nature biotechnology

Roadmap for revitalization?

The newly passed US Food and Drug Administration's (FDA) Amendments Act (FDAAA) sets the stage for key improvements to postmarketing surveillance as well as the preapproval process.

Every five years, US Congressmen, together with an assortment of lobby and special interest groups, lead FDA staff on a merry dance, seemingly to the edge of oblivion and back again. The dance involves reauthorization of the 1992 Prescription Drug User Fee Act (PDUFA), which provides the FDA with extra funding from user fees from industry in exchange for meeting drug-review performance goals. This time around, with 2,000 agency jobs on the line if user fees were not renewed by month's end, the dance finally ended on September 21, when a final version of FDAAA (including PDUFA IV) passed both houses by large majorities. The new legislation makes $392.8 million in user fees available for agency reviews of drugs and devices, representing a 29% hike in industry fees. Key sections of FDAAA also pave the way for enhancements to the effectiveness of premarket review and radical changes in postmarketing drug surveillance, hopefully laying the groundwork for a registration and reporting system capable of following products across their full life cycle.

According to one observer, the new legislation is "the mother of all FDA authorization bills," even though much of the 427 pages are taken up with what might be dismissed as administrative white noise: new reviews for direct-to-consumer advertising; six-months market exclusivity to encourage trials on new pediatric uses; and new codes to combat conflicts of interest on review committees.

Every time PDUFA is up for renewal, it is engulfed in the prevailing pharmaceutical zeitgeist. In the early 1990s, faster review for AIDS drugs was 'on message' and in 1997, streamlining and harmonizing biologic regulatory process was the buzz. This year, it is greater authority for safety oversight, with the outcries over Vioxx (rofecoxib), Seroxat (paroxetine), Epogen (epoetin-alpha) and, most recently, Avandia (rosiglitazone) clearly ringing in legislators' ears.

Reading between the lines (all 10,500 or so of them), the most important parts of this bill relate to infrastructure for the acquisition and hosting of trial data and the extension of postmarketing surveillance (phase 4 trials).

Phase 4 trials have long been the ugly duckling of drug development, left to languish untended because FDA has insufficient resources to enforce them and drugmakers would rather focus time and money on developing new products than discover problems with their existing ones. The scandalous disregard of sponsors for their commitments is borne out by the numbers: as of last year, three-quarters of phase 4 trials for small molecules and a third of those for biologics had yet to be launched.

Under FDAAA, the agency now has more teeth. It has the power to require a phase 4 commitment in cases where routine safety monitoring is deemed insufficient. It can also levy fines (on the order of $10,000 for the first 30 days, and then $10,000 every day thereafter) if manufacturers fail to meet their postmarketing requirements. Given the cost of phase 4 monitoring (millions), these fines do not represent much of a stick.

But three other factors seem likely to increase the chance of FDAAA leaving a marked impression on the regulatory landscape of the future.

The first of these is the specter of noncompliance on companies' public image. Although a monetary punishment could be swallowed (at least by most larger firms), 'noncompliant' branding is likely to damage both a company's reputation and its wider business.

Second, the new monitoring system to be implemented under the Act, which involves a publicly accessible clinical trial results database built onto the preexisting US clinical trials registry run by the US National Institutes of Health (http://www.clinicaltrials.gov/), is sorely needed to overhaul the FDA's current Byzantine and antiquated adverse event reporting system, which collects paper reports that are filed by physicians and sent by drug companies. Under the new system, phase 4 trials and adverse events will be uploaded directly by patients, providers, insurers and drug sponsors. The goals are ambitious: at least 25,000,000 patients by July 2010 and 100,000,000 patients by July 2012.

The system makes sense not only for regulators, but also for industry and the risk-minimization strategies of its products. For the former, more time can be invested in carefully designing phase 4 trials than before—several observers have cited the last-minute nature of postmarketing in the approval process and often less-than-optimal protocol design of these studies as a major reason for poor company compliance with postmarketing commitments. FDA can now work with companies to carefully tailor phase 4 studies to address the relevant safety questions.

For companies, the new system will enable early warning of toxicological problems, allowing firms to prepare their public relations responses more professionally and providing them with a development edge over competitors. After all, a clinically readied molecule is usually only one of a stable of molecules in development at any given company. With fast-following competitors poised in the wings, early access to carefully characterized, genotypically stratified response and toxicology data ought to be key in allowing innovative firms to stay ahead.

Finally, the ability to closely monitor drugs postapproval should also enable FDA to streamline the preapproval process before phase 4. This is good news for both companies and patients: streamlined approval will enable firms to move to revenue generation earlier and provide patients with more rapid access to medicines.

Thus, FDAAA is an important step forward toward a more rational, data-based drug development and monitoring process. Industry must now accept that the time has gone when it held data to itself as a dangerous substance. Indeed, there looks likely to be several benefits: potentially faster drug approvals; the generation of useful market segmentation data; and, most important of all, some small progress in restoring public faith in the regulators and regulated.