



January 28, 2019

Medical Product Regulation: Drugs, Biologics, and Devices

The Food and Drug Administration (FDA) regulates the safety and effectiveness of drugs, biologics, and devices (“medical products”) pursuant to its authorities under the Federal Food, Drug and Cosmetic Act (FFDCA) and the Public Health Service Act (PHSA). Drugs and devices are approved or cleared under the FFDCA, whereas biologics are licensed under the PHSA. Small molecule or chemical drugs are chemically synthesized, while biologics are derived from living organisms. All FDA-regulated medical products conceptually meet the definition of “drug.” Biologics are a subset of drugs, subject to many of the same regulatory requirements. A device—an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article—also meets the definition of “drug”; however, unlike a drug or biologic, it “does not achieve its primary intended purposes through chemical action within or on the body ... and is not dependent upon being metabolized for the achievement of its primary intended purposes” (FFDCA Section 201(h)). FDA’s Center for Biologics Evaluation and Research (CBER) oversees certain biologics (e.g., vaccines and gene therapies); the Center for Drug Evaluation and Research (CDER) oversees chemical drugs and therapeutic biologics; and the Center for Devices and Radiological Health (CDRH) oversees medical devices and radiologic products.

This In Focus broadly summarizes selected differences in statutory requirements among drugs, biologics, and devices. It does not address every difference and is not meant to be a comprehensive analysis of requirements.

Premarket Requirements

Under most circumstances, drugs, devices, and biologics may be marketed only if they have been approved, cleared, or licensed by FDA.

Prescription Drugs and Biologics

To market a new prescription drug, the sponsor (generally the manufacturer) must submit a new drug application (NDA) demonstrating that the drug is safe and effective for its proposed use. The law requires, among other things, *substantial evidence* of effectiveness, and the agency has some discretion to determine what evidence is necessary for NDA approval. During review, FDA officials evaluate the drug’s safety and effectiveness for the intended use (derived from clinical trials); adequacy of manufacturing methods to ensure the drug’s identity, strength, quality, and purity; and accuracy of the proposed labeling. Sponsors must comply with current good manufacturing practice (CGMP) regulations, which provide minimum requirements for the methods, facilities, and controls used in manufacturing a drug. For drugs with certain safety risks, FDA may require a risk evaluation and mitigation strategy (REMS) upon the

submission of an NDA, which may include restrictions on distribution or use of the drug.

While prescription drugs are *approved* via an NDA under Section 505 of the FFDCA, biologics are *licensed* via a biologics license application (BLA) under Section 351 of the PHSA. The exception to this is certain natural source biologics regulated as drugs under the FFDCA (e.g., insulin). However, this will no longer be the case in March 2020, when applications for biologics approved under the FFDCA will be deemed to be licenses under the PHSA. To obtain licensure, the sponsor must demonstrate in the BLA that the biologic and the facilities and processes for manufacturing the product are safe, pure, and potent. The requirements and review pathway for BLAs are generally similar to that for NDAs, and biologics are subject to certain FFDCA provisions (e.g., REMS).

Medical Devices

Medical devices are classified based on the risk posed to the consumer. Class I devices are low-risk (e.g., elastic bandages) and are generally exempt from premarket review. Class II and Class III devices are moderate-risk (e.g., powered wheelchairs) and high-risk (e.g., heart valves), respectively, and usually require premarket review. Unless specifically excluded by regulation, all devices must meet *general controls*, which include premarket and postmarket requirements; for example, registration, labeling, and compliance with CGMPs as set forth in FDA’s quality system regulations (QSRs). As QSRs apply to many different devices, the regulations are broad and flexible.

In addition to general controls, Class II devices must meet *special controls*, which are usually device-specific. Premarket special controls include performance standards and data requirements. Generally, Class II devices require 510(k) *clearance* demonstrating that a device is *substantially equivalent* to a device already on the market (i.e., a predicate device). A 510(k) application typically does not require submission of clinical data. Approximately 82% of total devices authorized for marketing in 2017 were cleared through the 510(k) clearance pathway. In November 2018, FDA announced changes to modernize the 510(k) *clearance* pathway, including sunseting certain older predicate devices. However, the agency may need additional guidance from Congress before proceeding.

Generally, Class III devices require a premarket approval application (PMA), with some exceptions. FDA issues an *approval order* when a PMA demonstrates *reasonable assurance* that a device is safe and effective for its intended use(s). Effectiveness must be based on well-controlled investigations, which generally means clinical trial data. However, the law provides that other evidence, when

appropriate, may be used to establish effectiveness (e.g., well-designed bench and/or animal testing) (see FFDCa §513(a)(3)(B) and “The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles; Final Guidance for FDA and Industry”).

Regardless of risk, a new device with no substantially equivalent predicate device is automatically designated Class III unless the manufacturer submits a reclassification request or petition. The de novo pathway allows for certain lower-risk, novel devices to be reclassified from a Class III designation to a Class I or II designation.

Figure 1. Select Premarket Requirements

	Prescription Drug	Biologic	Medical Device
Authorization	Approval	Licensure	Clearance or approval
Submission	NDA	BLA	<ul style="list-style-type: none"> • 510(k)—clearance • PMA—approval
Clinical trial	Yes	Yes	<ul style="list-style-type: none"> • 510(k)—no • PMA—yes, with some exceptions
Standard of evidence	Substantial evidence of effectiveness and adequate tests of safety	Safe, pure, and potent	<ul style="list-style-type: none"> • 510(k)—substantial equivalence • PMA—reasonable assurance that the device is safe and effective for its intended use(s)
Compliance with CGMPs	Yes	Yes	Yes (QSRs)

Source: FFDCa, PHSA, and regulations at 21 C.F.R. Title 21.

Postmarket Requirements

Medical products are subject to various mandatory and voluntary requirements once they are on the market.

Prescription Drugs and Biologics

Manufacturers must report all serious and unexpected adverse events to FDA within 15 days of becoming aware of them. Clinicians and patients may report adverse events to the agency at any time. Once a drug is on the market, FDA can require the manufacturer to conduct additional studies or clinical trials based on newly acquired information, and can require labeling changes based on information it gathers from mandatory and voluntary adverse event reports (FFDCa §505(o)). FDA may require a REMS after initial approval or licensing, if it becomes aware of certain new information and determines the REMS is necessary to ensure that the drug’s benefits outweigh the risks. FDA conducts surveillance inspections once a drug is on the market to assess compliance with manufacturing standards, as well as for-cause inspections to investigate concerns about product quality. The agency also monitors product integrity as the drug moves through the supply chain. FDA has mandatory recall authority over biologics, but generally not over drugs. However, FFDCa §569D, as added by the SUPPORT for Patients and Communities Act (P.L. 115-271), provides for the recall of a controlled substance that would cause serious adverse health consequences or death.

Medical Devices

Manufacturers must report device-related deaths, serious injuries, and malfunctions within 30 days of becoming aware of them and must submit a report to FDA within five

work days of becoming aware of an event that requires remedial action or a reportable event for which FDA made a written request. There are additional reporting requirements for importers and user facilities (e.g., hospitals). As with drugs and biologics, clinicians and patients may report adverse events to the agency any time.

Postmarket special controls for Class II devices include surveillance and patient registries. For Class III devices, FDA may impose additional postapproval controls in a PMA approval order or by regulation subsequent to approval. These controls may overlap with special controls for Class II devices but are generally more stringent and may include restriction of the sale, distribution or use of the device, and annual postapproval reports, among others.

FDA can indirectly require a device labeling change by (1) temporarily suspending a PMA approval order if, among other things, the labeling is false or misleading (FFDCa §515(e)), or (2) banning the device if it presents substantial deception in the labeling, as specified (FFDCa §516(a)). This is in contrast to the authority for drugs, which directly allows FDA to require a labeling change without affecting the drug’s approval status. FDA has mandatory recall authority over medical devices (FFDCa §518(e)(1)).

Figure 2. Select Postmarket Requirements

	Prescription Drug	Biologic	Medical Device
Adverse event reporting	Yes	Yes	Yes
FDA-mandated product recall	No (except for controlled substances)	Yes	Yes
FDA-mandated labeling changes	Yes	Yes	Yes
FDA-mandated studies or clinical trials	Yes	Yes	Yes

Source: FFDCa, PHSA, and regulations at 21 C.F.R. Title 21.

Product Classification Challenges

Generally, a product that meets the statutory definition of a drug or biologic and is assigned to CDER or CBER will have a higher standard of evidence, a potentially higher requirement for supporting data, and a higher user fee than a device assigned to CDRH. However, a product that is classified as a drug and assigned to CDER or CBER may be eligible for certain benefits that would not be available for a product assigned to CDRH, such as data or market protection in the form of regulatory exclusivity. At times, there has been disagreement between FDA and product sponsors regarding the jurisdictional determinations of certain drugs and devices and drug-device combination products. In addition, as new scientific evidence becomes available, FDA may reconsider previous determinations. For example, in December 2018, the agency announced its intent to consider appropriate classification of certain hyaluronic acid (HA) intra-articular products that have been regulated as Class III devices and marketed under a PMA. Recent scientific evidence suggests that HA achieves its primary intended purpose through chemical action within the body, which may not meet the definition of a device.

Agata Dabrowska, Analyst in Health Policy

Victoria R. Green, Analyst in Health Policy

Disclaimer

This document was prepared by the Congressional Research Service (CRS). CRS serves as nonpartisan shared staff to congressional committees and Members of Congress. It operates solely at the behest of and under the direction of Congress. Information in a CRS Report should not be relied upon for purposes other than public understanding of information that has been provided by CRS to Members of Congress in connection with CRS's institutional role. CRS Reports, as a work of the United States Government, are not subject to copyright protection in the United States. Any CRS Report may be reproduced and distributed in its entirety without permission from CRS. However, as a CRS Report may include copyrighted images or material from a third party, you may need to obtain the permission of the copyright holder if you wish to copy or otherwise use copyrighted material.