



JONES DAY
COMMENTARY

REGULATORY AND LEGISLATIVE RESPONSES TO DRUG SHORTAGES

Over the past year, the problem of drug shortages has received markedly increased attention from the federal government. This July, Congress passed new legislation addressing shortages (Title X of the Food and Drug Administration Safety and Innovation Act, which is better known as the User Fee Bill). President Obama issued an Executive Order last October. The Food and Drug Administration (“FDA”) has promulgated new regulations and a new guidance, and it has devoted increasing resources to addressing shortages.

This increased focus followed in the wake of the much-quoted statistic that the number of shortages tracked by the FDA almost tripled between 2005 and 2010, from 61 to 178. The number rose again in 2011, to 251, amid increasing attention from health-care providers and the mainstream media.¹

Despite the recent activity, drug shortages remain only lightly regulated. Manufacturers must report discontinuances, and a beefed-up reporting obligation is the centerpiece of the recent legislation. But the

FDA cannot demand that a manufacturer produce a drug, nor can the FDA control how a company prices or allocates its products. The FDA’s main tools to deal with shortages are diligence, discretion, and persuasion: helping manufacturers with quality problems return to the marketplace, allowing the distribution of drugs that would be prohibited by a strict interpretation of the regulations, and asking other companies to ramp up to fill the gaps.

The FDA reports that it is making progress. In the six months after the issuance of the Executive Order, the FDA claims to have prevented 128 drug shortages. It credits industry for providing “a six-fold increase in early notifications.”² Still, the problem continues. In the first four months of 2012, 42 new drugs were added to the shortage list,³ which continues to list more than 100 products.⁴

This article sets out the laws and policies framing the government’s responses to drug shortages, and how those laws and policies have changed over the past year.

PROXIMATE AND ROOT CAUSES OF DRUG SHORTAGES

The FDA tracks the immediate causes of supply disruptions. The resulting data show a significant limitation in the FDA's reliance on advance notification of manufacturing discontinuances: only 8 percent of supply disruptions resulted from planned discontinuances.

According to the FDA, the most common causes of shortages, by far, are "problems at manufacturing facility." Such problems are reportedly responsible for 43 percent of supply disruptions. The other reported causes are:

- Delays in manufacturing or shipping (15 percent);
- API shortage (10 percent);
- Loss of manufacturing site (5 percent);
- Non-API component shortage (4 percent);
- Demand increase (4 percent);
- Improper labeling (2 percent); and
- Other / unknown (9 percent).⁵

Manufacturing disruptions would not result in shortages if the affected company (or a competitor) could make up the shortfall through the use of other facilities. But this has proved to be increasingly difficult in recent years. Manufacturers tend to not have much excess capacity, making it hard to produce additional amounts of a drug even when supplies are tight. It is often difficult to convert existing facilities to production of a shortage drug. Many of the drugs in shortage have a complex manufacturing process, often requiring dedicated equipment. Supply chains are increasingly complex and increasingly reliant on outsourcing to overseas facilities. And inventories at all levels of distribution are kept lean, as "just-in-time" inventory systems are increasingly popular.⁶

There is no consensus as to the root causes of shortages or the market conditions that cause them, nor is there a consensus as to how to effect a long-term solution. An analysis by the Department of Health and Human Services is somewhat optimistic. According to this report, many of the shortages ultimately stemmed from the fact that demand for

certain products has soared in recent years, without a corresponding increase in capacity. However, projects to increase capacity are said to be underway. While it will take some time for supply to catch up, "[o]ver time, entry, and expansions in capacity in the industry, should lead to a situation where shortages due to supply disruptions are sporadic and rare." The report's primary recommendation is for the FDA to continue its policy of expediting review of new manufacturing capacity that could alleviate shortages.⁷

Others blame the pricing structure resulting from the 2003 Medicare Modernization Act. According to this theory, the Medicare Modernization Act drove down prices to the point where it is no longer economically feasible for drug manufacturers to maintain adequate capacity.⁸

A harshly worded staff report issued by the House of Representatives blames the FDA. This report concludes that "the crisis was largely sparked by actions of the Food and Drug Administration." According to the report, FDA enforcement activity caused the shutdown of significant manufacturing capacity: "58 percent of the drugs on the shortage list were produced by at least one facility undergoing FDA remediation." The report portrays the FDA's enforcement activity as excessive, claiming that there were no "instances where the shutdown was associated with reports of drugs harming customers."⁹

The FDA fired back in a letter dated July 23, 2012. In that letter, the FDA stated its position that the questioned enforcement activities were justified, that when "manufacturing conditions pose a safety threat to patients ... manufacturers generally must stop production to resolve the problem," that the FDA did not order any shutdowns, and that it is ultimately the responsibility of the manufacturers to ensure the safe production of their products.¹⁰

THE MANUFACTURERS' LEGAL OBLIGATIONS

The Food, Drug, and Cosmetic Act ("FD&C Act") contains many provisions controlling when a manufacturer cannot manufacture a drug, but it contains no affirmative obligation to produce a drug, even in a shortage situation. This remains true, notwithstanding the recent drug-shortage

legislation.¹¹ Similarly, a recent district court opinion held that there is no liability under state tort law for a failure to produce vital medicine.¹²

Section 506C of the FD&C Act addresses “discontinuance or interruption in the production of a lifesaving product.” As recently amended, this section calls for manufacturers of certain drugs to notify the FDA when the discontinuance or interruption of drug manufacturing “is likely to lead to a meaningful disruption in the supply of that drug.” The drugs covered under current Section 506C are those that are “life-supporting,” “life-sustaining,” or used to prevent or treat “a debilitating disease or condition.” Biological products are not currently covered by Section 506C, but the FDA is empowered to change that by regulation.

The manufacturers must give notice at least six months before the discontinuance or interruption. If this is not possible, the manufacturer must provide the notice “as soon as practicable.” Notification will not be construed as an admission of a regulatory violation, nor will it be construed as evidence of off-label marketing.

The current notice requirement reflects a strengthening of the previous version and its implementing regulations.¹³ Previously, the notification duty applied only to “the sole manufacturer” of a drug.

The new drug-shortage legislation also addresses, for the first time, the consequence of a manufacturer’s failure to provide the requisite notice. Under prior law, as the FDA acknowledged, “[t]he advance notification provision in section 506C ... does not include explicit enforcement authority.”¹⁴ Or, as the FDA stated more bluntly in a less-formal report, there is “[n]o consequence for failure to notify.”¹⁵

The current legislation still does not allow the FDA to use its primary enforcement tools. Most violations of the FD&C Act are deemed to be “prohibited acts” under Section 301. Sections 302 to 307 empower the FDA to respond to “prohibited acts” by seeking injunctions, criminal and civil penalties, product seizures, and other remedies. However, failure to provide advance notification of a discontinuance is not (and was not) a “prohibited act” under Section 301, nor did

any other section of the FD&C Act set out any means for the FDA to enforce that obligation.¹⁶

While the usual enforcement provisions of the FD&C Act remain unavailable, the new legislation contains a more creative remedy: The FDA will publicize failures to provide the requisite notice. The FDA is required to “issue a letter” to a noncompliant manufacturer pointing out the violation, and to then post the letter (and any response) on the FDA’s web site.

FORMAL GOVERNMENT EFFORTS TO ADDRESS DRUG SHORTAGES

The notification requirement (Section 506C) was added to the FD&C Act in 1997 through the FDA Modernization Act. The implementing regulations did not arrive until 10 years later.¹⁷ In contrast to this relaxed pace, the past year has seen a far greater focus on shortages; we have seen the issuance of an Executive Order, new regulations, new guidance documents and, in July, legislation. These measures have incrementally expanded the tools at the FDA’s disposal. But mostly, the new measures formalized or mandated existing FDA policy, which remains largely unchanged.

On October 31, 2011, President Obama issued an Executive Order titled “Reducing Prescription Drug Shortages.” The Executive Order requires the FDA to “use all appropriate administrative tools” to combat shortages. These tools include Section 506C, as well as “expand[ing] [the FDA’s] current efforts to expedite its regulatory reviews.” The Order does not identify any other “administrative tool” as available.

Responding to the President’s order, the FDA issued an interim final rule less than two months later.¹⁸ This rule amends the regulations implementing Section 506C. The amendments effectively broadened the notification obligation of Section 506C, to the extent supportable under the then-existing language.¹⁹

In February, the FDA issued a draft Guidance for Industry. The Guidance’s message boils down to: (i) the FDA can be effective in averting shortages given advance warning, and

(ii) manufacturers are requested to provide the FDA with as much notice as possible, even when notice is not required.²⁰

Lastly, Congress passed new legislation to address the subject, as part of the bill that also renews and expands upon the user fee programs. As discussed above, the centerpiece of the drug-shortage legislation is to expand the notification obligation in Section 506C. Another new feature reflects concern that the FDA has been causing shortages through overzealous enforcement. Before sending a warning letter or taking other enforcement action that might result in a shortage, enforcement personnel must communicate with personnel tasked with preventing drug shortages. Then, before acting, the FDA must evaluate the risk of a shortage, together with the risks associated with the contemplated action.²¹

Other provisions of the bill:

- Require the FDA to maintain and publish a drug-shortage list;
- Give priority to the drug applications and facility inspections that could result in mitigating or preventing a shortage;
- Call for the Drug Enforcement Agency (“DEA”) to increase production quotas of controlled substances in response to drug shortages, and to give priority for shortage-related quota requests;
- Make it easier for a hospital to divide and repackage drug doses for use within that hospital’s health system;
- Call for the FDA, the Government Accountability Office, and the DEA to provide reports and increase planning regarding shortage strategy; and
- Provide for implementing regulations.

FDA POLICIES AND INFORMAL EFFORTS TO PREVENT SHORTAGES

The FDA effort to mitigate drug shortages is led by employees of the Drug Shortage Program. Since the FDA lacks authority to impose mandates upon the manufacturers, the FDA’s main tools are publicity, prioritizing, arm-twisting, and “regulatory discretion.”

When first apprised of a shortage or a discontinuance, the FDA is required to inform physician, health-care provider, and patient organizations “to the maximum extent possible.” The FDA’s primary means of publicizing drug shortages is a “drug shortages” page on the FDA web site. The FDA had been posting this information without formal direction from Congress, but the FDA is now required to maintain the list pursuant to a new Section 506E. This publicity helps health-care providers plan for the possibility that they will not be able to obtain the listed drugs.

Publicity, however, is not an unmitigated benefit. The Executive Order found that “some participants in the market may use shortages as opportunities to hoard scarce drugs or charge exorbitant prices.” Where the FDA learns of such activity, it is directed to communicate that information to the Department of Justice to “determine whether these activities are consistent with applicable law.” Such so-called “gray market” transactions are also the subject of congressional scrutiny.²² Furthermore, the FDA and others cast doubt on whether the “gray market” drugs are properly “stored and handled or whether they are expired, counterfeit, or otherwise substandard”²³—and this August a distributor pled guilty to conspiracy to distribute drugs with false pedigrees.²⁴

However, there is widespread consensus that “gray market” transactions are a symptom, not a cause, of the drug shortage problem. There do not appear to be any laws prohibiting limiting redistribution of drugs at any mark-up.

Upon placing a drug on the shortage list, the FDA determines whether the affected drug is “medically necessary,” meaning that it is “used to treat or prevent a serious disease or medical condition for which there is no other adequately available drug product.” Unapproved drugs can be deemed medically necessary, as can unapproved (“off-label”) uses.²⁵ The FDA usually finds that shortage drugs are medically necessary. When the FDA identifies a drug as medically necessary, the FDA will then make it a priority to prevent or alleviate the shortage.

The FDA's simplest tool, and apparently its most effective, is to put filings concerning the shortage drug at the front of the line. Where the supply disruption resulted from manufacturing quality issues, the FDA can help by approving the restart of manufacturing operations as soon as the manufacturer fixes the problem. "Expedited review" can also involve the approval of a new manufacturer to make the product or the API. This February, the FDA expedited its review and approval of methotrexate, a drug used to treat children with leukemia.

The FDA estimates that 71 percent of the shortages it prevents were prevented through "expedited review."²⁶ The recent drug-shortage legislation has now formalized this long-standing policy in a new Section 506C(g).

When a shortage drug is manufactured by multiple suppliers, the FDA frequently will ask other firms to ramp up or initiate production. Where the shortage drug is subject to the Controlled Substances Act, increased production may be subject to quotas imposed by the DEA. The FDA has resolved a few shortages through coordination with the DEA. Under the new legislation, such coordination is now mandatory, and the DEA must respond to shortage-related quota requests within 30 days.²⁷

Lastly, the FDA will sometimes end or prevent shortages through the exercise of "regulatory discretion." This could mean allowing critical medicine to be sold notwithstanding unresolved quality problems. One example of this was allowing a drug to be sold even though it was contaminated with glass shards. A filter was provided with the product, along with instructions to pharmacists to filter the product before administration. The FDA's arsenal also includes permitting the import of unapproved drugs to substitute for a shortage drug. In February, the FDA issued a news release touting that it had addressed the shortage of Doxil, a cancer drug, by temporarily allowing the import of unapproved Lipodox.²⁸

CONCLUSION

Substantial efforts are underway to mitigate drug shortages. The FDA's Drug Shortage Program has gone from four employees to 11, Congress has given them additional tools, and both Congress and the President have demanded that the FDA make full use of these tools.

The challenge faced by both industry and government is to prove that the current remedies will substantially solve the drug-shortage problem. The drug industry is in most respects characterized by fierce competition among manufacturers that are highly protective of their confidential information. The industry is in many respects controlled by pervasive, mandatory regulations, implemented by a bureaucracy that is often more deliberate than speedy. Can the problem of drug shortages be resolved through reporting and cooperation by industry, guided by a nimble FDA that suggests solutions it cannot mandate?

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ENDNOTES

- 1 Surveys indicating the impact of drug shortages are discussed in: FDA, *A Review of FDA's Approach to Medical Product Shortages* (October 31, 2011) at 8–9, 12.
- 2 FDA Voice, *Six Month Check-Up: FDA's Work on Drug Shortages* (May 3, 2012). See also Letter from Jeanne Ireland (Assistant Commissioner for Legislation, FDA) to Representative Elijah E. Cummings (July 23, 2012) (reporting that the FDA averted 195 drug shortages in 2011 and more than 90 in 2012 as of the date of the letter).
- 3 FDA Voice, *Six Month Check-Up: FDA's Work on Drug Shortages* (May 3, 2012).
- 4 www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm050792.htm (last visited August 16, 2012).
- 5 FDA, *A Review of FDA's Approach to Medical Product Shortages* (October 31, 2011) at 16.
- 6 Government Accountability Office, *Drug Shortages; FDA's Ability to Respond Should Be Strengthened* at 5–8; FDA, *A Review of FDA's Approach to Medical Product Shortages* (October 31, 2011) at 29–32;
- 7 U.S. Dept. of Health and Human Services, Office of the Assistant Secretary for Planning and Evaluation, *ASPE Issue Brief; Economic Analysis of the Causes of Drug Shortages* (October 2011).
- 8 This was the consensus of witnesses who testified at a November 30, 2011, hearing before the House Subcommittee on Health Care, District of Columbia, Census and the National Archives. See also U.S. House of Representatives, Committee on Oversight and Government Reform, *FDA's Contribution to the Drug Shortage Crisis*, (staff report) (June 15, 2012) at 3–5.
- 9 U.S. House of Representatives, Committee on Oversight and Government Reform, *FDA's Contribution to the Drug Shortage Crisis*, (staff report) (June 15, 2012).
- 10 Letter from Jeanne Ireland (Assistant Commissioner for Legislation, FDA) to Representative Elijah E. Cummings (July 23, 2012).
- 11 This legislation is collected in Title X of the Food and Drug Administration Safety and Innovation Act ("FDASIA"), which was signed into law on July 9, 2012.
- 12 *Lacognata v. Hospira, Inc.*, Case No. 8:12-cv-822-T-30TGW (M.D. Fla. July 2, 2012).
- 13 21 C.F.R. §§ 341.81(b)(3)(iii), 314.92.
- 14 FDA, *A Review of FDA's Approach to Medical Product Shortages* (October 31, 2011) at 18.
- 15 FDA, *U.S. Drug Shortages* (September 30, 2011).
- 16 A notification of discontinuance is one of a number of post-approval reports required under 21 C.F.R. § 314.81. Under § 314.81(d), "[i]f an applicant fails to make reports required under this section, FDA may withdraw approval of the application and, thus, prohibit continued marketing of the drug product that is the subject of the application." However, the FDA has not identified § 314.81(d) as being applicable to notifications of discontinuance. More fundamentally, it would seem to be both overreaching and counterproductive to respond to a drug shortage by prohibiting a manufacturer from returning to the market.
- 17 72 FR 58999 (Oct. 18, 2007).
- 18 76 FR 78530 (Dec. 19, 2011).
- 19 See 21 C.F.R. § 314.81(b)(3)(iii)(d) (adding broad definitions of "discontinuance" and "sole manufacturer").
- 20 FDA, draft Guidance for Industry, *Notification to FDA of Issues that May Result in a Prescription Drug or Biological Product Shortage* (February 2012).
- 21 These provisions are codified as §§ 506D(a)(1)(B)(ii) and 506D(b) of the FD&C Act. The FDA contends that it is already its policy that the Office of Compliance consults with the Drug Shortage Program staff before issuing a warning letter. Letter from Jeanne Ireland (Assistant Commissioner for Legislation, FDA) to Representative Elijah E. Cummings (July 23, 2012) at 3.
- 22 In an effort to combat "gray market" sales, Representative Cummings has introduced a bill that would prohibit distributors from purchasing prescription drugs from pharmacies. See H.R. 5853. These transactions were also the focus of a July 25 Senate Committee hearing and a staff report. U.S. Congress, *Shining Light on the "Gray Market"; An Examination of Why Hospitals Are Forced To Pay Exorbitant Prices For Prescription Drugs Facing Critical Shortages*, (staff report) (July 25, 2012).
- 23 FDA, *A Review of FDA's Approach to Medical Product Shortages* (October 31, 2011) at 29.
- 24 On August 11, 2012, Altec Medical, Inc., pled guilty to one felony count of conspiracy. The predicate crimes were wire fraud and violation of the requirement that a wholesale distributor of a drug provide purchasers with "a statement ... identifying each prior sale, purchase, or trade of such drug." FD&C Act, § 503(e)(1)(A). Altec was aware that it was being supplied drugs that had passed through unlicensed suppliers, notwithstanding pedigrees that falsely stated that the drugs had come from nationally known drug distributors. *United States v. Altec Medical, Inc.*, Case 1:12-cr-20457-RNS (S.D. Fla., Aug. 11, 2012).
- 25 Center for Drug Evaluation and Research, Manual of Policies and Procedures 6003.1, *Drug Shortage Management* at 2–3.
- 26 FDA, *A Review of FDA's Approach to Medical Product Shortages* (October 31, 2011) at 21.
- 27 FD&C Act, §§ 506C(e), 506D(a)(1)(D); Controlled Substances Act, § 306(h).
- 28 FDA News Release, "FDA acts to bolster supply of critically needed cancer drugs" (Feb. 21, 2012).

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