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How to avoid another 'Vioxx'

Flaws in the regulatory system are apparent, but how to rectify them remains unclear.

Simon Frantz

In many ways, 2004 will be a year that the drug discovery community would prefer to forget. During the past 12 months, questions about pricing schemes, clinical trials registries and the role of government-funded research in drug discovery have been raised in public forums, and culminated in perhaps the biggest debacle to rock the industry in recent years —the withdrawal of rofecoxib (Vioxx; Merck) after a study in patients with colon cancer indicated that it doubled the risk of heart attacks and stroke in those who took it for longer than 18 months.

The circumstances surrounding the withdrawal highlights the problems that the FDA faces in attempting to strike the correct balance between the risks and benefits of a drug. Critics have suggested that this episode has exposed flaws in the system of drug regulation, and have called for profound changes in the way the FDA monitors drug safety.

Such calls for changes in the system aren't new, but this time things could be different, says Catherine DeAngelis, editor-in-chief of the *Journal of the American Medical Association*. "Now you have Congress involved, the public are involved, and people like me are involved," she says. The 1 December issue of *JAMA* contained a series of articles analysing the withdrawal of Bayer's cerivastatin (Baycol) in 2001, and were accompanied by an editorial calling for restructuring of the current system of post-marketing drug surveillance.

Arguments over the withdrawal of Vioxx have extended to the halls of Senate.

In this instance, however, some of the strongest criticism of the FDA is coming from within. At a Senate Finance Committee meeting chaired by Charles Grassley (R-Iowa), David Graham, Associate Director for Science and Medicine in the FDA Office of Drug Safety, and the person at the centre of a whistle-blowing scandal concerning the agency's suppression of his data, said, "I would argue that the FDA as currently configured is incapable of protecting America against another Vioxx."

"The problem is that safety issues such as with Vioxx are often very low prevalence, around 1% or 2%, and the clinical trials leading to drug approval are in relatively healthy and small numbers of patients," says Eric Topol, Chairman of the Department of Cardiovascular Medicine at the Cleveland Clinic Heart Center. "Only in the 'real world' situation with large numbers of sicker patients does the problem often truly manifest itself, and you have to be looking for it."

Accumulating long-term safety data cannot realistically be done at the pre-approval stage, and relies on a robust post-marketing surveillance system. The FDA has the power to recommend post-marketing studies but has no authority to enforce them, and instead relies on a voluntary spontaneous reporting system called MedWatch for reporting suspected cases. "MedWatch is very useful for events such as rhabdomyolysis in the case of Baycol, but you couldn't detect an association with myocardial infarction and Vioxx," says Bruce Psaty, Professor of Medicine & Epidemiology at the University of Washington, Seattle. "The spontaneous reporting system is really a

signal-generating system; if there is a rare and unexpected event, you would probably see it," says Susan Jick, Associate Professor of Epidemiology at the Boston University School of Public Health and co-director of the Boston Collaborative Drug Surveillance Program. "But you don't have any comparison or denominator information, and just because something has been reported it doesn't mean that it is an adverse event. Also, myocardial infarction is relatively common, so how do you know whether it has been caused by a drug?"

In response to the barrage of criticism, the FDA has commissioned an independent review of its safety-monitoring procedures by the Institute of Medicine. But critics are already clear about what changes are necessary. Senator Grassley has called for an autonomous board at the agency to track safety, and with the power to make label changes and withdraw drugs. Others have highlighted a possible conflict of interest between the FDA's Office of New Drugs and the Office of Drug Safety. Both are under the remit of the Center for Drug Evaluation and Research (CDER), but the Office of Drug Safety has no independent power to make labelling changes or withdrawals of approved drugs. This has led to the suggestion that CDER lacks incentives to look into post-marketing issues because it could undermine the perceived correctness of the decisions that they have made.

One proposal is for the formation of an independent drug safety office. "It's not necessarily a bad thing that the agency tries to protect its reputation," says Daniel Carpenter, professor at the Department of Government at Harvard University. "But we should then recognize that, when CDER has limitations, it might be better to give the Office of Drug Safety some independence from the leadership of CDER. I don't think, though, that we need an agency outside of the FDA."

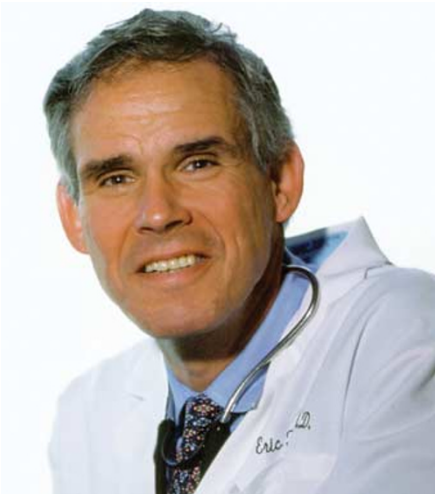
The current post-marketing surveillance system for drugs can't effectively spot adverse effects such as the association between heart attacks and Vioxx.

Any changes need to avoid knee-jerk reactions that only delay or prevent result in more defensive decisions that would prevent beneficial products from reaching consumers, says Henry Miller, Research Fellow at The Hoover Institution at Stanford University. Miller recommends the formation of an independent agency ombudsman that would regulate not only against approving a harmful product, but also against not approving a beneficial one. "The office would have to possess the following attributes: independence from the agency and the FDA commissioner; access to independent expertise in relevant disciplines, including medicine, pharmacology, science, regulation and law; and the power to levy sanctions against FDA employees found to be responsible, individually or collectively, for flawed decisions or policies that lead to severe, avoidable errors," says Miller.

"It's not necessarily a bad thing that the agency tries to protect its reputation. But we should then recognize that, when CDER has limitations, it might be better to give the Office of Drug Safety some independence from the leadership of CDER."

Another proposal is that the FDA should follow the post-marketing assessment procedures in Europe, in which an approved drug is re-reviewed after 5 years. "Right now, when a drug is approved in the USA, a company often agrees to do post-marketing studies, yet more than half of them aren't even started. So that's a failed system," says Psaty. "If a company knows that after 5 years its drug is going be re-reviewed, then this might serve as an incentive for some companies to move these along."

Any changes to the FDA are likely to require extra resources, but the current industry user fee model continues to raise eyebrows. However, Carpenter argues that the agency hasn't been compromised by its source of funding. His studies have shown that if Congress had just appropriated the fees, the reduction in review times still would have happened. "We've quantified the effect of every full-time employee hired under the user fee act and the bang for the buck that the public gets is, I think, overwhelming, unless that you think that individual reviews here are always being compromised, and I don't think that there's any reason why they have to be." Carpenter says that user fees have also allowed the FDA to grow in capacity in some areas in a time of general budgetary retrenchment in the USA. "Of course, there's the question of whether that's come at the cost of worsened safety," he says.



Eric Topol thinks that DTC advertising is a major liability. Cleveland Clinic Foundation

Initially, user fee money was only allowed to be directed specifically to pre-approval analysis, and not to post-marketing surveillance, a situation that is totally unacceptable, says DeAngelis. "Why should the FDA have seven people for approval reviews to one person for post-marketing safety? Whether it's in or out of the FDA, they have to have separate and equal authority," she says.

"It wasn't acceptable to us to not be putting money into post-marketing safety," says Sandra Kweder, Deputy Director at the FDA's Office of New Drugs. "We were directing appropriated resources over to post-marketing, and thereby undermining what the user fees were meant to be doing."

Kweder says they have suffered from cuts that undermine any benefit that would be expected from user fees. "For example, last year we did not have any increase in our budget because we had to use appropriated dollars to cover other burdens that we hadn't been allocated money for — for instance, pay rises." Kweder says a freeze on administrative hiring over the last year is impacting heavily on agency divisions. "I have whole divisions of 40-odd people with no secretary," says Kweder. "People are frustrated because they hear that help is coming but it doesn't come. It's really hard to shore up your staff when you're getting cuts from other places."

Any increase in authority or resources to monitor post-marketing safety will require the go-ahead from Congress. The cost of post-marketing studies is tiny relative to the cost of the clinical development, so these studies should be allowed to be carried out by the FDA, or even contracted out, says Jick. "Given that we have these databases it would only take about a couple of hundred thousand of dollars to carry out these studies," she says. "But for us to get this money is difficult, and that's absurd."

Without any great incentives to conduct post-marketing studies, pharmaceutical companies prefer to inform consumers through advertising, says Carpenter. "I don't necessarily blame them for this; they're just behaving rationally here," he says. "But it does mean that there is a dearth of information for the consumer and the public that the marketplace can't correct." Whether direct-to-consumer advertising has a role in the incidence of adverse effects is something that is likely to be investigated, says Kweder. "I'm not saying the industry isn't marketing responsibly, but they have responsibilities and taking a hard look at the effects of some of their promotional campaigns is part of that."

"Mass marketing via direct-to-consumer advertising is a major liability and this has to be seriously reviewed," says Topol. He says that radical changes are in order and suggests alternatives, such as considering allowing no DTC advertising at all; not allowing DTC until after a period of time in which long-term safety data are known; only allowing DTC for treatments that save lives or target critically important outcomes, such as prevention of heart attacks and strokes; or providing the FDA with more authority to regulate DTC advertisements.

"Given that we have these databases it would only take about a couple of hundred thousand of dollars to carry out these studies. But for us to get this money is difficult, and that's absurd."

Kweder's hope is that everyone will learn from this process and will be able to build some tools and technologies, and that funding will increase for doing a better job of post-marketing safety. "In our case, I think we can do a better job of communicating risks of products," says Kweder. "We can use things like public health advisories more often, which would allow us to express our concerns without having to speak through the industry and say what we think from a public health standpoint."

This isn't a new situation; post-marketing safety problems have come up many times in the past, adds Kweder. "But I don't think that the answer is a separate Office of Safety; it is not my experience, having worked in post-market safety and in pre-market safety, that this is what the solution is. I think that the problem is resources and focus."

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NEWS IN BRIEF

Novartis withdraws EU approval request

Novartis has announced the temporary withdrawal of its application for European Union approval of lumiracoxib (Prexige) while the company awaits the outcome of the European Medicines Agency (EMEA) safety review of all selective COX2 inhibitors. Although Novartis said it is 'committed' to the drug, given the current review of the category it felt that it was prudent to withdraw the filing for the time being, in spite of the drug being approved in 21 countries already. Lumiracoxib is thought to be one of Novartis' most important new drugs to help bolster earnings, and the company is relying on older products, such as the angiotensin II receptor antagonist valsartan (Diovan) for hypertension, to maintain sales growth until lumiracoxib is approved. The EU review is expected to be completed in the first half of 2005.

Lilly launches clinical trials registry

Eli Lilly has launched a publicly accessible registry of its clinical trials on its website (http://www.lillytrials.com). The registry will contain results from all Phase I–IV trials for its marketed drug products, and Lilly said it will post initiation data about all company-sponsored Phase II–IV clinical trials, as well as a comprehensive description of the trial design and methodology for each study.

FDA delays release of Critical Path Initiative

With issues such as safety concerns about marketed drugs needing to be urgently addressed, the publication of the FDA's Critical Path Initiative on the drug development process has been delayed. The report — which will identify key bottlenecks in the drug discovery and development process, and suggest ways to overcome these obstacles — was scheduled to be released this autumn, but will now not be available until early next year.

Antibody treatment for MS approved

Biogen Idec and Elan Pharmaceuticals have received FDA approval for their multiple sclerosis drug natalizumab (Tysabri, formerly known as Antegren). The antibody, which is the first new type of treatment for multiple sclerosis in eight years, targets α4 integrins on the surface of the blood cells that are thought to have a major role in causing the damage to the nervous system in multiple sclerosis, and interferes with their movement from the bloodstream into the brain and spinal cord. Biogen Idec said the FDA objected to the more familiar name Antegren because it was too similar to some existing drugs, such as Integrillin (Millennium).

Further warnings on antidepressants

The United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA) has requested new labelling on antidepressants. The agency wants to strengthen warnings about suicidality with selective serotonin-reuptake inhibitors (SSRIs) and the effects of drug withdrawal. The MHRA has also said that venlafaxine (Effexor; Wyeth) could cause irregular heart rhythms, withdrawal symptoms and have a higher rate of death from overdose than similar drugs. Wyeth responded that the changes are not consistent with scientific evidence. The FDA said that it does not find there is justification at this time for increased warnings or labelling changes for venlafaxine or SSRIs.

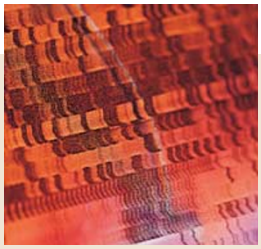
Female testosterone patch rejected by advisory committee

A testosterone patch for female sexual dysfunction (Intrinsa; Proctor & Gamble) has potential long-term risks that currently outweigh its benefits, said an FDA Advisory Committee. The committee voted unanimously against approval of Intrinsa due to safety concerns, such as a potential relationship to cardiovascular events and breast cancer. In the wake of findings from the Women's Health Initiative, hormonal combinations might need more extensive safety data, said the committee. The difference between placebo and Intrinsa was about one additional satisfying sexual episode per month. However, a P&G blinded exit interview of 132 patients from the two pivotal trials found a 52% meaningful response rate among the women treated with Intrinsa compared with 31% on placebo. The committee voted 14 to 3 that the effect of Intrinsa was clinically meaningful, but small.

Calcium-channel blocker benefits halts trial

A long-term study of the calcium-channel blocker amlodipine (Norvasc; Pfizer) has been stopped early because of the drug's significant benefits. The Europe-wide ASCOT study on ~20,000 patients was designed to compare a combination of Norvasc with the angiotensin-converting enzyme inhibitor perindopril over a combination of the beta-blocker atenolol and thiazide diuretic bendroflumethiazide in preventing cardiovascular events in patients with hypertension. As yet, Pfizer hasn't released any data on the observed benefits of amlodipine.

PATENTWATCH



Reasoning revealed behind Myriad's patent loss

Details behind the European Patent Office's (EPO) decision in May 2004 to revoke Myriad's 2001 *BRCA1* gene patent have now been made public. The main claim related to a method of diagnosing a predisposition to human breast/ovarian cancer by analysing mutations in the *BRCA1* gene. The gene was defined broadly by reference to a specific amino-acid sequence and variant sequences "with at least 95% identity to that sequence". The Opposition Division of the EPO rejected the claims of the granted patent on the grounds that there was inadequate basis in the application as originally filed for inserting the feature "with at least 95% identity" into claim 1 of the granted patent. Several sets of amended claims filed by Myriad were then considered in turn by the EPO.

Myriad first tried to avoid the limitation of the claims to a specific *BRCA1* sequence by removing the sequence from the claims, arguing that the term '*BRCA1* gene' was clear in itself and that the sequence of the gene was not necessary to carry out the invention. This was rejected by the EPO on the grounds that the sequence was an essential technical feature of the claim and also that its removal would illegally extend the scope of the patent. Myriad then tried to amend the claims to refer to the specific *BRCA1* gene sequence and also to several specific mutations that are characteristic of breast and ovarian cancers. The priority date of the claims then became a key issue, because a sequence of the *BRCA1* gene and details of all three mutations claimed by Myriad were published in the interval between the filing of Myriad's earliest US priority application and their European patent application. The claims were found not to be entitled to the earliest priority date, and therefore although they were held to be novel over the earlier publications, they were held not to be inventive. This decision illustrates the strict approach that the EPO takes regarding claim amendments and priority for gene sequences. Myriad has until 21 January 2005 to file an appeal.

No more royalties for Columbia

A federal judge in Boston has dismissed claims filed by Biogen, Genzyme and Abbott Laboratories alleging that Columbia University was illegally trying to extend its right to old patents that expired in 2000 — both sides are claiming victory. A number of the university patents expired in 2000, but in 2002 Columbia received a new patent derived from its previous patents with 17 more years of protection. The suit claimed that Columbia's 2002 patent (6,455,275) for creating protein-manufacturing cells is essentially the same technology as that covered in patents that lapsed 2 years earlier. The drug companies claim that together they have paid tens of millions of dollars in royalties to Columbia for using the technology in various pharmaceutical treatments, and that the new patent is invalid. At hearings, Columbia agreed it wouldn't assert certain claims against the drug companies or try to recover royalty payments. As a result, Judge Wolf granted Columbia's motion to dismiss the claims. In dismissing the claims, Wolf let Columbia's 2002 patent stand. Currently, the plaintiffs do not have any potential liability to Columbia, and Columbia is not explicitly or implicitly threatening to sue any of them as a result of their current activities. However, the '275 Columbia patent is being re-examined by the US Patent and Trademark Office, and, depending on the decision, the possibility exists of Columbia renewing its royalty demands.

Columbia's genetic engineering technology was licensed to more than 30 biotech companies, creating many of biotech's best sellers, and creating revenues of hundreds of millions of dollars for the use of the method.

New Act promotes collaborative research

US Congress has passed an Act that should benefit parties in collaborative research agreements when patenting inventions that arise from joint research. The Cooperative Research and Technology Enhancement (CREATE) Act of 2004 redefines the statutory term 'owned by the same person' so that it includes parties working under joint R&D agreements, and also means that subject matter previously considered as prior art can be excluded when considering patent applications if it arose from a collaboration. The Act applies to any patent granted after the date of enactment (20 November 2004), provided that the research collaboration was in effect before the invention; the invention clearly results from research activities carried out as part of the collaboration; and that all parties to the agreement are named in the patent application. The Act also covers inventions detailed in pending patent applications if the inventions were made under the joint R&D agreement, as well as patents re-issued after the date of enactment. The Act has several immediate implications: researchers working in collaborative projects are advised to make amendments to their research agreements to ensure that they qualify for the benefits of the Act; pending patents can be amended to disclose the names of all parties in the collaboration; and broadening re-issues of patents might be granted if the issued patent claims were restricted by prior art that is now excluded.

Full text of the CREATE Act:
http://www.aipla.org/html/reports/2004/FinalS2192.pdf

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PATENT PRIMER

Experimental support and patentability

Candi Soames

Recent decisions of the European Patent Office (EPO) indicate the ever-increasing need for experimental support in a patent application. This article reviews the experimental support requirement and looks at how the presence or absence of such support can influence the scope of patent protection obtained.

The European Patent Convention (EPC) contains no explicit requirement for a patent application to contain experimental data in support of the invention. It has therefore been possible to file speculative applications for inventions that are described theoretically, but not experimentally. This strategy permits applicants to obtain an early filing date, which is particularly advantageous in a competitive field of technology.

However, according to the EPC, the claims of an application for a patent must "…define the matter for which protection is sought. They must be clear and concise and supported by the description." Furthermore, "The description shall … describe in detail at least one way of carrying out the invention claimed using examples where appropriate." The EPC therefore infers a requirement for experimental support in an application. But how much 'experimental support' is adequate support? The case law of the Boards of Appeal, which is used to interpret the statutory provisions of the EPC, has provided guidance on this matter.

In the biotechnology field, early cases indicated that description of 'one way' of performing an invention was enough to support a claim of broad scope. For example, in the Genentech/bacterial-expression decision, broad claims were granted that protected a recombinant plasmid for transformation of a bacterial host comprising a regulatory element and DNA. Such claims were granted despite the presence of only one example in the application, which related to a specific bacterial species. In this case it was considered that the invention was generally applicable and that "there is nothing … that precludes a claim covering entities which may come into being in the future."

Proof of the invention

Recent case law indicates that there is a requirement for experimental support in an application in cases in which 'proof' of the invention is required. The reasoning behind the decision in a case involving Mycogen (see BOX) sums up the current thinking regarding the requirement for experimental support in an application.

If an invention embodies an idea or concept, which is not rendered obvious by prior art publications, then claims of a broad scope can be obtained with little or no experimental support. However, when the broad concept or idea is already in the public domain, the invention itself resting in the actual reduction to practice of the known or obvious idea, then the granted claims will be limited in scope to the breadth of experimental support in the application. In other words, if the invention is based on the achievement of a result, then the achievement of that result must be demonstrated over the whole scope of the claims.

Practically, this means that patent agents and inventors must carefully balance the need for an early patent filing date with the increasingly stringent requirement for experimental data in an application.

What is experimental support?

Just to muddy the waters a little more, it should be noted that 'experimental support' in an application does not necessarily mean 'methods and results of experiments that have been performed'. It can sometimes mean 'methods and the predicted results of experiments we might (or might not!) perform in the future' and which support the application on file. In essence, the experimental support in a patent application might be to a certain degree theoretical — the reasoning for this being that patents can be granted for inventions and a 'theoretical' experiment is an exemplification of the invention. This approach of using 'theoretical' examples must be used with caution, however, as the presence of 'unworkable embodiments' or irreproducible experiments in an application could cause sufficiency problems (described below), which might result in rejection of the patent application.

Finally, it is generally the case that further experiments can be presented, and theoretical experiments substantiated, during the prosecution of a patent application, and this must be taken into account in deciding when to file an initial application.

Support and Sufficiency

The need for support is linked with the requirement that a European patent application be sufficient — that is, according to the EPC it must "describe the invention in a manner clear and complete enough for it to be reproduced by one skilled in the art", without undue experimental burden. Recent case law has indicated that a patent application can be deemed insufficient if it contains aspects of an invention that do not work or are not reproducible. The danger of 'fabricating' aspects of an invention and 'experimental support' is, therefore, clear.

Experimental support and claim breadth

Are broad claims without substantial experimental support a thing of the past? It would seem not. Cases indicate that broad claims can be obtained with little or no experimental support. However, it seems that in general patent offices are becoming more stringent in their experimental support requirement and therefore the take-home message has to be 'the more the better'.

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TECHNICAL BOARD OF APPEAL DECISION T694/92: MYCOGEN

The Mycogen case relates to a method of genetically modifying a plant cell by forming a T-DNA–plant gene combination. The claims covered the use of any plant cell of any plant structural gene under the control of any plant promoter. The experimental data in the specification, however, related only to the expression of phaseolin in plant cells. Moreover, prior art in the field disclosed the method in theory, but acknowledged that the method had not been performed. In this case claims were granted which were restricted in scope to that of the example. The reasoning followed was that the invention in this case was not "a new general technique but the successful completion of experimentation".

OBITUARY

Sir John Vane FRS

William Harvey Research Institute

Sir John Vane's career as one of the greatest pharmacologists of the twentieth century was made all the more remarkable because of his accidental entrance into the field. As someone who had an all-consuming passion for chemistry experiments during his childhood — originating in the family kitchen using a Bunsen burner attached to the gas stove — John became frustrated by the lack of enthusiasm for his desire to experiment as a graduate at the University of Birmingham, UK. When offered the chance to do pharmacology at Oxford with J. H. Burn afterwards, John immediately accepted, followed almost as immediately by a visit the library to find out what pharmacology was all about. As John later admitted, this offer reshaped his career. It was an offer that also helped to reshape pharmacology.

After a 2-year-spell in the Department of Pharmacology at Yale with Arnold Welch, John returned to the UK. During his years with Gustav Born at the Royal College of Surgeons, John perfected his signature 'blood-bathed organ cascade' — a combination and extraordinary development of John Gaddum's parallel bioassay and superfusion techniques of 1953. Blood from animals, or sometimes humans, was passed continuously over a series of strips of smooth muscle chosen for their exquisite sensitivity to, and ability to differentiate between, the substances under investigation. This technique enabled John to measure instantaneously, dynamically and with great specificity the levels of one or more blood hormones, such as angiotensin and bradykinin.

Working with Sergio Ferreira, Mick Bakhle and others, John observed that the pulmonary circulation was a major site for the destruction of bradykinin as well as for the conversion of angiotensin I to angiotensin II. Speculating that both phenomena were attributable to the same enzyme, they deduced that the 'bradykinin potentiating factor' from *Bothrops jararaca* venom, which inhibited bradykinin proteolysis, might also block angiotensin I conversion and could prove a useful therapy for hypertension. John took the idea to Squibb, where Welch had become Research Director, and this led to the development of the revolutionary angiotensin-converting enzyme (ACE) inhibitors.

1971 brought another breakthrough. Aspirin had been developed in the 1890s, yet there had been no intellectually coherent explanation for its therapeutic action and side effects. One Monday, John walked into the lab proclaiming that over the weekend he had come up with a wonderful idea about how aspirin was linked to the cardiovascular system. John's interest in prostaglandins had been kindled some years earlier and he conceived the notion that aspirin worked by inhibiting the generation of these mediators. Almost overnight, he turned around the research focus of our lab to tackle his hunch; experimental proof was soon obtained and this concept, which he advanced mainly with Ferreira, Salvador Moncada and myself, profoundly influenced the field including the development of COX2 inhibitors, and helped to earn John the Nobel Prize in Physiology or Medicine in 1982.

In 1973 John moved to the Wellcome Foundation as R&D Director, and took Ferreira, Moncada, myself, Gerry Higgs and others with him to build a personal research group. Although friends discouraged him from moving into industry, John replied that those who believe that good science can only be achieved in academia were wrong. In 1976, working mainly with Moncada, Richard Gryglewski and Stuart Bunting, John's group discovered the potent vasodilator and anti-aggregatory prostaglandin 'X', later renamed prostacyclin (PGI_2). Analogues were later approved for the treatment of pulmonary hypertension and antithrombotic indications. Under John's management, Wellcome produced several other important drugs, including acyclovir (Zovirax), atracurium besylate (Tracrium) and lamotrigine (Lamictal).

"John walked into the lab proclaiming that over the weekend he had come up with a wonderful idea about how aspirin was linked to the cardiovascular system."

After an invitation from St Bartholomew's Hospital Medical School in 1986, and start-up funding from Glaxo Group Research, John brought together a new group — comprising Erik Änggård, Nigel Benjamin, Iain MacIntyre, David Tomlinson, Brendan Whittle, Derek Willoughby and his old colleagues Born and myself — to form The William Harvey Research Institute. Major funding from Ono Pharmaceuticals in Japan enabled his institute to expand rapidly and it soon became a pharmacological powerhouse, specializing in research into inflammation and cardiovascular disease. John even found time to start up (with Änggård) a new company, Vanguard Medica Ltd. (now Vernalis). He retired as full-time director of the institute in 1995 but remained Honorary Chairman of the charitable William Harvey Research Foundation until his death, from pneumonia, on Friday 19 November, aged 77.

John's legacy is not just in what he achieved, but in the manner in which he achieved it. He was an heir to the physiological tradition of pharmacology and, having watched the molecular biology revolution unfold from the sidelines, retained confidence in bioassays as an engine for the generation of new ideas and discoveries throughout his life. John created and moulded a generation of pharmacologists, gathered from many different countries, all captivated and inspired by his curiosity, his desire and his understanding of the research process. His phrases such as "Never ignore the unusual" and "Always do the simple experiment first" summed up his research ethics, and these phrases have been inherited by his willing students to inspire a new generation of pharmacologists.

On receiving his Nobel Prize, John said that he disagreed with those who said that the major discoveries had been made. There were still plenty of things to discover, he said; the trick is to find the right path from one to the other. Like John's vision and achievements, his message resonates as much now, if not more, in the field of drug discovery as it did then.

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