CHAPTER FIFTEEN

FDA's Public Health Imperative

An Increased Role for Active Postmarket Analysis

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THE FUNDAMENTAL purpose of the U.S. Food and Drug Administration (FDA) is to promote and protect the public health (Hamburg 2010). An integral component of the agency's public health mission is the creation and maintenance of a robust framework for regulating medical products. Experts at FDA and throughout the health care industry have long heralded a "life-cycle" approach to regulation, whereby safety and efficacy are examined both pre- and postmarket (IOM 2007a). Despite the documented need for life-cycle analysis, FDA has focused its regulatory efforts on premarket review and has exerted comparably little energy on postmarket analysis.

This imbalance is largely the result of statutory provisions that have been ingrained in FDA's fabric for decades—not only has Congress underfunded and overburdened FDA, it has incentivized speed in the premarket review process and has enacted legislation that, to varying degrees, has limited the agency's ability to mandate postmarket studies (Parasidis 2011). This dynamic has directly impacted the reliability of risk–benefit profiles for marketed products. Patients, providers, and payors are affected significantly, as each is deprived of evidence that

could prove integral to the decision of which treatment option to pursue, or whether a particular course of treatment is medically necessary. The risks borne by patients are exacerbated by preemption laws, which limit or preclude legal remedies in the event of adverse events, and an expanding commercial speech doctrine (discussed in part 3 of this volume), which hinders FDA's ability to regulate products once initial approval is granted.

In this chapter, I contend that the future of FDA as a public health agency is largely dependent on how well the agency is able to account for the current and evolving legal and political landscapes. In the context of medical products, this entails leveraging the agency's mandate and resources to address the limitations of premarket review and expand the instances in which postmarket analysis is required. Specifically, I argue that, in all cases where it has the authority to do so, FDA should require that sponsors conduct active postmarket analysis for the life of their products. As will be discussed, active postmarket analysis encompasses thorough, timely, and continuous monitoring of risks and benefits in real-world patients. Such monitoring includes utilization of health information technology (IT), observational studies, biomedical informatics, and, where appropriate, postmarket clinical trials. While FDA should assist in framing postmarket obligations and reviewing the results, sponsors must be held accountable for conducting and completing their postmarket studies.

I. THE ROLE OF POSTMARKET ANALYSIS IN THE DRUG REVIEW PROCESS

Since premarket clinical trials are limited in duration and scope, the risk–benefit profile that is derived from premarket studies is often inaccurate or incomplete. For example, premarket trials cannot capture latent adverse events nor can premarket studies sufficiently reveal adverse events that occur at low rates. In addition, premarket studies typically do not include patients with comorbidities; as such, the data do not always reflect how "real-world" patients react to treatment. Notwithstanding the ability of postmarket studies to mitigate the shortcomings of the premarket review process, decades of political and economic pressures have forced FDA to dedicate the majority of its resources to the premarket approval process (Parasidis 2011).

In situations where FDA has required postmarket studies, enforcement has been lax, and many sponsors have failed to complete their postmarket obligations (Kessler and Vladeck 2008).

In this section, I provide an overview of the framework under which FDA must work to fulfill its public health mission in the context of medical products. I begin by briefly summarizing FDA's passive framework for postmarket surveillance. I then discuss the symbiotic relationship between regulation and state tort claims, and explain how limitations on the availability of tort remedies have exacerbated the risks caused by FDA's passive postmarket surveillance regime. Although I will focus my discussion in this chapter on the regulation of pharmaceuticals, active postmarket analysis should be a component of all medical products, including medical devices and vaccines.

A. FDA's Passive Framework for Postmarket Surveillance

An influential report published by the Institute of Medicine (IOM) found that FDA has not historically had "adequate resources or procedures for translating preapproval safety signals into effective postmarketing studies, for monitoring and ascertaining the safety of new marketed drugs, for responding promptly to the safety problems that are discovered after marketing approval, and for quickly and effectively communicating appropriate risk information to the public" (IOM 2007a). Following the report—which was motivated in part by the public health catastrophe surrounding Vioxx, which caused thousands of deaths and tens of thousands of serious adverse events—Congress enacted the FDA Amendments Act of 2007 (FDAAA). Among its provisions, FDAAA requires that FDA create an active postmarket surveillance system.

In response to the legislative mandate, FDA established the Sentinel System. The Sentinel System is a nationwide electronic reporting system for monitoring medical products, which will have access to a wealth of health information that can be applied to study questions related to safety and efficacy. The Sentinel System supplements FDA's various postmarket surveillance schemes. For example, the FDA Adverse Event Reporting System (FAERS) has been FDA's primary source for managing and monitoring adverse events (Keuhn 2013). Under FAERS, formerly known as AERS, drug sponsors have

an obligation to report known adverse health events to FDA in a timely manner. Although FAERS provides a conduit through which adverse events can be reported to FDA, the Federal Food, Drug, and Cosmetic Act (FDCA) does not contain a provision that requires drug sponsors to monitor their products for adverse events.

A supplement to FAERS is MedWatch, where health professionals and patients may voluntarily report adverse events. Reports submitted through MedWatch are comparatively minimal, accounting for less than 5 percent of all reported adverse events. As with drug sponsors, physicians and patients do not have an affirmative duty to seek out information related to adverse events. Furthermore, unlike drug sponsors, who must report what they know, doctors and patients are not obligated to report known adverse events to FDA. Coupled with the Sentinel System, FAERS, and MedWatch, the FDA's Document Archiving, Reporting and Regulatory Tracking System (DARRTS) facilitates tracking of postmarket safety issues. DARRTS allows FDA to manage activities related to evaluations of safety issues, such as due dates and postmarket safety reports (IOM 2007a). FDA also maintains an adverse event database for vaccines (VAERS) and medical devices (MAUDE).

In addition to mandating that FDA adopt an active postmarket surveillance system, FDAAA grants FDA the ability to require that drug sponsors complete a Risk Evaluation and Mitigation Strategy (REMS). The goal of the REMS program is to detect adverse events as quickly as possible in order to provide FDA with timely and accurate information that may be utilized to determine whether proactive measures should be taken, such as changing a drug's label or removing the drug from the market. FDA can require a REMS before or after a drug is approved, and a REMS can be required for a specific drug or an entire drug class. While FDA can require a REMS as a condition of approval, if the agency seeks to require a REMS after a drug is approved, the agency must demonstrate that new safety information has arisen (Gilhooley 2008). New safety information is defined as "a serious risk associated with use of the drug which FDA has become aware since the drug was approved, since a REMS was required, or since the last assessment of the REMS" (FDA 2014).

Despite FDA's extensive postmarket surveillance tools, studies estimate that FDA's postmarket network captures less than one percent of serious adverse reactions. This is largely due to the fact that

sponsors do not have an affirmative duty to monitor their products for adverse events and that physicians do not have a duty to report known adverse events. Importantly, reported information is of limited clinical relevance because, from an epidemiological standpoint, "the FDA does not know how many people are using the drug and does not have adequate information about those who are"; as a result, FDA has "difficulty determining the incidence of a given adverse reaction" and whether it affects a particular subpopulation of patients (Kessler and Vladeck 2008). Taken together, FDA's postmarket surveillance framework has not consistently provided the agency with information sufficient to make intelligent decisions as to whether new safety risks should be communicated to the public.

B. Why Limitations on State Tort Claims Increase the Need for Active Postmarket Analysis

Since FDA does not have accurate information on postmarket risks, the agency is deprived of information that could help it make important decisions related to safety and efficacy of marketed products. This translates to an increased risk for patients and increased uncertainty on the part of providers and payors as to whether a particular treatment is medically necessary. Preemption of state tort claims—which refers to instances where patients injured from medical products are legally precluded from seeking remedies through the courts, a topic discussed in greater detail in other chapters of this volume—exacerbates the risks that stem from the regulatory regime.

In the context of FDA-regulated medical products, Congress has enacted targeted measures that immunize certain enterprises such as vaccine and generic drug manufacturers (Parasidis 2011). Preemption does not apply to manufacturers of brand-name drugs, nor does it apply to medical devices approved through the 510k process (contrast with medical devices approved through the PMA process, where preemption applies) (ibid.). Notably, in instances where preemption applies, a sponsor is not under a general obligation to research a marketed product for information related to safety and efficacy. In addition to federal immunities, a number of states have taken an active role in further limiting industry's liability exposure. These reforms include caps on noneconomic and punitive damages, a refusal to permit strict

liability claims, and recognition of a "regulatory compliance defense" (Tobias 2008).

Michigan's regulatory compliance defense is paradigmatic—in Michigan, an FDA-approved drug that contains an FDA-approved label is neither defective nor unreasonably dangerous as a matter of law. In Utah, conformity with FDA regulations establishes reasonable care or nondefectiveness as a matter of law, while Texas views compliance with FDA regulations as strong and substantial evidence that a product is not defective. In New Jersey, a label approved by FDA constitutes adequate warning as a matter of law. Various states have rejected strict liability claims for defective design and have solely permitted claims based in negligence. Several states shield pharmaceutical companies from punitive damages unless an injured plaintiff can show that the company fraudulently obtained FDA approval. As with federal preemption of state tort claims, there is no state reform measure that predicates limited liability on active postmarket analysis for safety and efficacy (Parasidis 2011).

Although fear of lawsuits may incentivize drug sponsors to disclose adequate information regarding safety and efficacy, civil litigation is not the optimal means of regulating the life-science industry. Civil suits are not the ideal vehicle for setting the standard of care or determining adequate product warnings. Lawsuits involve retrospective debate of medical information that, often times, was unavailable to the provider or patient at the time medical treatment was provided. Indeed, due to variations in civil judgments, a sponsor may be subject to different standards in different states.

Notably, tort law is not an efficient means of transferring costs from tortfeasor to victim (Goldberg and Zipursky 2010). While a civil judgment may provide monetary compensation and serve to vindicate wrongful conduct, studies have shown that approximately fifty cents of every dollar recovered through tort claims accommodate administrative costs and attorney fees (Polinsky and Shavell 2010). More importantly, when a product kills or severely injures a patient, monetary damages through tort law provide limited relief to patients and their families.

While tort claims may not be the best vehicle for addressing information asymmetries, the availability of tort claims serves as an incentive for industry to be diligent and forthcoming with risk-related information. This incentive is diminished when preemptions laws preclude injured patients from having their day in court.

II. COMBINING REGULATORY AUTHORITY AND HEALTH INFORMATION TECHNOLOGY TO FACILITATE ACTIVE POSTMARKET ANALYSIS

To help fulfill its public health mission, FDA must capitalize on innovations in health IT and leverage its regulatory authority to create a comprehensive framework for active postmarket analysis. This framework can be structured around the Sentinel System, which has access to electronic health care data for more than one hundred million patients. Advancements in electronic medical record (EMR) systems and biomedical informatics provide important avenues through which sponsors, FDA, and researchers can access robust data sets. Along with providing near real-time medical information, there is broad consensus that the adoption of EMR systems and utilization of health IT in the provision of medical care will significantly improve the efficiency and effectiveness of health care (Jha et al. 2009).

Since enactment of FDAAA, FDA has been exploring new methods and tools that will enable it to capitalize on existing large postmarket databases. For example, the agency has been collaborating with the Centers for Medicare and Medicaid Services (CMS) and the Department of Health and Human Services (HHS) on a postmarket surveillance project that utilizes Medicare and Medicaid data. Meanwhile, FDA has stated that it "is aggressively recruiting more epidemiologists, statisticians, medical officers, safety evaluators, statistical programmers, [and] data managers" (FDA 2009). These experts will be called upon to timely and effectively access and analyze new safety data. Through collaborative efforts, the agency is looking to leverage existing databases and emerging health information technologies to target science at every stage of a drug's life-cycle.

These substantial additions to the postmarket arsenal of FDA set the stage for a transition from passive monitoring of adverse events to active postmarket requirements. As numerous reports have discussed, passive surveillance has serious limitations, which include "underreporting, biased reporting, and difficulties in attributing an adverse event to a specific drug" (IOM 2007b). Replacing the passive system of postmarket surveillance with an active postmarket framework is an intelligent next step toward a stronger and more effective drug safety system.

Under existing regulations, FDA can mandate postmarket studies as a condition of approval or when a new safety signal arises. Accordingly, FDA's first step should be to mandate active postmarket analysis as a matter of course for the life of all newly approved products. Each sponsor should be responsible for fulfilling requirements outlined in a postmarket surveillance plan and REMS. For each product, the drug sponsor would be responsible for providing postmarket update reports to FDA and the public on a regular basis. If postmarket research reveals that the rate or severity of an adverse effect exceeds that which is identified on the label (whether for the general population or a specific subpopulation), or other information relevant to the risk–benefit profile of the underlying product, the sponsor should be responsible for filing a report with FDA and publicly disclosing this new information.

The public disclosure component could take many forms. For example, FDA could create a website that allows users to search by medical product. FDA's recent collaborations with Drugs.com, WedMD, and Medscape are particularly promising avenues through which the public disclosure requirement could be fulfilled. A product's page could contain the current label, a complete history of submitted postmarket reports, and FDA's analysis of submitted reports. The product page should also contain summary information that identifies ongoing postmarket obligations. All summary information should use language that the general public could understand, with links to more detailed scientific discussion that is geared toward providers.

Active postmarket analysis is particularly important for new molecular entities, since such drugs contain molecules that have never been approved for use in humans. Similarly, active postmarket analysis is indispensable for drugs approved on surrogate endpoints, since the drug sponsor was not obligated to demonstrate an actual clinical benefit during the premarket review process. These concerns are not merely theoretical. According to one recent study, between 2005 and 2011, nearly half of new molecular entity approvals were granted solely on the basis of surrogate endpoints (Downing et al. 2014).

While mandating active postmarket analysis for all new drug approvals will help produce real-world risk–benefit information and mitigate information asymmetries, it will only capture a small percentage of drugs that are on the market. The key to a robust active postmarket system is ensuring that *all* marketed products are being continually monitored and evaluated. Current guidelines grant FDA the authority

to mandate postmarket studies or REMS for approved products only where a new safety signal arises. The FDCA defines "new safety signal" to include serious risks that were previously unknown to the agency. The scope of this definition is unclear, and FDA has the discretion to define serious risks in a number of ways, either taking an expansive or limited view of the term.

Given the public health concerns raised by the existing pre- and postmarket framework, FDA should err on the side of patient safety and take an expansive approach to identifying the instances in which it has the authority to require a REMS or postmarket research for approved products. For example, a serious risk can include an instance where a drug is used for off-label purposes. Since off-label uses are not evaluated by FDA and drug labels do not provide guidance for off-label uses, the fact that patients are using a marketed product for an unapproved use raises a new safety signal. Selective publication that disproportionally favors positive findings is well documented, and the underreporting of negative results raises concerns for patients, providers, and payors, each of whom is left largely in the dark when it comes to determining whether a particular treatment is reasonable or medically necessary (Light 2010).

Under these circumstances, FDA could require active postmarket analysis as a condition of allowing the drug to remain on the market. There is nothing in the FDCA that limits the type of postmarket research that FDA could require. Rather, the FDCA sets the trigger that grants the agency the discretion to mandate postmarket studies. Although arguably FDA would have the authority to pull a drug from the market if adverse events from off-label uses occur, this is a drastic remedy that may preclude legitimate uses of an approved product. A more sensible alternative, and one that truly promotes the agency's public health mission, is using regulatory tools to bring forth meaningful information on each product's risks and benefits.

The Second Circuit's decision in *United States v. Caronia*, which opens the door to increased off-label promotion by drug sponsors, provides added justification for determining that off-label use constitutes a new safety signal for purposes of triggering FDA's ability to mandate active postmarket analysis (2012:149). An integral component of FDA's regulatory authority centers on the ability of the agency to monitor and limit drug marketing and advertising. As Kesselheim and Mello discuss in their chapter, *Caronia* casts doubt over

the agency's ability to enforce these regulations. Though the *Caronia* decision is only binding within the Second Circuit—which encompasses New York, Connecticut, and Vermont—other courts may adopt the reasoning of *Caronia* should a similar first amendment challenge to an FDCA violation arise. Equally as important, the *Caronia* decision raises serious questions as to the government's ability to prosecute off-label promotion under federal and state qui tam laws.

III. PROJECTED COSTS OF ACTIVE POSTMARKET ANALYSIS

FDA projects that a postmarket framework focused on active analysis will require funding and resources similar to those of premarket review (FDA 2009). In current dollars, this would set the cost at approximately $500 million per year. This is a negligible amount, representing 0.01 percent of the annual federal budget. Further, when one considers that an active postmarket framework will directly and significantly benefit all Americans, the cost per capita—$1.56 per person per year—is miniscule.

Of course, government expenditures are not the full picture. In addition to government costs associated with an active postmarket surveillance system, each drug sponsor will be responsible for funding the research related to its postmarket obligations. Although total costs per product will vary, a typical observational study that relies on primary- and secondary-data costs between $100,000 and $250,000 for small studies of less than two years of duration, and $1.5 million to $3 million for larger and lengthier studies (Holve and Pittman 2009). Though not insignificant amounts, these figures represent a fraction of the total cost for drug development. For instance, industry figures place the cost of developing one drug at approximately $1.2 billion (Adams and Brantner 2010). Thus, as with the projected federal expenditures, the projected postmarket research budgets are negligible when placed into context.

At one extreme, these costs may be passed on entirely to patients; at the other, industry would fully absorb the costs and decrease its return on investment. While industry's incentive may be to pass the costs to consumers, public and private payors have other levers, such as negotiated rates, which could help balance the impact of the costs

of an active postmarket system. To the extent current practices outside of the United States serve as a guide, Americans may be able to receive more postmarket analysis and cheaper drug prices. For example, although both Japan and the European Union maintain a more active postmarket system than that of the United States, drug prices in these regions are significantly lower than those in the United States. This is a direct result of nations negotiating drug prices with the drug sponsor. Unlike most industrialized nations, the United States generally does not negotiate drug prices with drug sponsors, though some large insurance companies and public payors do so. Legislation currently prohibits CMS—which is the largest payor, public or private, in the United States—from negotiating lower drug prices, although this prohibition has often been called into question.

As a result, Americans pay a significant premium for their drugs. In fact, prescription drug prices in the United States are among the highest in the world, and per capita prescription drug spending in the United States is substantially more than in all other nations (Kanavos et al. 2013). Even within the United States, the un-negotiated costs for individuals are more than double the negotiated costs. For example, within the public payor system in the United States, the Department of Veterans Affairs (VA) negotiates drug prices with pharmaceutical companies. These negotiations result in a 58 percent discount in drug prices for VA patients when compared to CMS patients (Steinberg and Bailey 2007).

At the macro level, the pharmaceutical industry is one of the most profitable in the world, earning over $900 billion in 2010, one-third of which came from sales in the United States. The industry had an average return on investment of 13.3% in 2010, which is 64 percent higher than the average return on investment across all industries. Between 2004 and 2008, the pharmaceutical industry's average return on investment was 19 percent, which places the industry among the highest of all industries. As Standard & Poor's concludes, this "lofty ratio" is "a function of the industry's . . . high profit margins" (Saftlas 2011). The operating profit margins of pharmaceutical companies averaged 32 percent in 2008, nearly double that for corporations in the S&P 500 index. "Net earnings as a percentage of sales averaged [approximately] 16% between 2004 and 2008," which is 150 percent more than the average of companies in the S&P 500 index. Notably, growth in the pharmaceutical industry is projected to increase at a margin twice that of the global market (ibid.).

In the United States, the pharmaceutical industry also enjoys significant government subsidies and tax incentives. Importantly, much of the initial pharmaceutical research in the United States is funded by American taxpayers through entities such as the National Institutes of Health. Once initial research demonstrates practical promise, industry will typically take over the development of the product. Balancing incentives to innovate with public health and rising health care costs is no simple task; that said, the pharmaceutical industry is a lucrative business in which there is room to incorporate active postmarket analysis as a component of marketed products.

IV. CONCLUSION

Because FDA's lackluster postmarket framework fails to capture the majority of adverse events, important information on safety and efficacy escapes the eyes of regulators, physicians, patients, and payors. While calls for increased postmarket analysis date back at least to the 1960s, FDA has not taken meaningful steps toward including active postmarket analysis as a regulatory requirement for all marketed products. Although an active postmarket framework comes at a cost, the projected savings are substantial. In the United States, it is estimated that adverse drug events cause more than 100,000 deaths and 2,000,000 serious injuries annually. The cost of treating patients with adverse drug events is approximately $1.6 to $5 billion per year, half of which may be preventable (Bond and Raehl 2006). This figure does not include the costs to patients and their families, or any resulting litigation. The figures also do not include the costs of lost productivity.

All stakeholders in the health care industry play an integral role in ensuring that maximum benefits flow from an active postmarket surveillance system. Patients must be mindful to fully disclose their medical histories and any adverse health events, while providers must ensure that their diagnosis and treatment regimens are carefully documented in the patients' records. Health IT experts are responsible for accurately transcribing patient records into searchable EMRs, creating a query system that captures pertinent medical information from the EMRs, and producing aggregated and de-identified data that are reflective of the underlying patient population. Sponsors must frame queries to capture relevant data and then interpret the data in

an honest, transparent, and scientifically sound manner. Regulators must guide sponsors in determining which queries are appropriate and interpret results in a manner that furthers the public health. Independent researchers work to supplement the inquiries and analyses of sponsors and regulators.

The Sentinel System has the ability to address the adverse event gap in the United States, but only if FDA combines the potential of Sentinel data with its regulatory authority and establishes an active duty on the part of drug sponsors to seek out and report information related to postmarket safety and efficacy. More accurate information on safety and efficacy will result in fewer injuries and deaths due to adverse health events. Better information will also reduce health care costs by prescreening high-risk patients before treatment. Not only will the patient be spared the potential side effects, payors will not incur costs associated with use of the product.

Industry stands to reduce costs as well. The costs of litigating civil claims are immense, with settlement funds reaching into the billions of dollars. Individual claims against drug companies, where the adverse drug event caused a permanent disability, averaged $4.3 million per patient. Claims for death and other serious adverse events also resulted in judgments or settlements in the millions per patient (ibid.). Taken together, the avoidance of these financial and reputational costs, coupled with the health benefits to patients, far outweighs the costs of active postmarket analysis.

While FDA's ability to mandate postmarket obligations is somewhat limited, the agency is supplied with an arsenal of regulatory tools that, if properly utilized, could go a long way toward bringing important data on risks and benefits to the forefront. By capitalizing on biomedical informatics techniques and the wealth of information available through the Sentinel System, FDA is poised to reinvent its regulatory agenda and assert its regulatory power in ways that will bring meaningful information to stakeholders throughout the health care industry.

In the context of FDA regulation of medical products, the agency must work to balance access and uncertainty, and ensure that providers, patients, and payors have the best available evidence of safety and efficacy. Americans pay more for their medications and receive less from their regulators in terms of postmarket review and analysis than citizens of other nations. Promoting and protecting the public health

requires that FDA modernize its approach to regulation by incorporating active postmarket analysis for all medical products.

NOTE

This chapter is based, in part, on E. Parasidis. 2011. "Patients Over Politics: Addressing Legislative Failure in the Regulation of Medical Products," *Wisconsin Law Review* 5: 929–1002.

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