



STRENGTHENING OUR NATIONAL SYSTEM FOR MEDICAL DEVICE POSTMARKET SURVEILLANCE

**CENTER FOR DEVICES AND RADIOLOGICAL HEALTH
U.S. FOOD AND DRUG ADMINISTRATION**

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TABLE OF CONTENTS

A	INTRODUCTION	03
B	CURRENT FDA MEDICAL DEVICE POSTMARKET SURVEILLANCE SYSTEM	05
	1 MEDICAL DEVICE REPORTING (MDR)	05
	2 MEDICAL PRODUCT SAFETY NETWORK (MEDSUN)	05
	3 POST-APPROVAL STUDIES	06
	4 POSTMARKET SURVEILLANCE STUDIES (“522 STUDIES”)	06
	5 FDA DISCRETIONARY STUDIES	06
	6 OTHER TOOLS	06
C	STRENGTHENING OUR NATIONAL SYSTEM FOR MEDICAL DEVICE POSTMARKET SURVEILLANCE	08
	1 ESTABLISH A UNIQUE DEVICE IDENTIFICATION SYSTEM AND PROMOTE ITS INCORPORATION INTO ELECTRONIC HEALTH INFORMATION	10
	2 PROMOTE THE DEVELOPMENT OF NATIONAL AND INTERNATIONAL DEVICE REGISTRIES FOR SELECTED PRODUCTS	10
	3 MODERNIZE ADVERSE EVENT REPORTING AND ANALYSIS	13
	3.1 DEVELOPMENT OF AUTOMATED ADVERSE EVENT REPORTING SYSTEMS	13
	3.2 INCREASE THE NUMBER OF MDRs RECEIVED ELECTRONICALLY	14
	3.3 DEVELOP A MOBILE APPLICATION FOR ADVERSE EVENT REPORTING	14
	3.4 MODERNIZE THE MEDICAL DEVICE ADVERSE EVENT DATABASE	14
	3.5 RAPIDLY IDENTIFY SAFETY SIGNALS	15
	4 DEVELOP AND USE NEW METHODS FOR EVIDENCE GENERATION, SYNTHESIS AND APPRAISAL	16
	4.1 QUANTITATIVE DECISION ANALYSIS TO EVALUATE BENEFITS AND RISKS	16
	4.2 EVIDENCE ASSESSMENT BY COMBINING DATA FROM DIVERSE DATA SOURCES	17
	4.3 AUTOMATED SIGNAL DETECTION	18
	4.4 REFINEMENT OF PROCESSES FOR SIGNAL DETECTION AND MANAGEMENT	18
D	CONCLUSION	21
E	APPENDIX	22
	CURRENT SELECTED MEDICAL DEVICE POSTMARKET AUTHORITIES	

A. INTRODUCTION

Several high-profile medical device performance concerns have led some to question whether the current United States postmarket surveillance system is optimally structured to meet the challenges of rapidly evolving medical devices and the changing nature of health care delivery and information technology. In their report entitled, “Medical Devices and the Public’s Health: The FDA 510(k) Clearance Process at 35 Years,” published in July 2011, the Institute of Medicine (IOM) recommended that the Food and Drug Administration (FDA) develop and implement a comprehensive medical device postmarket surveillance strategy to collect, analyze, and act on medical device postmarket performance information.

Medical device product evaluation presents unique challenges compared to drugs and biologics, related to the greater diversity and complexity of medical devices, and the rapid technological advances and iterative nature of medical device product development. FDA’s Center for Devices and Radiological Health (CDRH) has undertaken a number of actions since early 2011 to strengthen our premarket review program and facilitate the timely delivery of innovative, safe and effective products to American patients.¹ While

we strive to permit marketing of only those devices with a favorable benefit-risk profile, even a thorough premarket product evaluation can leave some unanswered questions about a medical device’s performance and associated clinical benefits and risks.

We believe that strengthening our National Medical Device Surveillance System will complement the improvements we have made to our premarket program. A medical device postmarket surveillance system should quickly identify poorly performing devices, accurately characterize and disseminate information about real-world device performance, including the clinical benefits and risks of marketed devices, and efficiently generate data to support premarket clearance or approval of new devices and new uses of currently marketed devices.

This document, in addition to providing an overview of FDA’s medical device postmarket authorities and the current United States medical device postmarket surveillance system, proposes four specific actions, using existing resources and under current authorities, to strengthen the medical device postmarket surveillance system in the United States.

¹ A description of the actions CDRH has taken can be found at: <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHReports/ucm239448.htm>.

These actions are:

1. Establish a Unique Device Identification System and Promote Its Incorporation into Electronic Health Information;
2. Promote the Development of National and International Device Registries for Selected Products;
3. Modernize Adverse Event Reporting and Analysis; and,
4. Develop and Use New Methods for Evidence Generation, Synthesis and Appraisal.

We are suggesting smart, tailored modifications to the existing postmarket surveillance program. Furthermore, we recognize that our postmarket vision cannot be implemented or achieved by the FDA alone. It requires the input and active participation of many other key domestic and foreign stakeholders including the medical device industry, health care providers, patients, academia, third-party payers, hospitals and other health care facilities, health care data holders, and other government agencies. In addition, CDRH is hosting four public meetings in September 2012 to garner stakeholder feedback.

B. CURRENT FDA MEDICAL DEVICE POSTMARKET SURVEILLANCE SYSTEM

Postmarket surveillance is the systematic collection, analysis, interpretation, and dissemination of health-related data to improve public health and reduce morbidity and mortality. Medical device postmarket surveillance presents unique challenges compared to drugs and biologics due to the great diversity and complexity of medical devices, the iterative nature of medical device product development, the learning curve associated with technology adoption, and the relatively short product life cycle. Proper medical device operation depends on optimal device design, the use environment, user training, and adherence to directions for use and maintenance. In some cases, these features limit the utility of relying on systems designed for the identification of drug-related adverse events.

Under its existing authorities,² the FDA uses a multifaceted postmarket surveillance approach that relies on various methods and techniques tailored to the specific device and public health need. This leverages a variety of data sources to monitor the safety and effectiveness of marketed medical devices, including repositories of spontaneous reports, device registries, administrative and claims data, data from integrated health systems, electronic health records,

and scientific and medical literature. The current United States medical device postmarket surveillance system depends primarily upon:

1. *Medical Device Reporting (MDR)* — Each year, the FDA receives several hundred thousand medical device reports of confirmed or possible device-associated serious injuries, deaths, and malfunctions. While MDRs are a valuable source of information, this passive surveillance system has notable limitations, including the potential submission of incomplete or inaccurate data, under-reporting of events, lack of denominator (exposure) data, and the lack of report timeliness.
2. *Medical Product Safety Network (MedSun)* — MedSun is an enhanced surveillance network comprised of approximately 280 hospitals nationwide that work interactively with the FDA to better understand and report on device use and adverse outcomes in the real-world clinical environment. The overall quality of the approximately 5,000 reports received annually via MedSun is significantly higher than those received via MDR. Specialty networks within

² See Appendix for a description of key, current FDA medical device postmarket authorities.

MedSun focus on device-specific areas such as cardiovascular devices (Heart-Net) and pediatric intensive care unit devices (KidNet). In addition, the network can be used for targeted surveys and focused clinical research.

3. *Post-Approval Studies* — The FDA may order a post-approval study as a condition of approval for a device approved under a premarket approval (PMA) order. Typically, post-approval studies are used to assess device safety, effectiveness, and/or reliability including longer-term, real-world device performance. Status updates for the more than 160 ongoing post-approval studies may be found on our website at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma_pas.cfm.
4. *Postmarket Surveillance Studies* — The FDA may order a manufacturer of certain Class II or Class III devices to conduct postmarket surveillance studies (often referred to as “522 studies”).³ Study approaches vary widely and may include non-clinical device testing, analysis of existing clinical databases, observational studies, and, rarely, randomized controlled trials. Status updates for ongoing postmarket surveillance studies covering approximately a dozen device types may be found on our website at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pss.cfm>.
5. *FDA Discretionary Studies* — In addition to medical device adverse event reports, post-approval and postmarket surveillance studies, the FDA also conducts its own research to monitor device performance, investigate adverse event signals and characterize device-associated benefits and risks to patient sub-populations. A variety of privacy-protected data sources are used including national registries, Medicare and Medicaid administrative and claims data, data from integrated health systems, electronic health records, and published scientific literature.
6. *Other Tools* — The FDA has other tools it may use in the postmarket setting to track devices, restrict or ban device use, and remove unsafe, adulterated, or misbranded products from the market (see Appendix).

3 Section 522 of the Food, Drug & Cosmetic Act (FD&C Act).

ROLE OF SENTINEL INITIATIVE IN MEDICAL DEVICE POSTMARKET SURVEILLANCE

The Food and Drug Administration Amendments Act of 2007 (FDAAA)⁴ required the FDA to collaborate with public, academic and private entities to develop methods for obtaining access to disparate health care data sources and to analyze health care safety data. In May 2008, the Secretary of Health and Human Services (HHS) and FDA's Commissioner announced the Sentinel Initiative, a long-term effort to create a national electronic system for monitoring FDA-regulated medical product safety. The Sentinel System will ultimately expand FDA's existing postmarket safety surveillance systems by enabling the FDA to conduct active surveillance and related observational studies on the safety and performance of its regulated medical products once they reach the market.

The Sentinel Initiative requires the FDA to collaborate with public, academic and private entities to develop methods for obtaining access to disparate health data sources and to validate means of linking and analyzing health care safety data from those sources. With this effort, the FDA seeks to create a privacy-protected, scalable, efficient, and sustainable system—the Sentinel System—that leverages existing electronic health care data from multiple sources to actively monitor the safety of regulated medical products. A key finding from the early work of the Sentinel Initiative is that a distributed data system is the preferred approach for performing active surveillance. A distributed system allows data to be maintained in local environments by current owners, as opposed to using a centralized approach, which would consolidate the data into one physical location. A key benefit of the distributed

approach is enabling the maintenance of patient privacy by keeping directly identifiable patient information behind local firewalls in its existing protected environment. Additionally, each health care data system retains physical and operational control over its own data, and provides important input into valid use and interpretation of the data.

The current Sentinel data model focuses on querying administrative and claims data maintained by partner organizations, who share aggregated results with the FDA. Direct identifiers, such as names, are removed from records before information is shared with the FDA. De-identified information includes outpatient pharmacy data, diagnoses and procedures, mortality, and select laboratory results. The FDA does not receive or hold personally identifiable information, but can query privacy-protected data and receive aggregated data from local environments that together total approximately 126 million patients. Unfortunately, most of these records lack manufacturer or brand-specific device identifiers and therefore cannot be leveraged to perform meaningful medical device postmarket surveillance.

As a result, complementary efforts are required to develop a comprehensive postmarket surveillance system for medical devices. The Food and Drug Administration Safety and Innovation Act of 2012 explicitly requires expansion of FDA's Sentinel System to include medical devices.

The FDA envisions using similar distributed data sources, which would include EHRs and registries, for the medical device Sentinel System to help maintain patient privacy, administrative and claims databases, and other external data sources.

4 Public Law 110-85.

STRENGTHENING OUR NATIONAL MEDICAL DEVICE POSTMARKET SURVEILLANCE SYSTEM

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FDA's vision for medical device postmarket surveillance is the creation of a national system that conducts active surveillance in near real-time using routinely collected electronic health information containing unique device identifiers, quickly identifies poorly performing devices, accurately characterizes the real-world clinical benefits and risks of marketed devices, and facilitates the development of new devices and new uses of existing devices through evidence generation, synthesis and appraisal. The system leverages privacy-protected distributed data systems and common data standards, and would augment, not replace, other mechanisms of surveillance such as FDA's MDR and MedSun.

Specifically, medical device postmarket surveillance should:

- Provide timely, accurate, systematic, and prioritized assessments of the benefits and risks of medical devices throughout their marketed life using high quality, standardized, structured, electronic health-related data;
- Identify potential safety signals in near real-time from a variety of privacy-protected data sources;
- Reduce burdens and costs of medical device postmarket surveillance; and,
- Facilitate the clearance and approval of new devices, or new uses for existing devices.

The FDA believes that four key steps are needed to strengthen medical device postmarket surveillance in the United States (*see Fig, p. 9*). These steps are:

1. Establish a Unique Device Identification (UDI) System and Promote Its Incorporation into Electronic Health Information;
2. Promote the Development of National and International Device Registries for Selected Products;
3. Modernize Adverse Event Reporting and Analysis; and,
4. Develop and Use New Methods for Evidence Generation, Synthesis and Appraisal.

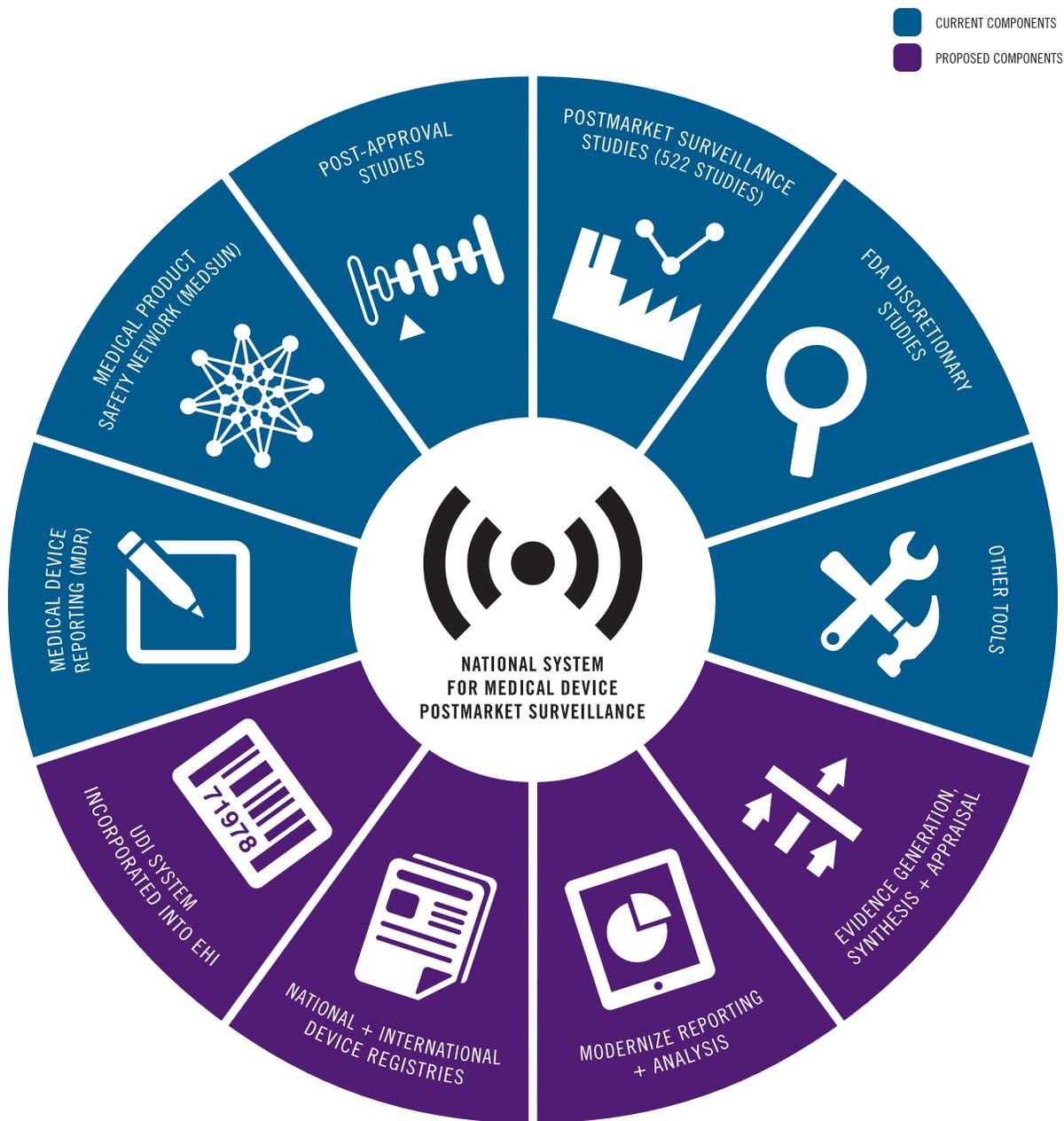


Figure. Strengthening Our National System for Medical Device Postmarket Surveillance.

The current medical device postmarket surveillance system in the United States depends primarily upon reporting of possible device-associated serious injuries, deaths and malfunctions (Medical Device Reporting – MDR), an enhanced surveillance network of approximately 280 hospitals (Medical Product Safety Network – MedSun), studies ordered by the FDA for selected devices (Post-Approval Studies and Postmarket Surveillance Studies), FDA research using other data sources (FDA Discretionary Studies), and other tools such as device tracking. The FDA suggests four specific actions that could be taken using existing resources and under current authorities to strengthen the medical device postmarket surveillance system in the United States. These actions are: 1) Establish a Unique Device Identification System (UDI) and Promote Its Incorporation into Electronic Health Information (EHI); 2) Promote the Development of National and International Device Registries for Selected Products; 3) Modernize Adverse Event Reporting and Analysis; and, 4) Develop and Use New Methods for Evidence Generation, Synthesis and Appraisal.

1. ESTABLISH A UNIQUE DEVICE IDENTIFICATION SYSTEM AND PROMOTE ITS INCORPORATION INTO ELECTRONIC HEALTH INFORMATION

FDAAA directed the FDA to promulgate regulations establishing a UDI system for all medical devices. In July 2012, the FDA issued a proposed rule for a UDI system.⁵ A UDI may contain two types of information: a unique numeric or alphanumeric code, specific to a device model, and an identifier that includes the production information for that specific device, such as the manufacturing lot or batch number, the serial number, manufacturing date, and expiration date.

UDIs will enhance postmarket surveillance activities by providing a standard and unambiguous way to document device use in EHRs, clinical information systems, and claims data sources. As a result, this information would potentially become available for use in assessing the benefits and risks of medical devices. UDIs will also allow the FDA, the health care community and industry to more accurately report and analyze device-related adverse events by ensuring that critical device information is included in the reports. These device identifiers may also help reduce medical errors by enabling health care professionals and others to rapidly and precisely identify a device, obtain important information concerning

the device's characteristics (e.g., whether it contains latex or is magnetic resonance imaging compatible) and improve the clinicians ability to trace the device through the supply chain to the point of patient use.

The incorporation of medical device identifiers into EHRs is another key step that would improve patient safety, make the conduct of postmarket surveillance more efficient, and make queries of and de-identified responses from electronic health information more readily usable to support device approval or clearance. Likewise, incorporation of UDIs into claims data would increase the utility of these data sources for medical device postmarket surveillance, and pilot studies suggest it is both technically feasible and cost-effective.

In short, a UDI system can improve the detection of medical device adverse events and product problems, enhance assessments of device benefit-risk profiles, streamline and help secure the domestic and global supply chain, facilitate more efficient and effective recalls, and facilitate the premarket evaluation of new devices and new uses of currently marketed devices.

2. PROMOTE THE DEVELOPMENT OF NATIONAL AND INTERNATIONAL DEVICE REGISTRIES FOR SELECTED PRODUCTS

A registry is a system that collects and

5 <https://www.federalregister.gov/articles/2012/07/10/2012-16621/unique-device-identification-system>

maintains structured records on a specific disease, condition, procedure, or medical product for a specified time period and population. Product registries include patients who have been exposed to a specific medical device, biologic or drug product. Health services registries consist of patients who have had a common procedure, clinical encounter or hospitalization. Disease or condition registries are defined by patients having the same diagnosis, such as diabetes mellitus or heart failure.

Procedure and device registries are often created and maintained by private organizations, such as the American College of Cardiology and its National Cardiovascular

Data Registry or the Society of Thoracic Surgeon's Adult Cardiac Surgery Database.

Importantly, the FDA is not seeking to develop a centralized repository of registry data. Rather each registry should retain physical and operational control over its own data, and provide important input into valid use and interpretation of its data. This also assures maintenance of patient privacy by keeping directly identifiable patient information behind local firewalls in its existing protected environment. In addition, the FDA envisions continuing to help facilitate the creation of registries. It is not seeking to regulate standards, such as business models

BOX C-1.

USING THE NATIONAL SYSTEM FOR MEDICAL DEVICE POSTMARKET SURVEILLANCE TO IDENTIFY NEW USES OF EXISTING DEVICES AND FACILITATE MARKET ACCESS FOR INNOVATIVE PRODUCTS

In addition to quickly identifying poorly performing devices and accurately characterizing the real-world clinical benefits and risks of marketed devices using routinely collected electronic health information, the National Medical Device Postmarket Surveillance System should facilitate the development of new technologies, new devices and new uses of currently marketed devices through evidence generation and analysis. The proposed system could do so by producing data to:

- Serve as the comparison group or “control arm” in scientific studies evaluating device performance;
- Identify new patient populations that benefit from device therapy;
- Be leveraged for expansion of labeled device indications to new groups; and,
- Demonstrate the relative safety of a device type to support downclassification and a reduction in the premarket evidentiary needs.

or taxonomy, for registries. The FDA currently partners with and uses registries to assess the real-world performance of medical products and procedures, to determine the clinical effectiveness and safety of a medical device, procedure or treatment, and to describe the natural history of a problem or disease. To be useful for device surveillance and assessment of benefits and risks, registries must contain sufficiently detailed patient, device and procedural data, and be linked to meaningful clinical outcomes.

Use of registries vary. For example, they may be voluntary or designed to meet FDA-mandated device postmarket surveillance requirements. Because well-designed registries provide valuable, unique insights into device performance and device-associated clinical benefits and risks, the FDA has encouraged the development of several device-specific registries and currently participates in more than a dozen registry efforts across a number of device areas involving cardiovascular, orthopedic, ophthalmic, and general surgery products.

For example, in 2011, the FDA helped to facilitate the creation of the International Consortium of Orthopedic Registries that consists of 29 registries from 14 nations and captures data from more than 3 million orthopedic procedures.

It is neither practical nor feasible to have

registries that address every medical device problem or issue. In addition, registry development and maintenance can be associated with significant costs and effort. For this reason, the creation of individual registries to meet the postmarket surveillance needs for a specific manufacturer or a specific product is not likely to be efficient or economical. For targeted areas, it may be more cost-effective to pursue nationwide medical device registries focused on certain product areas of high importance as reflected by a large public health need, patient exposure, uncertain long-term or real-world device performance, or societal cost. For other device areas where the benefit-risk profiles are well-understood, registries may not be needed.

The FDA believes that registry development in targeted product areas can both enhance public health and be cost-effective for industry, health care providers and payers. To foster the development of medical device registries in key product areas, CDRH will be convening registry experts and key stakeholders, including representatives from national and international registries, for Medical Device Registry public workshops⁶ to discuss how registries might voluntarily:

- Leverage experience and expertise to facilitate registry development and initiation;
- Establish common demographic, clinical, procedural and device-based data elements;

6 <http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/default.htm>

- Develop and share methodological tools for privacy-protected data collection, linking to longitudinal outcomes and analysis;
- Enhance interoperability with EHRs and claims data;
- Enhance incorporation of registry data into EHRs and EHR data into registries;
- Develop criteria that would render a registry automatically eligible to support an FDA-required post-approval study (voluntary certification);
- Create sustainable business models;
- Identify priority medical device types for which the establishment of a longitudinal registry is of significant public health importance, such as a subset of Class III or permanently implantable Class II medical devices; and,
- Adopt registry governance structures that promote rigorous design, conduct, analysis, reporting of key findings, and transparency.

Ideally, EHRs and claims data will one day routinely include UDIs. These data sources, therefore, may be used to complement and supplement data in device-specific or disease-specific registries. For example, a device-specific registry linked to an EHR

containing longitudinal clinical outcomes would collectively provide more information than either system alone and allow for more robust queries and de-identified data responses. Some health systems, such as Kaiser Permanente and the Veterans Health Administration, have successfully integrated registries into their EHR systems.

3. MODERNIZE ADVERSE EVENT REPORTING AND ANALYSIS

The FDA monitors postmarket device-related adverse events and product problems through both voluntary and mandatory reporting to detect signals of potential public health concern. Because of the limitations of spontaneous reporting systems, modernization of adverse event reporting and analysis is a key requirement of a comprehensive medical device postmarket surveillance system. Several ongoing or proposed activities will significantly enhance our surveillance capabilities.

3.1 Development of Automated Adverse Event Reporting Systems

We are working with partners to explore automated adverse event reporting systems that would facilitate the submission of device-related adverse events and minimize the effort required by the reporter. For example, we are working with 20 hospitals from our MedSun Network to develop software capabilities to export real-time adverse

event data with device identifiers from hospital incident reporting systems. The Adverse Spontaneous Triggered Events Reporting (ASTER) study demonstrated that facilitated, “triggered reporting” increased the number of adverse events reported by clinicians. CDRH is piloting ASTER-D to facilitate the use of hospital EHRs and Incident Reporting Systems to detect and automatically report select device associated adverse events to the FDA.

The creation of systems that facilitate triggered or automatic reporting of selected device-related adverse events via the EHR to the FDA as part of a clinician’s normal work flow is likely to increase the number and quality of adverse event reports, decrease under-reporting, and more regularly alert the FDA of potential device-related concerns. The FDA will continue to explore the development of automated or facilitated adverse event reporting.

3.2 Increase the Number of MDRs Received Electronically

Electronic reporting of device-related adverse event reports enhances timeliness, quality and efficiency of both reporting and postmarket surveillance. CDRH’s eMDR voluntary electronic reporting system provides the capability for electronic data entry and processing of MDRs and utilizes the Health Level Seven (HL7) Individual Case Safety Report standard. Currently, CDRH

receives 70 percent of MDRs electronically, significantly reducing data entry costs of paper reports and increasing the expediency of receiving reports. We anticipate that, ultimately, electronic reporting of MDRs will account for close to 95 percent of all reports.

3.3 Develop a Mobile Application for Adverse Event Reporting

We recognize the evolving societal role of mobile applications, their convenience and the potential role they may play in improving public health. CDRH has partnered with Boston Children’s Hospital in the development and implementation of a mobile app for securely reporting medical device adverse event reports. It is anticipated that this tool will facilitate the submission of voluntary reports by health care providers and patients. Work is currently underway to refine the app so that we may receive such reports through FDA’s electronic submission gateway.

3.4 Modernize the Medical Device Adverse Event Database

Reports of adverse events involving medical devices received by CDRH are contained in the Manufacturer and User Facility Device Experience (MAUDE) database (<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/search.cfm>).⁷ The database contains voluntary reports received since June 1993, user facility reports received since 1991, distributor reports received since

1993, and manufacturer reports received since August 1996. Online capability permits searches for information on medical devices that may have malfunctioned or caused a death or serious injury.

After 20 years of in-service use, the number of adverse event records contained in MAUDE is now exceeding its design capacity. Although CDRH instituted a voluntary electronic reporting program in 2007 in which we receive adverse events directly in electronic form, the base technology behind MAUDE is antiquated and is unable to handle the volume and complexity of device reports. In addition, MAUDE cannot take advantage of more modern streams of adverse event reporting (i.e. mobile apps, EHRs, registries, etc.) and the database platform cannot be extended further.

Therefore, a new adverse event reporting system is needed. The FDA is working to develop a new system, the FDA Adverse Event Reporting System (FAERS), with expanded capacity and modern analytic capability for identifying and extracting relevant information in automated fashion. In addition, the new FAERS system will accommodate receipt of adverse event data in more versatile reporting formats.

3.5 Rapidly Identify Safety Signals

Safety signals can be more rapidly identified

using automated, computerized statistical methods to discover patterns of associations or unexpected occurrences (i.e., “signals”) in large databases. CDRH has been exploring the use of these methods in its medical device adverse event reporting databases to systematically prioritize MDRs for CDRH evaluation and review.

Such methods offer a systematic, automated, and practical means of analyzing large datasets and improves efficiency by focusing signal detection efforts on key reporting associations. Importantly, it offers the potential to identify possible safety issues more quickly than traditional signal detection methods by providing statistically robust, automated data assessments that can also account for potentially confounding factors and adjust for chance observations.

To complement these report and data-driven efforts, we are developing semantic text mining techniques, which facilitate the automated extraction and analysis of the narrative text in large numbers of electronic documents. Using these methods, we are building a computerized search, retrieval and analysis system to quickly and systematically extract and evaluate information from our adverse event reporting databases. These efforts will improve our ability to detect adverse trends in device performance earlier, minimize patient exposure to under-performing products and maintain patients’ privacy.

7 MAUDE does not include reports made according to exemptions, variances, or alternative reporting requirements.

4. DEVELOP AND USE NEW METHODS FOR EVIDENCE GENERATION, SYNTHESIS AND APPRAISAL

The evolution of health-related electronic records, registries and adverse event reporting, as well as the increasingly global nature of product development and marketing, demands the strategic development of innovative methodological approaches for evidence generation, synthesis and appraisal.

In 2010, CDRH launched the Medical Device Epidemiology Network (MDEpiNet) Initiative motivated by the need to develop and apply innovative methodological strategies to address gaps in studying medical devices.⁸ The development and application of novel techniques to collect, analyze, synthesize, and communicate knowledge about medical devices can potentially reduce the burden and cost of postmarket surveillance, facilitate the premarket development and evaluation of new products, and improve the timeliness, quality and efficiency of postmarket decision-making by the FDA, the medical device industry, health care professionals, and the American public.

Some approaches are broadly applicable to all medical product areas, including medical devices, and are being developed as part of the FDA's Sentinel Initiative. For example, efforts to protect personal health information, maintain data security and integrity,

assure confidentiality of proprietary information, preserve intellectual property rights, and maintain transparency are currently being explored and developed.

However, as discussed previously, medical device postmarket surveillance has unique features that demand customized methodological approaches. The development of new tools and methods to generate, synthesize, and interpret postmarket information will improve the efficiency and quality of decision-making by identifying new and better ways to leverage existing data sources by providing more timely information about the benefits and risks of marketed products, and by translating data into knowledge to help better inform regulatory and clinical decisions.

Selected ongoing or proposed methodological approaches include:

4.1 Quantitative Decision Analysis to Evaluate Benefits and Risks

CDRH is exploring the use of quantitative decision analysis to help evaluate benefits and risks of medical devices. This statistical research method can be used to better quantify benefits and risks in an explicit and consistent way both before and after medical devices are marketed. Quantitative decision analysis can provide a reliable mechanism for incorporating patients' views on benefit

8 <http://www.fda.gov/MedicalDevices/ScienceandResearch/EpidemiologyMedicalDevices/MedicalDeviceEpidemiologyNetworkMDEpiNet/default.htm>

and risk into the assessment of clinical trial data, and can characterize and clarify bias and uncertainty in decision-making. Quantitative decision analysis can also provide context and enhance transparency to health care providers, industry and the public regarding our regulatory decisions, and provide information that will help individuals make important health care decisions.

4.2 Evidence Assessment by Combining Data from Diverse Data Sources

The ability to combine medical device performance and privacy-protected clinical outcome data from diverse sources would significantly improve the efficiency of post-market surveillance. Such efforts, for example, may permit linking of short-term, detailed procedural registry data with longitudinal outcomes data from a claims or administrative database or EHRs. Similarly, several small data sources may be combined using meta-analytic and other methods to generate a more accurate assessment of the benefits and risks of a device or class of devices.

Combining data from disparate sources is made easier and more straightforward by the development of common data standards and a strategy for master data management that allows seamless access to consistent high-quality data without the need to perform duplicate data entry or manipulation. Data standards promote the efficient sharing or exchange of information between

parties through the use of clear standards for protecting patient privacy as well as standardized data element names, definitions and formatting rules. Data standards often include information describing procedures, implementation guidelines and usage requirements. Standards facilitate electronic reporting, data transfer protocols, data sharing, and data quality.

The adoption of standard data exchange and vocabulary specifications and an effective master data management plan that includes patient privacy protection would facilitate the secure receipt, storage, access, and analysis of high-quality data. Notably, data standards must meet the needs of the FDA as well as external stakeholders. The FDA will continue to work with stakeholders, including industry, academia and international standards organizations, to promote adoption of effective data standards.

We have begun developing a formal evidence synthesis methodology framework that is capable of combining de-identified data from disparate sources including clinical trials, observational studies, patient registries, published literature, administrative and claims databases, and other external data sources. This framework will augment traditional regulatory tools and allow us to have a comprehensive, up-to-date, benefit-risk profile of a specific medical device at any point in its life cycle so that optimally informed decisions can be made and useful

information can be provided to practitioners, patients, and industry.

4.3 Automated Signal Detection

Increased use of near real-time large databases, such as EHRs or registries, offers promising opportunities. Modern statistical software and techniques can compare device performance and clinical outcomes among marketed products and identify early signals of concern. For example, the Data Extraction and Longitudinal Time Analysis (DELTA) system has been applied to cardiovascular device registries by the FDA and academic investigators to establish proof-of-concept for detection of safety signals of approved cardiovascular devices. While automated signal detection software can facilitate the identification of potentially underperforming products, the review and validation of the findings remain critical aspects of their use.

4.4 Refinement of Processes for Signal Detection and Management

A “safety signal” is information that arises from one or more sources, and suggests a new, potentially causal association, or a new aspect of a known association, between a medical device and an event or set of related events. The aim of signal detection is to identify promptly possible unwanted or unexpected effects associated with a product. The decision of

whether a finding represents a “safety signal” and whether it warrants further investigation can be challenging.

Factors that may influence the decision include the strength of the signal, whether or not the signal represents a new finding, the clinical importance and potential public health implications of the issue, and the potential for preventive measures to mitigate the adverse public health impact.

As part of the CDRH 2012 Strategic Priorities, we committed to develop a comprehensive framework for the timely evaluation and management of significant postmarket signals. Such a framework will consist of several phases including signal detection, risk assessment and signal prioritization, signal refinement, signal verification, and signal action. Key components of the signal evaluation and management framework will address issues of data transparency, stakeholder participation and timeliness of public communication.

BOX C-2.

CONTRASTING THE CURRENT AND FUTURE STATES OF MEDICAL DEVICE POSTMARKET SURVEILLANCE*

Example: Evaluation of Potential Safety Signal

CDRH becomes aware of unexpected adverse events associated with the use of a permanent neurological implant resulting in the need for early reoperation to have the implant replaced. After reviewing the available scientific data including published literature, adverse events submitted via its Medical Device Reporting system and information provided by manufacturers, CDRH cannot determine whether adverse events are occurring at a higher than expected rate and whether the poor outcomes are associated with one specific product or with all products of this type.

Current System: CDRH orders all companies who make this type of neurological implant to conduct a postmarket surveillance study (“522 study”) to determine whether their product is associated with an increased reoperation rate. Because of the lack of existing infrastructure and data collection capabilities, it is many months before the first patient is enrolled in the required study, and typically more than two years before the needed data are collected and available for analysis.

Future State: Relevant health care systems voluntarily access their EHRs containing unique device identifiers (UDIs) at the request of the FDA, and, working with the FDA, they help to determine in weeks rather than years that the increased reoperation rate is associated with a single model of a single manufacturer’s product. The problematic device is recalled and the other products remain on the market. Companies whose products are performing well are not required to conduct additional, expensive postmarket studies.

Example: New Device Receives FDA Approval — Postmarket Study Needed

CDRH approves a premarket approval (PMA) application for a novel implantable stent in the vasculature to treat arterial narrowings (stenosis) on the basis of a clinical study following several hundred patients that demonstrated patients receiving the stents are less likely to require vascular surgery within 12 months after stent implantation. Limited data on longer term follow-up are available at the time of approval.

Current System: The FDA, as a condition of approval, orders the company to complete a study of several hundred patients with 5-year follow-up to verify that the real-world, long-term benefit-risk profile of the device remains the same as that seen in the shorter-term premarket clinical study. The company organizes a multi-center, post-approval clinical registry — similar to other multi-center, post-approval registries sponsored by other companies with similar products. Because other similar products are available and patients

(continued)

* Examples are hypothetical and not intended to represent any specific product. They assume that all regulatory requirements have been met.

BOX C-2. (CONTINUED)

CONTRASTING THE CURRENT AND FUTURE STATES OF MEDICAL DEVICE POSTMARKET SURVEILLANCE*

can get the device outside of a research protocol, the company has trouble recruiting patients to participate in their registry.

Future State: During routine patient care, information about the newly approved stent, including its unique device identifier, is automatically incorporated into a National Vascular Stent Registry linked to a claims database, which the company can use instead of making a registry of their own. The data provides long-term (5-year) follow-up information including the rate of surgery among patients who receive the stent.

Example: Identification of Potential Safety Signal

CDRH approves several permanent cerebral (brain) implants to treat stroke patients.

Current System: CDRH monitors the MDRs it receives concerning the cerebral implants but many of the adverse event reports are incomplete or contain insufficient information to determine if the observed number of adverse events is higher than expected.

Future State: Automated surveillance software provides near real-time analysis of existing databases (registries or electronic health records) to monitor similar products, identify potentially underperforming ones and report de-identified data on product performance. Potential signals identifying poorly performing products are further evaluated to confirm the initial findings.

Example: Facilitating the Expansion of Labeled Indication

CDRH approves a medical device to treat male incontinence following prostate surgery. The manufacturer believes the device will also be effective for treating patients with incontinence due to other conditions.

Current State: The manufacturer is advised to conduct another clinical trial to demonstrate that the device is effective in treating patients with incontinence due to causes other than prostate surgery.

Future State: Analysis of de-identified EHR data containing unique device identifiers demonstrates that within the practice of medicine, physicians have been treating patients with incontinence due to other causes — and the data demonstrates the device is as effective as it is in patients with incontinence due to prostate surgery. The company submits the analysis and CDRH approves an expansion of the labeled indication solely on the basis of the collected postmarket data.

* Examples are hypothetical and not intended to represent any specific product. They assume that all regulatory requirements have been met.

D. CONCLUSION

Postmarket surveillance of medical devices presents unique challenges. Although the United States has a robust postmarket medical device surveillance system, we believe our system can be strengthened by implementing four key changes to our existing program. It bears emphasizing that modernizing medical device postmarket surveillance is a long-term effort. Our proposed strategic changes are intended to complement our existing programs.

CDRH is committed to strengthening our Medical Device Postmarket Surveillance System to collect, analyze and act on medical device postmarket performance information. We recognize that our postmarket vision cannot be implemented or achieved by the FDA alone. We have set out this draft plan as a first step and invite e-mail comments on our website and active participation at our September 2012 public meetings. We welcome e-mail comments and feedback on this proposal and encourage other ideas and suggestions on how we can strengthen our existing medical device postmarket surveillance system.

APPENDIX

CURRENT SELECTED MEDICAL DEVICE POSTMARKET AUTHORITIES

CDRH's postmarket authorities include the following:

- *Medical Device Reporting* — CDRH has the authority to require mandatory medical device reporting (MDR) from device manufacturers, user facilities and importers.⁹ Manufacturers, user facilities and importers must report under the MDR regulations whenever they become aware of an event that reasonably suggests that a device may have caused or contributed to a death or serious injury. In addition, certain malfunctions must be reported. Failure to comply with the MDR requirements will render the device “misbranded,”¹⁰ and may result in the issuance of an Untitled Letter, Warning Letter or more severe penalties such as injunction, seizure or civil money penalties. In addition, health professionals and consumers may voluntarily report to the FDA adverse events relating to the use of marketed medical devices.
- *Post-Approval Studies* — CDRH has the authority to order a Post-Approval

Study (PAS) for a device in a premarket approval application (PMA) order, or by regulation at the time of approval or subsequent to approval of the device. Post-approval requirements may include as a condition of approval of the device, continuing evaluation and periodic reporting of device safety, effectiveness and reliability.¹¹ The FDA states in the PMA approval order the reason or purpose for such requirement, the number of patients to be evaluated and the reports required to be submitted. There are no time limitations (e.g., length of study) for a PAS. Failure to comply with a PAS constitutes grounds for withdrawal of approval of a PMA.¹²

- *Postmarket Surveillance* — CDRH has the authority to order a Postmarket Surveillance Study (often referred to as “522 studies”) for certain Class II and III devices, generally for a duration of up to 36 months.¹³ Postmarket surveillance may be ordered if:

9 Section 519 of the FD&C Act; 21 CFR Part 803.

10 Section 502(t)(2) of the FD&C Act.

11 21 CFR 814.82.

12 21 CFR 814.82(c).

13 Section 522 of the FD&C Act. The study duration may exceed 36 months if the manufacturer agrees to extend the study timeframe, or if no agreement can be reached, after the completion of a dispute resolution process. If FDA's order is for a device that is expected to have significant use in pediatric populations, the study duration may exceed 36 months if such period is necessary in order to assess the impact of the device on growth and development, or the effects of growth, development, activity level, or other factors on the safety or efficacy of the device.

- device failure would be reasonably likely to have serious adverse health consequences;
- the device is expected to have significant use in pediatric populations;
- the device is intended to be implanted in the body for more than one year; or,
- the device is intended to be a life-sustaining or life-supporting device used outside a device user facility.¹⁴

The FDA may also order postmarket surveillance as condition of clearance of a device that is expected to have significant use in pediatric patients.¹⁵

- **Registration and Listing** — CDRH has the authority to require establishments that are involved in the manufacture, preparation, propagation, compounding or processing of medical devices intended for commercial distribution in the United States to initially register and thereafter register annually, and to submit device listing information. The required listing information includes, among other things, a list of all commercially distributed devices being manufactured or processed at the establishment and, in certain situations, the labeling for such devices.¹⁶

- **Recalls** — CDRH has the authority to issue a "cease distribution and notification" order, if, after providing the appropriate person with an opportunity to consult with the agency, CDRH determines that "there is a reasonable probability that the device would cause serious, adverse health consequences or death." The order may require the appropriate person to immediately:

- cease distribution of the device;
- notify health professionals and device user facilities of the order; and,
- instruct these professionals and device user facilities to cease use of the device.

CDRH may then amend the order to require a recall of such a device under certain conditions.¹⁷ A mandatory recall order from FDA will include, among others things, provisions for notification to individuals subject to the risk associated with the use of the device. If a significant number of such individuals cannot be identified, FDA may notify such individuals under section 705(b) of the FD&C Act.¹⁸

- **Device Tracking** — CDRH has the authority to require a manufacturer to

14 Section 522 of the FD&C Act.

15 Section 522(a)(1)(B) of the FD&C Act.

16 Section 510 of the FD&C Act; 21 CFR Part 807.

17 Section 518(e) of the FD&C Act; 21 CFR Part 810.

18 21 CFR 810.13(d). Under Section 705(b) of the FD&C Act, FDA may disseminate information regarding devices in situations involving "imminent danger to health, or gross deception of the consumer."

adopt a method of tracking for a Class II or Class III device, if the device meets one of the following three criteria and FDA issues an order to the manufacturer:

- the failure of the device would be reasonably likely to have serious adverse health consequences;
- the device is intended to be implanted in the human body for more than 1 year; or,
- the device is a life-sustaining or life-supporting device used outside a device user facility.¹⁹

CDRH's tracking authority is intended to ensure that the tracked device can be traced from the manufacturing facility to the person for whom the device is indicated (i.e., the patient).²⁰

- ***Repair, Replace, Refund*** — CDRH has the authority to order the manufacturer, importer, or distributor of a device to repair or replace it or to refund its purchase price if, after affording an opportunity for a hearing, CDRH determines that:
 - the device poses an unreasonable risk of substantial harm to the public health;
 - there are reasonable grounds to

believe that the device was not properly designed or manufactured with reference to the state of the art as it existed at the time of design or manufacture;

- there are reasonable grounds to believe that the unreasonable risk was not caused by failure of a person other than a manufacturer, importer, distributor, or retailer of the device to exercise due care in the installation, maintenance, repair, or use of the device; and,
- notifying device users would not by itself be sufficient to eliminate the unreasonable risk, and the repair, replacement, or refund is necessary to eliminate such risk.²¹

- ***Withdrawal of PMA Approval and Rescission of 510(k) Clearance*** — CDRH has the authority to withdraw a PMA approval²² and to rescind a 510(k) clearance, under certain circumstances.²³
- ***Ban Devices*** — CDRH has the authority to ban a device, by regulation, which would prevent it from being legally marketed, if the agency determines, on the basis of all available data and information, that the device presents a

19 Section 519(e) of the FD&C Act; 21 CFR Part 821.

20 21 CFR 821.1(b).

21 Section 518(b) of the FD&C Act.

22 515(e) of the FD&C Act; 21 CFR 814.46.

23 The FD&C Act does not expressly address rescission of a device clearance. However, agencies have inherent authority to reconsider their decisions in certain circumstances, such as where there has been fraud or error, or to correct their mistakes. See, e.g., *American Therapeutics, Inc. v. Sullivan*, 755 F. Supp. 1, 2, (D.D.C. 1990).

substantial deception or unreasonable and substantial risk of illness or injury which cannot or has not (after request) been corrected or eliminated by labeling or by a change in labeling, or by a change in advertising if the device is a restricted device.²⁴ The procedures for banning a device are described in 21 CFR Part 895.

- ***Restrict Devices*** — CDRH has the authority to, by regulation, restrict the sale, distribution, or use of a device if, because of its potentiality for harmful effect or the collateral measures necessary to its use, there cannot otherwise be reasonable assurance of its safety and effectiveness.²⁵ A regulation may restrict the device only to be sold upon receiving the oral or written authorization of a practitioner licensed by law to administer or use such device, or upon other conditions as prescribed by the regulation. If prescribed in the regulation, the label must include appropriate statements of any restrictions required by such regulation.²⁶ CDRH also has the authority to restrict PMA devices by requiring as a condition of approval that the device be restricted.²⁷
- ***Enforcement Actions*** — Failure to comply with certain postmarket requirements for devices will render the device

“adulterated” and/or “misbranded,” and/or will constitute a “prohibited act” under the FD&C Act.²⁸ CDRH has authority to initiate enforcement actions, including seizure of devices, injunctions, civil money penalties, and criminal penalties for violations involving adulterated or misbranded devices and for prohibited acts.²⁹

- ***Removal of a Device as a Predicate*** — Under Section 513(i)(2) of the FD&C Act, a device may not be found to be substantially equivalent to a predicate device that has been removed from the market at the initiative of the Secretary or that has been determined to be misbranded or adulterated by a judicial order.

24 Section 516 of the FD&C Act; 21 CFR Part 895.

25 Section 520(e) of the FD&C Act.

26 Section 520(e) of the FD&C Act.

27 Section 515(d)(1)(B)(ii) of the FD&C Act; 21 CFR 814.82(a)(1).

28 Sections 301, 501, and 502 of the FD&C Act.

29 Chapter III of the FD&C Act, Prohibited Acts and Penalties.



Food and Drug Administration
Center for Devices and Radiological Health
10903 New Hampshire Avenue
Silver Spring, MD 20993
<http://www.fda.gov/MedicalDevices>
<http://www.fda.gov/Radiation-EmittingProducts>