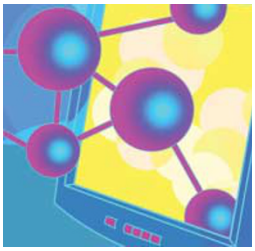

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Vioxx fears prompt call for user fee evaluation

The FDA is compromised by its funding source, but not in the way the public thinks, say experts.

Simon Frantz

Compromised? The FDA's user fee model has once again come under scrutiny.

Among the many casualties that lie in the wake of the worldwide withdrawal of rofecoxib (Vioxx; Merck), the FDA can in many ways be said to have taken the greatest hit. Many sections of the lay and academic press have once again accused the FDA of being in the pocket of the pharmaceutical industry by relying on industry's money to fund the drug approval process.

There is no doubt that the implementation of the Prescription Drugs User Fee Act (PDUFA) has intensified relationships between the agency and industry, but whether it has altered the FDA's objectivity is open to question.

The approval rate of new drugs has increased slightly from 76% for pre-PDUFA drugs to 81% since PDUFA. Drug safety, when measured in crude terms by drug withdrawals, has not increased noticeably, although this does not take into account the safety or risks of drugs still on the market.

What has dramatically changed is the increasing number of products approved in a single review cycle. More staff at the FDA, and greater dialogue between the agency and companies during the clinical development process, has helped, but so has introducing 6- or 12-month approval deadlines and performance goals.

These time limits mean that reviewers must in essence reject a New Drug Application if they want to see additional studies before approving the drug, says Mary Olson, Associate Professor of Health Policy and Administration at the Yale School of Public Health. "Reviewers may not be willing to reject a drug application that has evidence of efficacy even though they face some uncertainty about drug safety and would like to see an additional study of a safety-related question," says Olson. "This explains why agency requests for post-marketing safety studies have increased in the PDUFA era."

The main flaw with PDUFA is that it by and large allows funding to be used solely on reducing review time, says Raymond Woosley, President of The Critical Path Institute at the University of Arizona. "Restricting funds to mostly reviewing new drugs in effect compromises the FDA," says Woosley. "It's not anyone's intent to let user fees drive the agency, but the sheer weight of it does."

"What is desperately needed is increased funding from federal and/or filtered user-fee sources for post-marketing safety," says Eve Slater, who has worked at the US Department of Health and Human Services as well as Merck. The fee would go towards improving the IT systems and the personnel to process the data. "For the IT system, we're talking about an upgrade of around US$50 million and a head count of around 30 additional people," says Slater. "So we're not talking about a huge amount, relatively speaking."

Devoting more FDA funds to post-approval clinical trials and/or an expanded role of epidemiology studies would help restore some public confidence in the user fee system, says Daniel Carpenter, Professor of Government at Harvard University. "The fully capitalized benefits of regulatory approval are far in excess of the actual dollar value of a user fee — and that would be true even if the user fee was tripled or quadrupled."

"Will the public be reassured if they know safety studies are funded by user fees?" asks Kenneth Kaitin, Director of the Tufts Center for the Study of Drug Development. "In an ideal world Congress would commit the resources to fully fund the process, to eliminate the appearance of conflict of interest," says Kaitin. "But we don't live in an ideal world, and until I see evidence that the FDA is compromised by the current relationship with industry, I don't see an alternative or better system that is available at this point."

Share and share alike

Meeting aims to discuss tools that allow the safe exchange of chemical information.

David Bradley

Can researchers share relevant information on chemical compounds so they can test drug-discovery models and toxicity-prediction programmes without revealing structures to rivals? A meeting this month of two divisions of the American Chemical Society — Chemical Information (CINF) and Computers in Chemistry (COMP) in San Diego — aims to address this controversial question (http://oasys2.confex.com/acs/229nm/techprogram/).

"The pharmaceutical industry and academia want to share information, but proprietary and legal considerations mean that this cannot be done easily if there is a risk that chemical-structure information might be released," says Christopher Lipinski, Adjunct Senior Research Fellow at Pfizer Global R&D and co-chairman of the meeting. "We need an uncrackable system that lets information-poor academia gain information for testing its models and techniques, and allows industry to tap into academic expertise without compromising its intellectual property."

Quantitative structure–property relationship (QSPR) models rely on the quality and quantity of the experimental data they use, but the proprietary nature of industry data means that public-domain QSPR models rarely accomplish high-quality predictions. "This communication gap has created a cultural division between academic science and the industrial sector," says co-chairman Tudor Oprea, Professor and Director, Biocomputing at the University of New Mexico School of Medicine.

Some studies suggest that safe sharing would be impossible. For instance, Robert Pearlman and colleagues at the University of Texas have shown how software can deduce a chemical structure from a compound's descriptors, such as molecular mass.

Jean-Loup Faulon and colleagues at Sandia National Laboratories in California have shown that descriptors of molecular fragments might be used to 'reverse engineer' chemical structures. Dave Weininger and John Bradshaw from Daylight, a California-based chemical informatics company, use genetic algorithms that can 'guess' structures from chemical fingerprints in their databases.

Nevertheless, many researchers believe safe sharing is possible. Ruben Abagyan and colleagues at The Scripps Research Institute, La Jolla, have shown that adding artificial noise to data can mask structures. For example, knowing a compound's molecular mass to four decimal places could be enough to obtain a molecular formula, but lowering its precision to less than ten daltons precludes this.

Alexandru Balaban of Texas A&M University, Galveston, has used a similar approach based on topology to produce chemical identifiers that contain less information about structure. Even at lower accuracy, some druggability tools, such as Lipinski's 'rule of five', still work. Oprea warns, however, that software could 'model out' such seemingly random rounding of data.

An approach called Screens, developed by Nikolay Osadchiy and colleagues at ChemDiv, a chemical compound supplier, describes structural fragments but hides the manner in which they are connected. This can provide molecular diversity information and fill voids in chemical space while keeping structures secret.

Tripos, a supplier of products for chemistry research, suggests that topomers might be the answer. Company CSO Richard Cramer says

Europe supports plans for research on children

The European Union is encouraging development of new medicines for paediatric patients.

Peter Wrobel

The European Union has taken one step closer to launching US-style regulations that encourage the development of drugs designed specifically for use in children.

Leading figures from industry, clinical practice and regulatory affairs met in Brussels on 25–26 January under the auspices of the European Forum for Good Clinical Practice. A final decision by Europe's lawmakers might be more than a year away, but to judge by the talk inside and outside the conference hall, it is not a question of whether the European Parliament and Council will adopt the proposals, but what happens after it does.

Peter Arlett from the European Commission proposing the new initiatives for children.
BEN J. M. VERBEEK/EFGCP

Under the proposals, explained Peter Arlett from the European Commission, companies seeking approval for new medicines will either have to go to a new European Paediatrics Committee of the European Medicines Agency with data from paediatric clinical trials, or ask the committee to grant a waiver or a deferral. In return for completing studies, the makers of patented medicines will gain a 6-month 'patent extension' in Europe, rising to an extra 2 years for drugs for rare, or orphan, diseases.

So far, so pretty much a copy of the regulations introduced into the US in 1997 and confirmed by Congress in the Best Pharmaceuticals for Children Act of 2002. Things get more complex with generic, or off-patent drugs, and the European Commission has had to be a bit more innovative.

The Commission has come up with a new vehicle for granting intellectual property, a Paediatric Use Marketing Authorisation, or PUMA. This will allow innovation on older drugs to be rewarded with the intellectual property right — data protection — which gives an element of market exclusivity.

Questions remain about how effective in practice the provisions for older medicines will be in encouraging drug companies to produce medicines for children. Experience in the US since 1997 looks encouraging, said Diane Murphy, Director of the FDA's Office of Pediatric Therapeutics. Up to December 2004 the authorization procedure had led to 17 product labels carrying new dosing recommendations, 21 with new children-specific label information, and 11 with declarations that effectiveness in children had not been established.

that these topologically equivalent isomers look and behave similarly but not uniquely, so they could be used for druggability tests.

A related approach from Anthony Nicholls of Santa Fe company OpenEye Scientific Software, a producer of software for structure-based drug design, and Andrew Grant of AstraZeneca relies on the fact that different compounds can have a similar shape and electrostatic properties. These are key but not unique descriptors for druggability studies.

Oprea suggests that VolSurf — a descriptor system for pharmacokinetics and toxicity developed by Molecular Discovery, a UK-based software company — cannot be reverse engineered. Key molecular properties, such as the hydrophobic and polar surface areas, are reduced from thousands to 92 descriptors, but these still encode chemical information relevant to QSPR models.

The success of chemical masking techniques hinges on their integrity; any leaks and the system will inevitably fail. But Lipinski argues that success offers tremendous value to companies. "Software developers and academics would like to get their hands on the information," he says. "If they can share information without revealing structures, then useful research can be done."

Expertise in interpreting data will be a big issue. According to some of the attendants, it is estimated that there are no more than 12 trained paediatric clinical pharmacologists in Europe. As this expertise is mainly limited to the academic/clinical sector, industry is going to have to rely on this sector for expertise — which seems to echo the experience in the US.

Another stumbling block will be informed consent. There are already guidelines for informed consent from both parents and from the child when the child is capable of understanding what is going on. But there are a huge number of tricky areas, including situations involving divorced parents and sperm-donor parents.

Despite a small, nagging worry that some of Europe's MEPs might baulk at the very idea of clinical trials involving babies and children, there's a lot of confidence that most can be won over. And there is general agreement that the proposals would be a good start for Europe even if they will still leave the continent's researchers and companies nearly 10 years behind the US.

That said, the proposal for regulation in Europe has the advantage of drawing on US experience and has been able to plug the gaps that some consider to exist in the US laws.

NEWS IN BRIEF

Exanta's risk/benefit conundrum revealed

Two studies in the *Journal of the American Medical Association* place ximelagatran (Exanta; AstraZeneca) in the spotlight again for the first time since the FDA rejected approval of the thrombin inhibitor. The studies report the two Phase III trials, which showed that Exanta was as effective as warfarin and low-molecular-weight heparin for deep vein thrombosis and stroke prevention in atrial fibrillation. However, both studies raised questions about liver toxicity, and one trial raised suspicion of increased coronary events. A third article in the journal shows that Exanta is cost-effective only for patients with a high risk of intracranial haemorrhage or a low quality of life while taking warfarin. In an editorial accompanying the papers, Victor Gurewich from the Beth Israel Deaconess Hospital Medical Center, Boston, says the benefits of Exanta over warfarin, a drug that is notoriously difficult to manage and has adverse reactions with a number of other treatments, need to be considered. Gurewich suggests that the definition of these risks can be achieved only through post-marketing surveillance, not in a clinical trial.

http://jama.ama-assn.org/

Crawford nominated for permanent FDA commissioner post

The FDA's Acting Commissioner, Lester Crawford, has been nominated for the full-time post by President Bush. Although many are relieved that a permanent commissioner has been nominated, critics are disappointed that an outsider wasn't chosen, particularly in light of recent controversies about drug safety and the agency's relationship with drug companies. The FDA announced that it was creating a new independent Drug Safety Oversight Board to monitor approved medicines once on the market and to update physicians and patients with new information on risks and benefits. Full details were not released at the time of going to press, but Crawford said that the board would be made up of scientists throughout the federal government that will advise the FDA, although it will not have the independent power to force the withdrawal of drugs.

Pfizer to cut sales jobs?

A Lehman Brothers analyst has written in a research-note estimate that Pfizer could lay off up to 30% of its 38,000-member sales and marketing staff. A large-scale redundancy of as many as 11,000 sales reps would lower Pfizer's costs by US$1.5 billion to $1.7 billion a year and increase annual earnings by an estimated 17 cents a share, says C. Anthony Butler. Pfizer confirmed that it is looking at measures to streamline its business, but will provide details of the plan at a meeting with analysts in early April. Pfizer shares rose 2.6% to US$25.55 in response to the suggestions of job cuts.

HIV generic approved amongst a new climate of fear

South Africa's largest pharmaceutical company, Aspen Pharmacare, has become the first to receive approval from the FDA for the manufacture of a generic antiretroviral regimen containing lamivudine/zidovudine and nevirapine for the treatment of HIV/AIDS. Patents for lamivudine/zidovudine and nevirapine still belong to the original innovator companies, and the approval of this regimen is 'tentative', meaning that it cannot be marketed in the US, but it does meet the agency's standards for safety and bio-equivalence. The treatment will be available for use under the President's Emergency Plan for AIDS Relief, a 5-year global strategy. Meanwhile, New York City health officials announced that a man in New York has been infected with a highly virulent form of the HIV virus that is resistant to three of the four classes of anti-HIV drugs. Analysis by two independent labs confirmed that this form of the virus infects cells through CX4 cellular receptors, which are typically found only in those infected with HIV for a long time and in advanced stages of AIDS.

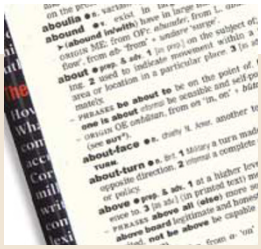
Adderall risks create difference in opinion

Health Canada have suspended sales of Adderall XR (Shire) for attention deficit hyperactivity disorder (ADHD) in light of reports that since 1994 the drug has been linked to 20 sudden deaths and 12 strokes. The FDA, however, said it had evaluated the same reports as Health Canada, yet believed that the data warranted an additional warning stating that Adderall XR should not be prescribed for people with structural cardiovascular abnormalities. Health Canada said it is asking manufacturers of related treatments for ADHD to provide a thorough review of their worldwide safety data.

Agreement reached over cancer vaccines

GlaxoSmithKline has said it will receive an upfront payment and unspecified royalties from Merck after settling a patent dispute with Merck concerning both of its cervical cancer vaccines. The agreement allows both companies to introduce their potential blockbuster human papillomavirus vaccines during the next couple of years, but GSK will get a share of Merck's revenues, estimated to be between 5–7% of global sales. Merck plans to file its vaccine for regulatory approval with the FDA in the second half of 2005, and GSK expects to file its vaccine for approval in Europe in 2006.

PATENTWATCH



Beware the lexicographer rule

Merck's patent claims for once-weekly administration of alendronate sodium (Fosamax) are invalid and obvious, according to the US Court of Appeals for the Federal Circuit in Washington DC. The verdict that the biggest-selling form of the drug is not covered by patent protection through to 2018 as previously thought hinged on Merck's use of the word 'about'.

The appellate court overturned the previous decision of the Delaware district court in August 2003, which found that Merck's US patent (5,994,329) was infringed by Teva Pharmaceuticals' Abbreviated New Drug Application (ANDA) filing. The district court determined that the claim term 'about' used to describe dose size was redefined by the patentee. The wording was intended to take into account variations in the molecular mass of the different derivatives of alendronic acid in order to deliver the exact dose stated.

Teva appealed the court's claim construction, and the Federal Circuit agreed, ruling that the term 'about' should be given its ordinary and accepted meaning of 'approximately', and not to mean 'exactly'. The court stated that when a patentee acts as his own lexicographer in redefining the meaning of particular claim terms away from their ordinary meaning, the patentee must clearly express that intent in the written description.

The district court's decision had discounted one piece of prior art that had been published in *Lunar News*, because the article was not published in a peer-reviewed journal or authored by one skilled in the relevant art. The federal circuit overturned this decision because the *Lunar News* article, which had clearly suggested once-weekly dosing to avoid or minimize problems related to dosing frequency, was written by one skilled in the art and that *Lunar News* was widely distributed among those working in the osteoporosis field.

In a strongly worded dissent, Judge Rader warned that the lexicographer option should be taken at one's own risk. Agreeing with the district court, Judge Rader wrote that Merck defined the phrase in question with precise values, but fell five letters short of success because the phrase included the word 'about'. He thought that the appellate court cast aside the lexicographer rule without a convincing explanation.

Teva believes that as a result of this ruling its ANDA will be eligible for final approval in February 2008 when Merck's original chemical matter patent (US 4,621,077) expires following its paediatric exclusivity period.

Merck & Co., Inc versus Teva Pharmaceuticals USA, Inc:
htpp://www.fedcir.gov/opinions/04-1005.pdf

Catch 22 for generics manufacturers?

The generics manufacturer Teva Pharmaceuticals has failed to persuade a Federal Circuit appeals court to maintain 180 days of exclusivity for a generic version of Pfizer's antidepressant sertraline (Zoloft).

The case illustrates the extent to which brand-name drug companies can work with manufacturers of their choosing to delay the entry of other generics.

According to the Hatch–Waxman Act, Pfizer had 45 days to sue Teva for patent infringement based on Teva's Abbreviated New Drug Application (ANDA) filings. However, Pfizer did not issue any proceedings. Teva then sought a ruling that its generic drug did not infringe Pfizer's patent (US 5,248,699), after Pfizer made a deal with Ivax Pharmaceuticals, the first company to seek permission to sell a generic version of sertraline.

Under Hatch–Waxman, the first generic company to seek approval for a drug gets 180 days of exclusively after the brand-name patents expire. However, major drug companies can use a legal loophole to make deals with the exclusive generic maker. The move, known as 'parking', delays the 180-day period and prevents competition.

The only means to stop any potential delay is to seek a pre-emptive, or declaratory, court order. But the Massachusetts district court rejected Teva's suit for failing to establish an actual controversy under the Declaratory Judgment Act.

On appeal, Teva argued that there was reasonable apprehension that Pfizer would bring suit against Teva for infringement of the patent. In support of this argument, Teva relied on the fact that Pfizer placed the patent in the Orange Book. However, the Federal Circuit noted that the listing of a patent in the FDA's Orange Book by an NDA filer is a Hatch–Waxman requirement, and that this should not be taken as a blanket threat to potential infringers.

Teva also argued that the Medicare Amendments of 2003 specifically allowed for a declaratory judgment action to be brought under these exact circumstances. However, the ruling in this case seems to make these provisions superfluous.

In his dissent, Judge Mayer argued that the filing of an NDA application combined with listing of the patents in the Orange Book does give rise to a reasonable apprehension that an ANDA filer and declaratory judgment plaintiff will face a patent-infringement suit. In addition, Pfizer had sued Ivax for patent infringement of the '699 patent and had refused to grant Teva a covenant not to sue for infringement of the '699 patent. He also explained that the inability of Teva to file a declaratory judgment action leads to an anomalous result.

Judge Mayer explained that although the 'parking' strategy is a win–win situation for the first ANDA filer and the branded drug manufacturer, subsequent ANDA filers, such as Teva, face a significant competitive disadvantage. Judge Mayer would have allowed Teva to file a declaratory judgment action to bring to a head the matter of infringement and validity for all generic manufacturers.

Teva Pharmaceuticals, Inc. versus Pfizer, Inc.:
http://www.fedcir.gov/opinions/04-1186.pdf

PATENT PRIMER

Third-party re-examination at the US PTO

Daniel M. Becker

US patent law lacks the robust post-grant opposition procedure available to third-party challengers under the European Patent Convention. Instead, US law offers two variants of post-issuance re-examination proceeding, each of which permits limited third-party challenge to patent validity. Neither is widely used, but *ex parte* re-examination, in which the third party is precluded from participating in the proceedings after filing the initial re-examination request, has proven to have some value as a tool in defence of actual or threatened infringement litigation.

Ex parte and *inter partes* re-examination

The original re-examination procedure, established in 1981, is conducted *ex parte*. This circumscription of third-party participation, coupled with constraints on the grounds on which re-examination can be requested, has substantially limited the use of *ex parte* re-examination: in 2003, only 239 third-party requests for *ex parte* re-examination were filed. Of these, an appreciable fraction were filed in the context of concurrent infringement litigation.

In an attempt to broaden the participatory role of the third-party challenger, Congress established an *inter partes* re-examination procedure 5 years ago in which the requester participates more fully. Even after statutory amendment in 2002, however, this procedure remains moribund, fatally afflicted by a statutory provision that prohibits the third-party requester from "asserting at a later time, in any civil action … any ground which the third-party requester raised *or could have raised* during the *inter partes* re-examination proceedings". In 2003, only 21 requests for *inter partes* re-examination were filed, of which 4 were known to the US Patent and Trademark Office (US PTO) to have related litigation.

Legislation that would establish an adversarial post-grant opposition procedure modelled after that available in the EPO was introduced in Congress in October 2004 (see box), but it seems unlikely to have an early passage.

Request for *ex parte* re-examination

At any time during the period of a patent's enforceability — from the day of issuance to the sixth anniversary of its expiry — any party can file a request for *ex parte* re-examination of any one or more of the patent's claims.

The request for *ex parte* re-examination must allege that prior art raises a substantial new question of patentability of at least one claim. Only printed prior art is cognizable, and the request must allege that the art compromises either the novelty of the claim or its 'originality', establishes the existence of a statutory bar, or calls into question the non-obviousness of the invention. The request can also allege statutory or non-statutory double-patenting over one or more of the patentee's other patents.

The patent office will not consider other grounds for challenging validity, such as improper inventorship, inequitable conduct, public use, failure of the patentee to disclose the best mode or the existence of an invalidating prior sale, and will only consider the adequacy of the specification's written description and enabling support to assess the patentee's entitlement to a priority date that precedes the effective date of a reference.

Ex parte re-examination proceedings

The re-examination request is assigned to a patent examiner in the relevant art group who had not earlier been involved in the patent's examination. The examiner must decide, within 3 months, whether the cited art raises a substantial new question of patentability. Under the US PTO's internal standard, the examiner must decide whether there is a substantial likelihood that a reasonable examiner would consider the prior art 'important' in deciding whether or not one or more claims is patentable. This standard is substantially less stringent than that used to reject claims during examination, and the re-examination request is almost invariably granted (almost 95% in 2003).

If re-examination is ordered, the patentee can file an optional statement. This is rarely, if ever, done, because such a response triggers the only formal opportunity for the third-party requester to file an additional paper.

Thereafter, prosecution re-opens and proceeds *ex parte* (albeit publicly), typically with examination of all claims, to issuance of a re-examination certificate. The certificate either confirms all claims as originally issued (30% of all re-examination certificates issued since 1981 in *ex parte* re-examinations requested by third parties), cancels all claims (12%) or confirms the patent with amended claims (58%).

Strategic value

Despite its significant limitations, *ex parte* re-examination offers certain limited advantages to third-party requesters in the face of actual or impending litigation: litigation, with its attendant costs, is typically stayed pending resolution of the re-examination; the burden of proving invalidity is reduced from the "clear and convincing" standard that is required in litigation to "preponderance of the evidence"; and even without invalidation or amendment of the claims, the re-examination proceeding can lead to further statements by the patentee that can be used to limit the construction of the confirmed claims.

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EXCERPTS FROM PROPOSED LEGISLATION HR 5299

- "A person may request that the grant … of a patent be reconsidered by the Patent and Trademark Office by filing an opposition seeking to invalidate one or more claims in the patent."
- "A person may not make an opposition request … later than 9 months after the grant of the patent … or later than 6 months after receiving notice from the patent holder alleging infringement of the patent."
- "The issues of invalidity that may be considered during the opposition proceeding are double patenting and any of the requirements for patentability set forth in sections 101, 102, 103, and 112 … except for … best mode … and any issue arising under subsection (c) [abandonment of the invention], (f) [derivation], or (g) [prior invention] of section 102."
- "The opposer in an opposition proceeding under this chapter shall have the burden to prove the invalidity of a claim by a preponderance of the evidence."
- "The Director shall assign the opposition proceeding to a panel of three administrative patent judges."
- "Any party to an opposition proceeding … may request an oral hearing…"

CAREER PATH

Chris Lipinski

Chris Lipinski, formulator of the 'rule of five' and Senior Adjunct Research Fellow at Pfizer's Groton laboratories, has successfully held a senior role in the pharmaceutical industry but has remained unencumbered by managerial responsibilities. He has followed a career path that allowed him to do something he really enjoys, and urges young scientists to do the same.

As a student, Lipinski was interested in the biological applications of chemistry and soon abandoned his medical studies, ultimately earning his Ph.D. in physical organic chemistry. "The principles that I was learning kept coming up in drug-industry literature, and got me interested in that field, but I knew I didn't have enough synthetic chemistry experience." Thanks to National Institute of General Medical Sciences postdoctoral funding from the US National Institutes of Health (NIH), Lipinski got the opportunity to work in Bob Ireland's synthetic chemistry laboratory at Caltech. "In general I am more a supporter of the private sector than the public sector but this particular NIH program helped me personally and this kind of opportunity for young scientists is exactly what the NIH should be funding."

Lipinski's only career regret is not publishing early. "It's important — your career is in your hands, and there's no assurance that the company you start working with will be the same company you retire with. Publishing is a great educational tool: it makes you go through the intricacies of the science, you have to review the literature and you go through the peer-review process. I think it really makes you a better scientist."

Frustrated with the conservative publication policy at Pfizer in the mid-1970s and having had applications to two prestigious conferences turned down, Lipinski decided to try and beat the obstacles in the Pfizer publication system of that era, and sought the advice of Joe Lombardino, an experienced medicinal chemist. "I greatly respected Joe and he had a very sound publication record. He told me there were some tricks you could use. So I started writing review articles and working in collaboration with people in other departments — work that was not part of any official Pfizer project specification."

It was at this time that Lipinski learned another useful attribute for the industrial scientist — information sharing. "A particularly influential manager, Hans-Jürgen Hess, Director of Medicinal Chemistry at Pfizer at that time, once said to me, 'If you want something from somebody, go to them with something first. Be outgoing and volunteer information, and be helpful even when there's no immediate payback, because somewhere along the line you might need a favour.'"

Another senior chemistry manager, Chuck Harbert, encouraged Lipinski to study the physical property measurements of drugs as a sideline. "It was in 1990 and our project was going very slowly. I explained my frustration to Chuck and was surprised when he asked what he could do to help." He indulged Lipinski's interests by providing US$30,000 on the condition that he find his own lab space and temporary scientific manning, and present his work regularly to the departmental management. "The scientific culture at Pfizer was fairly permissive — so as long as you weren't wasting your time, there was no problem." Later on, Harbert invited Lipinski to a meeting that ultimately led to the concept of the 'rule of five'. "There was a meeting of pharmaceutical scientists and chemistry managers, and Chuck wanted me to attend. I heard this litany of horror stories about the poor solubility of compounds coming out of our medicinal chemistry laboratories and knew we had to work on this. That meeting turned my entire lab around." Without asking for permission, he used his contacts and, in a conversation over hotdogs and sauerkraut with a developer at a Pittcon meeting, determined the specifications for the first automated solubility apparatus in the industry. "It was very primitive, but it worked, and we ran that assay for about 1,000 compounds. As a scientist you have to take the responsibility to go ahead with an idea — had this gone down in flames, I would have had to bear responsibility for it."

"Publishing is a great educational tool ... I think it really makes you a better scientist."

Despite being retired for two-and-a-half years, Lipinski speaks to us from his Pfizer office. It's a testament to how much he has enjoyed his career, and something he says is important for young scientists to consider. "Early on in your career you want to get exposed to as many fields as possible. Many organizations now support continuing education, which is a great way to explore different disciplines. Then, when an opportunity arises to hybridize between fields, you're in a good position to take it."

One thing that has changed since Lipinski joined Pfizer is the long-term career prospects for medicinal chemists. "When I joined Pfizer, starting as a medicinal chemist in a large pharmaceutical company meant you could expect to end your career there. I don't think you can count on that any more." With more of an onus on individuals to do their own career planning, it is also more important for young chemists to increase the breadth of their skill sets. "When I did my postdoctoral research, molecular genetic sciences did not exist, yet now it is increasingly a part of discovery research, especially with the advent of biomarkers." The interaction between chemistry and genomic disciplines means learning a completely different vocabulary and appreciating cultural differences, too. However, Lipinski thinks it's worth it: "There is more satisfaction and the team concept is more widespread than before. Many organizations have migrated away from departments separated by discipline. At Groton, there are no separate chemistry, biology or molecular genetics departments — everybody works in teams, which makes the local successes much more satisfying."

For medicinal chemists, the dream is to discover a drug. Lipinski did not achieve this directly, but he contributed a useful principle that might help others discover many drugs. He now intends to get involved in promoting data sharing between industry and academia, which he hopes will set a precedent for addressing other 'log-jams' in research. "Instead of criticizing the patent system or arguing about discovering drugs for profit, maybe we can begin to build bridges by starting at a technical level. I'm very excited about that."