Published in final edited form as:
Food Drug Law J. 2014 ; 69(1): 1–i.

Ensuring Medical Device Effectiveness and Safety: A Cross - National Comparison of Approaches to Regulation

Daniel B. Kramer, M.D.[*] **[Cardiac Electrophysiologist]**, **Yongtian T. Tan, MD/MBA**[**] **[candidate]**, **Chiaki Sato, Ph.D., LL.M.**[***] **[assistant professor]**, and **Aaron S. Kesselheim, M.D., J.D., M.P.H.**[****] **[assistant professor]**

[*]Beth Israel Deaconess Medical Center, an Assistant Scientist at the Hebrew SeniorLife Institute for Aging, and Instructor in Medicine at Harvard Medical School

[**]Harvard Medical School and Harvard Business School

[***]Graduate School of Public Policy/Policy Alternative Research Institute, the University of Tokyo, and a visiting scholar at the Engelberg Center for Healthcare Reform, the Brookings Institution

[****]Medicine at Harvard Medical School and the Director of the Program On Regulation, Therapeutics, And Law (PORTAL) in the Division of Pharmacoepidemiology and Pharmacoeconomics in the Department of Medicine at Brigham and Women's Hospital in Boston, MA

I. Introduction

Therapeutic interventions based on medical devices continue to grow in importance, reaching new markets worldwide and offering technological advances in disease management for a wide array of conditions. However, such interventions may also carry predictable as well as unforeseen risks, which in some circumstances, may lead to immediate life-threatening consequences. Regulatory bodies evaluating market approval for novel products must weigh the possible benefits of proposed treatment options against their potential risks. Accumulation of risk-benefit information about devices continues beyond the point of regulatory decision-making for market approval into the post-approval period. Various tools have been developed to specifically evaluate device performance in the post-approval setting.

The strengths and weaknesses of pre-approval and post-approval surveillance systems for medical devices have been hotly debated in numerous countries around the world in recent years in the wake of safety concerns involving implantable cardioverter-defibrillator leads,[1,2] orthopedic products,[3] and breast implants.[4] Interestingly, because of different regulatory environments, these crises have affected countries to varying degrees and inspired a range of responses. For example, when leaky breast implants using non-medical grade silicone made by Poly Implant Prosthese (PIP) was discovered in France, the products were removed from the market.[5,6] Subsequently, the French health authority urged patients to remove and replace the products, while the National Health Service in the UK did not recommend "routine removal" of the implants. Thus, discrepancies between regulatory regimes in different countries may be stark, with their approaches to pre-approval evaluation and post-approval surveillance leading to distinct patient outcomes.

Few studies have compared international approaches to medical device regulation. We have previously described how postmarket surveillance is organized differently in large, highly-developed countries (*e.g.*, the US and EU), small highly-developed countries (*e.g.*, Japan), and large emerging countries (*e.g.*, China).[7] In the current work, we use these same settings as the bases for in-depth comparisons of varying approaches to five key features of device regulation: regulatory authority, premarket evaluation, adverse event reporting, quality system regulation, post-approval studies, and postmarket regulatory actions. We also describe emerging tools in each setting that have the potential to revolutionize device regulation and promote efficient approval of the next generation of medical devices while minimizing public health risks.

II. Regulatory Authority

A. United States

Since the 1976 Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act (FDCA), the Food and Drug Administration (FDA) has been given a mandate to provide "reasonable assurance of safety and effectiveness" for new devices.[8] This legislation made FDA approval the sole mechanism for manufacturers to introduce medical devices in the US for use in patient care.[9] Later legislation added user fees for manufacturers and performance targets for the government in its evaluation times.[10,11] The 2012 FDA Safety and Innovation Act (FDASIA) preserved the general structure of device evaluation, renewing user fees and performance targets through 2017.[12,13]

B. European Union

Medical devices are regulated in the EU in a similar manner to other consumer products. There is no medical device equivalent to the European Medicines Agency: devices can be legally marketed in the EU after receiving a Conformité Européenne (CE) Mark from a Notified Body (NB), a private, for-profit organization based in a member state that specializes in evaluating medical devices or other consumer products.[14,15,16] A CE mark indicates that the device "conforms" to the relevant directives regarding its manufacturing, labeling, and expected performance and safety profile. Approval from any one of the more than 70 NBs in the EU permits marketing in all member states. Each country also has a governmental Competent Authority (CA), which oversees the NBs and has primary responsibility for post-approval surveillance. The structure, staffing, funding, and functions of CAs vary widely among individual countries. Individual CAs and NBs have flexibility in establishing procedures they deem sufficient for meeting the directives' requirements.

The legal structure of medical device regulation in the EU is established by the directives, which describe procedures and standards and are binding on member states. EU "guidance documents" provide definitions, recommendations for testing, information on specific topics such as integration of software into medical devices, and details on classifications for combination products and other complex devices.[17] Guidance documents help member states ensure they are meeting the directives. Together, directives and guidance documents outline the mechanics of pre- and post-approval regulation of medical devices in the EU. The directives covering medical devices are currently under review, though the basic

structure is not expected to change.[18,19] Any changes to the directives require approval both from the Council of Ministers and the European Parliament, a process that may take several years, particularly if legislation is proposed to create a more coordinated centrally-acting body.

Directives describe the fundamental post-approval requirements for manufacturers, including establishment of quality-control systems and responsibilities for adverse event reporting. Suggestions for CAs and manufacturers to meet these dual requirements are detailed in two guidance documents. A 2004 guidance document highlighting post-approval procedures notes that the inherent limitations of any pre-approval evaluation system obligates manufacturers to maintain quality assurance programs for all marketed devices, including systems for collecting and reporting adverse events and systems for conducting post-approval "clinical follow-up."[20] The need for post-approval clinical data varies according to the novelty, risk, and complexity of the device at issue, and manufacturers are urged to work with NBs to design systems appropriate to the device, like company-sponsored registries or surveys of health care providers.

Recently, a second guidance document described a more thorough framework for post-approval surveillance. This included greater detail regarding expected systems for both manufacturers and regulators to handle adverse events, and how to communicate safety concerns among EU member states and with the public. The document provides templates for standardizing data collection and reporting among stakeholders, including "clinical evaluation reports." Clinical evaluation reports are intended to provide an outline of the technology underlying a specific device and current clinical data supporting its use, ideally in reference to established standards or similar devices.[21] A clinical evaluation report is intended to be the main summary document included in the assessment by NBs to determine whether an approved device continues to perform as intended with an acceptable safety profile.

Guidance documents, however, remain nonbinding and each country has flexibility in meeting the essential requirements. Thus, in practice, there is substantial variation in the way each country interprets the basic requirements for quality assurance and adverse event reporting.

C. Japan

Device regulation in Japan is led centrally by the Pharmaceuticals and Medical Devices Agency (PMDA) and the Ministry of Health, Labor, and Welfare (MHLW).[22] Under Japan's Pharmaceutical Affairs Law, MHLW authorizes new device approvals and supervises post-approval surveillance activities.[23] MHLW decisions draw upon PMDA analysis including site inspections and premarket review of new technology, including both non-clinical and clinical asessments. The PMDA also establishes policies related to the testing, approval, marketing, distribution, and monitoring of medical devices. Local governments play a supporting role in administrative duties, coordinating periodic inspections and assessing adherence of manufacturers (termed "medical authorization holders [MAHs]") and their facilities to established standards. A basic organizing premise is that the MAH has primary responsibility for ensuring safety and effectiveness.[24] Post-

approval surveillance requirements naturally extend from this responsibility, and include systems for reporting foreign and domestic adverse events, identification of safety signals emerging from international markets, quality systems regulations, and post-approval studies.

D. China

China's medical device regulatory system was established fairly recently. The government's Ministry of Health (MOH) drafts basic regulations and oversees their implementation. *Regulations for the Supervision and Administration of Medical Devices*, issued in 2000, established legal requirements for regulatory approval in China through the State Food and Drug Administration (SFDA), which reports directly to the MOH.[25] Post-approval surveillance of the medical devices market was outlined in the *Interim Measures for the Administration of Adverse Medical Device Events Monitoring and Reevaluation* in 2008.[26] More recently, this agency was elevated to a ministerial-level position directly under the State Council and renamed the China Food and Drug Administration (CFDA).[27] The ministerial-level position affords the institution the ability to seek additional resources and greater regulatory authority overall.[28]

The CFDA divides responsibility for medical device regulation between the Center for Medical Device Evaluation (CMDE) and the National Center for Adverse Drug Reaction Monitoring. Unique to the Chinese system is the co-existence of provincial and municipal agencies that serve as first-line responders to reported adverse events and support the CFDA in monitoring and taking action at the regional level.[29]

III. Pre-Market Evaluation

A. United States

Device approval in the US is based on a risk classification system. All proposed new medical devices are assigned to one of three risk categories.[30,31,32] Low-risk (Class I) devices are subject to "general controls," which include adherence to predefined Good Manufacturing Practices (GMP), such as adequate manufacturing, packaging and storage.[33,34,35] Class I devices are registered with the FDA and most not subject to formal premarket review process. Medium-risk (Class II and complex Class I) devices must meet additional special controls, such as tests of biocompatibility or environmental interactions. The FDA evaluates most medium-risk products based on substantial equivalence to previously-marketed products, which is called the "510(k) process," after the section of the FDCA describing it.[36,37] A finding of substantial equivalence certifies that a device is similar to a previously-cleared device such that it raises no new safety or effectiveness concerns. For over 90% of medium-risk devices, manufacturers have demonstrated substantial equivalence without any new clinical data.[38]

The highest-risk (Class III) devices require Premarket Approval (PMA) applications.[39, 40] PMAs combine preclinical data (*e.g.*, animal studies) with clinical trials using clearly-defined objectives[41] to evaluate effectiveness and safety.[42] The FDA is statutorily required to follow the "least burdensome" approach in requesting specific study features.[32,43,44] Advisory committees of outside experts may provide recommendations regarding certain devices, including suggestions about post-approval studies, though panel recommendations

are non-binding on the FDA or manufacturers. High-risk devices in which the new feature is a relatively minor change—such as alterations in design, labeling, or manufacturing—to previously PMA-approved devices may be approved through a PMA supplement.[45] Though the FDA can require additional clinical data for PMA supplements, this is uncommon.[46] For example, two devices approved through PMA supplements—the Medtronic Sprint Fidelis and St. Jude Medical Riata implantable cardioverter-defibrillator (ICD) leads—were approved without new clinical data as part of their official FDA review process and were implanted in several hundred thousand patients before signals of higher-than-expected lead failure were detected,[47,48] leading to recalls in 2007 and 2012, respectively.

B. European Union

Device approval in the EU also involves risk-based classification.[49,50] Low-risk (Class I) devices are declared to the local CA, and must meet basic manufacturing standards.[51] Medium- and high-risk (Class IIa, IIb, and III) devices are presented to a NB chosen by the manufacturer, which reviews performance and reliability testing appropriate to the risks of the device's intended use.[52] Features such as engineering, durability, and sterility are tested in reference to guides published by organizations such as the International Organization for Standardization or European Committee for Standardization.

NBs commonly approve devices based on a "performance" standard, or demonstration that a device performs in the manner intended with expected benefits that outweigh expected risks.[53] This standard is considered to be more lenient than the FDA standard, in particular because it does not require proof of improvement in clinical endpoints for Class III devices. For example, a percutaneous device for exclusion of the left atrial appendage to prevent thromboembolism received a CE Mark in 2005 based on pilot data demonstrating that it could be safely delivered and deployed in patients.[54] By comparison, the same device was subject to a PMA application in the US, leading to a 700-patient study evaluating a clinical composite endpoint of stroke, systemic embolism, or cardiovascular death and a primary safety endpoint combining major bleeding, pericardial effusion, and device embolization.[55,56] Due to concerns about safety outcomes, it has not yet received FDA approval.[57] The clinical data forming the basis for devices approved in the EU are not systematically publicized and there is no requirement for NBs, manufacturers, or CAs to do so. These data may become available if published by investigators or posted by manufacturers themselves.

C. Japan

In Japan, prior to approval, medical devices are subject to a risk-based classification scheme (Class I are lowest risk; Class IV highest) that affects the pre- and post-approval requirements.[22] PMDA review includes inspections of facilities and document review related to basic manufacturing practices (collectively known as "quality management systems" or QMS), as well as review of engineering, biocompatibility, and other data including clinical investigations for scientific merit and conclusiveness. A summary report of this evaluation is generated after approval.[24]

For high-risk implantable devices, the premarket process involves PMDA assessment of post-approval surveillance operations, including training of physicians, erecting systems for monitoring usage, and protocols for evaluating outcomes. In general, the bar for approving new high-risk devices is closer to the FDA standard than the performance-based EU standard.[23] For example, clinical studies in Japanese patients were required for approval of devices for providing negative pressure to promote wound healing, an ultrasound-based bone-density system, and a unique artificial knee implant.[58] Private subcontractors play a limited role in evaluating devices that are low-risk and have established standards for approval, but these firms are not involved in post-approval surveillance for Class III or IV devices.

D. China

Medical device classification from Class I (low-risk) to Class III (high-risk) is broadly similar to that in the US.[59] For devices manufactured within China, Class I devices need only register with the municipal authority and Class II devices with the provincial authority, while Class III devices must register with the CFDA. This fragmentation has led to some variability in device approval, such as the same device being called different names. By contrast, all imported medical devices must register with the CFDA regardless of classification. For all Class III and some Class II imported medical devices not already approved overseas, the CFDA requires organization of clinical trials, as well as a determination as to demand for the device in China. Eight types of medical devices, including electrocardiographs, implantable pacemakers, X-ray equipment, and artificial lung-heart machines must also undergo electric safety and factory inspection tests in order to receive the a special product safety license called the China Compulsory Product Certification (3C) that also applies to certain non-medical consumer goods.

All Class III devices must undergo clinical testing, conducted at a minimum of two separate CFDA-approved medical institutions in China; however, devices previously approved overseas may be exempt. For novel devices and newer generation products, the CFDA organizes an expert panel of high-level physicians, regulators, and statisticians. The clinical trial requirements for newer therapies may vary.[60] For example, renal sympathetic denervation devices using radiofrequency ablation to treat resistant hypertension have been approved in the EU and have ongoing clinical trials in the US.[61] However, CFDA expert panels are still trying to determine clinical trial requirements in China. Each device is entered by the CFDA into a publicly searchable database that includes the approval date, manufacturer and distributor information, intended use and product standard references.[62] Data from clinical trials and other related testing remain under the proprietary control of the manufacturer and the CFDA. The CFDA also formed the China Medical Device Information Network, which is responsible for collecting, analyzing and processing records of all medical device products and their associated manufacturers.[63]

Every four years, a product approval must be renewed in a process requiring device vigilance reports of post-approval adverse events.[64] Chinese authorities are considering simplifying re-registration by focusing on important changes made in products in the intervening time. Post-approval studies are not formally required for devices,[65] but some

manufacturers of newer imported medical devices have compiled outcomes data from routine clinical experience.[66] Although nearly all renewal registrations have to repeat some testing, most have been granted renewals at the end of the process.[67]

IV. Adverse Event Reporting

A. United States

The FDA has promulgated regulations that outline the timing and content of adverse event reports. User facilities (*e.g.*, hospitals, surgical centers, nursing homes) are required to report device-related deaths or serious injuries within 10 business days to the FDA and manufacturer. Manufacturers and importers are required to report to the FDA events brought to their attention by user facilities or their own employees within 30 days, or within 5 days if the adverse event "requires remedial action to prevent an unreasonable risk of substantial harm to the public health."[68] These reports include patient demographic data, clinical information on the underlying medical conditions, and device and procedure details.

In 1993, the MedWatch program established a more streamlined adverse event reporting mechanism for consumers.[69] MedWatch collects voluntary submissions from health care providers and patients together with required reports from user facilities, importers, and manufacturers. Reports may be submitted by phone, fax, mail, or electronically, including by mobile applications currently under pilot investigation. FDA analysts evaluate the reports, which can lead to additional investigations or public safety alerts.

Since 1995, reports have been collected in a publicly available database called Manufacturer and User Facility Device Experience (MAUDE).[70] MAUDE is searchable by product class (*e.g.*, pacemakers), problem (*e.g.*, battery failure), manufacturer, brand name, or application number. MAUDE searches may also be narrowed by date and event type (*e.g.*, death, injury, or malfunction). Data from adverse events extracted from MAUDE have been used to describe mechanisms and clinical consequences of malfunctions for devices ranging from ICD leads,[2] to surgical staplers[71] However, MAUDE data have important limitations.[21] The reports are highly variable, as there are no standards for reporting clinical data, patient or practitioner features, or details of the suspected adverse event. Most submitted reports are from manufacturer representatives, who may be less likely to assign blame to the device versus practitioner errors or patient factors. Health care providers, by contrast, have no mandate to report suspected adverse events related to medical devices, and rarely do so in practice.

B. European Union

European Commission directives outline requirements for manufacturers and member states in reporting adverse events. Manufacturers are required to report "any deterioration in the characteristics and performances of a device, as well as any inaccuracies in the instruction leaflet which might lead to or might have led to the death of a patient or to deterioration in his state of health"[20] to CAs in the country where the event occurs. Manufacturers must also notify CAs of any "technical or medical reason resulting in a withdrawal of a device from the market."[20] Manufacturers must investigate incidents and include their analysis with the report. The information template (Manufacturer's Incident Form) requires identification of

the device risk class, its trade name and model, procedural information, patient information, description of the event itself and the manufacturer's assessment. Adverse events must be reported within two days for serious public health threats, 10 days for deaths or unanticipated serious events, and 30 days for other events, though it is recommended that all events be reported "immediately, without any delay that cannot be justified."

According to European Commission directives, CAs must have a centralized system for collecting reports from manufacturers, and also processes for relaying to manufacturers event reports submitted to CAs directly by patients or providers. CAs also have processes for assessing risks associated with reported incidents or recalls issued by manufacturers, working in collaboration with manufacturers to identify necessary further actions, and monitoring any corrective plan. CAs determine whether an event or recall appears specific to the device or device class (*e.g.*, a specific drug-eluting coronary stent or all drug-eluting coronary stents), and communicate their findings to manufacturers. Member states notify each other if an assessment of device-related events leads to specific measures taken to address potential adverse events.[72]

CAs submit adverse event and recall data to the European Databank on Medical Devices (EUDAMED), a central database run by the European Commission intended to improve vigilance by pooling data across member states.[73] EUDAMED is not publicly accessible, however, and though originally created in 1998, submission of event data only became mandatory in 2010. For these reasons, it has thus far provided limited utility for analysis or policy decisions. Proposals for improving post-approval surveillance in the EU include improving the function of EUDAMED by establishing a UDI system to support more standardized and efficient methods for tracking medical device use and performance. Some CAs maintain their own publicly-available databases of device postapproval information. For example, the Medicine and Healthcare Products Regulatory Agency in the United Kingdom coordinates adverse event and recall information in one searchable web portal.[74]

C. Japan

MAHs are required to report adverse events directly to MHLW within 15 or 30 days depending on seriousness of the problem.[75] Most adverse event reports come from MAHs, though other stakeholders (such as facilities and providers) can submit reports either to MAHs or directly to MHLW, which then shares these data with PMDA. Other entities involved in the manufacture and supply of devices, such as distributors, also must report to the MAH adverse events or events that otherwise factor into safety and effectiveness assessments. Health care providers are required by law to cooperate with MAHs during active investigation of safety problems. In addition, when providers "learn of cases of diseases, disabilities or deaths suspected to be caused by the use of medical devices, and they confirm that it is necessary to prevent the spread of hazards, they must report the fact to MHLW."[76]

After receiving adverse event reports, PMDA analysts evaluate the relationship between the device and the reported injuries or outcomes, trying to assess whether the outcome was related to user error, the underlying disease, or a device malfunction.[77] This assessment may conclude that further investigation is required by the MAH, or that the accumulated data

warranted additional safety measures, such as a change in labeling. MAHs may be encouraged to pursue further investigation in collaboration with ad hoc committees of outside experts. PMDA hosts a publicly searchable database of adverse event and recall data as well as a database for package inserts.

MAHs track and report events that occur outside Japan for similar or related devices, not just the device specifically sold in Japan. This obligation to collect foreign data is particularly important for Japanese regulators, as most medical devices used there are sold in other countries prior to entering clinical use in Japan. Ultimately, if a corrective action such as a recall or safety alert is issued in another country, the MAH must notify PMDA and analyze the likely impact on domestic devices or patients. If a recall, for example, is determined to relate to a manufacturing problem limited to devices sold outside of Japan, the MAH still must submit root cause analysis and evaluation, and determine whether systems in place are sufficient to prevent a similar problem from arising domestically.

PMDA's regulation of drugs includes providing remuneration to patients injured by adverse events related to approved pharmaceuticals. However, patients affected by device-related adverse events are not eligible for compensation, in part because determining cause and effect is more difficult.

D. China

China's post-approval surveillance system is overseen at the national level by the MOH and the CFDA, and conducted at the regional level by provincial health departments. A key characteristic of Chinese post-approval surveillance is regional autonomy in coordination with a tiered centralized system. Provincial health departments and regulatory authorities are the first line of response when adverse medical device events occur within each region. Although all adverse reports are eventually collected by the MOH and CFDA, they need to be reported first to the regional authority in a timely manner. In places without a provincial structure, such as municipalities (*e.g.*, Shanghai, Xi'an, Guangzhou) and in autonomous regions (*e.g.*, Tibet, Inner Mongolia, Xinjiang), regional health departments serve the same role.[78]

Within the CFDA is the National Center for ADR Monitoring, which is responsible for collecting, aggregating, and analyzing adverse event data from across all provinces and regions. Each province and region also has an ADR Center institution, which has faster and better access to local data than the National ADR Center, but less analytic capability. This regional autonomy may potentially create faster responses to adverse events and help with implementing policy changes. At the same time, central oversight by the CFDA and the National ADR Center allows for coordination across different regions and provides a platform for standardization.

Manufacturers, distributors, and users of medical devices must inform regional monitoring institutions of death-related adverse events within 5 days after their discovery and injury-related events within 15 days. Regional monitoring institutions are then responsible for passing on death-related reports to the National ADR Center, which completes final submission to the CFDA and MOH. By contrast, injury-related events only must be

submitted to CFDA and MOH once per quarter. Device manufacturers, distributors, and users can bypass regional monitoring institutions and directly report adverse events to national level authorities when they deem it necessary. However, they must still notify regional institutions.[79]

Manufacturers of Class II and Class III medical devices submit summaries of adverse events in the previous year to the regional monitoring institutions by the end of January. Regional institutions then pass these reports to the CFDA and MOH by the end of March.[79]

The 2009 ADR Monitoring Report described over 34 provincial monitoring institutions. In 2003, 366 adverse medical device events were reported, rising to 6,101 in 2006, 12,374 in 2007, 40,940 in 2008, and 53,304 in 2009.[78] In 2012, more than 180,000 suspicious medical device adverse events were reported, of which 13% resulted in serious injury and 0.06% led to death. Most (71%) of the ADR cases were reported by medical institutions, while 22% were reported by distributors, 3% were reported by manufacturers and 5% were reported by individuals.[80] Similar to premarket approvals, the CFDA hosts a central online database that tracks all reported adverse medical events. However, this database is not publicly available and is accessible only to CFDA regulators and industry leaders.[81] In 2011, the National ADR Center signed a two-year contract with Uppsala Monitoring Centre to enhance data exchange between China's ADR database and Vigibase, the World Health Organization's (WHO) international database consisting of over six million ADR reports.[82] This partnership may signal CFDA's alignment with the overall goals of the WHO Medical Device Unit towards prioritizing access to medical devices in developing nations with high standards of safety and effectiveness.[83]

V. Quality Systems Regulation

A. United States

Device manufacturers have post-approval responsibilities related to Quality System Regulation (QSR),[84] which includes the logistical guidelines manufacturers must follow for "the methods used in, and the facilities and controls used for, the design, manufacture, packaging, labeling, storage, installation, and servicing of all finished devices intended for human use." QSR also includes documenting, auditing, and managing design, production, storage, and distribution activities, all of which are commonly the focus of site inspections. QSR is tailored to the risk classification of the device, so Class II and III devices are typically subject to more stringent requirements and inspections than lower-risk devices.

As part of QSR, manufacturers must demonstrate a system for handling identified problems, known as Corrective and Preventive Action (CAPA). CAPA requires procedures to be in place for "Analyzing processes, work operations, concessions, quality audit reports, quality records, service records, complaints, returned product, and other sources of quality data to identify existing and potential causes of nonconforming product, or other quality problems."[85] CAPA programs collect reports of problems, investigate causes, and implement solutions ranging from manufacturing or labeling changes to initiation of recalls.

B. European Union

NBs' reviews of device applications include considerations of the post-approval surveillance needs and plans associated with use in clinical practice. The details of post-approval surveillance plans, however, are not made public. According to European Commission guidance documents, NBs are supposed to evaluate the vigilance system in place including QSR systems implemented to track, receive, and respond to adverse events related to specific devices. These include meeting accepted manufacturing standards such as those published by the International Organization for Standardization (ISO) covering biocompatibility and sterility testing. ISO arose in 1947 as a partnership among several national standardization agencies to develop consistent cross-border requirements and benchmarks for safety and quality. Other ISO standards are frequently used by manufacturers and NBs as benchmarks for meeting the more vague requirements outlined in the medical device directives.[86,87]

C. Japan

Pre-market approval in Japan is contingent upon establishment of "Quality Management Systems" (QMS), which includes compliance with regulations related to production and manufacturing standards, documentation,[23] and CAPA processes similar to the FDA's requirements.[88] QMS is tailored to the risk of devices, with higher-risk or more complex devices (such as those making use of radioactive materials) subject to more intense scrutiny.[89] Audits of QMS systems are typically performed in the pre-market phase and may be repeated in the post-market phase, typically at 5-year intervals.[80] These inspections may include site visits, document review, and review of processes and policies for quality assurance, particularly in light of deficiencies identified in past inspections.[97]

D. China

The CFDA implemented *Interim Good Manufacturing Practice Standards for Medical Devices* in January 2011, requiring medical device manufacturers to follow China's Good Manufacturing Practice (GMP) standards in the production process.[90] These measures lay out requirements for medical device manufacturers on production management, documentation and records, and adverse event monitoring. Manufacturers must fully document anticipated safety issues and risk control measures, establish standards for selection and evaluation of suppliers, and keep manufacturing records for each product batch.[98]

Manufacturers of Class I devices need to set up quality systems according to the measures, but only Class II and Class III device manufacturers must apply for GMP certification. However, no specific required certification due date has been issued. Manufacturers of implantable and sterile devices must obtain GMP certification before initial or renewal of registration with CFDA. Provincial authorities are responsible for GMP certification of Class II and Class III devices, while the CFDA is responsible for high-risk Class III devices. Provincial authorities also conduct GMP review for manufacturers of devices on the CFDA Priority Monitoring List at least once per year.[91]

In June 2012, the CFDA issued *Interim Working Procedures for Unannounced Inspection of Medical Device Manufacturers*, which allowed Chinese regulators to conduct surprise inspections of manufacturers. Violations could result in sanctions, although manufacturers may appeal, explain or immediately correct violations to reduce further penalties.[92]

VI. Post-Approval Studies

A. United States

The FDA may require manufacturers to perform post-market investigations under several circumstances.[93] These include at the time of approval of devices through the PMA or humanitarian device exemption (HDE) pathways to help assure continued safety and effectiveness (or continued probable benefit, in the case of an HDE). These post-approval studies may help clarify risks to patients emerging outside the strictly controlled setting of a clinical trial and also illustrate the adequacy of training programs. For example, a post-approval plan proposed by Cook Medical in support of its Zilver PTX drug-eluting stent for peripheral arterial disease included both longer-term follow-up of its pivotal trial population as well as a new registry of 900 patients receiving the device.[94] Listing of current post-approval studies and their completion status is also available online.[95] Failure to follow-through on post-approval commitments may by statute result in seizure, injunction, prosecution or fines as well as publicly posted warning letters to manufacturers.[96,97]

The FDA also has the authority to require post-market studies for Class II or III devices in which (1) failure would be reasonably likely to have serious adverse health consequences; (2) significant use in pediatric populations is expected; (3) implantation in the body for more than one year is anticipated; or (4) the devices are life-sustaining or life-supporting and are used outside of typical device user facility (*e.g.*, hospitals, physicians' offices).[98] Studies for these specialized situations are called "522 studies" for the FDCA section that outlines this regulatory power, and are typically ordered when a public health question arises in the post-market period. As of 2012, 522 studies must commence within 15 months of regulatory action.[99] The FDA provides public information about ongoing 522 studies, including the date the study was ordered and its current status.[100]

B. European Union

The European Commission's medical device directives do not grant authority to NBs or CAs to require post-market studies.[101] Rather, NBs as part of their review of individual device dossiers are expected to provide guidance, though it is not publicly released when postmarket studies have been required as conditions of assigning CE Marks.[102] Although CAs do not have the authority to require post-approval studies, individual payors (either private or public) may require further safety and/or effectiveness studies prior to authorizing reimbursement of a device.

C. Japan

PMDA analyses inform decisions about requirements for post-approval surveillance studies for selected devices. Approval of devices considered to be high risk or particularly novel may include requirements for MAHs to actively monitor domestic use of the device for up to

five years, or for a pre-specified number of cases.[23,80] For example, new drug-eluting coronary stents were approved with a requirement to have the first several thousand patients followed by the MAH, and for a cardiac resynchronization therapy device the MAH was required to monitor cases over the first three years of marketing.[103] Conditions of approval may also include review of physician training and experiences to ensure that qualified providers are being taught to use the device correctly.

A unique feature of device evaluation in Japan is the requirement to "re-file" applications for certain higher risk devices, which typically occurs 3–7 years after initial marketing approval.[104] For example, a surgical ablation system using ultrasound energy guided by magnetic resonance imaging[105] was approved in Japan in 2009, and was required to provide summary data describing real-world safety and effectiveness to PMDA within its reexamination period.[106]

In preparing for re-filing, MAHs aggregate information from health care providers, clinical trials, and published studies (such as foreign and domestic observational studies or registries), with the goal of ensuring that the device at issue is performing as intended and is providing the expected results. PMDA reviews the data submitted and submits reports to MHLW, which makes a final determination about ongoing marketing status and implements any necessary changes to labeling to reflect new knowledge about usage and safety problems.[23] The MHLW has never withdrawn marketing approval at the time of re-filing, even though it has the authority to do so.[112] One explanation is that MAHs' responsibilities to aggregate and report post-approval surveillance data during the initial approval period make it unlikely that the re-filing will unearth unexpected or important findings.

D. China

Post-approval studies, classified as "Phase IV Clinical Trials," are required for certain drug groups after approval in China to further evaluate benefits and risks and improve knowledge about dosing.[107] The CFDA has not set similar requirements for medical devices, beyond the quadrennial re-registration requirement. However, many manufacturers of newer generation imported medical devices are actively compiling real-world clinical outcomes data from routine clinical practice in China. For example, clinical outcomes for subjects receiving the PROMUS Element Stent System over the next five years will be evaluated in an observational study.[108] Over 2,600 patients have been enrolled in the post-approval observational study of the XIENCE V Everolimus Eluting Coronary Stent System, with completion expected in 2017.[109]

The CFDA office in Beijing has established pharmacovigilance centers within major Beijing hospitals, where more than two million patients are seen every year. The centers are staffed with safety specialists who monitor, aggregate, and report safety data based on patient outcomes. The close collaboration between the Beijing CFDA office and these hospitals allow both parties to act quickly in early detection of potential safety signals and work together in post-approval safety surveillance of new devices.[111]

VII. Postmarket Regulatory Actions

A. United States

When post-approval surveillance points to hazardous or malfunctioning devices or devices that no longer meet FDA requirements, the FDA may issue safety communications.[110] For example, a recent communication described the potential risk of burns for patients receiving MRI scans while wearing transdermal drug-delivery patches.[111] Communications usually include an overview of the clinical problem, ongoing efforts to update product labeling, and preventive or remedial steps for patients and clinicians. If actual patient harms have been documented, safety communications may be accompanied by medical device safety alerts from the FDA, manufacturers, or distributors. Safety alerts are intended to inform health professionals, patients, payers, and related institutions that a device may present an unreasonable risk of substantial harm.[112] For example, a safety alert was issued in March 2012 for a defective component in an automated external defibrillator that led to unexpected failure to deliver highvoltage therapy.[113]

Concerns about device safety may require issuing “recalls,” which reflect systemic concerns with a device and are classified by the FDA according to the likelihood of patient harm. The FDA is allowed to order mandatory recalls if a sufficient safety concern exists, or manufacturers can elect to conduct a recall voluntarily.[118] Recalls lead to either *corrections*, which address the problem in question at the point of use or sale (*e.g*. updates to software), or *removals* that take devices out of use or distribution. Class I recalls involve a reasonable probability that the use of a product will cause serious adverse health consequences or death. Class II recalls involve products that may result in temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote. Class III is invoked when the product is not likely to cause adverse health consequence, such as minor labeling errors. Class I and II recalls tend to invoke stricter FDA oversight, including follow-up and auditing of communication to providers or end-users, as well as more requirements for documentation and reporting. A manufacturer is responsible for developing the strategy for managing the logistics of a recall depending on the nature of the device, the problem, and the seriousness of the public health impact.

Two publicly-available databases track safety alert and recall information. A comprehensive listing of enforcement reports is published weekly.[114] The FDA also hosts a public database of Medical and Radiation Emitting Device Recalls, which has more detailed information on medical device recalls (since November 2002),[115] including the date and a narrative explanation for the recall and actions taken by the manufacturer. The database can be searched by date, manufacturer, recall class or number, or the reason for recall.

B. European Union

Manufacturers and regulators have obligations under the European Commission directives to manage adverse events and safety problems with marketed devices. Field Safety Corrective Actions (FSCAs) are “actions taken by manufacturers to reduce a risk of death or serious deterioration in the state of health associated with the use of a medical device” already on the market.[116] These actions range from changes in labeling to removal of products from the

market. Software upgrades and recommendations for clinical management changes are also considered FSCAs. The details of FSCAs are communicated by manufacturers to users (health care facilities or providers) in field safety notices (FSNs). For example, a FSN issued by a hip implant manufacturer in April 2011 described an FSCA resulting from a processing problem in which packaging for prostheses was mislabeled, leading to potential mismatching of implant size and patient size. The FSN outlined the expected impact of this mislabeling on clinical care, provided health care facilities with batch numbers to facilitate removal of the affected lots, and offered clinical recommendations for patient follow-up.[117] In this case, the identified problem occurred in France, and thus the FSN specified that the French CA was notified of the event. Each CA must submit National Competent Authority Reports (NCARs), which outline major safety issues for medical devices to keep other CAs up to date.

C. Japan

Postmarket actions taken by the MHLW include safety communications and recalls derived from mandatory reports from MAHs and voluntary reports provided by medical professionals.[23] The MHLW can issue safety communications directly to hospitals, medical associations, and health care providers, and facilitates publication and dissemination of “Dear Doctor” letters from MAHs.

For more significant safety concerns, are two routes to recall in the Japanese market. Serious problems are more likely to have manifested elsewhere first given Japan’s small population relative to the US or EU. Foreign recalls do not automatically trigger a recall in Japan, but companies themselves typically initiate a recall in Japan once they have done so elsewhere. If the sponsor is a global company, marketing a device in Japan that has been recalled elsewhere is generally untenable.

By contrast, recalls arising from domestic incidents may include problems with documentation or reporting, as well as those related to adverse events. For example, adverse events involving severe bleeding after use of a new surgical stapler were reported to PMDA in late 2010, leading PMDA to order the MAH to provide additional analysis and eventually issue a safety warning in Japan about use of this device in March of 2011. Nine months later, this same device was recalled in the US and EU.[118]

D. China

In July 2011, the MOH instituted the *Tentative Measures on the Administration of Recalls Concerning Medical Devices*, outlining rules to refine the device recall process in China.[119] The measures divide recalls into two types: proactive recalls and recalls on demand. Proactive recalls are initiated by medical device manufacturers based on self-investigation and assessment of product defects, ranging from eliminating defects through relabeling or software upgrades, to full market withdrawal. These measures contrast with China’s drug recall protocol, which only allows for product destruction.[98] Before initiating the recall, the manufacturer must submit a recall plan to the provincial ADR Center, which evaluates the recall plan and may demand changes to the original proposal, such as expansion of recall scope and reduction of recall lead time. The manufacturer must regularly update regional

authorities on the recall status, and submit a summary report within 10 days after recall completion.[120]

For a medical device that caused severe injuries or death, regional authorities and CFDA departments organize groups of representatives and experts from device monitoring institutions, manufacturers, and scientific research teams to conduct a full re-evaluation. The results help the authorities decide whether to revoke the device's original registration certificate. They may also institute a recall. Failure to recall defective medical devices subjects the manufacturers to monetary fines of three times of the value of the devices.

In October 2012, the CFDA and its provincial counterparts instituted a national disclosure system called the Drug Safety Blacklist, though it included medical devices as well. Manufacturers and companies will now be unable to secure regulatory approvals or licenses for two years if they are involved in the manufacturing of counterfeit or substandard products, or if they cause serious quality or safety events due to violation of drug/device laws. The disclosure system is accessible to the general public.[121]

VIII. Emerging Strategies

A. United States

Recognizing the complexity of post-approval surveillance and the need for a comprehensive, population-based approach to detect adverse events, the FDA established the Medical Product Safety Network (MedSun) network in 2002 to develop information about emerging safety signals.[122] MedSun facilities (approximately 280 as of 2012) submit reports of adverse events electronically, and typically with more detail than is the case for adverse event reports generally.[123] MedSun facilities may participate in "subnetworks" such as KidNet (for pediatric and neonatal intensive care units), and engage targeted research around real-world medical device use. MedSun can help estimate rates of specific problems, or provide more detailed user experiences that may distinguish whether adverse events are related to the devices or to user and patient factors that might be correctable without a recall.

Recently, the FDA outlined proposed revisions and improvements to its post-approval surveillance activities, organized more formally into a preliminary national strategy.[42] This strategy includes a rule for a unique device identifier (UDI) system.[124] UDIs may help identify specific devices used or implanted in individual patients, and therefore allow linkage of devices to clinical information that can enhance the context of adverse event reports. This has been piloted successfully in China, and is central to future plans in the EU and Japan as well. Theoretically, once UDIs are integrated into health care data sources, they will facilitate notification of devices' use and performance characteristics, support more accurate and timely aggreggation of adverse event data, and enable better coordination of recalls. Many technical hurdles remain, including integration of UDIs into the design of devices themselves as well as electronic medical record systems,[125] and draft guidance for industry was issued in September 2013.[126]

Another notable emerging post-approval surveillance strategy is the Medical Device Epidemiology Network (MDEpiNet), a public-private collaboration advanced by the FDA to

develop new sources of data and analytic techniques for post-approval surveillance. MDEpiNet working groups are currently focused on addressing issues such as the integration of UDIs into existing data sources, frameworks for device evaluation along a "total product life cycle,"[127,128] standardized classification schemes for orthopedic devices,[129] and the evaluation of software-based adverse event analytics to speed the identification of abnormal safety signals.[130] A closely related program is the FDA's Sentinel Initiative, started in 2008 to promote active, electronic monitoring of pharmaceutical safety. Expanding such a program to include medical devices will be aided by the integration of UDIs into medical records.[131]

B. European Union

The European Commission recently issued a detailed proposal for updating medical device regulation, including post-approval surveillance.[131] The post-approval surveillance provisions suggested in this document include use of UDIs and connecting UDIs to EUDAMED data. UDIs represent an opportunity to coordinate post-approval surveillance between markets, as advocates for this system intend identifiers to be consistent internationally. The provisions also include improved coordination among CAs, so that these isolated bodies may, for example, respond to emerging safety signals for specific devices by pooling of adverse event data.

Another important element of the proposed post-approval surveillance strategy is greater oversight of NBs.[132] Such oversight includes not only stricter guidance regarding the details of their "conformity assessment" activities in the pre-approval phase, but also clarification of their responsibility and authority to conduct unannounced inspections of manufacturing facilities and audits of collected documentation related to adverse events. Finally, the proposal emphasizes regular engagement with experts for specific post-approval surveillance questions, such as development of registries or clinical management of problems that arise.

C. Japan

Japan has pursued several new device surveillance strategies, including (1) securing an enhanced structure for PMDA,[133] (2) improving the effectiveness of QMS, and (3) establishing Health Information Database Network.[134] The first strategy entails enhancing government funding for PMDA to support hiring more personnel to speed device evaluation, and allow for more comprehensive post-approval surveillance assessments. The second thrust involves improving coordinating activities such as inspections among local government, PMDA, and private third-parties to streamline the process for lower-risk devices and preserve resources to focus on higher-risk products. The third initiative is the Health Information Database Network, often referred to as the "Sentinel Project in Japan" since its development in 2008 based upon FDA's Sentinel Initiative. The project seeks to establish 10 major health care delivery sites to collect and pool information on adverse events and performance of devices (as well as drugs) from an estimated 10 million patients. It is intended to provide a data source for novel statistical methods and analytic techniques to assess safety and effectiveness more actively than traditional approaches.

D. China

China's unique regional structure grants autonomy and authority to provincial CFDA agencies; each region is, in essence, responsible for overseeing medical device events within its geographic boundaries. This has fostered some regional competition in exploring new emerging strategies for post-approval surveillance. An illustrative example is Shanghai's development of a traceability program for implantable medical devices, adopting a UDI system that uses GS1 international traceability barcode standards to link implantable medical devices directly to patients.[135] In 2006, the Shanghai regional authority implemented this system across over 100 hospitals in Shanghai, covering high-risk devices such as breast implants, heart valves, pacemakers, catheters, and stents. Each device contains a UDI linked to its corresponding product name, model, lot number, registration certificate number, manufacturer, and distributor information. A hospital staff member scans the UDI and attaches it to the patient record via the hospital electronic data system. Hospitals then submit the information to a centralized Shanghai database, which serves as a resource for manufacturers, distributors, and hospitals. In the case of adverse events, the database can provide detailed records of potential patients involved and range of products with potentially similar issues, allowing the CFDA to hold back potentially dangerous products while still in inventory and limit future injuries.[144]

IX. Conclusion

Novel medical device technologies necessarily balance safety concerns with the promise of improved clinical care. A rigorous but efficient premarket regulatory evaluation process can help reduce the risk of harmful patient outcomes from new medical devices. We found that the device approval circumstances varied greatly among the settings we reviewed, including the degree of pre-approval testing required by the appropriate government authority. However, no amount of premarket testing can capture all potential patient health outcomes that will emerge a new device, either positive or negative, when it is introduced into clinical practice. We found that the US, EU, Japan and China share broad features in their approaches to post-approval monitoring, such as a heavy reliance on passive adverse event collection for marketed devices. This review also highlights the strengths and weaknesses in the way these systems aggregate and leverage post-market events for clinical and policy decisions.

The growing enthusiasm for shifting away from passive adverse event collection to more active and dynamic mechanisms such as UDI systems reflects the lessons learned from important past recalls and the public health burdens associated with malfunctioning devices. Yet transforming adverse event collection requires overcoming a host of legislative, technical, and logistical hurdles that may limit the short-term opportunities for improving public health. Our review suggests that current regulatory systems worldwide are beginning to experiment with strategies to identify unsafe or ineffective devices, but still require much progress before the promise of active surveillance can be achieved.

This review highlights a few ways in which different medical device regulatory systems around the world can learn from each other. For example, one opportunity for immediate improvement in the US and EU draws from the experiences in Japan (and emerging in

China) with scheduled re-examinations for selected devices. A formal regulatory re-evaluation of the marketing approval for select high-risk devices after 3–7 years enforces post-approval commitments while also providing feedback on the pre-approval requirements for individual devices and device classes. In the US and EU, appending a "sunset provision" to FDA-approval and the CE Mark for a subset of devices – selected on the basis of novelty, risk, or vulnerability of the intended population – would motivate both sponsors and regulators to provide a comprehensive, public reassessment of available safety and effectiveness data at predetermined intervals. Such a move would require changes in statutory authority through further revision to the Food Drug and Cosmetic Act (in the US) and the Medical Device Directives (in the EU), and thus would face significant political hurdles. Conversely, it appears that aspects of the US system are serving as templates for changes in the EU and potentially China, including stronger central oversight and better traceability of devices in the supply chain.[136] Cross-national comparisons can help strengthen a diversity of countries—highincome and low-income, those with a powerful regulatory apparatus and those with a weaker infrastructure—as policymakers pursue a common goal of encouraging medical device innovation and ensuring public safety.

Acknowledgments

This study was supported by funding from the Medical Device Initiative from the Pew Charitable Trusts. Dr. Kramer is the Lois Green Scholar at the Hebrew Senior Life Institute for Aging Research, and is additionally supported by an award from the Harvard Catalyst Clinical and Translational Science Center, and a Paul B. Beeson Career Development Award (K23AG045963). Dr. Kesselheim is also supported by a career development award from the Agency for Healthcare Research & Quality (K08HS18465-01), a Greenwall Faculty Scholarship in Bioethics, and a Robert Wood Johnson Foundation Investigator Award in Health Policy Research. Dr. Kramer reports serving as a consultant to Circulatory Systems Advisory Panel of the Food and Drug Administration. The authors would like to thank Yuka Sugamura of the Medical Device Safety Division at the Pharmaceuticals and Medical Devices Agency (Japan) as well as Liang Yan, head of Regulatory Affairs Division at the Shanghai Food and Drug Administration for their helpful conversations and insights.

Dr. Kramer's research focuses on policy, performance, and ethics questions surrounding the use of medical devices.

Yongtian Tina Tan research focuses on innovation at the intersection of medicine, business and technology, as well as on improving drug and medical device development.

Dr. Sato's research focuses on law and policy issues surroundings drugs and medical devices.

Aaron S. Kesselheim research focuses on the effects of intellectual property laws and regulatory policies on pharmaceutical development, the drug approval process, and the costs, availability, and use of prescription drugs both domestically and in resource-poor settings.

References

1. Hauser RG, Kallinen LM, Almquist AK, Gornick CC, Katsiyiannis WT. Early Failure of a Small-Diameter High-Voltage Implantable Cardioverter-Defibrillator Lead. Heart Rhythm. 2007 Jul; 4(7): 892–896. [PubMed: 17599673]
2. Hauser RG, Abdelhadi R, McGriff D, Retel LK. Deaths Caused by the Failure of Riata and Riata St Implantable Cardioverter-Defibrillator Leads. Heart Rhythm. 2012 Aug; 9(8):1227–1235. [PubMed: 22449741]
3. Jameson SS, Baker PN, Mason J, Porter ML, Deehan DJ, Reed MR. Independent Predictors of Revision Following Metal-On-Metal Hip Resurfacing: A Retrospective Cohort Study Using National Joint Registry Data. J Bone Joint Surg Br. 2012 Jun; 94(6):746–754. [PubMed: 22628587]
4. Horton R. A Serious Regulatory Failure, with Urgent Implications. Lancet. 2012; 379

5. Gallagher J. Pip Breast Implants: European Commission Says Reform Needed. BB C News. 2012 Jan 14. *available at*http://www.bbc.co.uk/news/health-1654332.
6. O'Dowd A. UK Launches Inquiry into Safetyof Pip Breast Implants. BMJ. 2012; 344:e11. [PubMed: 22214894]
7. Kramer DB, Tan YT, Sato C, Kesselheim AS. Postmarket Surveillance of Medical Devices: A Comparison of Strategies in the US, Eu, Japan, and China. PLoS Medicine. 2013 Sep. 10(9):e1001519. [PubMed: 24223035]
8. Medical Device Amendments. Pub. L. No. 94-295, 90 Stat. 539. 1976
9. Munsey RR. Trends and Events in Fda Regulation of Medical Devices Over the Last Fifty Years. Food Drug Law J. 1995; 50 Spec:163-77.
10. Medical Device User Fee and Modernization Act, Pub. L. No. 107-250, 116 Stat. 1588. 2002
11. Food and Drug Administration. [Accessed December 2, 2013] Information Related to MDUFMA II. *Available at*: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceUserFeeandModernizationActMDUFMA/ucm109316.htm.
12. United States Congress. [Accessed December 2, 2013] Food and Drug Administration Safety and Innovation Act. *Available at*: http://www.gpo.gov/fdsys/pkg/BILLS-112s3187enr/pdf/BILLS-112s3187enr.pdf.
13. Kramer DB, Kesselheim AS. User fees and beyond--the FDA Safety and Innovation Act of 2012. N Engl J Med. 2012; 367(14):1277–1279. [PubMed: 23034017]
14. European Union. Treaty Establishing the European Community, Rome Treaty. 1957 Mar 25.
15. European Union. Treaty on European Union, Treaty of Maastricht, 7 July 1992. Official Journal of the European Communities C 325/5. 2002 Dec 24.
16. European Union. Treaty of Lisbon Amending the Treaty on European Union and the Treaty Establishing the European Community, 13 December 2007, 2007/C 306/01. *Available at*: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2008:115:0047:0199:EN:PDF.
17. European Commission. Medical Devices: Guidance Meddevs. 2011 Jun 10. *Available at*: http://ec.europa.eu/health/medical-devices/documents/guidelines/index_en.htm.
18. European Commission. Proposals for Regulations of the European Parliament and of the Council on Medical Devices, and Amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009. *Available at*: http://ec.europa.eu/health/medical-devices/files/revision_docs/proposal_2012_542_en.pdf.
19. European Commission. Commission Staff Working Document Executive Summary Of The Impact Assessment On The Revision Of The Regulatory Framework For Medical Devices. *Available at*: http://ec.europa.eu/health/medical-devices/files/revision_docs/revision_ia_part1_en.pdf.
20. European Commission. Guidelines on Post Market Clinical Follow-Up (MEDDEV 2.12-2). 2004 May. *Available at*: http://ec.europa.eu/health/medical-devices/files/meddev/2_12-2_05-2004_en.pdf.
21. European Commission. Guidelines On Medical Devices. Clinical Evaluation: A Guide For Manufacturers And Notified Bodies. 2009 Dec. *Available at*: http://ec.europa.eu/health/medical-devices/files/meddev/2_7_1rev_3_en.pdf.
22. World Health Organization. Pharmaceutical Administration and Regulations in Japan. *Available at*: http://apps.who.int/medicinedocs/documents/s18577en/s18577en.pdf.
23. Japanese Pharmaceutical Affairs Law §§14 (1)–(2), No. 145 of 1960 (latest revisions by No. 44 of 2013).
24. Tamura A. Understanding Japanese Medical Device Requirements. 2011 AHC Workshop on Medical Devices: "Implementation of GHTF Documents". 2011 Jul 4. *Available at*: http://www.pmda.go.jp/regulatory/file/english_presentation/device/D-E3tamura.pdf.
25. State Food and Drug Administration, PR China. [Accessed December 2, 2013] Regulations for the Supervision and Administration of Medical Devices. *Available at*http://eng.sfda.gov.cn/WS03/CL0767/61641.html.
26. Center for Medical Device Evaluation, SFDA. Interim Measures for the Administration of Adverse Medical Device Events Monitoring and Reevaluation. *Available at*: http://www.cmde.org.cn.

27. Gaffney, Alexander. China's SFDA Becomes CFDA amidst Consolidation of Power and New Leadership. Regulatory Focus. 2013 Mar 25. *Available at*http://www.raps.org/focus-online/news/news-article-view/article/3073/chinas-sfda-becomes-cfda-amidst-consolidation-of-power-and-new-leadership.aspx.
28. Consolidation of China's SFDA Grants Agency More Prestige, Power. Regulatory Focus. 2013 Mar 11. *Available at*http://www.raps.org/focus-online/news/news-article-view/article/2993/consolidation-of-chinas-sfda-grants-agency-more-prestige-power.aspx.
29. State Food and Drug Administration, PR China. [Accessed December 2, 2013] Affiliated Organizations. *Available at*: http://former.sfda.gov.cn/cmsweb/webportal/W45255828/index.html.
30. Maisel WH. Medical device regulation: an introduction for the practicing physician. Ann Intern Med. 2004; 140:296–302. [PubMed: 14970153]
31. Food and Drug Administration. [Accessed December 2, 2013] Medical Device Classification. *Available at*: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/default.htm.
32. [Accessed December 2, 2013] United States Code, Title 21, Food and Drugs, Chapter 9, Federal Food, Drug and Cosmetic Act, Part A Sec 360.c: Classification of devices intended for human use.. *Available at*: http://www.gpo.gov/fdsys/granule/USCODE-2010-title21/USCODE-2010-title21-chap9-subchapV-partA-sec360c/content-detail.html.
33. Food and Drug Administration. [Accessed December 2, 2013] General Controls for Medical Devices. *Available at*: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/GeneralandSpecialControls/ucm055910.htm.
34. Food and Drug Administration. [Accessed December 2, 2013] General and Special Controls (Medical Devices). *Available at*: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/GeneralandSpecialControls/default.htm.
35. Medical devices; exemption from premarket notification and reserved devices; class I. Food and Drug Administration, HHS. Final rule. Fed Regist. 2000; 65(10):2296–2323.
36. Hall, RF. [Accessed December 2, 2013] Delicate balance: FDA and the reform of the medical device approval process. Written testimony for U.S. Senate Committee on Aging. 2011 Apr 13. *Available at*: http://aging.senate.gov/events/hr233hr.pdf.
37. [Accessed December 2, 2013] United States Code, Title 21, Food and Drugs, Chapter 9, Federal Food, Drug and Cosmetic Act, Part A, Sec 360.c: Classification of devices intended for human use. *Available at*: http://www.gpo.gov/fdsys/granule/USCODE-2010-title21/USCODE-2010-title21-chap9-subchapV-partA-sec360c/content-detail.html.
38. Food and Drug Administration. [Accessed December 2, 2013] CDRH preliminary internal evaluations—volume II. Task Force on the Utilization of Science in Regulatory Decision Making. Preliminary Report and Recommendations. 2010 Aug. *Available at*: http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHReports/UCM220783.pdf.
39. Safe Medical Devices Act. Pub L No. 101-629, 104 Stat 4511. 1990
40. [Accessed December 2, 2013] United States Code, Title 21, Food and Drugs, Chapter 9, Federal Food, Drug and Cosmetic Act, Part A, Sec 360.c: Classification of devices intended for human use. *Available at*: http://www.gpo.gov/fdsys/granule/USCODE-2010-title21/USCODE-2010-title21-chap9-subchapV-partA-sec360c/content-detail.html.
41. Food and Drug Administration. [Accessed December 2, 2013] PMA Clinical Studies. *Available at*: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/ucm050419.htm.
42. Sapirstein W, Alpert S, Callahan TJ. The role of clinical trials in the Food and Drug Administration approval process for cardiovascular devices. Circulation. 1994; 89:1900–1902. [PubMed: 8149556]
43. Food and Drug Administration Modernization Act of 1997. Pub L No. 105-115, 111 Stat 2295. 1997
44. Smith JJ, Shyjan AM. Defining "least burdensome means" under the Food and Drug Administration Modernization Act of 1997. Food Drug Law J. 2000; 55:435–447. [PubMed: 11824468]

45. [Accessed December 2, 2013] United States Code of Federal Regulations, Title 21, Volume 8; 814.82(a)(2): Postapproval Requirements. *Available at*: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=814.82.
46. [Accessed December 2, 2013] Food and Drug Administration, Guidance for Industry and FDA Staff: Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process, 2008. *Available at*http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm089274.htm.
47. Maisel WH. Semper Fidelis--Consumer Protection for Patients with Implanted Medical Devices. N Engl J Med. 2008 Mar 6; 358(10):985–987. [PubMed: 18322280]
48. Hauser RG. Here We Go Again--Failure of Postmarketing Device Surveillance. N Engl J Med. 2012; 366(10):873–875. [PubMed: 22332951]
49. European Commission. Classification of medical devices (MEDDEV 2.4/1 Rev. 9). 2010 Jun. *Available at*: http://ec.europa.eu/consumers/sectors/medical-devices/files/meddev/2_4_1_rev_9_classification_en.pdf.
50. European Commission. Classification criteria (Annex IX of Directive 93/42/EEC). 2010 Jun. *Available at*: http://www.lne-gmed.com/pdf/en/annex9-directive-93-42-amended.pdf.
51. European Commission. Enterprise and Industry. NANDO (New Approach Notified and Designated Organisations) Information System. Available at: http://ec.europa.eu/enterprise/newapproach/nando/.
52. European Commission. Commission communication in the framework of the implementation of Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices. 2011 Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2011:016:0001:0007:EN:PDF.
53. European Parliament and Council. Directive 98/79/EC, Annex IA. Available at: http://eur-lex.europa. eu/LexUriServ/LexUriServ.do?uri=OJ:L:1998:331:0001:0037:EN:PDF.
54. EuroScan international network website. WATCHMAN left atrial appendage closure device for nonvalvular atrial fibrillation. Available at: http://euroscan.org.uk/technologies/technology/view/1301.
55. Holmes DR, Reddy VY, Turi ZG, et al. Percutaneous Closure of the Left Atrial Appendage Versus Warfarin Therapy for Prevention of Stroke in Patients with Atrial Fibrillation: A Randomised Non-Inferiority Trial. Lancet. 2009; 374:534. [PubMed: 19683639]
56. Maisel WH. Left Atrial Appendage Occlusion--Closure or Just the Beginning? N Engl J Med. 2009; 360:2601–2603. [PubMed: 19474420]
57. Cingolani E, Stevens S, Shehata M, Diamond GA, Kaul S. Medical Device Regulatory Reform: Insights from the Watchman Left Atrial Appendage Closure Technology for Stroke Prophylaxis in Atrial Fibrillation. Arch Intern Med. 2011; 171(18):1670–1672. [PubMed: 21746999]
58. Pharmaceuticals and Medical Devices Agency. Report of Approved Devices. Available at: http://www.pmda.go.jp/english/service/pdf/list/NewmedicaldevicesFY2009.pdf.
59. The Chinese Medical Device Market: Riding the Dragon. Available at: http://www.neuvomedica.com/resources/free-white-paper/download-free-white-paper/.
60. Neuvomedica. The Chinese Medical Device Market: Riding the Dragon. Available at http://www.neuvomedica.com/resources/free-white-paper/download-free-white-paper/.
61. [Accessed December 2, 2013] Clinicaltrials.gov website entry for SYMPLICITY HTN-3 Trial: Renal Denervation in Patients with Uncontrolled Hypertension. Available at: http://clinicaltrials.gov/ct2/show/NCT01418261.
62. State Food and Drug Administration Database. [Accessed December 2, 2013] Available at: http://www.sfda.gov.cn/WS01/CL0135/.
63. China Medical Device Information Network. [Accessed December 2, 2013] Available at http://www.cmdi.gov.cn/cmdi/lmsetup.nsf/zydbsy?openform.
64. China develops new rules to simplify medical device re-registration process. Sidley Austin LLP Updates. 2013 Apr 1. Available at http://www.lexology.com/library/detail.aspx?g=70f3fdd2-c719-4a8c-99bb-2ffb670f08ee.
65. CFDA Drug Registration Regulations. [Accessed December 2, 2013] Available at: http://www.sfda.gov.cn/WS01/CL0053/24529/.html.

66. XIENCE V Everolimus Eluting Coronary Stent System (EECSS) China: Post-Approval, Single-Arm Study; Available at: http://clinical-trials.findthedata.org/l/31815/XIENCE-V-Everolimus-Eluting-Coronary-Stent-System-EECSS-China-Post-Approval-Single-Arm-Study.
67. Emergo Group: The Medical Device Approval Process in China. Available at: http://www.slideshare.net/emergogroup/the-medical-device-approval-process-in-china.
68. United States Code of Federal Regulations Title 21, Part 803, Subpart A. [Accessed December 2, 2013] Medical Device Reporting, General Provisions. Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=803.
69. Food and Drug Administration. [Accessed December 2, 2013] MedWatch: The FDA Safety Information and Adverse Event Reporting System. Available at: http://www.fda.gov/safety/medwatch/default.htm.
70. Food and Drug Administration. [Accessed December 2, 2013] Website for Manufacturer and User Facility Device Experience database. Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/search.CFM.
71. Hsi RS, Ojogho ON, Baldwin DD. Analysis of Techniques to Secure the Renal Hilum During Laparoscopic Donor Nephrectomy: Review of the FDA Database. Urology. 2009; 74(1):142–147. [PubMed: 19406458]
72. European Commission. Council Directive 90/385/EEC 1990 Article 8, paragraph 3. Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31990L0385:en:HTML.
73. European Commission. Website for European Databank on Medical Devices - EUDAMED. Available at: http://ec.europa.eu/consumers/sectors/medical-devices/market-surveillance-vigilance/eudamed/.
74. The Medicines and Healthcare products Regulatory Agency. [Accessed December 2, 2013] Medical Device Alerts website. Available at: http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/MedicalDeviceAlerts/index.htm.
75. Pharmaceutical Affairs Regulations §253 (2), No. 1 of 1961 (latest revisions by No. 109 of 2013.
76. Pharmaceuticals and Medical Devices Agency. Pharmaceutical Affairs Law 77-4-2.
77. Sugamura Y. (MHLW). Implementation of adverse event reporting. APEC Training Seminar on the implementation of GHTF guidance document. 2011 Jul 5. Available at: http://www.apec-ahc.org/files/tp201107/13_S5-(Yuka%20Sugamura)0705Implementation%20of%20Adverse%20Event%20Reporting%20 ((MHLW%20ver.pdf.
78. Guide to Medical Device Regulations and Practices in the People's Republic of China. Interfax China. 2010
79. Adverse Medical Event Reporting Process. [Accessed December 2, 2013] Center for Drug Reevaluation, SFDA. Available at: http://www.cdr.gov.cn/bszn/kyylqxblsjbglc/.
80. CFDA Releases 2012 Annual Report for National Adverse Events of Medical Devices Monitoring. Available at: http://chemlinked.com/en/news/pharmaceutical/cfda-releases-2012-annual-report-nationaladverse-events-medical-devices-monitoring.
81. National Adverse Drug Reactions Surveillance Database. Available at: http://114.255.93.220/sso/login?service=http%3A%2F%2F114.255.93.220%2FPF%2FcasAuthUser.
82. Uppsala Monitoring Center. Breakthrough collaboration in global patient safety information sharing: China and the WHO Programme for International Drug Monitoring agree to work closely together. Available at: http://www.who-umc.org/graphics/25071.pdf.
83. World Health Organization: Medical Devices. Available at: http://www.who.int/medical_devices/en/.
84. Food and Drug Administration. [Accessed December 2, 2013] Code of Federal Regulations Title 21, Part 820. Quality Systems Regulation. Available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=820.
85. Food and Drug Administration. [Accessed December 2, 2013] Code of Federal Regulations Title 21, Part 820, Subpart J, Sec 820.100: Corrective and Preventative Action. Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=820.100.
86. European Committee for Standardization website. Available at: http://www.cen.eu/cen/products/en/pages/default.aspx.

87. Emergo Group Medical Device Consulting website. ISO Requirements by Country/Region. Available at: http://www.iso13485.com/iso-13485-requirements.

88. QMS Ordinance Ch. 2, No. 169 of 2004; MHLW's Administrative Circular, Questions and Answers on relationships between QMS Ordinance and ISO13485-2003, May 30, 2011.

89. MHLW's GMP/QMS Inspection Guidance ch. 4, Nov. 30, 2005. See also Kenichi Ishibashi (PMDA). Medical device QMS/GMP system and audit. APEC Training Seminar on the implementation of GHTF guidance document. 2011 Jul 4.

90. SFDA, PR China. [Accessed August 1, 2013] Good Manufacturing Practice Standards for Medical Devices. Available at: http://www.sfda.gov.cn/WS01/CL0059/44657.html.

91. China Publishes medical device GMP regulations and proposes new draft drug GMP. Sidley Austin LLP. 2010 Jan 13. Available at: http://www.lexology.com/library/detail.aspx?g=6732bd03-e905-41b2-87d5-59e1b518960d.

92. SFDA, PR China. [Accessed December 2, 2013] SFDA Issues Working Procedures for Unannounced Inspection of Medical Device Manufacturers (interim). Available at: http://eng.sfda.gov.cn/WS03/CL0757/72894.html.

93. Food and Drug Administration. [Accessed December 2, 2013] Post-Approval Studies. Available at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/PostApprovaStudies/ucm135263.htm.

94. Food and Drug Administration, Cook Inc. [Accessed December 2, 2013] Zilver PTX Drug Eluting Stent; PMA P100022 Panel Package 1-1 Attachment 1 – Proposed Post-Approval Study Investigational Plan Zilver PTX Post-Approval Study Investigational Plan. Available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM273839 pdf.

95. Food and Drug Administration. [Accessed December 2, 2013] Post-Approval Studies. Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma_pas.cfm.

96. Food and Drug Administration. [Accessed December 2, 2013] Compliance and Enforcement. Available at: http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHTransparency/ucm199911.htm.

97. Food and Drug Administration. [Accessed December 2, 2013] Procedures for Handling Post-Approval Studies Imposed by PMA Order guidance document. Available at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070974.htm#9.

98. Food and Drug Administration. [Accessed December 2, 2013] Postmarket Surveillance Under Section 522 of the Federal Food, Drug and Cosmetic Act. Available at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm072517.htm.

99. Food and Drug Administration Safety and Innovation Act. [Accessed December 2, 2013] Sec 616: Postmarket Surveillance. Available at: http://www.gpo.gov/fdsys/pkg/BILLS-112s3187enr/pdf/BILLS-112s3187enr.pdf.

100. Food and Drug Administration. [Accessed December 2, 2013] 522 Postmarket Surveillance Studies. Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pss.cfm.

101. Global Harmonization Task Force. Review of current requirements on postmarket surveillance. 2005 May. Available at: http://www.ghtf.org/documents/sg2/sg2-n47r4.pdf.

102. European Commission. Guidelines on post market clinical follow-up (MEDDEV 2.12-2). 2004 May. Available at: http://ec.europa.eu/health/medical-devices/files/meddev/2_12-2_05-2004_en.pdf.

103. The Center for Reviewing Pharmaceuticals and Medical Devices at National Institute of Health Sciences. Reviewing Report on CYPHERR) Sirolimus-eluting Coronary Stent. 2004 Feb 18. See also Johnson & Johnson. Press Release on CYPHERR) Sirolimus-eluting Coronary Stent Approved for Marketing in Japan, Mar. 31, 2004.

104. MHLW: Re-filing and Re-evaluation, Feb. 28, 2011, at 8, available at www.cao.go.jp/consumer/history/01/.../tokuho/.../110228_shiryou5.pdf.

105. Dick EA, Gedroyc WM. Exablate Magnetic Resonance-Guided Focused Ultrasound System in Multiple Body Applications. Expert Rev Med Devices. 2010 Sep; 7(5):589–597. [PubMed: 20822382]

106. The PMDA. Reviewing Report to MHLW on ExAblate MR-guided Focused Ultrasound (MRgFUS) system for the treatment of women with uterine fibroids. 2009 Jun 10.
107. SFDA Drug Registration Regulations. [Accessed December 2, 2013] Available at: http://www.sfda.gov.cn/WS01/CL0053/24529.html.
108. ClinicalTrials.gov. [Accessed December 2, 2013] Post-Approval Study of PROMUS Element in China (PEChina). Available at: http://www.clinicaltrials.gov/ct2/show/NCT01677585.
109. XIENCE V Everolimus Eluting Coronary Stent System (EECSS) China: Post-Approval, Single-Arm Study. Available at: http://clinical-trials.findthedata.org/l/31815/XIENCE-V-Everolimus-Eluting-Coronary-Stent-System-EECSS-China-Post-Approval-Single-Arm-Study.
110. [Accessed December 2, 2013] United States Code, , Title 21, Section 360h : Notification and other remedies. Available at: http://www.gpo.gov/fdsys/granule/USCODE-2010-title21/USCODE-2010-title21-chap9-subchapV-partA-sec360h/content-detail.html.
111. Food and Drug Administration. [Accessed December 2, 2013] Public Health Advisory: Risk of burns during MRI scans from transdermal drug patches with metallic backings. Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm111313.htm.
112. Food and Drug Administration. Safety – Background and Definitions. Available at: http://www.fda.gov/Safety/Recalls/ucm165546.htm.
113. Food and Drug Administration. [Accessed December 2, 2013] Cardiac Science Powerheart, CardioVive, CardioLife; GE Responder and Responder Pro; Nihon-Kohden Automated External Defibrillators (AEDs): Class I Recall - Defective Component. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm294538.htm.
114. Food and Drug Administration. [Accessed December 2, 2013] Enforcement Reports Website. Available at: http://www.fda.gov/Safety/Recalls/EnforcementReports/default.htm.
115. Food and Drug Administration. [Accessed December 2, 2013] Medical & Radiation Emitting Device Recalls Website. Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRES/res.cfm.
116. European Commission. Guidelines on a Medical Device Vigilance System. Available at: http://ec.europa.eu/health/medical-devices/files/meddev/2_12_1-rev_6-12-2009_en.pdf.
117. Urgent Field Safety Notice: Corail AMT Size 9 and Size 10 Hip Implant. 2011 Aug 9. Available at: http://www.swissmedic.ch/recalllists_dl/04988/Vk_20110818_06-e1.pdf.
118. Food and Drug Administration. [Accessed December 2, 2013] Recall – Firm Press Release. Covidien Contraindicates The Use of Duet TRS for Thoracic Surgery, Implements a Voluntary Recall. Available at: http://www.fda.gov/Safety/Recalls/ucm288098.htm.
119. Center for Drug Reevaluation, CFDA. [Accessed December 2, 2013] Tentative Measures on the Administration of Recalls concerning Medical Devices. Available at: http://www.cdr.gov.cn/zcfg/ylqx/201108/t20110823_3172.html.
120. China's Health Ministry Issues Recall Rules for Medical Devices. Sidley Austin LLP News. 2011 Jun 23. Available at: http://m.sidley.com/chinas-health-ministry-issues-recall-rules-for-medicaldevices-06-23-2011/.
121. SFDA to enforce Blacklist System for unsafe drug and device products. Sidley Austin LLP Updates. 2012 Aug 21. Available at http://www.sidley.com/SFDA-to-Enforce-Blacklist-System--for-Unsafe-Drugand-Device-Products-08-21-2012/.
122. Food and Drug Administration. [Accessed December 2, 2013] About MedSun. Available at: http://www.fda.gov/medicaldevices/safety/medsunmedicalproductsafetynetwork/default.htm
123. Food and Drug Administration. [Accessed December 2, 2013] Strengthening our national system for medical device postmarket surveillance. Available at: http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHReports/UCM301924.pdf.
124. Food and Drug Administration. [Accessed December 2, 2013] Unique Device Identification System. Final Rule. Available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/UCM368961.pdf.

125. Gross TP, Crowley J. Unique Device Identification in the Service of Public Health. N Engl J Med. 2012; 367(17):1583–1585. [PubMed: 23013051]

126. Federal Register. [Accessed December 2 2013] Global Unique Device Identification Database; Draft Guidance for Industry. Available at: https://www.federalregister.gov/articles/2013/09/24/2013-23058/global-unique-deviceidentification-database-draft-guidance-for-industry-availability.

127. Food and Drug Administration. [Accessed December 2, 2013] Transcript for Public Workshop - Bridging the IDEAL and TPLC Approaches for Evidence Development for Surgical Medical Devices and Procedures. 2011 Dec 2. Available at: http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm288553.htm.

128. McCulloch P. The EU's System for Regulating Medical Devices. BMJ. 2012; 345:e7126. [PubMed: 23097545]

129. Sedrakyan A, Paxton EW, Phillips C, et al. The International Consortium of Orthopaedic Registries: Overview and Summary. J Bone Joint Surg Am. 2011; 93(Suppl 3):1–12. [PubMed: 22262417]

130. Matheny ME, Normand SL, Gross TP, et al. Evaluation of an Automated Safety Surveillance System Using Risk Adjusted Sequential Probability Ratio Testing. BMC Med Inform Decis Mak. 2011; 11:75. [PubMed: 22168892]

131. European Commission. Safe, effective and innovative medical devices and in vitro diagnostic medical devices for the benefit of patients, consumers and healthcare professionals. Available at: http://ec.europa.eu/health/medical-devices/documents/revision/.

132. European Commission. COMMISSION RECOMMENDATION of 24 September 2013 on the audits and assessments performed by notified bodies in the field of medical devices (Text with EEA relevance) (2013/473/EU). Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2013:253:0027:0035:EN:PDF.

133. Prime Minister and His Cabinet; Japan Revitalization Strategy - JAPAN is BACK, Cabinet Decision. 2013 Jun 14. Available at: http://www.kantei.go.jp/jp/singi/keizaisaisei/pdf/en_saikou_jpn_hon.pdf.

134. MHLW Advisory Committee Report on Safety and Trust in Using Pharmaceuticals and Medical Devices by Making Use of Electronic Medical Database ("The Sentinel Initiative" in Japan). 2010 Aug 25.

135. Implementation of a postmarket traceability program for implantable medical devices adopting unique device identification. 2009–2012 GS1 Healthcare Reference Book. Available at http://www.gs1.org/docs/healthcare/case_studies/Case%20study_Shanghai%20FDA_IMD%20Traceability.pdf.

136. European Commission. Regulation of the European Parliament and of the Council on medical devices, and amending directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009. EC. 2012 Available at: http://ec.europa.eu/health/medical-devices/files/revision_docs/proposal_2012_542_en.pdf..