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Review

Postmarketing Surveillance for "Modifed-Risk" Tobacco Products

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Abstract

Introduction: The U.S. Food and Drug Administration (FDA) acquired authority to regulate tobacco products in 2009. This authority will provide a structured process for manufacturers to introduce products that may have "modifed-risk" for morbidity or mortality relative to traditional tobacco products, with post-marketing surveillance and studies a condition of marketing.

Method: A narrative review approach was taken. The author searched and integrated publicly accessible literature on tobacco product surveillance as well as drug and medical device post-market activities currently performed by FDA.

Results: FDA relies on active and passive methods for postmarket surveillance and can require specifc studies and risk evaluation and mitigation strategies for certain products, including those with abuse liability. Past efforts at examining the individual and population effects of reduced harm tobacco products provide an example of integrating different data streams.

Discussion: Postmarket surveillance can be viewed in terms of the Agent–Host–Vector–Environment model, and concepts from diffusion of innovations are relevant to understanding factors associated with the adoption of new products by the population. Given that active and passive surveillance approaches have different strengths and weaknesses, multiple approaches may be necessary to evaluate population-level effects. Assuring that required studies are properly conducted and reported and that data indicating significant public health harms are quickly recognized will be important going forward.

Conclusions: The advent of broad regulatory authority over tobacco provides opportunities for policy evaluation research. The research community can provide FDA with the independent science it needs to evaluate the public health impact of novel tobacco products.

Introduction

The Family Smoking Prevention and Tobacco Control Act of 2009 granted the U.S. Food and Drug Administration (FDA) authority to regulate tobacco products through reducing initiation of tobacco use, public education, application of regulatory science to tobacco products, and engagement with the public health community and industry (Deyton, Sharfstein, & Hamburg, 2010). Unlike the agency's mandate for safety and effcacy for drugs and medical devices, tobacco products are regulated "for the protection of the public health" with a focus on reducing morbidity and mortality associated with tobacco product use. A signifcant component of the new regulation is a process for manufacturers to introduce products that may have "modifed-risk" for morbidity or mortality relative to tobacco products (MRTPs). Among other requirements, manufacturers wishing to make claims about MRTPs must frst submit them to a pre - market approvals (PMAs) process, where decisions are based on individual- and anticipated population-level risk or exposure reduction (Deyton et al., 2010). The legislation also requires postmarket surveillance and product studies as a condition for marketing MRTPs, a component of which is monitoring consumer perceptions. The specifc requirements related to post - market surveillance and studies in the Family Smoking Prevention and Tobacco Control Act (FSPTCA) are detailed in Table 1.

Postmarket activities are encompassed in the broader concept of pharmacovigilance, defned by the World Health Organization (WHO) as "the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problem." Pharmacovigilance studies the problems associated with the use of medical products in a societal context, encompassing issues such as unanticipated side effects, drug interactions, unapproved uses, illicit trade, and long-term effects of product use (WHO, 2002). In a broad sense, pharmacovigilance is necessary because of the limited ability to identify potentially serious problems from pre-approval effcacy-focused clinical trials, which generally enroll relatively small numbers of otherwise healthy patients who may or may not refect those people likely to use the product (Gross, Soffer, Bach, Rajkumar, & Forman, 2002). That is, once a new product enters the market, it is likely to be used by populations with comorbid conditions, taking other medications, or have interindividual differences that affect product effcacy (Woodcock, Behrman, & Dal Pan, 2011). Additionally, some drugs may have potential for abuse, could be recommended inappropriately by health care providers, or could be dangerous if children are

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Table 1. Text of Family Smoking Prevention and Tobacco Control Act Relevant to Postmarketing Activities[a]

"(i) POSTMARKET SURVEILLANCE AND STUDIES—
"(1) IN GENERAL—The Secretary shall require, with respect to a product for which an applicant obtained an order under subsection (g)(1), that the applicant conduct postmarket surveillance and studies for such a tobacco product to determine the impact of the order issuance on consumer perception, behavior, and health, to enable the Secretary to review the accuracy of the determinations upon which the order was based, and to provide information that the Secretary determines is otherwise necessary regarding the use or health risks involving the tobacco product. The results of postmarket surveillance and studies shall be submitted to the Secretary on an annual basis.
"(2) SURVEILLANCE PROTOCOL—Each applicant required to conduct a surveillance of a tobacco product under paragraph (1) shall, within 30 days after receiving notice that the applicant is required to conduct such surveillance, submit, for the approval of the Secretary, a protocol for the required surveillance. The Secretary, within 60 days of the receipt of such protocol, shall determine if the principal investigator proposed to be used in the surveillance has suffcient qualifcations and experience to conduct such surveillance and if such protocol will result in collection of the data or other information designated by the Secretary as necessary to protect the public health.
"(j) WITHDRAWAL OF AUTHORIZATION—The Secretary, after an opportunity for an informal hearing, shall withdraw an order under subsection (g) if the Secretary determines that— ....
"(3) any explicit or implicit representation that the product reduces risk or exposure is no longer valid, including if— ....
"(C) any postmarket surveillance or studies reveal that the order is no longer consistent with the protection of the public health;
"(4) the applicant failed to conduct or submit the postmarket surveillance and studies required under subsection (g)(2)(C)(ii) or subsection (i); or
"(5) the applicant failed to meet a condition imposed under subsection (h).
"(l) IMPLEMENTING REGULATIONS OR GUIDANCE—
"(1) SCIENTIFIC EVIDENCE—Not later than 2 years after the date of enactment of the Family Smoking Prevention and Tobacco Control Act, the Secretary shall issue regulations or guidance (or any combination thereof) on the scientifc evidence required for assessment and ongoing review of modifed risk tobacco products. Such regulations or guidance shall— . ...
"(C) establish minimum standards for postmarket studies, that shall include regular and long-term assessments of health outcomes and mortality, intermediate clinical endpoints, consumer perception of harm reduction, and the impact on quitting behavior and new use of tobacco products, as appropriate;
"(D) establish minimum standards for required postmarket surveillance, including ongoing assessments of consumer perception;
"(E) require that data from the required studies and surveillance be made available to the Secretary prior to the decision on renewal of a modifed risk tobacco product; and
"(F) establish a reasonable timetable for the Secretary to review an application under this section.
"(2) CONSULTATION—The regulations or guidance issued under paragraph (1) shall be developed in consultation with the Institute of Medicine, and with the input of other appropriate scientifc and medical experts, on the design and conduct of such studies and surveillance.
"(3) REVISION—The regulations or guidance under paragraph (1) shall be revised on a regular basis as new scientifc information becomes available.

[a]Full text of the Family Smoking Prevention and Tobacco Control act available at http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=111_cong_public_laws&docid=f:publ031.111.pdf.

accidentally exposed (Woodcock et al., 2011). So, additional data collection and research are necessary to capture emergent problems once the drug is being used in the broader population, particularly risks that are rare, have a long latency, or are more likely to affect specifc populations (Härmark & van Grootheest, 2008). So, pharmacovigilance systems must be able to help identify new risks, refine understanding of known adverse effects, and expand knowledge about the conditions under which the product can be used safely (Woodcock et al., 2011).

FDA's pharmacovigilance responsibilities and activities have evolved following the recall of several marketed drugs in the late 1990s and early 2000s (Brown, 1996; Hilts, 2003; Institute of Medicine [IOM], 2006). Recently, similar concerns were raised about the monitoring of medical devices (Lenzer & Brownlee, 2010; Levinson, 2009). A 2006 IOM report examined the drug safety system and recommended a "lifecycle approach" to drug risks and benefts, including the prospective availability of data, reassessment of risk and beneft over time, and use of consistent regulatory measures in preapproval and postmarket phases (IOM, 2006). Specifc recommendations included orga - nizational changes, evaluating and improving the adverse event reporting system (AERS), and developing "a more structured way to determine the level of postmarketing scrutiny and data requirements, in other words, to match the evaluation of drugs with the way that they will be used in the population" (IOM, 2006). Many of these proposed reforms were embodied in the Food and Drug Administration Amendments Act (FDAAA) of 2007, which placed greater emphasis on ongoing safety evaluation. The requirements of the FDAAA will be discussed later.

Just as FDA needs robust pharmacovigilance to monitor the population impact of medical products, it also needs vigorous systematic monitoring of MRTPs to minimize untoward population effects. Exactly how the Center for Tobacco Products (CTP) will operationalize its postmarketing surveillance requirements for MRTPs is yet to be determined, but current FDA practices regarding other regulated products may provide important insights. CTP may model its guidelines on approaches used by the Center for Drug Evaluation and Research (CDER) and the Center for Devices and Radiological Health (CDRH). Another important source of information is past practices of the industry regarding potential reduced exposure tobacco products (PREPs) and how consumers have reacted to novel products

claiming reduced health risks. This paper seeks to integrate postmarketing surveillance methods and practices and proposes research opportunities for the scientifc community as the FDA moves toward applying regulatory science to MRTPs.

Methods

Given the broad topic to be covered and the evolving nature of the feld, this paper utilizes a narrative review approach, which is a qualitative way to summarize and integrate the literature, driven primarily by the author (cf. Collins & Fauser, 2005). A series of searches of the published literature accessible via PubMed (http://www.ncbi.nlm.nih.gov/pubmed) was conducted in mid-2010 using search terms and combinations of postmarket, pharmacovigilance, surveillance, drug safety, FDA, adverse events, tobacco products, medical device, and risk. The FDA Web site search tools (http://www.fda.gov) were used for current guidance documents and reports issued by the relevant centers (i.e., CDER, CDRH, Center for Biologics Evaluation and Research, CTP).

Results

Results are organized into two broad sections. The frst section describes current postmarketing activities around drugs and medical devices, including key features such as signal identifcation, post - marketing requirements and commitments, and risk management and evaluation strategies. The second section describes approaches to surveillance of tobacco products, including a case study highlighting activities surrounding Eclipse (R.J. Reynolds [RJRT]).

Postmarketing Safety Signal Identifcation

As Härmark and van Grootheest (2008) noted, spontaneous reporting systems have traditionally formed the backbone of postmarketing surveillance. The AERS mandates the reporting of adverse events for prescription drugs and medical devices that come to the company's attention (Weaver, Grenade, Kwon, & Avigan, 2009; Wysowski & Swartz, 2005). In 1993, the FDA began the MedWatch program, which facilitated reporting of adverse events directly to FDA by physicians and patients. By nature, MedWatch is a spontaneous reporting system rather than a systematic surveillance structure, so, not all adverse events are captured, though the extent of underreporting is unknown (Weaver, Willy, & Avigan, 2008). FDA employs data mining techniques, particularly the empirical Bayes multiitem gamma Poisson shrinker algorithm, to explore the AERS database for safety signals, screening for unexpectedly high levels of a given adverse event (Bailey, Singh, Azadian, Huber, & Blum, 2010; Weaver et al., 2008).

Over the last twelve years, a variety of additional systems have been introduced to examine adverse events with medical products by leveraging multiple data streams to identify hazards associated with marketed products. Using 350 sentinel clinical sites to report real-world experiences, the MedSun program for medical devices is a step toward prospective tracking of adverse events (U.S. Department of Health and Human Services, 2009a). The Research on Adverse Drug events and Reports (RADAR) project was initiated by a consortium of 25 clinical investigators in 1998 to prospectively investigate serious adverse events (those causing death or requiring therapeutic intervention; Bennett et al., 2005). The RADAR process, described fully in Bennett et al. (2005), sought to develop hypotheses about possible mechanisms underlying the adverse event, followed by comprehensive summaries of the cases disseminated publicly through publications and presentations or directly to FDA and manufacturers. RADAR was shown to be more comprehensive than MedWatch, though increased data quality came at a cost in timeliness of dissemination (Bennett et al., 2007). The authors noted it would be impractical for FDA to implement such a prospective system on a large scale, so independent pharmacovigilance systems could be valuable for monitoring certain drugs (Bennett et al., 2007). A separate and similarly named surveillance system for controlled substances (Researched Abuse, Diversion, and Addiction-Related Surveillance [RADARS]; Cicero et al., 2007) integrates quarterly surveys of drug abuse experts, law enforcement data on drug diversion, and poison center reports of drug abuse and misuse to examine population-level abuse of prescription opiates, covering of 80% of the country's three-digit zip code areas. Similarly, Butler et al. (2008) have described a real-time addictions vigilance system (NAVIPPRO), designed to identify and prevent prescription drug abuse through product-specifc data collection on patients entering substance abuse treatment. DasGupta and Schnoll (2009) present a framework for signal detection that relies on public spontaneous reporting systems (AERS) as well as proprietary systems like those described above, together with signal verifcation using follow-up reports and feld investigations to derive recommendations for action, design of interventions, and evaluation of outcomes.

Postmarketing Requirements and Commitments

The FDAAA of 2007 represented an evolution in how the agency would approach postmarketing activities (Meyer, 2009; Woodcock et al., 2011). The law allows FDA to require certain studies as conditions of approval (termed "postmarket requirements" [PMRs]), and it also allows for manufacturer-proposed studies, termed "postmarket commitments" (PMCs; U.S. Department of Health and Human Services, 2009b). FDA is empowered to mandate PMRs for any new drug to assess known serious risks, assess signals of serious risks, and identify potential serious risks not identifed in preapproval clinical trials and that could not otherwise be adequately assessed using AERS or other pharmacovigilance systems (U.S. Department of Health and Human Services, 2009b). FDA can also require a postmarketing study or clinical trial for an approved drug if it becomes aware of new safety issues. PMR studies can cover the gamut of laboratory, animal, or human studies (U.S. Department of Health and Human Services, 2009b). PMCs can include studies or clinical trials undertaken voluntarily by manufacturers, such as pharmacoepidemiological studies to examine adverse event base rates, manufacturing stability studies, or clinical trials examining long-term drug effcacy (U.S. Department of Health and Human Services, 2009b). However, manufacturers making a PMC are still required to complete such studies and report the results to FDA. Via the PMR process, the FDA can require changes in product labeling, including changes to boxed warnings, contraindications, warnings, precautions, or adverse reactions (U.S. Department of Health and Human Services, 2009b).

Medical devices have different postmarketing requirements because devices themselves are grouped into three classes based

on likely risk of injury or harm (Maisel, 2004). Class I devices, considered low risk for harm, are generally exempt from pre- and postmarket activities (FDA, 2010a). Class II devices are generally covered by a premarket notifcation process (510[k]), which determines whether a new device is "substantially equivalent" (i.e., at least as safe and effective for the same intended use) to a reference device legally sold in the United States (Maisel, 2004; Monsein, 1997). Class III devices, which pose signifcant risk for harm, require PMA (Maisel, 2004). FDA may require specifc postmarket surveillance or studies for certain Class II and III devices where device failure poses a serious risk to health (U.S. Department of Health and Human Services, 2006, 2009d). As a condition of marketing for devices requiring a PMA, FDA may require postmarket studies to gather data on the performance of and experience with the new device.

Risk Evaluation and Mitigation Strategies

The 2007 FDAAA further authorized the agency to require Risk Evaluation and Mitigation Strategies (REMS) for approved drugs to assure that the benefts of the drug outweigh the risks (CDER/CBER, 2009b). Some guiding factors in requiring a REMS include the estimated size of the exposed population, the seriousness of the condition the drug is intended to treat, expected benefit, expected duration of use, and seriousness of known adverse consequences of use (Meyer, 2009; Shane, 2009). REMS can include medication guides, patient product inserts, and communication plans for patients and providers (U.S. Department of Health and Human Services, 2009c). In some cases, where a drug is known to have serious adverse effects, Elements to Assure Safe Use may be required to mitigate those known risks if other approaches would be insuffcient (U.S. Department of Health and Human Services, 2009c). The development of REMS is product specifc (though the same REMS apply to subsequent generic versions of products requiring a REMS) and relate to the specifc risks and benefts of the product and the population exposed (Shane, 2009). As a result, there is little standardization, which may pose challenges for implementation within the health care system (American Pharmacists Association, 2009). Shane (2009) has also noted that patients may be overwhelmed by large volumes of information about a drug.

One class of drugs where REMS are likely to evolve in importance is those having abuse liability (Wright, Schnoll, & Bernstein, 2008). A recent series of papers highlighted the importance and challenges of risk management and surveillance for drugs that have abuse potential (Balster, Johanson, & Walsh, 2009; Schuster, Barthwell, & Henningfeld, 2009). Leiderman (2009) notes that as risk management evolves, the roles of government and industry are likely to shift from merely providing information to providing more active tools and programs to support safe use of abuse-liable medications, particularly in assuring appropriate prescribing practices. Johanson et al. (2009) present a number of recommendations for risk management strategies for abuse-liable drugs. They note that laboratory abuse liability studies are good indicators of abuse in the real world, suggesting that premarket research can inform the development of REMS. Furthermore, they note the need to consider unintended consequences of REMS as part of monitoring, such as decreased availability of effective drugs, shifting use to less effective and/or more harmful drugs, disincentivizing drug innovation, and burdens on the medical system. Finally, they note the need for coordination and cooperation among FDA, state and federal public health entities, and the health care system to assure REMS compliance.

Recent Developments and Future Initiatives

In response to statutory obligations in the FDAAA of 2007, FDA has taken steps to be more proactive in pharmacovigilance (Psaty & Vandenbroucke, 2008). Yet, the agency remains largely dependent on the public to provide information about possible safety issues once a drug/device is in the marketplace (Woodcock et al., 2011). Under FDAAA, the agency was mandated to develop a new pharmacovigilance system that would facilitate risk identifcation and active surveillance using federal, private sector, and other electronic data while maintaining HIPAA compliance (Woodcock et al., 2011). FDA dubbed this new approach the Sentinel Initiative (FDA, 2008, 2010b). Sentinel relies on an architecture that would allow for querying of remote data sources, such as electronic medical records, medical claims, and the spontaneous reporting system, with a view to supporting dissemination of up-to-date information on medical products (Woodcock et al., 2011). Although it would not replace MedWatch or other reporting systems, once implemented, Sentinel is anticipated to be a key resource for identifying and verifying safety signals for medical products. A second spontaneous reporting system authorized under the FDAAA of 2007, the Safety Reporting Portal was launched in May 2010 and is currently operational for human and animal reportable foods, animal drugs, and pet foods. The new system aims to bring reporting of safety issues by consumers, manufacturers, and health care providers for FDA-regulated products under a single system accessible via the Internet. Unlike MedWatch, the Portal uses rational questionnaires to guide users through the reporting process, subsequently compiling the data into a standard report format (The Federal Adverse Event Task Force, 2010).

Tobacco Products Surveillance

Because tobacco products have not been regulated as intensively as drugs and medical devices, they have not been subjected to systematic postmarket surveillance, that is there is no adverse event reporting mechanism and the mechanisms of PMRs or REMS for new or modifed tobacco products do not exist. In its 2001 monograph on tobacco harm reduction, the IOM recommended that the health and behavioral effects of any modifed-risk product be monitored on a continuing basis after introduction (within a regulated marketplace), effectively promoting a postmarketing surveillance strategy (IOM, 2001). Specifcally, the IOM recommended the "development of a surveillance system to assess the impact of promotion and use of PREPs on the health of the public . . . " which would entail elements necessary to assess population impact, including " . . . attitudes, beliefs, product characteristics, distribution and usage patterns, marketing messages, . . . , incidence of initiation and quitting . . . ," as well as disease patterns (IOM 2001, p.8).

Population Indicators

Nonetheless, tobacco control researchers and advocates have a continuing interest in the emergence and effects of new tobacco products (see Giovino et al., 2009; O'Connor et al., 2009 for overviews). Giovino et al. (2009) conceptualized surveillance of tobacco product use within the Agent–Host–Vector–Environment framework of epidemiological research (see Cruz, 2009; Delnevo &

Bauer, 2009; Farrelly, 2009; Stellman & Djordjevic, 2009). These reviews discuss diverse data sources and study approaches for documenting the various aspects of tobacco product usage. Behavioral indicators, such as the prevalence of smoking, quitting rates, numbers of cigarettes smoked, and brand preferences, typically measured in surveys, constitute the foundation of tobacco surveillance and are likely to continue in importance in a regulated environment (Cummings, Hyland, Lewit, & Shopland, 1997; Cummings, Hyland, Pechacek, Orlandi, & Lynn, 1997; Giovino, 2002; Giovino et al., 1994; Morbidity and Mortality Weekly Report, 1990, 1992, 1994; Siegel et al., 1996). Large nationally representative surveys such as the Behavioral Risk Factor Surveillance System (BRFSS), National Health Interview Survey (NHIS), National Survey on Drug Use and Health (NSDUH), and the Tobacco Use Supplement to the Current Population Survey offer suffciently large samples to potentially track uptake of novel products over time. The National Health and Nutrition Examination Survey (NHANES) collects extensive information on cigarette brands and has the added beneft of extensive health data with which product information can be correlated (e.g., biomarkers of exposure, anthropometrics, medical examinations).

Consumer Perceptions

Surveillance of product awareness and uptake of marketed products is essential to establishing whether a given product may have a substantial public health impact (Giovino et al., 1996; Hamilton et al., 2004; Hughes, Keely, & Callas, 2005; Shiffman, Pillitteri, Burton, & Di Marino, 2004; Shiffman et al., 2007). Examining public perceptions of modifed-risk products have been a focus of intensive research (Bogen et al., 2009; Connolly, Rees, Kreslake, O'Connor, & Cummings, 2009; O'Connor, Hyland, Giovino, Fong, & Cummings, 2005; Parascandola, 2005; Parascandola, Hurd, & Augustson, 2008; Pederson & Nelson, 2007; Shiffman et al., 2002). Typical methods for examining consumer perceptions have been surveys (focusing on general awareness and beliefs), laboratory studies (measuring subjective effects of products), and focus groups (for more in-depth discussion of specifc products or to probe issues for larger studies; Connolly et al., 2009). However, the advent of collaborative web-based technologies such as Wikis (e.g., Trinkets and Trash [UMDNJ School of Public Health, 2006]; Tobacco Products Wiki [Wikiproducts, 2010]) affords nearly real-time surveillance of tobacco marketing activities and the introduction of novel products. Expanding such interactive systems to collect information directly from product users could be informative for product surveillance. Given the FDA's mandate to examine the health effects of modifed-risk products and consumer percep - tions, such research will continue to grow in importance.

Case Study in Tobacco Product Surveillance: R.J. Reynolds' Eclipse

It is instructive to examine a case study that demonstrates the integration of multiple data streams to identify concerns with a tobacco product marketed with claims of reduced health risks. One such example is RJRT's Eclipse, which frst emerged in test markets in 1996 and was eventually sold nationally. RJRT made explicit health claims for the product, including reduced risk for cancer and emphysema (Slade , Connolly, & Lymperis, 2002). A number of laboratories examined the evidence for health claims (Breland, Buchhalter, Evans, & Eissenberg, 2002; Breland, Kleykamp, & Eissenberg, 2006; Fagerstrom, Hughes, & Callas, 2002; Fagerstrom, Hughes, Rasmussen, & Callas, 2000; Lee, Malson, Moolchan, & Pickworth, 2004; Rennard et al., 2002; Stewart et al., 2006), generally fnding that nicotine levels were maintained, some biomarkers (e.g., 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone, alveolar epithelial injury) were reduced, and CO exposure was increased relative to traditional cigarettes. One research group reverse engineered the test marketed product and identifed a potential health issue associated with inhalation of the fberglass insulation around the carbon heating element (Pauly et al., 1998). Survey research attempted to document awareness and use of the product, with estimates of awareness ranging from 7% to 24% and use from 1% to 11% (Hund et al., 2006; O'Connor et al., 2005; Parascandola et al., 2008). Some of the discrepancy across surveys may be due to asking about Eclipse by name, which is shared with other consumer products, versus eliciting the name of the product from the respondent (see Bogen et al., 2009). In two studies, Shiffman et al. (2004, 2007) showed that smokers perceived Eclipse as reducing harm and that interest in using Eclipse was related to reduced intention to quit smoking. After seeing a single ad for the product and although none had ever tried the product, college students rated Eclipse less positively but also less negatively in terms of outcome expectancies relative to Marlboro Lights (O'Connor et al., 2007). Established smokers who took part in focus groups reported a signifcant dislike of the PREP cigarettes that they had tried, including Eclipse, and almost all of the participants reported that they would not recommend these products to other smokers (Caraballo, Pederson, & Gupta, 2006; O'Hegarty, Richter, & Pederson, 2007). Most reported that they felt the Eclipse cigarettes were too mild and did not deliver enough nicotine to satisfy their cravings, and many reported a dislike of the taste. One team of investigators identifed a sample of 173 Eclipse users, who were surveyed to determine their reactions to the product. Hughes et al. (2005) showed that smokers who had tried Eclipse generally did not like it, though they believed it to be safer than traditional cigarettes. The accumulated evidence on Eclipse eventually led the Attorney General of Vermont to fle suit against RJRT for deceptive advertising (State of Vermont v. R. J. Reynolds Tobacco Co. Chittenden Superior Court Docket No. S1087-05 CnC, 2010). The court found that RJRT misled consumers by extrapolating fndings from changes in biomarkers and smoke emissions without scientifc consensus that these changes would reduce disease risks, in particular noting:

> *Inasmuch as RJRT concedes there are no such epidemiological studies of Eclipse smokers—indeed, Reynolds argues that conducting such studies is an unreasonable, if not impossible requirement in this instance—its claim that a smoker switching to Eclipse will in fact face a lesser risk of contracting "cancer, chronic bronchitis, and possibly emphysema," . . . is deceptive and misleading as a matter of law* (State of Vermont v. R. J. Reynolds Tobacco Co. Chittenden Superior Court Docket No. S1087-05 CnC, 2010).

The experience with Eclipse underscores the need for post-market activities to serve as a monitor on whether fndings ob - served in preapproval studies continue when the study is in the market, especially where claims of reduced exposure and health risk are involved.

Discussion

Postmarket surveillance of modifed-risk products allowed for sale on the market will be crucial to determining their effects on

population health. The FDA CTP is charged with developing standards for postmarketing studies and surveillance for modifed-risk tobacco products, and other Centers within the agency have experience in this type of work. Table 2 summarizes the key features of postmarketing studies for drugs and devices under current FDA regulations as well as putative mechanisms for MRTP surveillance.

While postmarketing surveillance is formally mandated only for MRTPs, the principles of postmarketing surveillance and studies can be equally well applied to ongoing monitoring of the effectiveness of FDA regulations. For example, FDA has authority to mandate tobacco product performance standards (e.g., banning ingredients and/or imposing limits on specifc constituents). Such performance standards could be counterproductive for public health by making cigarettes appear to be safer, possibly encouraging uptake and/or impairing cessation efforts (e.g., Givel, 2008; Kozlowski, 2008). A systematic postmarketing surveillance effort could assess unintended consequences, such as increased uptake or decreased cessation, allowing the agency to adjust course as necessary.

Limitations of Current Postmarket Surveillance Systems and Strategies

Härmark and van Grootheest (2008) noted that pharmacovigilance methods fall into two broad categories, each with its advantages and disadvantages: descriptive studies and analytical studies. Descriptive studies are those that generate "signals" or hypotheses, including examination of spontaneous event reporting systems and intensive monitoring of patient cohorts. A major limitation of spontaneous reporting is capture—some have estimated that 94% of adverse event experiences go unreported (Hazell & Shakir, 2006), limiting the utility of spontaneous reporting systems for estimating the incidence of risks for specifc products. Additionally, proof of a causal relationship between product and event is not required to submit a report, making it diffcult to attribute events specifcally to product use (Shea, Hanson, Guglielmetti, & Levy, 2007). Still, the system represents an important source of data supporting safety actions, including product recalls and withdrawals (Wysowski & Swartz, 2005). Furthermore, parallel investigative systems, such as RADAR, RADARS, and NAVIPPRO, which draw data from multiple sources beyond the spontaneous reporting system, are necessarily limited by the accuracy and reliability of their data. O'Connor et al. (2009) have noted the challenges involved in ascertaining the reliability and validity of disparate data sources, many of which were originally collected for other purposes, for monitoring PREPs use. Just as FDA has developed advanced statistical tools for mining its spontaneous reporting databases for safety signals (e.g., Bailey et al., 2010), data mining techniques may need to be developed to examine and integrate signals from disparate data sources. Additionally, advanced statistical methods accommodating missing data may be necessary to obtain reliable prevalence estimates for the adoption of novel products.

Intensive monitoring approaches using cohorts of patients or medical record data offer the advantage of following a selected product over time in a group of naturalistic users. However, because there is no control group, it is difficult to ascertain whether observed events are higher or lower than background (Härmark & van Grootheest, 2008). Delnevo and Bauer (2009) have provided an excellent overview of issues related to survey research, another important form of descriptive pharmacovigilance. Two key problems to highlight are diminishing response rates and wireless substitution. For example, median response rates to BRFSS surveys have declined from about 70% in 1994

Table 2. Current Postmarketing Activity Regulations for Drugs and Medical Devices and Putative Requirements for Tobacco Products Under the FDA

	Drugs/biologics	Medical devices	Tobacco products
Applicable products	Prescription drugs and biological agents	Class II and III devices	Products with a "modifed-risk" or "reduced-exposure" claim
FDA can require postmarket study as condition of approval	Yes, via PMRs, including laboratory and epidemiological studies or clinical trials with safety endpoint	Yes, for products subject to PMA	Yes
FDA can require new postmarket study for already approved product	Yes, if signal identifed and existing reporting and surveillance systems are insuffcient	Yes, if signal identifed or product was recalled or subject to corrective action	Yes, on renewal of MRTP approval
Mandated reporting	AERS	AERS MAUDE	
Spontaneous reporting	MedWatch	MedWatch	
Surveillance structures	NEISS DAWN NSDUH	NEISS MedSUN	NSDUH NHIS NHANES CPS-TUS BRFSS
Risk evaluation and mitigation strategy	Yes, for selected products	No	

Note. AERS = adverse event reporting system; BRFSS = Behavioral Risk Factor Surveillance System; CPS-TUS = Current Population Survey Tobacco Use Supplement; DAWN = Drug Abuse Warning Network; NEISS = National Electronic Injury Surveillance System; NHANES = National Health and Nutrition Examination Survey; NHIS = National Health Interview Survey; NSDUH = National Survey on Drug Use and Health; MedSUN = Medical Product Safety Network; MRTP = modifed-risk tobacco product; PMA = premarket approval; PMR = postmarketing requirement.

to just over 50% in 2009, raising issues of biased prevalence estimates and differential nonresponse (CDC, 2010). Indeed, Schneider Clark, Rakowski, and Lapane (2010) found that women, minorities, and younger people were underrepresented in the 2000 BRFSS relative to the contemporaneous Census survey. A related issue is the increasing proportion of persons foregoing "land lines" for cellular telephones. The most recent NHIS estimate notes that one in five households is wireless-only posing a significant problem for representing this subset of the population in traditional random-digit-dialed telephone surveys (Blumberg & Luke, 2009). Those in wireless households tended to be current smokers, Hispanic or non-Hispanic Black, younger than 45 years of age, and living near or below the poverty line. Therefore, a growing number of research groups are using mixed mode surveying (e.g., telephone and Internet, mail and telephone) to reduce nonresponse bias (e.g., Link & Mokdad, 2005; McCabe, Diez, Boyd, Nelson, & Weitzman, 2006). The use of national surveys is also hampered by the inability to rapidly change and field surveys, practical limits on the number of questions that can be asked, and limited ability to tap underrepresented populations (reviewed in Delnevo & Bauer, 2009). Panel or cohort studies could offer advantages over cross-sectional surveys, such as tracking response to interventions and new product introductions in a well-characterized population (cf. Fong et al., 2006; International Agency for Research on Cancer, 2008; Thompson et al., 2006). Panels do suffer from attrition, which is likely to be nonrandom (e.g., Young, Powers, & Bell, 2006), making the cohort less representative over time, though not precluding meaningful analysis of change (Powers & Loxton, 2010; Thompson et al., 2006).

Analytical studies encompass typical epidemiological and clinical study designs, such as case–control, cohort, and even clinical trials having safety endpoints. Analytical studies tend to involve select populations and study conditions that may not to reflect the real-world context of use. It is sometimes possible to construct retrospective or nested case–control or cohort studies in ongoing systematic data collections to answer safety questions (Härmark & van Grootheest, 2008; Strom, 2005). Beyond the practical aspects of study design and analysis are the ethical issues involved in specifically studying the safety of marketed products, a topic currently under examination by the IOM (2010). In its preliminary report, IOM (2010) recommended that FDA require such trials only in those situations where there is a "significant question about the public health risks." Communicating the sometimes complicated risks and benefits issues for trial participants was a particular concern, and the committee advised against a "kitchen-sink" approach to risk information, noting that informed consent involves participants understanding the risks, not merely having them disclosed (IOM, 2010). This has implications for the study of modified-risk tobacco products, where explanations of risks and benefits occur in the context of an already risky activity (smoking). Overall, though both descriptive and analytic approaches to pharmacovigilance serve to enhance understanding of the performance of medical products in the real world.

FDA has been criticized in the past for not fulfilling its obligations for ongoing surveillance of medical product safety (Brown, 1996; Hilts, 2003; IOM, 2006). For any postmarketing surveillance activities to have their intended effect of avoiding untoward consequences of introducing an MRTP, the Agency must use the full power of its authority to ensure the following: (a) studies required as a condition of approval are properly conducted and reported, (b) ongoing data collection activities (e.g., surveys, spontaneous reporting) are fit for their purpose, and (c) data indicating significant public health harms will be fed back quickly to reevaluate the marketing approval.

A Framework for Postmarket Surveillance for Tobacco Products

The 2002 National Tobacco Monitoring, Research, and Evaluation Workshop (Giovino et al., 2009) compiled a series of reviews covering tobacco surveillance with respect to the agent (product characteristics; Stellman & Djordjevic, 2009), vector (industry activities; Cruz, 2009), host (tobacco user characteristics; Delnevo & Bauer, 2009), and environment (regulations and policies; Farrelly, 2009). The tracking of a newly introduced product into the population may be further conceptualized by diffusion approaches (e.g., Rogers, 2003; Wejnert, 2002). Such models are explicitly concerned with the rate of uptake of the product of interest, among whom the product is first adopted, and what characteristics of the product relate to adoption. Indeed, one might frame the entire enterprise of postmarketing surveillance as a study of product diffusion and its sequelae. Wejnert (2002) attempted to integrate the component variables of various models of innovation diffusion, noting that they fell into three broad categories: (a) characteristics of the innovation itself, (b) characteristics of users that influence likelihood of adoption, and (c) environmental context. These categories map well onto the epidemiological framework, and Table 3 frames diffusion issues within the context of the Agent–Host–Vector–Environment model to outline potential areas of postmarket surveillance for modified-risk tobacco products. Others have more comprehensively reviewed frameworks to evaluate potentially reduced harm tobacco products (e.g., IOM, 2001; Zeller & Hatsukami, 2009), so herein are presented selected examples in each area.

Agent (i.e., the modified-risk product)

We are primarily interested in the characteristics of the product per se that lead to its adoption. For tobacco products, this is likely to relate at least in part to its nicotine delivery and to its relative health benefits (ostensibly the reason it was approved for marketing as "modified-risk"). Independent testing to verify product contents and emissions should be conducted prospectively while the product is on the market to verify manufacturer disclosures and to confirm product stability. Similar to abuse-liable products, investigating design tamperability that may increase health risks to users (or nonusers) may be important (Cone, 2006; Grudzinskas et al., 2006). An example of tamperability with tobacco products that led to disastrous public health consequences was the blocking of filter vent holes on low-tar cigarettes, which enabled smokers to obtain higher levels of toxins (Kozlowski & O'Connor, 2002). Cost may also be an issue driving adoption, depending on whether the novel product is offered at a premium or discount relative to traditional products, so monitoring retail prices and sales figures may provide context to other data sources on usage patterns. Other costs may be social in nature, such as feeling embarrassed or silly using the novel product (cf. Caraballo et al., 2006).

Vector

In the case of the MRTP, vector comprises the manufacturer, competing companies, and retailers (i.e., those who have a

Table 3. Epidemiological Model of Postmarketing Surveillance Issues, Coupled to Related Concepts From Diffusion Theory

	Surveillance targets	Surveillance variables	Diffusion concepts[a]
Agent	Modifed-risk tobacco product (MRTP)	Product stability	Benefts of use
		Product performance	Costs of use
		Nicotine delivery	Consequences of use
Vector	MRTP manufacturer	Compliance with approved marketing	
	Other manufacturers	Marketing practices	
		Competitive pricing	
		Competing products	
	Retailers	Pricing, placement, promotion	
	Users	Viral marketing	
Host	MRTP users	Perceptions of absolute and relative risk	Demographics
			Socioeconomic status
		Health beliefs	Social position
		Intentions to quit	Familiarity
	Nonusers	Perceptions of absolute and relative risk	
		Health beliefs	
		Trial of MRTPs	
		Intentions to use product	
Environment	Availability	Number and location of retailers stocking MRTP	Geography
			Culture
	Regulations	Clean indoor air laws	Political conditions
		Local sales and advertising restrictions	Institutionalization
		Taxation	

[a]Adapted from Wejnert (2002).

financial stake in the success or failure of the novel product; Cruz, 2009). Under FDA regulation, the agency requires reporting from manufacturers to address most concerns about vector activities. However, from a diffusion perspective, an important vector for spreading information about a new product is other users (e.g., early adopters). Indeed, such "viral" marketing was one means explored by RJRT to promote the Eclipse product (Anderson & Ling, 2008). Viral and buzz marketing, enabled by the Internet and user-generated content sites like YouTube and Facebook, may become increasingly important as more traditional means of promotion are restricted (Freeman & Chapman, 2008). Furthermore, there is evidence that the Internet is a forum for sharing information and experiences among drug users (e.g., Cone, 2006; Deluca, Schifano, & Psychonaut 2002 Research Group, 2007). Therefore, monitoring the Internet for signals indicating possible viral marketing could be an important component of postmarketing surveillance activity.

Host

The FSPTCA requires FDA to consider not only users of the "modifed-risk" product but also impacts on nonusers of tobacco (including former smokers and youth). From a diffusion perspective, the host is the "innovator" or the person adopting the innovation of interest. Understanding the demographics of early adopters may provide important insights into the appeal of the product (i.e., WHO are the users of the "modifed-risk" product and WHY they are using it). How FDA deals with drugs having abuse potential may present a reasonable framework for MRTPs, as they share a common concern about use by persons other than the intended consumers. Dart (2009) and Dasgupta and Schnoll (2009) outline the types of data sources that can be applied in postmarketing surveillance of controlled substances, and many of these data sources overlap with or are conceptually similar to those that can be used to monitor tobacco products (cf. Cruz, 2009; Farrelly, 2009; O'Connor et al., 2009).

Of course, usage patterns are only one aspect of the concerns at the host level—product perceptions and beliefs about health effects are equally important. With regard to consumer perceptions, very few studies outside the tobacco industry have examined naturalistic adoption of novel products (e.g., Hughes et al., 2005). However, given that laboratory studies of abuse liability are predictive of the abuse of prescription drugs (Carter & Griffths, 2009), laboratory evaluations of modifed-risk prod - ucts may similarly inform on the likelihood of misuse by nonusers and youth (for reviews of methods and measures, see Carter et al., 2009; Hanson, O'Connor, & Hatsukami, 2009; Hatsukami et al., 2009; Rees et al., 2009). Research on consumer perceptions to tobacco products, and in particular, how those perceptions relate to use, is imperative because such data provide insight into why someone might be interested in using a product as well as how a product might be used by consumers (e.g., complete vs. partial substitution of traditional tobacco products, context for use; Rees et al., 2009). Periodic examination of health claims with small groups of smokers, nonsmokers, and youth might be required to assess understanding of claims, necessitating larger-scale follow-up studies.

Environment

The broader milieu into which an MRTP is introduced can have an impact into its adoption and use in the population. Historically, novel products have been introduced in test market in limited geographic areas, so initially, only smokers in selected areas may have access to the product. As with most regulatory

processes, political pressures and priorities may impact the Agency's zeal in enforcing requirements (Hilts, 2003). While FDA has jurisdiction over the products, states and localities are free to regulate the sale of tobacco products, which may ultimately impact the availability of "modifed-risk" products in different locales (cf. Slater, Giovino, & Chaloupka, 2008). Localities may also differ in regulations regarding clean indoor air, taxation, and support for smoking cessation, which could have an impact on the relative attractiveness of "modifed-risk" products. This is a relatively understudied aspect of adoption of novel tobacco products.

Opportunities for Future Research

The advent of broad regulatory authority over tobacco provides opportunities for policy evaluation research. The research community can provide FDA with the independent science it needs to complement mandated reporting and studies to provide a broad picture of the public health impact of MRTPs that are approved for marketing. Postmarketing surveillance of MRTPs will draw on existing experience and expertise for guidance on effective mechanisms. However, there are still opportunities to examine the relative merits of different approaches. Drawing on the above review, a series of eight questions is posed in no particular order—over time, doubtless some of these questions will be addressed and new ones will evolve.

1. Should priority for postmarketing surveillance requirements be placed on laboratory and epidemiological studies or on clinical trial designs?
2. What should constitute a reportable adverse event with a modified-risk tobacco product? Given that "safe" use of tobacco is unlikely, the standard for which AEs are judged may need special consideration.
3. Should REMS or similar risk management plans be required for modifed-risk tobacco products? If so, what form would they take?
4. What is the most effcient mechanism to monitor consumer perceptions prospectively? Ongoing survey instruments such as BRFSS, NHIS, NHANES, or NSDUH are available but are limited in terms of the amount of data that can reasonably be collected. A consortium of independent investigators might be useful to conduct smaller scale studies that address specifc hypotheses.
5. How long should postmarket surveillance last, and should activity be more intensive earlier in the product's lifespan? Some untoward outcomes (such as adoption by nonsmokers) might be evident in the shorter term, while adverse health effects might only manifest in the medium to long term (i.e., years after introduction).
6. Can adequate adverse event monitoring be achieved through existing and/or developing FDA systems (e.g., MedWatch, Safety Reporting Portal), or will complementary independent systems (akin to RADAR) need to be developed?
7. At what point should regulators become concerned by the consumer appeal of a product in the market? A potential conundrum arises in that an unappealing modifed-risk product is unlikely to be used, thus not benefting public health, but one that is excessively appealing to nonusers and youth would increase health burden and be detrimental to public health.
8. What role do state and local regulations, such as clean indoor air, taxation, and retail, play in the adoption of "modifed-risk" products?

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RJOC has served as a member of the Tobacco Constituents Subcommittee of the Tobacco Products Scientifc Advisory Committee for the Food and Drug Administration.

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