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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 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 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 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 biologic and the facilities and processes for manufacturing the product are safe, pure, and potent (i.e., effective). 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 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, and listing and compliance with CGMPs as set forth in FDA's quality system regulations (QSRs). Almost all Class I devices are exempt from the 510(k) premarket notification requirement. In addition to general controls, Class II devices must meet *special controls*, which are usually device-specific. Premarket special controls include performance standards and premarket data requirements. Almost all Class II devices require 510(k) *clearance*, demonstrating that a device is *substantially equivalent* to a predicate device, prior to marketing. A 510(k) application typically does not require submission of clinical data. In November 2018, FDA announced changes to modernize the 510(k) *clearance* pathway, including sunsetting certain older predicate devices.

Class III devices are subject to premarket approval application (PMA) requirements, with some exceptions, in addition to having to meet 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). 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) (FFDCA §513(a)(3)(B) and "The Least Burdensome Provisions of the FDA Modernization Act of 1997"). 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*.

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 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 §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 things, 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)). (This is in contrast to the authority for drugs, which 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

	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 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. For example, in 2019, Genus Medical Technologies sued FDA for its decision to classify barium sulfate contrast imaging agents as drugs rather than devices. In August 2021, FDA announced that following a decision in that case, the agency could be requiring some approved products to transition from drug to device status (86 FR 43553). In addition, FDA notes that the agency intends to regulate products that meet *both* the device and drug definition as devices, except where statute indicates that Congress intended a different classification. 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 and marketed under a PMA (83 FR 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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