I n one looking for an example of why the Food and Drug Administration (FDA) appears increasingly concerned about the quality of generic drugs in the U.S., one need look no further than the Indian company Ranbaxy Laboratories. In the past few years, it has on its own and at the FDA’s insistence recalled bottles of atorvastatin calcium (generic Lipitor) and been barred from exporting to the U.S. products made at a plant in Toansa, India. In 2013, Ranbaxy, owned by the Japanese drug company Daiichi Sankyo, paid a $500 million fine and pled guilty to criminal charges of selling adulterated drugs and making false statements to the FDA.1

The FDA also banned sales in the U.S. from Indian facilities owned by a second Indian company, Wockhardt Ltd. In a long letter dated July 18, 2013, to Habil Khorakiwala, Wockhardt’s Chairman and Group Chief Executive Officer, Michael D. Smedley, Acting Director of the FDA’s Office of Manufacturing and Product Quality, wrote that FDA inspectors had found significant violations of current good manufacturing practice regulations at the Wockhardt plant in Aurangabad, India. The company “withheld truthful information, and delayed and limited the inspection.” Smedley added.2

Of course, Ranbaxy, Wockhardt, and other major generic manufacturers such as Teva Pharmaceutical Industries Ltd., Sandoz, Actavis PLC, Mylan Inc., Hospira Inc., Sanofi, Aspen Pharmacare Holdings Ltd., and STADA Arzneimittel AG are more often the good guys, selling important drugs at significant discounts to patented alternatives. Those lower prices ease the financial strain on millions of Americans every year. Generic pharmaceuticals fill 84 percent of the prescriptions dispensed in the U.S. but account for just 27 percent of the total drug spending, according to the Generic Pharmaceutical Association (GPhA).3

Despite their financial advantages to consumers, however, generics may have a greater chance than brand-name products of causing adverse reactions because so many are in use. When they do, they prompt headlines atop stories that often very quickly mention that the company making the offending drug is headquartered outside the U.S., along with most or all of its manufacturing plants. Questions about adequate FDA inspection of overseas facilities come up just as quickly thereafter. Eighty percent of active pharmaceutical ingredients are imported to the U.S., as are 40 percent of finished drugs, according to the FDA.4 There are no good statistics on what percentage of finished generic drugs are imported.

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bioequivalent to Wellbutrin. (Activis and Watson had merged prior to the announcement.)

**Hamburg Trip to India Yields Very Modest Results**

Concerns about generic drug quality have been percolating at the FDA for years, of course. But new regulatory requirements, funding streams, and expanding generic use on private and public formularies have forced the FDA to step up the pressure it exerts on the industry. FDA Commissioner Margaret Hamburg, MD, took her first trip to India at the end of February. While there, she signed a statement of intent with her counterpart, the Drug Controller General of India, Gyanendra Singh, PhD. The statement is fairly general, and its impact and impact have been somewhat diluted by comments Dr. Singh made after Dr. Hamburg’s visit. Dr. Singh said, according to a journalist participating in a conference call with Dr. Hamburg upon her return, that if he had to follow U.S. standards in inspecting facilities he “would have to shut almost all of those.”

Actually, there was no need for Dr. Singh to devalue Dr. Hamburg’s efforts. The statement of intent commits India to do very little of substance beyond information-sharing and scientific collaboration. There is no talk of hiring additional inspectors, improving quality standards, or anything of that nature. And the statement allows India to forego even potential softball actions when “taking into account the limitations of existing human and financial resources and within the parameters of domestic legal and administrative requirements.”

 Asked whether the FDA was perturbed by Dr. Singh’s comment, a spokesman says, “Within five years, we will be able to conduct biennial inspections for both domestic and foreign facilities, allowing us to identify any noncompliant players in the drug supply chain—wherever they are based—so we can focus on the generic drug industry worldwide.”

Five years is a long time when lives are at stake. Questions about the quality and safety of generics become more important by the day as formularies for Medicare, Medicaid, employer health plans, and Affordable Care Act plans for independents by the day as formularies for Medicare, Medicaid, employer health plans, and Affordable Care Act plans for independents heavily weight their tier-one drug offerings with generics. The announcement by Eli Lilly & Company in late March that it was eliminating pay raises for most employees in 2014 reflects the growing dominance of generics. Lilly said the loss of patient protection for Cymbalta, its best-selling drug, and Evista ent protection for Cymbalta, its best-selling drug, and Evista when it passed the Generic Drug User Fee Act (GDUFA) in 2012. The law required generic manufacturers to pay fees to the FDA for the first time. The agency uses those fees (which came to $300 million in 2013) to finance critical and measurable enhancements in generic drug programs. Generic drug facilities, sites, and organizations around the world must provide identification information annually to the FDA.

The GDUFA dictated a number of FDA actions and indirectly associated with inflammatory bowel disease in patients without

**GDUFA Fees Let FDA Expand Regulatory Reach**

Congress was aware of the generic surge, as well as its potential for both health care savings and safety problems, when it passed the Generic Drug User Fee Act (GDUFA) in 2012. The law required generic manufacturers to pay fees to the FDA for the first time. The agency uses those fees (which came to $300 million in 2013) to finance critical and measurable enhancements in generic drug programs. Generic drug facilities, sites, and organizations around the world must provide identification information annually to the FDA.

The GDUFA dictated a number of FDA actions and indirectly led to others. In addition to a key proposed rule and a testing program farmed out to academic medical centers, the FDA has published a draft guidance explaining when the agency could “refuse to receive” an abbreviated new drug application (ANDA). Before marketing a new product, generic companies submit an ANDA, which must be approved by the FDA. The guidance, which has not been finalized, delves into important issues such as whether the agency will accept a claim that a generic is “bioequivalent” to its brand-name counterpart.

A proposed rule issued last November by the FDA allowing generic companies to change their safety labeling before the reference brand-name product does so has been among the most controversial of the FDA’s recent actions. The reason for the proposed rule is that generic companies are as likely to be alerted to adverse reactions as brand-name companies. But under current law, only the brand-name company can submit a “changes being effected” (CBE-0) supplement to the FDA. That allows the company to make certain labeling changes without FDA approval: for example, to add or strengthen a contraindication, warning, or precaution, or to strengthen a statement about drug abuse or an instruction about dosage. Once the revised labeling goes into effect, all generic products on the market are required to make their labeling conform within 30 days. This policy dates back to 1982.

But because only the brand-name manufacturer can make CBE-0 labeling changes, only the brand-name company is liable in court for adverse reactions. Generic companies cannot be sued for failing to update labels. Under the FDA proposal, generic drug makers could be sued—a prospect that displeases them.

The generic industry is arguing that the change in labeling policy would create nightmares for pharmacists and others as generic companies selling the same active ingredient were freed to change the labels of their individual products in any way they wanted. Uniformity would not be required. A number of pharmacy groups, including the Academy of Managed Care Pharmacy, American Association of Colleges of Pharmacy, American Pharmacists Association, and American Society of Health-System Pharmacists, signed on to a letter that the GPhA originated in March to comment on the rule. They said they were most concerned about the dangerous confusion multiple labels would cause and about the increased costs of and reduced access to generic medicines for patients who need them most. The letter stated that pharmacists could be exposed to liability as well as the generic drug companies.

Allison Zieve, Director of the Public Citizen Litigation Group, doubts the validity of the “labeling confusion” argument. “Numerous different newly discovered safety risks are unlikely to come to light for a single drug at the same time,” she states. To buttress the contention, she refers to classes of brand-name drugs where there are several competitors. Take the selective serotonin reuptake inhibitor class of antidepressants, for example. Fluoxetine hydrochloride (Prozac, Eli Lilly), sertraline hydrochloride (Zoloft, Pfizer), and paroxetine hydrochloride (Paxil, GlaxoSmithKline) are sold by different manufacturers. “We do not see the manufacturers discovering a variety of new safety risks all at about the same time,” she explains. "If several manufacturers submit changes at or near the same time, the changes are likely to address the same risk—and it will hardly confuse physicians and patients if, for instance, one generic warns that its drug ‘has been associated with inflammatory bowel disease in patients without
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a prior history of intestinal disorders,’ while another warns that ‘long-term use is associated with serious intestinal problems, including ulcerative colitis and Crohn’s disease,’ and a third warns that ‘patients taking this product should be monitored closely for signs of inflammatory bowel disease.”11

Guidance Would Turn Back Flawed ANDAs

Labeling also comes up in the context of the draft guidance on “refuse to receive” that the FDA issued last October.10 This guidance, which the FDA has yet to finalize, was issued as a result of a GDUFA provision. It describes what should be included in an ANDA and highlights serious deficiencies that may cause the FDA to refuse to receive an ANDA. A refuse-to-receive decision indicates that the FDA has determined the ANDA is incomplete on its face, usually because of omissions. The draft guidance covers labeling, chemistry, and bioequivalence issues. Guidance, however, is advisory; the FDA cannot penalize a company for violation of guidance, as it can for violation of rules.

Underlining concerns about generic quality and safety, the draft points out that the FDA office of generic drugs refused to receive 497 ANDAs between 2009 and 2012. “Recent data underscore the need for improvement in the quality of original ANDA submissions,” the draft states. In 2012, of the 100 ANDAs that the office of generic drugs refused to receive, 40 were refused because of serious bioequivalence deficiencies, 36 because of serious chemistry deficiencies, 13 because of format or organizational flaws, six because of clinical deficiencies, four because of inadequate microbiology (sterility assurance) information, and one because an incorrect reference drug was cited. Those 100 accounted for approximately 10 percent of the ANDAs the agency received in 2012.11

The draft makes some minor and potentially major changes in current FDA policy. “There are several new criteria presented in the guidance document that will require ANDA applicants time to revise product designs and development strategies,” says David R. Gaugh, RPh, the GPhA’s Senior Vice President for Sciences and Regulatory Affairs. He is concerned, for example, with new guidance for oral liquid product formulations. “It would be inappropriate to require ANDA applicants to reformulate products, repeat clinical studies, and potentially forfeit a first-to-file opportunity by imposing the new refuse-to-receive criterion without ample time to adjust to the new standard,” he emphasizes.

The guidance says the FDA would reject an ANDA if it contains 10 minor deficiencies or one major deficiency. The sponsor may decide to submit additional materials to correct the deficiencies, but the resulting amended ANDA will be considered a new ANDA submission, received as of the new date and requiring a new GDUFA fee.

The “10-or-more” standard perturbs a number of companies. “Apotex is of the opinion that assigning a specific requirement on the total number to the deficiencies in the ANDA submission creates variability,” says Kiran Krishnan, Vice President of U.S. Regulatory Affairs for Apotex Corp. “Apotex is of the opinion that the number and nature of the deficiencies should not be used as a threshold to refuse an ANDA without giving the firms an opportunity to justify.”

Questions on Testing Requirements for Generics

Still, some industry experts believe the FDA needs to require more from generic companies before approving ANDAs. “‘The current standards, criteria, and regulations governing approval and monitoring of generic drugs are inadequate,’” say pharmacologist Joe Graedon, MS, and medical anthropologist Teresa Graedon, PhD. The Graedons write a syndicated newspaper column, host a health-talk show syndicated on public radio, and are founders and directors of the website www.PeoplesPharmacy.com. Their June 2013 comment letter responded to an FDA request for input on the agency’s generics regulatory science initiatives.

The major challenge generic companies face in seeking FDA approval of their ANDAs is proving their products are bioequivalent to the reference product. That involves dissolution testing: The rate at which a drug dissolves from a dosage form is measured, typically in the same medium used by the reference company’s product in its dissolution testing. The results can be used to determine whether the generic will have the same potency in a patient’s body as the reference drug. At least that is the theory—that an in vitro test can predict in vivo results. “But that translation doesn’t work reliably in all cases,” states Dr. Amidon, the Michigan professor who worked for major drug manufacturers for nearly three decades and now directs UM’s Pharmaceutical Engineering Program. His program has received money from the FDA to develop and check new dissolution test methods and computer modeling techniques that may prove more accurate for predicting in vivo results.

Better dissolution methods and computer modeling might allow the FDA to waive in vivo bioequivalence testing, which it already does for some generics. But even some generic companies oppose easing those requirements. For example, Teva submitted a petition to the FDA in December 2013 pleading with the agency to require immunogenicity testing for companies submitting ANDAs for its branded product Copaxone (glatiramer acetate injection), a drug for patients with relapsing-remitting multiple sclerosis. The Teva petition asked the FDA not to provide any waiver of in vivo bioequivalence testing because Copaxone is a colloidal suspension rather than a true solution. In January 2014, Teva published data in the online scientific journal PLOS ONE purporting to show significant differences in biological and immunological effects between Copaxone and a generic glatiramer acetate marketed in India by Natco Pharma Ltd. Teva argued the differences have potential clinical ramifications.14 Natco and Mylan have filed an ANDA for glatiramer acetate injections, as have Momenta Pharmaceuticals and Sandoz. There has been patent litigation between Teva and the other two teams for years. The Copaxone patent expires in 2015.

Sandoz has not started manufacturing generic glatiramer acetate injections, of course, and it is not clear when and where that manufacturing will take place. The company has manufacturing sites in India. But Sandoz has had plenty of trouble with the FDA over its U.S. manufacturing sites, proving that generics manufacturing quality is a worldwide issue. The FDA issued warning letters to Sandoz manufacturing sites in Colorado, North Carolina, and Canada in 2011.15 In 2013, Sandoz, the world’s second-largest generics manufacturer, announced that it was recalling injectibles manufactured in continued on page 364

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Austria because of particles in vials.

So even with its new GDUFA authorities and funds, the FDA has its hands full ensuring the safety and effectiveness of generic drugs. The manufacturers take their responsibilities seriously, no question about that. But can they ever be serious enough?

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