

out clinical testing of safety and efficacy, provided they are deemed substantially equivalent to devices already on the market. Despite 1990 legislation ordering the agency to begin requiring more extensive clinical studies of class III devices (those implanted in the body) before approval, most are still approved with minimal testing.⁵ An “improved” pacemaker wire that was approved in this manner recently caused deaths when it fractured after being implanted in patients.

Regarding drugs, the FDA must continue to focus on striking the right balance between safety and efficacy and on promptly sharing emerging safety concerns with doctors and the public. There is consensus on the need for companies to conduct more postmarketing studies of newly approved medicines to look for adverse ef-

fects and measure long-term effectiveness, and the FDA has begun working with organizations that maintain large databases of information on patients to establish the Sentinel System, in which a drug’s safety profile can be efficiently evaluated by epidemiologists. The goal is to have 25 million records available for such studies by 2010, an FDA official said.

Although commissioners often take on the job because they are interested in a specific issue, fixing the FDA will require a leader who is passionate about the agency and its mission as a whole. By restoring science to its rightful status, by forcefully advocating for needed resources, and by improving the FDA’s record as a guardian of public health, the new commissioner will most effectively serve the American people.

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Dr. Okie is a national correspondent for the *Journal*.

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Safe Drugs and the Cost of Good Intentions

Hans-Georg Eichler, M.D., Eric Abadie, M.D., June M. Raine, M.D., and Tomas Salmonson, Ph.D.

In recent years, the pendulum of opinion on the health benefits and risks of drugs has swung back from what were often unrealistically high hopes to much grimmer expectations. This shift has resulted from several high-profile incidents related to the drugs’ risks and the perception that drug companies downplayed safety findings. Not only has the reputation of the pharmaceutical industry become tarnished as a result, but the performance of drug-regulatory agencies has also come under renewed scrutiny. Some observers have concluded that the entire regulatory system must be revamped because

regulators have failed to apply sufficient counterpressure on companies.

Legislators and drug-regulatory agencies in many jurisdictions have taken heed of the calls for a stronger emphasis on drug safety. By 2003, the European Union had instituted a proactive risk-management strategy. In 2005, new European legislation conferred on regulatory agencies the power to require companies to submit, along with their application for marketing authorization, a risk-management plan comprising detailed commitments for postmarketing pharmacovigilance.

Other jurisdictions, including the United States, have introduced or are considering similar legal provisions.

These legislative and regulatory changes have been complemented by research initiatives designed to improve safety-evaluation methods. Regulators will probably soon have at their disposal substantially more powerful tools with which to scan the horizon for adverse drug effects, including ever-larger clinical trials, more widespread use of (preplanned) meta-analyses of trials of individual drugs or drug classes, and results from observational studies involving elec-

tronic records that link drug-use data to health outcomes for millions of patients. Sophisticated data-mining tools are now available that permit real-time analysis of spontaneous reports of adverse drug reactions.

It would be surprising if these powerful tools did not lead to the detection of new drug-safety signals for both new and well-established drugs. These developments are good news — but there are a number of unintended but foreseeable consequences that will need to be addressed before these advances can be translated into real public health benefits.

First, the number of false safety signals is likely to increase. The interpretation of meta-analyses of adverse drug events is not always straightforward, and observational studies may sometimes produce unreliable findings implying the presence of risks that are later proven to be phantoms. All initial safety signals require further verification to justify regulatory action. That is where the difficulty starts: for example, if the validity of observational findings is questioned, it is usually not because adverse events (especially those in large observational studies) may be attributable to chance, but because of potential bias or confounding.¹ Ideally, safety signals would be validated and quantified in randomized, controlled trials, but this approach is often impossible because of the size and duration of the trials that would be required to detect rare adverse drug reactions. So we are often left with very rare but worrisome adverse effects, the risk of which cannot be convincingly verified or refuted without great cost or delay. Such scenarios can result in the loss of public trust and, some-

times, harm to public health from the underuse of potentially life-saving vaccines and drugs. If regulatory decisions were made on the basis of spurious safety signals, we would end up denying patients — often those with life-threatening conditions — access to drugs even if their overall benefit-risk profiles were favorable.

Second, the push for “safe drugs” means that regulators are coming under increasing pressure to raise the bar and to refuse, restrict, or revoke drug licenses. Some may see such increased stringency as an intended consequence, but would it reflect society's preference? There is a common belief that society is becoming increasingly risk-averse, being less willing to accept risk for a given benefit. But we have not seen convincing evidence of such a change with respect to drugs. Calls for “safe” products can be inappropriately interpreted as demanding zero risk. What if patients and consumers have not become more risk-averse but merely more risk-aware? Media coverage (among other things) can disproportionately increase the public visibility of adverse events, inducing biased judgments.² If we have merely become more aware of risks as a result of more widespread reporting of the downside of drug treatment, then denying or delaying access to drugs could lead to more, not fewer, disconnects between regulators and their primary stakeholders, patients and health care professionals.

Third, simply putting more emphasis on drug safety may well fail to buy back trust in drugs. Indeed, it is difficult to conceive how increasing the profile of adverse-effect findings and related communications and adding to

the media coverage would reassure patients, consumers, and health care professionals. In fact, we may instead witness an upward spiral of risk awareness, in which better pharmacovigilance tools will detect more safety signals (some true and some false), which will draw more attention to the downside of medicines and, in turn, give rise to a call for greater emphasis on safety and better pharmacovigilance tools, and so on.

We believe that such a negative scenario is preventable, if the more intense surveillance of drug safety is complemented by additional measures. For instance, regulators need to refine their methods of assessing benefit-risk balances and switch from “implicit” to “explicit” decision making — that is, to an approach involving explicit descriptions not only of all decision criteria and interpretations of data but also valuations, such as the weighting factors for potential treatment outcomes.

Ideally, regulators should also shift from the use of qualitative statements to quantitative descriptions of the size of the net health benefits. We believe that such refined assessments would provide greater transparency and consistency to the decision-making process. This improvement would provide an opportunity to systematically incorporate patients' values and preferences into decisions and create a better communication tool, enabling regulators to publicly justify decisions.

Drug regulators should also lead the way in developing a consensus on what is considered a tolerable level of risk. Experts in other areas of risk regulation, such as the regulation of carcinogenic residues in food or of nuclear power, have long recog-

nized that calls for zero tolerance of risk are untenable and have instead established a consensus definition of “negligible” and “tolerable” risk levels. There is evidence that patients are willing to accept a finite level of risk for a given benefit. For example, a recent survey of patients with multiple sclerosis found that a majority would “definitely” or “probably” use a treatment that was “significantly more effective than currently available drugs,” even with a 1-in-1000 chance of a fatal side effect.³ This information has been factored into a quantitative benefit–risk analysis of natalizumab⁴ — work that offers an interesting case study for regulatory decision making about drugs with a low probability of serious adverse effects. We believe that the public health would be better served if patients’ views of acceptable risk levels were incorporated into benefit–risk assessments.

At the European Medicines Agency (EMA), we no longer use terms like “ensuring drug safety” in public communications, instead striving to ensure a “positive benefit–risk profile” — a phrase implying the concept of tolerability of risk. Indeed, we consider the debate over “safe drugs” to be unhelpful, since words trigger expectations — and every drug is unsafe under some conditions. We also believe that regulators should begin to communicate about benefits and risks, rather than just risks — by presenting, in quantifiable terms that patients can

understand, the benefits of taking a drug and the odds of experiencing adverse effects. Currently, companies, though required to communicate risks, naturally focus on promoting their drugs’ benefits, whereas regulators emphasize the risks — leaving patients and health care providers searching for balanced information. Historically, regulators shied away from communication about benefits for fear of being perceived as doing the industry’s marketing, and certainly more detailed emphasis by regulators on drugs’ health benefits will draw some negative responses. But the alternative seems to be a lack of comprehensive and balanced information on drugs, progression of the spiral of risk awareness, and further erosion of the public trust in drug treatments.

In addition to shifts in regulatory behavior, some changes are needed in physicians’ prescribing practices with respect to off-label use of drugs.⁵ Prescribers need to be fully conversant with a drug’s license and need to discuss with their patients the probable risks and benefits of an off-label use. We also foresee a role for third-party payers, who need to carefully evaluate when to fund off-label drug treatment.

As the early-20th-century satirist Kurt Tucholsky wryly noted, “The opposite of ‘good’ is ‘good intention.’” Although uncritical calls for “ensuring drug safety” are probably well meant, they may be doing harm as well as good. If, however, we make the most of

emerging pharmacovigilance tools and new legislative provisions, we should be able not only to refine benefit–risk assessments but also to maximize the public health benefit of new medical treatments.

Drs. Eichler, Abadie, Raine, and Salmonson report being full-time employees of drug-regulatory agencies. No other potential conflict of interest relevant to this article was reported.

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Dr. Eichler is the senior medical officer of EMA, London. Dr. Abadie is the chair of the Committee for Medicinal Products for Human Use (CHMP) of EMA and scientific advisor to the General Directorate of the Agence Française de Sécurité Sanitaire des Produits de Santé, Saint-Denis, France. Dr. Raine is the chair of the Pharmacovigilance Working Party of CHMP and director of vigilance and risk management of medicines at the Medicines and Healthcare Products Regulatory Agency, London. Dr. Salmonson is the vice chair of CHMP and senior expert at Läkemedelverket (the Medical Products Agency), Uppsala, Sweden.

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