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FDA's Role in the Medical Product Supply Chain and Considerations During COVID-19

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SUMMARY

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FDA's Role in the Medical Product Supply Chain and Considerations During COVID-19

The Coronavirus Disease 2019 (COVID-19) pandemic has affected the medical product supply chain globally and domestically. Although concerns about the U.S. medical product supply chain predate the emergence of COVID-19, the ongoing pandemic has underscored the importance of understanding the supply chain—in particular, U.S. reliance on foreign sources of medical products and the federal government's ability to oversee the supply chain and mitigate future disruptions.

The Food and Drug Administration (FDA), within the Department of Health and Human Services (HHS), is the federal agency responsible for ensuring the safety and effectiveness of medical products—drugs and medical devices—marketed in the United States. The FDA therefore plays a critical role in overseeing aspects of the U.S. medical product supply chain. Drug and medical device ("device") manufacturers are subject to FDA-mandated reporting requirements related to the supply chain. For example, establishments that manufacture drugs and devices are required to register with FDA and must report various manufacturing-related information to the agency. These requirements apply to both domestic and foreign establishments that import drugs and devices into the United States. However, concerns have been raised that certain manufacturers, such as those producing medical products or components that are not imported directly into the United States, may not be registered with FDA. This potential blind spot may limit the agency's ability to oversee the medical product supply chain and monitor the entities manufacturing such products for the U.S. market.

In response to concerns about FDA regulation of drugs and devices in the global supply chain, Congress has introduced and passed legislation to help regulators, stakeholders, and the public better understand the medical product supply chain both during and beyond public health emergencies. The recently enacted Coronavirus Aid, Relief, and Economic Security Act (CARES Act; P.L. 116-136), for example, expanded drug listing and reporting requirements to help quantify for regulators the volume of finished drug products and active pharmaceutical ingredients (APIs) manufactured domestically and abroad for the U.S. market. The CARES Act also provided FDA the explicit authority to require certain device manufacturers to report interruptions or discontinuances in manufacturing during public health emergencies. More broadly, the CARES Act requires the National Academies of Science, Engineering, and Medicine (NASEM) to examine and report on the security of the U.S. medical product supply chain, including U.S. dependence on critical drugs and devices from other countries.

However, some stakeholders and Members of Congress contend that issues remain regarding the medical product supply chain in the context of FDA's existing authority. These issues include

- gaps or loopholes in reporting requirements to FDA, which may limit the agency's ability to oversee the medical product supply chain;
- limitations in currently available supply chain data, which make it challenging to determine the extent of U.S. reliance on foreign medical product manufacturers; and
- a lack of transparency in the medical product supply chain, which may contribute to product shortages and pose a risk to national security.

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Background

The Coronavirus Disease 2019 (COVID-19) pandemic has affected the medical product supply chain globally and domestically. Although certain concerns about the U.S. medical product supply chain predate the emergence of COVID-19, the ongoing pandemic has made addressing those concerns and understanding the supply chain a more urgent priority. Of particular concern for some are the United States' reliance on foreign sources of medical products and the federal government's ability to oversee the supply chain and mitigate future disruptions.

Federal Role in Overseeing the Medical Supply Chain

The Food and Drug Administration (FDA), within the Department of Health and Human Services (HHS), is the federal agency responsible for ensuring the safety and effectiveness of medical products, which include drugs, biological products (biologics), and medical devices marketed in the United States. Small molecule, chemically synthesized drugs and medical devices are approved or cleared by FDA under the Federal Food, Drug, and Cosmetic Act (FFDCA), whereas biologics—therapeutics derived from living organisms—are licensed by FDA under the Public Health Service Act (PHSA). For the purpose of this report, unless otherwise noted, the term *drugs* generally includes finished drug products, active pharmaceutical ingredients (APIs or *drug substances*),[1] as well as biologics, which are subject to most FFDCA drug requirements. Medical devices are referred to as *devices*, consistent with the term's definition in the FFDCA.[2]

As the federal regulator of drugs and devices, FDA plays a critical role in overseeing aspects of the U.S. medical product supply chain. Drug and device manufacturers are required, by law, to report to FDA certain supply chain-related information, with some exceptions for emergency circumstances.[3] For example, establishments that manufacture drugs and devices are required to register with FDA and list the drugs and devices they manufacture for U.S. commercial distribution. This registration helps FDA maintain a catalog of all drugs, biologics, and devices in commercial distribution in the United States.[4] FDA relies on establishment registration and listing information to carry out various programs and activities, including establishment inspections, postmarketing surveillance, recalls, drug quality reports, adverse event reports, monitoring of drug and device shortages and availability, supply chain security, and identification of products marketed without an approved application.[5]

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[1] FDA regulations define a *finished drug product* to mean a finished dosage form (e.g., tablet, capsule, or solution) that contains at least one API and typically "in association with other ingredients in finished package form suitable for distribution to pharmacies, hospitals, or other sellers or dispensers of the drug product to patients or consumers." An API refers to "any substance that is intended for incorporation into a finished drug product and is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body. Active pharmaceutical ingredient does not include intermediates used in the synthesis of the substance." An *unfinished drug* refers to an API either alone or with one or more other ingredients but does not include finished drug products. 21 C.F.R. §207.1.

[2] FFDCA §201(h); 21 U.S.C. §321(h).

[3] For more information on emergency use authorization (EUA), see CRS In Focus IF10745, *Emergency Use Authorization and FDA's Related Authorities*.

[4] FDA, "CY 2018 Annual Report on Inspections of Establishments," https://www.fda.gov/media/123480/download.

[5] FDA, "Drugs Intended for Human Use That Are Improperly Listed Due to Lack of Annual Certification or Identification of a Manufacturing Establishment Not Duly Registered With the Food and Drug Administration; Action Dates," 84 *Federal Register* 40417-40419, August 14, 2019. See also, FDA, "Implementation of Device Registration and Listing Requirements Enacted in the Public Health Security and Bioterrorism Preparedness and Response Act of

Although registration and listing requirements apply to both domestic and foreign establishments that import drugs and devices into the United States, concerns have been raised that certain entities that manufacture drugs or their ingredients may not be registering with FDA. For example, according to October 2019 congressional testimony from Dr. Janet Woodcock, the Director of FDA's Center for Drug Evaluation and Research (CDER),

> CDER has limited information about API suppliers for products that do not need an approved application from FDA to be marketed, such as compounded and OTC [over-the-counter] monograph drugs. API suppliers for such products may not register their facility with FDA if they are sending material to a drug product manufacturer outside the United States to make the FDF [finished dosage form], which is then sold in the United States.[6]

These potential gaps in registration information may limit FDA's ability to oversee the entire supply chain and monitor the entities manufacturing drugs for the U.S. market.

In response to these concerns, Congress has passed legislation to help regulators, stakeholders, and the public better understand the medical product supply chain. The recently enacted Coronavirus Aid, Relief, and Economic Security Act (CARES Act; P.L. 116-136), for example, expanded drug listing and reporting requirements to help quantify for regulators the amount of finished drug products and APIs manufactured domestically and abroad for the U.S. market, and provided FDA the explicit authority to require certain device manufacturers to report interruptions or disruptions in manufacturing during a public health emergency. More broadly, the CARES Act requires the National Academies of Science, Engineering, and Medicine (NASEM) to examine and report on the security of the U.S. medical product supply chain, including U.S. dependence on critical drugs and devices from other countries.

Scope of This Report

In light of recent legislation and ongoing congressional interest regarding the medical product supply chain, this report provides an overview of current FDA-mandated supply chain-related reporting requirements that apply to drug and device manufacturers. Specifically, the report

- describes the registration and listing requirements that apply to domestic and foreign drug and device manufacturers;
- describes marketing authorization, importation, and manufacturing requirements related to FDA's monitoring of the supply chain;
- provides a brief overview of the types of facility inspections conducted by FDA and the supply-chain related information available to the agency during inspections; and
- discusses further issues for congressional consideration.

Appendix A includes a legislative history of laws that have authorized and amended the registration and reporting requirements described in this report, **Appendix B** provides an overview of legislative proposals introduced in the 116th Congress related to the medical product

2002, the Medical Device User Fee and Modernization Act of 2002, and Title II of the Food and Drug Administration Amendments Act of 2007," 77 *Federal Register* 45927-45944, August 2, 2012.

[6] FDA, Testimony of Dr. Janet Woodcock, Director the Center for Drug Evaluation and Research, *Safeguarding Pharmaceutical Supply Chains in a Global Economy*, before the U.S. Congress, House Committee on Energy and Commerce, Subcommittee on Health, 116th Cong., 1st sess., October 30, 2019, https://www.fda.gov/news-events/congressional-testimony/safeguarding-pharmaceutical-supply-chains-global-economy-10302019, (hereinafter, FDA, Testimony of Dr. Janet Woodcock, "Safeguarding Pharmaceutical Supply Chains in a Global Economy").

supply chain, **Appendix C** lists medical product supply chain resources, and **Appendix D** includes a list of acronyms used in this report.

It is not the purpose of this report to compare and contrast FDA drug and device reporting requirements. Rather, the purpose is to broadly describe, in the context of supply chain transparency, existing reporting requirements for entities that manufacture drugs and devices for the U.S. market and to identify gaps in those requirements. This report does not describe every reporting requirement (e.g., adverse event reports); instead, it aims to provide a picture of the data and information that must be submitted to FDA to enable the agency to monitor the medical product supply chain.

Registration and Listing Requirements for Drugs and Devices

FDA's authority to regulate drugs and devices derives from the FFDCA. The FFDCA imposes various requirements on entities engaged in the "manufacture, preparation, propagation, compounding, or processing" (hereinafter referred to as *manufacture*) of drugs and devices.[7] The FFDCA and FDA regulations require establishments to submit specific information to the HHS Secretary (FDA, by delegation of authority) about the drugs and devices they manufacture for the U.S. market. This requirement is distinct from other requirements, such as marketing authorization (discussed in the "Submission of Supply Chain Information as Part of Marketing Authorization" section), and the information gained from registration and listing allows FDA to carry out various programs and activities, including establishment inspections, postmarketing surveillance, and product recalls, among other things. Such information must be submitted electronically (with certain exceptions)[8] and is generally publicly available.[9] However, FDA does not disclose which products are made at which establishments.

Establishment Registration Requirements

Domestic and foreign establishments that manufacture drugs and devices must be registered with FDA. Domestic establishments are those located in a state or territory of the United States, the District of Columbia, and the Commonwealth of Puerto Rico;[10] foreign establishments are those located in foreign countries and that import or offer for import drugs and devices into the United States. Generally, facilities that manufacture the source or raw materials used in the manufacturing of drugs or devices (e.g., starting materials used to make an API or a valve in a ventilator) are not required to register with FDA.[11]

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[7] As used in this report, the term *manufacture* refers to all activities that trigger establishment registration obligations under FFDCA Section 510 and in FDA regulation at 21 C.F.R. Part 207 for drugs (including drug repacking, relabeling, and salvaging) and 21 C.F.R. Part 807 for devices (including device assembly and repackaging).

[8] FFDCA §510(p); 21 U.S.C. §360(p).

[9] FDA, "Drug Establishments Current Registration Site," https://www.fda.gov/drugs/drug-approvals-and-databases/drug-establishments-current-registration-site. FDA, "Establishment Registration & Device Listing," https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRL/rl.cfm.

[10] 21 C.F.R. §207.1.

[11] 21 C.F.R. §§207.13 and 807.65. See also FDA, "Electronic Drug Registration and Listing Instructions," https://www.fda.gov/drugs/drug-registration-and-listing-system-drls-and-edrls/electronic-drug-registration-and-listing-instructions, and "Who Must Register, List, and Pay the Fee," September 27, 2018, https://www.fda.gov/medical-devices/device-registration-and-listing/who-must-register-list-and-pay-fee.

With respect to *domestic* facilities, a person who owns or operates an establishment that manufactures drugs or devices must register with FDA and submit specified information. The registration requirement applies regardless of whether the manufactured drug or device is intended for U.S. commercial distribution.[12] A person must register an establishment upon first engaging in the manufacture of a drug or device, and the establishment must be registered annually thereafter between October 1 and December 31.[13] Registrants must immediately register any additional establishments they own in which a drug or device is initially manufactured.[14] For drugs, the registration must include the name of the owner or operator of each establishment; each establishment's name, physical address, and telephone number(s); all names of the establishment; the registration number, if assigned by FDA; the unique facility identifier (UFI); all types of operations performed at the establishment; and specified contact information.[15] FDA regulations further specify that registrants must register each domestic establishment no later than five calendar days after beginning drug manufacturing. For devices, the registration must include the name, place of business, specified contact information, and all such establishments that engage in the manufacture of a device or devices.[16] FDA regulations specify that registrants must initially register each domestic (and foreign) establishment no later than 30 days after beginning any process of device manufacturing.

With respect to *foreign* facilities, as with domestic facilities, a person who owns or operates an establishment in a foreign country that manufactures drugs or devices for import into the United States must register with FDA upon engaging in the manufacture of a drug or device, and the establishment must be registered annually thereafter between October 1 and December 31.[17] Registrants generally must submit the same information that is required for domestic facilities. However, registration information for a foreign establishment must also include the name, mailing address, telephone number, and email address of the U.S. agent of each establishment, each importer of the drug in the United States that is known to the establishment, and each person who imports or offers for import the drug to the United States.[18] Similarly, for devices, the registration must include the name and place of business of the establishment, the name of the U.S. agent for the establishment, the name of each importer of the device in the United States known to the establishment, and the name of each person who imports or offers for import the device to the United States.[19] Foreign establishments are required to update registration

[12] FDA, "Requirements for Foreign and Domestic Establishment Registration and Listing for Human Drugs, Including Drugs That Are Regulated Under a Biologics License Application, and Animal Drugs," 81 *Federal Register* 60169, August 31, 2016, and FDA, "Implementation of Device Registration and Listing Requirements Enacted in the Public Health Security and Bioterrorism Preparedness and Response Act of 2002, the Medical Device User Fee and Modernization Act of 2002, and Title II of the Food and Drug Administration Amendments Act of 2007," 77 *Federal Register* 45941, August 2, 2012.

[13] FFDCA §510(b) and (c) [21 U.S.C. §360(b) and (c)].

[14] FFDCA §510(d) [21 U.S.C. §360(d)].

[15] FFDCA §510(b)(1) [21 U.S.C. §360(b)(1)] and 21 C.F.R. Part 207 Subpart B. FDA, *Guidance for Industry, Specification of the Unique Facility Identifier (UFI) System for Drug Establishment Registration*, November 2014, https://www.fda.gov/media/89926/download.

[16] FFDCA §510(b)(2) [21 U.S.C. §360(b)(2)]; 21 C.F.R. Part 807 Subpart B.

[17] FFDCA §510(i) [21 U.S.C. §360(i)].

[18] FFDCA §510(i)(1)(A)(i) [21 U.S.C. §360(i)(1)(A)(i)] and 21 C.F.R. Part 207 Subpart B. FDA, "Electronic Drug Registration and Listing Instructions," https://www.fda.gov/drugs/drug-registration-and-listing-system-drls-and-edrls/electronic-drug-registration-and-listing-instructions.

[19] FFDCA §510(i)(1)(A)(ii) [21 U.S.C. §360(i)(1)(A)(ii)] and 21 C.F.R. Part 807 Subpart C.

information to reflect any changes in a U.S. agent's name, address, or phone number within 10 business days.

FDA regulations include additional requirements that apply to *both* domestic and foreign establishments. For example, for both drugs and devices, per agency regulations, if covered operations are conducted at more than one establishment under common ownership and control, the parent, subsidiary, or affiliate company may submit registration information for all establishments. FDA regulations further require registrants of drug establishments to update their registration information no later than 30 calendar days after certain changes are made: after closing or selling an establishment; after changing an establishment's name or physical address; or after changing the name, mailing address, telephone number, or email address of the official contact or the United States agent.[20] Similarly, for devices, registrants are required to update their registration no later than 30 calendar days after changing the name, mailing address, or website address (if any) of the device establishment; the name, address, phone number, fax number, and email address of the owner or operator; the name, address, phone number, fax number, and email address of the establishment's official correspondent; or all trade names used by the establishment.[21]

Certain entities are exempt from the registration requirements, including

- pharmacies;
- licensed health care practitioners;
- persons who manufacture drugs or devices not for sale but solely for research, teaching, or chemical analysis;
- wholesale distributors of devices; and
- other classes of persons exempted by FDA by regulation.[22]

Specific to drugs, for example, manufacturers of "harmless inactive ingredients such as excipients, colorings, flavorings, emulsifiers, lubricants, preservatives, or solvents that become components of drugs" are exempt from registration requirements.[23] In device regulation, for example, manufacturers of raw materials and components that are distributed to a finished device[24] manufacturer and manufacturers of devices for veterinary purposes are exempted from registration.[25]

Listing Requirements

Every person who registers with FDA, must, at the time of registration, file with FDA a list of drugs and devices—by their established and proprietary names—being manufactured for commercial distribution. As with registration, information gained from listing allows FDA to carry out various activities, such as completing adverse event reports, monitoring drug and device

[20] 21 C.F.R. §207.29.

[21] 21 C.F.R. §807.25(b).

[22] FFDCA §510(g) [21 U.S.C. §360(g)]; 21 C.F.R. Part 207.

[23] 21 C.F.R. §207.13. In guidance, FDA defines *excipient* to mean any inactive ingredients that are intentionally added to therapeutic and diagnostic products. FDA, *Guidance for Industry: Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*, May 2005, https://www.fda.gov/media/72260/download.

[24] Pursuant to 21 C.F.R. §820.3, a finished device is defined as any device or accessory to any device that is suitable for use or capable of functioning, whether or not it is packaged, labeled, or sterilized.

[25] 21 C.F.R. §807.65.

shortages and availability, and identifying products that are marketed without an approved application, among other things. Drug and device requirements are described below.

Drugs

Registrants must "list" each drug (i.e., finished drug and API) manufactured at their establishments for commercial distribution upon establishment registration; the listing information must be reviewed and updated biannually. More specifically, each person who registers a drug manufacturing establishment with FDA under FFDCA Section 510 must submit, within three calendar days of initial registration, a list of drugs that it manufactures for commercial distribution.[26] Registrants must also list, at the time of annual establishment registration—between October 1 and December 31—any drugs manufactured for commercial distribution that had not been listed previously.[27]

The FFDCA and FDA regulations specify what information must be submitted as part of drug listing. Some of these requirements differ depending on whether the drug is subject to the approval requirements under FFDCA Section 505 (or FFDCA Section 512 for new animal drugs), whether the drug is exempt from approval, and whether the drug is available by prescription only or over-the-counter (OTC).[28] For example, for a drug subject to approval via a new drug application (NDA) or abbreviated new drug application (ANDA), the list must include a reference to the authority for marketing the drug (e.g., the approved U.S. application number).[29] For a drug exempt from approval (e.g., an OTC monograph drug), the list must include a brief statement explaining how the registrant determined that the drug is not subject to approval; certain labeling information, which varies depending on whether the drug is by prescription only or OTC; and a quantitative listing of the drug's active ingredients. As part of the listing information for all drugs, the registrant must provide information about the excipients in the drug, including the name and place of business of each manufacturer of such excipient. In addition, FDA may require registrants to submit a list of each drug product being manufactured for commercial distribution that contains a particular ingredient.[30]

FDA regulations further require a registrant to provide, as part of drug listing, the name and UFI of every other establishment where manufacturing is performed for the drug and the type of operation performed at each establishment.[31] A registrant must also obtain for each drug subject to the listing requirements a national drug code (NDC) from FDA.[32] The registrant must propose a new NDC if certain changes are made to a drug after its initial marketing (e.g., a change in its name, API, or dosage form). The NDC is a universal product identifier for human drugs manufactured for commercial distribution. The listing of a drug is not indicative of marketing approval, as FDA does not review or approve unfinished drugs or APIs. Thus, a drug may have an NDC but may not be FDA-approved.[33]

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[26] FFDCA §510(j)(1) [21 U.S.C. §360(j)(1)]; 21 C.F.R. §207.45.

[27] 21 C.F.R. §207.57.

[28] FFDCA §510(j)(1) [21 U.S.C. §360(j)(1)].

[29] FDA regulations extend this requirement to biologics licensed (i.e., "approved") under a biologics license application or BLA.

[30] FFDCA §510(j)(3); 21 U.S.C. §360(j)(3).

[31] 21 C.F.R. Part 207 Subpart D. FDA regulations differentiate between what listing information must be provided by a registrant that manufactures drugs, repacks or relabels drugs, and salvages drugs.

[32] 21 C.F.R. Part 207 Subpart C.

[33] 21 C.F.R. Part 207 Subpart C. See also FDA, "National Drug Code Directory," https://www.fda.gov/drugs/drug-

Registrants must review and update their drug listing information biannually—once in June and once in December of each year. During this biannual review, a registrant must (1) provide a list of drugs introduced for commercial distribution that were not included on any previously submitted list; (2) report if the manufacture of any previously listed drug has been discontinued since the last report (or resumed if previously discontinued); and (3) report any material change to previously submitted information. If there are no changes to report in June or December, the registrant must certify that no changes subject to reporting have occurred since the last report.[34] Registrants are encouraged, but not required, to submit listing information at the time of making any change affecting information previously submitted.

Each person who registers with FDA under FFDCA Section 510 must report annually on the amount of each listed drug manufactured for commercial distribution. FDA may require that this information be submitted at the time a public health emergency is declared under Section 319 of the Public Health Service Act. Certain biologics may be exempted from this reporting requirement if FDA determines that applying such requirements to biologics is not necessary to protect the public health.[35]

Devices

Similar to drug requirements, registering a device establishment with FDA requires registrants to file a list of all devices being manufactured for commercial distribution. Device listing generally occurs at two times: (1) at initial registration and listing, which must occur within 30 days of commencing device manufacturing, and (2) at annual registration and listing, which occurs between October 1 and December 31 of each year. A registrant may—but is not required—to make changes to listing information at other times, such as when a device is first introduced into commercial distribution.[36]

Specified information is required at the time of initial listing. A brief explanation about why the device is not being listed as a drug must accompany each device in the list.[37] In addition, a reference to the authority under which certain devices are being marketed (e.g., an FDA-assigned premarket application number), including the reasoning for not marketing devices under certain authorities, is required.[38] A description of each activity or process that contributes to the device (e.g., manufacturing, sterilization) must be provided, including which part of the process occurred at which establishment under the owner or operator's control.[39] Regarding labeling and advertising information, listings for restricted devices—those that can be sold only under authorization from a licensed health care provider or under conditions specified in regulation[40]—must include a copy of all labeling and a representative sampling of advertisements. If requested

approvals-and-databases/national-drug-code-directory.

[34] FFDCA §510(j)(2) [21 U.S.C. §360(j)(2)] and 21 C.F.R. §207.57.

[35] FFDCA §510(j)(3)(A) [21 U.S.C. §360(j)(3)(A)], as added by §3112(e) of the CARES Act (P.L. 116-136).

[36] FDA, "When to Register and List," December 23, 2017, https://www.fda.gov/medical-devices/device-registration-and-listing/when-register-and-list.

[37] Per FDA guidance, "Conceptually, all FDA-regulated medical products meet the definition of "drug" under section 201(g) of the FD&C Act, due to the broader scope of the drug definition." For a medical product to meet the definition of a device under the FFDCA, it must meet specified conditions. For more information, see FDA, *Guidance for Industry and FDA Staff: Classification of Products as Drugs and Devices & Additional Product Classification Issues*, September 2017, https://www.fda.gov/media/80384/download.

[38] FFDCA §510(j)(1); 21 U.S.C. §360(j)(1).

[39] 21 C.F.R. §807.25(g).

[40] FFDCA §520(e); 21 U.S.C. §360j(e).

by FDA for a good cause, a copy of *all* advertisements for the restricted device must be submitted. For all other devices, the label and package insert for a device and a representative sampling of any other labeling must be submitted.[41]

Each registrant must review and submit additional device listing information on an annual basis between October 1 and December 31. As with drug requirements, registrants must (1) provide a list of devices introduced for commercial distribution that were not included on any previously submitted list; (2) report if the manufacture of any previously listed device has been discontinued since the last report (or resumed if previously discontinued); and (3) report any material change to previously submitted information.[42] Registrants must maintain in a historical file any material changes to labeling or advertisements made after the initial listing, and must maintain this file in a secure location, with additional storage requirements specified in regulation.[43]

Submission of Supply Chain Information as Part of Marketing Authorization

With limited exceptions, a drug, biologic, or device may not be marketed in the United States unless it has been authorized for marketing (i.e., approved, licensed, or cleared) by FDA. This marketing authorization requirement applies regardless of whether a product is manufactured domestically or in a foreign country. As mentioned above, for drugs and some devices, this requirement is distinct from establishment registration and product listing.[44] The FFDCA and FDA regulations require that certain information about where a medical product is manufactured be submitted to FDA as part of the drug, biologic, and device approval, licensure, and clearance processes.[45] In addition, the FFDCA and FDA regulations impose postmarket reporting requirements that apply to holders of approved regulatory submissions. Because drugs and biologics are approved under separate mechanisms, this section differentiates between requirements for the two medical product types.

To market a new drug, the sponsor (typically the manufacturer) must submit to FDA an NDA demonstrating that the drug is safe and effective for its proposed use.[46] In the case of a generic drug, the sponsor must submit an ANDA. Although most drugs are subject to premarket approval through the NDA or ANDA process, there are some exceptions; for example, most OTC drugs are not covered by an approved NDA or ANDA and may be marketed by complying with a *monograph*.[47] To market a new biologic, the sponsor must submit to FDA a biologics license

[41] FFDCA §510(j)(1)(B); 21 U.S.C. §360(j)(1)(B).

[42] FFDCA §510(j)(2) [21 U.S.C. §360(j)(2)] and 21 C.F.R. §807.22(b)(3) and §807.28.

[43] 21 C.F.R. §807.26.

[44] For devices subject to premarket review, the device must be cleared or approved before an establishment can register and list the device. See FDA, "When to Register and List," December 2017, https://www.fda.gov/medical-devices/device-registration-and-listing/when-register-and-list.

[45] Labeling included on drug and device packaging is also included as a part of a premarket application reviewed by FDA prior to marketing authorization.

[46] FFDCA §505 [21 U.S.C. §355].

[47] A *monograph* establishes conditions—active ingredient(s) and related conditions (e.g., dosage level, combination of active ingredients, labeled indications, warnings and adequate directions for use)—under which an OTC drug in a given therapeutic category (e.g., sunscreen, antacid) is considered generally recognized as safe and effective (GRASE) for use. See the section "Subtitle F—Over-the-Counter Drugs" in CRS Report R46334, *Selected Health Provisions in Title III of the CARES Act (P.L. 116-136)*.

application (BLA) demonstrating that the biologic and the facilities in which it is manufactured meet standards to ensure its safety, potency (i.e., effectiveness), and purity.[48]

Most medical devices must be reviewed by FDA prior to marketing; the most common premarket review mechanisms are premarket notification (i.e., 510(k)) and premarket approval (PMA). The applicable premarket review mechanism depends on the regulatory class of the device—FDA's categorization of devices based on the risk they pose to the consumer. The three regulatory classes of medical devices with different applicable requirements are class I (low risk), class II (moderate risk), and class III (high risk). Certain class I devices (e.g., surgical gloves) and most class II devices (e.g., surgical masks, ventilators) are subject to premarket notification via a 510(k), in which manufacturers are required to submit specified information to FDA at least 90 days prior to marketing.[49] To receive a 510(k) *clearance*, a manufacturer must demonstrate that the device proposed to be marketed is substantially equivalent to a device already on the market (i.e., predicate device). To market and receive *approval* for a class III device, a sponsor must submit a PMA application demonstrating that the device provides reasonable assurance of safety and effectiveness.[50]

Drugs and Biologics

For drugs that are subject to premarket approval—the vast majority of prescription drugs and some nonprescription (OTC) drugs—information about the API and finished drug manufacturing facilities must be provided as part of an NDA, ANDA, or BLA. In particular, an NDA or ANDA must include, as part of the *chemistry, manufacturing and controls* section of the application, the name and address of the manufacturer of the drug substance (i.e., API) and the name and address of each manufacturer of the drug product (i.e., finished drug).[51] Similarly, a BLA must include the address of each location involved in the manufacture of a biologic.[52] An application holder is required to submit to FDA a supplemental submission to reflect any change(s) to the "drug substance, drug product, production process, quality controls, equipment, or facilities that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product."[53] For drugs that do not require premarket approval (e.g., compounded drugs or OTC monograph drugs), manufacturers are not subject to these requirements.

Holders of approved applications must submit certain supply chain information to FDA once the product is on the market. For example, FDA regulations require an approved NDA or ANDA holder to submit in annual reports, among other things, information about the quantity of the drug product (i.e., finished drug) distributed under the approved application, including the drug quantity distributed to distributors. The information must include the total number of dosage units of each strength or potency distributed and the quantities distributed for domestic and foreign use.[54] For biologics, information about the quantity of the product distributed under an approved BLA, as specified, must be submitted to FDA in six-month increments or in another time frame

[48] PHSA §351 [42 U.S.C. §262]. See also CRS Report R44620, *Biologics and Biosimilars: Background and Key Issues*.

[49] FFDCA §510(k); 21 U.S.C. §360(k).

[50] FFDCA §515(k); 21 U.S.C. §360e.

[51] 21 C.F.R. §314.50(d)(1) and §314.94(a)(9).

[52] 21 C.F.R. §601.2(a).

[53] 21 C.F.R. §314.70. See also FFDCA §506A [21 U.S.C. §356a], 21 C.F.R. §314.97 and §601.12.

[54] 21 C.F.R. §314.81.

determined by the agency.[55] Reporting distribution data under an NDA, ANDA, or BLA is separate from that in FFDCA Section 510 requiring each person who registers with FDA to report annually on the amount of each drug manufactured for commercial distribution (see the "Drugs" section of this report).

FFDCA Section 506I requires the holder of an approved NDA or ANDA (but not BLA) to notify FDA of any changes to the marketing status of a drug.[56] The holder of an approved NDA or ANDA must notify FDA in writing six months before withdrawing an approved drug from sale (or as soon as practicable) and must notify FDA within six months of approval if the drug will not be available for sale within six months of approval. This requirement is separate from the one in FFDCA Section 510(j) that each registrant report to FDA in the biannual drug listing information if the manufacture of any previously listed drug has been discontinued since the last report.

In addition, FDA obtains information about facilities that manufacture generic drugs, pursuant to requirements under the Generic Drug User Fee Amendments (GDUFA). Under GDUFA, generic drug manufacturers are subject to three types of facility fees that must be paid annually: (1) an API facility fee, (2) a finished dosage form (FDF) facility fee, and (3) a contract manufacturing organization (CMO) facility fee.[57] Facility owners incur a fee if their facility is referenced in an approved generic drug submission (an ANDA) and the facility is engaged in manufacturing or processing an API or FDF. The owner of such facility must submit certain identification information to FDA, including whether the facility manufactures an API, FDF, or both, and whether it is located in the United States.[58] FDA publishes on its website several lists of facilities that are subject to GDUFA, including a list of facilities that have paid the fees, as well as those on an arrears list for failing to pay.[59] Brand-name drugs, biologics, and biosimilars are not subject to establishment fees under their respective user fee programs.[60]

Devices

Fewer explicit FDA requirements exist for devices than for drugs regarding the inclusion of supply chain information in premarket applications for marketing, particularly regarding the disclosure of location of facilities. The FFDCA and FDA regulations for PMA submissions do not require that the name and address of each manufacturer involved in the production of the device be included in the application. Rather, PMA regulations specify that the name and address of the applicant must be included in the PMA submission; if the applicant is a foreign establishment, an authorized representative must sign the application and include the representative's name and address in the United States.[61] Similarly, statute and regulations for 510(k) submissions do not require that each manufacturer involved in the production of the device be identified in the

[55] 21 C.F.R. §600.81.

[56] FFDCA §506I [21 U.S.C. §356I], added by Section 804 of FDARA (P.L. 115-52).

[57] FFDCA §744B(a)(4) [21 U.S.C. §379j-42(a)(4)].

[58] FFDCA §744B(f) [21 U.S.C. §379j-42(f)].

[59] FDA, Generic Drug User Fee Amendments; see "User Fee Lists" https://www.fda.gov/industry/fda-user-fee-programs/generic-drug-user-fee-amendments.

[60] Brand-name drugs and biologics are subject to the Prescription Drug User Fee Act (PDUFA), and biosimilar biologics are subject to the Biosimilar User Fee Act (BsUFA). Neither PDUFA nor BsUFA require payment of an establishment fee. For additional information, see CRS Report R44750, *FDA Human Medical Product User Fee Programs: In Brief.*

[61] 21 C.F.R. §814.20.

submission. Instead, the name and address of the individual preparing the submissions is included.[62]

If a manufacturer makes certain changes to a cleared or approved device, FDA needs to be notified via a new 510(k) submission[63] or a PMA supplement,[64] respectively. A PMA supplement would need to be submitted if a different establishment—whether it is domestic or foreign—is being used to manufacture the device, but the regulations do not specify requiring other information about the establishment (e.g., address of establishment, manufacturing capabilities).[65] Statute, regulation, and FDA guidance do not explicitly state that a change in location of manufacturing would trigger a new 510(k). However, a new 510(k) would be triggered by a significant change in method of manufacture or manufacturing process that could affect the safety and effectiveness of the device.[66] Regardless, FDA generally obtains information about a new device facility through registration and listing.

Regarding postapproval requirements, FDA requires devices authorized under a PMA to report certain information annually to the agency. These annual reporting requirements do not apply to devices subject to 510(k) clearance or those exempt from premarket review. While the postapproval PMA report is not required to include a discussion of location of manufacturing, certain distribution information must be included. For example, in approval orders issued after August 1, 2009, FDA requires applicants to provide the number of devices shipped or sold, or in the case of device implants, the number of devices implanted.[67]

FDA also obtains information about device facilities pursuant to requirements under the Medical Device User Fee Amendments (MDUFA). Under MDUFA, each establishment that intends to distribute a device commercially is required to pay a user fee at the time of registration and listing, as well as each year thereafter.[68] (For devices subject to premarket review, this occurs after clearance or approval is received.) In required MDUFA quarterly reports, FDA publishes data on current active registrations by type of facility (e.g., manufacturer, initial importer) and specifies whether these facilities are domestic or foreign.[69]

Submission of Supply Chain Information Upon Importation

All products offered for importation into the United States must be declared to U.S. Customs and Border Protection (CBP), and product entry information must be filed in the Automated Commercial Environment (ACE) system.[70] CBP refers all FDA-regulated products to FDA for

[62] 21 C.F.R. §807.92(a)(1).

[63] 21 C.F.R. §807.81(a)(3).

[64] 21 C.F.R. §814.39.

[65] 21 C.F.R. §814.39(a)(3).

[66] 21 C.F.R. §807.81(a)(3)(i).

[67] 21 C.F.R. §814.82. See also FDA, *Guidance for Industry and Food and Drug Administration Staff: Annual Reports for Approved Premarket Approval Applications (PMA)*, p. 6, December 16, 2019, https://www.fda.gov/media/73391/download.

[68] FFDCA §738(a)(3); 21 U.S.C. §379j(a)(3).

[69] See, for example, FDA, "Quarterly Update on Medical Device Performance Goals, MDUFA IV CDRH Performance Data," p. 303, February 21, 2020, https://www.fda.gov/media/135471/download.

[70] FDA, "Import Basics," https://www.fda.gov/industry/import-program-food-and-drug-administration-fda/import-basics. See also "Automated Commercial Environment/International Trade Data System (ACE/ITDS),"

review and determination of admissibility. Imported FDA-regulated products may be refused admission into the United States for a variety of reasons, including if FDA determines that a product appears to be adulterated or misbranded.[71] FDA may destroy certain drugs that have been refused admission into the United States.[72]

To facilitate admissibility determinations, the agency has promulgated regulations that require importers to submit certain data elements in ACE for all imported FDA-regulated products and additional information for specific product types (e.g., drugs, devices). FDA-regulated products submitted to ACE must include the following general data elements:[73]

- **FDA country of production.** The country where the article was last manufactured, processed, or grown. FDA regulations clarify that "the FDA Country of Production for an article that has undergone any manufacturing or processing is the country where that activity occurred provided that the manufacturing or processing had more than a minor, negligible, or insignificant effect on the article." For example, if an API is made in one country but exported into another to be encapsulated into the final dosage form, the country where the drug was encapsulated would be the FDA country of production. This data element is different from CBP's use of the substantial transformation test to determine country of origin.[74]
- **FDA product code.** An alphanumeric code used to describe a specific product.[75]
- **Full intended use code.** A code used to denote the intended use of the product (e.g., whether the product is an API intended for investigational use, personal use, or commercial use).
- **Importer of record contact information.** The telephone and email address of the importer.

In general, medical products made in foreign countries and imported into the United States for commercial distribution must comply with the same FFDCA requirements as domestically manufactured medical products, including registration, listing, and premarket authorization.[76] As such, for drugs and biologics regulated by FDA's Center for Drug Evaluation and Research (CDER), the filer must also submit in ACE the registration and listing information for the drug or biologic, as well as the approved application number or investigational new drug application number (in the case of a drug being imported for clinical testing in humans).[77] For a device

https://www.fda.gov/industry/import-systems/automated-commercial-environmentinternational-trade-data-system-aceitds.

[71] FFDCA §801(a); 21 U.S.C. §381(a).

[72] FFDCA §801(a); 21 U.S.C. §381(a). See also FDA, "Administrative Destruction of Certain Drugs Refused Admission to the United States," 80 *Federal Register* 55237, September 15, 2015.

[73] 21 C.F.R. §1.72.

[74] FDA, "Submission of Food and Drug Administration Import Data in the Automated Commercial Environment," 81 *Federal Register* 85854, November 29, 2016. CBP's substantial transformation test contends that "substantial transformation occurs in the country where the article acquired the name, character, or intended use that matches the article identified in the entry."

[75] FDA, "Product Codes and Product Code Builder," https://www.fda.gov/industry/import-program-resources/product-codes-and-product-code-builder.

[76] Requirements governing importation of prescription drugs are discussed in more detail in CRS In Focus IF11056, *Prescription Drug Importation*.

[77] 21 C.F.R. §1.74.

regulated by the Center for Devices and Radiological Health (CDRH), the ACE filing information must include the registration and listing information; the investigational device exemption number or premarket number, if applicable; and "an affirmation identifying that the article being imported or offered for import is a component that requires further processing or inclusion into a finished medical device," if applicable.[78] In addition, the regulations require an "affirmation of compliance" for specific devices or device components (e.g., lead wires/patient cables). For biologics and devices (e.g., certain in vitro diagnostics) regulated by the Center for Biologics Evaluation and Research (CBER), the filer must submit in ACE the product application number, the registration and listing information, the product name, and, if applicable, the tracking number for the BLA and other device-related information.[79]

In certain cases, medical products or their components may be imported into the United States for further processing and subsequent exportation. In such cases, the importer must submit to FDA a statement providing that such article is intended to be further processed and exported; indicating the manufacturer of the article and each other entity that had possession of the article from the manufacturer to the importer of the article; and providing a certificate of analysis to identify such article unless it is a device or blood product.[80] Provided these conditions are met, a foreign establishment that imports drugs or drug components for further processing into the United States for exportation is exempt from registration and listing requirements.[81]

Medical products also may be manufactured in their entirety in the United States solely for export purposes. Foreign companies or governments may require an exporting company to provide an export certificate containing information about a product's regulatory or marketing status. FDA is required to issue export certificates, upon request, for (1) drugs and devices manufactured in the United States that meet applicable FFDCA requirements and may be lawfully marketed in the United States, or (2) for drugs and devices that may not lawfully be marketed in the United States (e.g., lack marketing authorization) but may be lawfully exported.[82]

Collection of Supply Chain Information as Part of Facility Inspections

FDA obtains information about drug and device manufacturing through establishment inspections, which are conducted throughout the lifecycle of a drug or device (i.e., premarket and postmarket). The agency conducts inspections to verify that FDA-regulated products are manufactured in compliance with current good manufacturing practices (CGMPs) and other FFDCA and regulatory requirements. Other federal agencies, particularly the Government Accountability Office (GAO), have investigated how FDA inspects drug manufacturers. To avoid duplication of work with GAO, in this report facility inspections are discussed only in the context of the supply chain related-information that FDA obtains from such inspections. (See **Appendix**

[78] 21 C.F.R. §1.76.

[79] 21 C.F.R. §1.78.

[80] FFDCA §801(d)(3) [21 U.S.C. §381(d)(3)].

[81] 21 C.F.R. §207.13. FDA, "Requirements for Foreign and Domestic Establishment Registration and Listing for Human Drugs, Including Drugs That Are Regulated Under a Biologics License Application, and Animal Drugs," 81 *Federal Register* 60184, August 31, 2016.

[82] FFDCA §801(e)(4) [21 U.S.C. §381(e)(4)]. FDA, CPG Sec. 110.100 Certification for Exports, April 2000, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cpg-sec-110100-certification-exports.

C for further resources pertaining to facility inspections—including foreign facility inspections—and other medical supply chain-related resources.)

Current Good Manufacturing Practices (CGMPs)

As noted above, FDA-regulated products, including medical products, are subject to CGMPs. Manufacturers of drugs—finished drugs and APIs—must comply with CGMPs to ensure that the products are safe and meet their purported or represented purity, strength, identity, and quality characteristics. For drugs, CGMPs include "the implementation of oversight and controls over the manufacture of drugs to ensure quality, including managing the risk of and establishing the safety of raw materials, materials used in the manufacturing of drugs, and finished drug products."[83] FDA has promulgated CGMP regulations for the manufacture of finished drugs,[84] which provide minimum requirements for the methods, facilities, and controls used in manufacturing. FDA has not issued CGMP regulations for API manufacturing. However, the agency recognizes that the CGMP regulations for finished drugs "are valid and applicable in concept to [API] manufacturing."[85] Device manufacturers must also comply with CGMPs to ensure that their products are safe, effective, and otherwise in compliance with the FFDCA.[86] FDA has promulgated CGMP regulations for devices through the quality system (QS) regulation.[87]

Generally, records required to be kept as part of drug CGMPs or in compliance with the device QS regulation do not need to be proactively reported by manufacturers; instead, they are subject to FDA review during facility inspections.[88] For drugs, manufacturers must maintain distribution records containing the name and strength of the product and description of the dosage form, name and address of the consignee, date and quantity shipped, and lot or control number of the drug product.[89] In addition, certain distribution records are required for all finished devices, including accessories to any device that are suitable for use or capable of functioning, regardless of whether they are packaged, labeled, or sterilized.[90] Specifically, each manufacturer is required to maintain distribution records that include the name and address of the initial consignee, as well as the identification and the quantity of devices shipped.[91] In addition, manufacturers are required to maintain a device history file (DHF), which must include the quantity of devices manufactured and distributed, among other things.[92]

Types of Facility Inspections

FDA generally conducts three types of inspections for drugs and devices:

[83] FFDCA §501 [21 U.S.C. §351].

[84] 21 C.F.R. Parts 210 and 211.

[85] FDA, Compliance Program 7356.002F, Active Pharmaceutical Ingredient (API) Process Inspection, p. 4, https://www.fda.gov/media/75201/download.

[86] FFDCA §520(f); 21 U.S.C. §360j(f).

[87] 21 C.F.R. Part 820.

[88] 21 C.F.R. §§211.180 and 820.180.

[89] 21 C.F.R. §211.196.

[90] 21 C.F.R. §820.3(l).

[91] 21 C.F.R. §820.160(b).

[92] 21 C.F.R. §820.184.

- **Preapproval inspections** are conducted as part of the drug review process before approving an NDA, ANDA, or BLA, and as part of the device review process for devices subject to a PMA or PMA supplement.
- **For-cause inspections** are conducted in response to specific issues, for example, consumer complaints or as a follow-up to previous FDA regulatory action.
- **Surveillance inspections** assess manufacturer compliance with CGMPs once a drug or device is on the market.

Pursuant to changes made by the FDA Safety Innovation Act of 2012 (FDASIA, P.L. 112-144), FDA must inspect both domestic and foreign drug and device establishments on a risk-based schedule.[93] Prior to FDASIA, FDA was required to inspect domestic establishments every two years, with no comparable requirement for foreign establishments. FDASIA required a risk-based schedule for all establishments, regardless of location. The law also directed FDA to institute a risk-based inspection schedule that considers the safety risks of an establishment, for example, its compliance history and the inherent risk of the drug or device.[94] According to FDA, this statutory change was consistent with the CDER Site Selection Model (SSM) used by FDA since 2005 and explicitly allowed FDA to place less emphasis on a set frequency of inspection.[95] CDER runs its SSM twice a year to determine which manufacturing establishments should be prioritized for surveillance inspections. CDRH lists its priorities for surveillance inspections in its compliance program guidance manual. The manual provides a list of firms that are considered higher risk (e.g., those that manufacture class III [high risk] devices that have never been inspected) and should be prioritized. Manufacturers of class I (low risk) devices, per the handbook, should receive lowest inspectional priority unless certain circumstances warrant an inspection sooner (e.g., health hazard is apparent).[96]

FDA may enter into agreements with foreign governments to recognize surveillance inspections conducted by foreign regulatory authorities of registered foreign drug and device manufacturing establishments. For example, FDA has a mutual recognition agreement (MRA) with the European Union (EU) and recognizes the surveillance inspection conducted by certain regulatory authorities in the EU.[97]

Records from Facility Inspections

At the conclusion of an inspection, the FDA inspector issues a Form 483 to the owner or agent in charge of the establishment. This form lists any conditions observed during the inspection that may render an FDA-regulated product to be adulterated and in violation of the FFDCA.[98] Form

[93] FFDCA §510(h); 21 U.S.C. §360(h).

[94] FFDCA §510(h)(4). FDA is also required to consider the record, history, and nature of recalls linked to the establishment; "the inspection frequency and history of the establishment, including whether the establishment has been inspected pursuant to section 704 within the last 4 years; whether the establishment has been inspected by a foreign government or an agency of a foreign government recognized under section 809; and any other criteria deemed necessary and appropriate by the Secretary for purposes of allocating inspection resources."

[95] FDA, Center for Drug Evaluation and Research (CDER), Office of Pharmaceutical Quality, MAPP 5014.1, Understanding CDER's Risk-Based Site Selection Model, https://www.fda.gov/media/116004/download.

[96] FDA, Compliance Program Guidance Material, Program 7382.845, Inspection of Medical Device Manufacturers, https://www.fda.gov/media/80195/download.

[97] FDA, "Mutual Recognition Agreement (MRA)," https://www.fda.gov/international-programs/international-arrangements/mutual-recognition-agreement-mra; FDA, "List of Devices for MRA Review," https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/mra.cfm?panel=AN.

[98] FFDCA §704 (b)(1) [21 U.S.C. §374(b)(1)]. FDA, "FDA Form 483 Frequently Asked Questions,"

483 is not an all-inclusive listing of potential FFDCA violations, nor does it constitute a final agency determination of whether an establishment is in violation of the FFDCA. After completing a facility inspection, the inspector prepares an Establishment Inspection Report (EIR), which documents inspection findings and provides a preliminary recommendation regarding whether enforcement action should be taken. The recommendation is made using one of three classifications: no action indicated (NAI), voluntary action indicated (VAI), or official action indicated (OAI).[99] For surveillance inspections, NAI and VAI recommendations are reviewed within the Office of Regulatory Affairs (ORA). OAI recommendations are sent to the appropriate FDA Center (e.g., CDER for drugs, CDRH for devices), which reviews the recommendation and determines whether regulatory action is needed. Regarding for-cause inspections, the appropriate FDA Center is to review the inspection reports and initial classification recommendations, regardless of whether it was classified as OAI.[100]

FDA maintains a public Inspection Classification Database, which lists inspections conducted by the agency and its assessments of regulated establishments' compliance with FDA law and regulation. The database does not include all inspections conducted by FDA. For example, preapproval inspections are excluded from the database, and the database does not disclose which drugs or devices are made in a specific facility.[101] However, the database does allow the public to see how FDA classified the inspection of a specific manufacturing establishment (e.g., OAI, NAI) and where that establishment is located (i.e., city, state, and country). On occasion, FDA makes available redacted inspection records (e.g., a Form 483 or an EIR) requested pursuant to a Freedom of Information Act (FOIA) request.

For drugs, FDA can require manufacturers to submit records or other information subject to inspection in advance prior to or in lieu of an inspection.[102] For example, FDA appears to have relied upon this authority during the COVID-19 pandemic, when the agency's ability to inspect drug establishments was limited.[103] Device manufacturers are not subject to this requirement, but they may choose to comply if the agency makes such a request.

Other Supply Chain Reporting Requirements

To enhance FDA's capacity to assess the medical product supply chain and manufacturing, Congress has created additional legislative requirements for reporting drug and device manufacturing interruptions and for tracking drugs as they are distributed to consumers.[104]

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https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/fda-form-483-frequently-asked-questions.

[99] GAO, "Preliminary Findings Indicate Persistent Challenges with FDA Foreign Inspections," GAO-20-262T, December 2019, p. 9, https://www.gao.gov/assets/710/703078.pdf.

[100] GAO, "Drug Safety: COVID-19 Complicates Already Challenged FDA Foreign Inspection Program," June 2, 2020, p. 8, https://www.gao.gov/assets/710/707345.pdf.

[101] FDA, "Inspections Database Frequently Asked Questions," https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/inspections-database-frequently-asked-questions.

[102] FFDCA §704(a)(4) [21 U.S.C. §374(a)(4)].

[103] FDA, *Guidance for Industry: Manufacturing, Supply Chain, and Drug and Biological Product Inspections During COVID-19 Public Health Emergency Questions and Answers*, August 2020, https://www.fda.gov/media/141312/download.

[104] This is not intended to be an exhaustive list of all reporting requirements in the FFDCA. For example, the FFDCA and FDA regulations mandate reporting of serious adverse events associated with use of a drug or device and while adverse event reports may trigger FDA facility inspections or regulatory action, these reporting requirements are

Manufacturing Interruptions, Discontinuances, and Shortages

To help prevent and mitigate shortages, manufacturers of certain drugs and devices must notify FDA of any interruptions or discontinuances in their manufacturing. FDA is required to take certain mitigating actions in response to such notification. For example, FDA must prioritize and expedite facility inspections and review of certain regulatory submissions. When FDA receives notifications from drug and device manufacturers reporting an interruption in manufacturing, the agency generally does not make this information public on its website. However, FDA is required to distribute this information to appropriate organizations (e.g., physicians, supply chain partners) unless such a disclosure would adversely affect the public's health.[105] If a manufacturer fails to submit the required information, FDA must submit a letter to the manufacturer documenting this failure. The manufacturer is required to respond with reasons for noncompliance, as well as with information on interruptions or discontinuances as originally required, within 30 days. FDA makes such information public within 45 days of receipt but is not permitted to disclose any information considered confidential or a trade secret.[106]

Notably, drug manufacturers are required to report such interruptions or discontinuances at any time, while device manufacturers are subject to this requirement only in the context of a public health emergency. The reporting requirements specific to drugs and devices are described in more detail below.

Drugs

Congress first required certain drug manufacturers to report shortage-related information to FDA in 1997, with enactment of the Food and Drug Administration Modernization Act of 1997 (FDAMA; P.L. 105-115). Subsequent legislation—FDASIA (P.L. 112-144) and the CARES Act (P.L. 116-136)—expanded these requirements.[107] As amended, the FFDCA requires a manufacturer of a drug that is life-supporting, life-sustaining, or intended to prevent or treat a debilitating disease or condition to notify FDA of any permanent discontinuance or interruption in the manufacture of the drug (or API of such drug) that is likely to disrupt its U.S. supply.[108] The notification must include the reasons for the interruption or discontinuance, information about the source of the API and alternative sources, and whether any associated device used in the preparation or administration of the drug has contributed to the shortage, among other information. In addition, as mandated by the CARES Act amendments to the FFDCA, a manufacturer of a drug, API, or associated medical device subject to these notification requirements must develop, maintain, and implement a redundancy risk management plan, as appropriate, for each establishment that manufactures such a drug or its API.[109] The risk

generally outside the scope of this report.

[105] FFDCA §506C(c) [21 U.S.C. §356c(c)]; FFDCA §506J(c); 21 U.S.C. §356j(c).

[106] FFDCA §506C(d) and (f) [21 U.S.C. §356c(d) and (f)]; FFDCA §506J(e) [21 U.S.C. §356j(e)].

[107] Section 131 of FDAMA established FFDCA Section 506C requiring that a sole-source manufacturer of an approved drug that is life-supporting, life-sustaining, or intended for use in the prevention or treatment of a debilitating disease or condition notify FDA of any discontinuance in the manufacture of the drug. Section 1001(a) of FDASIA amended FFDCA Section 506C, among other things, to expand these reporting requirements beyond sole-source manufacturers and to require notification of any interruption in manufacturing, not just discontinuance. Section 3112 of the CARES Act further amended FFDCA Section 506C to require a manufacturer to notify FDA of any permanent discontinuance or interruption in the manufacture of an API—not just the finished drug—that is likely to lead to a meaningful disruption in the supply of the API of such drug.

[108] FFDCA §506C(a); 21 U.S.C. §356c(a).

[109] FFDCA §506C(j); 21 U.S.C. §356c(j).

management plan, which is subject to inspection and copying by FDA, should identify and evaluate risks to the supply of the drug, as applicable, for each facility in which the drug or API is manufactured.

Devices

As mandated by the CARES Act (P.L. 116-136), device manufacturers are required to report to FDA during or prior to a public health emergency any permanent discontinuance of production, or interruption in production, likely to lead to a significant disruption in the supply of a device, including the reasons for the discontinuance or interruption.[110] This information must be reported to FDA at least six months prior to occurrence, or as soon as is practical.[111]

FDA has issued guidance to help affected manufacturers implement this provision in the context of COVID-19.[112] The guidance, in addition to outlining the requirements specified in statute, specifies additional voluntary information that would help the agency identify shortages. Such information includes, among other things, how COVID-19 has affected the ability to manufacture or distribute a device, and how reliance on a critical supplier affected by COVID-19 may have an adverse impact on the ability to manufacture a device.[113]

Shortage Lists

To make the public aware of supply chain disruptions, FDA is required, by law, to maintain public, up-to-date lists of drugs and devices that are in short supply.[114] FDA publishes lists of drugs and devices that the agency determines are in shortage based on the information it receives from various entities. Such lists must include the name of the drug in shortage, the name of the manufacturer, and the estimated duration of and reason for the shortage, as determined by FDA. The agency maintains this list in the form of a searchable database for drugs.[115] FDA publishes a separate list of CBER-regulated biologics that are in shortage.[116]

Similarly, FDA is required to establish and maintain a device shortage list. This list includes, among other things, the category or name of the device in shortage and, as determined by FDA, the reason(s) for the shortage (e.g., demand increase for the device) and the expected duration of the shortage, in the context of a public health emergency. For example, FDA has recently published a list of devices that are in shortage during the COVID-19 public health emergency.[117]

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[110] FFDCA §506J(a); 21 U.S.C. §356j(a).

[111] FFDCA §506J(b); 21 U.S.C. §356j(b). Per FDA guidance, FDA interprets "as soon as is practicable" to mean no later than seven calendar days after the discontinuance or interruption in manufacturing occurs. FDA, *Guidance for Industry and Food and Drug Administration Staff: Notifying CDRH of a Permanent Discontinuance or Interruption in Manufacturing of a Device Under Section 506J of the FD&C Act During the COVID-19 Public Health Emergency*, p. 5, June 2020, https://www.fda.gov/media/137712/download, (hereinafter FDA, *Guidance: Notifying CDRH of a Permanent Discontinuance or Interruption in Manufacturing of a Device Under Section 506J of the FD&C Act During the COVID-19 Public Health Emergency*).

[112] FDA, *Guidance: Notifying CDRH of a Permanent Discontinuance or Interruption in Manufacturing of a Device Under Section 506J of the FD&C Act During the COVID-19 Public Health Emergency*.

[113] FDA, *Guidance: Notifying CDRH of a Permanent Discontinuance or Interruption in Manufacturing of a Device Under Section 506J of the FD&C Act During the COVID-19 Public Health Emergency*, pp. 11-12.

[114] FFDCA §506E [21 U.S.C. §356e]; FFDCA §506J(g) [21 U.S.C. §356j(e)].

[115] FDA, "FDA Drug Shortages," https://www.accessdata.fda.gov/scripts/drugshortages/.

[116] FDA, "CBER-Regulated Products: Current Shortages," https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/cber-regulated-products-current-shortages.

[117] FDA, "Medical Device Shortages During the COVID-19 Public Health Emergency," https://www.fda.gov/medical-

The FFDCA requires that such drug and device shortage information be made public unless it is considered confidential, a trade secret, or determined by FDA to be harmful to the public (e.g., increases the possibility of hoarding). These drug and device shortage lists do not disclose the location of the manufacturers.

Drug Supply Chain and Security

The Drug Supply Chain Security Act (DSCSA), enacted as Title II of the Drug Quality and Security Act (DQSA, P.L. 113-54), expanded FDA's authority to monitor the drug supply chain and prevent suspect or illegitimate drugs (e.g., counterfeit or diverted drugs) from getting to consumers.[118] Pursuant to changes made by the DSCSA, certain trading partners (i.e., manufacturers, repackagers, wholesale distributors, and dispensers) are required to maintain and exchange certain transaction information (e.g., drug product name, NDC, shipment date) with respect to a drug.[119] Manufacturers and repackagers are required to affix a "product identifier" on packages for certain prescription drugs. If a trading partner determines itself to be in possession of a drug that is suspect or illegitimate, the trading partner must take certain steps to prevent the drug from being distributed (e.g., quarantine or dispose of the product, notify FDA and other trading partners). The law requires that not later than 10 years after enactment, an electronic, interoperable system be used to identify and trace at the package level certain prescription drugs as they are distributed in the United States.[120] The DSCSA is required to be implemented over time. As such, certain requirements have taken effect (e.g., establishment of product verification systems by trading partners), while others (e.g., establishment of an electronic interoperable system) have not.[121] Certain DSCSA requirements may be waived if the HHS Secretary declares a public health emergency under PHSA Section 319. There are no parallel requirements for devices.

Select Issues for Congress

Certain concerns about the U.S. medical product supply chain existed prior to the emergence of COVID-19. In the context of the ongoing pandemic, however, addressing those concerns has become more urgent. Of particular importance to many are gaining a better understanding of certain aspects of the medical product supply chain, U.S. reliance on foreign sources of medical products, and the federal government's ability to oversee the supply chain and mitigate future disruptions. In particular, some stakeholders and Members of Congress have raised concerns about the lack of information sharing and publicly available data regarding location and quantity of medical product manufacturing. However, the publication of certain medical product-related information and data may be constrained when regarded as a trade secret or confidential commercial information. This section discusses three overarching issues in the context of FDA's existing authority:

1. Gaps or loopholes in reporting requirements to FDA limit the agency's ability to oversee the medical product supply chain.

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devices/coronavirus-covid-19-and-medical-devices/medical-device-shortages-during-covid-19-public-health-emergency.

[118] The DQSA, enacted on November 27, 2013, amended FFDCA Chapter V to add a new Subchapter H "Pharmaceutical Distribution Supply Chain."

[119] FFDCA §582(a)-(e); 21 U.S.C. §360eee-1(a)-(e).

[120] FFDCA §582(g); 21 U.S.C. §360eee-1(g).

[121] FDA, "Drug Supply Chain Security Act (DSCSA)," https://www.fda.gov/drugs/drug-supply-chain-integrity/drug-supply-chain-security-act-dscsa.

2. Limitations in currently available supply chain data make it challenging to determine how reliant the United States is on foreign medical product manufacturers.
3. A lack of transparency in the medical product supply chain may contribute to product shortages and pose a risk to national security.

These issues are discussed in further detail below, along with potential considerations for policymakers.

Gaps in Reporting Requirements and Limits to FDA Oversight

CDER maintains a catalog of all establishments manufacturing drugs for the United States, whether they are doing so through an approved application or by registering and listing to supply drugs for the U.S. market. The catalog includes establishments making API and finished drugs. However, the data available to CDER are limited. For example, CDER has limited information about establishments that provide API for drug products that do not need an approved application from FDA to be marketed (e.g., OTC monograph drugs). According to testimony from CDER Director Janet Woodcock, "API suppliers for such products may not register their facility with FDA if they are sending material to a drug product manufacturer outside the United States to make the FDF, which is then sold in the United States."[123] As an example, in the case of an establishment in China manufacturing an API that is exported to Germany to be made into a finished OTC monograph drug that is then exported to the United States, the establishment in China may not be registered with FDA, since it is not importing directly to the United States. The facility in Germany would be required to register with FDA and provide, as part of the listing information, the name and UFI of every other establishment that manufactures the drug (e.g., the facility in China) and the type of operation performed at each such establishment.[124] However, the API facility in China may not be captured by the listing requirements or annual manufacturing quantity reporting requirements established by the CARES Act. As mentioned, while FDA may also obtain information about a foreign API manufacturer through the NDA process, the agency has limited information about upstream

Exceptions During Emergencies

Under emergency circumstances such as the COVID-19 pandemic, FDA may waive some of the requirements discussed in this report. In particular, an emergency use authorization (EUA) allowing for the distribution and use of an unapproved medical product enables FDA to waive CGMPs and exempts EUA products from the registration and listing requirements. FDA has issued several EUAs during the COVID-19 pandemic. While the purpose of these EUAs was to increase availability of and access to PPE, ventilators, drugs, and other medical products, waiving or modifying regulatory requirements is not without risk and may affect the safety, effectiveness, and quality of the medical product. For example, in April 2020, FDA issued an EUA allowing certain non-FDA-cleared respirators to be imported from China. However, FDA subsequently amended the EUA to exclude certain previously authorized respirators because they failed to demonstrate adequate filtration performance in later testing.[122]

[122] FDA, "Certain Filtering Facepiece Respirators from China May Not Provide Adequate Respiratory Protection - Letter to Health Care Providers," June 7, 2020, https://www.fda.gov/medical-devices/letters-health-care-providers/certain-filtering-facepiece-respirators-china-may-not-provide-adequate-respiratory-protection-letter.

[123] FDA, Testimony of Dr. Janet Woodcock, "Safeguarding Pharmaceutical Supply Chains in a Global Economy."

[124] 21 C.F.R. §207.49(a)(12)(ii). See also GAO-10-961, *FDA Has Conducted More Foreign Inspections and Begun to Improve Its Information on Foreign Establishments, but More Progress Is Needed*, September 2010, p. 10, https://www.gao.gov/new.items/d10961.pdf.

establishments involved in the manufacture of drug products that are not subject to an NDA or ANDA (e.g., compounded drugs or OTC monograph drugs).[125]

Given the gaps in existing requirements, legislation has been introduced that would explicitly require a foreign-based establishment to register with FDA, list the drugs manufactured for commercial distribution, and report quarterly on quantity manufactured, regardless of whether the finished drug or API undergoes further manufacture or processing at a separate establishment prior to being imported or offered for import into the United States.[126]

Limitations also have been identified in reporting requirements related to drug and device shortages. As mentioned, the CARES Act established new requirements for devices and expanded existing reporting requirements for drugs to include interruptions in manufacturing of API (see the "Drugs" section of this report). However, manufacturers are not required to report to FDA if a shortage is due to other factors, for example, an increase in product demand or an export restriction imposed by the country in which the product is manufactured. The CARES Act provision regarding devices is applicable only in the context of a public health emergency. Although reported shortages of personal protective equipment (PPE) and ventilators have occurred during the COVID-19 public health emergency, device shortages can occur under other circumstances. For example, prior to COVID-19, concerns about medical device shortages arose due to the closure of ethylene oxide sterilization facilities that were not in compliance with U.S. Environmental Protection Agency (EPA) standards.[127] When the facilities closed, FDA relied on the manufacturers' voluntary reports on the device shortages. Legislation has been introduced that would expand reporting of device manufacturing interruptions, as well as device shortage lists, beyond the context of public health emergencies.[128] In addition, some legislation that has been introduced would allow for importation of unapproved devices in the case of a device shortage,[129] an authority that currently exists for drugs, but not for devices.[130]

The addition of registration and reporting requirements raises an inherent tension between providing FDA with needed, timely information and placing additional, potentially burdensome requirements on manufacturers. If such registration and reporting requirements are added, it is unclear whether they will give FDA the information needed in real-time to proactively mitigate disruptions in the medical product supply chain. Further, some companies do not properly comply with the registration and listing requirements, which can hinder the agency's ability to access accurate, up-to-date information.[131] To address this issue, as described earlier in this report, there are certain reporting requirements for discontinuances or interruptions in manufacturing. Some legislation that has been introduced would require quarterly reporting of certain information, such

[125] FDA, Testimony of Dr. Janet Woodcock, "Safeguarding Pharmaceutical Supply Chains in a Global Economy." See also GAO, *DRUG SAFETY, Better Data Management and More Inspections Are Needed to Strengthen FDA's Foreign Drug Inspection Program*, GAO-08-970, September 2008, p. 18, https://www.gao.gov/assets/290/281366.pdf.

[126] H.R. 6800 (116th Congress) §30515 and S. 3781 (116th Congress).

[127] FDA, "Statement on concerns with medical device availability due to certain sterilization facility closures," October 25, 2019, https://www.fda.gov/news-events/press-announcements/statement-concerns-medical-device-availability-due-certain-sterilization-facility-closures.

[128] H.R. 6049 (116th Congress); H.R. 6062 (116th Congress); S. 3468 (116th Congress); S. 3343 (116th Congress).

[129] H.R. 6062 (116th Congress).

[130] FFDCA §801(d)(1)(B) [21 U.S.C. §381(d)(1)(B)]

[131] See, for example, FDA, "Warning Letter: NuCare Pharmaceuticals Inc," September 26, 2019, https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/nucare-pharmaceuticals-inc-588096-09262019.

as the amount of drug or device manufactured.[132] However, it is unclear whether increasing the frequency of reporting information already submitted to the agency will be useful.

Limitations of Currently Available Data

The COVID-19 pandemic has underscored concerns regarding U.S. reliance on foreign countries for medical products, particularly drugs and APIs. A frequently cited figure is that 80% of APIs are made overseas, although questions remain about the origin of this figure.[133] Regardless, the extent to which the United States relies on other countries for medical products is not entirely known due to limitations in data collected by FDA and trade data. Limitations in FDA data are described below; trade data are discussed in CRS Report R46304, *COVID-19: China Medical Supply Chains and Broader Trade Issues*.

API

Historically, FDA has been able to describe, in general, where drug manufacturing sites are located (e.g., what percentage of API facilities manufacturing drugs for the U.S. market are located outside the United States or in a specific country), but not the volume of API manufactured.[134] According to Dr. Woodcock's 2019 congressional testimony,

> Although CDER can describe the locations of API manufacturing facilities, we cannot determine with any precision the volume of API that China is actually producing, or the volume of APIs manufactured in China that is entering the U.S. market, either directly or indirectly by incorporation into finished dosages manufactured in China or other parts of the world.[135]

This limitation exists because although drug manufacturers are required to register their establishments with FDA and list the drugs they produce for commercial distribution, registrants are not required to report to FDA on the volume they are manufacturing. In addition, APIs made in registered establishments may be used to make finished drugs for both the U.S. market and other countries, and some APIs sold in the United States are subsequently formulated into finished drugs that are then exported.[136] As such, FDA generally has been able to determine which facilities are manufacturing a drug but unable to determine the quantity manufactured at each facility, particularly in the case of API. Provisions in the CARES Act attempt to remedy this gap

[132] H.R. 6800 (116th Congress) §30515(c); S. 3781 (116th Congress).

[133] For example, the 2019 annual report to Congress from the U.S.-China Economic and Security Review Commission states that the United States sources 80% of its APIs from foreign countries and has identified China as the world's largest producer of APIs. A 2011 FDA report, *Pathway to Global Product Safety and Quality*, states that 80% of APIs come from overseas and cites the 1998 GAO report *Improvements Needed in the Foreign Drug Inspection Program* as the source of this number. The 1998 GAO report, in turn, states, "According to FDA, as much as 80 percent of the bulk pharmaceutical chemicals used by U.S. manufacturers to produce prescription drugs is imported."

[134] FDA, Testimony of Judith McMeekin, Associate Commissioner for Regulatory Affairs, Mark Abdoo, Associate Commissioner for Global Policy and Strategy, and Douglas Throckmorton, Deputy Director for Regulatory Programs—Center for Drug Evaluation and Research, "COVID-19 and Beyond: Oversight of the FDA's Foreign Drug Manufacturing Inspection Process," June 2, 2020, https://www.fda.gov/news-events/congressional-testimony/covid-19-and-beyond-oversight-fdas-foreign-drug-manufacturing-inspection-process-06022020, (hereinafter, FDA, Testimony of Judith McMeekin, Mark Abdoo, and Douglas Throckmorton, "CDER COVID-19 and Beyond: Oversight of the FDA's Foreign Drug Manufacturing Inspection Process").

[135] FDA, Testimony of Dr. Janet Woodcock, "Safeguarding Pharmaceutical Supply Chains in a Global Economy."

[136] FDA, Testimony of Dr. Janet Woodcock, "Safeguarding Pharmaceutical Supply Chains in a Global Economy."

by establishing annual reporting requirements for manufacturing quantity of drugs,[137] and legislation has been introduced to further expand this reporting requirement.[138]

FDA reports that between 70%-90% of API facilities are located outside of the United States, and that these numbers vary over time. For example,

- According to June 2020 congressional testimony from FDA officials, "As of May 2020, 26 percent of facilities manufacturing APIs and 46 percent of the facilities producing finished dosage forms (FDFs) of human drugs for the U.S. market were located in the U.S."[139]
- According to October 2019 congressional testimony from FDA CDER Director Janet Woodcock, "As of August 2019, only 28 percent of the manufacturing facilities making APIs to supply the U.S. market were in our country. By contrast, the remaining 72 percent of the API manufacturers supplying the U.S. market were overseas, and 13 percent are in China."[140]
- According to FDA's October 2019 drug shortages report, "In 2018, 88 percent of the manufacturing sites making APIs and 63 percent of sites making finished dosage forms (FDFs) were located overseas (FDA Internal Memorandum 2019; Van Den Bos 2009)."[141]
- According to FDA's October 2019 At a Glance fact sheet, "about 80 percent of active pharmaceutical ingredients manufacturers are located outside of the U.S."[142]

As FDA has noted, information in the CDER site catalog is continually updated, and the numbers regarding facility location generally represent "a snapshot at a point in time."[143]

Other Medical Product Data

FDA reports some data on foreign-sourced products in terms of import lines. FDA uses the term *import line* to denote each distinct regulated product within a shipment through CBP.[144] An import line does not indicate volume or quantity imported, nor does it necessarily comport with other figures provided by FDA. For example, according to the agency's import summary dashboard, in FY2019, 45,220,000 total lines of FDA-regulated products were imported, of which 21,487,882 were devices (48%) and 1,011,202 (2%) were drugs and biologics.[145] However, according to the

[137] FFDCA §510(j)(3) [21 U.S.C. §360(j)(3)], as amended by §3112(e) of the CARES Act.

[138] See, for example, H.R. 6800 (116th Congress) §30515.

[139] FDA, Testimony of Judith McMeekin, Mark Abdoo, and Douglas Throckmorton, "CDER COVID-19 and Beyond: Oversight of the FDA's Foreign Drug Manufacturing Inspection Process."

[140] FDA, Testimony of Dr. Janet Woodcock, "Safeguarding Pharmaceutical Supply Chains in a Global Economy."

[141] FDA, "Drug Shortages: Root Causes and Potential Solutions," initial report was published in October 2019 and subsequently updated in March 2020, p. 27, https://www.fda.gov/media/131130/download.

[142] FDA, "Fact Sheet: FDA at a Glance," October 18, 2019, https://www.fda.gov/about-fda/fda-basics/fact-sheet-fda-glance, (hereinafter, FDA, "Fact Sheet: FDA at a Glance").

[143] FDA, Testimony of Dr. Janet Woodcock, "Safeguarding Pharmaceutical Supply Chains in a Global Economy."

[144] According to Chapter 6 of the FDA Investigations Operations Manual, p. 33, https://www.fda.gov/media/75256/download: "A line is each portion of an entry which is listed as a separate item on an entry document. An importer may identify goods in an entry in as many portions as he chooses, except each item in the entry having a different tariff description and rate must be listed separately."

[145] FDA, "Imports Summary," https://datadashboard.fda.gov/ora/cd/impsummary.htm. The remaining 50% of FDA-regulated product import lines include cosmetics, human foods, animal feed, houseware- and food-related products,

agency's October 2019 fact sheet, about 35% of devices used in the United States are imports, and 70% of biologics sales are imports.[146] Given that FDA generally does not make public how these metrics are calculated or what data source they are based on, precisely determining U.S. reliance on foreign sources of medical supplies is difficult. Further, limited data on volume manufactured makes it difficult to ascertain how much of a medical product or its components is manufactured in a specific country.

In October 2019, FDA reported that 52% of registered facilities manufacturing devices are located in the United States.[147] However, as noted above, FDA data do not provide a detailed breakdown of where specific devices or device components are made and do not quantify the amount or proportion of devices made in a specific country. Other resources provide some insight regarding where select device components are made. For example, proceedings from a 2018 NASEM meeting note that "90 percent of the latex for sterile gloves is produced in Malaysia ... and a significant portion of surgical hand instruments are manufactured in Pakistan."[148] However, the report generated from those proceedings did not specify how these data were determined, and did not provide more comprehensive data across the range of devices on the market. Different medical device industry reports by country[149] and trade data may be used to determine where some devices or device components are made, but these data have limitations as well.[150]

Lack of Transparency in the Supply Chain

The location or locations in which a finished drug or its ingredients are manufactured are not required to be disclosed on the drug's label. This also applies to devices. Instead, a drug or device in finished package form must contain the name and place of business of the manufacturer, packer, *or* distributor.[151] As mentioned above, product labeling and public FDA databases do not disclose the country of origin or the location of drug and device manufacturers. Health care providers and health care facilities may be particularly affected by this omission. For example, hospitals often make purchasing decisions without any information about drug manufacturing location or data on manufacturing quality.[152] A hospital may not know that a critical drug is made in a hurricane-prone location or in a country that has imposed export restrictions, or that the establishment manufacturing the drug has a history of violating FDA requirements. This lack of transparency may make it difficult for hospitals to anticipate supply chain interruptions and drug shortages. In addition, although drug manufacturers must comply with CGMPs, few incentives exist for drug manufacturers to engage in mature quality management systems that go beyond CGMPs. As such, FDA has supported the idea of providing information to purchasers for health care systems, and potentially consumers more broadly, about the quality management systems of

radiological health products, and tobacco products.

[146] FDA, "Fact Sheet: FDA at a Glance."

[147] FDA, "Fact Sheet: FDA at a Glance."

[148] NASEM, "Impact of the Global Medical Supply Chain on SNS Operations and Communications: Proceedings of a Workshop," July 18, 2018, p. 10, https://www.ncbi.nlm.nih.gov/books/NBK525648/ doi: 10.17226/25149.

[149] See for example, IBISWorld, "Medical Device Manufacturing Industry in the US - Market Research Report," April 2020, https://www.ibisworld.com/united-states/market-research-reports/medical-device-manufacturing-industry/.

[150] CRS Report R46304, *COVID-19: China Medical Supply Chains and Broader Trade Issues*.

[151] FFDCA §502(b)(1) [21 U.S.C. §352(b)(1)]. 21 C.F.R. §201.1(a) and §801.1.

[152] ASHP, "Statement for the Record: Improving Safety and Transparency in America's Food and Drugs," Energy and Commerce Subcommittee on Health, January 29, 2020, https://www.ashp.org/Advocacy-and-Issues/Key-Issues/Drug-Pricing/Energy-and-Commerce-Jan-29.

the facilities in which drugs are manufactured.[153] To implement this idea, the agency would assign a quality rating to a manufacturing facility and drug companies could, at their discretion, disclose this rating to purchasers and the general public.[154] It is not clear how many manufacturers would be willing to participate in such a program—particularly those without mature quality management systems in place—and to disclose publicly a rating that is less than favorable.

Safety concerns regarding drugs can stem from manufacturing quality issues. In contrast, safety concerns and adverse events regarding certain devices are more commonly associated with device premarket review mechanisms, which can be less stringent than those for drugs.[155] In an effort to enhance postmarket surveillance of devices, the FDA Amendments Act of 2007 (FDAAA) and FDASIA required FDA to issue regulations establishing a unique device identification (UDI) system for devices. The UDI system enables rapid identification of a device and its attributes, especially those that could affect its safety and effectiveness. Among other things, the UDI system is intended to reduce medical error, simplify integration of device use information into data systems, and rapidly identify devices with associated adverse events.[156] A device labeler (or its designated contact) is required to provide FDA with certain information, which is then entered into the publically available Global Unique Device Identification Database (GUDID).[157] Supply chain data (e.g., location of manufacturing and large-scale distribution data) are generally not required to be reported as part of the UDI system. The location information of the labeler (or its designated contact) is reported. This contact information is not always made available to the public through the GUDID. Distribution data are available only in the context of the number of individual single-use devices produced in a single device package.[158] Furthermore, certain EUA-authorized PPE distributed and used during the COVID-19 public health emergency have been exempted from these UDI requirements altogether.[159] Although the UDI system is intended to address the issue of device safety concerns and adverse events, Congress may consider requiring device labelers to include certain supply chain information on the UDI label and in the GUDID.

Some stakeholders have expressed concern that U.S. consumers do not know where their drugs are coming from and that they may be unknowingly accepting risks associated with drugs made in certain countries. Such stakeholders have recommended that this information be publicly available. For example, the 2019 annual report to Congress of the U.S.-China Economic and Security Review Commission recommended that "Congress enact legislation requiring drug companies to list active pharmaceutical ingredients and their countries of origin on labels of imported and domestically produced finished drug products."[160] Other stakeholders have made

[153] FDA, "To Help Reduce Drug Shortages, We Need Manufacturers to Sell Quality—Not Just Medicine," October 24, 2019, https://www.fda.gov/news-events/fda-voices/help-reduce-drug-shortages-we-need-manufacturers-sell-quality-not-just-medicine, (hereinafter, FDA, "To Help Reduce Drug Shortages, We Need Manufacturers to Sell Quality—Not Just Medicine").

[154] FDA, "To Help Reduce Drug Shortages, We Need Manufacturers to Sell Quality—Not Just Medicine."

[155] See, for example, IOM (Institute of Medicine), Medical Devices and the Public's Health: The FDA 510(k) Clearance Process at 35 Years, Washington, DC, July 2011.

[156] FDA, "Unique Device Identification System," 78 *Federal Register* 58785, September 24, 2013.

[157] 21 C.F.R. Part 830 subpart E.

[158] FDA, *Guidance for Industry and Food and Drug Administration Staff: Global Unique Device Identification Database (GUDID)*, June 2014, https://www.fda.gov/media/86569/download.

[159] FDA, "Emergency Use Authorization (EUA) for Face Masks," revised letter dated April 24, 2020, https://www.fda.gov/media/137121/download.

[160] U.S.-China Economic and Security Review Commission, 2019 Annual Report to Congress, Chapter 3 Section 3-Growing U.S. Reliance on China's Biotech and Pharmaceutical Products, https://www.uscc.gov/annual-report/2019-annual-report.

similar recommendations, for example, to require disclosure of country of origin of drugs that are sold to the Department of Defense.[161] Legislation has been introduced that would require disclosure of this information in some manner for drugs. For example, some proposals would require that drug labels specify the country of origin of each active ingredient contained in the drug[162] and disclose the location of the manufacturer of each active and inactive ingredient.[163] Other proposals would require that the drug manufacturer maintain on its website information about each country in which a drug is manufactured.[164] None of these proposals have been enacted, and it is unclear how this information would affect consumer decision making, particularly for sole-source drugs made in a foreign country for which there is no U.S.-made alternative.

Concluding Observations

For years, stakeholders have expressed concern regarding the transparency and resilience of the medical product supply chain. In light of the COVID-19 pandemic, these concerns have been brought to the forefront. Given the potential for disruptions in the supply chain globally, some have argued that U.S. medical products should be primarily manufactured domestically. However, others have argued that despite concerns over shortages, particularly shortages of drugs and APIs said to be made in China, those shortages have not fully transpired as the pandemic has continued. As a result, some stakeholders argue that the supply chain may be more robust when it relies on multiple domestic and foreign establishments—as would be the case, for example, if domestic establishments were severely affected by a surge in COVID-19 cases in a U.S. community with many medical product manufacturers.

The issues raised in this report pertaining to the U.S. medical product supply chain are generally described in the context of FDA's role. The lack of transparency in the medical product supply chain and purported reliance on foreign-made medical products has been framed as a national security issue, particularly with respect to U.S. dependence on China and India for medical products. However, the extent of this dependence is not clear.[165]

In response to these issues, Congress has introduced legislation that would require various government and nongovernment entities to study the U.S. medical product supply chain. For example, the recently enacted CARES Act requires the NASEM to examine and report on the security of the U.S. medical product supply chain, including U.S. dependence on critical drugs and devices from other countries.[166] The report must assess and evaluate U.S. dependence on critical drugs and devices from other countries; provide recommendations (e.g., a plan to improve resiliency of the supply chain); and address any supply vulnerabilities or potential disruptions that

[161] Testimony of Rosemary Gibson, Author of "China Rx: Exposing the Risks of America's Dependence on China for Medicine" before the U.S. Congress, House Committee on Energy and Commerce, Subcommittee on Health, 116th Cong., 1st sess., October 30, 2019, https://energycommerce.house.gov/sites/democrats.energycommerce.house.gov/files/documents/Testimony-Gibson-API_103019.pdf.

[162] S. 3757 (116th Congress), §2 Subsection (c).

[163] S. 3633 (110th Congress).

[164] S. 3105 (115th Congress).

[165] For example, FDA data indicate that 13% of facilities that make API for the U.S. market are located in China and 19% are located in India, but the volume of drugs manufactured in these countries is unknown. See FDA, Testimony of Judith McMeekin, Mark Abdoo, and Douglas Throckmorton, "CDER COVID-19 and Beyond: Oversight of the FDA's Foreign Drug Manufacturing Inspection Process."

[166] P.L. 116-136, §3101.

would significantly affect or pose a threat to public health or national security, as appropriate. In conducting the study and developing the report, NASEM must consider input from federal departments and agencies and consult with stakeholders through public meetings and other forms of engagement. In addition, legislation has been introduced that would require the Secretaries of HHS, Homeland Security, and Defense to individually conduct annual risk assessments of the medical product supply chain and to submit those assessment to Congress.[167] Although drug and device manufacturers are required to report various supply chain information to FDA, this information generally has not been required to be shared with other agencies or departments. As such, legislation has been introduced that would require FDA to share certain supply chain information with the Assistant Secretary for Preparedness and Response (ASPR) and the Department of Defense.[168]

Various legislative proposals related to the medical product supply chain have been introduced in the 116th Congress (see **Appendix B**). These proposals include, among other things, commissioning studies; expanding manufacturer reporting requirements and information sharing across agencies; restricting federal health programs from purchasing foreign-made drugs; and expanding and incentivizing use of advanced manufacturing technologies for domestic drug and device manufacturing.

[167] See, for example, S. 3780 (116th Congress).

[168] See, for example, S. 3781 (116th Congress).

Appendix A. Selected Laws Authorizing and Amending Registration and Reporting Requirements

Year	Law	Summaries of Selected Provisions
1938	The Federal Food, Drug, and Cosmetic Act (FFDCA, P.L. 75-717)	Drug Approval Requirements: Required that a drug is demonstrated to be safe prior to marketing. The FFDCA, as subsequently amended, authorizes FDA to regulate the safety and effectiveness of drugs and devices (and other products).
1962	The Kefauver-Harris Drug Amendments to the FFDCA (P.L. 87-781)	Drug Establishment Registration: Established new FFDCA Section 510 requiring that domestic entities engaged in the manufacture of drugs annually register their establishments with the Secretary and allowing foreign entities engaged in the manufacture of drugs to register their establishments pursuant to regulations promulgated by the Secretary.
1972	The Drug Listing Act of 1972 (P.L. 92-387)	Drug Listing: Amended FFDCA Section 510 to add a subsection (j) requiring registrants to file with the Secretary biannually a list of drugs being manufactured by them for commercial distribution.
1976	The Medical Device Amendments of 1976 (MDA, P.L. 94-295)	Device Establishment Registration and Listing: Amended FFDCA Section 510 to extend registration and listing requirements to device manufacturers.
1997	The FDA Modernization Act (FDAMA, P.L. 105-115)	Foreign Drug Establishment Registration and Listing: Amended FFDCA Section 510(i) to require (rather than allow) establishments that manufacture drugs or devices in foreign countries for importation into the United States to register with the Secretary and to provide specified drug and device listing information. Notification of Drug Discontinuance: Created FFDCA Section 506C to require that a sole-source manufacturer of an approved drug that is life-supporting, life-sustaining, or intended for use in the prevention or treatment of a debilitating disease or condition to notify the Secretary of any discontinuance in the manufacture of the drug.
2002	The Public Health Security and Bioterrorism Preparedness Response Act (P.L. 107-188)	Annual Registration of Foreign Establishments: Amended FFDCA Section 510(i) to require foreign drug and device establishments to register with the Secretary *annually* and expanded the information that must be provided during registration. Importation Statement of Registration: Amended FFDCA Section 801 to allow an imported drug or device to be refused admission into the United States if the importer, owner, or consignee does not, at the time of offering the drug or device for import, submit to the Secretary a statement that identifies the registration under FFDCA Section 510(i) of each establishment involved in the manufacture of that drug or device.
2002	Medical Device User Fee and Modernization Act of 2002 (MDUFMA, P.L. 107-250)	Electronic Registration: Amended FFDCA Section 510 to require that facility registration is submitted to the Secretary electronically. Inspections by Accredited Persons: Amended FFDCA Section 510 to require the Secretary to accredit persons to conduct surveillance inspections of device establishments.
2007	The FDA Amendments Act (FDAAA, P.L. 110-85)	Registration of Domestic Device Establishments: Amended FFDCA Section 510(b) to require that annual registration of domestic device establishments takes place during the period beginning on October 1 and ending on December 31 of each year. Registration of Foreign Establishments: Amended FFDCA Section 510(i) to require foreign establishments to register upon first engaging in the

Year	Law	Summaries of Selected Provisions
		manufacture of a drug or device, and maintained the requirement to register annually thereafter. Device Listing: Amended FFDCA Section 510(j) to require submission of annual, rather than biannual, listing information for devices. Electronic Registration and Listing: Amended FFDCA Section 510 to require that registration and listing information be submitted to the Secretary electronically unless waived by the Secretary. Unique Device Identification System: Amended FFDCA Section 519 to require FDA to promulgate regulations establishing a unique device identification system that requires the label of devices to bear a unique identifier.
2012	The FDA Safety and Innovation Act (FDASIA, P.L. 112-144), Title VII	Registration of Establishments: Amended FFDCA Section 510 to require that annual registration of domestic and foreign drug establishments, as well as foreign device establishments, takes place during the period beginning on October 1 and ending on December 31 of each year; that the registrant provide the unique facility identifier (UFI) of each such drug establishment and a point of contact email address; and that the Secretary specify the UFI system for registration of domestic and foreign drug establishments. Drug Listing and Excipient Information: Amended FFDCA Section 510(j) to require that listing information include the name and place of business of each manufacturer of an excipient of the listed drug. Electronic Registration and Listing: Amended FFDCA Section 510 to require the Secretary to maintain an electronic database to enable FDA personnel to search the database by any field of information submitted in a registration and that uses the UFI system. Risk-based Inspection Frequency: Amended FFDCA Section 510(h) to require FDA to conduct surveillance inspections of foreign and domestic drug and device establishments on a risk-based schedule. Records for inspection: Amended FFDCA Section 704(a) to allow the Secretary to require that drug establishments submit records or other information subject to inspection in advance prior to or in lieu of an inspection. Notification of Interruption of Discontinuance of Drug Production: Amended FFDCA Section 506C to require the manufacturer of a drug that is life-supporting, life-sustaining, or intended for use in the prevention or treatment of a debilitating disease or condition to notify the Secretary of any discontinuance or interruption in its manufacturing. Unique Device Identifier: Amended FFDCA Section 519 to require the Secretary to promulgate regulations regarding the unique device identification system on a specified timeline.
2013	Drug Quality and Security Act (DQSA, P.L. 113-54)	Drug Supply Chain Security: Amended FFDCA Ch. V to add a new subchapter H ("Pharmaceutical Distribution Supply Chain") requiring trading partners within the drug supply chain to maintain and exchange certain transaction information with respect to a drug, among other things.
2017	FDA Reauthorization Act (FDARA, P.L. 115-52)	Improvements to Inspections Process for Device Establishments: Amended FFDCA Section 704 to require the Secretary to review and update processes and standards applicable to domestic and foreign device establishment inspections, other than for-cause inspections, and issue guidance implementing these changes. Such standards must provide for, among other things, pre-announcing the inspection within a reasonable time before it takes place.

Year	Law	Summaries of Selected Provisions
2020	The Coronavirus Aid, Relief, and Economic Security Act (CARES Act, P.L. 116-136)	Notification of Interruption of Discontinuance of API Production: Amended FFDCA Section 506C to require a manufacturer to notify the Secretary of any permanent discontinuance or interruption in the manufacture of an API—not just the finished drug—that is likely to lead to a meaningful disruption in the supply of the API of such drug. Additional Drug Manufacturer Reporting Requirements: Amended FFDCA Section 510(j) to require a registrant to report annually on the amount of each listed drug manufactured for commercial distribution. Notification of Interruption of Discontinuance of Device Production: Added FFDCA Section 506J to require a manufacturer to notify FDA, prior to or during a public health emergency, of any permanent discontinuance or interruption in the manufacture of a device that is likely to lead to a meaningful disruption in the supply of the device.

Source: Created by CRS.

Notes: This table is meant to summarize key laws authorizing and amending the reporting and registration requirements described in this report. Summaries were written by the authors of this report and are not intended to be comprehensive. This table does not include the Biologics Control Act (P.L. 57-244), enacted in 1902, which required annual licensure by the Public Health Service (PHS) of establishments manufacturing biological products for interstate commerce. The Biologics Control Act was revised and recodified (42 U.S.C. §262) when the Public Health Service Act (PHSA) was enacted in 1944. The PHSA provides that a biological product licensed for marketing under the PHSA is also subject to regulation (though not approval) under the FFDCA. As such, biologics are generally subject to the registration and listing requirements in FFDCA Section 510.

Appendix B. Selected Medical Product Supply Chain Legislation Introduced in the 116th Congress

Bill Title	Bill Number	Summary
Prescription for American Drug Independence Act of 2020	H.R. 6670	Would require the HHS Secretary to enter into a contract with NASEM to establish a committee of experts on drug production; conduct a public symposium to analyze U.S. dependence on foreign-made drugs and recommend strategies to end such dependence; and submit a report to Congress on the symposium's proceedings.
Commission on America's Medical Security Act	H.R. 6282; S. 3478	Would require the HHS Secretary to enter into a contract with NASEM to assess and evaluate U.S. dependence on critical drugs and devices that are sourced or manufactured outside of the United States and provide recommendations to address the resiliency of the supply chain for critical drugs and devices.
Protecting Our Pharmaceutical Supply Chain from China Act of 2020	S. 3635; H.R. 6482	Would require the HHS Secretary to (1) compile and maintain a list of all FDA-approved drugs and any API in such drugs that are manufactured outside of the United States and (2) maintain a separate list of drugs based on the first list that are exclusively manufactured in China, or use API or inactive ingredients manufactured in China. Would deem a drug misbranded if its labeling does not specify the country of origin of each API in the drug. Would prohibit the use of federal funds for the purchase of, or reimbursement for, drugs manufactured in China.
Take Responsibility for Workers and Families Act	H.R. 6379	Would require manufacturers or certain sterilizers of essential devices to report to the HHS Secretary a permanent discontinuance or interruption in manufacturing or other circumstances that would lead to a shortage or meaningful disruption in the supply of the device in the United States. Essential devices would be defined as those critical to preventing, screening, diagnosing, treating, or mitigating the spread of a disease or condition during a public health emergency declared under PHSA Section 319. The HHS Secretary would be required to make a list of essential devices publicly available on FDA's website. Would authorize the HHS Secretary to destroy counterfeit devices valued at $2,500 or less (or such higher amount as the Secretary of the Treasury may set by regulation). Would explicitly require establishments in a foreign country engaged in the manufacture of a drug (including API) to register with the HHS Secretary, regardless of whether the drug or API undergoes further manufacture outside the United States prior to importation. Would expand the information that must be submitted as part of drug listing to include certification that the registrant has (1) identified every other establishment where manufacturing is performed for the drug and (2) notified each known foreign establishment manufacturing the drug or API of its inclusion on the list and obligation to register. Would amend the reporting requirement on quantity of drug manufactured added by the CARES Act to make it quarterly instead of annual and would allow the Secretary to require this information to be further delineated.

Bill Title	Bill Number	Summary
		Would require the HHS Secretary, acting through FDA, to designate an institution of higher education as a National Center of Excellence in Continuous Pharmaceutical Manufacturing.
The Pharmaceutical Accountability, Responsibility, and Transparency (PART) Act	S. 3781	Would require drug and device manufacturers to notify the HHS Secretary of (1) any increases in demand of a drug or device that they will be unable to meet and (2) any export restrictions or other limitations imposed on manufacturing or export of a drug (or its APIs) or device (or its components) by the country in which it is manufactured. Would explicitly require establishments within a foreign country engaged in the manufacture of a drug (including API) or device to register with the HHS Secretary, regardless of whether the drug, API, or device undergoes further manufacture outside the United States prior to importation. Would expand the information that must be submitted as part of drug listing to include certification that the registrant has (1) identified every other establishment where manufacturing is performed for the drug and (2) notified each known foreign establishment manufacturing the drug or API of its inclusion on the list and obligation to register. Would amend the reporting requirement on quantity of drug manufactured added by the CARES Act to make it quarterly instead of annual and would expand the information that must be reported, including to devices. Would require FDA to share with ASPR and the Assistant Secretary of Defense for Health Affairs specified drug and device manufacturing data.
The Heroes Act	H.R. 6800	Would explicitly require establishments within a foreign country engaged in the manufacture of a drug (including API) to register with the HHS Secretary, regardless of whether the drug or API undergoes further manufacture outside the United States prior to importation. Would expand the information that must be submitted as part of drug listing to include certification that the registrant has (1) identified every other establishment where manufacturing is performed for the drug and (2) notified each known foreign establishment manufacturing the drug or API of its inclusion on the list and the obligation to register. Would amend the reporting requirement on quantity of drug manufactured added by the CARES Act to make it quarterly instead of annual.
Limit Ongoing Shortages and Stabilize Supply Act of 2020, LOSS Act	H.R. 6660	Would require drug manufacturers to conduct risk assessments to identify vulnerabilities to the supply of a drug and to develop risk mitigation plans. Would expand required reporting of manufacturing interruptions and discontinuances to APIs.
Safe and Secure Medicine Supply for Hardworking Americans Act of 2020	H.R. 6885	Would prohibit the importation of a drug or device that was manufactured at a banned foreign facility, which would be defined in statute. Would also impose duties on drugs from certain countries and create a fund in the Treasury for purposes of incentivizing drug or device companies to increase U.S. manufacturing capacity. Would require the HHS Secretary to (1) compile and maintain a registry of all FDA-approved drugs and any API in such drugs that are manufactured outside of the United States and (2) maintain a separate list of drugs included in the registry for

Bill Title	Bill Number	Summary
		which 50% or more of their API are manufactured outside the United States. Would deem a drug misbranded if its labeling does not specify the country of origin of each API in the drug.
Manufacturing API, Drugs, and Excipients (MADE) in America Act of 2020	H.R. 6930	Would require the HHS Secretary to report to Congress on barriers to domestic manufacturing of APIs, drugs, and devices; expand or establish initiatives for mutual sharing of review and inspection criteria between drug regulatory authorities; report annually on select drug and device inspections conducted in the prior year; continue the program to evaluate and approve new drug manufacturing technologies that are included in drug applications; and designate certain methods of drug manufacturing as advanced manufacturing technologies and take actions to expedite the development and implementation of such method of manufacture for purposes of approval. Would establish a tax credit for drug and device production activities in distressed zones.
Buy American Medical Supply Chain Act of 2020	H.R. 6879	Would require the HHS Secretary to establish and implement a program to maintain U.S. industrial production capacity for items in the SNS "at a level needed to ensure that domestic needs can be met during a surge in worldwide demand due to a pandemic or other widespread emergency."
Help Onshore Manufacturing Efficiencies for Drugs and Devices Act; HOME Act	S. 3780	Would establish within ASPR the Center for Domestic Advanced Manufacturing of Critical Drugs and Devices (Center); require the Center to compile a list of critical drugs and devices to be prioritized for domestic advanced manufacturing and increased domestic production; and establish and oversee a grant and forgivable loan program to support advanced manufacturing and domestic production. Would require FDA to expedite supplemental applications for drugs on the critical drugs and devices list, if approval of the supplemental application would enable incorporation of a manufacturing change intended to enhance drug quality, increase domestic manufacturing of the drug, or incorporate the use of advanced manufacturing. Would allow HHS and DOD to enter into contracts to purchase critical drugs or devices in order to invest in preparedness, the SNS, and mitigate drug and device shortages. Would require the Secretaries of DHS, HHS, and DOD to each conduct separate independent risk assessments of the medical supply chain and report findings to Congress.
Medical Supply Chain Security Act	H.R. 6049; S. 3343	Would require manufacturers of certain devices to notify the HHS Secretary of a permanent discontinuance or interruption in the manufacture of the device that would lead to a meaningful disruption in its supply in the United States. Would require the HHS Secretary, as appropriate, to expedite the review of a device subject to a PMA in which there is, or likely to be, a shortage of the device. Would require manufacturers of drugs or devices that have submitted a notification regarding a permanent discontinuance or interruption to report on an annual basis, or more frequently at the request of the HHS Secretary, information related to manufacturing capacity of such drug or device. Would require device manufacturers that have submitted a notification of permanent discontinuance or interruption to

Bill Title	Bill Number	Summary
		report to select committees of Congress information related to device shortages on an annual basis.
Preventing Essential Medical Device Shortages Act of 2020	S. 3468	Would require manufacturers of essential devices to notify the HHS Secretary of a permanent discontinuance or interruption in the manufacture of the device that would lead to a meaningful disruption in its supply in the United States. The term *essential device* would be defined in regulations that would be required to be promulgated one year after enactment of the act. Would allow for the HHS Secretary to expedite the review of certain premarket applications for devices that are or are likely to be in shortage. The HHS Secretary would be required to publish a public list, updated annually, of essential devices that had received expedited premarket review, among other things. Would additionally require the HHS Secretary to maintain a public up-to-date list of devices that are determined to be in shortage in the United States. Would require a GAO report examining FDA intra-agency coordination, communication, and decision-making in assessing device shortages, including FDA efforts to mitigate any essential device shortages.
To amend certain provisions in the Federal Food, Drug, and Cosmetic Act relating to the discontinuance or interruption in the production of life-saving drugs so as to apply such provisions with respect to life-saving devices, and for other purposes.	H.R. 6062	Would require manufacturers of certain devices to notify the HHS Secretary of a permanent discontinuance or interruption in the manufacture of the device that would lead to a meaningful disruption in its supply in the United States. Would require the HHS Secretary, as appropriate, to expedite select premarket review applications of devices in which there is, or is likely to be, a shortage. Would require device manufacturers that have submitted a notification of permanent discontinuance or interruption to report to select committees of Congress information related to device shortages on an annual basis. Would require the HHS Secretary to maintain a public up-to-date list of devices that are determined to be in shortage in the United States. Would allow for importation of devices not cleared or approved by FDA in the case of a shortage of such device.
Safeguarding Therapeutics Act	H.R. 5663	Would authorize the HHS Secretary to destroy a counterfeit device valued at $2,500 or less (or such higher amount as the Secretary of the Treasury may set by regulation).
Safe Medicine Act	H.R. 5982	Would require the HHS Secretary, in consultation with other appropriate federal departments and agencies, to submit to Congress a report on vulnerabilities to the U.S. medicine supply chain. Would allow FDA to issue a temporary order deeming certain drugs to be misbranded if the drug or its APIs are manufactured in a country that FDA determines may be producing contaminated drugs or APIs as a result of systemic problems of supervision in manufacturing and the labeling does not bear a boxed warning of the potential for contamination.
Securing America's Medicine Cabinet Act of 2020	S. 3432; H.R. 6708	Would require the HHS Secretary to continue the program to evaluate and approve new drug manufacturing technologies that are included in drug applications; to designate certain methods

Bill Title	Bill Number	Summary
		of drug manufacturing as advanced manufacturing technologies and take actions to expedite the development and implementation of such method of manufacture for purposes of approval of drugs and biologics; and to designate eligible institutions of higher education as National Centers of Excellence in Advanced Pharmaceutical Manufacturing.
COVID-19 Emergency Medical Supplies Enhancement Act of 2020	H.R. 6858	"To enhance authorities under the Defense Production Act of 1950 to respond to the COVID–19 emergency, to provide additional oversight of such authorities, and to require a strategy on securing supply chains for medical materials, and for other purposes."
Medical Supply Chain Emergency Act of 2020	S. 3568, H.R. 6390	Would require the President to use authorities under the Defense Production Act of 1950 to require emergency production of medical equipment (e.g., N95 respirators, ventilators) to address the COVID-19 pandemic, and to coordinate and direct the allocation of medical equipment based on requests from governors and the needs of the states, as specified.
Medical Supplies for Pandemics Act of 2020	H.R. 6531	Would require the HHS Secretary to "enhance medical supply chain elasticity and establish and maintain domestic reserves of critical medical supplies (including personal protective equipment, ancillary medical supplies, and other applicable supplies required for the administration of drugs, vaccines and other biological products, medical devices, and diagnostic tests) by creating incentives for manufacturers of medical supplies" to increase emergency stock of critical medical supplies, geographically diversify production, and take other specified actions.
Securing America's Pharmaceutical Supply Chain Act	H.R. 6731	Would allow an executive agency to purchase a drug only if the drug is over 50% sourced, manufactured, and assembled in the United States, except for during emergencies or if the drug is not available in sufficient quantity or quality as over 50% sourced, manufactured, and assembled in the United States. Also would require modification to trade agreements to exclude coverage of essential medicines and medical countermeasures.
Strengthening America's Supply Chain and National Security Act	S. 3538, H.R. 6393	Would require the DOD Secretary, in coordination with the HHS Secretary, to submit to Congress a classified report on DOD's reliance on drugs made at least in part in certain countries; modify how country of origin is determined for drugs; and require the sponsor of a drug to submit, as part of the annual postmarket reporting requirements, information about the source of each active and inactive ingredient in the drug and the percentage of the aggregate amounts of such ingredients from each source.
Country Of Origin Labeling (COOL) Online Act	S. 3707	Would require disclosure of country-of-origin labeling for products "introduced, sold, advertised, or offered for sale" on the internet and would prohibit false and misleading representation of U.S. origin in any labeling, advertising, or other promotional materials of a product.
National Defense Authorization Act for FY2020	H.R. 2500	Section 739 would require the DOD Secretary to conduct a study on the effectiveness of readiness contracts managed by the Customer Pharmacy Operations Center of the Defense Logistics Agency in meeting the military's drug supply needs, as

Bill Title	Bill Number	Summary
		specified, including "an analysis of how the contractual approach to manage drug shortages for military health care can be a model for responding to drug shortages in the civilian health care market in the United States."
Securing America's Medical Supply Chain and Advancing the Production of Life Saving Medicines Act	S. 3942	Would establish the Chief Pharmaceutical and Medical Supply Chain Negotiator in the Office of the United States Trade Representative, who would be responsible for "conducting trade negotiations and enforcing trade agreements related to acts, policies, and practices of foreign governments that fail to appropriately reward United States innovation with respect to pharmaceuticals, to advance domestic production of life-saving medicines, and to secure the United States medical supply chain to eliminate reliance on foreign governments, and for other purposes."
PPE Supply Chain Transparency Act of 2020.	S. 4158	Would require the Administrator of FEMA, in consultation with the HHS Secretary, to submit to select committees of Congress and to make publicly available a report on the supply chain for PPE during the COVID-19 pandemic.

Source: Created by CRS.

Notes: Bills were identified by searching Congress.gov for legislation introduced in the 116th Congress that would amend 21 U.S.C. §360, 21 U.S.C. §356c, or 21 U.S.C. §356j, and includes terms related to drugs or medical devices and the supply chain. The authors of this report selected relevant bills from the result lists. Note that these searches may not have identified all applicable legislation. Bill summaries were written by the authors of this report to describe key provisions and are not intended to be comprehensive.

Abbreviations: API=Active Pharmaceutical Ingredient; ASPR=Assistant Secretary for Preparedness and Response; CARES=Coronavirus Aid, Relief, and Economic Security; DOD=Department of Defense; DHS=Department of Homeland Security; FDA=Food and Drug Administration; FEMA=Federal Emergency Management Agency; GAO=Government Accountability Office; HHS=Department of Health and Human Services; NASEM=National Academies of Science, Engineering and Medicine; PPE=Personal Protective Equipment; PHSA=Public Health Service Act; PMA=Premarket Approval; and SNS=Strategic National Stockpile.

Appendix C. Selected Medical Product Supply Chain Resources

Congressional Hearings

The following congressional hearings feature testimony from Food and Drug Administration (FDA) officials regarding FDA oversight of the medical supply chain.

- U.S. Congress, Senate Finance Committee, *COVID-19 and Beyond: Oversight of the FDA's Foreign Drug Manufacturing Inspection Process*, hearings, 116th Congress, 2nd session, June 2, 2020, https://www.finance.senate.gov/hearings/covid-19-and-beyond-oversight-of-the-fdas-foreign-drug-manufacturing-inspection-process.
- U.S. Congress, House Committee on Energy and Commerce, Subcommittee on Oversight and Investigations, *Securing the U.S. Drug Supply Chain: Oversight of FDA's Foreign Inspection Program*, hearings, 116th Congress, 1st session, December 10, 2019, https://energycommerce.house.gov/committee-activity/hearings/hearing-on-securing-the-us-drug-supply-chain-oversight-of-fda-s-foreign.
- U.S. Congress, House Committee on Energy and Commerce, Subcommittee on Health, *Safeguarding Pharmaceutical Supply Chains in a Global Economy*, hearings, 116th Congress, 1st session, October 30, 2019, https://energycommerce.house.gov/committee-activity/hearings/hearing-on-safeguarding-pharmaceutical-supply-chains-in-a-global-economy.
- U.S. Congress, U.S. - China Economic and Security Review Commission, *Exploring the Growing U.S. Reliance on China's Biotech and Pharmaceutical Products*, hearings, 116th Congress, 1st session, July 31, 2019, https://www.uscc.gov/hearings/exploring-growing-us-reliance-chinas-biotech-and-pharmaceutical-products.

Food and Drug Administration (FDA)

Reports

- U.S. Food and Drug Administration, Drug Shortages Task Force, *Drug Shortages: Root Causes and Potential Solutions*, Updated February 21, 2020, https://www.fda.gov/media/131130/download.
- U.S. Food and Drug Administration, Office of Pharmaceutical Quality (OPQ), *Report on the State of Pharmaceutical Quality, Fiscal Year 2019*, https://www.fda.gov/media/138711/download.
- U.S. Food and Drug Administration, Office of Pharmaceutical Quality (OPQ), *Report on the State of Pharmaceutical Quality, Fiscal Year 2018*, https://www.fda.gov/media/125001/download.

News Releases and Communications

- U.S. Food and Drug Administration, *Coronavirus (COVID-19) Update: FDA prepares for resumption of domestic inspections with new risk assessment system*,

July 10, 2020, https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-prepares-resumption-domestic-inspections-new-risk-assessment-system.

- U.S. Food and Drug Administration, *Coronavirus (COVID-19) Update: FDA updates on surveillance inspections during COVID-19*, May 11, 2020, https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-updates-surveillance-inspections-during-covid-19.
- U.S. Food and Drug Administration, *FDA at a Glance: Regulated Products and Facilities*, October 2019, https://www.fda.gov/media/131874/download.
- U.S. Food and Drug Administration, *Statement on concerns with medical device availability due to certain sterilization facility closures*, October 25, 2019, https://www.fda.gov/news-events/press-announcements/statement-concerns-medical-device-availability-due-certain-sterilization-facility-closures.
- U.S. Food and Drug Administration*, CDER Conversation: Assuring Drug Quality Around the Globe,* May 10, 2019, https://www.fda.gov/drugs/news-events-human-drugs/cder-conversation-assuring-drug-quality-around-globe.
- U.S. Food and Drug Administration, *Statement from FDA Commissioner Scott Gottlieb, M.D., and Director of FDA's Center for Drug Evaluation and Research Janet Woodcock, M.D., on the FDA's continuing efforts to maintain its strong oversight of generic drug quality issues domestically and abroad,* February 22, 2019, https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-and-director-fdas-center-drug-evaluation-and-research-0.

Government Accountability Office (GAO)

Drugs

- U.S. Government Accountability Office, *COVID-19 Complicates Already Challenged FDA Foreign Inspection Program,* GAO-20-626T, June 2, 2020, https://www.gao.gov/products/GAO-20-626T.
- U.S. Government Accountability Office, *Preliminary Findings Indicate Persistent Challenges with FDA Foreign Inspections*, GAO-20-262T, December 2019, https://www.gao.gov/products/GAO-20-262T.
- U.S. Government Accountability Office, *FDA Should Take Additional Steps to Address Factors That May Affect Approval Rates in the First Review Cycle,* GAO-19-565, August 2019, https://www.gao.gov/products/GAO-19-565.
- U.S. Government Accountability Office, *FDA Has Improved Its Foreign Drug Inspection Program, but Needs to Assess the Effectiveness and Staffing of Its Foreign Offices,* GAO-17-143, December 2016, https://www.gao.gov/products/GAO-17-143.
- U.S. Government Accountability Office, *FDA Has Conducted More Foreign Inspections and Begun to Improve Its Information on Foreign Establishments, but More Progress Is Needed*, GAO-10-961, September 2010, https://www.gao.gov/products/GAO-10-961.

- U.S. Government Accountability Office, *Better Data Management and More Inspections Are Needed to Strengthen FDA's Foreign Drug Inspection Program,* GAO-08-970, September 2008, https://www.gao.gov/products/GAO-08-970.
- U.S. Government Accountability Office, *Preliminary Findings Suggest Recent FDA Initiatives Have Potential, but Do Not Fully Address Weaknesses in Its Foreign Drug Inspection Program*, GAO-08-701T, April 2008, https://www.gao.gov/products/GAO-08-701T.
- U.S. Government Accountability Office, *Preliminary Findings Suggest Weaknesses in FDA's Program for Inspecting Foreign Drug Manufacturers*, GAO-08-224T, November 2007, https://www.gao.gov/products/GAO-08-224T.
- U.S. Government Accountability Office, *Improvements Needed in the Foreign Drug Inspection Program,* HEHS-98-21, March 1998, https://www.gao.gov/products/HEHS-98-21.

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- U.S. Government Accountability Office, *Shortcomings in FDA's Premarket Review, Postmarket Surveillance, and Inspections of Device Manufacturing Establishments*, GAO-09-370T, June 2009, https://www.gao.gov/products/GAO-09-370T.
- U.S. Government Accountability Office, *FDA Faces Challenges in Conducting Inspections of Foreign Manufacturing Establishments*, GAO-08-780T, May 14, 2008, https://www.gao.gov/products/GAO-08-780T.
- U.S. Government Accountability Office, *Challenges for FDA in Conducting Manufacturer Inspections*, GAO-08-428T, January 2008, https://www.gao.gov/products/GAO-08-428T.
- U.S. Government Accountability Office, *Status of FDA's Program for Inspections by Accredited Organizations*, GAO-07-147, January 2007, https://www.gao.gov/products/GAO-07-157.

Appendix D. Acronyms Used in this Report

ACE	Automated Commercial Environment System
ANDA	Abbreviated New Drug Application
API	Active Pharmaceutical Ingredient
ASPR	Assistant Secretary for Preparedness and Response
BLA	Biologic License Application
BsUFA	Biosimilar User Fee Act
CARES	Coronavirus Aid, Relief, and Economic Security Act
CBER	Center for Biologics Evaluation and Research
CBP	U.S. Customs and Border Protection
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CGMP	Current Good Manufacturing Practice
CMO	Contract Manufacturing Organization
COVID-19	Coronavirus Disease 2019
DECRS	Drug Establishment Current Registration Site
DHF	Device History File
DSCSA	Drug Supply Chain Security Act
DQSA	Drug Quality and Security Act
EIR	Establishment Inspection Report
EPA	U.S. Environmental Protection Agency
FDA	Food and Drug Administration
FDAAA	FDA Amendments Act of 2007
FDAMA	Food and Drug Administration Modernization Act of 1997
FDASIA	FDA Safety Innovation Act of 2012
FDF	Finished Dosage Form
FFDCA	Federal Food, Drug, and Cosmetic Act
FOIA	Freedom of Information Act
GAO	Government Accountability Office
GDUFA	Generic Drug User Fee Amendments
GUDID	Global Unique Device Identification Database
HHS	Department of Health and Human Services
MDUFA	Medical Device User Fee Amendments
MRA	Mutual Recognition Agreement
NAI	No Action Indicated
NASEM	National Academies of Sciences, Engineering, and Medicine
NDA	New Drug Application

NDC	National Drug Code
OAI	Official Action Indicated
ORA	Office of Regulatory Affairs
OTC	Over-the-Counter
PHSA	Public Health Service Act
PMA	Premarket Approval
QS	Quality System
SSM	Site Selection Model
UDI	Unique Device Identification
VAI	Voluntary Action Indicated

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