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analysis

The good, the bad and the ugly red tape of biomedical research

How could regulators lower bureaucratic hurdles in clinical research without compromising the safety of patients?

Biomedical scientists have long felt the tension between their desire to perform innovative clinical research and the bureaucratic red tape that aims to protect patients. For years, scientists have been complaining about the rules and regulations that can hold up the progression of their biomedical research from the bench to the bedside. A recent study has once again highlighted this problem (Contopoulos-Ioannidis *et al*, 2008). The authors examined 32 scientific papers describing effective medical interventions, each with more than 1,000 citations, which, they argue, suggests that the publications represent 'scientific milestones'. Within the scope of the study, the average 'translational lag'—the time between a discovery and the first highly cited study showing its clinical usefulness—was 16.5 years, with a range of 0–221 years.

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Sometimes, of course, the translation from research to clinical application occurs relatively rapidly. Indinavir (Crixivan®; Merck Sharp and Dome, Whitehouse Station, NJ, USA), part of the HAART (highly active antiretroviral therapy) combination therapy for HIV/AIDS, and abciximab (ReoPro®; Eli Lilly, Indianapolis, IN, USA), used to prevent thrombosis after certain cardiovascular procedures, both needed just four years to progress from the initial patent to the publication of a highly cited, randomized study. By way of a rather extreme contrast, the discovery of nitric oxide as a chemical substance was made in 1772. Yet, the first highly cited article—relating to its clinical use in adult respiratory distress syndrome—was not published until 1993. "Successful translation of medical interventions is very demanding and takes a lot of time," commented John Ioannidis, senior author of the 2008 study and chairman of the Department of Hygiene and Epidemiology at the University of Ioannina School of Medicine in Greece.

"Two counter-forces determine the speed at which advances move from the laboratory to the clinic," explained Brian Walker, Professor of Endocrinology and Chair of the Masters Programme in Translational Medicine at Edinburgh University in Scotland, UK. "On the one hand, there is the desire to test technical advances, such as stem cells and gene therapy, in the clinic as soon as possible. On the other hand, layers of regulation, bureaucracy and a conservative attitude among regulators hinder implementation of new advances."

According to Jonathan Weber, Director of Research at the UK's Academic Health Science Centre—a partnership between Imperial College London and Imperial College Healthcare NHS Trust—the 2004 EU clinical trials' regulations increased the complexity, cost and time needed to gain approval for clinical trials. These regulations impose heavy responsibilities on universities, Weber commented. "The 2004 act makes Good Clinical Practice a responsibility under criminal law rather than a moral obligation, and the thought of a vice-chancellor going to prison focussed universities' attention," he said by way of example.

"Every serious clinical researcher has several examples of ludicrous bureaucratic restrictions hindering their investigations," added Paul Stewart, Professor of Medicine and Director of Research at the University of Birmingham's College of Medical & Dental Sciences, UK. He noted that four or five separate bodies evaluate a research protocol and that completing the forms can take 60–70 man hours, followed by up to four or five months before approval is given. Stewart and colleagues have, therefore, argued that the current regulations pose a "real threat to clinical research" (Stewart *et al*, 2008). "It's galling when we can't even use a urine sample without filling in seemingly endless forms," he said.

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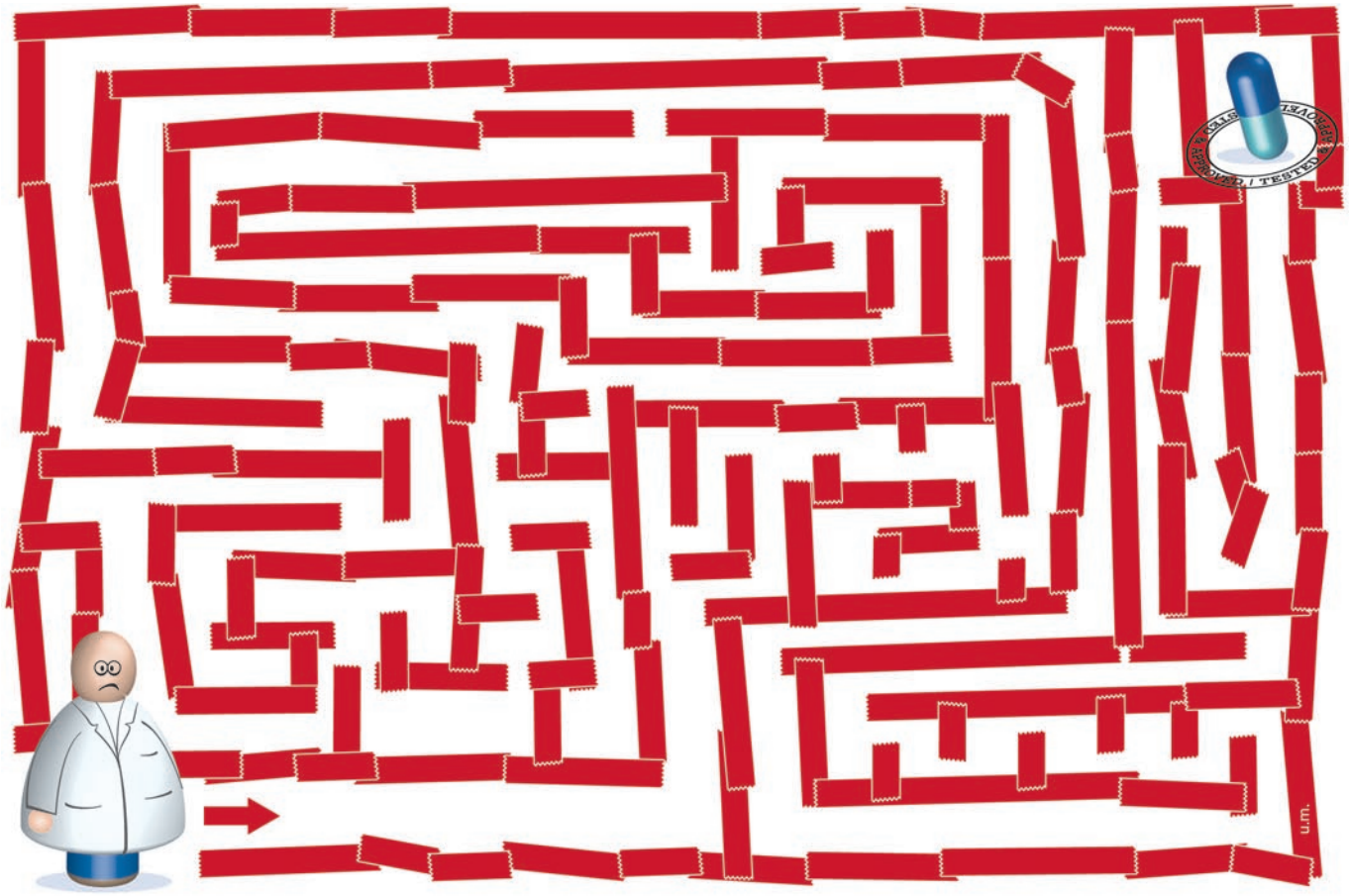
"There's no doubt that the way the regulations have grown makes the system too cumbersome," Walker agreed. "Each regulation seems rational and sensible when considered in isolation. However, together they create a trap for innovative translational research. It's hard to find a way through even for experienced researchers. The average multi-tasking clinician often finds the system too cumbersome and, therefore, doesn't perform research."

In theory, the regulations governing clinical research should apply across the EU; however, their implementation varies between countries. In Italy, for example,



surgical consent generally includes the provision to store tissue samples for future research. "In the UK and, to a lesser extent in France, these samples just end up as clinical waste," Stewart noted.

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"The UK takes the letter of the law quite strictly, and this adds to our burden compared to some European countries where a more relaxed interpretation of the regulations exists," Weber commented. "A consistent approach across the EU would be helpful, and personally, I should like to see a reduction in intensity of monitoring for university-based, publicly funded clinical trials. The rules appear to favour a high barrier to clinical trials, which favours pharma-funded research disproportionally."

Despite all the bureaucracy, the system is not infallible. In 2006, six healthy volunteers received the candidate T-cell stimulant TGN1412 and subsequently experienced life-threatening cytokine release syndrome during a phase I study at Northwick Park Hospital in London, UK. The high-profile case contributed to increasing concerns over the safety of patients and volunteers in clinical studies. "As a society generally and in medical research particularly, we have become very risk averse. We seem unwilling to accept almost any element of risk," Walker remarked. "If we are to make advances, we need to accept that episodes such as Northwick Park can happen. Researchers, regulators and politicians need to help change the way society views risk."

Furthermore, Walker commented that occasionally his research into steroid action reveals specific effects that could cause adverse reactions, which the current clinical development guidelines would miss. "Despite being cumbersome enough to obstruct research, the system does not effectively spot problems," he said. "We need a more dynamic system."

Against this background, how can researchers and regulators improve the translation from research to clinic? "There is some risk in generalizing," Ioannidis warned. "However, I believe that four features contributed to the rapid translation of indinavir and abciximab." First, Ioannidis' research suggests that new technologies tend to reach highly cited status more rapidly than studies of older drugs. Second, a targeted research effort supported both drugs; and third, cooperation of basic and clinical scientists helped to move indinavir and abciximab rapidly from preclinical development to clinical testing. "Basic scientists should actively try to link their efforts with clinical researchers and vice versa," Ioannidis suggested. Finally, indinavir and abciximab underwent large trials with clinical, as opposed to surrogate, endpoints. "When done correctly, large trials with clinical endpoints can provide answers rapidly,"

he said. "By contrast, surrogate endpoints often mislead."

Walker, however, believes that greater use of biomarkers and genetic stratification could speed translation; although, he thinks that the value of biomarkers in early clinical development needs assessment by formal experimentation. "Pharmaceutical companies need to demonstrate that using biomarkers more extensively speeds up development without compromising safety," he said. "But some companies will need to take a lead. The status quo is not an option."

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Indeed, the pharmaceutical sector seems to recognize the need for change. The Innovative Medicines Initiative is a Public–Private Partnership between the European Commission and the European Federation of Pharmaceutical Industries and Associations (EFPIA; Brussels, Belgium). The Initiative aims to increase "the systematic use of biomarkers […] applying innovative technologies such as genomics and proteomics in combination with appropriate knowledge management capabilities" and facilitating "a smooth transition from basic science to clinical research and regulatory standards".

Meanwhile, Weber would like to see an expansion of the 'academic health science centre'. "If academically based clinical research is to be facilitated within the current regulatory environment, then we need to create an infrastructure that eases the pain of translation," he said. "Clinical research needs to be professionally organised under the 2004 act. So we need to create the university-based structures to facilitate research." In line with this, Stewart favours a single, web-based system to submit and review protocols rather than having to apply separately to individual bodies.

Weber also advocates drawing a regulatory distinction between academic and industry-sponsored studies. "For licensing studies, pharma and biotech would retain the high degree of regulatory attention, but university-based clinical research, which is aiming to explore mechanisms of action rather than licensure, might be subject to a lower level of regulation, as was the case before 2004," he said. "A more 'relaxed' approach to studies sponsored by universities would help unblock the regulatory pipeline."

Although loosening the bureaucratic hold on academic research should help to speed up translation, regulators still need to be able to protect patients, especially in the light of several recent high-profile safety concerns, including those surrounding cerivastatin (Baycol®), rofecoxib (Vioxx®), tegaserod (Zelmac®), rosiglitazone (Avandia®) and, most recently, Acomplia® (rimonabant; Sanofi-Aventis, Paris, France). In October 2008, the European Medicines Agency (EMEA; London, UK) suspended marketing authorization for the anti-obesity drug after the Committee for Medicinal Products for Human Use (CHMP) noted "an approximate doubling of the risk of psychiatric disorders in obese or overweight patients taking Acomplia compared to those taking [a] placebo." The committee added that new data suggested that serious psychiatric disorders might "be more common than in the clinical trials used in the initial assessment" (EMEA, 2008).

Such high-profile cases bolster the case of scientists and consumer advocacy groups who offer, in the words of a recent review, "mounting criticism of regulatory agencies for allowing drugs on the market too early" (Eichler *et al*, 2008). Such commentators typically call for more comprehensive pre-marketing safety data and more rigorous assessment, which would protract the time to market. Conversely, the review notes the increasing number of patients' organizations, some non-governmental organizations, and several commentators in the pharmaceutical industry, who "denounce what is perceived as an increasingly risk-averse regulatory culture" (Eichler *et al*, 2008). For example, a 2004 report by the World Health Organization (WHO; Geneva, Switzerland) commented that "[p]harmaceutical innovation in Europe could be improved through reforms of regulatory and pricing policies" (Kaplan & Laing, 2004).

Improving post-marketing surveillance should help, Stewart believes, to balance the competing tensions of more rapid development and patient safety. Conditional marketing authorization offers another possible approach. In July 2006, the EMEA issued the first conditional approval for sunitinib (Sutent®; Pfizer, New York, NY, USA), which is used to treat refractory metastatic renal cancer. The EMEA considered that, despite "methodological shortcomings" in some of the studies, the tumour shrinkage of around 36% of previously treated patients was "unprecedented" and, therefore, recommended conditional approval. Pfizer had to provide evidence within a specified time that sunitinib prolonged progression-free survival or overall survival. After Pfizer provided adequate data, the EMEA switched sunitinib to a standard marketing authorization in January 2007 (Eichler *et al*, 2008).

Such initiatives are particularly important given that many of the products of modern research are monoclonal antibodies and other biopharmaceuticals. Biologicals accounted for 22% of new chemical entities approved by the EMEA between 2003 and 2006. However, approximately 25% of the biologicals approved between January 1995 and June 2007 in the USA or Europe received safety-related, post-marketing regulatory actions, which ranged from letters to doctors to the inclusion of black box warnings on the US label.

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One recent study found that 'first in class' biopharmaceuticals—the first members of a new group of medicines—were the most likely to attract safety-related, post-marketing regulatory action (Giezen *et al*, 2008). "The study provided an insight into the safety problems identified in the post-marketing setting," commented author Thijs Giezen, from the Utrecht Institute for Pharmaceutical Sciences and the Dutch Medicines Evaluation Board. "We hope that post-marketing studies can specifically focus on these problems based, in large part, on the knowledge provided by pharmacology, pre-clinical and clinical studies," he remarked. "More in-depth evaluation of the mode of action of biologicals during the pre-registration phase may help to better predict potential risks that should subsequently be monitored during the post-marketing phase." Giezen added that basic

and clinical researchers will need to collaborate more closely together with regulators to prevent the increased mechanistic evaluation from further delaying translation.

"We should try to identify new safety issues as soon as possible using close monitoring and enhancing spontaneous reporting; and regulatory authorities should be actively involved in the design of the post-marketing safety studies," commented Aukje Mantel-Teeuwisse, also from the Utrecht Institute for Pharmaceutical Sciences and the Dutch Medicines Evaluation Board.

Overall, lowering some of the bureaucratic hurdles, particularly for academics, and increasing the scrutiny in licensing studies, particularly after launch, could help to speed up the translation from bench to bedside while still ensuring patient safety. Such a shift would move the regulatory onus from academics to the pharmaceutical sector—after all, as Stewart remarked, pharmaceutical studies account for only about 30% of biomedical research in his institution. According to many researchers, the current regulations, although established with good intent, are stifling academic research and hindering patients' access to innovative technology. "It's not really surprising that there are delays getting research from the bench to the bedside," Stewart concluded. "The bureaucracy makes conducting research feel as if you're swimming through porridge."

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