

GUEST EDITORIAL

THE INSTITUTE OF MEDICINE REPORT ON THE FDA:
WHERE IS THE SCIENCE?

In the past several years, the United States has witnessed a perceived drug safety crisis. The withdrawal of Vioxx, the potentially unsafe decrease in drug approval times due to the controversial Prescription Drug User Fee Acts (PDUFA), and the undue industry influence that these Acts may have entailed have fueled these sentiments. It is in this context that the Institute of Medicine (IOM), at the request of the Food and Drug Administration's (FDA) Center for Drug Evaluation and Research (CDER), released its final recommendations for reforming the US drug safety system this past September (Institute of Medicine, 2006). The goal of the IOM panel was laudable, since despite the agency's strict adherence to evidence-based evaluation of the products it oversees, less evidence and evaluation exist on its own safety and efficacy. Put differently, no product application would pass the FDA approval process with the quality and type of evidence that currently exist for evaluating the FDA policies themselves.

Though the scope of the drug safety system is wide and diverse, the IOM report naturally focused its attention on the main regulatory body in the US responsible for both pre- and post-marketing assessments of the safety and efficacy of pharmaceutical products, the FDA. Its highly detailed recommendations can generally be divided into improvements in: (1) the organizational structure of the FDA; (2) the methodology and infrastructure to assess drug safety; (3) communication across stakeholders in the drug safety system, e.g. the FDA, patients, and physicians; (4) the regulatory power of the FDA, in particular, during the period of post-approval marketing; and (5) the resources required to fund these recommendations.

Despite the strengths of several of the Institute's recommendations, the main weakness of the report is that it is premised, with little evidence, on a perceived drug safety crisis in the US. Much of this perception centers on heavily publicized drug withdrawals, such as the withdrawal of Vioxx, as well as the PDUFA of 1992, 1997, and 2002. These Acts were designed to lower drug approval times by financing the evaluation process with user fees levied on entities applying for FDA approval. As the IOM report notes, PDUFA has been controversial for several reasons, among the most relevant being the 'too-close' relationship between the industry and the FDA, the potentially unsafe rush towards drug approval, and the pressure imposed on FDA staff due to this rush. *Is there an empirical basis for these concerns and, more importantly, is there evidence that too many unsafe drugs enter the market?*

With regard to PDUFA, while the IOM report nicely documents the decrease in approval times due to these Acts, there is no discussion of whether these reductions were 'rushed' in the sense that the safety and well-being of consumers were compromised. More generally, the report makes no effort to assess whether the decrease in safety due to lower approval times and the additional burden imposed on FDA staff were outweighed by the benefit to those able to consume the drug earlier, an argument suggested by existing evidence. For example, Philipson *et al.* (2005) found that the social benefit generated by reductions in drug approval times in the PDUFA era substantially outweighed any decreases in safety associated with more rapid approval. Focusing on 662 new molecular entities approved from 1979 to 2002 – this includes the period of Vioxx – the authors estimate that the societal gains from reduced approval times amount to \$16–\$32 billion dollars, an amount equivalent to 180–310 thousand life-years. In the extreme case that all drug withdrawals that took place during the PDUFA era were due to lapses from more rapid approval, the number of life-years lost would be 58 thousand. For the case of PDUFA, the trade-off between speed and safety appears to have been quite favorable in the sense of raising

economic efficiency. The popular press quickly picked up on the inconsistency between this study and the IOM report (Wall Street Journal, Editorial, 2006).

As for Vioxx and other heavily publicized drug withdrawals, while they are regrettable, they are not necessarily evidence of a non-optimal approval process. As stated by the IOM report, the drug approval process involves balancing the competing interests of speed and safety. While more extensive pre-approval testing would lead to safer drugs and fewer withdrawals, it would also entail a larger delay for drugs to reach the market. It is very likely that the optimal balance between speed and safety allows for the possibility that some unsafe drugs will reach the market, and therefore, the existence of drug withdrawals is not necessarily evidence of a drug safety crisis in the sense that too many drugs are withdrawn. Rather, it may simply be the necessary consequence of a policy that appropriately balances the speed–safety trade-off. Moreover, given the tremendous value of new medicines estimated by others (Philipson and Jena, 2005; Murphy and Topel, 2006), the potentially negative safety consequences of new drugs would have to be huge to dwarf the gains associated with increased access and speed to the masses of beneficial drugs.

Many of the report's recommendations seem to be predicated on the existence of a 'drug safety' crisis. For example, one of its strong recommendations is a 2 year moratorium on Direct-to-Consumer-Advertising (DTCA) for newly approved drugs. The report's main argument for this moratorium is that newer drugs have not undergone the same post-market surveillance and assessment as other established products, and that DTCA may lead to more consumers being exposed to the unsafe new drugs. However, the converse is also true – DTCA restrictions will also reduce patient access to potentially useful new drugs. We believe that the latter is more likely, given the evidence that the vast majority of approved drugs are safe and have tremendous value. Moreover, while it seems reasonable to assume that DTCA (and marketing more generally) increases usage and can alter prescribing patterns¹ – otherwise, spending would be wasted by manufacturers – given its small share in total advertising (15%, according to the United States Government Accounting Office, 2002), it is unclear how much DTCA restrictions would restrict quantity in the first place. Indeed, assessing the effects of DTCA is similar to assessing the effects of PDUFA, since both increase access to drugs. Unfortunately, despite its strong stance, the IOM report offers no empirical evidence on whether DTCA has decreased or increased social welfare.

Despite its weaknesses, we agree with the IOM report on several issues. The current focus on pre-market assessments, routinely done through gold-standard randomized controlled trials, should be coupled with equally vigilant post-market studies of a drug's safety and efficacy. The science of approval is far more elaborate than the science of withdrawal, many times done under great political pressure. This is particularly important since pre-market assessments often rely on small, select groups of patients while post-approval use is typically characterized by a far larger and more heterogeneous population, one for whom a drug may act differently or elicit rare and therefore previously unnoticed side-effects. Furthermore, there is a clear need for stronger FDA commitments to post-approval studies, since pharmaceutical companies have little incentive to engage in such studies as they can only lower profits and, as the IOM report notes, the FDA's current legal authority over post-market study commitments is weak or unclear.

Finally, the IOM report recommends several measures to prevent 'regulatory capture' of the FDA by the pharmaceutical industry. In the first instance, we reiterate that, given the evidence of the tremendous net value of new medicines, it is unclear that any regulatory capture has had negative social effects. Moreover, the IOM report provides little evidence of regulatory capture, and indeed a recent study (Lurie *et al.*, 2006) published in JAMA suggests that the conflicts of interest, argued to be an important drawback of PDUFA, have played little or no role in the FDA's approval decisions. The report also

¹ The effects of DTCA on prescription drug usage are detailed in Chapter 5 of the IOM report.

argues that PDUFA user fees should be raised from taxes on prescriptions, drug advertising, or general taxation. However, user fees have several advantages over the other proposed taxation methods as the stakeholders in the drug safety system pay the taxes, regardless of their incidence across those stakeholders.

Overall then, the IOM report contains some strong recommendations. However, we believe that the scientific, as opposed to rhetorical, case of a 'drug safety crisis' is misplaced and that the recommendations in the IOM report must be interpreted in this light. The lack of science or empirical evidence backing the IOM recommendations is unfortunate, as so much opinion about the FDA lacks a scientific basis already.

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