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CHAPTER TWENTY-SIX

A New Regulatory Function for E-Prescriptions

Linking FDA to Physicians and Patient Records

ANDREW ENGLISH, DAVID ROSENBERG, AND HUAOU YAN

I. INTRODUCTION

In this chapter, we propose broadening the conventional use of electronic-prescription (e-prescription) technology to include a new regulatory function. Currently, e-prescriptions mainly provide digital means for more efficiently accomplishing the time-honored purchase-order function of paper prescriptions[1] (Kannry 2011; Stross 2012). We propose deploying this technology to also serve FDA regulatory objectives in overseeing the postmarket safety and efficacy of medical products.[2]

FDA faces significant difficulties in monitoring the postmarket safety and efficacy of medical products. A recent example is the diabetes drug Avandia. Approved in 1999, Avandia reportedly caused more than 47,000 people to suffer heart attacks, strokes, or death before FDA recognized the potential risk and intervened in 2010 to curtail the drug's marketing (Harris 2010). Indeed, the risk was first uncovered not by FDA but by plaintiffs' lawyers prosecuting product liability claims against the manufacturer, with medical studies subsequently

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confirming the drug's dangers based on data publicly divulged as a result of the litigation's settlement (ibid.). The case of all-metal hip replacements demonstrates that inadequate monitoring also hobbles FDA's oversight of medical devices. As early as 2008, DePuy Orthopaedics knew that its hip replacements were failing prematurely; even earlier, the company was alerted that the metallic implants were leaking chromium and cobalt into surrounding tissue, resulting in damage to vital organs, muscle, and bone (Editorial 2013; Jaslow 2012). Yet, FDA took no action until 2011, despite the 300 complaints it received during the preceding three years (Meier 2013; Meier 2010a).[3]

Achieving physician compliance with its warnings, advisories, and practice guidelines is another major problem for FDA. This regulatory failure stems both from FDA difficulties in communicating content in a timely, informative, and attention-getting manner and from physicians lacking adequate time, training, and willingness to keep abreast with and adhere to the agency's prescriptions regarding the safe and efficacious use of medical products. The sedative triazolam provides an example. After a protracted debate over its safety, FDA directed the manufacturer to issue a new warning that the drug should only be prescribed for seven to ten days (Moore et al. 1998). Yet follow-up studies found that 85 percent of triazolam prescriptions were for significantly longer periods (ibid.). Similarly, despite a two-year informational campaign about the addictive properties of propoxyphene conducted by FDA and the drug's manufacturer, there was no material effect on prescription volume or on the number of overdose deaths (Soumerai et al. 1987). Furthermore, concern about its advice being ignored prompted FDA originally to severely restrict Avandia's use rather than rely on additional warnings (Harris 2010; Tavernise 2013).

The regulatory function we advance for e-prescriptions can simultaneously and substantially improve FDA's accomplishment of its two objectives of compliance and monitoring by interfacing the agency with physicians and computerized patient records.

In particular, the e-prescription could be used to encourage physicians' compliance with FDA advisories and more generally with the norms of best medical practice by increasing their awareness of and focusing their attention on up-to-date FDA warnings, notices, and actions at the critical point of issuing the purchase order, together with access to the underlying studies and reports concerning the safety and efficacy of medical products. Simultaneously, the e-prescription

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system will dramatically improve FDA monitoring of medical product usage for risk signals and patterns and hence for early regulatory intervention. This system would represent a significant advance over the agency's current reliance on voluntary, relatively circumscribed modes of oversight. Our proposal would require physicians to specify on the e-prescription their treatment purpose for the prescribed medical product and would be called upon to report their knowledge of the medical outcomes, both favorable and unfavorable. By collecting and evaluating these data, e-prescription technology will provide FDA with a long sought experiential and evidentiary basis for reliable and expeditious formulation, implementation, and review of regulatory decisions.

The major FDA regulatory role we are proposing has not previously been considered in the literature or by policy makers. Most safety-related studies concern the technology's purchase-order function, for example, in eliminating mistakes due to illegible handwriting or incorrect specification of the dose level or frequency (Shamliyan et al. 2008; Nanji et al. 2011). Researchers have also investigated linking e-prescriptions to patient records to provide physicians and pharmacists with computer programmed alerts, dosage defaults, and other checks against potentially dangerous interactions between the newly prescribed treatment and a patient's ongoing medical conditions and product usage (Kaushal et al. 2010; Denekamp 2007; Gandhi et al. 2005; Nanji et al. 2011). Beyond the purchase-order function, e-prescriptions are increasingly used to provide doctors with clinical guidelines on recommended protocols and practices for treating certain diseases or conditions (Lang et al. 2007; Kawamoto et al. 2005), but critically, they do not involve a regulatory linkage between e-prescriptions and FDA designed to facilitate the agency in accomplishing its compliance and monitoring objectives. A small-scale e-prescription system initiated by McGill University goes the furthest of any we have found in tracking indications for which physicians prescribe drugs as well as providing them with current information regarding product uses, risks, generic alternatives, pricing, and best practice protocols (Tamblyn et al. 2006; Buckeridge et al. 2007; Eguale et al. 2010). This program, however, stops well short of our proposal, which, in contrast to McGill's, is primarily aimed at promoting regulatory objectives. To that end, the e-prescription system we propose would comprehensively collect data for continuous agency assessment, algorithmically

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and otherwise, relating not only to the diagnostic, therapeutic, and other indications prompting the physicians to prescribe a given medical product but also, to a matter of utmost regulatory importance: the safety and efficacy of the prescribed course and outcome of treatment.

In part 2, we outline the operational mechanics of an e-prescription system tasked to serve FDA regulatory objectives of compliance and monitoring. In part 3, we discuss the system's regulatory benefits, including augmentation of existing regulatory oversight. In part 4, we assess potential costs of our proposal.

II. OPERATIONAL OVERVIEW OF PROPOSED E-PRESCRIPTION SYSTEM

Our aim is to introduce the concept of an e-prescription technology that would provide as capacious, directive, and wide-ranging an interface between physicians and patient records on the one hand and FDA on the other as the agency needs to achieve its regulatory goals. As such, we will not consider how FDA implements our proposal, including its determination of how much and how insistently information should be communicated and elicited through e-prescriptions. Similarly, we do not address technical matters of software and content design.

A. Compliance

On opening an e-prescription form, the physician would be prompted to enter a user-identification and password, patient medical identification number, and then the name (brand, generic, chemical) or class, type, and function of the particular drug or device in question. The program would offer the option of viewing (or in response to a search request, provide) a list of and comparative information on safety, efficacy, and pricing of alternative products.

Having entered a particular product, the physician will be asked to select from a dropdown menu of FDA-approved medical indications or conditions for the given product. The physician can also enter another, "unapproved" (e.g., "off-label," warned against) use. Choosing an off-label or other unapproved course of treatment at this juncture will

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trigger an "override" feature of the e-prescription program, which we discuss below.

The heart of the compliance function will be notifying physicians of FDA warnings, cautions, best practice guidance, and other safety and efficacy information (including a link to the product insert) regarding a drug's or device's proposed use. Crucially, this advisory will be delivered at the moment of its greatest relevance and effectiveness, when the physician decides to prescribe the product (Kawamoto et al. 2005). The particular notices would be ordered and presented to optimally effectuate their clear and concise communication consistent with FDA priorities, with each soliciting a physician response indicating either understanding of the content or, if not, the difficulty involved. The program will indicate whether, when, and the extent to which notices have been upgraded (or downgraded) in seriousness or supplemented by new adverse event data and studies. If desirable, the system could be designed to allow physicians who have recently submitted e-prescriptions for the given product to skip all but contraindications and major warnings contained in the previously sent advisories.

Furthermore, to foster the best treatment outcome, the program will search the patient's computerized records for problematic factors in his/her medical history and for potentially harmful interactions from concomitant drug or device uses. The program will seek to identify such hazards by comparing the entire array of FDA warnings and cautions against the patient's records for available information relating to prior or ongoing drug and device use, medical conditions, treatment experiences, family background, and other risk-related factors and behaviors.

A physician response or search of patient records indicating use of the medical product for an FDA unapproved course of treatment or one that might pose concomitant drug or other usage risks of a patient-specific nature would trigger an "override" feature. Consistent with the agency's predominantly informational approach that affords physicians latitude in treatment, the override feature will condition but not preclude submission of the e-prescription for the unapproved use. To satisfy the condition, the physician will be required to expressly select from a menu of unapproved uses or to specify the unlisted, unapproved use. At that point, FDA contraindications, warnings, cautions, guidelines, and other contrary recommendations would appear sequentially, each with a request for the doctor to acknowledge having

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read and understood the advisory. This interrogatory process will not only serve the compliance function but also will be critical to promoting the monitoring function.

B. Monitoring

Our proposal's monitoring feature is designed to identify how medical products are being used and how safely and effectively they are performing in practice. The information sought includes not only adverse but also positive results. Although outcomes may often be described simply in terms of the use, for example, that the patient showed no evidence of malady X after use of product Y, the goal of our proposal is to secure more detailed accounts. Thus, for devices, it would be most helpful to know how long and under what type of circumstances the particular product was in use, and if and when the need arose to repair or replace it. As far as practicable, e-prescription monitoring would produce calibrated appraisals.

The primary monitoring feature of the proposal would be activated upon completion and submission of the e-prescription. At that point, not only will the purchase order be transmitted to the pharmacy but all entries on the e-prescription and all physician acknowledgments will automatically be conveyed to both FDA (appropriately anonymized) and to the patient's computerized records.

Although completed, the e-prescription would remain open until the physician's final report of the treatment outcome. Frequently, the outcome report will be based on information supplied by the patient in the normal course, for example, during a follow-up examination. In cases determined by FDA to present particular regulatory concerns, such as those involving use of especially risky products or investigation of a newly emergent danger, the physician may be prompted by the program to contact the patient for relevant information. The program will permanently close the e-prescription when the physician submits a report designated as final.

Many other cases may involve long-term courses of treatment, the outcome of which may be delayed and the prescribing physician's connection with the patient may lapse. Here, the program may be designed to allow the physician to reassign the reporting obligation directly or via an existing medical record to the patient's subsequent health care

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providers, enlisting them as coadministrators of the e-prescription and responsible for entering updated treatment results. The e-prescription technology can also respond to the "open" prescription case by searching pertinent entries in computerized patient records for information about the outcome of the treatment in question that would suffice to effect closure.

Despite these features, there will be cases where the follow-up effort required to close a prescription is not practical. When obstacles prevent meaningful follow-up, the physician may close the e-prescription by entering a final report of "outcome unascertainable."

Reporting gaps are likely to be random and surmountable through appropriate statistical techniques. Thus the e-prescription system should provide an unprecedented wealth of information about drugs and devices, their medical effects, both positive and negative, and how and for what condition they are being used; and it will do so in real-time.

III. EXPECTED BENEFITS

E-prescription technology will improve compliance by providing easy and timely access to complete, up-to-date information through a directive and interactive transmission medium—physicians must acknowledge receipt and appreciation of FDA prescriptions. Moreover, to authorize off-label and other unapproved uses, physicians must explain their choice.

Furthermore, the two regulatory functions of our proposal reinforce each other. Facilitating compliance with timely risk and practice guidance should diminish the need and cost for monitoring; and monitoring will encourage compliance as physicians realize that their responses to e-prescription queries are being recorded and scrutinized by FDA.

With respect to monitoring, reporting would be an automatic part of every prescription, and the data accumulated would be subject to FDA's direct unmediated access. This mode of surveillance contrasts markedly with existing FDA systems that are voluntary and fragmented in nature, such as MedWatch, which creates its database of adverse events from physicians, patients, and others who choose to report them, and disseminates alerts to physicians who choose to receive

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them (FDA 2012; Craigle 2007). FDA established MedSun to monitor adverse events in the use of medical devices based on reports from a network of voluntarily participating health care facilities, and upon investigation, to share the findings with the members of the network (FDA 2012a). However, as of 2010, only about four hundred hospitals had signed up (FDA 2010), limiting the information collected and disseminated. Similarly, Sentinel involves medical insurers/providers volunteering to search their proprietary databases for relevant information upon FDA request, but crucially, the system depends on the agency having otherwise already acquired evidence of adverse reactions or inefficacy before requesting database mining (Mini-Sentinel Coordinating Center 2011). These FDA programs provide vital information but, as exemplified by performance of MedWatch, are prone to underreporting and unreliability due in part to their voluntariness (Meier 2010a; Meier 2010b).

There are evident regulatory benefits from combining a comprehensive and more dependable database with constant evaluation of incoming information. Naturally, the feed of information from every e-prescription generated represents an enormous increase in response rate over current, voluntary programs. The e-prescription generated databases can create real-time, continuous analysis by algorithms designed to catch problems quickly as well as provide researchers with information for developing causal hypotheses and testing them against the compiled evidence, indeed, even by using the postapproval data to run retroactive randomized clinical investigations of a given product's safety and efficacy.[4] The vast amount of data could be examined as a whole or parsed as needed to scale monitoring up to the national level or down to those served by a particular physician group or hospital.

Of particular importance, the e-prescription system would provide FDA with currently unavailable information on off-label medications, which accounts for as much as 21 percent of the prescriptions for some drugs (Radley 2006). Clinical trials run for an approved use may not capture the adverse effects of other, unapproved uses (Stafford 2008). And off-label prescriptions are often written notwithstanding the lack of evidence on safety and efficacy (ibid.). Our proposal enables FDA to evaluate the efficacy and safety of off-label and other unapproved medical product uses, set alerts for new or increased use of medical products for unapproved purposes, correlate such uses with adverse (or positive) patient outcomes, and adjust its policies and advisories accordingly.

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Furthermore, our e-prescription proposal would promote FDA compliance objectives in the same manner as the agency pursues them. Physician adherence to rules and norms is encouraged mainly through information provided in approved product labels, inserts, and directions, and augmented as needed through specially issued warnings and updates. Medical malpractice suits and products liability deter nonconformity as well. However, physicians' compliance remains largely a matter of their conscious choice to become aware of and follow agency prescriptions. Although our proposal requires physicians to report their treatment decisions and outcomes, it leaves them free to choose the course of treatment, consistent with the general medical practice exemption from FDA regulation.[5]

The proposed e-prescription system could also be readily integrated with FDA's existing voluntary data reporting and sharing systems, incorporating and supplementing their databases. The e-prescription system can supplement Sentinel by providing a comprehensive database on treatment outcomes for all patients. It would also complement MedWatch. MedWatch would continue to allow consumers and require pharmaceutical companies to report adverse reactions, while our system would provide algorithmically generated warning signals from its vast database. Moreover, our proposed e-prescription system would render existing nongovernmental registries and databases, which are limited to specific types of medical devices or are proprietary, unnecessary as researchers could subject the e-prescription database to virtually unlimited types and combinations of investigative searches.

IV. POTENTIAL COSTS

The foregoing benefits are substantial. However, difficulties will arise in establishing an e-prescription system that can effectively serve FDA regulatory objectives. To begin with, building a fully integrated nationwide system will require federal funding and the expertise of FDA and other agencies with allied regulatory jurisdiction such as the Centers for Disease Control and Prevention. Next, we review the chief design problems, concluding that despite the challenges they present, none poses a significant obstacle to effectuating our proposal.

Development of the information technology component of the system is a nontrivial challenge. The system must be standardized and

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operate across multiple public and private entities. Given the many different preexisting systems, either the design of the overarching system must be able to encompass a wide variety of platforms or a major overhaul of infrastructure would need to occur.

The creation and editing of the content for the compliance function of the e-prescription system also poses significant design hurdles. Effectuation of that function hinges on informational prompts and questions whenever physicians fill out a prescription. The information being conveyed cannot regurgitate scientific studies, requiring significant effort by physicians to glean the meaning of the relevant reports. Nor should it simply provide links to lists of alerts that physicians can choose to access, as this would replicate the voluntary participation problems that undermine the reliability of MedWatch and other existing programs. Rather, FDA notices must be translated into straightforward prompts and questions that cogently and compellingly inform doctors of the relevant problems and side effects with the prescribed product. These cues would have to be carefully formulated, prioritized, and curated by FDA, and the agency would need to balance the value of conveying more information against not overloading the physician at this critical decision point. This process may be laborious and expensive in its initial setup as well as in continually updating the system. Moreover, these high capital investments will have to be undertaken despite relatively little empirical and experiential basis for anticipating the actual operating costs and benefits of the system.[6]

Our proposal will require continued expenditure from individual health care providers on necessary information technology and training. However, although the providers will bear most of these relatively fixed costs, they will reap a small amount of the benefits, which largely accrue to consumers and insurers in the form of better and less expensive treatment. Such a collective action problem could inhibit investment in the e-prescription system. FDA supervision as well as subsidization of participation by health care providers in system development would be required and costly.

Moreover, the system must not overtax the prescribing physician at the critical but typically brief moment of prescription. At least one study of e-prescription systems with clinical decision support suggested that clinicians override most medication alerts (Isaac 2009). Thus, physicians have to be trained on the software so that they can effectively and efficiently use the system and understand

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the importance of the alerts and questions generated rather than viewing the software as a burden (Drazen 2009). Beyond training costs, funding will be required for designing software and content to reduce "alert fatigue" and physicians' overall burden, for example, by minimizing the number and complexity of questions while at the same time countering their "clicking-through" and similar short-cutting behaviors by randomizing the sequence and varying the grammar of questions.

Any attempt to gather patient health information on the scale we propose raises privacy concerns. Our proposal must conform to the current federal patient privacy framework (DHHS 2002). Under DHHS privacy rules, protected health information that is individually identifiable cannot ordinarily be used without the person's consent. Thus, the collected data must be carefully stripped of its identifying characteristics while still maintaining to the greatest extent the research and monitoring value of the data set. If investigation of an FDA risk signal or pattern requires direct contact with patients, access to identifying information must be available, whether on some showing to a court or neutral FDA arbiter.[7] Furthermore, the number of breaches of patient privacy has corresponded with the increasing digitization of medical records (Perlroth 2011). To ensure privacy, this process will entail expenditures not only for training those entrusted with patient data but also for vigilance and oversight to prevent security lapses and assure compliance (McGilchrist 2007).

Finally, we note the possible costs of allowing a physician's e-prescription responses to be admitted into evidence to prove or disprove medical malpractice. This concern is speculative. A study of the McGill e-prescription system indicates physicians reported treatment indications with a high rate of completeness and accuracy (Eguale et al. 2010). Moreover, physician responses will add little to what can be readily gleaned from the treatment context, for example, from a patient's record showing that the doctor prescribed a drug approved only for adults to treat an infant. Although admission could motivate misreporting, the e-prescription system might also lower the rate and degree of liability findings by (1) reducing the number of medical errors and thus the number of lawsuits and (2) documenting physicians' answers to questions about potential side effects, thereby demonstrating reasonable care by the prescriber (Ransbotham 2011). While e-prescriptions might provide clear evidence of physician error,

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this kind of definitive evidence could reduce malpractice costs by encouraging settlement (ibid.). Moreover, the fact that these acknowledgements could later be used in litigation might encourage doctors to take the warnings seriously, thereby leading to fewer adverse effects, lower rates of defensive medicine, and stronger legal barriers against the filing of weak malpractice claims. And critically, regardless of the effects on liability, e-prescription evidence would render judicial determinations less prone to error.

V. CONCLUSION

It is critically important for the FDA to possess a robust, comprehensive postmarketing system of oversight to continuously surveil medical product usage, safety, and efficacy, and to ensure physician awareness of and compliance with its regulatory prescriptions. Leveraging e-prescription technology can provide FDA with such a system, the capability of which in acquiring monitoring and compliance data would far exceed its existing programs and those operated by other regulators and nongovernmental organizations. At the same time, the system could deliver critical warnings regarding drug and device use to practitioners at the very moment they need that information the most. Our proposal for developing e-prescription technology thus would not merely improve the purchase-order process but also would crucially and powerfully enhance FDA regulatory capacity to assure the safety and efficacy of medical products and delivery of medical services on which everyone's health and well-being depends.

NOTES

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1. For convenient reference, the e-prescription "purchase-order" function includes orders issued by health care providers to pharmacies or other private or public suppliers of FDA-regulated pharmaceuticals and medical devices.

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2. "Medical products" encompasses the full range of drugs, devices, and other items, and related methods, means, and protocols for their use subject to FDA jurisdiction and control pursuant to 21 USC § 301 et seq.

3. The manufacturer issued a warning about the high early failure rate in 2010 (Meier 2010b).

4. Opening the database to non-FDA researchers would provide additional resources for monitoring the safe and efficacious use of medical products. It would also facilitate investigations related to the host of recommended medical procedures and therapies that are advanced by nongovernmental organizations, such as the recent study showing widespread failure to adopt improved cancer therapies (Editorial 2013a).

5. However, the admonitory approach is not a necessary feature. Thus, our proposal is also fully compatible with FDA initiatives, such as the Risk Evaluation and Mitigation Strategy (REMS) Program, that impose more control over the use of certain medical products involving particularly pronounced risk (National Comprehensive Cancer Network 2013).

6. Electronic medical-record systems have not produced the anticipated amount of benefits (Abelson 2013).

7. The precise mechanism to evaluate the need for anonymity will need to be determined later. A balance must be struck between society's need for the best medical products and practices and a patient's desire for privacy, but no patient should be allowed to absolutely veto such access at will.

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