Eye on Safety: Is the FDA Targeting Dermatology?

Multiple recent warnings confirm that the FDA is targeting safety of approved drugs.

Observers give context for the focus on safety.

By Paul Winnington, Editorial Director

If you started your day with a bowl of Cheerios, the toasted oat Os may have seemed innocent enough. But FDA officials say the cereal has been violating Federal law. According to a warning letter sent by the agency to General Mills in May, package labeling stating that Cheerios consumption can help lower cholesterol amounts to an efficacy claim, thus making the cereal a drug. If it wants to tout cholesterol-lowering properties of Cheerios, FDA says, General Mills must submit an NDA (New Drug Application) for the almost 70-year-old product. That a beleaguered agency complaining of insufficient staffing and funding would invest time and energy into claims on a cereal box—which no one contends are false—fueled criticisms.

The FDA has certainly been busy in recent months, and a lot of its attention seems to be directed at dermatology. Some clinicians are still stung by the controversial boxed warnings assigned to Protopic and Elidel a few years ago. In the last few months, the specialty has seen the voluntary withdrawal of Raptiva, boxed warnings and new REMS for botulinum toxins and biologics, and warnings about advertisements for Galderma’s Tri-Luma and Allergan’s Aczone. Some in the specialty worry that the agency is hyper-focused on safety, particularly when it comes to dermatologic therapies.

It’s not that clinicians see warnings as frivolous; they question whether some are overstated, redundant, or unnecessarily alarming to patients. Some critics contend that scrutiny of drugs already on the market is hindering efforts to usher new molecular entities through the approval process. With just 24 new drugs approved by the FDA in 2008 and a paltry 18 in 2007, the rate of approvals has dropped notably in the last 10 years (there were 39
Approvals in 1997 and 30 in 1998). At the same time, an agency that most observers and insiders already agree is stretched too thin has now been charged with oversight of tobacco products and may even monitor soft drinks.

With a new commissioner at the helm and the Obama administration seeking significant funding for it, FDA watchers wonder what’s next for the agency. One thing that seems certain is that scrutiny and more warnings for drugs already on the market will continue. And though it means challenges for clinicians, some observers say that isn’t necessarily a bad thing.

Focus on Safety

Discussion about the FDA’s current scrutiny of approved drugs inevitably leads to mention of Vioxx. Three years after Merck’s pain reliever was pulled from the market in light of safety data withheld from agency reviewers and omitted from peer-reviewed studies, many feel the FDA is still taking reactionary measures to assure the safety of drugs.

“Recent, highly publicized cases of withdrawn drugs such as Vioxx have put the FDA in a bad light and have the FDA in an extremely cautious mode,” notes Alex Tabarrok, Director of Research at The Independent Institute (www.Independent.org). “Extreme FDA caution is a danger to patients,” he maintains.

It’s not that increased scrutiny is worthless. “Greater FDA scrutiny of new drugs has some benefits, the quality of drugs that eventually reach the marketplace will be higher,” Mr. Tabarrok, who is also Bartley J. Madden Chair in Economics at the Mercatus Center at George Mason University, says. “But there are trade-offs. The greater the costs of producing new drugs the fewer new drugs will be produced, hence more testing means drug loss. More testing also means that beneficial drugs take longer to reach the market—drug lag.”

According to Jonathan Moreno, PhD, a Senior Fellow at the Center for American Progress (Americanprogress.org), “There is very little evidence” that the regulatory process slows drug development and discourages innovation. In fact, the David and Lyn Silfen University professor of ethics and professor of Medical Ethics at the University of Pennsylvania notes, innovation “started to explode” in the 1960s to coincide with Congressional passage of the Drug Amendments of 1962. Prior to this legislation, developers had little guidance for demonstrating the safety and efficacy of a drug. “A company doesn’t want to get involved in the process if it doesn’t know what the rules are. This legislation told them what the rules of the road are,” he notes.

But Mr. Tabarrok and others suggest that when FDA becomes too stringent, patients and physicians suffer, arguing that drug loss and drug lag mean potentially more deaths from disease. “The FDA, however, is much more concerned about deaths from approving a bad drug than about the deaths caused by drug loss and drug lag,” Mr. Tabarrok says. “When the FDA approves a drug that kills or has some unexpected side-effects, there are newspaper reports and Congressional hearings. When the FDA slows the approval of a new drug and people die because the drug is not available, these deaths are hidden. Even more hidden are the deaths that occur because some new drugs were never discovered, because FDA scrutiny meant that it wasn’t worthwhile to even begin the necessary R&D.”

Information Overload?

Some dermatologists have maintained that the FDA historically has been biased against dermatology, charging that agency reviewers expect higher levels of safety for drugs to treat cutaneous diseases. Essentially, they argue, FDA suggests that skin disease isn’t “serious enough” to warrant a notable level of risk. This apparent bias may result from what Mr. Tabarrok describes as FDA’s “one-size-doesn’t-fit-all policy,” which, “is increasingly
anachronistic. Medicine is becoming more personalized, but FDA policy is behind the curve in recognizing heterogeneity.” Noting that individuals may respond differently to the same drug, he notes that, “what works for one patient may not work for another. As a result, it’s beneficial for physicians to have access to multiple drugs. Even if the risk-safety profile for one drug appears to be generally worse than for another drug, it’s beneficial to have access to the second drug when the first drug has been tried and failed.”

As medicine becomes more personalized, access to safety data can be helpful in making medical decisions. A potential glut of information, “is the price we pay for keeping informed,” Dr. Moreno suggests. However, ongoing safety monitoring, collection of data, and issuance of warnings is critical to educate the public and ensure patient safety, Dr. Moreno maintains. “It is very very hard to predict once you let a drug out what it’s going to do,” he says. That’s why ongoing surveillance is key.

Just last month, FDA proposed mandatory electronic safety reporting to streamline data collection processes. The proposed rules, which apply to medical devices, drugs, and biologic products, do not change the types of events to be reported but require that all reports be submitted electronically, “to improve the agency’s ability to obtain safety information more quickly, which will help lead to faster identification of potential safety problems,” said David Buckles, PhD, Director of the Division of Postmarket Surveillance at the FDA’s Center for Devices and Radiological Health, in a statement. Currently, reports may be submitted on paper and are manually reviewed and entered into databases by agency staff.

Another challenge facing dermatology compared to other specialties is the difficulty of assessing patient improvement, particularly in terms of more subjective measures. “The FDA is also not very good at taking into account difficult to quantify characteristics, such as the quality of pain relief or the benefits of cosmetic improvements,” Mr. Tabarrok states. This makes it difficult for the agency to measure the risk/benefit of a particular agent. “In the case of Vioxx, for example, many patients found that despite the risks, Vioxx improved their quality of life in a way that no other drugs were able to duplicate. These are the kinds of benefits that may be discovered by doctors and patients as they test different treatment regimens on an individual, personal level but that cannot be taken into account by the FDA.”

In a sense, then, the focus on safety reviews and warnings may be a benefit to patients and physicians, observers suggest, because it provides data needed to support decision-making. Mr. Tabarrok does not endorse the FDA’s current, “one choice to rule them all,” approval process. Instead, he advocates, “What I call the Consumer Reports model that would meet the needs of diverse health-care consumers much better.” He explains, “Consumer Reports, a magazine run by a non-profit foundation, doesn’t try to replace consumer choice. Instead, by carefully evaluating and testing new products and providing this information to readers, Consumer Reports helps consumers to make better choices. Similarly, a less paternalistic FDA would provide more information to patients and doctors, but it would also leave more choices in their hands, because only patients and their doctors have the particular knowledge that allows each patient to be treated as an individual. In this sense, black box warnings are much preferable to an FDA that simply fails to approve many new drugs.”

Within the current system, as reporting of drug safety information and new warnings continues to expand, the expertise of the physician becomes increasingly important. “The public doesn’t really understand very well what it means for a drug to be approved,” Dr. Moreno contends. First, few individuals understand that a drug is investigated and approved for a specific indication. On the other hand, they often don’t understand that appropriate “off-label” use poses no particular risks and is acceptable. Noting that “Doctor means Teacher;” Dr. Moreno sees an opportunity for physicians to inform patients about the drug approval process, drug safety, and, at the clinical level, the therapeutic selection process.
Technology is influencing the process, he says. Whereas just a decade ago he says many physicians expressed displeasure and frustration when patients challenged them with health information gathered from the Internet, today, most physicians seem to welcome the opportunity to educate an engaged patient. Sometimes patients even bring information to a physician’s attention for the first time, he notes, meaning that the educational process is two-sided.

Of course, physicians are not typically well compensated for “time” spent with patients, often making it difficult for them to justify the work needed to walk patients through the therapeutic evaluation and decision-making process. For Dr. Moreno, the recent hubbub over end-of-life counseling within healthcare reform legislation is unfortunate. Essentially, under proposals the government would have established payment for a physician’s time spent in educating/counseling patients and coordinating care relevant to end of life decisions. Besides being an important benefit to terminal patients, the initiative could serve as a model for other initiatives aimed at reimbursing a doctor’s activities beyond traditional evaluation and management. Negative reaction to the effort has led to its abandonment.

Interest in Conflicts

Another result of the Vioxx withdrawal and other recent scandals has been increased attention paid to conflicts of interest. Among two primary areas of ongoing concern at FDA, according to Dr. Moreno, are understaffing, about which “there has been a level of concern for some time,” and conflicts of interest. FDA announced this summer that it will step up efforts to identify and ban or debar individuals known to have broken the law from working with or for companies with approved or pending drug applications before the agency. According to a report from FDA, new efforts will be supported by an increase in staff and a focus on centralized coordination of efforts. Debarment proceedings will be posted on an FDA website.

Last month reports emerged that the Inspector General of Health and Human Services (HHS) has launched an investigation into alleged product-review bias by Janet Woodcock, M.D., Director of FDA’s Center for Drug Evaluation and Research (CDER). Neither HHS nor FDA confirmed the report, published by the Wall Street Journal. Reportedly, generic-drug manufacturer Amphastar Pharmaceuticals filed a complaint that Dr. Woodcock had an inappropriate relationship with a competitive manufacturer.

The merits of Amphastar’s complaints are unknown. However, recent investigations have identified verifiable problems associated with disclosure of conflicts of interest among some investigators involved in drug trials. Many conflict issues have come to light due to high profile investigations spearheaded by Senator Chuck Grassley (R-Iowa), points out Patricia Tereskerz, JD, PhD, Director of the Program in Ethics and Policy in Healthcare in the Center for Biomedical Ethics and Humanities at the University of Virginia School of Medicine. FDA has guidelines in place for recognizing and addressing conflicts of interest, and there are indications that the agency seeks to further strengthen its efforts to weed out conflicts. Dr. Tereskerz notes that there are initiatives underway outside of the agency to address conflicts. Among these are new reporting programs at institutions and pharmaceutical companies, including on-line registries that disclose payments made to individuals and

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institutions. To those who react negatively to such reporting, Dr. Tereskerz argues that it helps ensure full disclosure so that researchers, subjects, analysts, evaluators, clinical care providers, and patients can critically assess information that comes out of trials.

Anytime a researcher or author has a relationship with a company, “there is always at least the appearance of impropriety,” Dr. Tereskerz says. That’s not too suggest that impropriety is common; in fact, “It’s very difficult but not impossible to prove that a conflict of interests even influenced particular results.” Still, Dr. Tereskerz says, it’s best that investigators not have any financial stake in a company whose products they are testing. When it comes to conflicts of interest, the emphasis should be on “prevention rather than management.”

Ironically, Dr. Tereskerz points out, conflicts of interest have been almost inherent in drug development over the last few years. Legislation passed in the 1980s to encourage innovation incentivized researchers and institutions to have an ownership stake in novel therapies. That legislation bolstered the therapeutic pipeline in the US but “failed to control for the inevitable and obvious conflicts that would arise,” she says. When individuals complain that registries or disclosure requirements go too far, Dr. Tereskerz points out that such concern often gets to the heart of the need for disclosures. “The very reason you don’t want to disclose is the reason you should be disclosing,” she says.

An important element of changing the culture of conflict recognition and reporting is investigator education, Dr. Tereskerz says. If an investigator fears subjects won’t enroll in trials if the investigator has a vested interest, then it’s important for that investigator to understand the nature of full disclosure and the need to properly inform patients. Education will contribute to transparency, she maintains.

Dr. Tereskerz also points out the role of institutions in improving transparency. She chairs the University of Virginia’s Conflict of Interest committee. There, when an investigator has a strong apparent or potential conflict of interest, the case is referred to a university-wide oversight panel that includes representatives from other schools within the institution, not just the medical school. Whereas a committee comprised only of medical school members may be sympathetic to an investigator, representatives from other schools typically lack such “loyalty.”

Additional steps to ensure transparency may include the creation of an independent committee to oversee data analysis, or, in the case of a junior faculty member or research assistant who may feel pressured by a senior researcher, the appointment of an independent ombudsman to work with that junior investigator.

As with safety issues, clinicians bear responsibilities related to conflicts of interest, Dr. Tereskerz says. Prescribers have a responsibility to inform patients if they have an equity interest, do talks, participate in research, or otherwise have a relationship with the manufacturer of any product prescribed. In the rare event that the physician earns a referral fee for directing a patient to a study, that should also be disclosed. These disclosures should be simple and direct and provided when the therapy is recommended, along with a rationale for choosing the therapy and a discussion of its risks and benefits.

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FDA is without doubt an agency in transition. From staffing changes at the top, to new oversight responsibilities, demand for better management of food safety, modifications to the device approval process, and anticipated expansion of its budget, much in the federal agency is likely to change in the months and years ahead. Sometimes hyper sensitivity to safety is not likely to change. Given this reality, dermatologists must be prepared to deal with the consequences of new warnings as they are disseminated. Clinicians must help patients understand the rationale for warnings and risks as they apply to the individual.

Upcoming articles will address FDA approval processes for innovator and generic drugs and for devices, which are subject to possible new regulations.