

# Review of the Processes for FDA Oversight of Drugs, Medical Devices, and Combination Products

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In the United States, drugs and medical devices are regulated by different divisions of the U.S. Food and Drug Administration (FDA). While defined similarly, drugs and medical devices differ in their modes of action. Both are products that are labeled, promoted, or used in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease. A device, however, does not achieve its intended purpose through a chemical action within or on the body or by being metabolized by the body.<sup>1</sup> Although both drugs and medical devices must comply with federal regulations regarding labeling, advertising, production, and postmarketing surveillance, there are differences in the FDA premarket review and approval processes. FDA clearance and prescription status of a device do not necessarily mean that safety and efficacy have been shown for the product or that clinical trials have been conducted. We conducted a literature review to (a) examine the historical legislation and approval processes for drugs, medical devices, and combination products and (b) discuss implications of the differences in FDA review processes for clinicians and payers.

## Methods

A MEDLINE search (1950 to September 2010) for English-language articles was conducted using the following search terms: *drug approval, device approval, combination products, and US Food and Drug Administration* (Figure 1). The reference citations from identified articles were reviewed for additional resources, and the FDA website was searched for specific subject areas within the Federal Register, Code of Federal Regulations (CFR), Center for Drug Evaluation and Research (CDER), Center for Devices and Radiological Health (CDRH), and general FDA regulatory documents.

## Results

### Key Laws and Regulations

Over the past century, there have been significant changes and advances in the regulation of drugs by the FDA. These changes evolved in response to catastrophic events in history, because of the advancement of science, and in response to consumer expectations (Figure 2). Prior to the twentieth century, there were essentially no regulations protecting the public from drugs.<sup>2</sup> Manufacturers were able to make curative claims and advertise useless remedies with little fear of repercussions.

The first step towards organizing federal regulation of drugs did not occur until 1902 when Harvey Wiley, a chemist in the Department of Agriculture, began to assess drug ingredients

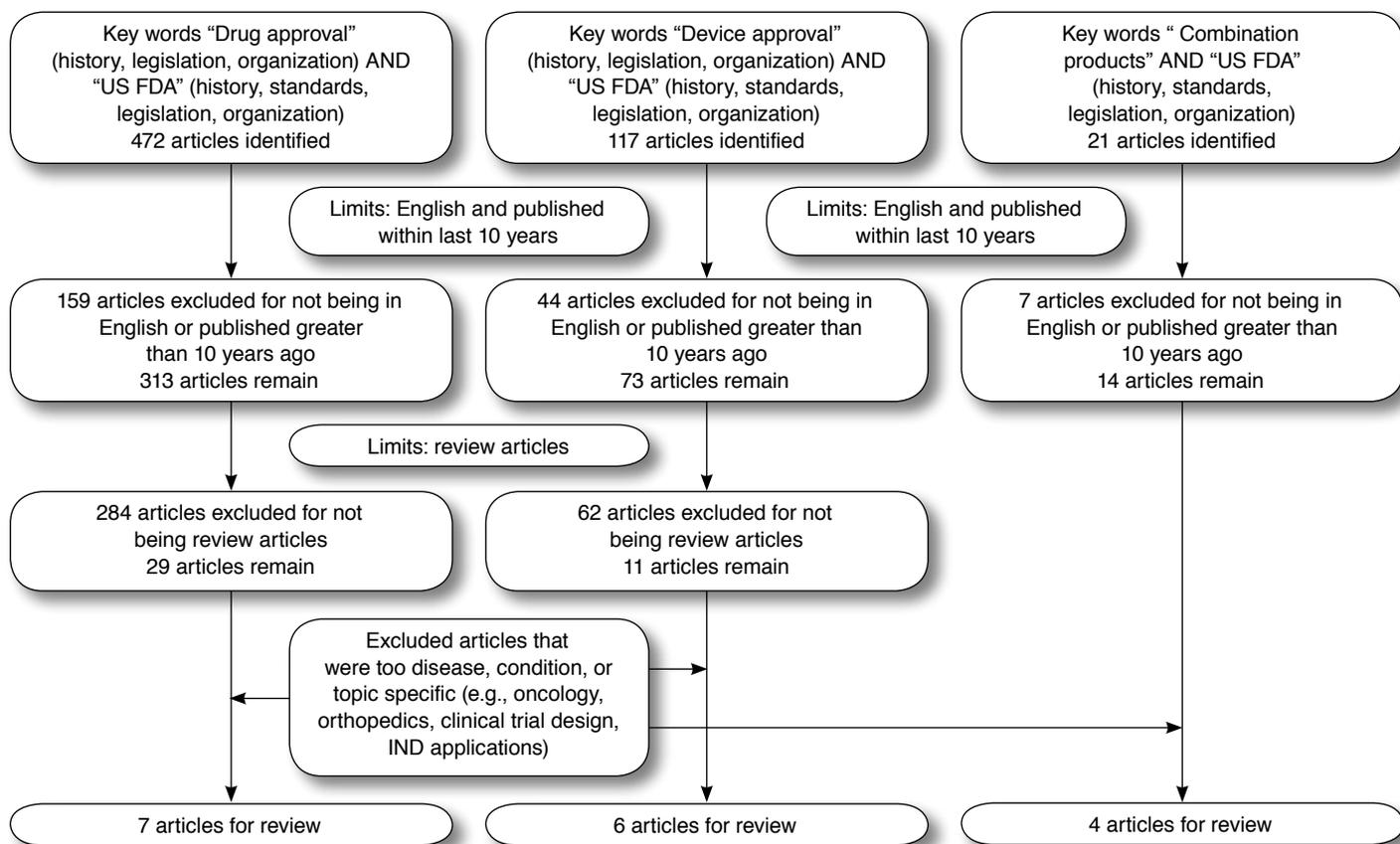
through the Drug Laboratory Program. This process eventually led to the Federal Food and Drugs Act, a law enacted in 1906 that prohibited interstate commerce of misbranded or adulterated foods and drugs and required that drugs meet standards of strength and purity set by the United States Pharmacopeia (USP).<sup>2-4</sup> The 1906 act, however, did not require that any information be submitted to the FDA prior to marketing to establish safety or efficacy, leaving the government responsible to prove with a preponderance of evidence that a drug's labeling was false before it could be removed from the market.<sup>2</sup> Six years later, in 1912, the Sherley Amendment was passed prohibiting manufacturers from labeling medications with false therapeutic claims intended to defraud the consumer. Prior to this amendment, false claims for effectiveness did not fall under the scope of the FDA. Although the 1912 amendment was a step in the right direction, it remained difficult for the FDA to prove intent to defraud the consumer.<sup>2,5</sup>

Although the 1906 Food and Drugs Act was a big step in consumer advocacy, various events occurred over the next 30 years that clearly indicated additional legislation was necessary. In 1933, the FDA produced an exhibit known as the "Chamber of Horrors," which chronicled the drug- and cosmetic-related adverse events for products brought to market legally under the then-current legislation.<sup>5</sup> In 1937, an antimicrobial product known as "Elixir of Sulfanilamide" came to market in a liquid formulation. Diethylene glycol was used as the base solution, a product that had never been examined for safety in the laboratory or in humans. Ultimately, its use led to more than 100 deaths, many of whom were children.<sup>6</sup> Because there was no standing legislation requiring manufacturers to establish safety before bringing a drug to market, the FDA was able to charge the manufacturer only with misbranding, as it called the drug an elixir when it contained no alcohol.<sup>2</sup>

In 1938, after a 5-year debate, the FDA recommended revisions to the 1906 legislation, and Congress passed the Federal Food, Drug and Cosmetic Act (FDCA).<sup>3,7</sup> For the first time in history, manufacturers had to submit an application to receive approval from the FDA prior to marketing a new drug. The FDCA required that new drugs be proven safe prior to marketing, but there was no requirement to prove efficacy. The FDCA also expanded the authority of the FDA to control therapeutic devices, although this regulation was limited to ensuring that devices were not adulterated or misbranded.<sup>8</sup> Although the FDCA offered great improvements, particularly in the regulation of drugs, there continued to be flaws.

Drugs were not required to demonstrate proof of efficacy

**FIGURE 1** Selection of Articles for Review



FDA = U.S. Food and Drug Administration; IND = Investigational New Drug.

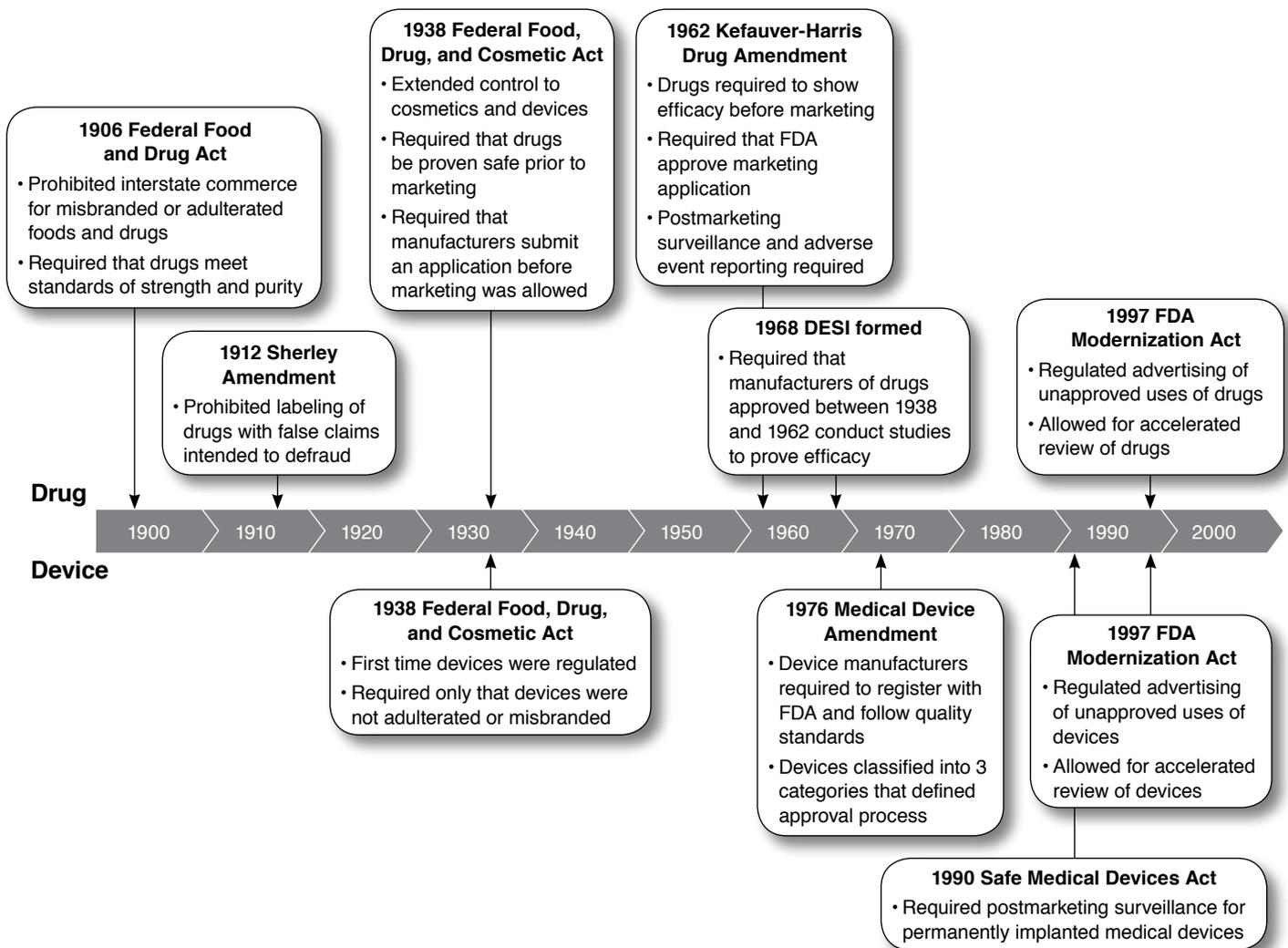
prior to marketing until 1962 when the Kefauver-Harris Drug Amendment was passed.<sup>7,9,10</sup> This amendment was a response to the thalidomide tragedy in Europe, where horrible birth defects were seen in babies born to mothers who received this sleeping pill. The extent of the tragedy was reduced in the United States because of the fortunate delay by 1 reviewer in the FDA who was concerned with the safety of the drug.<sup>11</sup> The 1962 amendment applied to all drugs (prescription and over-the-counter) and required, for the first time, that adequate and well-controlled studies be conducted to prove a drug's efficacy. It also defined rules for obtaining informed consent from research subjects and required that the FDA approve the marketing application prior to the availability of a new drug.<sup>3,8</sup>

While the regulation of drugs began in 1906 with the Federal Food and Drug Act, regulation of medical devices did not begin until enactment of the FDCA in 1938 (Figure 2).<sup>8,12</sup> It was not until the passage of the Medical Device Amendment in 1976 that manufacturers of medical devices were required to register with the FDA and to follow quality control standards prior to marketing.<sup>7,8,12</sup> This legislation was enacted largely

because of increasing reports of injuries associated with medical devices, perhaps the most notable being the thousands of women injured by the Dalkon Shield intrauterine device (IUD), which caused second-trimester septic abortions and maternal deaths.<sup>13</sup> Postmarketing surveillance and adverse event reporting of permanently implanted devices became required in 1990 through the Safe Medical Device Act, in part because of the 1986 market withdrawal of a mechanical heart valve that had premature strut failure, which affected hundreds of patients.<sup>13</sup> In contrast, postmarketing monitoring and safety features for drugs had been in place since 1962.<sup>12</sup>

Over the last 2 decades, multiple amendments have been enacted in an effort to bring safer and more effective drugs and medical devices to market efficiently.<sup>7</sup> The 1997 Food and Drug Administration Modernization Act brought about the most wide-ranging reforms since 1938, including regulation of advertising for unapproved (off-label) uses for drugs and devices, a step that has resulted in a growing number of warning letters to manufacturers for off-label promotion.<sup>14</sup> It also provided for accelerated reviews of drugs and medical

**FIGURE 2** Timeline of Key Laws and Regulations for Drugs and Devices in the United States



DESI = Drug Efficacy Study Implementation; FDA = U.S. Food and Drug Administration.

devices using less stringent thresholds (e.g., use of surrogate markers to assess efficacy and requiring only 1 well-controlled trial to assess safety and efficacy) to allow new therapies to be brought to market sooner for products used to treat very rare diseases (i.e., orphan drugs) or serious medical conditions for which there are no currently available treatment options (e.g., treatment-resistant malignancies). In addition, fees associated with product applications were imposed on manufacturers of drugs through the Prescription Drug User Fee Act (1992) and for medical devices through the Medical Device User Fee Modernization Act (2002) to provide additional funding to the FDA for the new product review process.<sup>12</sup>

The regulation of drugs and medical devices is currently handled through 3 centers within the FDA: CDER, Center for

Biologics Evaluation and Research (CBER), and CDRH. The regulation of biopharmaceuticals, biologicals such as interferon or monoclonal antibodies that are used for therapeutic purposes, was transferred from CBER to CDER in 2003.<sup>7,15</sup>

### FDA Approval Process

It is generally recognized that all drugs and medical devices carry some level of risk. In fact, each year approximately 1-2 drugs and 6-8 medical devices are removed from the U.S. market because of safety concerns.<sup>12</sup> The FDA is charged with reviewing the safety and efficacy of drugs and medical devices and assessing the benefit versus risk of each product.<sup>16</sup> However, the FDA approval processes used for drugs and devices can differ widely.

**Drug Approval Process.** Drugs and biopharmaceuticals are regulated through CDER. The drug development process, which takes an average of 8 to 10 years, begins with pre-clinical studies that assess safety and biological activity in various animal models.<sup>7,17</sup> The manufacturer must then submit to the FDA an Investigational New Drug (IND) application to show results of preclinical testing before testing in humans can occur. Studies in humans are typically done in 4 phases, 3 of which must occur prior to FDA approval.<sup>7,18,19</sup> Phase I studies are the first studies done in humans and are designed to establish the safety, pharmacology, pharmacokinetics, and safe dose range of the drug. These studies typically involve a small number of subjects, often normal healthy volunteers. Phase II studies include patients with the target disease state. The primary goal of the phase II studies is to identify the optimal dose for the phase III studies to maximize efficacy while minimizing toxicity. These studies produce preliminary data on efficacy and identify the most common short-term adverse effects, but they are not generally powered to evaluate efficacy. Phase III studies are the large, pivotal trials that are often used for the FDA approval of a drug. They usually include a large sample size (hundreds to thousands of patients) and are designed to evaluate efficacy.<sup>20</sup>

Typically, once a drug has made it through phase III testing, a manufacturer submits to the FDA a New Drug Application (NDA), a formal proposal requesting approval to market a new drug in the United States.<sup>3,7</sup> CDER reviews the preclinical and clinical data for the proposed indication and makes a determination of approval status. In some cases, conditional approval is granted requiring the manufacturer to complete phase IV postmarketing studies to assess efficacy or safety concerns or to address quality of life or cost/benefit issues.<sup>7</sup> From 2003 through September 2008, the average time required for FDA review of a standard NDA was 12.2 months (range 10 to 15 months).<sup>21</sup> As noted earlier, orphan drugs or drugs used to treat conditions for which there are no good treatment alternatives may undergo expedited review and gain approval based on surrogate markers and phase II data. The process for new generic formulations is somewhat shortened, allowing the manufacturer to submit an Abbreviated NDA (ANDA), which requires data supporting bioequivalence of the generic drug to the innovator product but does not require that clinical trials be conducted.<sup>7</sup> This abbreviated process was made possible in 1984 through the Hatch-Waxman Act in an effort to make generic drugs available sooner.<sup>10</sup>

**Device Approval Process.** The medical device industry, which is very large and diverse, is regulated through CDRH. Although all medical devices marketed in the United States must adhere to controls outlined in the FDCA (i.e., compliance with good manufacturing practices [GMPs], proper labeling, adequate packaging, registration with the FDA), the majority of devices reach the U.S. market through an approval process that is less demanding than that required for drugs and which does not require a true clinical trial testing for safety and efficacy.<sup>12,22</sup>

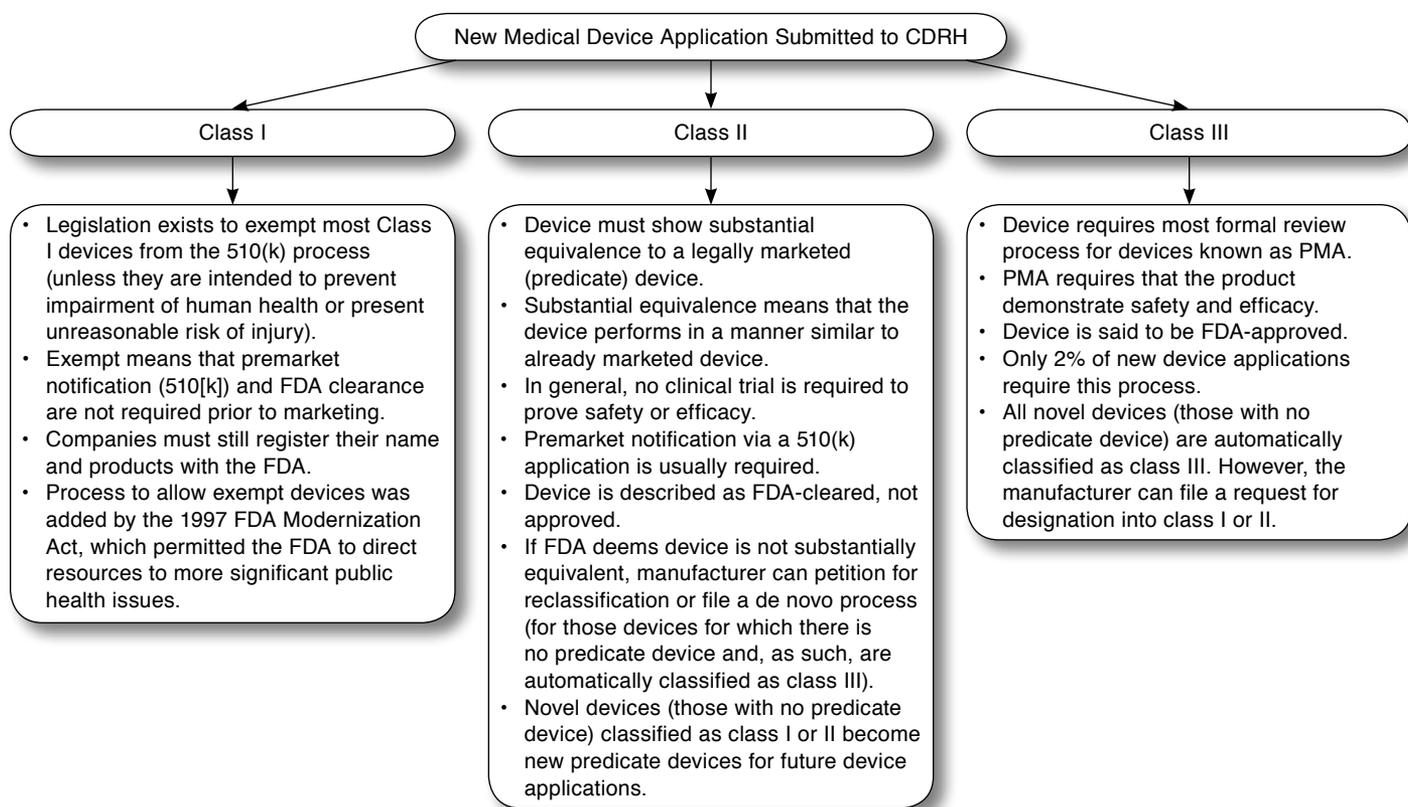
Since 1990, the FDA device evaluations have become more rigorous, requiring more information about the risks and benefits of new medical devices.<sup>16</sup> However, few new device evaluations use randomized controlled trials (RCTs). There are several reasons for the lack of RCTs, including federal regulations for devices; methodological difficulties for device evaluations (e.g., randomization, appropriate and ethical control groups, measurable outcomes in a reasonable time frame); and the sheer volume of device applications, which forces the FDA to prioritize its review specific to safety over efficacy.<sup>22,23</sup>

Because of the wide variety of devices that exist (e.g., latex gloves to coronary stents), the Medical Device Amendment of 1976 recognized that not all devices require the same level of regulation. According to this legislation, the FDA classifies all existing and future devices into 1 of 3 categories based on the level of risk posed to the patient, a classification that is well defined in the CFR<sup>24</sup> and that determines the level of FDA review a device receives prior to marketing.<sup>3,25</sup> Devices on the market prior to 1976 were classified and grandfathered in; they required no retrospective review for marketing to demonstrate safety or efficacy.<sup>25</sup> These pre-1976 devices became known as predicate devices, products that serve as a comparison for pre-market review of new devices brought to market.<sup>12,25,26</sup> Class I devices have the lowest level of risk and include products such as tongue depressors and band-aids. Class II devices pose more risk and include items such as forceps and surgical lasers. Class III devices are products that support or sustain life or prevent health impairment. They pose the highest risk for injury or illness to the patient and include products such as drug-eluting stents and pacemakers.<sup>12,25</sup>

All devices brought to market after 1976 must be reviewed by the FDA to determine the most appropriate approval process. There are essentially 2 pathways that a new device can follow to gain approval for marketing in the United States: Premarket Notification (known as the 510[k] submission) or the Premarket Application (PMA) (Figure 3).<sup>26-28</sup> Which process is followed is determined by the CDRH based on the classification of the device. As the risk of harm to the patient increases, so do the requirements for premarket review.<sup>8,12</sup>

All medical devices, regardless of classification, are subject to FDA regulations for adulteration and misbranding, and companies are required to register their information and products with the FDA.<sup>12,25</sup> The FDA is required by statute to exempt most class I and some class II devices from the formal premarket review processes (510[k]), thereby minimizing FDA premarket scrutiny.<sup>27</sup> Most class II and a few class III devices undergo a traditional 510(k), a process requiring that devices demonstrate substantial equivalence to a predicate device (either a pre-1976 device or a post-1976 device that has received FDA clearance). Substantial equivalence means that the new device performs in a similar manner and is at least as safe and effective as the predicate device, which was never required to prove safety and efficacy and may in fact not be safe or effective.<sup>29</sup> It does not mean that the new and predicate devices

**FIGURE 3** Overview of Medical Device Approval Process<sup>26-28</sup>



CDRH = Center for Devices and Radiological Health; FDA = U.S. Food and Drug Administration; PMA = premarket application.

are identical, differing from generic drugs where bioequivalence must be proven.<sup>9</sup> Most studies that support a 510(k) are not true clinical trials demonstrating safety and efficacy.<sup>22,23</sup> Medical devices reviewed through the 510(k) process are said to be FDA-cleared, not FDA-approved.<sup>12,26</sup> In September 2009, the FDA announced that the Institute of Medicine will study the 510(k) process to ensure it continues to meet the needs of the dramatically changing device industry.<sup>30</sup> This decision is particularly important because many of the predicate devices to which substantial equivalence must be shown were on the market prior to 1976 and demonstrating equivalence to a product more than 30 years old may no longer be sufficient.<sup>31</sup>

The PMA is the most rigorous device application and is required for most class III devices.<sup>32</sup> PMA is the device-evaluation process that is most similar to that required for drugs.<sup>12,13</sup> Like the NDA process for drugs, PMA requires demonstration of safety and efficacy, which are higher standards than substantial equivalence. Medical devices reviewed through a PMA are said to be FDA-approved. These products must provide sufficient scientific evidence to demonstrate the safety and efficacy of the device for its intended use. It is important to note, though, that

only 2% of devices are approved by the PMA process. Between 2003 and 2007, there were 13,199 submissions for class I and II devices via the 510(k) process, compared with only 217 original PMA submissions.<sup>31</sup> Similar numbers were reported in 2008, when there were 3,363 510(k) submissions and only 26 original PMA submissions.<sup>33</sup> New device applications that are not substantially equivalent to a predicate device automatically fall into class III.<sup>24</sup> The manufacturer must either submit a PMA or petition the FDA to reclassify the device into class I or II before the product can be commercially distributed.<sup>32</sup>

**Comparison of Drug and Device Approval Processes.** While there are differences between the drug and medical device approval processes, there are also some similarities. Manufacturers of drugs or medical devices can market products only for their intended use once approved or cleared by the FDA.<sup>12</sup> Both drugs and devices must comply with federal regulations for labeling, advertising, production, and postmarketing surveillance.<sup>8,12</sup> Both drugs and medical devices offer a means of providing products to patients for humanitarian use (Orphan Drug or Humanitarian Device Exemption processes, respectively). And, both have a process to allow for the

study of the product in humans (Investigational New Drug or Investigational Device Exemption, respectively).

However, there are also some key differences in the requirements for drugs and medical devices. While all drugs are required to demonstrate safety and efficacy in humans, only class III devices have this same requirement. Generic drugs are required to demonstrate bioequivalence to the predicate drug, a higher standard than the substantial equivalence required for 510(k)-cleared devices. And, while all manufacturers of drugs must undergo FDA inspections, manufacturers of medical devices are often not inspected.<sup>12,26,34</sup> Despite these differences, and the overall more rigorous review process required for drugs, the FDA review processes for both drugs and medical devices are perhaps the best in the world.<sup>3,7</sup>

**Combination Products.** Some products regulated by the FDA do not fit exclusively into the category of drug or device but are instead a combination of 2 or more single-entity products (e.g., drug, biological, and device). A wide variety of combination products exist, but they generally fall into one of a few categories: those that are physically, chemically, or otherwise combined and produced as a single entity (e.g., drug-eluting stents or a patch-containing drug such as Neupro); those that consist of individual products that are packaged together (e.g., surgical trays); and those that have products packaged separately but which must be used together to fulfill the indication for use (e.g., tositumomab and iodine-131 tositumomab [Bexxar; GlaxoSmithKline]).<sup>35,36</sup> With increasingly innovative diagnostic and therapeutic products becoming available and technology advancing drug delivery systems, the market of combination products continues to grow with 330 submissions reviewed in 2008 compared with 251 in 2004.<sup>37</sup>

The FDA formed the Office of Combination Products (OCP) in 2002 in response to requirements defined in the Medical Devices User Fee and Modernization Act.<sup>35</sup> The OCP is responsible for classifying each combination product as a drug, device, or biological based on the primary mode of action (PMOA) and then assigning the review of that product to the most appropriate center (CDER, CBER, or CDRH). The PMOA is defined as the single mode of action that provides the most important therapeutic action of the combination product.<sup>36</sup> For some products there may not be an obvious PMOA, or the combination product may have 2 distinct mechanisms of action. In these situations, the OCP uses an algorithm to assist in the determination of the PMOA. If no center has experience regulating similar products, the OCP determines the regulatory center that has experience in evaluating the most important safety and efficacy issues that may surround the product.<sup>36</sup>

Once a product's PMOA has been determined by the OCP, it can be assigned to the primary regulatory center. If manufacturers disagree with the determination of the PMOA, they can appeal for reconsideration and reclassification by submitting a formal determination for primary jurisdiction known as a Request for Designation.<sup>38</sup> A combination product is held to the usual and customary premarket approval and regulatory

processes of a single-entity product regulated under that same center.<sup>35</sup> Postmarketing safety reporting and GMP requirements have been less clearly defined for combination products than for single-entity products. In 2009, the FDA issued proposed rules to (a) codify the current GMP requirements applicable to combination products and (b) clarify the postmarketing safety reporting requirements that apply to combination products.<sup>39,40</sup>

### **Classification of Products— Not as Obvious as You Might Think**

Although classification as drug or medical device can be very clear for some products, for others it is not so obvious. Some products that may intuitively be considered a drug may, in fact, actually be classified as a device, and vice versa. It is important to remember that the classification of a product is determined by its mechanism of action, or PMOA for combination products.

After the formation of the OCP, a retrospective review of existing combination products was conducted to determine which center should assume primary responsibility for review and regulation. One of the more notable decisions that resulted from this review was the reclassification of heparin flushes from drug to device in October 2006.<sup>41</sup> In the announcement of transfer, the FDA stated that heparin flushes exert their PMOA by physically occupying space and applying pressure within the catheter, similar to the mechanism of saline flushes.<sup>42</sup> The mechanism of heparin preventing thrombotic occlusions was determined to be a secondary function of the product.<sup>41</sup> Both saline and heparin flushes are now classified as class II devices requiring 510(k) clearance for marketing.<sup>41-43</sup> This change surprised many health care providers because heparin is considered a high-alert medication.<sup>44</sup> Although used to restore rather than maintain catheter patency, alteplase (Cathflo, Activase [LyticExperience; Genentech]) syringes are administered in a manner similar to heparin or saline flush solutions. However, alteplase syringes work to restore the function to venous access devices by chemically initiating local fibrinolysis of a thrombus in an occluded catheter.<sup>45</sup> As such, alteplase syringes are regulated as a drug (biological product) under CDER.<sup>46</sup> Because all 3 products are used in a similar manner for similar purposes (maintain or restore patency of venous catheters), many health care providers may intuitively consider them to be drugs. They may not be aware that, as class II devices, saline and heparin flush solutions only had to demonstrate substantial equivalence to a device already on the market to obtain FDA clearance.<sup>26</sup>

The previous example outlined a situation in which a product that may be thought of as a drug (e.g., heparin flush) is regulated as a device. The opposite can also be true. There are currently 2 IUDs on the U.S. market, T 380A intrauterine copper contraceptive (ParaGard [Duramed Pharmaceuticals]) and levonorgestrel-releasing intrauterine system (Mirena [Bayer]). Although both are combination products, they were approved by the FDA as drugs, requiring an NDA for marketing; both

were approved prior to the formation of the OCP in 2002. ParaGard is a copper IUD consisting of a T-frame made of polyethylene and barium sulfate (device component) and a copper wire (drug component). While the exact mechanism of action is not fully understood, it is believed that copper interferes with sperm transport and fertilization and, therefore, prevents egg implantation.<sup>47</sup> Mirena is a levonorgestrel-releasing intrauterine system that also consists of a T-shaped polyethylene frame with the levonorgestrel reservoir around a vertical stem. It is thought to act by causing a thickening of the cervical mucosa, inhibiting sperm survival, and altering the endometrial environment.<sup>48</sup> In both cases, the device component causes changes in the lining of the uterus and fallopian tubes that affect movement of sperm so that fertilization does not occur. Although their names may be misleading, IUDs are combination products that are classified and regulated by the FDA as drugs.

As noted earlier, the classification of a product as a drug or device is determined by its mechanism of action, with drugs achieving their primary intended purpose through chemical or metabolic action in the body. Topical creams used to treat minor dermatologic conditions are commonly thought to be drugs. However, some topical creams are considered to be barriers and are classified as devices because they impart no chemical or metabolic action and have no active ingredients.<sup>3</sup> Tropazone CR (Midlothian Laboratories) is one example of a prescription-only cream used for the management of superficial wounds and first- and second-degree burns.<sup>49</sup> This emulsion contains moisturizers that work to keep the area moist and was approved through the 510(k) process, showing technological comparisons to 4 predicate devices. Clinical testing involved only insult patch testing in 50 human subjects, showing it to be a nonprimary irritant or skin sensitizer. No efficacy studies showing benefit to the healing process were reported in the 510(k) application.

Sometimes products with very similar indications for use may be classified and, therefore, regulated differently. Osteoarthritis is a common medical condition that is often managed using intra-articular injections of corticosteroids (e.g., triamcinolone hexacetonide) or tissue stabilizers (e.g., hyaluronan). Both of these products are indicated for the treatment of pain associated with osteoarthritis.<sup>50,51</sup> Corticosteroids are regulated as drugs because they impart their action by reducing inflammation. Hyaluronan (Synvisc [Genzyme]), however, is regulated as a class III device because it works as a tissue stabilizer and elastoviscous shock absorber, thereby imparting its action through nonchemical means.<sup>52</sup>

Formulation of a product may also affect its classification as drug or device. Oral sucralfate (Carafate) acts chemically with hydrochloric acid in a patient's stomach to form a barrier paste inside the body, thereby creating a protective barrier at ulcer sites.<sup>53</sup> The FDA classifies oral sucralfate as a drug because it acts chemically within the body to perform its action. In contrast, sucralfate topical paste (Carapaste [McGrath Pharmaceuticals]) is mixed with hydrochloric acid prior to

use, forming a paste that is then applied to oral lesions. The resulting product acts physically as a protective barrier and is classified as a device.<sup>54</sup>

As illustrated with these few examples and in others shown in Table 1,<sup>42,43,45-48,50-66</sup> the classification of a product as drug or device is not always intuitively obvious to the practicing clinician.

### Discussion

The classification of a product as a drug or medical device can have an impact on clinicians and payers. Some of these practical considerations are described below.

### Clinical Considerations

As discussed earlier, all drugs must prove safety and efficacy prior to marketing, although they are not required to prove benefit over existing therapies. A similar requirement exists for most class III devices that undergo the PMA process. However, most devices enter the market through the less rigorous 510(k) process where they, at most, need only to show equivalence to a predicate device, indicating that the device does what it is intended to do and is reasonably safe. Demonstration of efficacy is not required for approval.<sup>16</sup> It is important that clinicians are aware of these differences in premarketing scrutiny and take them into consideration when selecting treatment for a patient.<sup>67</sup> Incorporation of medical devices into routine clinical practice without adequate safety and efficacy data can mean that products are used that have little benefit over existing alternatives or, worse, that they offer no benefit at all. For example, in the late 1990s the FDA continued to receive 510(k) applications for intermittent positive pressure breathing devices even after the Agency for Health Care Policy and Research determined that they offered no benefit to patients.<sup>23,68</sup>

The level of premarket scrutiny is relevant not only to the level of clinical evidence available, but also to standards for quality of the product. Medical devices cleared through the 510(k) process are required to submit notification to the FDA of their intent to market a new device at least 90 days prior to marketing. The 510(k) process does not require FDA inspection of the manufacturing plant prior to marketing, although the manufacturer must be prepared for a quality inspection at any time after clearance.<sup>26</sup> This process has resulted in adverse patient consequences such as when marketed heparin flush solutions were found to be contaminated with *Serratia marcescens*, causing infections in more than 40 patients.<sup>34,69</sup> The affected heparin flush solution was brought to market legally as a class II device by demonstrating substantial equivalence to a predicate device, but the quality standards of the manufacturing facility were not adequate. Notably, when the FDA shifted all heparin flush solutions from CDER to CDRH in 2006, it recognized the potential for serious patient consequences if a suboptimal product came to market and, as such, required a premarket plant inspection prior to FDA clearance of this product.<sup>41</sup>

## Review of the Processes for FDA Oversight of Drugs, Medical Devices, and Combination Products

**TABLE 1** Examples of Various Product Classifications by the U.S. Food and Drug Administration

Category	Product	Indication for Use	Mechanism of Action	FDA Classification [Rx Status]	Review Requirement/References
<b>Products with Similar Indications</b>					
Catheter patency	Saline flush	Enhance the performance and maintain patency of indwelling catheters Flush of IV catheters and IV tubing before and after administration of intermittent medications	Physically occupies space within the catheter and exerts pressure on the patient's circulating blood, thereby preventing blood from back filling into the catheter and clotting	Device (Class II) [Prescription]	510(k) <sup>42</sup>
	Heparin flush	Enhance the performance and maintain patency of indwelling catheters	Device: Physically occupies space within the catheter and exerts pressure on the patient's circulating blood (PMOA) Drug: Heparin acts chemically to prevent thrombotic occlusions within the catheter	Device (Class II) [Prescription] Combination product <sup>a</sup>	510(k) <sup>43</sup>
	Alteplase (Activase CathFlo)	Restore function to venous access devices that have become occluded	Acts chemically to initiate local fibrinolysis of a thrombus within the catheter, thereby restoring catheter function	Drug [Prescription]	NDA <sup>45,46</sup>
Osteoarthritis	Hyaluronan (e.g., Synvisc)	Treatment of pain associated with osteoarthritis of the knee	Tissue stabilizer and elastoviscous shock absorber that is injected into the affected joint	Device (Class III) [Prescription]	PMA <sup>50,52</sup>
	Triamcinolone hexacetonide (Aristospan)	Treatment of pain associated with osteoarthritis	Corticosteroid that is injected into the affected joint, which reduces inflammation through limiting capillary dilation and permeability of vasculature	Drug [Prescription]	NDA <sup>51</sup>
Topical analgesic or antipruritic	Tetrix topical cream	To relieve itching and burning associated with various dermatoses including atopic dermatitis and contact dermatitis	Maintains a moist wound and skin environment, which is beneficial to the healing process	Device (Class I) [Prescription]	510(k) <sup>55</sup>
	Epiceram skin barrier emulsion	To improve dry skin and relieve burning and itching associated with various dermatoses including atopic and contact dermatitis	Maintains a moist wound and skin environment	Device (Class I) [Prescription]	510(k) <sup>56</sup>
	Benadryl topical cream	To relieve pain and itching associated with insect bites, minor burns, and contact dermatitis	Blocks the action of histamine and provides topical analgesia	Drug [OTC]	OTC monograph <sup>57,58</sup>
Topical anesthetic or analgesic	Ethyl chloride spray	Topical anesthetic and vapocoolant (skin refrigerant)	Provides numbness by freezing the skin	Device (Class I) [Prescription]	510(k) <sup>59</sup>
	Benzocaine	Fast-acting topical anesthetic spray	Local anesthetic that numbs the skin	Drug [OTC]	OTC monograph <sup>58</sup>
Wrinkles	Hyaluronic acid (Restylane)	Dermal filler	Injected into the skin to temporarily restore volume to fill moderate to severe wrinkles.	Device (Class III) [Prescription]	PMA <sup>60</sup>
	Onabotulinum toxin A (Botox)	For temporary improvement in the appearance of moderate to severe lines associated with aging	Blocks neuromuscular transmission by inhibiting release of acetylcholine, which causes denervation of the muscle	Drug [Prescription]	NDA <sup>61</sup>
Electrolyte solutions for dialysis	Normocarb sterile bicarbonate renal dialysis concentrate	Dialysate for use in hemodialysis	Physically applies pressure inside the filter to help push toxins and excess water in the blood through the dialysis filter	Device (Class II) [Prescription]	510(k) <sup>62</sup>
	Normocarb HF	Prefilter hemofiltration solution for CRRT	Electrolyte, fluid replacement and pH balancing during CRRT	Drug [Prescription]	NDA <sup>63,64</sup>
Sucralfate	Carapaste topical	Barrier used to relieve pain of oral wounds and protect against further irritation	Product is mixed with hydrochloric acid prior to use and is then applied to oral lesions; physically adheres to and forms a protective layer over the oral mucosa	Device (Class I) [Prescription]	510(k) <sup>54</sup>
	Carafate oral tablets	Barrier used for healing of duodenal ulcers and protection against further irritation	Reacts with hydrochloric acid in the stomach to form a paste-like substance that adheres to proteins on the surface of ulcers	Drug [Prescription]	NDA <sup>53</sup>
<b>Miscellaneous Products</b>					
Intrauterine devices	Mirena ParaGard	Intrauterine contraception	Device: causes changes in the lining of the uterus and fallopian tubes that affects movement of sperm so that fertilization does not occur Drug: Thickens cervical mucus, inhibits sperm survival and alters endometrium, thereby affecting fertilization	Drug [Prescription] Combination product <sup>a</sup>	NDA <sup>47,48</sup>
Viscoelastic device, ophthalmic	Sodium hyaluronate (Healon Ophthalmic)	A nongaseous fluid injected into the eye to aid performance of surgery	Physically occupies space in the eye during surgery; maintains anterior chamber depth, preserves tissue integrity, protects tissue from surgical trauma	Device (Class III) [Prescription]	PMA <sup>65</sup>
Tissue glue	Indermil tissue adhesive	Closure of topical skin incisions in areas of low skin tension	Cyanoacrylate-based synthetic tissue adhesive that closes wounds painlessly in seconds	Device (Class III) [Prescription]	PMA <sup>66</sup>

<sup>a</sup>Denotes a product that does not fit exclusively into the category of drug or device but is instead a combination of 2 or more of these single-entity products (e.g., drug, biological, and device). CRRT = continuous renal replacement therapy; FDA = U.S. Food and Drug Administration; IV = intravenous; NDA = New Drug Approval; OTC = over-the-counter; PMA = Premarket Approval; PMOA = primary mode of action; Rx = prescription.

### Payer Considerations

Centers for Medicare and Medicaid Services (CMS) projected prescription drug expenditures for 2010 are \$260.1 billion, or 10.1% of all national health care expenditures.<sup>70</sup> From a payer's perspective, dollars are best spent on evidence-based, value-added prescription products given the limited funding resources available to support health care. Although both drugs and devices must be approved or cleared through the FDA, such review does not guarantee coverage by government or third-party payers. For example, when heparin flushes were reclassified as devices, notices were distributed to Medicaid medical directors informing them of future noncoverage of these products under the pharmacy benefit since they were no longer classified as drugs. Heparin flushes are also not covered under Medicare Part D because they are not prescription drugs.<sup>71</sup>

Prescription drug claims payable by third parties (e.g., employers, union groups, Medicaid, and Medicare) are typically processed at point-of-sale through a pharmacy benefit management (PBM) company or claims processor. Rules of coverage are established within the claims processing system to determine drug coverage status, copayments, coinsurance, quantity limits, and any number of plan coverage parameters. Prescription claims processed by a PBM on behalf of a third-party payer will cascade through a set of plan coverage and payment rules. Coverage rules are typically established at the highest possible level of product classification, on an exclusion basis, with continued greater specificity as required to obtain the third-party payer's coverage intent. For example, the rules may be set to exclude all over-the-counter (OTC) products with the exception of such products as OTC insulin and syringes. Because the highest level of exclusion is typically the prescription/OTC status of a product, all prescription devices will automatically be covered unless excluded by lower-level rules. Unfortunately, the current system is not well equipped to exclude prescription devices or to provide a trigger to the managed care pharmacist prompting the need to review a new product.

There are primarily 2 companies that market product files to pharmacy claims processors: First DataBank (First DataBank, Inc., San Francisco, CA) and Medi-Span (Wolters Kluwer Health, Indianapolis, IN). Until 2008, neither company's product file contained an indicator denoting the FDA review or approval path taken for a given product. In 2008, First DataBank added an indicator noting if a drug product was approved by an NDA or an ANDA and will be adding biologics license application (BLA) information in late 2010. The Medi-Span product file currently contains NDA, ANDA, and BLA information. Neither company has a notation for products reviewed as medical devices. The absence of an FDA drug approval indicator is the only prompt that the managed care pharmacist has to suggest that the product may be regulated as a medical device, and the pharmacists see these items

only if they review each line item added to these databases on a regular basis.

Because an efficient method to determine the review or approval path for a given product is not currently available, prescription devices often gain unintended prescription plan coverage simply because they were coded as prescription products. Depending on the device manufacturer's marketing efforts, these products can prove to be costly to individual prescription drug plans. For example, several emollient products were approved through the device process: Tropazone CR, Biafine (Ortho Dermatologics), and Zenieva (Gorbec Pharmaceutical Services, Inc).<sup>49</sup> There are no active ingredients in these products, all of which were approved as prescription devices through the 510(k) process, with each claiming substantial equivalence to the others. As stated earlier, there were no clinical trials reported in the 510(k) application for Tropazone CR showing improved wound healing. Yet, all of these products require a prescription, and their costs are not insignificant: average prices range from \$54 per 90 grams (Biafine) to \$122 per 140 grams (Tropazone) from drugstore.com.<sup>72</sup> These costs are considerably higher than those of many of the OTC alternatives. Unless a health plan specifically coded these products for noncoverage, their claims would be paid.

This example illustrates how understanding the differences between drugs and medical devices and being aware of the current limitations of the drug product files available to process claims can assist payers in making informed prescription drug coverage decisions. Many pharmacy benefit plans have rules that exclude coverage of prescription devices. However, it is difficult for plans to manage this coverage exclusion given the limited functionality of the current information systems to provide the needed information in a user-friendly manner. Further improvements in the information sources available to plans to include the FDA review designation of devices coupled with a thorough understanding by plan managers of the differences in the drug and device review processes (i.e., the typical lack of RCTs demonstrating clinical outcomes for many devices) will help plans provide a sustainable, quality prescription drug benefit.

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DISCLOSURES

The authors report no financial relationships or other potential conflicts of interest related to this review. Sweet designed the study with the assistance of Schwemm. Sweet and Schwemm collected and interpreted the data and wrote the manuscript. Sweet revised the manuscript with the assistance of Schwemm and Parsons.

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