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IN FOCUS

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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 §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 other biologics (e.g., certain monoclonal antibodies and immunomodulators); 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 drug, the sponsor (generally the manufacturer) must submit to FDA for review a new drug application (NDA) demonstrating that the drug is safe and effective for its proposed use. FDA has some discretion when determining what evidence is necessary for NDA approval. During review, FDA officials evaluate the drug's safety and effectiveness (derived from clinical trials) for its intended use; adequacy of manufacturing methods to ensure the drug's identity, strength, quality, and purity; and accuracy of the proposed labeling. Sponsors for both drug and biologic products must comply with current good manufacturing practice (CGMP) regulations, which provide minimum requirements for the methods, facilities, and controls used in manufacturing.

While 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. To obtain licensure, the sponsor must demonstrate in the BLA that the facilities and processes for biologics manufacturing meet standards ensuring the product is safe, pure, and potent (i.e., effective). The requirements and review pathway for BLAs are generally similar to those for NDAs, and biologics are subject to certain FFDCA provisions.

For prescription drugs and biologics 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 or biologic.

Medical Devices

Medical devices are regulated based on the risk posed to the consumer: Class I devices are low-risk, Class II devices are moderate-risk, and Class III devices are high-risk. Unless specifically excluded by regulation, all devices must meet *general controls*, which include both premarket and postmarket requirements. General controls include, for example, 510(k) premarket notification, registration, listing, and compliance with CGMPs as set forth in FDA's quality system regulation (QSR). Class II devices must meet, in addition to general controls, *special controls*, which are usually device-specific. Premarket special controls include performance standards and premarket data requirements. Almost all Class I devices are exempt from the 510(k) premarket notification requirement, whereas almost all Class II devices require 510(k) clearance prior to marketing. A 510(k) submission must demonstrate that a device is *substantially equivalent* to a legally marketed predicate device, which typically does not require submission of clinical data, although it may in certain cases. In November 2018, FDA announced proposed changes to modernize the 510(k) clearance pathway, including the preferential use of modern predicate devices and development of updated pathways.

Class III devices are subject to premarket approval application (PMA) requirements, with some exceptions, in addition to general controls. FDA issues an *approval* order when a PMA demonstrates *reasonable assurance* that a device is safe and effective for its intended use(s). Safety and effectiveness must be based on valid scientific evidence, which is generally derived from well-controlled investigations, usually clinical trials. However, the law provides that other evidence, when appropriate, may be used to establish effectiveness (e.g., well-designed bench and/or animal testing) (FFDCA §513(a)(3)(B) and "The Least Burdensome Provisions: Concept and Principles"). 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 Class III to Class I or II; devices reviewed through this pathway successfully are *authorized for marketing*, create a new device type, and may serve as a predicate going forward.

Figure 1. Select Premarket Requirements

	Drug	Biologic	Device
Authorization	Approval	Licensure	Clearance or approval
Submission	NDA	BLA	• 510(k)—clearance • PMA—approval
Clinical trial	Yes	Yes	• 510(k)—no • PMA—yes, with some exceptions
Standard of evidence	Substantial evidence of effectiveness and adequate tests of safety	Safe, pure, and potent (i.e., effective, same standard as for drugs)	• 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 various types of inspections, including 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. FDA also monitors product integrity as a drug moves through the supply chain. FDA has mandatory recall authority over biologics, but generally not drugs. However, FFDCA Section 569D, added by 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 (1) an event that requires remedial action, or (2) a reportable event for which FDA made a written request. There are additional reporting requirements for importers and user facilities (e.g., hospitals). Clinicians and patients may report adverse events to the agency at any time. Postmarket special controls for Class II devices include postmarket surveillance (e.g., mandated studies) 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 postapproval studies; restriction of the sale, distribution or use of the device; and postapproval reports. FDA can indirectly require a device labeling change by (1) temporarily suspending a PMA approval order if, among other reasons, the labeling is false or misleading (FFDCA §515(e)), or (2) banning a device if it presents substantial deception in the labeling (FFDCA §516(a)). FDA has mandatory recall authority over medical devices (FFDCA §518(e)), although this authority is rarely used.

Figure 2. Select Postmarket Requirements

	Drug	Biologic	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 necessitate a higher standard of evidence, user fee, and requirement for supporting data than will 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 for certain drugs and devices and drug-device combination products. For example, in 2019, Genus Medical Technologies sued FDA for its decision to classify barium sulfate contrast imaging agents as drugs rather than devices. This was ultimately settled legislatively, as Section 3621 of the Consolidated Appropriations Act, 2023 (P.L. 117-328), deemed any contrast agent, among other substances, to be a drug under the FFDCA. Additionally, as new scientific evidence becomes available, FDA may reconsider *previous* determinations. For example, in December 2018, the agency announced its intent to reconsider classification of certain hyaluronic acid (HA) intra-articular products that have been regulated as Class III devices (83 *Federal Register* 64844). New evidence suggests that HA achieves its primary intended purpose through chemical action within the body, which may not meet the definition of a device.

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