It's the Law

By Linda Horton, JD

A Toolkit for Fixing FDA: Hearing Aids, Plate Glass and a Crystal Ball

In recent months, the best minds in American medicine, public policy and journalism have contributed ideas to the debate about "fixing FDA." There emerges no consensus about whether FDA is broken or, among those who think it is, what should be done to fix the agency's perceived flaws.

Those of us whose résumés include a substantial period as FDA insiders—in my case, for precisely a third of a century—are sought out for commentaries such as this one. Most FDA veterans empathize with its current leaders. In fact, the agency's alumni association issued a statement expressing continued confidence in the agency (www.fdaaa.org). However, those few who had spent their FDA careers battling with its management seemed delighted that the agency was getting its just due, and piled on criticisms of their own. Few of us are in favor of separating premarket drug evaluation from postmarket drug safety oversight; the dilution of relevant expertise would be too high a price, considering that other mechanisms exist to guard against loss of objectivity by those who recommended approval of a product in the first place.

The common ground for all FDA insiders is that the current "perfect storm" is but one in a series of recurrent drug safety crises that the agency has faced in the past century. Whether one starts with the infectious horse serum that took several young lives and stimulated passage of the 1902 biologics law, or the Elixir of Sulfanilamide tragedy that took the lives of another 100 children and led to the new drug law, it is clear that drug safety issues are nothing new for FDA. Other periods in which drug safety issues erupted included the Cutter polio vaccine episode of the 1950s, thalidomide and its birth defects (leading to the 1962 drug amendments), FDA drug decisions in the 1960s highlighted in Congressman Fountain's hearings, the agency decisions debated in the 1970s hearings by Senator Kennedy and involving "the FDA dissidents," the early 1980s advocacy for better drug availability by both anti-regulation economists and AIDS activists, the generic drug scandal of the late 1980s and the withdrawals of Baycol, "fen phen" and Rezulin in the 1990s.

Observers may discern in this history a trend that we could call the FDA Pendulum: it swings to one extreme, where the agency is extraordinarily cautious, demanding, and slow in its new drug decisions and then—following much-publicized deregulatory reforms—the pendulum swings to the opposite extreme, with a speed-up in drug approvals (which agency critics attack as throwing caution to the wind). Then, after some unexpected patient events, followed by FDA regulatory reforms, that pendulum goes back to the super-cautious mode. Some view the FDA Pendulum as evidence that the agency is "damned if it does and damned if it doesn't," given its demanding stakeholders in Congress, consumer groups, and the industry.

The past year's trio of problems—antidepressants and suicidality, flu vaccine production failures and the explosive COX-2 safety debate—mark the first drug safety debacle of the new millennium. Will the FDA Pendulum now veer back to the cautious side and what would be the impact of such a move? Such a swing would be applauded by those who believe that recent FDA decisions cavalierly disregarded public health, while those who want predictable decisions on new therapies try to project when the return swing of the FDA Pendulum might occur.

There is evidence to support the view that each pendulum swing is an essential prelude to change; every drug safety crisis in FDA history has led to improvements in the regulatory system. Indeed, I would argue that the FDA Pendulum's oscillatory motion serves as an energy source for an institution with a lot of fondness for its past and the status quo. Without the pendulum's energy, there is little incentive for reform. We should not wish for the swinging of the FDA Pendulum to cease any more than we would wish for a clock whose pendulum has ceased movement. A pendulum in equilibrium is found only on a clock that is no longer working, with its face fixed forever in the inertia of yesteryear. This is not where a dynamic institution like FDA needs to be.

I, for one, would hope that while this FDA Pendulum is on the cautious side, there will be more attention to the safety problems inherent in proposals to relax controls for drug importation and follow-on proteins. These issues present health threats as compelling as others that have dominated the recent drug safety debate, yet are seen by many as economic and competitive matters.

And, if the current turmoil is the fuel of FDA progress, what changes should FDA make?

A legion of regulatory doctors has been issuing prescriptions for FDA reform. For its part, FDA has trotted out a new drug safety infrastructure—immediately attacked by critics as insufficiently independent—along with a raft

of new agency guidance documents and long-delayed risk management plans for several specific drugs. Among the proposals are longer and bigger clinical trials; elimination of user fees; greater use of patient registries; imposition of conditions or time limits on approvals; or restrictions of direct-to-consumer advertising, empowering FDA to order postmarketing studies or fine companies failing to complete them and clarifying the agency's authority to order labeling changes. An article in *Forbes Magazine's* January 2005 issue, entitled "Five Ways to Fix the FDA," advocated better funding, more authority, better tracking of side effects and more government-conducted trials, admitted that labeling is not working and sought better ways to implement drug safety management decisions. This article returns later to this set of five ideas, choosing first to address the *Forbes* reform proposals.

Rather than offering my own tweaks of the drug safety system, I have imagined a new FDA tool kit to help correct some weak spots in the current decision-making processes. My sundry assortment of tools would include a hearing aid, some plate glass and a crystal ball.

Hearing Aid

FDA has developed "big ears" on the outside, to hear what its external stakeholders are saying, but can be a bit deaf when it comes to its own staff. Therefore, to better hear what its staff is saying, FDA needs a hearing aid, so that it reaps the benefit of its own staff's wealth of great ideas that often are not vetted, much less adopted, due to the difficulty employees encounter penetrating the bureaucratic layers without being viewed as whistleblowers rather than team players. As mentioned earlier, few experienced FDAers would separate premarket evaluation from postmarket surveillance. One mechanism to ensure that the organization that approved a product maintains its necessary objectivity is for the agency to have a robust mechanism for listening to its own people, including those who have doubts about drug safety.

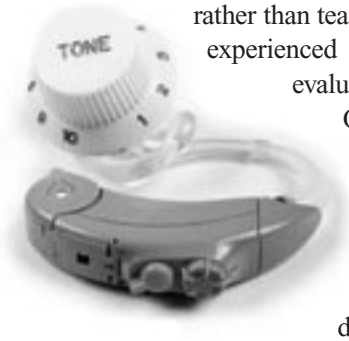

Plate Glass

FDA's much-praised transparency is incomplete. It is time for the agency to establish a system in which there is a public docket for each pending marketing approval applications including: new drug applications, abbreviated new drug applications, biologics licensing applications, medical device premarket approval applications, premarket notifications (510(k)), and new animal drug applications. Although much information in these applications is confidential, commercial information or trade secrets that could not be submitted to a public docket, establishment of a docket at the time of application submission to FDA will enhance transparency and give the public a focal point for comments. FDA traditionally has regarded the existence of a pending application for marketing authorization as confidential commercial information. Under this view, FDA will not even disclose that it has received a new drug application or similar submission unless it has clear evidence that the applicant has itself disclosed the submission. The legal basis for this position has been weak for many years; more than 20 years ago FDA proposed a rule taking the position that a pending application is not confidential commercial information. This idea should be dusted off, updated and reissued for comment.

Crystal Ball

Alternatives are needed to existing adverse event reporting systems, which have limited capacity to reveal or predict drugs' side effects. My view is that the general media ascribe far too much importance to adverse event reporting, and I foresee world peace before I foresee an effective spontaneous adverse event reporting system. Why the pessimism?

Health professionals and hospitals do not have time to file reports; even if they did, they lack the motivation to file reports that might attract liability suits. Reports, when filed, tend to be woefully incomplete, and even as to relatively complete filings, drug regulators cannot determine whether the drug, the underlying disease or some other variable caused the effect in question. Around the world, regulators have masses of undecipherable, confusing, incomplete and duplicative reports. Automation and terminology harmonization will not correct the problem; all the electronic systems and MedDRA (Medical Dictionary for Regulatory Activities) systems in the world cannot fix a system that is fundamentally doomed to failure.

We should stop pretending that the adverse reaction reporting system is fixable; it is not. At best, adverse event reporting systems can signal problems with marketed products, but they cannot answer any other questions, including incidence (the numerator and the true denominator). Adverse event reporting systems cannot be eliminated altogether, due to their occasional detection of a safety problem. Still, more attention should be paid to mechanisms that offer greater promise as means of detecting valid scientific information on drug safety issues, e.g., adequate, well-controlled,

postmarketing, clinical trials and patient registries. Several experts quoted in the *Forbes* article discussed these tools, and an International Conference on Harmonization guidance document recently published by FDA contains a useful checklist to some of these science-based alternatives (or complements) to adverse event reporting.[1]

Replying to *Forbes*

I will respond to the *Forbes* five-point plan from the perspective of someone who spent 33 years in FDA and another three observing it closely from the outside, as a partner in a global law firm. Does FDA need more money? More authority? Better tracking of adverse events? More government-funded studies so that there are sources of clinical data other than those generated by drug-company sponsors? Better ways than labeling to ensure that restrictions on drug use are better observed?

More money

It is difficult to quibble with this one. While FDA's budget is, without doubt, the envy of the agency's counterparts around the world, FDA plays a global role as gatekeeper to new medical therapies that is unrivalled anywhere. This big job requires big money. An unglamorous fact is that every government agency must have a budgetary increase each year just to stay at status quo.

More authority

Whether FDA needs new legislative authority is more controversial, even among FDA officials. A senior FDA drug approval official, Dr. Sandra Kweder, told Congress that the agency could use more authority to direct companies to make specific labeling changes. That position was reversed by a more senior official, Dr. Janet Woodcock. (Apparently FDA and Merck discussed for several months the new labeling for VIOXX, a process that some in FDA blame for delaying the public announcement about the findings of cardiovascular risk.)

My view is that FDA has immense power if it chooses to use it. However, FDA may find it difficult to follow through on a threat to withdraw approval of a marketed drug because the agency may strongly favor the continued marketing of the product, albeit with revised labeling. Many of these labeling debates also drag on, not because of lack of authority, but because the agency has other priorities and does not always ride herd on timely conclusion of a dialogue with a company.

On the issue of penalties, I was quoted in a recent issue of *Business Week* that FDA lacks authority that even the youthful European Medicines Agency will soon possess to impose monetary fines on companies that fail to submit complete information with their applications for marketing authorization, fail to complete condition-to-approval post-authorization studies or violate regulations on adverse event reporting, advertising or marketing controls or other requirements.

What is much more effective than monetary fines for companies with a reputation to protect is adverse publicity, i.e., the "name and shame" policies under discussion in various European contexts. However, any usage of publicity to effect compliance should be tempered with procedural safeguards. Except where there is an imminent public health emergency, before a company is publicly "named" as being non-compliant, the regulatory agency should give the company prior notice and an opportunity either to fall in line with what the agency has requested or to submit information and views on why it should not be compelled to do so. Such procedural safeguards help ensure that use of publicity is not abused and aid the agency in ensuring it has all relevant information before making a decision.

Better tracking of adverse events

As explained above, I believe more effort should be put into alternatives to spontaneous adverse event reporting systems.

More government-funded studies of drugs.

Government-funded research has a place: where would we be without the contributions of the National Institutes of Health to early-stage scientific discovery, and (as mentioned in the *Forbes* article) from time to time the government performs a vital public service by funding longitudinal studies of long-marketed drugs, such as the one on post-menopausal hormone-replacement therapy. Also, public funding can help start-ups with promising therapies to overcome the gaping, billion-dollar abyss between laboratory and medicine chest.

This idea of governmental funding of drug studies is not a new one: I remember that, as a young legislative analyst in the early 1970s, I was assigned to analyze a proposal by then-Senator Gaylord Nelson to establish a National Center for Drug Testing. A new government agency would conduct clinical trials, paid for by industry. I believed then, and I believe now, that large-scale involvement of government in doing primary testing of drugs would be a mistake. Government needs to be able to operate as a check and balance overseeing research done by others, and if government is put in charge of the testing,

there will be a loss of the objectivity needed at the stage of data review.

Admit to the shortcomings of labeling.
Forbes said we should "Forget Labels." I disagree. We cannot give up on labeling; after all, it is a product's charter, defining what indications have been found by FDA to be supported by adequate evidence of safety and effectiveness.

Conclusion

In sum, of *Forbes*' proposals, I would support additional resources for FDA and better alternatives to spontaneous adverse event reporting (like my Crystal Ball), but question those for giving FDA new authority, performance of drug testing by the government or scrapping labels.

So, the toolkit that I would send along to FDA would have in it a rather fat money roll along with the Hearing Aid, Plate Glass and Crystal Ball.

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REFERENCES

1. FDA, *Guidance for Industry, E2E Pharmacovigilance Planning*, April 2005. An Annex to this guidance lists for consideration a number of "pharmacovigilance methods:"
   - passive surveillance systems such as conventional adverse event reporting
   - various forms of active surveillance seeking to ascertain completely the number of adverse events via a continuous pre-organized process such as the follow-up of patients treated with a particular drug through a risk management program
   - reviewing medical records or interviewing patients and/or physicians in a sample of sentinel sites
   - drug event monitoring in which patients might be identified from electronic prescription data or automated health insurance claims for follow-up questionnaires sent to each prescribing physician or patient at pre-specified intervals)
   - patient registries
   - comparative observational studies, including cross-sectional studies (surveys), case-control studies, and cohort studies
   - targeted clinical investigations
   - descriptive studies of the natural history of a disease and of drug utilization (studies that describe how a drug is marketed, prescribed, and used in a population, and how these factors influence outcomes, including clinical, social, and economic outcomes)