Case study

Managing the risk aspects of the product development process at the Upjohn Company

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Abstract
Purpose – The aim of this paper is to describe an innovative practice that has implication for new product developers within and outside the pharmaceutical industry.
Design/methodology/approach – The case describes an approach to managing the risk inherent in marketing drugs. The organization’s original name has been retained, although individual managers’ names have been changed at its request. Interviews with former company employees and publicly available data were used to write the case study.
Findings – The paper provides information and action approaches to new product developers that may reduce the risk of losing products to regulatory action. The subject company devised a risk management response to its product development. Their results offer direct implications for new product development teams in the drug industry. By extension, the implications may aid traditional companies outside of the pharmaceutical industry.
Research limitations/implications – As in all case studies, the specific conditions found in one organization may not be found more generally in others. Readers are cautioned that the conclusions drawn in the case may have limited applicability.
Practical implications – The case depicts an innovative application of the risk minimization to the new product development process. Other organizations may find the technique of value in their own efforts.
Originality/value – The case is the first to describe a successful application of risk management to the product development/product management process. It offers the potential of improving the lifetime of pharmaceutical products in the marketplace, allowing the company a longer time to reap profits.

Keywords Product development, Risk analysis, Risk management, Pharmaceuticals industry

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Introduction
W.E. Upjohn, a physician practicing in the city of Kalamazoo, Michigan in the late 1800s, founded the Upjohn Company. The local population included a number of followers of the Seventh Day Adventist faith, whose beliefs discourage meat eating. As a result, there were significant health issues related to iron deficiency anemia. To remedy the situation, the physician started to compound “iron” pills to provide the important mineral to his patients who had to rely on vegetable sources. The pills were not Dr Upjohn’s primary focus and he assigned the “pill-rolling” operation to one of his brothers who implemented sound business practices and hired a sales force. Within several years, the operation spawned a number of competitors. One finding startled the brothers. Some iron pills on the market were so hard that a man wielding a hammer could pound them into a soft pine board. The pills passed through the body without being absorbed. It became a standard technique to arm salespeople with hammers, boards, and competitor’s pills and demonstrate their hardness. In contrast, the Upjohn Company’s pills could be crushed to a powder by a salesperson’s thumb. That demonstration vitalized the company’s devotion to purity and quality.

The regulatory environment
In many industries, the level of devotion to product quality would be sufficient to insure success. For example, the Federal Trade Commission and the Consumer Product Safety Commission regulate most products and their safety. These agencies have limited enforcement powers and in egregious cases of dangerous products can do little more than sue, warn the public and negotiate a product recall.
However, in drug industries worldwide, government regulation is often intense. In the USA, the Food and Drug Administration (FDA) is charged with protecting the population from dangerous or ineffective pharmaceuticals. Accordingly, it possesses extraordinary powers. Every day it seizes and destroys food and pharmaceutical products deemed ...
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defective. They may not be dangerous per se but if they do not meet FDA standards, they are in jeopardy. The cost of tainted, defective, or unsafe foods and drugs is enormous. While the producer bears the cost of the product seizure, ultimately the consumer pays.

To protect the welfare of the public, the FDA created a complex, highly monitored series of procedures to introduce a new pharmaceutical product into the US market. The process is a highly articulated series of stages and gates familiar to new product developers. Each stage requires a detailed, scientifically designed, and highly measured set of results. The overall process is a scientific experiment that measures the effectiveness, and side effects of a given product. The implications for public health are highly important. The implications for the pharmaceutical industry are staggering.

Dick Bost, Vice President for FDA Compliance, once stated that in a production process, the further along in the process a mistake occurs, the higher the cost. For example, if an iron ingot were damaged at the start of the process, the cost would be relatively minor; restricted to the cost of the ingot. In contrast, if the ingot were turned into a rough part, then machined into a finished part, installed into a complex machine and then failed, the cost would include all the manufacturing and assembly steps and would be much higher.

The idea he expressed was to increase the success of the drug development and testing process. If possible, he wanted to weed out product ideas as early as possible. Bost and other managers decided to hedge their bets as much as possible. To do so, they partnered with European firms to market in the US drugs successfully introduced into Europe. The US drug introduction process remained in place but the likelihood of an accepted drug making it through that process increased. Even if a drug passed through the process successful, the FDA might still order it withdrawn from the market after introduction.

Marketing other companies’ drugs had limited potential. As an example, Upjohn successfully introduced two generations of antidiabetes agents from Germany’s Hoechst Pharmaceutical into the US market. However, Hoechst decided to prepare to assume lucrative US marketing. Thus, Upjohn found itself competing with Hoechst in the third generation introduction. The situation forced Upjohn to look for strategic partners. It found one in Sweden’s Pharmacia. Pharmacia had a robust new product development (NPD) and introduction system and the marriage seemed blessed. The new entity, called Pharmacia and Upjohn, was controlled by Upjohn and despite differences in managerial culture; the flow of new products from Europe was attractive.

Recent changes

Recently the FDA imposed new requirements on pharmaceutical developers. They accelerated the rapidity with which drugs were withdrawn from the market. In the early 1970s, the FDA halted sales of about two to four drugs each year. Twenty years later the average annual withdrawal rate surged to ten drugs. Bost reacted swiftly. In order to minimize the risk of the loss of an expensively tested product, he formed an internal group dedicated to minimizing the risk of losing a product to regulation. The group, a task force, reviewed industry developments and internal policies. There were several strategic changes. Bost realized that this changed marketing and new product development’s role as well.

To accomplish a successful pharmaceutical introduction, NPD’s job was twofold. First it had to shepherd the product through the FDA new drug application process. That process followed a rigidly prescribed series of steps to prove a drug’s efficacy and safety. The process can be divided roughly into two parts: discovery and clinical trials. Discovery involves finding targets for the drug and optimizing its composition for the best effects. Clinical trials involve four phases, Phases I to IV. Phase IV represents the stage at which a drug is approved for sale and the research efforts aim at discovering negative and positive effects of its use.

As a result, new drug applicants started with a series of tests on animal subjects to gauge safety and toxicity. In the classic stage-gate process, serious problems uncovered using lower animals like rats and rabbits would stop further development. If no problems were encountered, the tests would proceed up the evolutionary chain to other mammals. The detailed studies often took years and involved double blind studies in which some subjects received the drug and others received a placebo. At the end of the process, scientists knew much about how the drug affects the body, which organs were affected, and whether the drug actually worked. If results merited further testing, human volunteers were included. The road from rats to humans consumed enormous amounts of time and resources. If the drug made it to market, the NPD team would be involved in post introduction surveillance to insure that physicians used the drug safely.

The second task the NPD team faced was determining the drug’s indications and contraindications. Simply put, an indication is the condition or disease entity for which the product should be used. In contrast, contraindications are warning of situations in which the drug should not be used. If, for example, long-term use of a drug can damage a person’s liver, underlying liver disease is a contraindication and those with the condition should use the drug.

If the NPD team performed either scientific task less than perfectly, the company could suffer costly problems. Even if their job was done flawlessly, success also depended on marketing. Previously, marketing’s job was to achieve peak sales as soon as possible. Companies stressed the need to recover product development investments as quickly as possible. Often the funds were needed to help start the next development cycle. As a result, marketing’s focus was early and widespread adoption. It is still an important consideration. However, companies have come to realize that the long-term financial benefits of keeping the drug on the market throughout its lifecycle. In most countries, pharmaceutical firms face a limited period of patent protection until their products become generic. Any competitor can market generic products. While expiration of a patent does not force a company to exit the market, it usually signals a decline in sales.

Consequently, the marketing team must focus on both early and long-term sales. It is important to insure that a promising drug is not withdrawn from the market for safety reasons. The development team has done its job and marketers must avoid missteps that prematurely end a product’s lifetime. Thus, marketers must focus on risk management.

In fact, the Upjohn Company has always been sensitive to promoting its products in the most careful way. Within the company, lawyers play a powerful role. Compliance with all
the FDA regulations is recognized as vital to organizational existence. The industry recognizes that pharmaceuticals are highly complex products used in an equally complex environment. Unforeseen factors come into play frequently and must be managed. As an example, the company produced a tranquilizer called Maolate. The product was in the monoamine oxidase (MAO) inhibitor class. It passed every animal test and was tested on human volunteers, who were prisoners at Jackson State Penitentiary about 100 miles away from Kalamazoo. Results were exciting the product worked with very few side effects. Upjohn released the product with high hopes and good early efficacy. Marketing exploited the information and impressed a number of physicians. About eight months after market introduction, a patient on Maolate died. During the next few months several other Maolate patients died. Upjohn and the FDA investigated and learned that the malt in beer caused an adverse reaction that led to the deaths. The prisoner human volunteers had no access to beer in confinement during their part of the drug tests. The company faced a choice: label drinking beer as a contraindication and keep the drug on the market or, voluntarily pull the product and lose the promised stream of revenue. Upjohn pulled the product to avoid further deaths, even though a warning would have protected it from lawsuits. That episode of laudable corporate responsibility emphasized the need to manage risk.

Risk management in the pharmaceutical industry

By definition, risk management is the process of minimizing a drug’s risk during the product’s life cycle. Developing an inherently safe drug is vital. However, marketers must also maximize the drug’s benefits while minimizing its risks. In this context, risk management has two key components: risk assessment and risk minimization.

Bost convened his task force and started a discussion about how the company could accomplish both components. Immediately, opposition surfaced. Ward Studebaker, the vice president of Sales, complained that the effort was unnecessary. He cited the extensive sales force training that inculcated a culture of caution and concern. All salespeople were trained to promote company pharmaceuticals only in accordance with the FDA approved package insert. The package insert is a document unique to the pharmaceutical industry. It contains information about dosage, indications, contraindications, adverse reactions, and side effects. It communicates all the relevant information about a drug product and is completely supported with fact. It forms an advisory tool for physicians and is the legal protection for the manufacturer.

Studebaker was clear that the company enforced compliance with the package insert and had terminated several sales people who were found to violate that directive. In addition, he cited the extensive post introduction surveillance that the compliance department performed. The department monitored the worldwide performance of each product daily. When an adverse reaction occurred, even in New Zealand, the company knew about it almost immediately and prepared an appropriate and timely response. Studebaker described these two mechanisms as double-barreled protection from both lawsuits and FDA intervention. He wanted to use the resources to further marketing and sales.

There was a lively and heated debate about risk management, which was not resolved by the end of the meeting. Bost approached Dan Karel, the Harvard Law School trained CEO. Karel immediately saw the need to reduce the company’s exposure to suits and seizure and authorized Bost to design a risk management program. He assigned Robert Schleifer, the corporate counsel to help with the design. Schleifer offered several operating principles to guide their efforts. As prescribing experience grows, the medical profession learns more about how a given drug acts in a population. Some times the newly discovered effects can be beneficial. In others, experience can uncover negatives. Schleifer stated that pharmaceutical companies can reduce risk by demonstrating active efforts to warn the public and FDA about any untoward effects of one of their products. In doing so, the company becomes a partner in the public health effort.

Schleifer outlined three common elements to aid in risk management:
1. traditional education;
2. reminder programs; and
3. controlled access.

Traditional education programs might involve information booklets, letters to doctors, and letters to patients. Reminder programs include things like informed consent agreement documents that spell out potential risks to patients and require a patient signature. The third element, controlled access, limits the distribution of the drug to certain types of patients.

Both Bost and Schleifer wanted the aid of an expert. They found one in Frank Paine at the University of Michigan Health Systems Management program. He had specific experience in regulatory compliance. Paine met with both managers and laid out four basic questions that were the foundation of a pharmaceutical risk management effort:
1. Who should not use the drug?
2. How is the drug used?
3. What things do patients need to avoid when taking the drug?
4. To what extent are there issues of informed consent?

Paine advocated a systematic approach to actions and communications.

The design of a risk management effort

When to start the effort

Bost and Schleifer liked Paine’s approach and hired him to help them start their design. They arranged for an all day retreat for the risk management task force. Paine was there as a facilitator and leader and started with a basic question about the timing of a company’s risk management and risk minimization efforts. He asked, “When is the right time to begin developing a risk management program?”

That question was really a loaded one and prompted an earlier rather than later response. In fact, one task force member suggested the process should begin as early as possible. FDA guidance documents exist and if combined with some common sense, a team would have a sense about the level of risk to follow. Even early in the process there are steps that can be taken.

In other words, certain risk minimization actions become apparent. The picture is not all clear. There is usually little
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experience and it is difficult to know what the risks are at the early stages. Another member agreed it is important to start as early as possible, but real data usually come much later. In the drug development process potential risks are not apparent until close to the end of mammalian or human testing.

After further discussion Paine got agreement that once there was an understanding of possible risks, companies could start to minimize them. In fact, most companies do not start thinking about risk minimization until late in clinical trials, perhaps as late as Phase III trials are complete or nearly complete, just before the drug is cleared for sale. The task force agreed in principle that risk assessment should be an ongoing process and should begin as early in the discovery phase as possible.

At that point, Paine divided the task force into two teams. Each group was given an hour to consider the tradeoffs and benefits associated with early versus late risk management efforts. Both groups felt that beginning early and being proactive is important since it helps to understand the risks and all potential risks for a drug. Paine led a discussion that concluded that there are two basic types of risk associated with a pharmaceutical drug candidate. The first is the known risk; the second, unknown risk.

There was agreement that discovery phase information and knowledge of the type of patients will help predict the known risks of the drug candidate. Moreover, there was a consensus that identifying risk early can aid in planning the proper management response.

The lawyer on the task force noted something about the drug submission process. It is after all a regulatory process overseen by bureaucrats. If a company discovers risk early in the process, it can devise testing protocols in Phase II and Phase III that respond to the risk. When those modified protocols are included in a drug application submission, they and the submission may be viewed favorably.

Composition of the risk management team
Borrowing from the new product development literature and practice, team membership should be broad. There are examples in which there are not enough people involved in risk management. There are also cases in which there are too many decision makers involved.

The task force agreed that there are some vital experts. They include safety, risk management, regulatory affairs, medical affairs, medical communications, marketing, sales, epidemiology, and the legal department. Paine then explored the great professional difference among the experts and addressed the next issue.

Risk management team organization
It is important for all the groups to work together effectively. The professional differences can create management problems that hinder that effectiveness. One solution may be in using clearly defined roles and responsibilities. Paine stressed that there must be a clear leader with reward power. Some task force members worried about how to implement a risk management team even with Paine’s guidelines. The solution seemed to be to use the new product development/brand management team as an analogy. Upjohn employed a rather standard cross-functional team composed of members from a variety of functional areas but led by marketing. The team makes all of the key decisions for the product. In essence it “owns” the product. As owners, team members earn rewards based on their – and their product’s – success. Team performance as well as individual contributions would yield an individual’s performance evaluation.

The team can be divided into two major parts: product developers and product commercializers. Each subgroup is significant and each assumes different importance in the new drug application process. In the pre-release stage, the new product developers have great importance since they are close to the research and other internal processes that shape the product. After the product is released, the commercializers assume greater importance since they are responsible for defending the brand against competition and in fine tuning the promotion and marketing action plan for the target market.

The resulting risk management team organization duplicates the new product development/brand management team’s organization. The key differences focus on team leadership and target audiences. Marketing leads the NPD team. The regulatory affairs office leads the risk management team. Analogous to the developer/commercializer classification, the risk management team can be divided into two groups: those focused on prerelease phases and those whose primary focus is the post-release phase. This division makes sense. The first group is responsible for proving the safety and efficacy of their products. The second responds to issues not necessarily related to product safety.

Extended challenges
Safe products face many risks after their launch that may not related to their inherent safety. There are external factors, which could tarnish the drug’s appearance of safety. For example, physicians may prescribe a drug inappropriately, using it with patients for whom it may be contraindicated. Dosing may be a problem. Upjohn faced this issue with one of its anti-staphylococcus antibiotics, Cleocin. Its dose was 150 milligrams four times a day. The standard dose of penicillin was 250-500 milligrams four times a day. Some doctors were prescribing 450 milligrams of Cleocin, four times a day, which increased adverse reactions. Other examples focus on lower than effective doses which call a drug’s efficacy into question.

One other aspect that is unique to the pharmaceutical industry is the immense important of regulatory influence. Arguably, the FDA wields greater power than any other regulatory agency in a democracy. FDA personnel are motivated by the basic desire to protect the population from medical mistakes and unsafe foods and drugs. They are highly devoted to their duties but are also thoughtful in applying rules and regulations. The agency is well aware of the potential problems that new drugs face when they are pass through the clinical stages. Since not all information can be known or anticipated, regulators respect drug companies that perform extreme due diligence. The feeling is that the companies are acted somewhat like partners in safeguarding the public rather than self-interested organizations seeking profit above all else.

During the time period in which the company evaluated the need for a risk management strategy policy, company representatives presented new drug applications to the FDA. Establishing a risk management team, led to a natural pairing of team members with the company’s FDA representation team. It provided the necessary breadth of experience needed to answer the continuum of questions that might arise. Not
only was the choice of members simplified, but also their experience in the risk management group made them more effective as representatives.

In the event that the new drug application is approved, other requirements are necessary. Most companies use post-approval surveillance. If performed well, surveillance may reduce the number of interventions by the FDA. The key is to use a rigorous surveillance system and take action when an event occurs. Post-approval surveillance may also have benefits before another product's launch. If the new product is similar to a company's previous products, the risk management plan may help ward off FDA intervention. Similarly, totally new products that are the first in a product class, may avoid intervention also.

Implications for marketers and product managers

Upjohn was one of the earliest drug companies to address the risk management issue within the pharmaceutical regulatory process. The basic facts in the case are well documented, but some details have been changed to protect confidentiality. Recently, Pharmacia and Upjohn merged with Pfizer, another proactive player in the market. Presumably, the new entity benefits from groundbreaking work done in the past. It must be stressed that few organizations have extensive experience operating risk management programs. The basic application area is still suffering growing pains and there are no definitive best ways to proceed. The risk management process will become more effective as companies in the pharmaceutical industry learn more about what works and does not.

Outside of the pharmaceutical industry, manufacturers face different sources of risk that might be managed with a suitable response. For automobile, toy, or basically any other item, risks in how consumers use products abound. The lessons learned in the pharmaceutical industry show that having a basically safe product does not mean that people will use it safely. There was a famous example of two men who wanted to trim a hedge and did not have hedge trimmers. They used a gasoline-powered lawn mower. To do so they each lifted the unit by holding one side. After a slip, they lost several fingers. The act was foolish but the manufacturer worried about a lawsuit and regulatory involvement. If the company had a functioning risk management program in place, it might have been using at least a traditional education program to alert users to dangers. The important thing to remember is that managers can address most challenges.