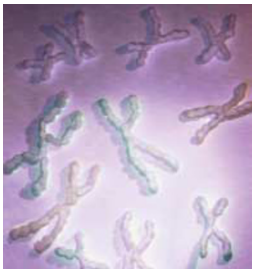
NEWS & ANALYSIS



Long-term study proposed for COX2 inhibitors

To truly evaluate the risks of the COX2 inhibitors, more needs to be known about older treatments.

Melanie Brazil

What we know about the safety of selective cyclooxygenase 2 (COX2) inhibitors is dwarfed by what we don't know — this was the message that emerged from the FDA's joint Arthritis Drugs/Drug Safety & Risk Management Advisory Committee meeting held in Gaithersburg, Maryland, USA, last month.

After 3 days of testimonies, deliberations and often heated exchanges the committees voted that the selective COX2 inhibitors celecoxib (Celebrex; Pfizer), rofecoxib (Vioxx; Merck) and valdecoxib (Bextra; Pfizer) show an increased risk of cardiovascular events and should have a black-box warning on the label — the strongest warning the FDA can give to a drug.

There was agreement that the increase in cardiovascular events was greatest in Vioxx and Bextra, and was only apparent in the highest doses of Celebrex. But assessing the true risk of these drugs is difficult. Trials have used different populations with different comparator drugs, and often lacked a placebo arm, said Robert Temple, Associate Director for Medical Policy at the FDA, in his presentation to the committees.

Temple raised the question of running a large, long-term trial, similar to the National Institutes of Health-funded ALLHAT study (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial), which compared commonly prescribed classes of antihypertensives without a placebo arm.

The proposed trial would compare the cardiovascular and gastrointestinal risk in Celebrex with the traditional non-steroidal anti-inflammatory drugs (NSAIDs) ibuprofen, naproxen and diclofenac, which differ with respect to their degree of COX2 selectivity. Ideally, said Temple, aspirin plus a proton-pump inhibitor (PPI) would be included too.

Thomas Fleming, Professor of Biostatistics at the University of Washington and an FDA consultant, believes that this trial could and should be done. "This trial should be carried out in an osteoarthritis or rheumatoid arthritis setting and should enrol 10,000 patients per arm with 2–3 years follow-up," he says.

With a placebo arm being unethical, as it would leave some patients without any pain medication, comparator consistency in these trials is crucial, says Steven Nissen, Vice-Chairman of the Department of Cardiovascular Medicine at the Cleveland Clinic.

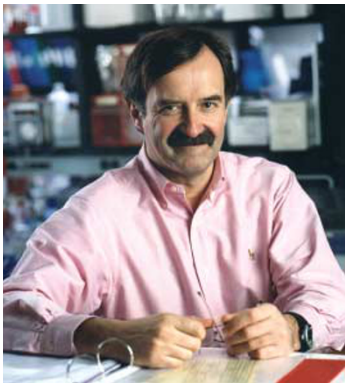
Nissen's trial proposal would compare celecoxib with naproxen, and have a third arm of another traditional NSAID, such as diclofenac. "If it is true, as Garret FitzGerald believes, that diclofenac and celecoxib are very similar with respect to their cardiovascular profile, as they are with respect to their COX2 selectivity, then diclofenac is not a neutral comparator," says Nissen, who was also on the Advisory Committees panel.

With a placebo arm being unethical, as it would leave some patients without any pain medication, comparator consistency in these trials is crucial.

Robert Temple at the FDA has proposed an ALLHAT-like trial to assess the risk of COX2 inhibitors.
US FOOD AND DRUG ADMINISTRATION

Alastair Wood, Professor of Medicine at Vanderbilt University, and Chair of the joint committee meeting says that more needs to be known about naproxen for naproxen-plus-PPI to become the standard comparator for trials. "First, we need a naproxen-plus-PPI versus placebo comparison to establish whether naproxen is or is not [cardio]protective," says Wood.

But FitzGerald, Professor of Medicine and Pharmacology at the University of Pennsylvania, is against performing a large study of all NSAIDs at the taxpayer's expense. A black-box label for COX2 inhibitors will provide a motive to their manufacturers to perform safety studies,



Garret FitzGerald is against running a large, long-term trial to examine all NSAIDs. UNIVERSITY OF PENNSYLVANIA

but the challenges are different with NSAIDs, he says.

"In the case of diclofenac, I believe the evidence exists to word a non-black-box precaution in a way that suggested that the precautions of selective COX2 inhibitors should probably apply," says FitzGerald.

Comparative data indicate that either naproxen is cardioprotective and COX2 agents are neutral, or naproxen is neutral and selective COX2 agents have a higher cardiovascular risk. "Either way, naproxen looks better than a selective COX2 inhibitor," says FitzGerald.

With efficacy and safety variations within the NSAIDs needing to be clearly defined, the whole NSAID class should have a warning to indicate a possible cardiovascular risk, says John Cush, Chief of Rheumatology and Clinical Immunology at the Presbyterian Hospital of Dallas, and member of the Arthritis Advisory committee. "Performing a trial against naproxen as comparator and demonstrating equal or better risk profile would allow the warning to be removed," he says.

Although Cush supports the idea of the ALLHAT-like trial, he does have some concerns. "In my experience, patients frequently switch NSAID therapies in the first year, which would confound long-term analysis," he says. "The trial design will be difficult and must include input from rheumatologists who specialize in such trials."

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Industry shrugs off NIH consulting ban

Many pharmaceutical company representatives think that politics is driving new conflict-of-interest rules.

Mark Ratner

When Elias Zerhouni, director of the National Institutes of Health (NIH), announced a tightening of conflict-of-interest rules with NIH scientists on 1 February — in effect, significantly expanding the restrictions placed on senior members of NIH last year and extending them to all 5,000-plus NIH scientists — pharmaceutical companies were left quietly puzzled by the move.

Those in industry polled for this story said that the sweeping ban on links between NIH scientists and companies would have no real effect on their businesses, but they were unwilling to speak on the record, citing legal concerns should they stir up the waters, as well as some confusion over the requirements set by the NIH.

The new restrictions prohibit interactions with companies, health-care providers, insurers, trade groups and NIH-supported research institutions. Designated interactions include consulting, participation on scientific and other boards, and compensated teaching, speaking or writing. Such activities must cease within 30 days of the announcement, with some narrow provision for extending the deadline. NIH scientists and their spouses and children must also divest all but nominal stock holdings in health-care affiliated companies, irrespective of whether they have other ties to them.

Despite the fact that affected NIH scientists have little time to act on this interim final rule, some details of implementation remain sketchy. Stock ownership more than US$15,000, for example, is prohibited. But what if a stock shoots up one day, then pulls back? What is the trigger to sell — a one-day closing price?

"We don't know how it's going to shake out," says a spokesman for the National Academy of Sciences. "Some things are not clear; the NIH has to work through their process."

How many scientists are affected by the rulings is also not clear. Approximately 600 scientists have been implicated, and around 100 researchers were named by a congressional committee as failing to notify the agency about their outside deals. But a week later, an NIH review found that 50–80% of these scientists might be mistakenly implicated because of confusion over similar names, the time period for which data were collected and differences in data coding.

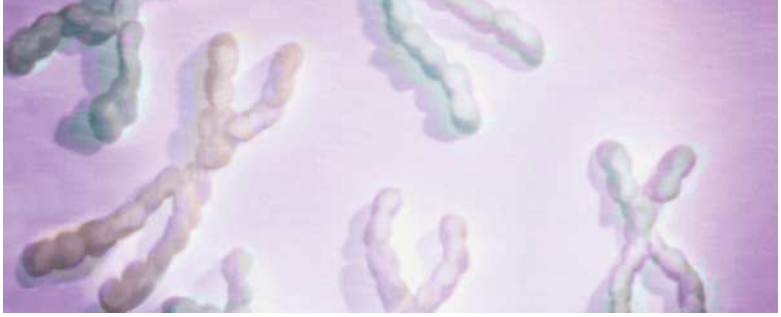
Also unclear is the amount of money at issue as a result of existing relationships. The NIH has promised to provide some quantitative information, but after the 30-day deadline for implementation the last post on its website is dated 3 February. "The process is ongoing," explains Don Ralbovsky of the NIH Office of Communications.

Companies are waiting for NIH colleagues to contact them. Wyeth, for example, on seeing the announcement, immediately searched its databases to find out who they were paying, and for what, according to President of Wyeth research, Robert Ruffolo, Jr. But he was not aware of any NIH scientists who had contacted the company.

Ruffolo expects little impact on Wyeth. "The influence NIH has over what we do is so relatively small. I don't know anyone who sees this as an issue that needed to be fixed."

"What we saw was a very quick, not well-considered, reaction to some political pressure, which should have been resisted," says Raymond Warrell, Jr., CEO of Genta Inc. and a former long time consultant to industry. A more reasonable approach is to require full disclose, he suggests, along the lines of what the NIH imposed last year on its senior staff. "No one is countenancing a mechanism that does not involve doing that in a public forum, but there's no reason to go beyond that."

NIH could take a lesson from the way the FDA handled accusations of bias in the approvals of cyclooxygenase 2 (COX2) inhibitors, says Warrell. The FDA called a meeting, including its own whistleblower, and put it to a vote to see what people thought. The NIH has been reactive, not proactive, during a time that calls for leadership."



Cancer drugs could now discover X factor

X chromosome sequence provides opportunity to study unexplored aspect of epigenetic-based oncology treatments.

Simon Frantz

The secrets of the X chromosome have now been revealed with the publication of its sequence (Ross, M. T. *et al. Nature* 434, 325–337 (2005)), and information hidden within this data could help promising cancer drugs that target epigenetic mechanisms.

The X chromosome is unique in that the expression of most of the genes on one of the two X chromosomes in female mammals are inactivated. Inactivating one X ensures that females by and large have the same dosage of gene products as males, who only have one X chromosome.

This X-chromosome inactivation process is driven by epigenetic regulation — the heritable silencing of genes without changes to their coding sequences. The *Nature* paper reveals that mobile genetic sequence elements called L1 repeats could serve as booster signals for this process.

Cancer researchers have long been interested in the roles that epigenetic mechanisms have in the activation and silencing of genes in tumours. Inhibitors are being developed against DNA methylation and the protein histone deacetylase (HDAC), both of which reactivate genes that have been epigenetically silenced. One DNA methylation inhibitor, 5-azacytidine (Vidaza; Pharmion), was approved for myelodysplastic syndrome by the FDA in May 2004.

Little is known about the long-term effects of these inhibitors, and no study has looked specifically at whether genes on the inactive X chromosome are reactivated. Many research groups, wary of the effects of reactivating previously inactive genes, are using microarray studies on cancer cells in culture treated with 5-azacytidine or HDAC inhibitors to see which genes are modulated.

A paper recently published in *PNAS* shows that different HDAC inhibitors alter transcription of a large and common set of genes that control several molecular pathways that are involved in cell survival and apoptosis (Peart, M. J. *et al. PNAS* 102, 3697–3702 (2005)).

"Our findings show that HDAC inhibitors are quite selective in the genes whose transcription is altered," says Paul Marks, President Emeritus and Member at the Memorial Sloan-Kettering Cancer Center, New York, and one of the co-authors of the paper.

Susan Clark is investigating the effects of 5-azacytidine and other DNA-methylation agents. "We were not specifically looking for X-linked genes but we did see X-linked genes as well as genes from the chromosomes that had become increased in expression," says Clark, Epigenetic Research Group Leader at The Garvan Institute of Medical Research, Darlinghurst, Australia.

Whether these are from the inactive X chromosome is difficult to tell. "Without polymorphic markers it is impossible to interpret whether the X-linked genes that are activated by treatment are from the inactive X or if the increase in expression is from the active X," says Clark.

But with the sequence of the X chromosome in hand the identification of polymorphic markers could now be possible, and other aspects of epigenetic mechanisms in cancer might be revealed. "The X chromosome provides a model system for understanding epigenetic regulation and misregulation," says Edith Heard, at the Mammalian Developmental Epigenetics Group, Curie Institute Paris. "The behaviour of the inactive X following various treatments will be critical."

NEWS IN BRIEF

MS treatment temporarily suspended

Biogen Idec and Elan have suspended sales of their multiple-sclerosis drug natalizumab (Tysabri) after two patients died from a rare disease of the central nervous system. At the time of the announcement on 28 February one person had died from progressive multifocal leukoencephalopathy after 2 years of therapy with Tysabri and interferon β-1a (Avonex; Biogen Idec), and another patient suspected of contracting the disease later died. Shares in both companies went into a tailspin on the day of the announcement. Biogen shares fell US$28.63, or nearly 43%, and Elan shares dropped US$18.90, or more than 70%. At least seven lawsuits seeking class-action status on behalf of shareholders have already been filed in federal courts against Biogen Idec and Elan. The lawsuits allege that the companies artificially inflated the value of their stocks by concealing the problems between 18 February, when the companies knew about the cases, and the date of the public announcement. Thomas Bucknum, a lawyer at Biogen, resigned after it was revealed that he sold 89,700 shares of Biogen Idec stock on 18 February.

Novartis becomes biggest generic manufacturer

Novartis has overtaken Teva Pharmaceuticals as the biggest generic-drug producer by agreeing to pay €5.65 billion (US$7.46 million) in cash to buy German firm Hexal and around two-thirds of the US-based company Eon Labs, offering to buy the remaining Eon shares. The deal expands the portfolio of the generic subsidiary of Novartis, Sandoz, to 600 products, generating $5.1 billion in annual sales, compared with Novartis' total sales of $28.25 billion last year. Global generics sales are around 10% of the estimated $450-billion global market for branded drugs, but are expected to grow at about 22% annually during the next 5 years, in contrast to less than 10% annually for branded-drug sales. Novartis' foray into the generics markets hasn't been followed by other large companies; only Sanofi–Aventis has shown an interest in generics through acquisition.

Treatments compete to lower cholesterol

A 5-year study involving 10,001 patients has shown that the highest dose of atorvastatin (Lipitor; Pfizer) significantly reduces the rate of heart attacks and strokes among people with stable heart disease (LaRosa, J. C. *et al. NEJM* published online 8 March 2005 (doi:10.1056/NEJMoa 050461)). The results were presented at the American College of Cardiology meeting in Orlando, and reinforce many cardiologists' opinion that aggressive lowering of low-density lipoprotein cholesterol in stable coronary heart disease patients to <70 mg per dl — substantially below the current target in the US of <100 mg per dl — results in a better clinical outcome. In another presentation at the meeting, a 6-week head-to-head study of 1,902 people showed that the combination treatment simvastatin/ ezetimibe (Vytorin; Merck/Schering Plough) reduced LDL cholesterol levels even more than Lipitor. Vytorin reduced LDL cholesterol by 59%, compared with 49% for Lipitor, and 57% of high-risk patients taking Vytorin achieved an LDL level of <70 mg per dl, compared with 23% of Lipitor patients.

PATENTWATCH

Yale assigned Nobel Prize winner's patent

John Fenn, winner of the 2002 Nobel Prize in Chemistry, owes Yale University more than US$1 million in royalties and legal fees for secretly patenting his prize-winning electrospray ionization process (ESI), according to Connecticut District Court judge Christopher Droney.

Fenn invented the ESI in the late 1980s, which enables mass spectrometric analysis of large molecules, such as proteins, nucleic acids and carbohydrates. However, by not informing the university when he applied for a patent while a professor at Yale, Fenn violated the university's intellectual property policy.

The patent (US 5,130,538), which was issued to Fenn in 1992, has generated more than US$5 million in royalties, and will not expire for another 6 years. Yale's policy allows the first $100,000 royalties to be split equally between the inventor and the university; the inventor retains 40% of the second $100,000 and, if royalties exceed $200,000, the proportion retained by the inventor drops to 30%. Fenn's patent has already earned more than $5 million in royalties and will not expire for another 6 years.

When Yale found out about the patent, it claimed rights to it and asked Fenn to re-assign the patent to the university, but Fenn refused. Fenn sued Yale after the University struck a licensing deal with Analytica without his involvement, alleging theft, tortuous interference with business relations and violations of the Connecticut Unfair Trade Practices Act. Yale responded to Fenn's lawsuit by counterclaiming for breach of contract, fraud, negligent misrepresentation, theft, unjust enrichment and seeking assignment of the '538 patent.

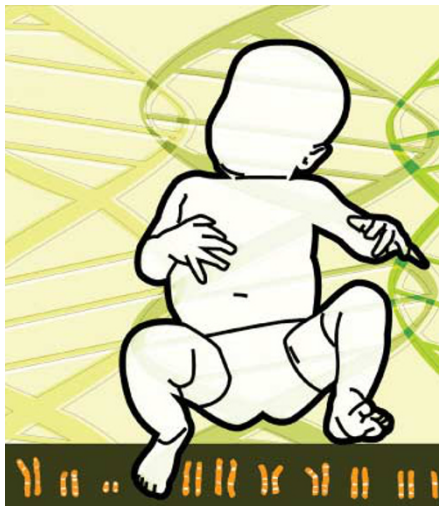
Although Fenn argued that he had rights to his discovery under the Bayh–Dole Act — which gives US universities the right to own inventions arising from federally funded research and license the technologies to companies for commercial development — the judge determined that Fenn knew Yale rightfully owned his invention under the University's official patenting policy. The judge also agreed with the university that Fenn had concealed material facts from Yale so that his actions, even after applying for the patent, would not be discovered. The court assigned the '538 patent to Yale, and awarded them treble damages of US$545,114 and punitive damages of US$492,435, in addition to any attorney fees incurred.

Hybrid too human to patent

A New York scientist's 7-year attempt to patent a human–animal chimera has failed because the hybrid could be too human. Stuart Newman of New York Medical College and his collaborator Jeremy Rifkin claim a victory nonetheless because they never intended to make the animal anyway. Rather, as opponents of patents on living organisms, they simply wanted to find out whether such an invention would be patentable and prevent others from profiting from similar inventions.

Newman's application described a technique for combining human embryo cells with embryonic cells from another animal to create a chimera with many potential medical applications. "Back in 1997, we made claims for the chimera's intended use that at the time seemed quite wild but are much more feasible today." For example, given the current prohibitive legislation concerning the use of human embryos for medical research, one likely use of this technology would be to enable the study of stem-cell therapies for neurodegenerative disorders. The chimeras could also be used to generate bone marrow and neuronal stem cells for reparative transplantation. Indeed, studies with a sheep–goat hybrid have already shown that transplanted cells from the chimeric animal had reduced ability to provoke immunorejection in the recipient animal. Newman notes that tissues from a human hybrid that have become more 'humanized' might be more effective for transplantation. He also proposed that if the chimeras can be grown to full-term, they could be used to facilitate drug toxicity testing: "The prohibitions on doing drug testing and cardiovascular stress experiments would be much less than they currently are for experiments on humans and so the technology could be useful to drug companies," he says.

The crucial bone of contention for the US Patent and Trademark Office (USPTO), however, was exactly how human the hybrid would be, and the office still lacks a criterion for determining how human a genetically engineered organism is. "But if you could genetically engineer the chimera so that the human component will be a known percentage of the organism then the USPTO might be better satisfied," says Newman. "I don't think that the rejection of this patent will impede research in the field. I do hope, however, that it stimulates legislative guidelines. With commercial incentive alone it is only a matter of time before such an organism is made."



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PATENT PRIMER

Experimental use provision

Candi Soames

Patent systems were designed to encourage and reward innovation. A system that prevents research into the subject matter covered by a patent would be inconsistent with such goals, and so the patent systems of most countries contain a provision that exempts from infringement experiments performed relating to the subject matter of a patent. In this article, the extent of the exclusion for experimental acts in Europe, particularly the UK, is discussed. I consider what constitutes an experimental act and to what extent the experimental use provision can effect scientific development.

The UK experimental use exemption

According to the UK Patents Act of 1977, a patent is infringed if, for instance, a person 'makes or uses' a product covered by the patent within the UK. However, an exemption is provided such that "an act which … would constitute an infringement of a patent for an invention shall not do so if … it is done for experimental purposes relating to the subject matter of the invention."

UK case law

In interpreting the meaning of the terms 'experimental purposes' and 'subject matter of the invention', certain decisions of the UK courts are relied upon. In particular, the case still used for the interpretation of the scope of these terms is Monsanto versus Stauffer (see BOX), which is now 20 years old. In the case in question, Stauffer wished to undertake field trials using a herbicide that was known to infringe a patent held by Monsanto in order to obtain regulatory clearance for this product.

This case established the principle that experiments carried out for the purpose of gaining regulatory approval for a product would not be exempt from being regarded as acts of infringement in the UK, because they could not be regarded as acts which were done for 'experimental purposes'. However, it seems that 'experiments' performed to find out something new — that is, which advance scientific knowledge — might be exempt from being regarded as acts of infringement, in so far as they relate to the subject matter of the invention. According to this case, an exempt act can have 'an ultimate commercial purpose'.

With respect to the meaning of the term the 'subject matter of the invention', the UK courts currently consider that the nature of the subject matter should be assessed by considering the contents of the patent as a whole. Furthermore, it is considered that the experimental purpose must have a 'real and direct' connection with that subject matter. There is an important distinction between research relating to the invention, which is exempted, and research using the invention, which is not. For example, use of a patented sequencing technology in an experiment to further develop sequencing technologies might be exempted, but it is very unlikely that the use of the same technology in an experiment to determine the sequence of a nucleic acid would be exempted.

Practically, what does the 'experimental use' exemption in the UK permit? It is clear that the scope of the exemption is currently interpreted narrowly: experiments that are performed to further scientific knowledge and discover 'something new' can be exempted from being classed as an infringing act, in so far as the experiments performed have a 'direct' connection with the invention described in the patent. However, experiments performed purely for gaining regulatory approval, such as field trials or clinical trials, might not be considered to be exempt from being classed as an infringing act in the UK at present.

Exemption in other parts of Europe

In other parts of Europe, recent decisions indicate that the 'experimental use' exemption is being interpreted more generously. For example, recent decisions in Germany have indicated that clinical trials on a patented compound to find out whether the compound is effective in other indications, or to obtain further information about certain characteristics of a compound, can be considered exempt from infringement irrespective of whether the clinical trials are carried out for commercial purposes.

Moreover, a recent decision in France has deemed that under certain circumstances Phase III clinical trials can be exempted from infringement.

The pharmaceutical regulatory directive

On 11 March 2004 the EU adopted a new European pharmaceutical regulatory directive apparently with the aim of facilitating the movement of generic products to the European market. The directive provides that "conducting the necessary studies and trials … shall not be regarded as contrary to patent rights." This exemption applies to generic medicinal products and also to non-generics, but only those that are similar to the reference product and which do not fulfil the generic definition for specified reasons.

It seems, then, that the effect of this directive might be to provide a more generous interpretation of the experimental use provision, in the UK at least. But beware, the directive does not have to be implemented until 30 October 2005!

Summary

Experiments can be performed using patented products, but only with caution. Experiments designed to elicit new knowledge — that is, which can be considered to advance scientific knowledge — might be exempted. However, at least in the UK, those experiments performed purely for commercial purposes currently do not benefit from the 'experimental use' exemption. It is hoped that the new EU directive will clarify the position.

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MONSANTO VERSUS STAUFFER: REPORTS OF PATENT CASES [1985] 515

The case in question related to the testing of a particular herbicide, Touchdown, which was being produced by Stauffer. Tests were being performed using Touchdown in an attempt to seek regulatory approval for the product. Monsanto sued Stauffer for infringement. Stauffer argued that the act of performing field trials using Touchdown was exempt from infringement because the trials were "done for experimental purposes relating to the subject matter of the invention." The UK Court of Appeal held that experiments exempt from infringement can have a commercial purpose, such as experiments designed to establish whether "the experimenter could manufacture a quality product commercially in accordance with the … patent." However, it was further held that the field trials being performed for the purpose of obtaining regulatory approval of Touchdown could not be considered to be performed for these purposes and therefore were considered acts of infringement.

AN AUDIENCE WITH...

John L. LaMattina

John L. LaMattina, Senior Vice President and President of Global R&D, Pfizer.

John L. LaMattina is Senior Vice President, Pfizer, and President, Pfizer Global Research and Development. He joined Pfizer in 1977 in Groton, Connecticut where his research involved seeking new therapeutic agents for the treatment of gastrointestinal disorders and asthma. He received his Ph.D. in organic chemistry from the University of New Hampshire in 1975 before moving onto Princeton University as a National Institutes of Health (NIH) Postdoctoral Fellow.

Does the pharmaceutical industry adequately explain the complexity of drug discovery to its stakeholders?
No, and there are several reasons for this. First, the modern pharmaceutical research enterprise is remarkably complex — even for those who are immersed in it. Second, our stakeholders comprise a broad cross-section of society and it is a challenging task to explain a complex system to this diverse group. We need to increase the engagement of the industry with its stakeholders. At Pfizer we bring them to our major R&D sites to learn about what we do. In our experience this is a remarkably effective way to overcome the misperceptions that exist about the industry. But it's a two-way street: visiting our sites takes time and a commitment from our stakeholders to learn about us.

People need to understand who does the 'heavy lifting' in discovering and developing new medicines. Too many people believe that the NIH discovers and develops new medicines and that industry simply manufactures them. The NIH itself has made clear that the vast majority of new medicines are discovered by industry and has published data showing that it has played a role in only 3 of the top 48 major drugs recently discovered (EPO/Procrit (Amgen/J&J); Neupogen (Amgen) and Taxol (BMS)). The NIH funds valuable early studies but relies on industry for the further development and manufacturing. The important discovery work that is needed to prove or disprove these fundamental biological mechanisms, and the subsequent long-term testing to demonstrate the safety and efficacy of new molecules is largely the responsibility of the pharmaceutical industry. In the case of Taxol, there were very challenging issues with synthesis of the drug that nearly prevented its development.

More than anything our stakeholders need to understand the quality and integrity of the research we do and the standards that are in place to validate it, and the best way to demonstrate this is to continue to produce remarkable new medicines.

Does talking publicly about preclinical failures make stakeholders more aware of the challenges of drug discovery and development?
One can, in fact, talk publicly about failures and Pfizer did so in a *Wall Street Journal* article (2 May 2002) that detailed many years of R&D and the resulting US$71 million that we invested in our attempt to develop a growth-hormone-releasing-peptide mimetic to treat frailty in the elderly. However, people are not generally interested in reading about failures, they'd rather hear about the next new medicine. In addition, preclinical failures are rarely the result of a single flaw. Over the course of several years and various hurdles, we might get a compound with the necessary credentials or we might face the difficult decision to terminate the programme. At that point, there is little to gain in publicizing this.

Failures do not generally make a great media story, and they rarely rate acceptance in major journals. The discovery and development of successful products is far more fascinating. Each success story has its own set of decision points: crossroads at which insight, creativity, sweat and, yes, a bit of luck, led to a product that benefited millions of people around the world. Those are the stories to tell.

The industry seems at liberty to release whatever information it wishes. How do you decide which failures to highlight?
I must first correct any impression that we control data releases and hide failures — that is certainly not the case, nor is it even possible. When we proceed to regulatory filing, we must include all data, including negative results. Clinical trials and post-marketing studies are conducted by leading academics and clinicians, and their trust and partnership are of paramount importance. Recently, journal editors and others have demanded access to trial databases, which Pfizer is willing to co-operate with. But, should we publish everything? No. We don't issue press releases on early undisclosed candidates because the majority of these fail. In the case of the growth-hormone mimic, we disclosed some early details because the science was exciting and the project was well-known. After development stopped, the *Wall Street Journal* approached us and we allowed their correspondent to talk to the project team. We did so to show how medical progress relies on our industry's willingness and ability to take financial risks.

How have recent setbacks for the industry altered its relationship with the public?
The relationship is about trust. For 155 years Pfizer has delivered medicines that improve and extend lives and, during that time, we have gained knowledge that enables us to more effectively measure the risk–benefit of drugs. But there have been profound changes in the doctor–patient relationship. Patients used to rely on their doctors to make risk–benefit judgments. The FDA then began taking a major role, and now patients demand far more authority and information, and are encouraged in this by lawyers, advocates, journalists and politicians. Although empowerment is positive, there is also confusion amid this wealth of data. Patients are not sure whom to trust. However, the professional, ethical and scientific standards in the pharmaceutical industry have never been higher. We all understand that causing harm to the customer is a guaranteed path to failure.