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Product Pipelines and Pharmaceutical Risk Management in the New Era of Strict Regulatory Scrutiny

William K. Sietsema[1,2]

1 Clinical and Regulatory Strategic Planning, Kendle International Inc., Cincinnati, Ohio, USA
2 Pharmaceutical Sciences, University of Cincinnati, College of Pharmacy, Cincinnati, Ohio, USA

Abstract

The value of a pharmaceutical company may be defined as its pipeline or portfolio of products and their potential value in the marketplace. One strategy to help mitigate the multitude of risks in pharmaceutical product development is to balance a portfolio across therapeutic areas, levels of risk and potential for returns. Risks include unexpected toxicities, therapeutic failure and inappropriate risk-benefit for the patient, as well as technical, financial, regulatory, political or social failure. Strategic reviews of a company's portfolio will help ensure its product line-up is balanced appropriately to meet corporate goals and that product risks have been considered.

Following the withdrawal of Vioxx™ from the marketplace, a higher level of scrutiny has been focused on the safety of new pharmaceutical products. There is preliminary evidence that the overall number of approvals for new molecular entities decreased in 2005 relative to 2004. Certainly, all approvals of new COX-2 inhibitors have been suspended, leaving lumiracoxib and etoricoxib with an uncertain fate.

Accusations have been voiced that the Vioxx™ withdrawal was a result of shortened regulatory review times in the US, promulgated by the Prescription Drug User Fee Act. However, analysis by the Tufts Center for the Study of Drug Development has shown drug withdrawals, pre- and post-Act, are the same – withdrawn drugs did not have shorter review times than drugs remaining on the market.

Options are being sought by the industry and regulators to find better ways to uncover unexpected toxicities early in development and monitor evolving toxicity profiles during a product's marketing phase. Most agree, it is undesirable to delay the approval of new products, as this would stifle innovation and leave patients without needed therapies.

1. Product Pipelines

A pharmaceutical product pipeline may be defined as a portfolio of products in various development stages, each with its own potential risks and rewards, together defining the overall potential of a company. Pharmaceutical product pipelines are much like financial portfolios, strengthened by diversification. A well diversified portfolio is shown in tables I and II. Note the mixture of products ranging from preclinical, through each of the development stages, and including products marketed in the US and the European Union (EU). This portfolio is also balanced across therapeutic areas, as it includes entries in endocrinology, inflammation, gastroenterology, skeletal disease and central nervous system disease.

An additional consideration in a product pipeline is the depth of its components. Some of the strongest pipelines are those that contain multiple compounds within a therapeutic area and at different stages of development. In this way, the less mature compounds can serve as 'backups' if a more mature compound is discontinued.

Attention should be given also to patent life for compounds within the portfolio. If the company's presence in a therapeutic area depends on a single marketed compound for which the patent(s) will soon expire, it can be especially important to strengthen the pipeline with development candidates in that therapeutic area. Additionally, it may be possible to extend the lifecycle of such a compound with product improvements and fresh patent protection.

Table I. Sample product pipeline, balanced with respect to therapeutic areas and development stages for partnered products (data supplied by NPS Pharmaceuticals)

Product[a]	Indication	Corporate partner	Market territory	Comment
Sensipar® (cinacalcet HCl)	Secondary HPT	Amgen	US	Market launch April 2004 (discovered by NPS Pharmaceuticals; developed/marketed by Amgen)
Mimpara® (cinacalcet)	Secondary HPT	Amgen	EU	Market launch October 2004 (discovered by NPS Pharmaceuticals; developed/marketed by Amgen)
Kineret® (anakinra)	Rheumatoid arthritis	Amgen	US	NPS Pharmaceuticals promotion launch March 2005 (discovered/owned by Amgen; promoted by NPS Pharmaceuticals in the US)
Restasis® (cyclosporine ophthalmic emulsion 0.05%)	Chronic dry eye (keratoconjunctivitis sicca)	Allergan	US	NPS Pharmaceuticals promotion launch November 2005 (owned by Allergan; promoted by NPS Pharmaceuticals to rheumatologists in the US)

a The use of trade names is for product identification purposes only and does not imply endorsement.

EU = European Union; **HPT** = hyperparathyroidism.

2. Risks Faced in Modern Drug Development

There are many risks faced in drug development, categorised as scientific and medical, technical, financial and regulatory. The scientific and medical risks include the possibility that the new agent may not be efficacious in humans despite findings in preclinical studies, or it may not be safe in humans, or the risk-benefit equation may not be favourable.

Safety risks related to infrequent events are particularly difficult to quantify during the drug development process. The average development programme exposes somewhere between 1000 and 10 000 patients to a new medication prior to approval. Reasonably, this would allow one to detect adverse events that occur at a rate of 1 in 300 to 1 in 3000. But one would not expect to detect more infrequent adverse events until the product has been exposed to hundreds of thousands or even millions of patients after product approval.

Technical risks include such things as the inability to manufacture the product consistently, insurmountable stability problems or the inability to develop a delivery system with acceptable bioavailability.

Financial risks can be, quite simply, not having enough monetary resources to complete the product's development. Most drug development programmes will encounter unexpected issues that require supplementary funding. Many a biotechnology or drug delivery company has been forced to close its doors before its star product could be brought to market successfully due to a lack of funding. Additionally, financial risks may relate to the inability of a product to compete successfully in the marketplace. Sometimes the development of a product is discontinued due to a realisation that its evolving profile of safety and efficacy will not make it a popular choice among patients and physicians.

Regulatory risks primarily revolve around differences of opinions with regulatory authorities about what is needed for an approval.

Many of these risks can be mitigated with the careful planning of a robust development programme, and by enlisting the right

Table II. Sample product pipeline, balanced with respect to therapeutic areas and development stages for proprietary and partnered development programmes (data supplied by NPS Pharmaceuticals)

Product candidate[a]	Therapeutic area	Product developer	Stage of development				File registration date
			preclinical	phase I	phase II	phase III	
PREOS® (*parathyroid hormone)	Osteoporosis	NPS Pharmaceuticals (US)	Y	Y	Y	Y	5/2005
Preotact™ (*parathyroid hormone)	Osteoporosis	Nycomed (EU)	Y	Y	Y	Y	3/2005
Teduglutide	SBS	NPS Pharmaceuticals	Y	Y	Y	Started	
Teduglutide	Crohn's disease	NPS Pharmaceuticals	Y	Y	Started		
Isovaleramide	CNS	NPS Pharmaceuticals	Y	Y			
Calcilytics	Osteoporosis	GlaxoSmithKline	Y	Started			
GlyT-1	Schizophrenia	Janssen	Y	Started			
mGluRs	CNS/GI	AstraZeneca	Y	Started			

a The use of trade names is for product identification purposes only and does not imply endorsement.

CNS = central nervous system; **GI** = gastrointestinal; **SBS** = short bowel syndrome.

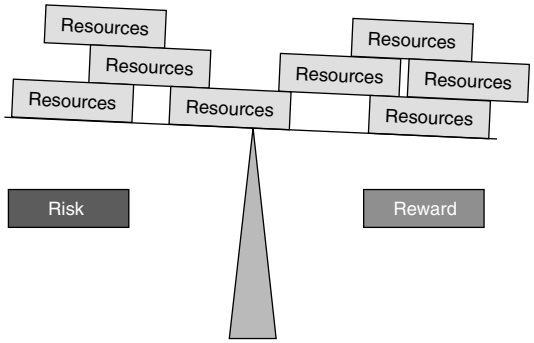

Fig. 1. Portfolio management means balancing the available resources (people, money and time) across projects so as to create the right ratio of risk versus reward.

experts to contribute to strategic planning, challenge assumptions and to look for potential gaps that could hamper a registration.

3. Portfolio Management and Reviews

Many pharmaceutical, biotechnology and drug delivery companies will manage their portfolios with an annual or semi-annual review process. These management reviews provide insight into the value of individual projects and allow the management team to gauge the contribution of each project to corporate aims. Additionally, they help the company optimise resources across projects, providing more resources to projects with near-term revenue opportunity and higher probability of success, and more modest resources to the projects that are 'long shots'.

Portfolio review also allows companies to define gaps in the pipeline, which may be filled by in-licensing, or to define excesses in the pipeline, which may be opportunities for out-licensing, possibly generating revenues to boost an underfunded programme.

Overall, portfolio reviews provide companies with an opportunity to evaluate multiple potential candidates and to grow/acquire/support those projects to obtain the right portfolio balance (see figure 1). This portfolio balancing helps the company manage the consumption of resources versus its generation of revenue so as to optimise growth and profitability. Thus, it improves the quality and value of corporate decisions.

A number of issues should be taken into consideration during a portfolio review. These include:

- the scientific strength of the technology;
- the stage of development (how much farther does it have to go to be marketed?);
- the robustness of the underlying science;
- the number and strength of the competition (other companies working in the area);
- the degree of medical advancement this would provide (is this a big step forward?);
- the diversity of targets across the portfolio;
- the potential risks and rewards of each project.

As a means of reviewing projects across a portfolio, many companies will group them according to potential risks and rewards, using a 'four-box' as shown in figure 2.[1] This view helps balance a portfolio by emphasising a variety of projects, some with high probability of success and low potential returns, and others with a lower probability of success but high potential returns. Although it may seem reasonable to maintain a portfolio which consists entirely of low-risk projects, such a portfolio is unlikely to provide satisfactory financial returns. A portfolio should contain projects at different risk levels and should not avoid some high-risk projects, as these could become the next blockbuster drug.

Another portfolio management tool uses 'isoquants', or lines of equivalent value, instead of the four quadrants, plotted on the same axes of probability of success versus potential returns (see figure 3).[20]

4. The Vioxx™ Story

The withdrawal of Vioxx™ (rofecoxib) from the global market on 30 September 2004 was an important day in drug development history. It created broad repercussions within the

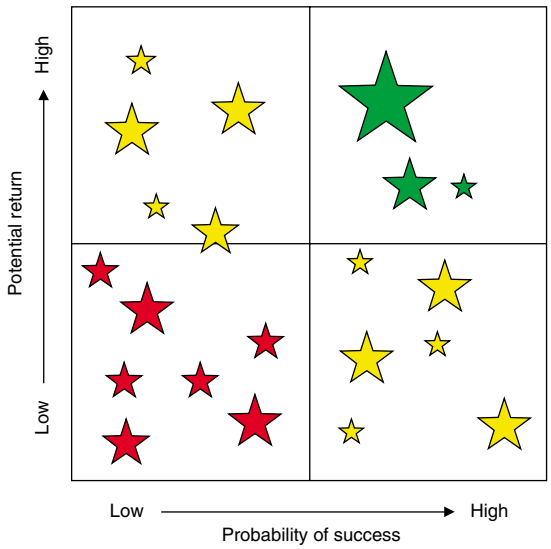

Fig. 2. A four-box comparing the probability of success and potential return on projects within a portfolio. The size of the star indicates the quantity of resources required to adequately staff each project and the colour emphasises the overall attractiveness, with green representing high attractiveness, yellow moderate and red poor attractiveness.

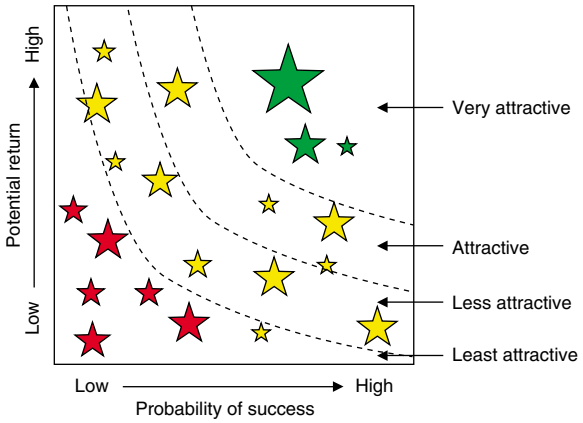

Fig. 3. Portfolio management tool showing 'isoquants' of equivalent value, based on a combination of probability of success and potential return. The size of each star reflects the quantity of resources required to staff the project and the colour emphasises the overall attractiveness, with green representing high attractiveness, yellow moderate and red poor attractiveness.

pharmaceutical industry, including a sudden and unpleasant public awareness that seemingly safe medicines can have infrequent but serious adverse events, as well as a change in expectations for drug safety on the part of regulatory agencies and the public.

Following the Vioxx™ withdrawal, there has been considerable medical, regulatory and legal turmoil, including finger-pointing and fault-finding. Some felt Merck was primarily at fault, others accused the US Food and Drug Administration (FDA) of being inadequately staffed and with inadequate procedures, and others blamed inadequate legislation.[3]

Since 30 September 2004, regulatory agencies have increased their focus on the safety of currently marketed products, especially on an ability to analyse infrequent events in large populations. This increased safety focus has been particularly directed towards cardiovascular events, such as myocardial infarction and stroke, and on increased incidence of certain cancers. There has been greater scrutiny of data also during the approval process, which has led to delays in the approval of the newer COX2 inhibitors lumiracoxib[4] and etoricoxib.[5]

5. Food and Drug Administration Approvals Since Vioxx™

In spite of the newer COX2 inhibitors lumiracoxib[4] and etoricoxib, whose approval has been delayed because of the Vioxx™ withdrawal, it does not appear that product approvals overall in the US have been delayed. The FDA makes data available on approvals on its website,[6] and an analysis of 196 new drug application (NDA) approvals in 2004 and through November 2005 fails to suggest a decrease in the overall rate of approvals (see figure 4). However, a closer look at approvals is afforded by isolating only the new molecular entities (NMEs), accounting for 51 approvals in 2004 and through November 2005 (figure 5). This analysis shows a decrease in NME approvals in the January through August timeframe, with 10 approvals for this same period in 2005 compared to 20 approvals for the same period in 2004. Interestingly, when looking at just the NME approvals, one can see the approval gaps that occur during summer holidays and in January, as well as the approval spike that always occurs in December. Whether there will be an overall decrease in number of NMEs approved in 2005 will not be known until the full 2005 approval statistics are available on the FDA website during 2006.

6. Review of Drug Withdrawals Since 1980

Drug withdrawals are not new and a study conducted by the Tufts Center for the Study of Drug Development (CSDD) has examined these withdrawals to determine whether there is a relationship between the implementation of expedited review procedures and the number of subsequent withdrawals.[7] Tufts CSDD evaluated a total of 648 new drug approvals since 1980 and noted there were 20 subsequent withdrawals – an overall withdrawal rate of about 3.1%. Interestingly, while the withdrawal rate has fluctuated somewhat over the years, it has been the lowest (1.6%) in recent years (2000–2004), concurrent with a reduction in the average time required for the FDA to approve a drug. When approval times were evaluated for drugs by therapeutic category, it appeared that the approval time for a drug not withdrawn from the market is similar to a drug that was later withdrawn from the market. Thus, withdrawals do not appear to be directly related to inadequate review time.

7. Changing Regulatory Expectations

Will the 'bar' for approval of new drugs be raised, or has it been raised already?[8,9]

Some have called for a tightening of the requirements for approval of new medications, such as requiring large outcomes studies.[5] In fact, development programmes for COX2 inhibitors have always included large outcome studies. For celecoxib, there were the CLASS (Celecoxib Long-term Arthritis Safety Study) studies[10] involving a total of about 8000 patients; for Vioxx™, there was the VIGOR (Vioxx™ GI Outcomes Research) study,[11] also involving about 8000 patients; and for lumiracoxib, the TARGET (Therapeutic Arthritis Research and Gastrointestinal Event Trial) studies[12] were performed in more than 18 000 patients. With etoricoxib, there was the EDGE (Etoricoxib-

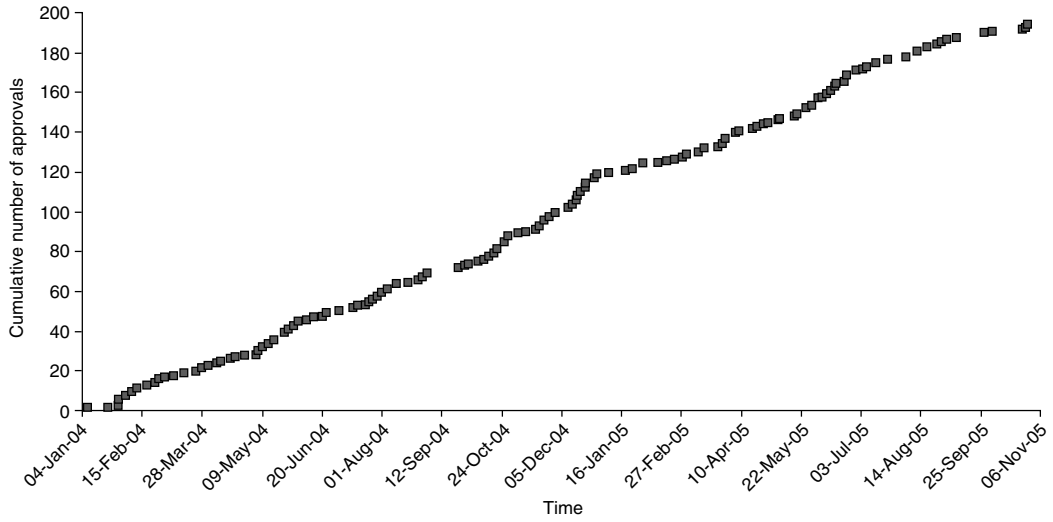

Fig. 4. Analysis of all new drug application approvals in the US in 2004 and up until November 2005, demonstrating that there has not been a decrease in the overall number of approvals following the Vioxx™ (rofecoxib) withdrawal.

Diclofenac Gastrointestinal Evaluation) trial with more than 7000 patients, as well as the ongoing MEDAL (Multinational Etoricoxib and Diclofenac Arthritis Long-term) trial with more than 23 000 patients.

While these studies have contributed significantly to an understanding of these agents, these large outcomes studies are extraordinarily expensive, costing $US20 million–$US40 million or more, and it is hoped that they will not become a requirement for all medications.

8. The Changing Risk-Benefit Equation

Most would agree we could all benefit from a better understanding of the safety issues surrounding new medications.[13] Preclinical studies can effectively identify major risks of frequent events that may occur with a medication, but generally are not useful for identifying infrequent, idiopathic events. A better understanding of potential adverse events versus expected benefits would help physicians and their patients make the right decisions

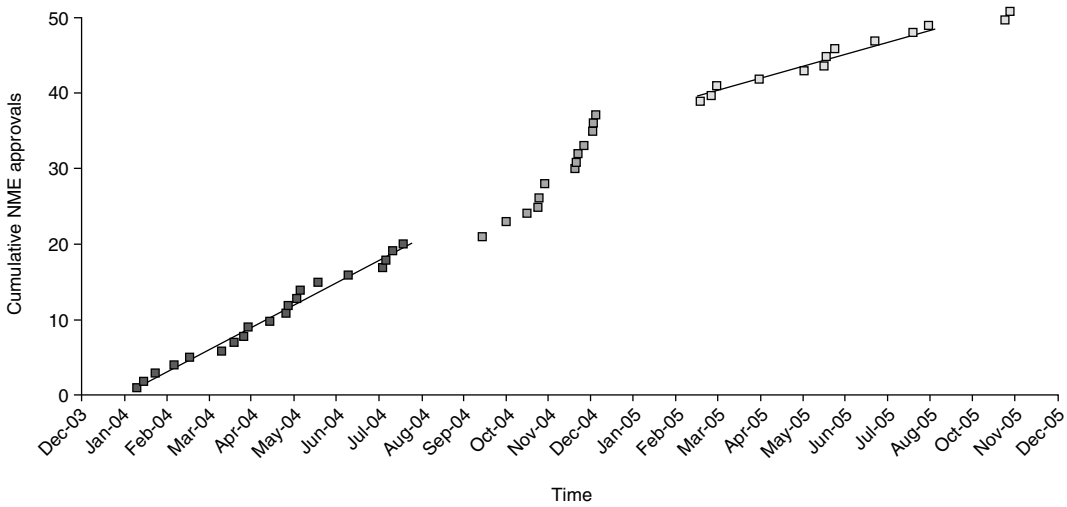

Fig. 5. Analysis of new molecular entity (NME) new drug application approvals in the US in 2004 and up until December 2005, demonstrating that there has been a slight decrease in the number of NME approvals following the Vioxx™ (rofecoxib) withdrawal. Note the usual summer approval gaps in August and September, the usual winter approval gap in January and February, and the usual approval spike in December. Trend lines are shown for comparable time frames in January through August.

on a case-by-case basis. However, as previously mentioned, it is not practical, or even possible, to fully understand the infrequent adverse events that may be related to a new product until at least hundreds of thousands (perhaps even millions) of patients have been exposed to it – which may never happen in the case of orphan indications.

Accordingly, the risks of infrequent but serious events could be addressed by exposing more patients for longer periods of time, prior to approval. But this would increase the cost of innovation and would lengthen the development time, making new medications more costly and delaying their availability to the public.

If regulatory agencies were to require more patients to be exposed to a new medication before approval, it would adversely affect innovation by drawing funds away from discovery research, causing biopharmaceutical companies to focus only on very large disease indications, and ultimately reducing the number of innovative new medicines. A reasonable alternative would be to raise expectations for postmarketing surveillance of new medications, increasing the level of surveillance with the size of the population being treated in proportion to the risk-benefit of the new medicine.[13] It has even been suggested that patent extensions be granted to accommodate the completion of post-approval, long-term safety studies.[14]

9. Estimating Adverse Event Rates

The best adverse event rate data comes from prospective, randomised and blinded studies. It is imperative that appropriate control groups are included in such designs, or it may not be possible to put the resulting data in proper perspective.

Two other approaches for evaluating event rates for infrequent adverse events should be mentioned. The first is the use of spontaneous adverse event reporting. This approach may help identify rare events, but generally is not useful for estimating event rates, due to an inability to determine the extent to which such events are under-reported, and the difficulty of estimating the denominator to apply to the estimate.

Another approach is to 'data mine' large health databases, searching for infrequent adverse events in association with product usage. Again, while this may be useful in identifying rare events, it does not provide reliable estimates of event rates and is, therefore, difficult to compare apparent event rates between products reliably. A data mining approach is best at defining large differences (10× or greater) in relative risk between two treatment options.

10. Economic Modelling in Drug Development

With the changing expectations in pharmaceutical development, modelling of the economics of a new medicine becomes more important as part of the 'go/no go' decision in development.[15] Such modelling allows biopharmaceutical companies to account for costs prior to product approval as well as costs versus expected revenues after approval. Following the Vioxx™ withdrawal, companies should account for the impact of additional preclinical and clinical safety data, pre- and postmarketing. These increased expenses must be balanced against expected revenue. It is worth considering whether spending additional funds to generate a more robust safety database may lead to increased prescribing, hence greater market share and revenue.

11. Selection of Indication as a Means of Altering Risk-Benefit Ratios

Most products in development have the potential for treating more than one indication. Often one of these indications stands out as a large patient population with the potential for the drug to become a blockbuster, generating revenues in excess of $US1 billion. Other indications have smaller potential revenue. For example, COX2 inhibitors have been developed primarily for osteoarthritis and rheumatoid arthritis (the largest markets), with less attention on diseases with more limited patient populations (such as ankylosing spondylitis). As it turns out, the largest indications are often the indications for which alternate medications are already available, whereas the smaller indications often have few therapeutic options. As a result, patients with rare diseases that have few therapeutic options may be willing to tolerate more risk to have an effective treatment.

In the past, most companies have focused their development efforts on the largest indications as a means to generate the most revenue, as soon as possible, following launch. However, with the changing risk-benefit equation, the choice of lead indication may be influenced more heavily by other factors. More and more, biopharmaceutical companies are selecting lead indications on the basis of the risk-benefit ratio to the target patient population, and choosing indications for which greater risk would be acceptable. Thus, approval may be granted with less safety data or with a less favourable safety profile. Such undertreated diseases may even accommodate higher pricing, making up, in part, for a smaller revenue base.

Additionally, acute indications, where patients are treated for a short period of time, may be more attractive as lead indication than a chronic indication, due to the fact that there will be less concern for adverse events that may only emerge after long-

term treatment. It also follows that untreated indications, where there are few therapeutic options, may be more attractive than indications where multiple therapeutic options already exist.

Rituximab is an early example of this principle in action. Rituximab is an antibody which targets and reduces the number of B cells within the body. Several diseases may benefit from such treatment, among them non-Hodgkin's lymphoma (NHL) and rheumatoid arthritis. NHL is a smaller market size, but was the lead indication for initial development of rituximab because patients would accept greater risk and pay a higher price, since satisfactory treatments did not exist. Rituximab was first approved in 1997 and has been a great success for the treatment of NHL. Efforts are now underway to gain an approval for rheumatoid arthritis, which has a larger market size, but for which multiple other treatments exist.

12. Rebuilding Trust

Prior to September 2004 the public was mistrustful of biopharmaceutical companies, largely due to a perception that pricing was unfair. This was especially true in the US where pharmaceutical prices are among the highest in the world. The withdrawal of Vioxx™ and the accusations that followed have degraded trust even further, not only of biopharmaceutical companies, but of the drug regulatory process. The discovery of sales memos directing Merck's detailing force to downplay the potential cardiovascular adverse events was particularly troublesome.[16]

Since 2004, another cause of mistrust has been the apparent withholding of full information related to the safety of drug products. This lack of transparency appears to have been the case with cardiovascular events and Vioxx™,[17] as well as with the use of antidepressants in children.[18]

But in fact the drug regulatory processes in the US and around the world were more robust in 2004 than ever before. Merck and the regulators were aware of the slight and variable cardiovascular signals with Vioxx™ and had been watching closely to see whether a clearer picture would emerge. Finally, when data from the APPROVE (Adenomatous Polyp Prevention on VIOXX) trial were analysed, there was definitive evidence of a small increase in the relative risk for cardiovascular events, such as heart attack and stroke, in patients treated for 18 months or more. Even though the increase in relative risk was small, Merck reacted with the immediate withdrawal of Vioxx™ from the market. This abrupt action had a number of dramatic effects. While a few patients made calls to their lawyers, a greater number of patients were making calls to their pharmacist. Vioxx™ was a medication that worked to treat their arthritis and, to them, the small potential risk was worth the benefit.

Nonetheless, trust in Pharma companies and the regulators has diminished and needs to be rebuilt. One way to begin rebuilding trust is to help government officials, lawyers, and the general public understand how the regulatory process works. Education can go a long way to help these factions develop trust in a regulatory process that has been well thoughtout and functioning reasonably for many years.

This is not to say that the regulatory process should not be improved, and most would agree that a better system is needed for collecting and analysing adverse drug reaction data. The limitations of our current adverse event reporting system have long been acknowledged[13] but cost-effective and satisfactory solutions have not been found. One of the positive effects of the Vioxx™ withdrawal has been a strengthening of efforts to improve adverse event reporting systems around the world.

Biopharmaceutical companies can build trust by making their operations more transparent and by educating the public about the drug development process. Pharmaceuticals provide good value and make up one of the smallest sectors of healthcare spending, far less than hospital care, which in the US has been out of control for many years.[19] It is an under-appreciated fact that in the US the average consumer spends more going out to eat ($US4.04 daily per capita) than on pharmaceuticals ($US2.34 daily per capita).[20] While this statistic fails to emphasise that senior citizens may bear more than the per-capita share of pharmaceuticals, it does help put pharmaceuticals spending in perspective relative to other categories.

13. Summary

The withdrawal of Vioxx™ in 2004 has led to a change in public and regulatory scrutiny of new and existing products, and a change in the way pharmaceutical pipelines are managed. Greater attention is now being given to uncovering the potential for infrequent but serious adverse drug reactions. This includes more careful evaluation of NMEs at the preclinical stage, as well as greater scrutiny during the approval process, and closer monitoring in a postmarketing environment. While there may be an expectation for exposing more humans (and for longer periods of time) to a NME prior to approval, this would increase the cost of drug development and would adversely impact innovation, making fewer new medicines available in the long run. A better option would be to improve adverse event surveillance systems in the postmarketing environment and to do a better job of educating the general public about potential risks versus benefits of medications so that informed choices can be made.

Distrust has developed regarding the drug development and drug regulatory processes. Trust can be rebuilt by making these processes more transparent and by continuing to strive for improvements in our adverse event monitoring systems.

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Correspondence and offprints: Dr *William K. Sietsema*, Clinical and Regulatory Strategic Planning, Kendle International Inc., 441 Vine St, Suite 1200, Cincinnati, OH 45202, USA.
E-mail: sietsema.william@kendle.com