack of strong leadership at the head of the FDA and the fact that the agency is partly funded by the pharmaceutical companies created an environment favorable to the pharmaceutical companies where the FDA was less prone to question pharmaceutical companies and impose costly Phase IV studies.

Finally, the FDA did not have either the authority or the data to recall the drug. A study done by OSE in 2001 was not conclusive enough to recall the drug and the post-market data available at the time was not sufficient to establish that Vioxx was causally related to the serious cardiovascular events, which were common in that age group. The inconclusive results can in part be explained by the fact that OSE only has access to a very limited set of information sources and did not have access to the studies run by the pharmaceutical companies that showed more clearly the link between Vioxx and the cardiovascular events (GAO, 2006). Graham was

eventually capable of showing a clear link between the two, but he used an external database maintained by Kaiser Permanente.

FDA Advisory Boards

General Information

The FDA currently has 48 committees and panels that provide independent expert advice on scientific, technical, and policy matters (FDA, 2010). Out of those 48 committees, 16 have drug related responsibilities, such as the "Drug Safety and Risk Management Advisory Committee" or the "Arthritis Drug Advisory Committee". The committees can include Academician/Practitioners, consumers, industry representatives and patient representatives. The number of people on each committee varies depending on its role. The FDA usually follows the recommendations of the committees, but it is not bound to do so.

Summary of Accident Causal Factors

Safety Requirements

The FDA Advisory Boards are responsible for providing independent advice and recommendations to the FDA in the best interest of the general public. Members of the committees are expected to disclose conflicts of interest related to subjects on which advice is being given.

Context in Which Decisions Were Made

Members and potential members have financial ties to interested companies and have close working relationships with drug companies, typically through highly paid consulting work. It is also common for patients and patient advocate groups to provide testimonials during committee meetings.

Inadequate Control Actions

Some members with conflicts of interest did not recuse themselves from the decisions about Vioxx and, as mentioned previously, four of the six members on the approval committee for Vioxx required waivers because of conflicts of interest (Angell, 2005).

Similarly, ten of the 32 members of the advisory committee gave their opinion on the drug recall without needing to disclose their financial interests to the panel. The panel members were absolved from this requirement by an agency secretary because the committee agenda involved "issues of broad applicability and there are no products being approved", further adding that "[t]he Food and Drug Administration acknowledges that there may be potential conflicts of interest, but because of the general nature of the discussions before the committee, these potential conflicts are mitigated" (Harris & Berenson, 2005). Yet the committee took nine votes on issues ranging from whether to continue marketing drugs to what restrictions should be applied to those drugs.

The conflicts of interests were of course not limited to the committees dealing with Vioxx. A USA TODAY study found that more than 54% of the time, experts advising the FDA had direct financial interests in the drug or topic they were asked to review. Between 1998 and 2000, the FDA waived the conflict of interest restrictions more than 800 times (Cauchon, 2000).

A USA TODAY analysis of financial conflicts at 159 FDA advisory committee meetings from Jan. 1, 1998, through […] June 30, 2000 found:

- At 92% of the meetings, at least one member had a financial conflict of interest.
- At 55% of meetings, half or more of the FDA advisers had conflicts of interest.
- Conflicts were most frequent at the 57 meetings when broader issues were discussed: 92% of members had conflicts.
- At the 102 meetings dealing with the fate of a specific drug, 33% of the experts had a financial conflict.

Table 3 – USA TODAY study results (Cauchon, 2000)

Another interesting aspect of the committees is that, as mentioned in the context section, they allow for public testimonials, in this case from people who were using the COX-2 inhibitors (such as Vioxx) and wanted them to stay on the market. Yet such testimonials have very little scientific value (especially if they are not balanced by testimonials from those who have been injured by the drug) but can have a significant influence on the panel (Angell, 2005).

Payers / Insurers

General Information

In the United States there are two types of insurers: private and public. Private insurance companies (e.g., Blue Cross, Blue Shield, Cigna) are often offered as a benefit by employers and provide medical coverage (medical visits and drugs) for the people insured. Like all insurance, the costs are spread out across everyone who is insured. The public healthcare insurance systems (Medicare, Medicaid, and the VA healthcare system) provide medical coverage to a narrow selection of people (children, elderly and veterans).

Safety Requirements:

1. Pay medical costs for the people insured as needed
2. Only reimburse for drugs that are safe and effective

Context in Which Decisions Were Made:

1. Private insurers are expected to be profitable
2. Private insurance contracts are often negotiated by companies
3. Public insurance has to work with a tight budget

Inadequate Control Actions:

1. Picked the drug to be put on the formulary not based on its effectiveness but based on the price they could negotiate or because of pressures from the pharmaceutical companies

Summary of Accident Causal Factors

Safety Requirements

Medical insurers are expected to pay for the medical costs of the people they insure. Furthermore, by approving a drug, an insurer indirectly endorses it and gives it its "seal of approval". Why would they pay for it otherwise? In that sense, the insurers have the responsibility to only pay for drugs that have potential benefits to the patients (G. M. Anderson, et al., 2008).

Context in Which Decisions Were Made

Medical insurance companies are business entities, and they are expected to make a profit by distributing the health risks across their insured population and negotiating deals with the doctors, hospitals and drug companies to reduce costs. Private insurers often work directly with companies to provide insurance as an employment benefit. However, the individual needs of the employees are not necessarily completely satisfy by this insurance policy and, because the insurance is offered by the employer, it is difficult for them to switch to another provider. Insurers have little incentive to focus on the needs of the patients but rather focus on the partnerships with the firms.

For patients over the age of 65, most medical costs are covered by Medicare, which is funded through a 2.9% tax on wages and salary earnings and now represents an estimated 13% of the federal budget, and has been constantly rising over the past few years. Medicare, Medicaid and the other federal healthcare programs are therefore at the center of the discussion on how to moderate healthcare spending in the United States. These programs have to face the dual challenge of providing for increasingly expensive medical care while trying to keep costs down (Kaiser Foundation, 2009).

Inadequate Control Actions

The insurance companies initially tried to limit the prescription of Vioxx and Celebrex and imposed strict conditions for patients to meet before paying for the drugs because they were about eight times the cost of a generic prescription pain reliever. However, the pharmaceutical companies argued that all patients should be taking COX-2 because they had a better safety profile (W. B. Anderson, 2001). In 2004, Merck had managed to position Vioxx as the preferred formulary drug for about 90 percent of managed care firms (Wadhwani, 2004). Vioxx became the drug of choice for both doctors and patients, even if it was not the most appropriate for the needs of the patients—alternative generic treatments might have been as effective, possibly safer, and definitely cheaper.

Scientific Journals

General Information

Scientific, and in particular medical journals, are one of the primary sources of information for doctors and are an avenue for researchers to publish their work. Typically, scientific journals are peer-reviewed and focus on a specific field. In medicine, some of the main journals are the Annals of Internal Medicine, the Archives of Internal Medicine, the British Medical Journal, the Canadian Medical Association Journal, the Journal of the American Medical Association, The Lancet, Nature Medicine, and the New England Journal of Medicine.

Summary of Accident Causal Factors

Safety Requirements:

1. Publish only articles of high scientific quality
2. Provide accurate and balanced information to doctors

Context in Which Decisions Were Made:

1. Difficult to get well-qualified reviewers
2. Pressures to meet deadlines, limited ability to check for accuracy
3. Can only publish articles that are submitted, cannot force people to publish negative results
4. Difficult to check that the authors have declared all their conflicts of interests and whether they are the primary authors for the articles or not
5. Pharmaceutical companies pay medical journals for article reprints, advertising space and journal supplements

Inadequate Control Actions:

1. Published ghostwritten articles about Vioxx
2. Created a journal of questionable legitimacy in Australia to publish Vioxx and Fosamax articles
3. Did not require or did not check disclosure of financial interests for authors
4. Did not require independent statistical analysis of the data
5. Did not publish articles that showed negative results and warned of the CV risks

Safety Requirements

Scientific journals are judged on the quality of the articles they publish, and it is expected they will only publish papers of high scientific quality while providing accurate and balanced information.

Context in Which Decisions Were Made

However, it can be hard for journals to find qualified reviewers, and they are under pressure to meet deadlines, which limits their capacity to check papers for accuracy. Similarly, it is near impossible for journals to check whether the authors have declared all their conflicts of interests and whether they are the primary authors of the articles or not.

Furthermore, journals can only publish articles that are submitted and many negative studies are never submitted if the authors (or their sponsors) do not want the results to be known. Finally, note that a significant part of journal's profits come from article reprints, adds and supplements paid for by pharmaceutical companies (Lexchin & Light, 2006; R. Smith, 2003).

Inadequate Control Actions

Medical journals published ghostwritten articles on Vioxx without requiring proper financial disclosure from the authors, they did not require independent statistical analysis of the data, and, in the case of The Australasian Journal of Bone and Joint Medicine, the publishing house created a journal of questionable legitimacy to publish Vioxx and Fosamax articles (see the discussion in the Merck section on Elsevier).

Furthermore, journals did not publish articles showing negative results that could have help give a more accurate view of the risks associated with Vioxx: negative results tend to be published less often and with a longer delay than studies with positive results. Note that results with indecisive results take even longer to be published (Stern & Simes, 1997). The disparity between the number of positive and negative results can be explained in two ways: 1) negative results are rarely submitted for publications and 2) it is in the interest of medical journals to avoid printing articles that are not favorable to drug manufacturers because the journal makes a large profit from reprints and other forms of advertisement. This arrangement tends to bias journals in favor of the pharmaceutical companies and incentivizes them against publishing negative results (Garfield, 2009).

Research Scientists/Centers

General Information

Research Scientists typically work in universities and do independent research, usually funded by the government (for example by NIH). Note that in the medical field, the research scientists are typically also medical doctors but here the role of practicing physicians is so different than that of researchers that they are modeled separately.

Summary of Accident Causal Factors

Safety Requirement:

1. Provide independent and objective research on drug's safety, efficacy and new uses
    a. Researchers should disclose all their conflicts of interests when publishing
    b. Researchers should only take credit for papers on which they have significantly contributed
2. Give their unbiased expert opinion when it is requested by the FDA

Context in Which Decisions Were Made:

1. Limited amount of NIH funding. Most funding now comes from industry
2. The research culture rewards people with more publications
3. Clinical trials data about drugs is often not released, or released with a long delay, to scientists for independent analysis
4. Bayh-Dole allowed financial gain from research and researchers started to see themselves as partners of industry leading to a blurring of the boundaries between academia and industry
5. Drug companies are often involved in the details of studies including design, analysis, and decision on whether or not to publish the results
6. Competition from CROs led to research scientists and academic institutions becoming more accommodating to industry sponsors
7. Faculty researchers often have lucrative financial arrangements with drug company sponsors

Inadequate Control Actions:

1. Allowed their names to be put on studies ghostwritten by Merck employees and did not divulge their financial ties with Merck
2. Few researchers focused on potential negative side effects of the drug
3. Some researchers sitting on advisory committees had financial ties with Merck
4. Research results from studies sponsored by pharmaceutical companies were often biased in favor of the product manufactured by the sponsor

Safety Requirements

Research scientists are expected to provide independent and objective research on a drug's safety, efficacy and new uses. They should disclose all their conflicts of interests when publishing and should only take credit for papers on which they have significantly contributed. As independent experts, they can also be asked to work with the FDA and it is expected that when they do work for an FDA Advisory Board they will give their unbiased expert opinion.

Context in Which Decisions Were Made

In most fields the research culture rewards people with more publications which forces researchers to continuously look for new funding and publication opportunities. In the current academic climate, there has been limited federal funding available to researchers, creating incentives for researchers to turn to other sources of funding, typically pharmaceutical companies. For example, it has historically been common practice for academically affiliated research centers to conduct clinical trials for pharmaceutical companies. However, in the last 10 years, there has been a spectacular growth in the number of Contract Research Organizations (CROs). Those organizations are more accommodating to pharmaceutical companies, offering them more control over the way the studies are conducted and often can run the studies faster and for a lower cost. Researcher scientists and academic institutions who compete with CROs for studies therefore have to be more accommodating to industry sponsors and potentially lower their standards (Bodenheimer, 2000).

The entrance of CROs in the field has had repercussions on the quality and quantity of data published because more and more often, drug companies are involved in the details of studies, including design, analysis, and decisions on whether or not to publish the results. Because of the competition between CROs and academic centers, pharmaceutical company's control over studies has started to permeated research done by academics. In 1995, Dong was not able to publish a study she conducted for Flint Laboratories because the results were not favorable to the pharmaceutical firm (Rennie, 1997). Similarly, a contract between Apotex and a researcher forbade disclosure of results for three years after the study without prior approval from the company (Bodenheimer, 2000).

When researchers are not directly conducting studies for pharmaceutical companies, they often have other lucrative financial arrangements with the companies. For example, it is fairly common for pharmaceutical companies to hire researchers as consultants and speakers to either help them during the clinical trials or to represent the pharmaceutical company at conferences and meetings. These consultants are often referred to as "Thought Leaders" as their voice and opinion can influence a large number of doctors.

More and more, the research enterprise is the result of grater cooperation between academic researchers and pharmaceutical companies, cooperation encouraged by the Bayh-Dole act, adopted in 1980, which allows academic institutions supported by federal grants to patent or license their new discoveries. Recently, the strong links between academics and pharmaceutical companies has led to a blurring of the boundaries between the two groups, which can also explain to some extent the pro-industry bias reported in the literature (Bhandari, et al., 2004).

Finally, when researchers do try to work independently from the pharmaceutical company, they often find themselves stifled by the lack of data available. As mentioned previously, pharmaceutical companies are not required to publish their results and the FDA has to treat the clinical information as confidential, which means that the research scientists do not have access to the data to run an independent analysis. In the case of Vioxx, the drug was approved in 1999 but "the data were not submitted to a peer-reviewed journal until the following year and did not appear in print until November 23, 2000, one and a half years after commercial approval had been granted" (Topol, 2004).

Inadequate Control Actions

In general, there is not enough independent research done on drug safety, a situation that can be explained by a multitude of factors: studies are very expensive, there is not enough government funding for this kind of research and it is difficult for researchers to have access to data that is often proprietary. For example, clinical trials submitted to the FDA are often considered trade secrets and are not released to independent researchers for analysis.

When research is financed by the pharmaceutical companies, there is a potential for the results to be biased. In a study published in JAMA, Friedberg argued that pharmaceutical sponsorship of economic analysis is associated with a reduced likelihood of reporting unfavorable results (Friedberg, Saffran, Stinson, Nelson, & Bennett, 1999) potentially because researchers are worried that if they do not find positive results, the pharmaceutical companies will turn to CROs for their next study (Bodenheimer, 2000). For example in Vioxx's Alzheimer studies, the intention-to-treat analyses, which showed an increased risk of mortality, were not published but rather the results were presented to the FDA as on-treatment, which minimized the appearance of the mortality risk (Psaty & Kronmal, 2008).

Researchers with strong ties to pharmaceutical companies are, as discussed previously in the Merck section, more likely to partake in ghostwriting and guest authorship. This practice would be impossible if the doctors refused to put their names as primary investigators on studies in which they only marginally contributed. According to a study led by Flanagin, 11% of published articles studied had evidence of ghost authors and 19% had evidence of honorary authors (Flanagin, et al., 1998). The behavior of researchers can in part be seen as the result of an academic research culture where scientists are evaluated by the number of articles they publish each year, which creates pressures for researchers to accept authorship of articles on which they only contributed minimally.

Finally, as it was made clear during the advisory meetings dealing with the recall of Vioxx, several researchers sitting on FDA advisory committees had financial ties with Merck. These financial ties come in many forms, for example as grants or highly paid consulting fees. Such financial deals mean that the researchers are no longer impartial and therefore should need a waiver if ever consulted by an FDA Advisory Board. In themselves the ties are not a problem, but it becomes an issue when the ties are not disclosed and the researchers give potentially biased advice.

Congress

General Information

Congress has authority over financial and budgetary matters, and it has the responsibility to investigate and oversee the executive branch. Congress frequently mandates committees to study various aspects of the government. Examples of relevant committees for the Vioxx case are the Committee on Government Reform and the Committee of Finance where Sandra Kweder, the Deputy Director of the Office of New Drugs, and David J. Graham, Associate Director for Science, provided statements (Graham, 2004; Kweder, 2004).

Summary of Accident Causal Factors

Safety Requirements:

1. Provide guidance to FDA by passing laws and providing directives
2. Provide necessary legislation to ensure drug safety
3. Ensure that the FDA has enough funding to operate independently
4. Provide legislative oversight on effectiveness of FDA activities
5. Hold committee hearings and investigations on industry practices

Context in Which Decisions Were Made:

1. Congress is lobbied by the pharmaceutical companies. There is a "revolving door" between government and lobbyists
2. Industry provides large amounts of political contributions
3. Industry funds "grassroots" organizations to promote its interests in the media and pressure Congress

Inadequate Control Actions:

1. Congress did not pass regulation that could have prevented or helped mitigate the accident
2. Congress underfunded the FDA, in particularly OSE

Safety Requirements

Congress is expected to provide guidance to FDA through laws and directives. It established the FDA in 1906 by the passage of the Federal Food and Drugs Act which added regulatory functions to the agency's then scientific mission. This act was the first of more than 200 laws that helped established the FDA (FDA, 2009g). It is Congress' responsibility to make sure that as products and needs evolve the agency can keep on fulfilling its mission. Part of Congress' responsibility is then to ensure that the legislation is up-to-date to provide the FDA with the tools and powers it needs to properly ensure drug (and food and cosmetics) safety. New types of drugs, like biologics and nanotechnology, create the need for new legislation.

Similarly, Congress is expected to ensure that the FDA has enough funding to operate independently; it is also expected to provide legislative oversight on the effectiveness of the FDA activities and hold committee hearings and investigations on industry practices.

Context in Which Decisions Were Made

As all large industries, pharmaceutical companies have a lobby to represent them in Washington, with a "revolving door" between the government and lobbyists. The pharmaceutical lobby, named the Pharmaceutical Research and Manufacturers of America (PhRMA), is one of the largest in the United States and has a powerful influence over Congress. Senator Richard J. Durbin, Democrat of Illinois, has been quoted as saying: "PhRMA, this lobby, has a death grip on Congress" (Pear, 2003). Indeed, "[s]ince 1998, drug companies have spent $758 million on lobbying—more than any other industry, according to government records analyzed by the Center for Public Integrity, a watchdog group. In Washington, the industry has 1,274 lobbyists—more than two for every member of Congress" (Drinkard, 2005).

Similarly, in 2000, the pharmaceutical manufacturers contributed over $19 million to federal candidates and parties with a strong bias towards Republican candidates (23% to Democrats, 77% to Republicans). According to the website Opensecrets.org, the Pharmaceutical products industry was the 20th biggest contributor to members of Congress (OpenSecrets.org, 2009).

Finally, in a more subtle form of lobbying, industry funds "grassroots" organizations to promote its interests in the media and put pressure on Congress: "I don't think there is a patient-advocacy group in America that does not receive some level of funding from a pharmaceutical company" (Drinkard, 2005).

Inadequate Control Actions

Congress did not pass regulation that could have prevented or helped mitigate the losses associated with Vioxx. At the time, the legislative environment was pro-industry and favored pharmaceutical companies. Indeed President Bush seemed to favor deregulation in all domains (banks, environment, healthcare…).

Furthermore, congress underfunded the FDA, in particular OSE. The agency was underfunded during the years before the accident, and it had to increasingly rely on funding from the

pharmaceutical companies, making it more susceptible to pressures from those companies. Several departments were particularly underfunded, such as DDMAC and OSE. This situation has been documented in an IOM report and several studies done after the Vioxx accident (Institute of Medicine, et al., 2007; Rosen, 2007).

Summary of Inadequate Control Actions

Patients

1. Some patients pressured their doctor into prescribing Vioxx, even if it was not necessarily the most appropriate treatment

Physicians

1. Doctors prescribed Vioxx, both on and off label, for patients for whom it was not indicated

Merck

1. Merck did not run studies that might have found negative CV results. Company executives rejected doing a study of Vioxx's CV risks
2. Merck's studies, and the results the firm published, inadequately represented the risk/benefit profile of the drug
    e. The studies were motivated by marketing goals
    f. If the results were published, they were typically released very late or only partially released
    g. The results were biased to appear better than they were
    h. Some of the studies that were run did not have an active Data and Safety Monitoring Board (DSMB) to monitor the clinical trials and protect the patients. The safety of the patients was solely in the hands of the Merck investigators
3. Merck published and disseminated misleading information about the safety profile of Vioxx
    e. Merck aggressively promoted drug usage with a task force trained to avoid CV questions
    f. Merck used promotional activities and materials that were false, lacking in fair balance or otherwise misleading. The company continued to minimize unfavorable findings up to a month before withdrawing Vioxx
    g. Merck published or promoted publication using guest authorship or ghostwriting; Merck employees' involvement in the writing process was often not mentioned and the financial ties of the main authors were not always disclosed
    h. Merck created journals made to look like independent peer-reviewed journals. These journals were actually marketing compilations of articles promoting Vioxx and another drug made by Merck

FDA/CDER

Agency Wide

1. Allowed waivers of conflict of interest rules for advisory panel members
2. Pressured an FDA employee to change conclusions and recommendations on a study of Vioxx and prevented publication of the results
3. Was not able to provide quality adverse event reports for researchers to use

OND

4. Gave expedited review and approval to Vioxx even though the drug did not meet the criteria for expedited review
5. Did not check whether clinical trial safety requirements were being enforced (e.g., that protocol 078 had an active DSMB)
6. Approved Vioxx without requiring a Phase IV study even though the long term risks were unclear
7. Did not update the Vioxx label in a timely fashion
8. Delayed the recall of Vioxx. Did not act fast or effectively enough

DDMAC

9. Original warning letter was not followed by subsequent warnings; false and misleading promotional material went un-reviewed

OSE

10. Did not properly monitor the drug for long term risks. Could not differentiate normal adverse events from the ones due to the drug within the population affected
11. Did not insist that Merck launch a large-scale clinical trial when suspicions first arose
12. Could not require a recall of the drug

FDA Advisory Boards

1. Members with conflicts did not recuse themselves from the decisions about Vioxx
2. Members did not reveal conflicts of interest
3. Recommendations were potentially influenced by external pressures

Payers / Insurers

1. Picked the drug to be put on the formulary not based on its effectiveness but based on the price they could negotiate or because of pressures from the pharmaceutical companies

Scientific Journals

1. Published ghostwritten articles about Vioxx
2. Publishers created a journal of questionable legitimacy in Australia to publish Vioxx and Fosamax articles
3. Did not require or did not check disclosure of financial interests for authors
4. Do not require independent statistical analysis of the data
5. Did not publish articles that showed negative results and warned of the CV risks

Research Scientists/Centers

1. Allowed their names to be put on studies ghostwritten by Merck employees and did not divulge their financial ties with Merck
2. Few researchers focused on potential negative side effects of the drug
3. Some researchers sitting on advisory committees had financial ties with Merck
4. Research results from studies sponsored by pharmaceutical companies were often biased in favor of the product manufactured by the sponsor

Congress

1. Congress did not pass regulation that could have prevented or helped mitigate the accident
2. Congress underfunded the FDA, in particularly OSE

While this list looks like everyone did the wrong thing, it is important to focus more on "why" each part of the safety control structure acted the way they did. In the discussion above, the context and the mental models (information each person had) when taking these actions help to explain the reasons for these unsafe actions. It is impossible to change humans, but human behavior can be altered by modifying the information available to decision makers and by assisting them in making better decisions.

The STAMP models provided so far describe the static control structure of the drug safety control system in the US and the flawed behavior of the components of this system that contributed to the events in the Vioxx saga. A model of the system dynamics is also used in the analysis. System dynamics models provide an executable and analyzable model of the context for each of the unsafe control actions listed above and help to explain the pressures in the system that led to the flawed decisions.

Section 3: Background information on System Dynamics

The field of System Dynamics was invented in the 1950's by Jay W. Forrester at the Massachusetts Institute of Technology. He first presented the philosophy and methodology of System Dynamics in *Industrial Dynamics* (Forrester, 2000).

System Dynamics provides a framework for dealing with dynamic complexity and can be used to help decision-makers learn about the structure and dynamics of complex systems. It can also be used to test high leverage policies and model policy resistance. It is grounded in the theory of non-linear dynamics and feedback control but also draws on cognitive and social psychology, organization theory, economics, and other social sciences.

> *"All too often, well-intentioned efforts to solve pressing problems create unanticipated 'side effects.' Our decisions provoke reactions we did not foresee. Today's solutions become tomorrow's problems. The result is policy resistance, the tendency for interventions to be defeated by the response of the system to the intervention itself. From California's failed electricity reforms, to road building programs that create suburban sprawl and actually increase traffic congestion, to pathogens that evolve resistance to antibiotics, our best efforts to solve problems often make them worse. At the root of this phenomenon lies the narrow, event-oriented, reductionist worldview most people live by. We have been trained to see the world as a series of events, to view our situation as the result of forces outside ourselves, forces largely unpredictable and uncontrollable…System dynamics helps us expand the boundaries of our Mental Model Flaws so that we become aware of and take responsibility for the feedbacks created by our decisions."* – John Sterman (Sterman, 2002)

For a more thorough description of how System Dynamics works, see *Business Dynamics* (Sterman, 2000)

System Dynamics framework

System Dynamics uses two different tools to model a system: 1) Causal loop diagrams and 2) Stocks and Flows diagrams. In this thesis, only the former were used and mostly for illustration purposes.

Stock and Flow diagrams were not used for two main reasons: 1) it was impossible to gather enough data to create operational stock and flow diagrams. Most of the data needed is proprietary and because of litigation issues was never released making it impossible to calibrate and validate the models using real data and therefore made quantitative predictions useless. Furthermore, the large number of variables used made sensitivity analysis futile; 2) part of the analysis relies on the behavior of the different components (doctors, patients, FDA…) of the system. It is possible to model the reaction of these components to different pressures qualitatively but it would have been inappropriate to model those responses quantitatively. For example, a doctor's decision to prescribe a drug is influenced both by sales pitches made by pharmaceutical companies and by patients requests, but it is impossible to tell how much the

decision was influence by either of those pressures. Both of those points were strong argument as to why stock and flow diagrams were not practical options for this research.

Causal loop diagrams

Causal loop diagrams are used to model a System Dynamics hypothesis, help develop more complex models and illustrate the main feedback systems existing in a system. Causal loop diagrams typically are not executable.

Causal loops diagrams are made up of variables and arrows representing the causal influence between the variables. The arrows, known as causal links, have a polarity (positive or negative). A positive link means that if the first variable increases then the second variable increases as a consequence of the change in the first variable (see Figure 8). A negative link means that if the first variable increases then the second variable decreases as a consequence of the change in the first variable (Sterman, 2000).

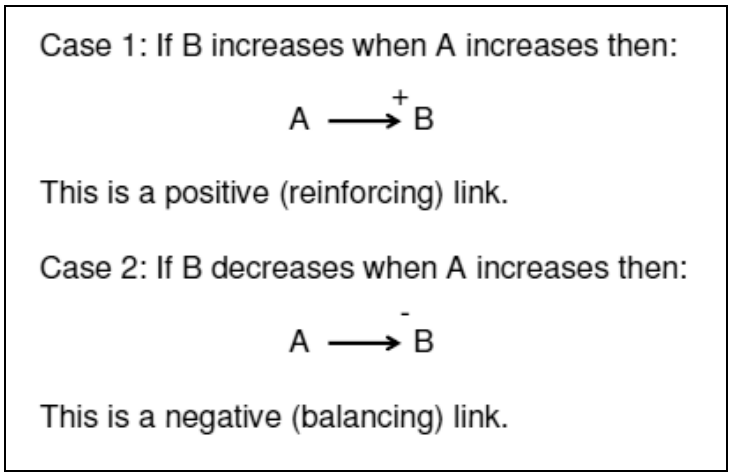
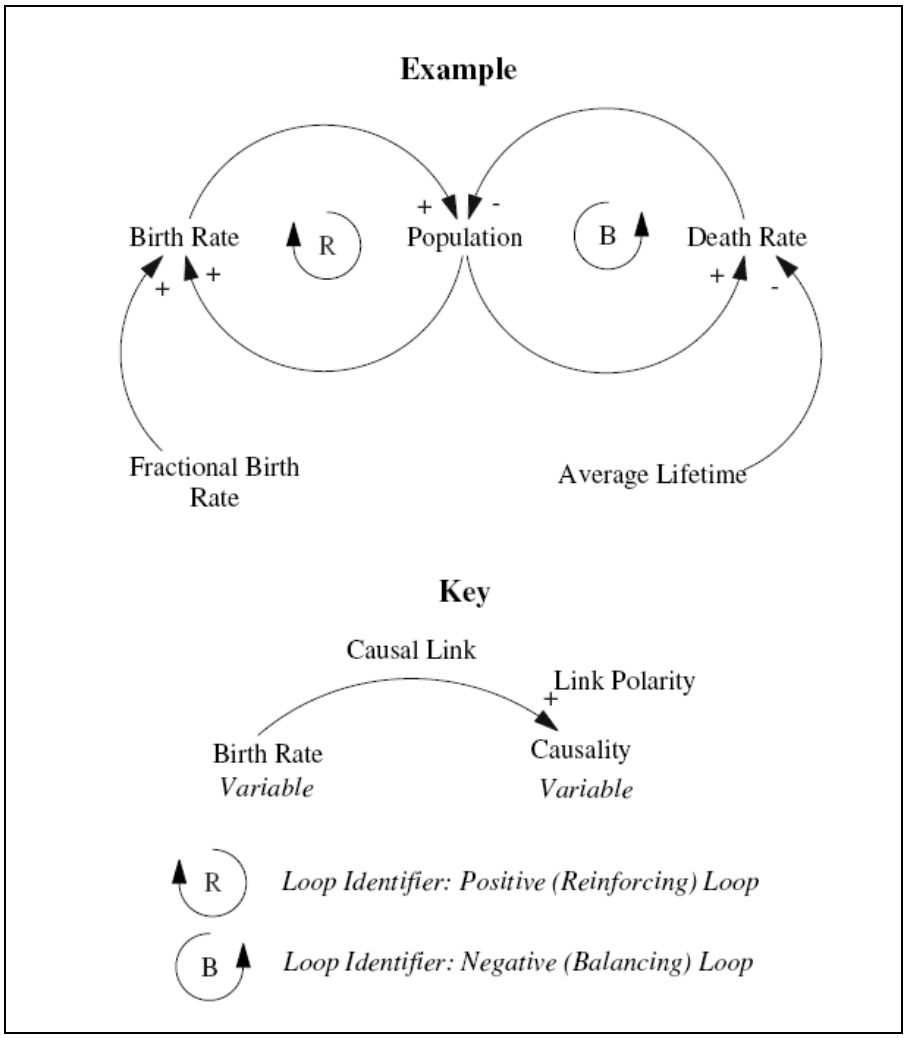


Figure 8 – Causal links

The causal links and variable often combine to create loops that can, like arrows, have a polarity. A loop can either be reinforcing (positive) if the effect is positively related to the cause or balancing (negative) if the effect counteracts change.

The figure below shows both a positive and a negative loop. If the population increases, the birth rate increases (more people have more babies) which entails an increase in population. These dynamics are a positive loop and without any controls, the population would grow exponentially. In this model the positive loop is moderated by the death rate: a larger population means a higher death rate (for example because there is less food per person). The balancing loop controls the population growth.



Adapted from (Sterman, 2000).

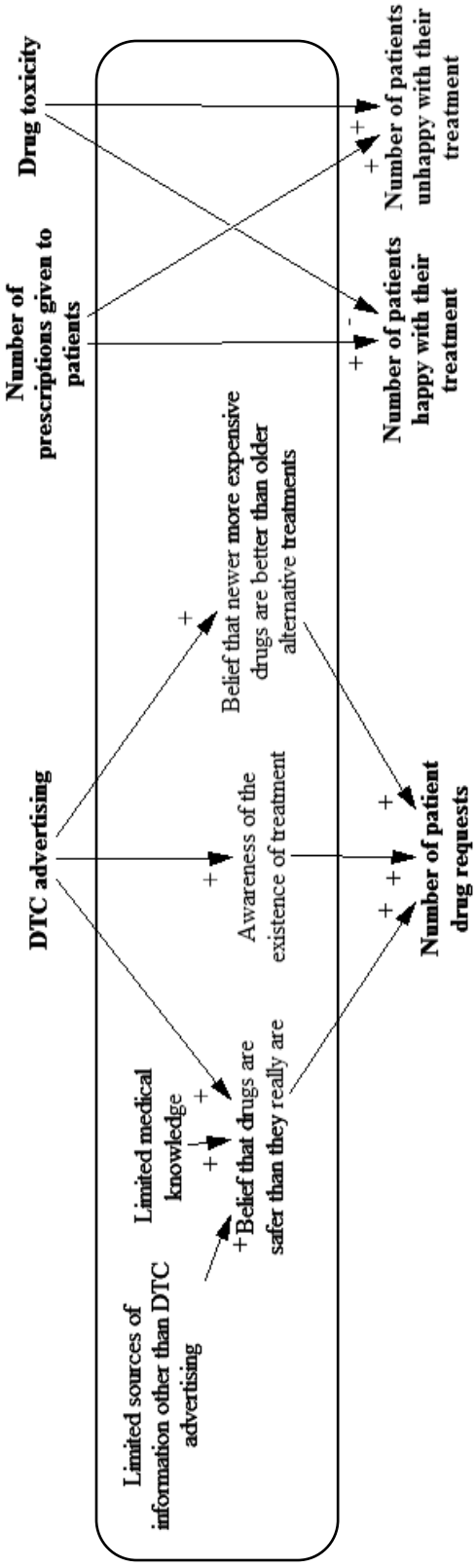
Figure 9 – Causal loop diagram notation

Variables, causal links and loops represent the foundation of causal loop diagrams. With this set of tools, it is possible to model most non-linear systems with balancing and reinforcing feedback mechanisms.

System Dynamics Models of the Pharmaceutical Safety System

Models are first created for each of the independent components of the safety control structure and then they are connected to show the dynamics of the overall pharmaceutical safety control structure. Each component model represents the way a controller operates with the information and control inputs coming in at the top (in bold), and the control process within the component and the information/control instructions leaving the component from the bottom (in bold). The outputs of one component can then be used as inputs for another component. Note that much of the information within the individual component models is simply the same information provided in the "context" section of the models in Chapter 2.

Example of a component model – Patients



This model of the Patients component is an example of a component model. It has three inputs (DTC advertising, Number of prescriptions given to patients and Drug toxicity) and three outputs (Number of patient drug requests, Number of patients happy with their treatment and Number of patients unhappy with their treatment). The external inputs are used by the patients in combination with two internal variables (Limited source of information other than DTC advertising and Limited medical knowledge) and result in the three output variables. This can be translated in mathematical terms:

Number of patients happy with their treatment
= f (Number of prescriptions given to patients, Drug toxicity)

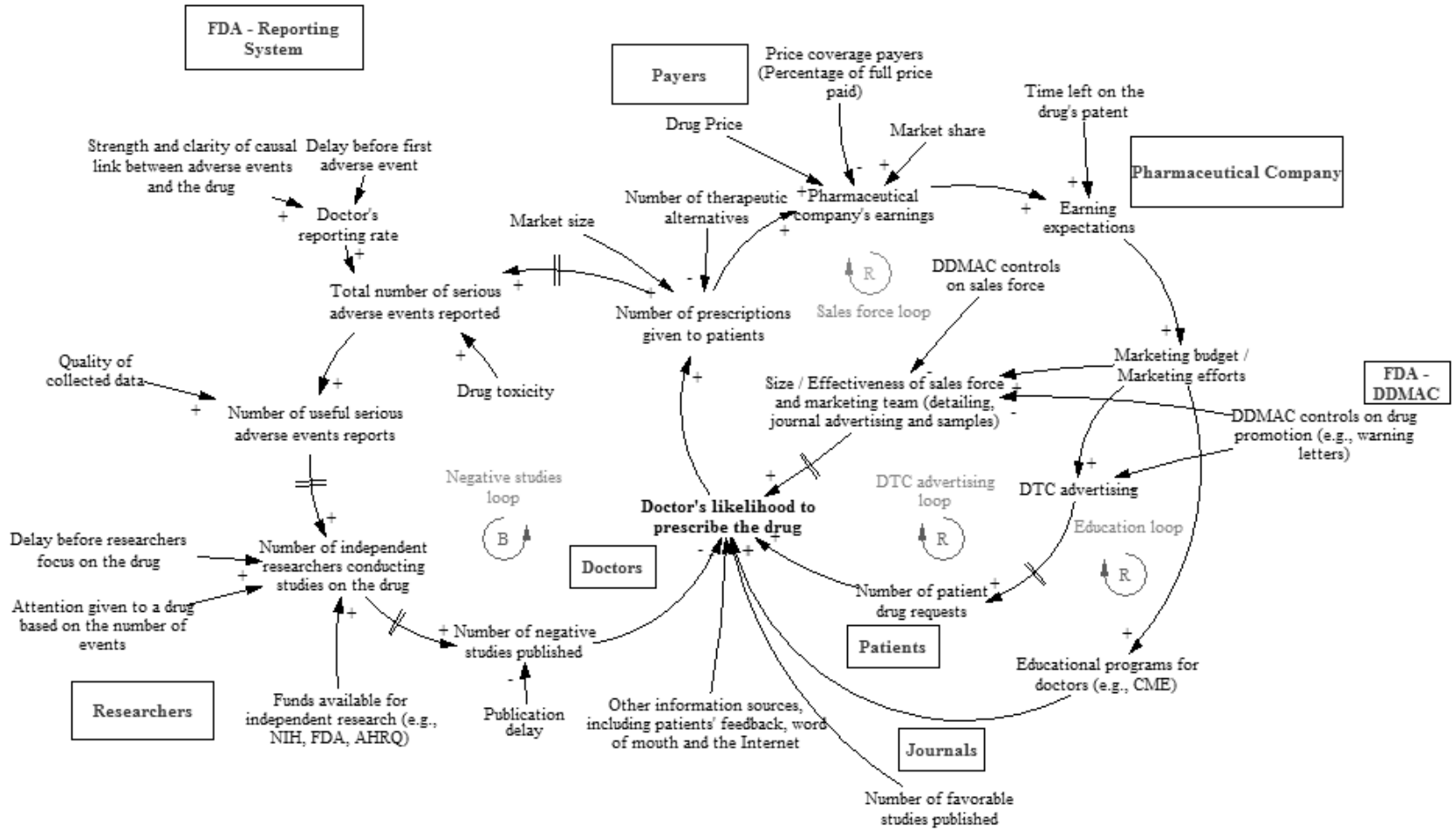
All component models have the same underlying structure and combine internal variables with external inputs to generate a set of new variables that can be used for another component.

System Models

When the different controller models are combined two larger model of the healthcare system emerge, each centered on a key processes: 1) the prescription of Vioxx by doctors and 2) the recall of Vioxx by the FDA or pharmaceutical companies. These two processes are critical because they represent key gate-keeping points: Without a prescription from doctors, patients do not have access to the drug and if the drug is recalled from the market, doctors simply cannot prescribe it. The two new systems can be studied as separate System Dynamics models, each with its own set of pressures driving the gate-keeping decisions.

Physicians Prescriptions Habits

The first large Causal loop diagram models the pressures that influenced the prescription habits of physicians, ignoring the recall of the drug (which is treated as a separate event). The model was built around the pressures identified in the Vioxx case but is general enough to be applied to most pharmaceutical products.



Model 1 – Physicians Prescription Habits

The main focus of this model is the Doctor's likelihood to prescribe the drug, which is at the core of the different loops at play here. It is central to the analysis because Vioxx was a prescription drug and therefore patients could only get the drug through their doctors and the number of prescriptions is highly correlated with the pharmaceutical company's earnings.

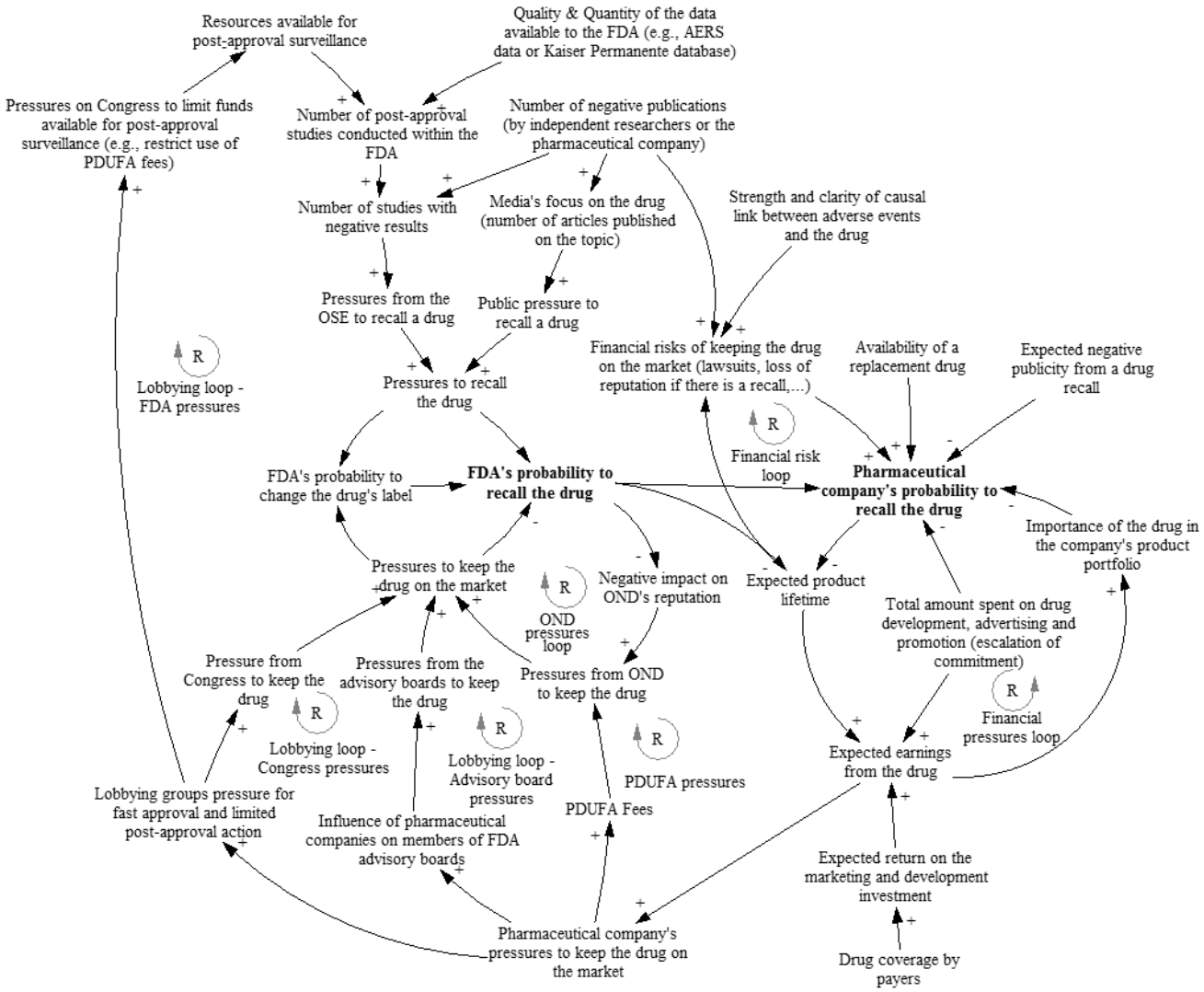
On the right side of the model the pressures on the doctors come from the pharmaceutical companies and create three reinforcing loops through which a pharmaceutical company can influence doctors: 1) a pharmaceutical company can pressure doctors through its sales force (`Sales force loop`), either by increasing the size of the sales force or by asking the sales representatives to be more aggressive in their marketing; 2) a pharmaceutical company can target the patients directly through direct-to-consumer advertising (`DTC advertising loop`) and hope that the patients will request the drug from their doctors; 3) or a pharmaceutical company can influence doctors through education programs, for example CME (`Education loop`). The model also includes the number of positive studies published because they have a strong influence on doctors perceptions but they appear as an independent external influence and not a loop (`Total number of favorable studies published`).

Two forces balance the pressures to prescribe: 1) when a drug is prescribed to a large segment of the population and that adverse events are starting to appear, independent researchers are likely to start studying the drug. Independent research, and the negative results that it can uncover, helps balance the positive studies published by the pharmaceutical companies, giving a more accurate model of the risks associated with the drug (`negative studies loop`); 2) Patient feedback, word of mouth and online sources, which were modeled as a single external influence (`Other information sources, including patients feedback, word of mouth and the Internet`). Note that there is no direct feedback loop between patients and doctors after negative events because in the case of Vioxx the adverse events typically occurred after a long delay and doctors were unlikely to associate the events with the Vioxx prescription.

To conclude, this model shows the different pressures that affect the likelihood that a doctor will prescribe the drug, the reinforcing pressures coming from the pharmaceutical companies and the balancing loops that help control them.

The Dynamics of a Drug Recall

This model focuses on the interplay between the FDA and manufacturers and the factors that can lead either of them to recall a drug. In the Vioxx case, the drug was recalled by Merck before the FDA decided Vioxx was dangerous.



Model 2 – Drug Recall

The two main variables in this model are `FDA's probability to recall the drug` and `Pharmaceutical Company's probability to recall the drug`. The model is split into two parts with the left side of the diagram focusing on the pressures relevant to the FDA and on the right, the ones that affect the pharmaceutical company. In each half there are both balancing and reinforcing loops that keep the model in equilibrium (no recall) until the system reaches a tipping point and the drug is recalled, either by the pharmaceutical company or the manufacturer.

The left side of the model shows the pressures that influence an FDA recall. A combination of pressures prevent drugs from being recalled for example `Political pressures to keep the drug on the market`, typically the result of lobbying from the pharmaceutical companies and

Pressures from OND to keep the drug on the market (which is in turn fueled by pressures existing with the agency and pressures external to the agency). At the same time public pressure can build up against a drug (Public pressure to recall a drug) and force an FDA recall.

The right side of the model shows the pressures and influences on the pharmaceutical companies. A drug like Vioxx represents an important investment for a company and it is harder to recall a product that represents a large investment (Total amount spent on drug development, advertising and promotion) and a large share of the company's income, as was the case for Vioxx. On the other hand, a company is more likely to recall the drug if it believes that the FDA will recall it in the near future or if the company believes that the costs associated with keeping the drugs on the market (e.g., Negative publicity from the drug, Financial risks of keeping the drug on the market) outweigh the benefits. Finally, if the company has a replacement drug in the pipeline, it is more likely to recall the older drug to focus on the new entrant (Availability of a replacement drug). To conclude, this model serves to illustrate the mechanisms and pressures that drive drug recalls from either the FDA or the pharmaceutical company's side: There is always a tension between pressures to keep the drug on the market and pressures to recall the drug.

The two models presented above represent the system as it was when Vioxx was prescribed and eventually recalled. They provide insights on how the system works and illustrate the different influences at play. However, the healthcare system has changed since the recall, in part to correct problems identified in the wake of the Vioxx recall. The two models above serve as a starting point for the rest of the analysis: Section 4 introduces the legislative changes that followed the Vioxx recall and add the new constraints to the existing model; Section 5 outlines new recommendations that go beyond what was proposed by the FDA and again add new safety constraints to the models.

Section 4 - Legislative changes following the recall of Vioxx

In the wake of the Vioxx recall numerous newspaper articles, books, and reports were published on the topic tackling both issues directly related to Vioxx and the more general problem of drug approval. This section is centered on the main reports, their recommendations, and the regulatory changes they prompted. Those changes are then modeled using the STAMP analysis to determine whether the changes proposed could help prevent "a new Vioxx".

Three main reports were released after the Vioxx recall, the first one published by a government agency (U.S. Government Accountability Office - *Report - Drug Safety – Improvements Needed in FDA's Postmarket Decision-making and Oversight Process*), the second one published by a third party agency (Institute Of Medicine Report - *The future of drug safety: promoting and protecting the health of the public*), and the third one commissioned by Merck (*Report of The Honorable John S. Marin, JR. to the Special Committee of the Board of Directors of Merck & Co., Inc. Concerning the Conduct of Senior Management in the Development and Marketing of Vioxx*).

The publication of these three reports led to two waves of changes, first within the FDA (FDA's response to the IOM report) and the second from Congress (Food and Drug Administration Amendments Act of 2007). Many of the suggested changes are still in the process of being implemented and little has been published on the short or long term effects of the changes.

Reports

GAO report

In March 2006, the United States Government Accountability Office published a report entitled *Drug Safety – Improvements Needed in FDA's Postmarket Decision-making and Oversight Process* (GAO, 2006). In this report, the GAO 1) describes FDA's organizational structure and the process for postmarket drug safety decision making, 2) assesses the effectiveness of FDA's postmarket drug safety decision-making process and 3) assesses the steps the FDA is taking to improve post-marketing safety.

The report concludes that there are opportunities within the FDA to improve the approval process, in particular when it comes to dealing with tensions between OND and ODS (now OSE). The report also added that the information available to the FDA for drug approval is limited and that Congress should consider expanding the FDA's authority to require drug sponsors to conduct post-approval studies to collect additional data on drug safety when needed.

Recommendations from the report:

- Establish a mechanism for systematically tracking ODS's recommendations and subsequent safety actions;
- With input from the Drug Safety Oversight Board (DSB) and the Process Improvement Teams, revise and implement the FDA's proposed draft policy on major postmarket drug safety decisions;
- Improve CDER's dispute resolution process by revising the FDA's pilot program on conflict resolution by increasing its independence; and
- Clarify ODS's role in FDA's scientific advisory committee meetings involving postmarket drug safety issues (GAO, 2006).

IOM report

In September 2006, 2 years after the recall, the Institute Of Medicine released *The future of drug safety: promoting and protecting the health of the public,* the result of a 15 month investigation by the IOM committee. The committee reviewed the FDA's regulatory authority, its organizational function and capabilities, and the resources and scientific data available to it and came up with a list of 25 recommendations intended to help the FDA strengthen its post-approval processes with the end goal of reaching a lifecycle approach to drug safety. The recommendations focused on eight main topics: Clarifying the FDA's regulatory authority, requiring symbols to alert consumers to new products and denote heighted regulatory attention, establishing performance goals for safety, holding industry and researchers accountable for making drug safety study results public, appropriating adequate resources for drug safety, stabilizing the leadership of FDA, improving FDA's communication to the public and a list of other recommendations of particular interest to Congress.

No.	*IOM Committee Recommends That*
3.1	FDA commissioner be appointed for a 6-year term
3.2	Secretary of HHS appoint an External Management Advisory Board to transform CDER's culture
3.3	FDA Commission, CDER director, and management advisory board develop a comprehensive plan for sustained cultural change
3.4	CDER assign joint authority to OND and OSE for postapproval regulatory actions related to safety
3.5	Congress introduce specific safety-related performance goals in PDUFA IV
4.1	CDER conduct a systematic review of AERS
4.2	CDER increase access to large health care databases and develop active surveillance for some drugs and diseases
4.3	Secretary of HHS develop a public-private partnership to prioritize, plan, and organize funding for safety and efficacy studies of public health importance
4.4	CDER ensure performance and timely evaluation of sponsors' risk minimization action plans
4.5	CDER develop and continually improve a systematic approach to risk-benefit analysis
4.6	CDER build internal epidemiologic and informatics capacity to improve postmarketing assessment of drugs
4.7	FDA commissioner demonstrate a commitment to building the agency's scientific research capacity
4.8	FDA have its advisory committees review all new molecular entities either before or after approval
4.9	All FDA advisory committees include public health expertise
4.10	FDA establish a requirement that a substantial majority of advisory committee members be free of significant financial conflicts
4.11	Congress require sponsors to register in a timely manner all phase 2-4 clinical trials and post efficacy and safety results
4.12	FDA post all NDA review packages on its Web site
4.13	CDER review teams analyze all postmarketing study results and make public their risk-benefit assessments
5.1	Congress ensure that FDA has the regulatory authorities to require postmarketing risk assessments and risk management to ensure safe use of drug products
5.2	Congress provide FDA with increased enforcement authority and better enforcement tools
5.3	Congress require the use of a symbol to identify new drugs and FDA restrict direct-to-consumer advertising during symbol's use
5.4	FDA evaluate all new data on new molecular entities not later than 5 years after approval
6.1	Congress establish a new FDA advisory committee on communications with patients and physicians
6.2	FDA develop a cohesive risk communication plan
7.1	Administration request and Congress approve substantially increased resources in funds and personnel for the FDA

Adapted from (Psaty & Charo, 2007)

Table 4 – IOM Recommendations

For a more detailed list of the recommendations see Appendix G.

Martin Report

A few months after the Vioxx Recall, in December 2004, a Special Committee of the Board of Directors at Merck & Co., Inc. retained John S. Martin Jr. to review the conduct of senior management in connection with Vioxx. Judge Martin and his team led a 20-month investigation during which they interviewed 115 witnesses and reviewed millions of pages of documents. The subsequent report was then made public.

The report concluded that "management acted with integrity and had legitimate reasons for making the decisions that it made, in light of the knowledge available at the time" (Martin, 2006).

Changes prompted by the Reports

The IOM report and the public pressure following the recall forced the FDA and Congress to act and initiate much needed change within the agency. The first changes were proposed by the FDA Commissioner, but the changes were inherently limited by the FDA's mandate, a problem corrected by Congress in the Food and Drug Administration Amendments Act.

FDA's response to the IOM report

In January 2007 the FDA took the unusual step of providing a detailed, 38 page public response (FDA, 2007) to the IOM report (Institute of Medicine, et al., 2007) indicating the changes it intended to make to deal with the issues outlined in the report. In this report, the FDA outlined its three main goals: Strengthening the science that supports the U.S. medical product safety system, improving communication and information flows and improving operations and management to strengthen the drug safety system.

A. STRENGTHENING THE SCIENCE THAT SUPPORTS OUR MEDICAL PRODUCT SAFETY SYSTEM

1. Upgrading methods of benefit and risk analysis and risk management
2. Strengthening methods and tools of safety surveillance
3. Developing new scientific approaches to detecting, understanding, predicting, and preventing adverse events

B. IMPROVING COMMUNICATION AND INFORMATION FLOWS

1. Conducting a comprehensive review of current public communication tools
2. Establishing an Advisory Committee on communication
3. Using fees to fund improvements in communication among staff on safety issues
4. Issuing drug safety information guidance
5. Publishing a newsletter on postmarket findings
6. Posting reviews of NDA supplements and assessments of postmarket safety studies

C. IMPROVING OPERATIONS AND MANAGEMENT TO STRENGTHEN THE DRUG SAFETY SYSTEM

1. Engaging external management consultants to help CDER/FDA develop a comprehensive strategy for improving CDER/FDA's organizational culture
2. Making specific organizational and management changes to increase communications among review and safety staff
3. Improving our use of Advisory Committees

Adapted from (FDA, 2007)

Table 5 – FDA's Response to the IOM Report

See Appendix H for a more detailed list of FDA proposed changes.

In the appendix to the report, the FDA matched point-by-point the proposed changes to the recommendations of the IOM. As shown in the appendix, some of the IOM recommendations were addressed yet many issues remained unresolved: the powers available to the FDA limited its capacity to deal with all the recommendations proposed by the IOM and a Congressional mandate was required to implement them.

Congress' response to the IOM report – Food and Drug Administration Amendments Act (FDAAA)

In September 2007, Congress passed the Food and Drug Administration Amendments Act, which amends the Federal Food, Drug, and Cosmetic Act and extends the user-fee programs for prescription drugs and medical devices while enhancing the postmarket authorities of the Food and Drug Administration with respect to the safety of drugs and food. Congress answered many of the IOM committee recommendations and dealt with some of the issues the FDA was not able to address on its own. Several sections of the act are relevant to post-approval safety namely, Title I: PDUFA, Title VI: Reagan-Udall foundation, Title VII: Conflicts of Interest, Title VIII: Clinical trial databases and Title IX: Enhanced authorities regarding postmarket safety of drugs.

Most notably, the act gives the FDA the authority to require post-marketing studies, to initiate label changes and to require Risk Evaluation and Mitigation Strategies (REMS) to make sure that a drug's benefits outweighs its risks. The act also requires the FDA to establish an active post-marketing surveillance system and to enforce the registration of all phase II, III, or IV drug trials. Finally, the act increases the resources available to the FDA for post-approval safety by allowing a greater share of user fees to be used for safety monitoring and pushes for a change in the dynamics between OND and OSE.

Key Drug-Safety Provisions in the FDAAA.
Power to require postmarketing studies, to order changes in a drug's label, and to restrict distribution of a drug
New resources of $225 million over 5 years for drug safety
Modernization of the Adverse Event Reporting System and access to large governmental and private databases on adverse drug reactions
Elevation of the drug-safety group's organizational status

Source (Schultz, 2007)

Figure 10 – Key Drug-Safety Provisions in FDAAA

With the combination of the changes proposed by the FDA and Congress all but one IOM recommendation has been addressed (3.1 – FDA commissioner be appointed for a 6-year term).

Analysis of the changes

The goal of this section is to determine how the changes made map to the underlying issues found in the first part of the analysis and study how the changes affect the context within which the system operates.

Analysis of the FDA's response to the IOM report

After the publication of the IOM report, the FDA deemed it necessary to publish a response and implement some of the recommended changes. Those changes were then mapped to the control structure to identify the repercussions of the implemented changes (see Appendix I for the summary of this analysis).

Effects of the changes

The FDA's responses to the IOM recommendations were of two types: 1) the agency does not have the authority to implement the proposed changes, which will require a Congressional amendment or 2) the FDA will run a pilot study or project to test the effects of the recommendations.

Recommendations requiring congressional amendments:

- FDA commissioner appointed for a 6-year term
- Require sponsors to register clinical trials
- Ensure the FDA has regulatory authority to require post-marketing risk assessments
- Provide the FDA with increased enforcement authority and better enforcement tools

- Require the use of a symbol to identify new drugs
- Appropriation of more funds for the agency

Recommendations under study by the FDA:

- Pilot project to evaluate models of OSE involvement
- Memorandum of understanding with the VA for sharing of data
- Pilot for review of NME
- New guidance documents on disclosure of conflicts for advisory committees

It is hard to determine whether the proposed changes will be effective because so many of them are in the planning and testing phases and at this point it is not clear what part of the system they will affect and in what manner. However, the proposed changes are very limited compared to what is suggested in the IOM report.

Published criticism of FDA's response to the IOM recommendations

Smith, in a perspective article published in the New England Journal of Medicine (S. W. Smith, 2007), argues that the changes proposed by the FDA fall short of the recommendations made by the IOM, in particular because OND and OSE are still separate entities, with OSE serving as consultants to OND. She argues that the new pilot study proposed (IOM 3.4) is redundant because a similar study was done 10 years ago by Greg Burkhart, with positive results. Finally, she points out that OSE still does not have the authority to recall drugs. Overall, she criticizes the FDA for not doing enough to move towards a more safety-focused culture.

In his Journal of American Medicine paper on the topic, Psaty pointed out that the fact that only one of the recommendations from the IOM report was really new and suggests that the FDA is slow to react to change and casts doubt on how fast the FDA will be implementing the new changes. He also mentions the fact that the proposed changes seem to fall short of the IOM recommendations, especially when dealing with cultural changes within the agency. For example the agency "made no commitment to joint authority" for issues that affect both OSE and OND. He commented that overall, "while the FDA responses represent incremental progress, they also suggest that the agency failed to embrace fully the values of transparency, independent review, and equality between the preapproval and post-approval activities of the agency" (Psaty & Charo, 2007).

Analysis of FDAAA

The Food and Drug Administration Amendments Act brings significant and much needed changes to the FDA and it is hopped that those changes will enhance the capacity of the FDA to monitor drugs throughout their whole lifecycle and help protect the American public from unsafe drugs. The recommendation can be divided in two groups based on whether the STAMP analysis suggest that the changes will increase overall safety or if the changes will not be as effective as anticipated by Congress. A third group includes all the recommendations omitted by Congress the potential consequences of this oversight. The first two groups are then added to the existing System Dynamics models to show the potential dynamic effects of the policy changes.

To determine the effects of the FDAAA changes on the healthcare system, each recommendation was mapped onto the system to determine what component it was most likely to affect. The repercussions of this change can then followed throughout the system as a whole. For a table summarizing those finding see Appendix J**.**

Changes with positive effects

The Food and Drug Administration Amendment Act represents a major improvement in two areas: 1) quality and quantity of information available to the FDA and the public and 2) authority given to the FDA.

FDAAA ensures that the FDA will have access to more information through a large cohort of electronic medical records ("Sentinel Initiative"), systematic reviews of the existing AERS data, registration of new clinical trials and detailed risk evaluation and mitigation strategy plans. The information can then be communicated to the public through an improved and more transparent FDA website while a committee on risk communication studies other ways to disseminate the information. Properly used, the new data can theoretically help with the monitoring of drugs and the early detection of unknown risks. More efficient and transparent communication means that this information is then readily communicated to doctors and patients so that they can make optimal treatment decisions. Potential difficulties exist, however, in actually implementing such a large and complex information system. The effect will depend on how well these new information systems are designed and operated.

FDAAA also gives increased legal authority to the FDA. The agency can now require postmarketing studies, label changes, restrictions on distribution or use of new drugs and new civil penalties discouraging non-compliance. This new authority means that the FDA can react faster and with more flexibility than before when its only means of control was the threat of a drug recall. The agency can now better tailor its response, for example by requiring the drug label to be updated, when new risks are suspected or discovered.

Changes likely to be less effective than anticipated

The analysis suggests that many of the proposed changes in FDAAA are likely to be less effective than anticipated by the IOM and Congress because many of the recommendations are

resource intensive, because the OND is still captured by the industry it is supposed to regulated, and because FDAAA does not deal with some the important communication and leadership issues that plague the FDA. That is, many of the most important contextual factors leading to the poor decision-making with regard to Vioxx still exist.

The first major problem is that contrary to the IOM recommendation, most of the resources still come from user fees and not Congressional appropriations, retaining the situation where a large part of the agency's budget comes from the industry it is in charge of regulating. FDAAA potentially magnifies this problem because close to 10 percent of user fees are now directed to OSE rather than simply OND. The increase in resources for post-approval safety is positive, but the requirements attached to their use might negate, or at least dampen, the positive effects. The second significant problem is that FDAAA does little to alleviate the tension between OND and OSE: OSE still serves as a consultant to OND without the power to enforce its safety findings and resources are still skewed towards approval of new drugs.

Similar dampening effects can be found for many of the FDAAA recommendations:

- Systematic review of the AERS data: Asking the FDA to review the AERS data at regular intervals for signs of adverse events will only be useful if the quality of the data in the AERS database is improved. Reviewing poor data on a regular basis will not make the American public safer.
- Gradual reduction in permitted waivers for conflict of interest: The FDA assumes that it will be able to find enough researchers with the appropriate qualifications and without ties to pharmaceutical companies to sit on the committees. However, without appropriate incentives, potential committee members have no reason to turn down lucrative consulting salaries or speaker fees.
- The creation of the office of chief scientist: This position can be effective only if the FDA has a stable and consistent leadership at both the agency and centers level.
- Review of AERS, REMS, EHR, and DTC Advertising data: Many of the FDAAA changes are resource intensive, but the FDA does not currently have the personnel to meet the increased workload. Without significant increase in the allocations of funds for DDMAC and OSE, it is unlikely that the centers will be able to meet their new safety goals.

Recommendation not addressed in FDAAA

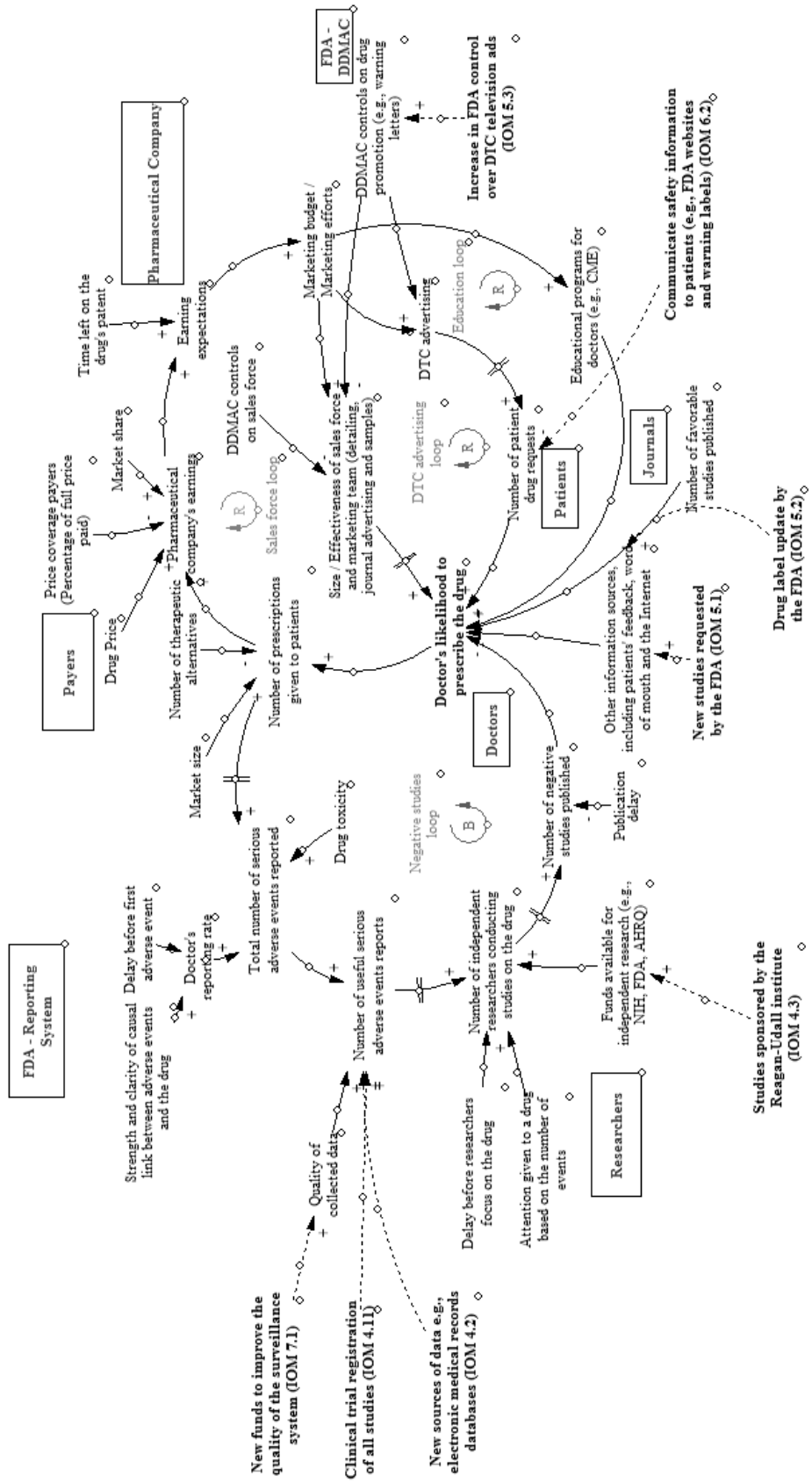
Congress decided to ignore the IOM's recommendation to fund the agency through appropriations from general revenues rather than user fees. Similarly FDAAA leaves OSE to serve as an advisory to OND, without significant authority, which can be a serious problem if OND has indeed been captured by the industry. FDAAA also does not mandate the Reagan-Udall institute to plan, design or fund safety and efficacy studies, it does not require the use of a symbol to identify new drugs as was done in the UK, and it does not appoint the FDA commissioner for a 6-year term as was suggested in the IOM report.

Finally, it is important to point out that the changes focus solely on the FDA and the pressures and contextual influences on the behavior of the doctors, pharmaceutical companies, patients, payers and journals have largely been ignored. Because of this limited focus, the proposed

solutions may not be enough to significantly improve the safety of the overall system. Other parts of the safety control structure are likely to react to the changes in the FDA, resulting in little overall improvement in drug safety.

System Dynamics analysis

In this part of the analysis the models created in Section 3 were used as a basis for new models which include the safety constraints defined by the FDAAA and the repercussions of those changes throughout the structure. The new recommendations were added in bold and linked to the FDAAA changes using the IOM recommendation numbers.



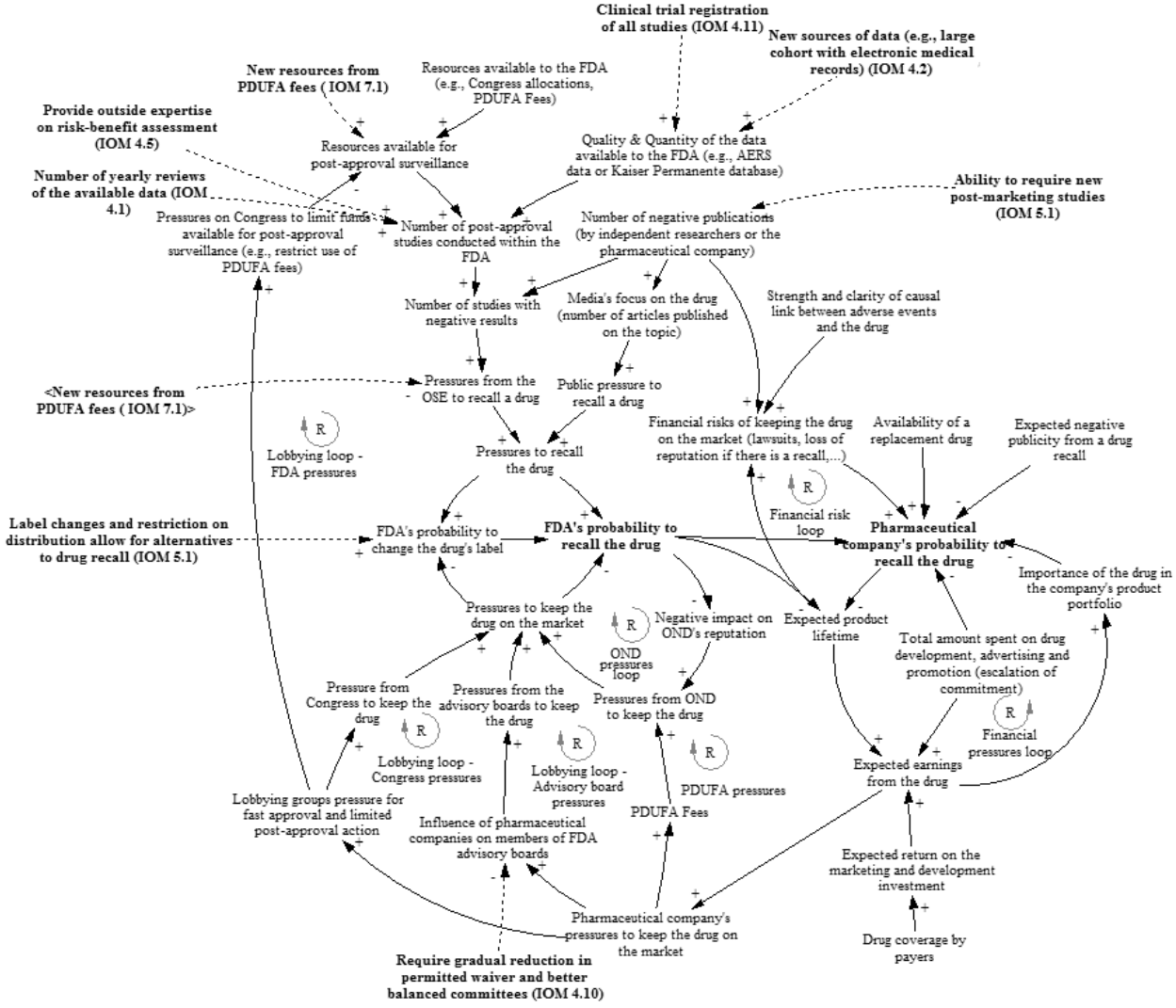
Model 3 – Physicians Prescription Habits with FDAAA controls

In this model, eight different recommendations are relevant to physician drug prescription behavior, four of which deal with how new adverse events are reported, monitored and analyzed (left side of the model), two deal with risk communication (bottom part of the model) and two with advertising (right side of the model).

The first four recommendations (IOM 4.2, 4.3, 4.11 and 7.1) moderate the negative studies loop to ensure that more accurate information is collected and that more funds are available to analyze this data. If the drug is dangerous the controls will reduce the doctor's likelihood to prescribe the drug. However, even with those new pressures, there are still some inherent delays in the system (time to collect data, time to run the studies…) that mitigate the effects of the changes.

The other four changes deal with information propagation. The first two (IOM 5.1 and 5.2) deal with collecting and publishing more information to help better inform the doctors and the last two (IOM 5.3 and 6.2) try to control pharmaceutical company marketing efforts by either providing alternative information to the patients or by increasing the funds for the FDA office in charge of controlling advertisement. Those four changes can help give doctors and patients a more balanced view of the effects of the drug prescribed.

The model suggests that the proposed changes will lead to faster recalls and that the magnitude of the changes will depend on how effective the new monitoring system is. However, there are inherent time delays due to the drug effects and reporting times that will limit the effectiveness of the proposed changes and make it impossible to make the system "completely" safe.



Model 4 – Drug recall with FDAAA controls

In this model eight recommendations and their effects on drug recalls are added. Most of the changes (IOM 4.1, 4.2, 4.5, 4.11 5.1 and 7.1) focus on the number and quality of post-approval studies conducted within or for the FDA and how often the data is reviewed. This creation of new knowledge is important because it helps foster a better scientific consensus around the effects of a given drug. However, many of those efforts are paid for by PDUFA fees. On the face of it, new resources for post-approval surveillance are a positive change because they increase the FDA's capacity to monitor and recall dangerous drugs. However as was mentioned in the earlier analysis of the proposed changes two issues might limit the effects of this change: 1) if OSE has no authority to recall drugs, then newly sponsored studies might not be acted upon, or at least not fast enough especially if the tension between OND and OSE is not resolved; and 2) it is possible that the sponsoring of OSE through PDUFA funds will create a situation similar to the one currently existing within OND, where pharmaceutical companies are seen as a "client" more than a group to be regulated, creating an inherent conflict of interest within the office and leading to biased work.

The FDA's new authority to change labels without prior approval from the pharmaceutical companies (Label change – IOM 5.1) gives the agency an important alternative to recalls and allows it to take action when new risks are discovered, without having to deal with a full recall. The effectiveness of this change will depend on how often the FDA actually uses this clause, how much the pharmaceutical companies fight its use, and how it is perceived by the public at large.

The gradual reduction in conflict of interest waivers required by the FAAA (IOM 4.10) will help limit the external pressures on the OND and should help keep the advisory committees more neutral. However, this proposed change might have little effect since the pressures coming from the PDUFA fees are so strong and already bias OND in favor of pharmaceutical companies.

In this section the changes that followed the Vioxx recall were analyzed using both the static control structures and the two system dynamics models. While most of the changes are theoretically positive, they are focused too much on the FDA only and not on preventing the other parts of the control structure to adapt and mitigate the potentially positive effects. The narrow focus may also lead to unintended consequences. The next section proposes a more complete set of recommended changes.

Section 5 - Policy recommendations

The changes proposed by the FDA and the subsequent changes brought by the Food and Drug Administration Amendments Act represent an important first step towards better protecting the American public from unsafe drugs. However, to enhance drug safety, the entire safety control structure needs to be re-engineered to provide contextual influences that encourage safer decision making on the part of everyone

This section proposes a number of recommendations based on the system analysis. The STAMP model was used to trace back the inadequate control actions to the context in which the different controllers operate and to suggest changes that will help encourage better decision making. The details of the analysis can be found in Appendix I.

Recommendations

Physicians

If the new sources of information about drug safety are available and usable by physicians, many of the current problems will be solved. However, in addition:

1. Doctors should be required to pay for their own Continuing Medical Education programs to ensure that the content of the presentation is neutral and not biased in favor of the pharmaceutical companies who typically sponsor such events.

Pharmaceutical Companies

The recommendations outlined in this section are not focused on ways to control the behavior of pharmaceutical company or the safety of the products they sell. The FDA already has the responsibility to make sure that all pharmaceutical products are safe (of course, FDA's control over the pharmaceutical company can still be improved on and some of recommendations in the FDA section aim at doing just that). Instead, the recommendations outlined below focus on what the pharmaceutical companies can do to avoid being in a situation where they have to recall one of their major source of revenue. Nevertheless, it is important to note that the recommendations can have an indirect impact on safety if they result in the pharmaceutical companies recalling dangerous products faster.

2. By diversifying its drug portfolio a drug company can better protect itself from the negative impacts of a drug recall and will be more open to recognizing early warning signs associated with any one product.

3. If pharmaceutical company's managers want to have the best available information when making safety decisions they need to ensure that adequate skepticism and critical thinking are maintained during research and development phases. To achieve this goal, pharmaceutical companies need to:

- isolate the research department from marketing and sales group
- incentivize the early detection of critical drug flaws

FDA

Proposals echoing the IOM recommendations

4. The FDA needs to develop a new adverse event reporting system based on existing EHR databases and continuously expand it to include new EHR databases as they are deployed. A larger high quality dataset can help detect warning signs early on.

5. The FDA needs to establish a database to track ongoing clinical trials and periodically check if the trials are still running. If a trial has been interrupted, the FDA should be notified as to why and be given access to the intermediary results.

6. The FDA needs to have the authority and tools to force pharmaceutical companies to follow up on their Phase IV studies commitments (for example, with fines or by delaying approval of other drugs).

Recommendations on communication

7. The FDA should ensure that patients have access to the information they need to understand their disease and treatment. The FDA should actively focus on patient education. Web based resources are starting to help fill this gap.

8. The FDA needs to improve the way information about newly marketed drugs is communicated to patients. In particular the FDA needs to communicate the fact that little is known about new drugs' long-term side effects.

9. The FDA should provide targeted information to the doctors based on the population they treat or the prescriptions they make. This information is already used by the pharmaceutical companies when marketing new drugs and could be used by the FDA to help inform doctors.

10. The FDA needs to ensure that DTC advertisements are accurate and provide balanced information to the patients. Ultimately, the FDA should consider banning full direct-to-consumer advertising, a position that has been adopted by all other developed countries.

Comparative studies

11a. The FDA should sponsor comparative studies between alternative treatments and adequately communicate the results to doctors and patients.

11b. The FDA should require pharmaceutical companies to test new drugs not only against placebos but also against existing treatments, using comparable dosages to help understand what drug is most efficient for each part of the population.

Structural recommendations

12. OSE and OND

12a. The FDA needs to the give OSE the authority to recall a drug without requiring OND approval. The two centers have to be able to work independently to limit conflicts of interest within the agency.

12b. The FDA needs to give OSE the authority to request new safety studies. It is important that OSE has this authority, independently of what OND decides, in particular if suspicion of new risks arises after the drug has been approved.

13. The FDA needs to lower its standard for drug recalls. The burden of proof for a recall should not be as stringent as the one for the approval of a drug—protection of the public should be the agency's first consideration.

14[4]. The FDA needs to set standards for clinical trials to be respected by both CROs and academic researchers to ensure that the subjects are adequately protected, in particular when dealing with multicenter studies.

FDA Advisory Boards

15. The FDA needs to strictly enforce waiver rules in advisory committees to limit conflicts of interest and make sure that the committees' recommendations can be trusted.

16. The FDA should make it rewarding financially, professionally or academically to be selected for an FDA committee which would make it easier for the FDA to fill vacancies in its committees.

17a. FDA committees should not allow patients to testify since testimonies give a biased representation of the drug efficacy. Often only patients who benefit from the drug testify.

17b. Alternatively, the FDA needs to ensure that patients representing both sides of the issue testify in committee hearings.

Journals

18. Questionable journals should be investigated for fraud.

19. Medical journals should create and maintain a database where authors' affiliations and conflict of interests are listed. Such a database would help ensure consistency across journals and would make it easier for journals to keep track of sources of funding. The database could then be audited by an external board or patient advocacy groups for accuracy.

[4] This recommendation does not appear in the SD models

20. Journals should write precise guidelines on ghostwriting and guest authorship and should establish strong penalties for authors who do not respect the guidelines (for example, ban them from publication).

Congress & Executive Branch

Proposals echoing the IOM recommendations

21. The FDA must be given the authority to require new safety studies to be conducted, even after the drug has been approved.

22. The FDA must be given the authority to recall unsafe drugs.

23. The FDA must be given the authority to change a drug's label without requiring the approval of the drug manufacturer.

24. The FDA must be given the authority to add a special symbol similar to the one used in the UK to signal that a drug is new. A warning symbol would help dispel the consumer belief that new drugs are necessarily safer than older drugs and would serve as a potential reminder to doctors that all risks associated with the drug might not yet be known.

25. Congress needs to fund the FDA through appropriations from general revenue rather than user fees.

26. OSE needs to have access to a larger dataset and should have access to databases maintained by private medical providers such as Kaiser Permanente and databases maintained by other government agencies like the VA.

Novel recommendations

27. The president should appoint a strong leader as the head of the FDA, who in turn would appoint capable people at the head of CDER, OND and OSE.

28. Congress needs to relax the PDUFA requirements so that the FDA is not under a timeline pressure to approve drugs.

29. Congress should require Pharmaceutical companies to release the results of all trials to both the FDA and external researchers, especially when the results are negative. Without this information the data available to researchers, doctors and patients is not representative of the real risk–benefit profile of the drug.

30. Congress should create transparency rules so that researchers, research centers, and pharmaceutical companies are required to disclose their financial engagements.

31. Congress should establish civil penalties for researchers signing off on ghostwritten studies or the professional societies, funding agencies, and journals should establish penalties.

Funding recommendations

32. Congress needs to ensure that funds are properly allocated between OND and OSE and that OND is not significantly larger, both in staff size and budget, than OSE.

33. Congress should increase the allocations for OSE.

34. Congress should increase the allocations for DDMAC.

35. Congress needs to increase NIH/AHRQ funding for post-approval safety research and for comparative studies.

Now that the recommendations have been outlined, it is possible to map them on the System Dynamics models to see how they affect the system as a whole and what balancing influences are likely to either enhance or limit their effects.

System Dynamics Analysis

In this section the recommendations are modeled in addition to the FDAAA changes. Again the changes from the original model are in bold. When the new recommendations overlap with the existing FDAAA changes, the recommendations are referred to with both their IOM and STAMP number. For completely new changes only the STAMP number were used.

Physicians Prescription Habits

Model 5 – Physician Prescription Habits with STAMP controls

In this model, seventeen new constraints are imposed on the system, nine of them specific to the STAMP analysis.

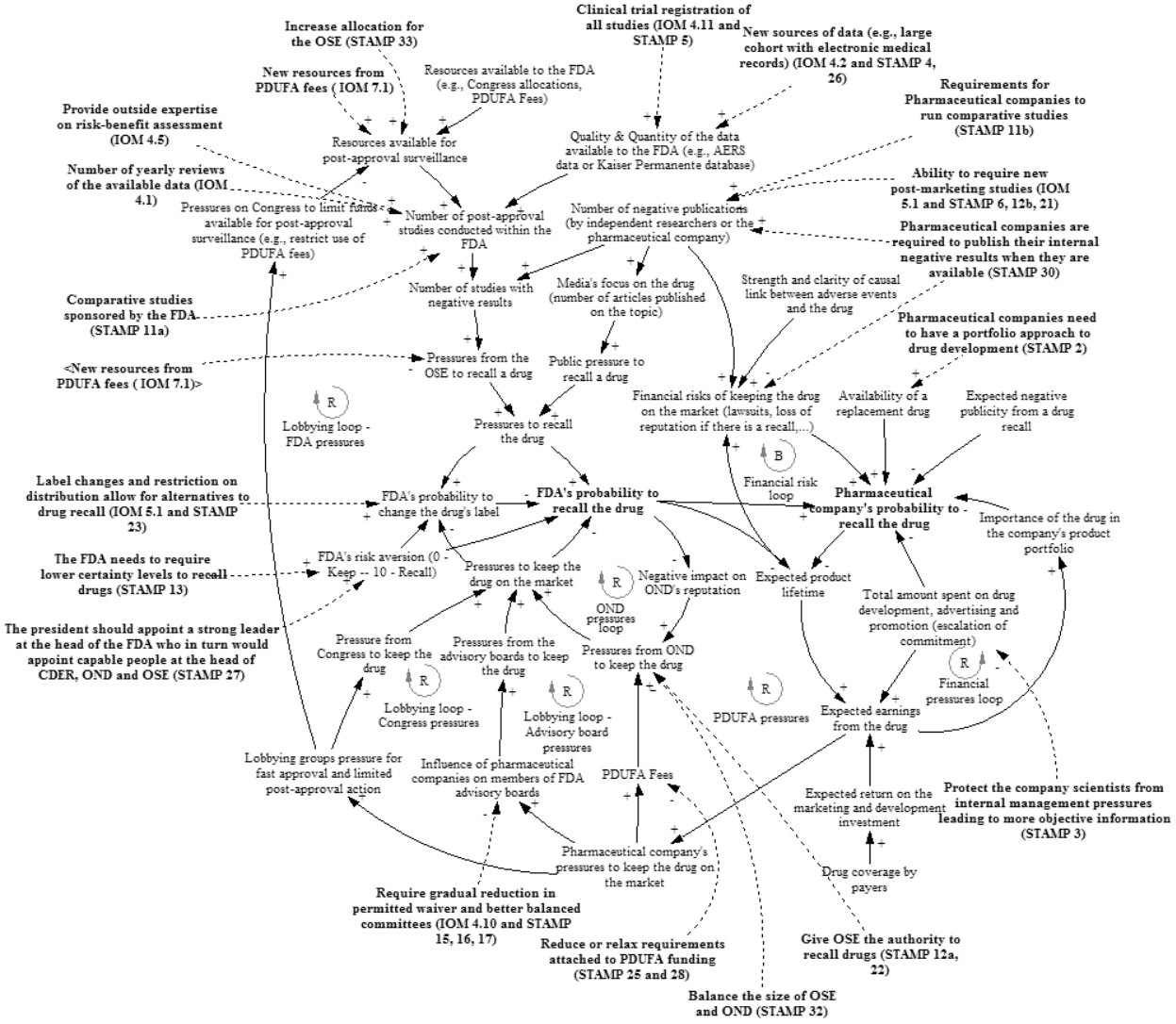
Four of the new proposed changes focus on improving the information available to doctors either by increasing the number of comparative studies that are run (STAMP 11a and 11b), by labeling new drugs with a specific warning (STAMP 24) or by imposing stricter controls on the information published (STAMP 18, 19 …).

Another set of three changes (STAMP 9, 10 and 34) focus on controlling how drugs are advertised, first by balancing the information provided to doctors by pharmaceutical companies with information provided by the FDA (STAMP 9), second by giving greater control to DDMAC over DTC advertising (STAMP 10) and third by making sure that DDMAC is adequately funded (STAMP 34).

One change aims at reducing the biases inherent in the way CME programs are currently organized by forcing doctors to pay for their own continuing medical education instead of having the events sponsored by the drug companies (STAMP 1). This change may be impractical unless the Federal Government allows such education fees to be a tax write-off, essentially funding the education through tax dollars.

Finally, the last two changes are recommendations for the pharmaceutical companies to help them avoid being in a situation where they have to recall one of their major source of revenue. Companies can diversify the risk associated with a single drug by encouraging early on the development of as many products as possible (STAMP 2) and can ensure that they have more accurate information about their own products if they isolate the research department from marketing and sales group and incentivize the early detection of critical drug flaws (STAMP 3).

The proposed changes target almost all the different components of the system. The models suggest that dangerous drugs can be detected earlier and information about adverse events propagated faster, while at the same time limiting the amount of biased information that influences both patients and doctors. Again, there are inherent delays in the system and it will always take time to learn about long-term side effects, but the changes will allow negative side effects to be detected as soon as possible and information about them propagated and acted upon more quickly.



Model 6 – Drug Recall with STAMP controls

There are nineteen proposed changes affecting the drug recall model, eleven of which originated from the STAMP analysis. Again, the changes target a wide range of components within the system.

Most of changes focus on increasing the quality of the post-approval surveillance system by increasing the resources available to OSE and sponsoring new studies (STAMP 11a and STAMP 33) or on easing the tension between OSE and OND by increasing the budget for OSE (STAMP 32) or by giving it more authority (STAMP 12a, 22). Other changes deal with the way the FDA handles drug recalls (STAMP 13), how to ensure that a strong leader is in charge of the agency (STAMP 27) and hot to limit the pressures on OND (STAMP 25 and 28).

Another two recommendation (STAMP 11b and STAMP 30) are constraints that should be imposed by the FDA on the pharmaceutical companies to enhance post-approval safety: 1) they should be required to run comparative studies (STAMP 11b) they should be required to release the data they have on marketed products (STAMP 30).

As in to the previous model, the final two recommendations (STAMP 2 and 3) are observations intended to help pharmaceutical companies protect themselves from having to recall one of their major source of revenue.

The recommendations outlined in this model intend to create a more accurate and reactive system will limiting the external pressures on the FDA. They have the potential to lead to earlier recalls for potentially dangerous drugs or faster label changes for drugs that are more dangerous than first expected.

Conclusions

Creating a completely safe healthcare system is impossible but that does not mean that it is not important to learn from past mistakes and work to improve the existing system. This thesis focused on understanding the healthcare system and how the Vioxx tragedy happened by first studying the system as a whole and outlining the control structure that dictates the way safety is enforced. The second step was to identify the main clusters of power (Pharmaceutical companies, FDA, Congress, Doctors, Patients…) and map the way they interact with each other. Third, the different components of the system were studied individually to look for ways in which they violated their safety responsibilities and to try to understand what motivated the controllers by recreating the environment in which they operated at the time.

Based on this contextual analysis, each of the components were modeled using System Dynamics tools and connected the components to create two larger multi-component models. The first model illustrates the drug prescription process and focuses in particular on the way pharmaceutical companies can influence doctors. The second model is centered on the recall of a drug. Those two models help to understand how drugs evolve after they receive FDA approval because both focus on major safety control points: the way doctors control patient access to the drug and the way the FDA or pharmaceutical companies control market access.

The drug safety control structure has evolved since the Vioxx events, due in part to changes imposed by the Food and Drug Administration Amendment Act of 2007. Those recommendations were divided in two groups: those likely to have positive effects and those likely to be less effective. A third group of recommendations were part of the Institute Of Medicine report but were not included in FDAAA. The first two groups of recommendations were included in an enhanced set of System Dynamics models that was used to study how the new changes affect the system and to try to predict what factors might either reinforce or limit the effects of those changes.

The analysis found that the proposed changes were very narrowly focused so the STAMP analysis was used to generate a new set of 35 recommendations that target all the controllers. Again, the changes were modeled on a new set of System Dynamics diagrams to illustrate how recommendations would lead to earlier recall of dangerous drugs and would help doctors make better treatment decisions.

However even those recommendations should not be expected to be enough to protect the American public in the long term. The healthcare system will keep evolving and new medical treatments will bring new and unknown risks, risks that the current safety structure is not configured to handle. It is important to keep in mind that the system is constantly evolving and that it is necessary to monitor the way each of the components adapts to new changes and how they affect the system as a whole. It is only by proactively monitoring the changes that future drug safety problems can be prevented.

Appendices

Appendix A – A Vioxx timeline

Date	Merck	FDA	Other
1994	Vioxx molecule discovered		
-----/-/----	----------/-/----------	----------/-/----------	----------/-/----------
11/1998	Seeks FDA approval		
12/1998			Celebrex approved by the FDA
1/1999	VIGOR Trial Begins		
2/1999	First Alzheimer's disease trial		
3/1999			
4/1999			
5/1999		FDA approves Vioxx for the relief of osteoarthritis symptoms and management of acute pain	
-----/-/----	----------/-/----------	----------/-/----------	----------/-/----------
10/1999	APPROVe trial protocol finalized		
11/1999	The Vigor DSMB meets to discuss heart problems		
12/1999			Vioxx has more than 40% of new prescriptions in its class
1/2000			
2/2000	Start of the APPROVe study		
3/2000	● Merck gets results of the VIGOR trial ● Publishes results from Alzheimer trial (no CV problems found)		
4/2000		FDA recommends that Merck conduct an animal study with Vioxx to evaluate CV safety	
5/2000	Publishes the results from the Vigor study in the NEJM. The data include only 17 of the 20 heart attacks Vioxx patients have		
6/2000	Submits data from the VIGOR study to the FDA: Shows a 4x higher risk of heart attacks compared with naproxen		
-----/-/----	----------/-/----------	----------/-/----------	----------/-/----------
10/2000	Merck tells the FDA about three other heart attacks from the Vigor study		

11/2000		FDA requests complete Clinical study report for ADVANTAGE	The NEJM publishes the results from the Vigor study
12/2000			
1/2001			
2/2001		FDA Arthritis Advisory Committee meets to discuss the gastrointestinal VIGOR study	
3/2001	Merck submits final data from ADVANTAGE to FDA		
-----/-/----	----------/-/----------	----------/-/----------	----------/-/----------
8/2001			A meta-analysis is published in JAMA casting serious doubts on the safety of Vioxx
9/2001			
10/2001		Label negotiations were initiated by the FDA	
11/2001	Merck rejects FDA proposed labeling		
-----/-/----	----------/-/----------	----------/-/----------	----------/-/----------
4/2002		FDA approves changes to Vioxx label which include cardiovascular risks, gastrointestinal benefits and a new use to treat rheumatoid arthritis	
-----/-/----	----------/-/----------	----------/-/----------	----------/-/----------
8/2004		Graham presented his results at a scientific meeting in France (Vioxx users had a higher rate of heart attacks and sudden cardiac deaths than Celebrex users)	
9/2004	• APPROVe shows that the drug raises the risk of heart attacks after 18 months • **Announces withdrawal of Vioxx**		
10/2004	Merck receives conditional approval for Arcoxia, Vioxx's replacement (already sold in 48 countries)		
11/2004			Graham testifies in front of the Senate
12/2004			Congress holds hearing on Merck and the FDA's handling of the drug's safety issues

Adapted from (Martin, 2006; Reuters, 2005)

Appendix B – Gap analysis

#	Safety Requirements and Constraints	Controller	Responsibility
1	***Pharmaceutical products are developed to enhance long-term health***		
1.a.	Continuous appropriate incentives exist to develop and market needed drugs	Government	Help ensure the development of new drugs for rare diseases (e.g., Orphan drugs Act)
		Market	Sets price and where research funds are allocated within a firm
1.b.	New scientific knowledge and technology is developed to create new drugs	Pharmaceutical companies	Conduct or sponsor research which can be useful for the development of new drugs and treatments
		NIH/NAS	Basic biology research is sponsored by the NAS
1.c.	New drugs are developed and manufactured when the scientific and technical knowledge is available	Pharmaceutical companies	Provide safe and effective drugs
2	***Drugs on the market are adequately safe and effective***		
2.a.	Drugs are subjected to effective and timely safety testing	Pharmaceutical companies	Test drugs for effectiveness
		FDA - OND	Set the requirements and process for the approval of new drugs
2.b.	New drugs are approved by the FDA based upon a validated and reproducible decision-making process	FDA - OND	Critically examine a sponsor's claim that a drug is safe for intended use (conduct an NDA Safety Review). Impartially evaluate new drugs for safety and efficacy and approve them for sale if deemed appropriate
		Pharmaceutical companies	b. Provide all available information about the safety of the drug to the FDA
2.c.	Drugs are not unnecessarily delayed	FDA - OND	Do not unnecessarily delay drugs that may have a beneficial effect
2.d.	The labels attached to drugs provide correct information about safety and efficacy	Pharmaceutical companies	Properly label the drugs
		FDA - OND	Upon approval set the label for the drug
		FDA - OSE	Update the label information when new information about drug safety is discovered
2.e.	Drugs are manufactured according to Good Manufacturing Practices	Pharmaceutical companies	Manufacture the drugs according to Good Manufacturing Practices
		FDA	Inspect plants and check that GMP are upheld
2.f.	Marketed drugs are monitored for known and unknown adverse events, side effects, and potential negative interactions	FDA - OSE	Conduct on-going reviews of product safety, efficacy, and quality. Perform statistical analysis on adverse event data received to determine whether there is a safety problem
		Physicians	Report adverse events potentially linked to drugs
		Pharmaceutical companies	Run new trials to test for potential safety hazards
2.g.	Long term studies are conducted, even after the drug as been approved, to validate the FDA's approval decision (e.g., Phase IV studies) both on the long term and for subpopulations	Pharmaceutical companies	Run long-term post-approval studies as required by the FDA
			Provide, maintain, and incentivize adverse-event reporting channels
		FDA - OND	Require phase IV safety testing if there is a potential long term safety risk
		Researchers	Provide independent and objective research on

			drug's safety, efficacy and new uses
2.h.	New information about potential safety risks is reviewed by an independent advisory board	FDA - Commissioner	Select competent advisory committee members and establish and enforce conflict of interest rules
		FDA Advisory Board	Provide independent advice and recommendations to FDA in the best interest of the general public
		Researchers	Give their unbiased expert opinion when it is requested by the FDA
2.i.	Marketed drugs found to be unsafe after they are approved are removed, recalled, restricted, or appropriate risk/benefit information is provided	Pharmaceutical companies	Remove drug from the market if it is no longer considered safe
			Inform the FDA of potential new safety issues in a timely manner
		FDA - OSE	Re-assess risks based on new data learned after a drug is marketed and recommend ways to manage risk
			Remove a drug from the market if new evidence shows that the risks outweigh the benefits
3	***Patients get and use the drugs they need for good health***		
3.a.	Drugs are obtainable by patients	Payers	Pay medical costs for the people insured as needed
3.b.	Accurate information is available to support decision-making about risks and benefits	Pharmaceutical companies	Do not promote unsafe uses of the drugs
			Educate doctors
		FDA - DDMAC	Monitor the marketing and promotion of drugs. Approve information that can be disseminated on controlled substances. Review advertisements for accuracy and balance
		Journals	Publish only articles of high scientific quality
			Provide accurate and balanced information to doctors
		AHRQ	Provide new comparative information
3.c.	Patients get the best intervention reasonable for their health needs	Physicians	Make treatment decisions based on the best interests of their patients
			Weight the risks of treatment and non-treatment
3.d.	Patients get drugs with the required dosage and purity	Physicians	Prescribe drugs according to the limitations on the label
4	***Patients take the drugs in a safe and effective manner***		
4.a.	Patients get correct instructions about dosage and follow them	Patients	Follow their physicians instructions and take drugs as prescribed
		Physicians	Prescribe drugs according to the limitations on the label
4.b.	Patients do not take unsafe combinations of drugs	Patients	Accede to doctor's superior knowledge when appropriate
			Patients must go through a doctor to get a prescription for drugs like Vioxx
		Physicians	Maintain up-to-date information about drug safety, efficacy and the risk/benefit profile of the drugs they are prescribing
4.c.	Patients are properly followed by a physician while they are being treated	Physicians	Monitor symptoms of their patients under treatment for adverse events and negative interactions
4.d.	Patients are not subjected to unacceptable risk during clinical trials	Pharmaceutical companies	Protect patients during clinical trials by properly monitoring the trial

		FDA - OND	Oversee all U.S. human trials and development programs for investigational medical products to assure safety of participants in clinical trials. Provide oversight of IRBs that perform these functions for the FDA
5	**The necessary legislative and judiciary infrastructure exists to ensure that the public is protected**	Congress	Provide guidance to FDA by passing laws and providing directives
			Provide necessary legislation to ensure drug safety
			Ensure that the FDA has enough funding to operate independently
			Provide legislative oversight on effectiveness of FDA activities
			Hold committee hearings and investigations on industry practices

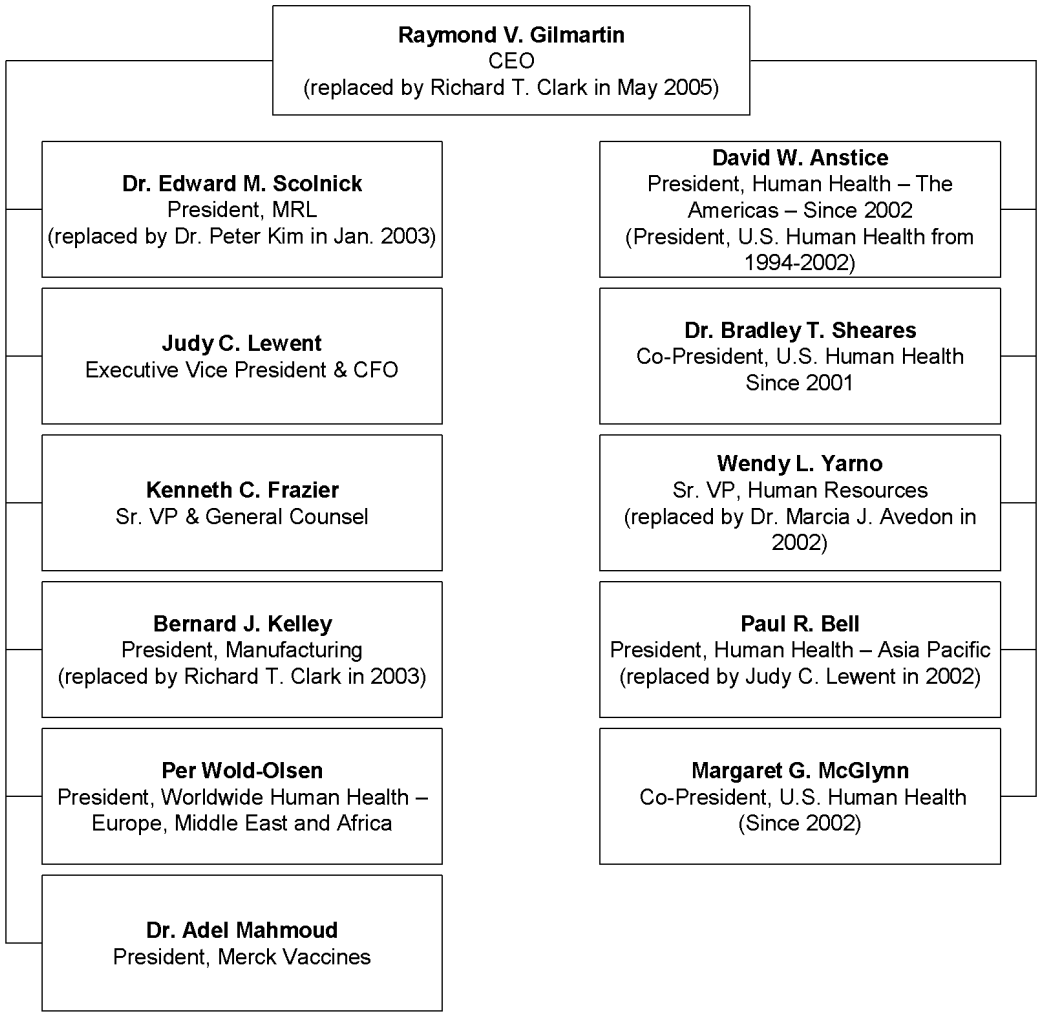
Appendix C – Structure of Merck between 1994 and 2004

CEO: Mr. Raymond Gilmartin

Merck Divisions:

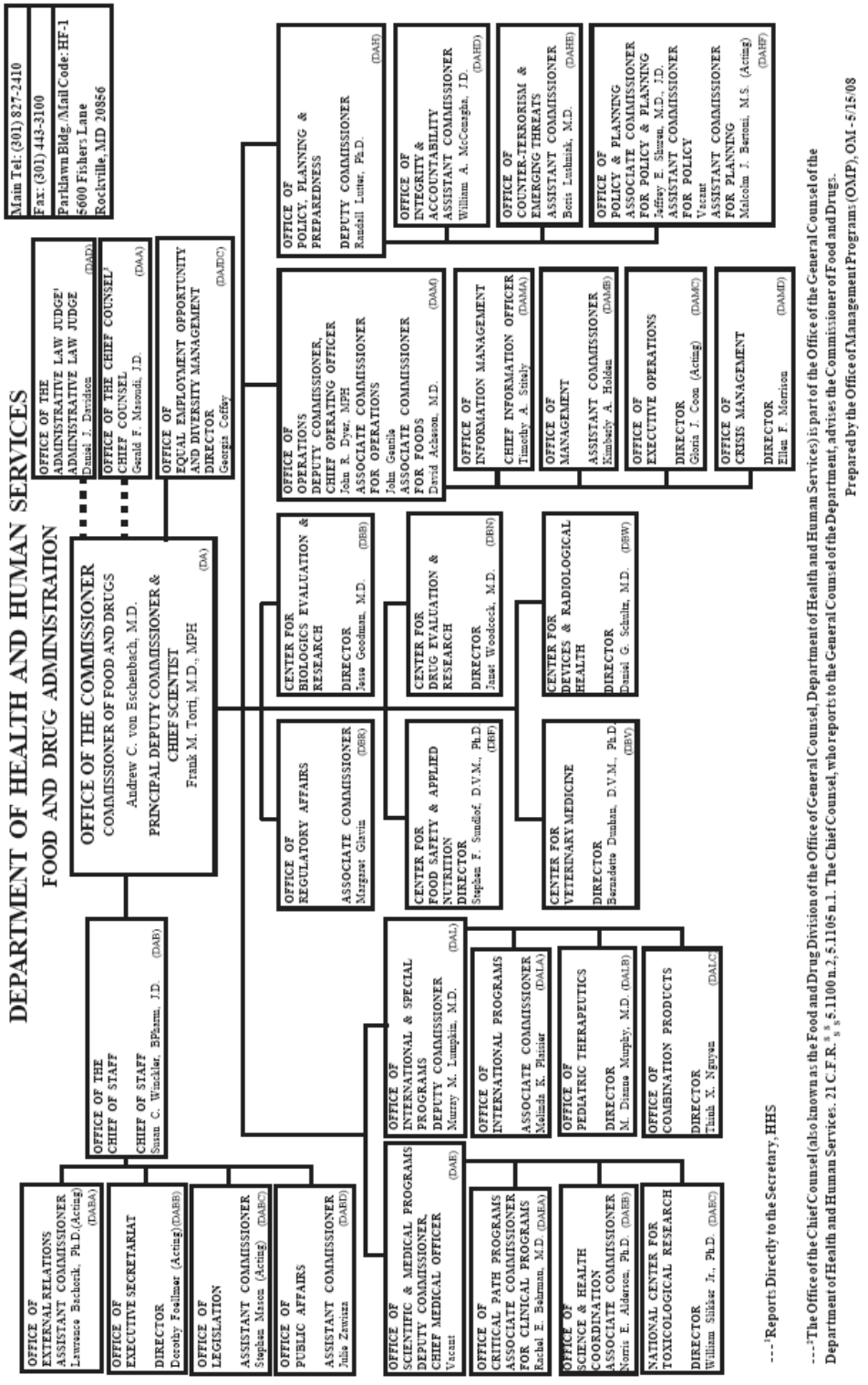
- Research: Merck Research Laboratories (MRL)
- Marketing/Sales: Division named Human Health and is organized by geographical region
- Public Affairs: Works closely with the Marketing/Sales division

Senior Management:



Source: Martin Report – Exhibit 1 (Martin, 2006)

Appendix D – Structure of the FDA and CDER in 2008



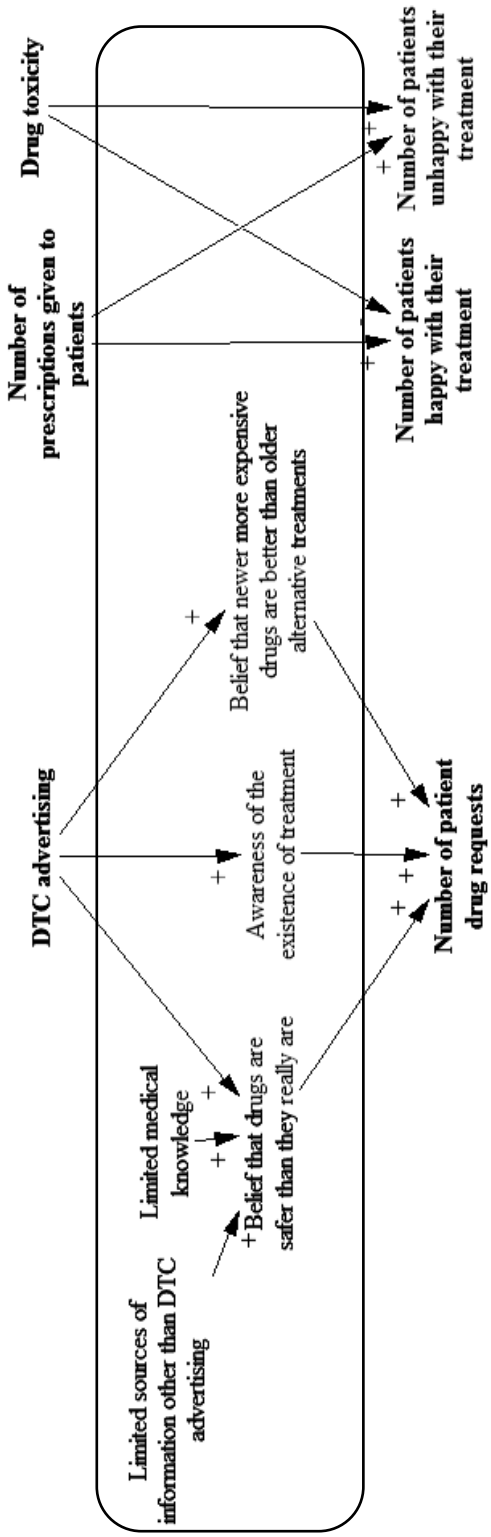
Source: FDA website (http://www.fda.gov/oc/orgcharts/orgchart.html)

Appendix E – List of acronyms used in this paper

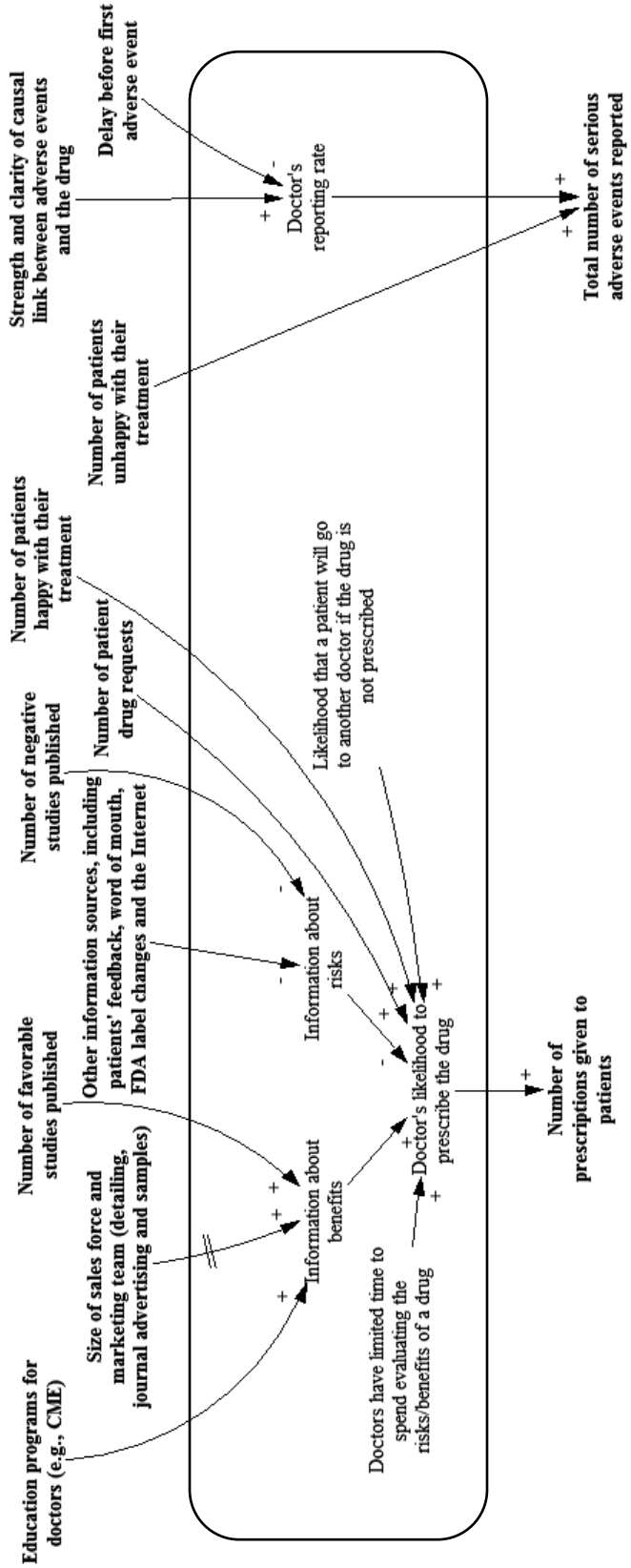
ADVANTAGE	Assessment of Differences between Vioxx and Naproxen To Ascertain Gastrointestinal Tolerability and Effectiveness
AERS	Adverse Event Reporting System
AHRQ	Agency for Healthcare Research and Quality
APPROVe	Adenomatous Polyp Prevention on Vioxx
BMJ	British Medical Journal
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CME	Continuing Medical Education
CRO	Contract Research Organization
CV	Cardio-Vascular
DDMAC	Division of Drug Marketing, Advertising and Communications
DSMB	Data and Safety Monitoring Board
DTC	Direct-To-Consumer
DTCA	Direct-To-Consumer Advertising
EHR	Electronic Health Records
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
GAO	Government Accountability Office
GMP	Good Manufacturing Practice
IRB	Institutional Review Board
JAMA	Journal of the American Medical Association
NDA	New Drug Application
NEJM	New England Journal of Medicine
NSAIDs	Nonsteroidal anti-inflammatory drugs
ODS	Office of Drug Safety (now OSE)
OMB	Office of Management and Budget
OND	Office of New Drugs
OSE	Office of Surveillance and Epidemiology
OTC	Over-the-counter (not prescription)
PDUFA	Prescription Drug User Fee Act
PhRMA	Pharmaceutical Research and Manufacturers of America
REMS	Risk Evaluation and Mitigation Strategies
ROI	Return On Investment
SD	System Dynamics
STAMP	Systems-Theoretic Accident Modeling and Processes
VA	Veterans Affairs
VIGOR	Vioxx Gastrointestinal Outcomes Research

Appendix F – Component System Dynamics Models

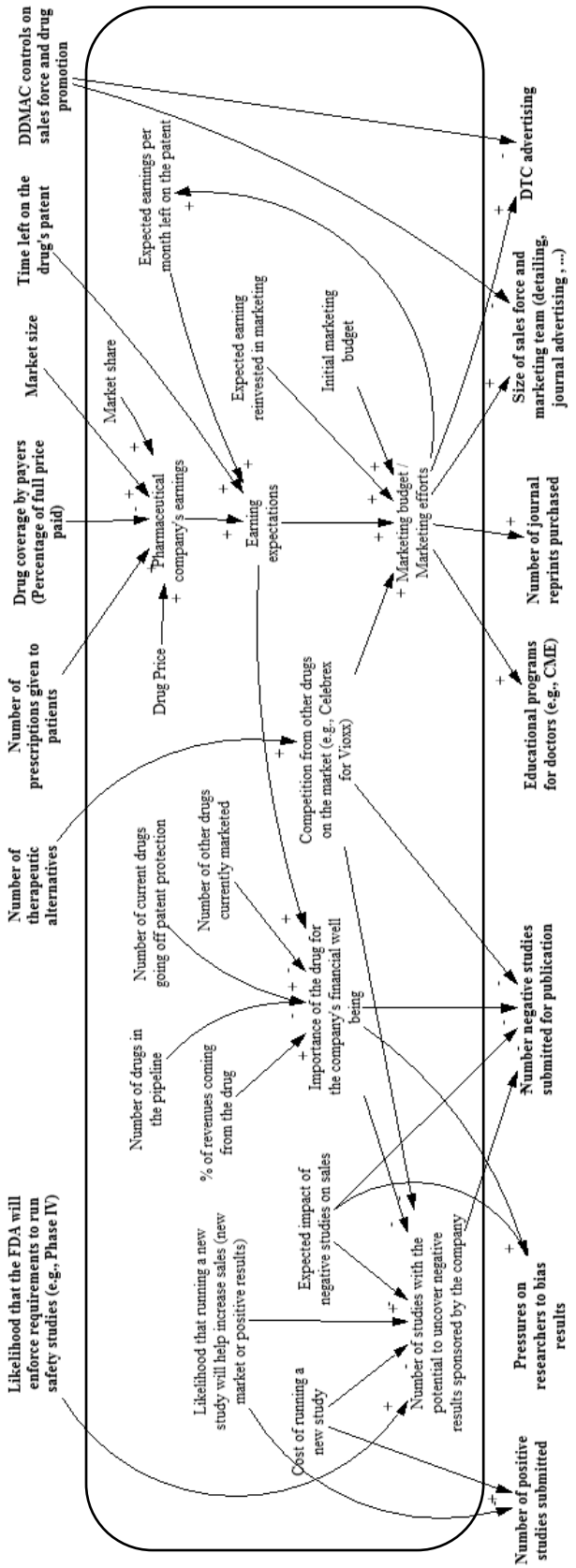
Patients

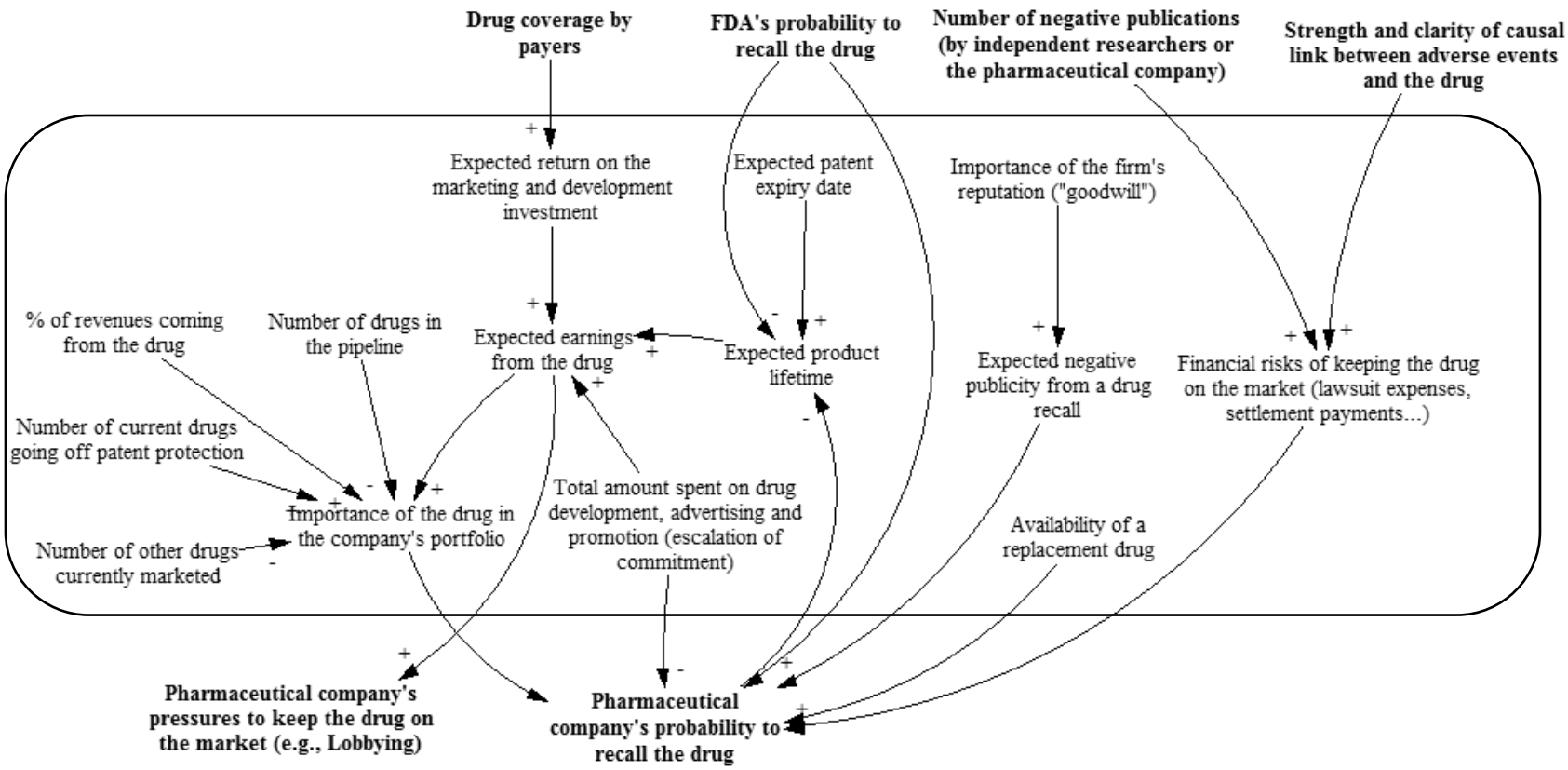


Physicians

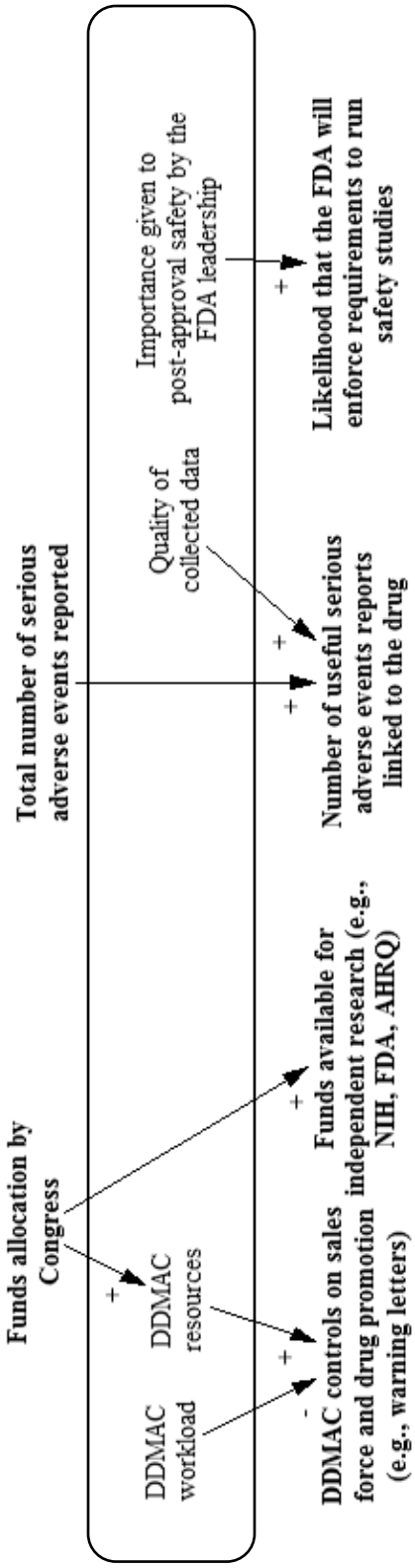

Strength and clarity of causal link between adverse events and the drug
Delay before first adverse event
Doctor's reporting rate
Total number of serious adverse events reported
Number of patients unhappy with their treatment
Number of patients happy with their treatment
Likelihood that a patient will go to another doctor if the drug is not prescribed
Number of patient drug requests
Number of negative studies published
Other information sources, including patients' feedback, word of mouth, FDA label changes and the Internet
Information about risks
Number of favorable studies published
Size of sales force and marketing team (detailing, journal advertising and samples)
Information about benefits
Doctors have limited time to spend evaluating the risks/benefits of a drug
Doctor's likelihood to prescribe the drug
Number of prescriptions given to patients
Education programs for doctors (e.g., CME)

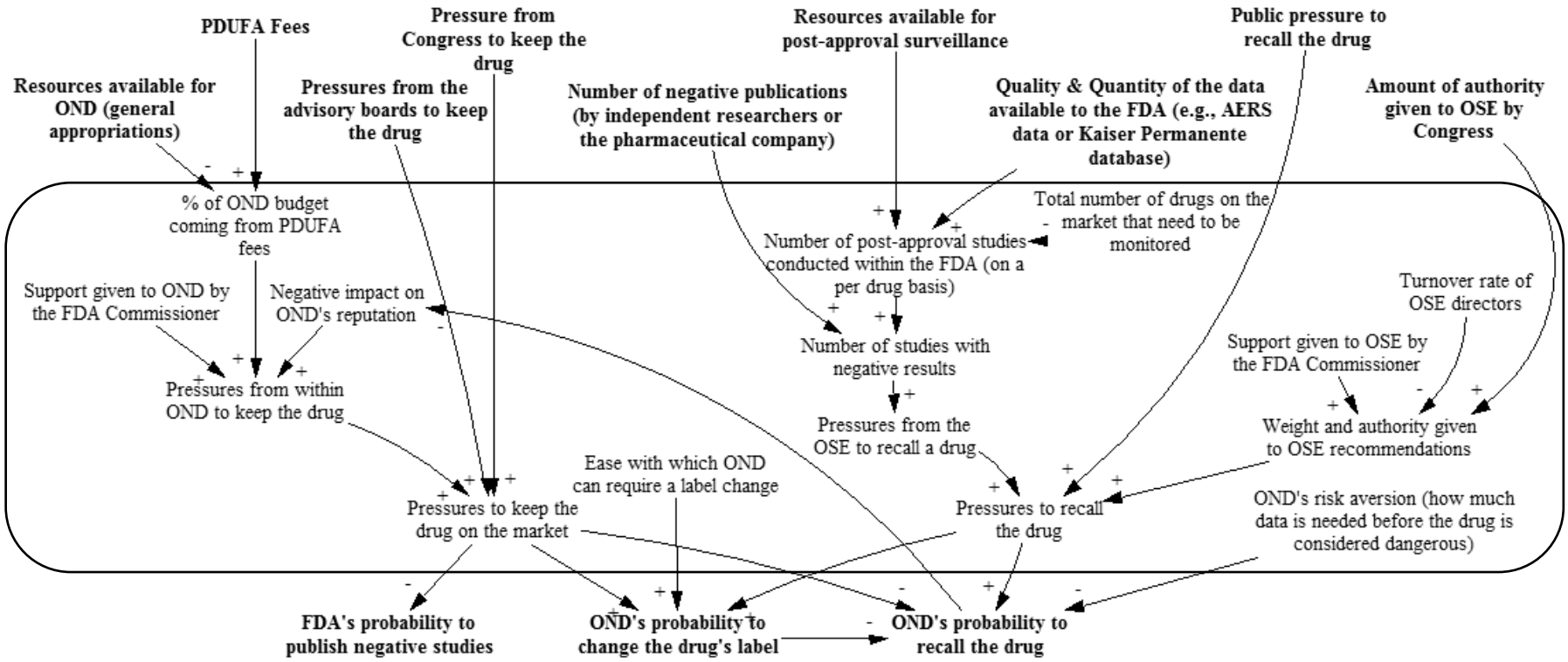
Merck – 2 models



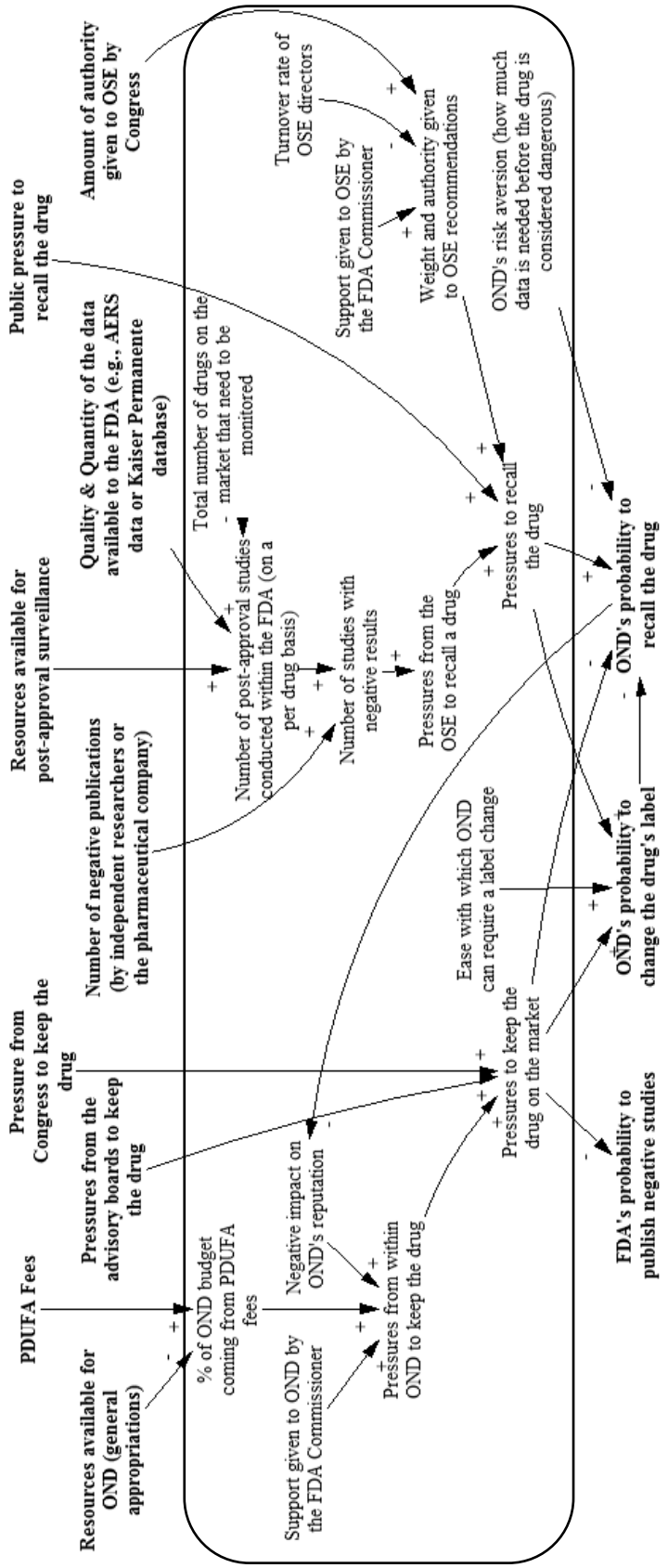

Drug coverage by payers
FDA's probability to recall the drug
Number of negative publications (by independent researchers or the pharmaceutical company)
Strength and clarity of causal link between adverse events and the drug
Expected return on the marketing and development investment
Expected patent expiry date
Importance of the firm's reputation ("goodwill")
% of revenues coming from the drug
Number of drugs in the pipeline
Expected earnings from the drug
Expected product lifetime
Expected negative publicity from a drug recall
Financial risks of keeping the drug on the market (lawsuit expenses, settlement payments...)
Number of current drugs going off patent protection
Importance of the drug in the company's portfolio
Total amount spent on drug development, advertising and promotion (escalation of commitment)
Number of other drugs currently marketed
Availability of a replacement drug
Pharmaceutical company's pressures to keep the drug on the market (e.g., Lobbying)
Pharmaceutical company's probability to recall the drug

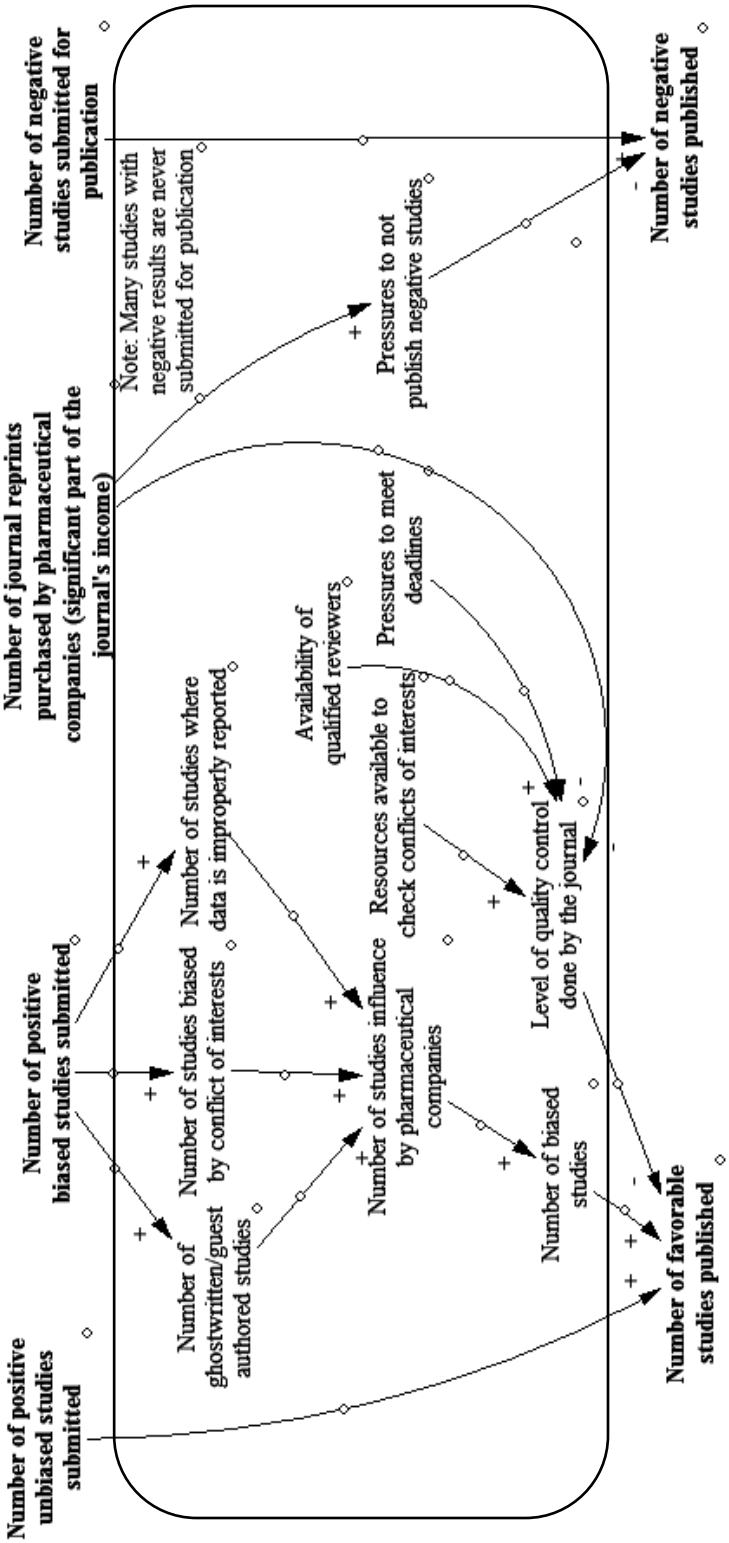
FDA/CDER – 2 models



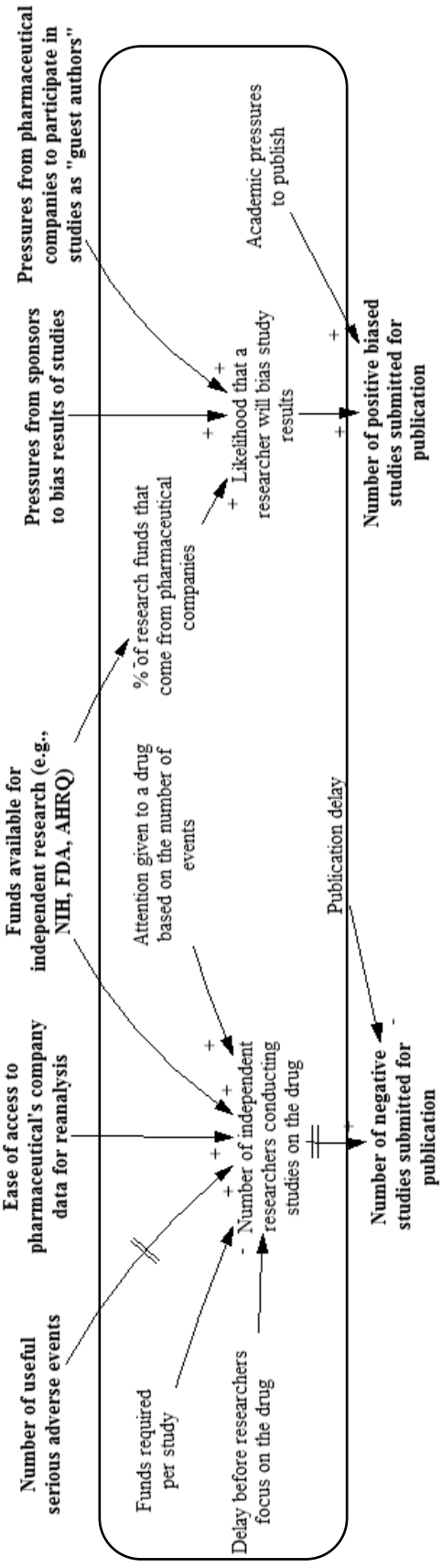

PDUFA Fees
Pressure from Congress to keep the drug
Resources available for post-approval surveillance
Public pressure to recall the drug
Resources available for OND (general appropriations)
Pressures from the advisory boards to keep the drug
Number of negative publications (by independent researchers or the pharmaceutical company)
Quality & Quantity of the data available to the FDA (e.g., AERS data or Kaiser Permanente database)
Amount of authority given to OSE by Congress
% of OND budget coming from PDUFA fees
Total number of drugs on the market that need to be monitored
Number of post-approval studies conducted within the FDA (on a per drug basis)
Support given to OND by the FDA Commissioner
Negative impact on OND's reputation
Turnover rate of OSE directors
Number of studies with negative results
Support given to OSE by the FDA Commissioner
Pressures from within OND to keep the drug
Pressures from the OSE to recall a drug
Weight and authority given to OSE recommendations
Ease with which OND can require a label change
Pressures to keep the drug on the market
Pressures to recall the drug
OND's risk aversion (how much data is needed before the drug is considered dangerous)
FDA's probability to publish negative studies
OND's probability to change the drug's label
OND's probability to recall the drug

FDA Advisory Boards

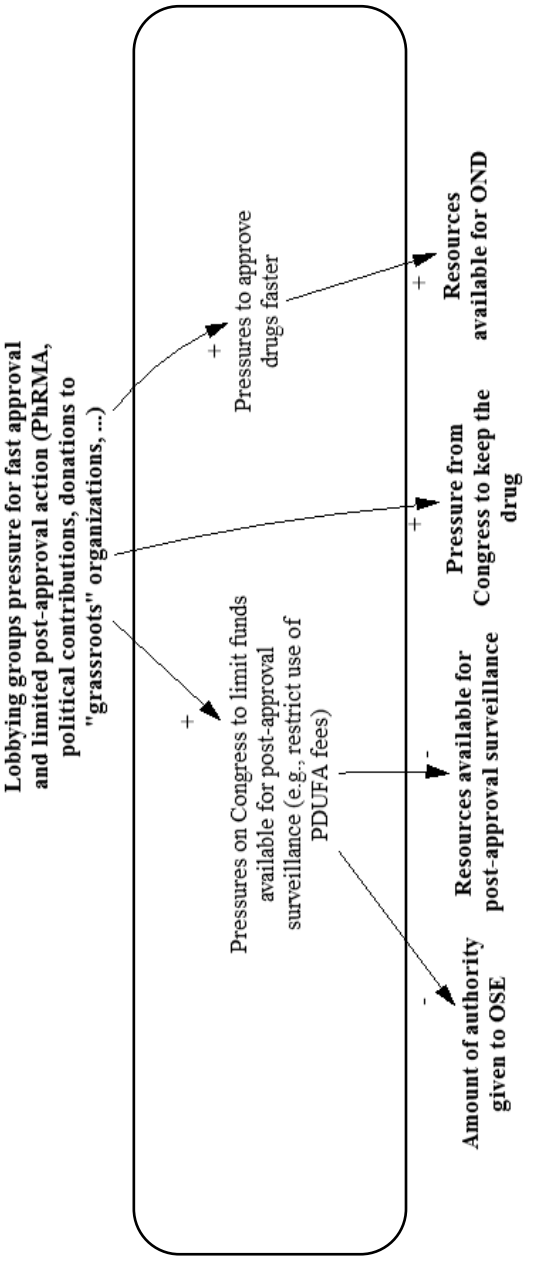



Number of positive unbiased studies submitted
Number of positive biased studies submitted
Number of journal reprints purchased by pharmaceutical companies (significant part of the journal's income)
Number of negative studies submitted for publication
Number of negative studies published
Number of favorable studies published
Number of ghostwritten/guest authored studies
Number of studies biased by conflict of interests
Number of studies where data is improperly reported
Number of studies influence by pharmaceutical companies
Number of biased studies
Availability of qualified reviewers
Resources available to check conflicts of interests
Pressures to meet deadlines
Level of quality control done by the journal
Pressures to not publish negative studies
Note: Many studies with negative results are never submitted for publication

Research Scientists/Centers



Congress


Lobbying groups pressure for fast approval and limited post-approval action (PhRMA, political contributions, donations to "grassroots" organizations, ...)
+
Pressures to approve drugs faster
+
Resources available for OND
+
Pressure from Congress to keep the drug
+
Pressures on Congress to limit funds available for post-approval surveillance (e.g., restrict use of PDUFA fees)
-
Resources available for post-approval surveillance
-
Amount of authority given to OSE

Appendix G – IOM Report recommendations

3.1: The committee recommends that the FD&C Act be amended to require that the FDA Commissioner currently appointed by the President with the advice and consent of the Senate also be appointed for a 6-year term of office. The Commissioner should be an individual with appropriate expertise to head a science-based agency, demonstrated capacity to lead and inspire, and a proven commitment to public health, scientific integrity, transparency, and communication. The President may remove the Commissioner from office only for reasons of inefficiency, neglect of duty, or malfeasance in office.

3.2: The committee recommends that an external Management Advisory Board be appointed by the Secretary of HHS to advise the FDA commissioner in shepherding CDER (and the agency as a whole) to implement and sustain the changes necessary to transform the center's culture—by improving morale and retention of professional staff, strengthening transparency, restoring credibility, and creating a culture of safety based upon a lifecycle approach to risk-benefit.

3.3: The committee recommends the Secretary of HHS direct the FDA commissioner and Director of CDER, with the assistance of the Management Advisory Board, to develop a comprehensive strategy for sustained cultural change that positions the agency to fulfill its mission, including protecting the health of the public.

3.4: The committee recommends that CDER appoint an OSE staff member to each New Drug Application review team and assign joint authority to OND and OSE for postapproval regulatory actions related to safety.

3.5: To restore appropriate balance between the FDA's dual goals of speeding access to innovative drugs and ensuring drug safety over the product's lifecycle, the committee recommends that Congress should introduce specific safety-related performance goals in the Prescription Drug User Fee Act IV in 2007.

4.1: The committee recommends that in order to improve the generation of new safety signals and hypotheses, CDER (a) conduct a systematic, scientific review of the AERS system, (b) identify and implement changes in key factors that could lead to a more efficient system, and (c) systematically implement statistical-surveillance methods on a regular and routine basis for the automated generation of new safety signals.

4.2: The committee recommends that in order to facilitate the formulation and testing of drug safety hypotheses, CDER (a) increase their intramural and extramural programs that access and study data from large automated healthcare databases and (b) include in these programs studies on drug utilization patterns and background incidence rates for adverse events of interest, and (c) develop and implement active surveillance of specific drugs and diseases as needed in a variety of settings.

4.3: The committee recommends that the Secretary of HHS, working with the Secretaries of Veterans Affairs and Defense, develop a public-private partnership with drug sponsors, public

and private insurers, for-profit and not-for-profit health care provider organizations, consumer groups, and large pharmaceutical companies to prioritize, plan, and organize funding for confirmatory drug safety and efficacy studies of public health importance. Congress should capitalize the public share of this partnership.

4.4: The committee recommends that CDER assure the performance of timely and scientifically-valid evaluations (whether done internally or by industry sponsors) of Risk Minimization Action Plans (RiskMAPs).

4.5: The committee recommends that CDER develop and continually improve a systematic approach to risk-benefit analysis for use throughout the FDA in the preapproval and postapproval settings.

4.6: The committee recommends that CDER build internal epidemiologic and informatics capacity in order to improve the postmarket assessment of drugs.

4.7: The committee recommends that the Commissioner of FDA demonstrate commitment to building the Agency's scientific research capacity by:

a. Appointing a Chief Scientist in the office of the Commissioner with responsibility for overseeing, coordinating, and ensuring the quality and regulatory focus of the agency's intramural research programs.
b. Designating the FDA's Science Board as the extramural advisory committee to the Chief Scientist.
c. Including research capacity in the Agency's mission statement.
d. Applying resources to support intramural research approved by the Chief Scientist.
e. Ensuring that adequate funding to support the intramural research program is requested in the Agency's annual budget request to Congress.

4.8: The committee recommends that FDA have its advisory committees review all NMEs either prior to approval or soon after approval to advise in the process of ensuring drug safety and efficacy or managing drug risks.

4.9: The committee recommends that all FDA drug product advisory committees, and any other peer-review effort such as mentioned above for CDER-reviewed product safety, include a pharmacoepidemiologist or an individual with comparable public health expertise in studying the safety of medical products.

4.10: The committee recommends FDA establish a requirement that a substantial majority of the members of each advisory committee be free of significant financial involvement with companies whose interests may be affected by the committee's deliberations.

4.11: To ensure that trial registration is mandatory, systematic, standardized, and complete, and that the registration site is able to accommodate the reporting of trial results, the committee recommends that Congress require industry sponsors to register in a timely manner at clinicaltrials.gov, at a minimum, all Phase 2 through 4 clinical trials, wherever they may have

been conducted, if data from the trials are intended to be submitted to the FDA as part of an NDA, sNDA, or to fulfill a postmarket commitment. The committee further recommends that this requirement include the posting of a structured field summary of the efficacy and safety results of the studies.

4.12: The committee recommends that FDA post all NDA review packages on the agency's Web site.

4:13: The committee recommends that the CDER review teams regularly and systematically analyze all postmarket study results and make public their assessment of the significance of the results with regard to the integration of risk and benefit information.

5.1: The committee recommends that Congress ensure that the Food and Drug Administration has the ability to require such postmarketing risk assessment and risk management programs as are needed to monitor and ensure safe use of drug products. These conditions may be imposed both before and after approval of a new drug, new indication, or new dosage, as well as after identification of new contraindications or patterns of adverse events. The limitations imposed should match the specific safety concerns and benefits presented by the drug product. The risk assessment and risk management program may include:

1. Distribution conditioned on compliance with agency-initiated changes in drug labels.
2. Distribution conditioned on specific warnings to be incorporated into all promotional materials (including broadcast direct-to-consumer [DTC] advertising).
3. Distribution conditioned on a moratorium on DTC advertising.
4. Distribution restricted to certain facilities, pharmacists, or physicians with special training or experience.
5. Distribution conditioned on the performance of specified medical procedures.
6. Distribution conditioned on the performance of specified additional clinical trials or other studies.
7. Distribution conditioned on the maintenance of an active adverse event surveillance system.

5.2: The committee recommends that Congress provide oversight and enact any needed legislation to ensure compliance by both the Food and Drug Administration and drug sponsors with the provisions listed above. FDA needs increased enforcement authority and better enforcement tools directed at drug sponsors, which should include fines, injunctions, and withdrawal of drug approval.

5.3: The committee recommends that Congress amend the Food, Drug and Cosmetic Act to require that product labels carry a special symbol such as the black triangle used in the UK or an equivalent symbol for new drugs, new combinations of active substances, and new systems of delivery of existing drugs. The Food and Drug Administration should restrict direct-to-consumer advertising during the period of time the special symbol is in effect.

5.4: The committee recommends that FDA evaluate all new data on new molecular entities no later than 5 years after approval. Sponsors will submit a report of accumulated data relevant to

drug safety and efficacy, including any additional data published in a peer-reviewed journal, and will report on the status of any applicable conditions imposed on the distribution of the drug called for at or after the time of approval.

6.1: The committee recommends that Congress enact legislation establishing a new FDA advisory committee on communication with patients and consumers. The committee would be composed of members who represent consumer and patient perspectives and organizations. The advisory committee would advise CDER and other centers on communication issues related to efficacy, safety, and use during the lifecycle of drugs and other medical products, and it would support the centers in their mission to "help the public get the accurate, science-based information they need to use medicines and foods to improve their health."

6.2: The committee recommends that the new Office of Drug Safety Policy and Communication should develop a cohesive risk communication plan that includes, at a minimum, a review of all center risk communication activities, evaluation and revision of communication tools for clarity and consistency, and priority-setting to ensure efficient use of resources.

7.1: To support improvements in drug safety and efficacy activities over a product's lifecycle, the committee recommends that the Administration should request and Congress should approve substantially increased resources in both funds and personnel for the Food and Drug Administration.

Appendix H – FDA's response to the IOM Report

A. STRENGTHENING THE SCIENCE THAT SUPPORTS OUR MEDICAL PRODUCT SAFETY SYSTEM

1. Upgrading methods of benefit and risk analysis and risk management
• Developing and incorporating new quantitative tools in the assessment of benefit and risk
• Developing and validating risk management and risk communication tools
• Conducting a pilot program beginning in 2007 for routine new molecular entity postmarketing evaluations to assess their utility

2. Strengthening methods and tools of safety surveillance
• Maximizing the public health benefit of adverse event information (AE) collection throughout the product life cycle
• Upgrading AERS II
• Expanding safety database resources
• Proposing a Sentinel Network
• Developing and issuing guidance on epidemiology best practices

3. Developing new scientific approaches to detecting, understanding, predicting, and preventing adverse events
• Developing and qualifying techniques for predictive toxicology
• Identifying cardiovascular risk of drugs
• Preventing drug-induced liver injury
• Using pharmacogenomic information to guide safer and more effective use of drugs
• Using new scientific tools to enhance blood safety
• Enhancing the long-term safety of gene therapy
• Improving the science of drug development by providing guidance for industry

B. IMPROVING COMMUNICATION AND INFORMATION FLOWS

1. Conducting a comprehensive review of current public communication tools
2. Establishing an Advisory Committee on communication
3. Using fees to fund improvements in communication among staff on safety issues
4. Issuing drug safety information guidance
5. Publishing a newsletter on postmarket findings
6. Posting reviews of NDA supplements and assessments of postmarket safety studies

C. IMPROVING OPERATIONS AND MANAGEMENT TO STRENGTHEN THE DRUG SAFETY SYSTEM

1. Engaging external management consultants to help CDER/FDA develop a comprehensive strategy for improving CDER/FDA's organizational culture

2. Making specific organizational and management changes to increase communications among review and safety staff
• Process improvement teams have recommended specific organizational changes
• Involving OSE personnel in new drug reviews
• Creating procedures to improve the decision-making processes related to postmarketing drug safety
• Creating an electronic postmarket drug safety tracking system
• Applying a quality systems approach to improve drug adverse event detection

3. Improving our use of Advisory Committees
• Creating a standard operating procedure for presenting postmarket safety issues to an Advisory Committee or other body
• Increase epidemiology expertise in Advisory Committee meetings
• Strengthening FDA Advisory Committee management

Appendix I – Analysis of the FDA proposed changes

Table. Summary of Institute of Medicine (IOM) Recommendations and US Food and Drug Administration (FDA) Responses*

IOM No.	*FDA Response*	*How it changes the context*	*Effects on the system*
3.2	FDA is engaging external management consultants and proposed the creation of the Office of Chief Medical Officer.	None	Effects depend on recommendations from consultants and how well they are followed.
3.4	FDA is initiating pilot projects to evaluate various models of Office of Surveillance and Epidemiology involvement	None	Again, depends on the results of the pilot project and how the resulting recommendations will be implemented.
3.5	FDA lists a number of activities but no safety-related performance goals	Conditional on Congress approval.	This is dependent on Congress approving the changes in PDUFA IV.
4.1	FDA plans a number of activities, including an upgrade of the AERS system (and the development of Sentinel)	Conditional on Congress approval.	This is dependent on Congress approving the changes in PDUFA IV.
4.2	FDA would use PDUFA funds to obtain access to new databases	Conditional on Congress approval.	This is dependent on Congress approving the changes in PDUFA IV.
	Work with AHRQ to get access to more data	FDA.Context.18: Increases the number of sources available to OSE for monitoring.	Positive effect since it would provide the FDA with new sources of data.
4.3	FDA announces memorandum of understanding with the Veterans Health Administration to allow sharing of some data.	FDA.Context.18: Increases the number of sources available to OSE for monitoring.	Positive effect since it would provide the FDA with new sources of data.
4.4	FDA plans to identify tools, develop evaluation plans, and do 1 or 2 evaluations	Patient.Context.1: Increase the quality of the information available to patients.	Positive effects if it means an improvement to the Risk Maps, better risk communication, and lower compliance costs for the pharmaceutical companies.
4.5	FDA held workshop, created Quantitative Safety and Pharmacoepidemiology Group	Limited effects	Positive if it can help standardize and the post-approval safety process. However does not deal with the fact that OSE still has no power in drug recalls.
4.6	See responses to 3.5 and 4.2	Conditional on Congress approval	--
4.7	FDA commissioner requested FDA Science Board undertake a formal review	None	Depends on the results of the formal review.
4.8	FDA plans pilot for review of new molecular entities	None	Positive if it can help the FDA improve the process. Again, depends on the results of the pilots study and how those results are used.

4.9	FDA will do so when safety is important	FDA Advisory Board.Context.1: Should help balance pro-pharmaceutical representatives on the committees	Positive if done often enough and the experts are not biased.
4.10	No commitment to limit conflict, but plans for 3 new guidance documents	FDA Advisory Board.Context.1: Stricter waiver policy will limit bias of committees.	Overall positive but will depend on the quality of the guidelines and how well they will be enforced.
4.12	Not accepted	None	None
4.13	Public disclosure of assessments of safety studies decided on case-by-case basis	Patient.Context.1: Increase the quantity of the information available to patients.	Positive but depends on how many cases are released.
5.4	CDER is conducting a pilot study of review of new molecular entities	See 4.8	See 4.8
6.1	FDA established a new advisory committee to improve agency's communication policies	Patient.Context.1: Improves communication of information to patients. Physicians.Context.3: Same for doctors.	Positive since it will help communication with patients and doctors.
6.2	Several activities under way or planned	Patient.Context.1: Improves communication of information to patients. Physicians.Context.3: Same for doctors.	Positive since it will help communication with patients and doctors.

Adapted from (Psaty & Charo, 2007)

Appendix J – Analysis of the FDAAA proposed changes

Table. IOM Committee Recommendations and the FDA Amendments Act			
No.	*FDA Amendments Act of 2007*	*How it changes the context*	*Effects on the system*
3.1	Not addressed	---	---
3.2		---	---
3.3		---	---
3.4	Does not give joint authority to OND and OSE; requires consultation with both OND and OSE in REMS; requires a report on the implementation of joint OND-OSE efforts in REMS	---	No effect, since OSE still does not have control over recall and OND still has the final say in drug recall.
3.5	Requires chief scientist to develop rigorous safety performance measures (see 4.7)	Depends on the implementation	Possible positive effects, depending on the actual implementation
4.1	Requires regular review and quarterly posting of new adverse event information; for new molecular entities, summary at 18 months or 10 000 users	FDA.Context.17: Should lead to a more thorough and regular analysis of the AERS data (if data quality is improved).	No effect since the quality of the AERS data is not improved
4.2	Implements active postmarketing risk identification plans to include large cohort with electronic medical records and complementary approaches as needed	FDA.Context.18: Increases the number of sources available to OSE for monitoring	Positive effect since it will provide new sources of information (hopefully more reliable than AERS) for OSE. This might however be of limited use if OSE does not have the staff and resources to analyze the databases. Finally, OSE does not have the authority to act on its finding which might further limit the benefits of this change.
4.3	Establishes Reagan-Udall Institute to accelerate innovation in drug development, but no mandate to plan, design, or fund large safety and efficacy studies	Physicians.Context.3: Will increase physicians access to unbiased information.	Positive effect if it helps fund independent analysis of drugs (balances studies published by the pharmaceutical company). Effects can be mitigated by advertising and attacks from the pharmaceutical companies (e.g.. Allhat)

			Positive effects in enforcing long term follow-up of safety. However this is an increased burden on the pharmaceutical company and positive effects can be mitigated if it becomes extra paperwork without any real follow through from the FDA. Again, requires a lot of resources on the side of the FDA to evaluate systematically the REMS plans
4.4	Establishes requirement for evaluating REMS at 18 months, 3 years, and 7 years	Not discussed in our analysis	
4.5	Requires collaborations for advanced analyses of drug safety issues, including risk-benefit assessments	FDA.Context.10: By establishing clear risk-benefit assessment standards, the FDA can establish a clear metric used for drug recalls.	Positive effects if it helps clarify the post-approval safety monitoring process and can help the pharmaceutical companies better monitor the drugs
4.6	See 4.2	See 4.2	See 4.2
4.7	Creates the office of chief scientist, who will develop and advocate for a budget	FDA.Context.1: Helps establish a clear leadership for the FDA, especially with regards to post-approval safety	Positive effect if it helps bring leadership to the FDA and especially OSE. Effect can be mitigated if nobody is appointed or there is a high turnover
4.8	Requires that all new molecular entities be referred to an advisory committee or provide explanation why not in action letter	Not discussed in our analysis	Positive effect if it helps provide an external control. However, effects can be mitigated if conflict of interest rules are not enforced for those committees
4.10	Requires gradual reduction in permitted waivers over 5 years (for 2008, reduction to 95% of 2007 waivers; for 2012, reduction to 75% of 2007 waivers)	FDA Advisory Boards.Context.1: Helps lower the number of potentially biased members on the committees	Positive effect since it should help make the advisory committees more neutral. However, this assumes that the FDA can find enough experts who do not require waivers to sit on

			the committees. Need to make sure that the incentives for the experts to sit on the boards exist
4.11	Expands clinical trial registration to include all phase 2-4 studies and requires the development of database to house clinical trial results	FDA.Context.8b: Allows the FDA to keep track of ongoing trials FDA.Context.16: Helps enforce Post-Marketing requirements FDA.Context.18: Provides a new source of information for the FDA	Positive effect since it will help in enforcing Phase IV studies and provide more data for the clinical research. It will depend however on how well populated the databases are, who has access to the data (FDA only or also open to independent researchers) and whether the FDA has the resources to analyze this data
4.12	Requires FDA to post summary new molecular entity (NME) review within 48 hours and full action package within 30 days of approval; for non-NMEs, within 30 days of third request	---	---
4.13	See 4.12		
5.1	Provides FDA with new legal authorities to require postmarketing studies, label changes, or restrictions on distribution or use of new drug through REMS	FDA.Context.9: Allows the FDA to require label changes FDA.Context.16: Allows the FDA to require post-marketing studies	Positive change if the FDA enforces its new authority. Again, can be balanced by pressures on the FDA or by tensions within OND but it does offer a wide range of options and therefore can help avoid the loss-of-face issue has was in the case of a recall
5.2	Provides for civil penalties for failure to comply with study requirements, label changes, or restrictions	Not discussed in our analysis	Positive changes if the civil penalties are enough to make the companies comply
5.3	Provides authority to require review of direct-to-consumer television ads; consider use of unique symbol and date of approval as communication tools	Patients.Context.1: Allows for a better control of the DTC advertisements shown to patients	Positive changes if enforced. Effectiveness will depend on resources allocated to DDMAC to actually review all

			the television ads
5.4	Requires evaluation only for drugs with REMS (see 4.4)	See 4.4	See 4.4
6.1	Creation of new advisory committee on risk communication	Not discussed in our analysis	Positive change if the committee if the FDA follows the recommendations of committee (assuming it has not been captured by a specific interest group)
6.2	Requires implementation of Web site to improve transparency and communication; requires partnering with professional groups to develop system for communicating about emerging risks	Physicians.Context.2&3: Increases rapid dissemination of information to physicians	Positive change if it means that the doctors are faster informed about newly discovered drug risks
7.1	Increases user fee target; directs some user fees, about 10% to safety; provides for $25 million per year to develop active surveillance system	FDA.Context.4: Increases the resources in personnel and budget available to the FDA, especially for OSE	This can foster positive change since it provides new resources to the FDA, especially much needed resources for the safety and surveillance. However, as often with user fees, it puts the agency in a position where it is dependent on the industry it is suppose to regulate

Adapted from (Psaty & Korn, 2007)

Appendix K – Analysis leading to the recommendations

Controller	Inadequate Control action	Process model	Context	#	Recommendations
Patients	Some patients pressured their doctors into prescribing Vioxx	Patients believed that the drug was safer than it really was	Vioxx was approved by the FDA	1	The FDA needs to improve the way information about newly marketed drugs is communicated to patients
			Patients had limited information sources about the safety and effectiveness of Vioxx (mostly DTCA)	2	The FDA needs to ensure that DTCAs are accurate and provide balanced information
			Patients have limited medical knowledge about both their disease and the medication they are taking	3	The FDA should ensure that patients have access to the information they need to understand their disease and treatment. The FDA should actively focus on patient education. Web based resources are starting to help fill this gap
		Patients believe that newer, more expensive drugs are better than older alternative treatments		4	The FDA should run comparative studies between new and old treatments and adequately propagate the results
Physicians	Physicians had an inaccurate mental model of the risk/benefits of the drug	Belief that new drugs are better than existing treatments	Studies of new drugs are typically done against placebos	5	The FDA should require pharmaceutical companies to test new drugs not only against placebos but also against existing treatments, using comparable dosages
		Physicians did not understand the risk/benefit tradeoffs of Vioxx	Doctors have limited access to unbiased information	6	The FDA should provide targeted information to the doctors based on the population they treat or the prescriptions they make. This kind of information is already used by the

					pharmaceutical companies when marketing new drugs and could be used by the FDA to help inform doctors
			Doctors are notoriously busy and their time is limited		
			Insurers paid for Vioxx, providing a tacit endorsement		
		Belief that information from pharmaceutical companies is accurate	Doctors learn about new products mostly through drug companies' representatives	7	Doctors should be required to pay for their own Continuing Medical Education programs to ensure that the content of the presentation is neutral and not biased in favor of the pharmaceutical companies who typically sponsor such events
	Physicians prescribed the drug for populations outside the indicated label	Doctors believed that patients might go somewhere else if Vioxx was not prescribed	Doctors are part of the service industry and do not want to alienate their patients.		
Merck	Merck published and disseminated misleading information about the safety profile of Vioxx	Merck could convince doctors to prescribe the drug despite the potential CV risks	Most clinical research on drugs sponsored by companies that make them		
			Drug companies have no incentive to do Phase IV safety testing	8	The FDA needs to have the authority to enforce Phase IV studies. Need to include fines or other means of pressure (e.g. delay approval of other drugs) if the pharmaceutical companies do not comply
		Merck had to aggressively promote the	Merck was facing fierce competition		

		drug to be competitive with Celebrex	from a rival drug, Celebrex		
			The drug pipeline was dwindling, older drugs were going off patent protection		
	Some of the studies did not have an active (DSMB)	Could not allow negative study results to impact sales	Vioxx was extremely profitable and a major source of Merck's revenue	9	Pharmaceutical companies need to have a portfolio approach to drug development so that the failure or recall of one drug does not significantly impact the firm
	Merck did not run the studies that might have found negative CV results		Merck has a fiduciary duty to shareholders		
	Merck's studies were inappropriate to help evaluate the risk/benefit profile of the drug	Vioxx did not cause any CV events, the competitor's drugs protected the patients' hearts	Primary results could be interpreted as a protective action from naproxen	10	Pharmaceutical companies need to protect their researchers from the influence of management to ensure that the conclusions of preliminary research are unbiased and that adequate skepticism and critical thinking are maintained during the research and development phases -- Internal studies need to be unbiased so that management can have the best information available when making decisions
		Negative results in studies would negatively impact the firm's reputation	Merck had a reputation to maintain	11	Pharmaceutical companies need to create a culture where the publication of a negative study is seen as a strength for the company. By being open about negative results and publishing them early companies can help restore their standing with the general

				pubic and establish once again a reputation as ethical firms
FDA - General	Allowed waivers of conflict of interest rules for advisory panel members	Lack of strong leadership at the head of the FDA, high turnover and unfilled positions	12	The president should appoint a strong leaders at the head of the FDA who in turn would appoint capable people at the head of CDER, OND and OSE
		It is hard to find experts who do not have ties with pharmaceutical companies	13	The FDA needs to enforce waiver rules in advisory committees
			14	The FDA should make it rewarding financially, professionally or academically to be selected for a FDA committee
	Pressured an FDA employee to change conclusions on a study of Vioxx and prevented publication of the results	Political and congressional pressures		See recommendation 12
		Tensions between the Office of New Drugs (OND) and the Office of Surveillance and Epidemiology (OSE)	15	Congress needs to ensure that funds are properly allocated between OND and OSE and that OND is not significantly larger than OSE
			16	The FDA needs to establish a neutral committee to help deal with issues between OND and OSE
			17	Congress needs to give OSE the authority to recall drugs
FDA - OND	Did not check whether clinical trial safety requirements were being enforced	Limited resources in personnel and budget	18	Congress needs to increase allocation to the FDA
		Lack of strong leadership at the head of the FDA, high turnover and unfilled positions		See recommendation 12
	Gave expedited review and approval but Vioxx did not			
		PDUFA leads to pressure to reduce approval time	19	Congress needs to replace PDUFA by

	meet the criteria for expedited review			allocations
	Approved Vioxx without requiring a Phase IV study even though the long term risks were unclear		20	Congress needs to relax the requirements attached to PDUFA so that the FDA is not under a timeline pressure to approve drugs
		For pre-market review, the FDA only has information provided by company		
	Delayed the recall of Vioxx. Did not act fast or effectively enough	A very high certainty that the drug is dangerous is required before it is recalled	21	The FDA needs to lower its standard for drug recalls - they should not require the same levels of confidence as the approval of drugs
		PDUFA fees represent more than 50% of OND budget		See recommendations 19 and 20
	Did not update the Vioxx label in a timely fashion	The people who approve a drug are also the people in charge of recalling it.		See recommendation 17
		Legislation makes it difficult for the FDA to require label changes	22	Congress needs to give the FDA the authority to change the label on a drug without requiring the approval of the drug manufacturer
FDA -DDMAC	Original warning letter was not followed by subsequent warnings	Limited resources in personnel and budget	23	Congress should increase the allocations for DDMAC
FDA - OSE	Did not insist Merck launch a large-scale clinical trial when suspicions first arose	No legal authority to require additional safety studies after approval	24	OSE should have the authority to require new safety studies to be conducted, even once the drug has been approved
	Did not properly monitor the drug for long term risks	High turnover of ODS directors		See recommendation 12
		Adverse event reporting (AERS) limited	25	The FDA needs to develop a new reporting system based on existing EHR databases and continuously expand it to include new EHR databases as they

				are deployed
		Very limited sources of information about adverse events	26	OSE needs to have access to a larger dataset and for example should have access to databases maintained by private medical providers like Kaiser permanente and databases maintained by other government agencies like the VA
		The FDA is unable to keep track of ongoing clinical trials	27	The FDA needs to establish a database to track ongoing clinical trials and periodically check if the trials are still running. If a trial has been interrupted, the FDA should be made aware as to why and be given access to the intermediary results
	Was not able to require a recall of the drug	Limited resources in personnel and budget	28	Resources for OSE need to be increased either through Congress allocations or by allocating a larger share of the PDUFA fees to post-approval safety
		Does not have independent decision-making responsibility		See recommendation 17
FDA advisory committees	Some members did not reveal conflicts of interests	Many members have financial ties or close working relationships to interested companies		See recommendation 13
	Some members with conflicts did not recuse themselves			
	Recommendations from the committees were potentially influenced	Committee meetings often have patients and patient advocates providing testimony	29	FDA committees should not allow patients to testify since testimonies give a biased representation of the drug efficacy (typically only patients who benefit

				from the drug testify)
			30	The FDA needs to ensure that patients representing both sides of the issue testify in committee hearings
Payers / Insurers	Chose drugs not based on their effectiveness but because of marketing pressures	Public Insurance has to work with a tight budget		See recommendation 4
		Private insurers are public companies, with the goal of making a profit		
		Private insurance contracts are often negotiation by companies		
Scientific Journals	Do not require independent statistical analysis of the data	Hard to get well qualified reviewers		
	Created a journal of questionable legitimacy in Australia to publish Vioxx and Fosamax articles	Pressures to meet deadlines, limited ability to check for accuracy	31	Questionable journals should be investigated for marketing fraud
	Published ghostwritten articles about Vioxx	Pharmaceutical companies pay medical journals for article reprints		
	Did not require or did not check disclosure of financial interests of authors	It can be difficult for the journals to check that the authors have declared all their conflicts of interests	32	Medical journals should create and maintain a database where authors affiliations and conflict of interests are listed. This will help ensure consistency across journals and will make it easier for journals to keep track of sources of funding. This database can then be audited by an external board or patient advocacy groups for accuracy
			33	Medical journals should create and maintain a database where authors affiliations and conflict of interests are listed. This will

				help ensure consistency across journals and will make it easier for journals to keep track of sources of funding. This database can then be audited by an external board or patient advocacy groups for accuracy
Research Scientists	Few researchers focused on potential negative side effects of the drug	Limited amount of NIH funding. Most funding now comes from industry	34	Congress needs to increase NIH funding for post-approval safety research and for comparative studies
		Clinical trials data about drugs is often not released, or released with a long delay	35	Pharmaceutical companies need to release the results of trials to both the FDA and external researchers even when the results are negative
		Drug companies are often involved in details of studies	36	The FDA needs to set standards for clinical trials to be respected by both CROs and academic researchers to ensure that the subjects are adequately protected, in particular when dealing with multicenter studies
	Research results from studies sponsored by pharmaceutical companies are often biased	Competition from CROs led to research scientists to become more accommodating		
	Researchers signed off on ghostwritten studies; Did not divulge their financial ties	Bayh-Dole allowed financial gains from research		
		The research culture rewards people with more publications	37	Congress should establish civil penalties for researchers signing-off on ghostwritten studies
	Some researchers sitting on advisory committees had financial ties with Merck	Faculty researchers have lucrative arrangements with drug company sponsors		
				See recommendation 13
Congress	Congress did not pass regulation that could have prevented or helped mitigate the accident	Congress is lobbied by the pharmaceutical companies		
		Industry funds “grassroots” organizations to promote its interests in the media and put pressure on Congress		
		Industry provides large	38	Congress should set

	Congress underfunded the FDA, in particularly OSE	amounts of political contributions		a cap on the amount of political contributions allowed by the pharmaceutical companies
		Belief that the free market will provide adequate controls on safety		

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