December 19, 2024

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Sent by e-mail

Declaratory Order: Resolution of Shortages of Tirzepatide Injection Products (Mounjaro and Zepbound)

Tirzepatide injection products were first added to FDA's drug shortage list on December 15, 2022. The Agency determined that the shortage was resolved and removed tirzepatide injection products from FDA's drug shortage list on October 2, 2024.[1] FDA has now reevaluated that decision.[2]

This order has been prepared to allow for its public disclosure. It does not include any of the confidential commercial information and/or trade secret information provided by Eli Lilly and Company that FDA analyzed for the purpose of making the determination set forth herein.

This order revokes and replaces FDA's October 2, 2024 decision on the same subject.

I. Determination

FDA determines that the tirzepatide injection product shortage is resolved. This determination is based on the analysis set forth in FDA's decision memorandum dated December 19, 2024, "Resolution of Tirzepatide Injection Product Shortage and Supply Status," (Decision Memorandum") and summarized below.

FDA is instructed to "maintain an up-to-date list of drugs that are determined by [FDA] to be in shortage in the United States,"[3] and a "shortage" is "a period of time when the demand or projected demand for the drug within the United States exceeds the supply of the drug."[4] Eli Lilly and Company ("Lilly"), the manufacturer of the relevant tirzepatide injection drug

[1] https://dps.fda.gov/drugshortages/resolved/tirzepatide-injection
[2] On October 7, 2024, FDA was sued in the U.S. District Court for the Northern District of Texas by the Outsourcing Facilities Association and North American Custom Laboratories, LLC d/b/a Farmakeio Custom Compounding regarding removal of tirzepatide injection from FDA's drug shortages list. On October 11, 2024, upon FDA's motion, a court order remanded the decision to the Agency for reevaluation. *See Outsourcing Facilities Ass'n v. FDA*, No. 4:24-cv-953, ECF Nos. 27, 28 (N.D. Tex.).
[3] Section 506E(a) of the FD&C Act.
[4] Section 506C(h)(2) of the FD&C Act; 21 CFR 314.81(b)(3)(iii)(f).

products, has provided FDA with detailed information and data regarding its production and inventory of these drug products at various points in time, including stock reports that show quantities supplied and demanded, and inventory held in stock, for all strengths of these drug products; cumulative quantities supplied to and demanded by its customers in the year 2024; projected demand and supply in future months; and wholesaler inventory data, among other information. We conclude that the information and data Lilly has provided to FDA demonstrate that Lilly's supply is currently meeting or exceeding demand for these drug products, and that Lilly has developed reserves that it now holds in its finished product inventory, plus significant units of semi-finished product, and has scheduled substantial additional production over the coming months, such that supply will meet or exceed projected demand.

FDA has also considered potentially relevant information regarding the shortage determination from patients, healthcare providers, and others, including compounders, along with data from other sources that we independently identified. After carefully evaluating this information, we find that it has important limitations. We conclude that this information does not undermine or outweigh the evidence demonstrating that Lilly's supply is currently meeting or exceeding demand and that, based on our best judgment, it will meet or exceed projected demand.

For example, FDA received reports that some patients and pharmacists are not able to obtain the approved drugs, and that a substantial amount of tirzepatide compounding is occurring. The information provided in Lilly's submissions demonstrate that the company is currently meeting or exceeding demand for Mounjaro and Zepbound. That is not inconsistent with some, and even many, individuals having had some trouble getting prescriptions for the affected drugs filled over the course of the shortage, and some individuals may still be currently encountering such challenges, even though Lilly's supply is now meeting or exceeding demand nationally. In our assessment, intermittent challenges of this kind are most likely explained not by a continuing national shortage of supply, but by the practical dynamics of the portion of the supply chain between Lilly and the individual customers, including wholesale distributors and retailers. We recognize that significant compounding of tirzepatide injection products is occurring, and that some number of patients currently receiving those products can be expected to seek Lilly's approved products at a future point when compounding is curtailed. However, the additional information provided by patients, healthcare providers, and others, including compounders does not demonstrate that Lilly will be unable to meet projected demand, especially when weighed against the Lilly-provided data.

For all of these reasons and as explained further in the Decision Memorandum, we determine that the shortage is resolved. Our determination is based on our conclusions that supply meets or exceeds current demand, and that, based on our best judgment looking at the available information with its limitations, supply will also meet or exceed projected demand.

FDA will continue to monitor supply and demand for these products, and whether any tirzepatide injection products should be included on the drug shortage list in the future, as appropriate.[5]

[5] Notwithstanding resolution of the shortage, FDA understands that patients and prescribers may still see intermittent localized supply disruptions as the products move through the supply chain from the manufacturer to wholesale distributors and pharmacies.

This order also explains that, in addition to the representations FDA made regarding enforcement in October 2024 in connection with litigation,[6] FDA does not intend to take action against compounders for violations of the Federal Food, Drug, and Cosmetic Act (FD&C Act) arising from conditions that depend on tirzepatide injection products' inclusion on the FDA drug shortage list (see section 506E of the FD&C Act) [i.e., section 503A(b)(1)(D) (compounded drugs that are essentially a copy of a commercially available drug product) or sections 503B(a)(2)(A) (bulk drug substances used in compounding) and (a)(5) (compounded drugs that are essentially a copy of an FDA-approved drug product)] for the following time periods from the date of this order:

- For state-licensed pharmacists or physicians compounding under section 503A of the FD&C Act, 60 calendar days from the date of this order, until February 18, 2025; and
- For outsourcing facilities under section 503B of the FD&C Act, 90 calendar days from the date of this order, until March 19, 2025.

II. Background

FDA maintains an up-to-date list of drugs that are determined by the Agency to be in shortage in the United States.[7] FDA's drug shortage list is publicly available on the Agency's website.[8] FDA's drug shortage list includes the names and National Drug Code (NDC) numbers for such drugs; the name of each applicant for such drugs, the reason for the shortage as determined by FDA, and the estimated duration of the shortage.[9]

In this context, a drug shortage means "a period of time when the demand or projected demand for the drug within the United States exceeds the supply of the drug."[10] As such, in determining whether a drug is in shortage for purposes of the FD&C Act, FDA evaluates the supply and demand or projected demand of the drug on a nationwide level, across the entire market, not at

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[6] *See* Defendants' Unopposed Motion for Voluntary Remand and Stay, *Outsourcing Facilities Ass'n v. FDA*, No. 4:24-cv-953, ECF No. 27, at 3. *See also* Letter from Gail Bormel, Office Director, CDER Office of Compounding Quality and Compliance, to Scott Brunner, Chief Executive Officer, Alliance for Pharmacy Compounding (APC) (Oct. 17, 2024), available at https://www.fda.gov/media/182948/download?attachment.

[7] See section 506E(a) of the FD&C Act (21 U.S.C. 356e) and 21 CFR 314.81(b)(3)(iii)(*d*)(*1*). Manufacturers of certain prescription drug products must notify FDA of a permanent discontinuance in the manufacture of the drug product, or an interruption in manufacturing of the drug product that is likely to lead to a meaningful disruption in supply of that drug in the United States, and the reasons for such discontinuance or interruption. For the same drugs, manufacturers are also required to report a permanent discontinuance in the manufacture of an active pharmaceutical ingredient of the drug or an interruption in the manufacture of an active pharmaceutical ingredient likely to lead to a meaningful disruption in supply of the manufacturer's drug, and the reasons for the discontinuance or interruption. See section 506C of the FD&C Act and 21 CFR 314.81(b)(3)(iii).

[8] https://dps.fda.gov/drugshortages. See section 506E(c) of the FD&C Act and 21 CFR 314.81(b)(3)(iii)(*d*)(*1*).

[9] See section 506E(b) of the FD&C Act and 21 CFR 314.81(b)(3)(iii)(*d*)(*1*). FDA cannot disclose trade secret or commercial or financial information that is considered confidential or privileged. See sections 506C(d) and 506E(c)(2) of the FD&C Act and 21 CFR 314.81(b)(3)(iii)(*d*)(*2*). Additionally, FDA may choose not to make drug shortage information publicly available if FDA determines that disclosure of such information would adversely affect the public health (such as by increasing the possibility of hoarding or other disruption of the availability of drug products to patients). See section 506E(c)(3) of the FD&C Act and 21 CFR 314.81(b)(3)(iii)(*d*)(*2*).

[10] Section 506C(h)(2) (21 U.S.C. 356c) of the FD&C Act; see also 21 CFR 314.81(b)(3)(iii)(*f*).

the local level.[11] The Agency acknowledges that even when a shortage is considered resolved, patients and prescribers may still see intermittent localized supply disruptions as products move through the supply chain from the manufacturer and distributors to local pharmacies.

FDA receives input regarding drug shortages from numerous stakeholders, including manufacturers, patients, healthcare providers, and others, including compounders.[12] In particular, manufacturers are required to notify FDA about discontinuances and manufacturing interruptions pertaining to certain drugs pursuant to statutory and regulatory requirements,[13] and they may voluntarily provide additional information as relevant about quality issues, increases in demand, recalls, or other events (e.g., relevant supply and demand conditions).

Tirzepatide is a glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor agonist. Mounjaro and Zepbound are the only FDA-approved tirzepatide products. Mounjaro (tirzepatide) injection, for subcutaneous use, is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Mounjaro is approved as pre-filled single-dose pens in several strengths (2.5 mg/0.5 mL, 5 mg/0.5 mL, 7.5 mg/0.5 mL, 10 mg/0.5 mL, 12.5 mg/0.5 mL, and 15 mg/0.5 mL). The Mounjaro pen products were approved by FDA in May 2022 (NDA 215866) and added to FDA's drug shortage list in December 2022 due to high demand. Mounjaro single-dose vial products in the same strengths were approved in a supplement to NDA 215866 in July 2023, but are not currently marketed in the United States and have not been on FDA's drug shortage list. Zepbound (tirzepatide) injection, for subcutaneous use, is indicated in combination with a reduced-calorie diet and increased physical activity to reduce excess body weight and maintain weight reduction long term in adults with obesity or adults with overweight in the presence of at least one weight-related comorbid condition. Zepbound is also approved as pre-filled single-dose pens and single-dose vials in the same strengths as Mounjaro (2.5 mg/0.5 mL, 5 mg/0.5 mL, 7.5 mg/0.5 mL, 10 mg/0.5 mL, 12.5 mg/0.5 mL, and 15 mg/0.5 mL). The Zepbound pen products were approved by FDA in November 2023 (NDA 217806) and added to FDA's drug shortage list in April 2024 due to high demand. The Zepbound single-dose vial products were approved in a supplement to NDA 217806 in March 2024, but only the 2.5 mg and 5.0 mg strengths are currently being marketed in the United States. The Zepbound vial products have never been on the shortage list.

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[11] See FDA Strategic Plan for Preventing and Mitigating Drug Shortages (October 2013), available at https://www.fda.gov/media/86907/download. See also CDER's manual of policies and procedures on drug shortage management (MAPP 4190.1 Rev. 4), available at https://www.fda.gov/media/72447/download; and FDA's draft guidance for industry, *Notifying FDA of a Discontinuance or Interruption in Manufacturing of Finished Products or Active Pharmaceutical Ingredients Under Section 506C of the FD&C Act* (February 2024), available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/notifying-fda-discontinuance-or-interruption-manufacturing-finished-products-or-active. This draft guidance, when finalized, will represent FDA's current thinking on this topic.

[12] FDA's website includes information about drug shortage notifications for industry and a public portal for patients, healthcare providers, and organizations to report new shortages, available at https://www.fda.gov/drugs/drug-safety-and-availability/drug-shortages.

[13] Section 506C(h)(2) of the FD&C Act; 21 CFR 314.81(b)(3)(iii)(f).

III. Procedural Considerations

This declaratory order is the product of an informal adjudication in which FDA evaluated the information available to the agency to make a determination of the relevant facts regarding the affected drug products, and applied the statutory standard for drug shortages to those facts. Under 5 U.S.C. 554(e) (section 5(d) of the Administrative Procedure Act (APA)), an agency, "in its sound discretion, may issue a declaratory order to terminate a controversy or remove uncertainty." The APA defines "order" as "the whole or a part of a final disposition, whether affirmative, negative, injunctive, or declaratory in form, of an agency in a matter other than rulemaking but including licensing." 5 U.S.C. 551(6). The APA defines "adjudication" as "agency process for the formulation of an order." 5 U.S.C. 551(7). FDA's regulations, consistent with the APA, define "order" to mean "the final agency disposition, other than the issuance of a regulation, in a proceeding concerning any matter . . . ." 21 CFR 10.3(a). Our regulations also define "proceeding and administrative proceeding" to mean "any undertaking to issue, amend, or revoke a regulation or order, or to take or not to take any other form of administrative action, under the laws administered by the Food and Drug Administration." 21 CFR 10.3(a). Moreover, our regulations establish that the Commissioner may initiate an administrative proceeding to issue, amend, or revoke an order. 21 CFR 10.25(b).

The statute does not explicitly provide the procedure FDA must use to make a determination regarding whether a drug product is in shortage, or whether such a shortage has resolved. As explained below, FDA has determined that its drug shortage authority is more compatible with adjudication than with rulemaking, and, consistent with the agency's past practice, FDA continues to implement this authority through adjudication. "The choice between rule-making or declaratory order is primarily one for the agency regardless of whether the decision may affect policy and have general prospective application." *Viacom v. FCC*, 672 F.2d 1034, 1042 (2d Cir. 1982). *See also SEC v. Chenery*, 332 U.S. 194, 203 (1947); *NLRB v. Wyman-Gordon Co.*, 394 U.S. 759 (1969); *NLRB v. Bell Aerospace Co.*, 416 U.S. 267, 294 (1974); *Almy v. Sebelius*, 679 F.3d 297, 303 (4th Cir. 2012); *City of Arlington, Texas v. FCC*, 133 S. Ct. 1863, 1874 (2013); *Qwest Servs. Corp. v. FCC*, 509 F.3d 531, 536– 37 (D.C. Cir. 2007) ("Most norms that emerge from a rulemaking are equally capable of emerging (legitimately) from an adjudication, and accordingly agencies have very broad discretion whether to proceed by way of adjudication or rulemaking" (internal citations and quotations omitted)). Courts "accord significant deference to an agency's characterization of its own action" when determining whether it is a rule or an order for APA purposes. *Am. Airlines, Inc. v. Dep't of Transp.*, 202 F.3d 788, 797–98 (5th Cir. 2000) (citing and quoting *British Caledonian Airways, Ltd. v. Civil Aeronautics Bd.*, 584 F.2d 982, 992 (D.C. Cir. 1978) ("In the present case we have, moreover, the Board's own assertion that its order is purely interpretive, and this contention in itself is entitled to a significant degree of credence.... While declaratory orders differ in some respects from interpretive rules, the same rationale should apply equally to an agency's characterization of one of its rulings as a declaratory order.")).

Making a determination regarding drug shortage status in a declaratory order issued as a product of informal adjudication is well within FDA's discretion under the FD&C Act and the APA.

Whether an affected drug product is (or is no longer) in shortage is a "concrete and narrow question[]"—in this case involving a drug product manufactured by a single pharmaceutical company—"the resolution[] of which would have an immediate and determinable impact on specific factual scenarios." *City of Arlington v. FCC*, 668 F.3d 229, 243 (5th Cir. 2012); *see also Qwest Servs. Corp.*, 509 F.3d at 536–37; *Chisholm v. FCC*, 538 F.2d 349, 364–66 (D.C. Cir. 1976). FDA is issuing this declaratory order to remove uncertainty as to the status of the shortages of tirzepatide injection drug products, specifically, Mounjaro 2.5 mg, 5.0 mg, 7.5 mg, 10 mg, 12.5 mg, and 15 mg; and Zepbound 2.5 mg, 5.0 mg, 7.5 mg, 10 mg, 12.5 mg, and 15 mg.

This adjudication requires FDA to make determinations about the relevant facts, using the information available to the agency, and apply the statutory standard for drug shortages to those facts. Such applications of law to facts do not create new law and accordingly do not require FDA to engage in rulemaking, even if they include some amount of interpretation. "The feature which distinguishes declaratory orders and other interpretative rulings from those legislative rules which must conform with the procedures established by the APA for rulemaking is not the extent of their effect, but rather that the order or ruling *instead of creating new law serves only to clarify and state an agency's interpretation of an existing statute or regulation*." *British Caledonian Airways v. Civil Aeronautics Board*, 584 F.2d 982, 990 (D.C. Cir. 1978) (emphasis added); *see also Trans International Airlines v. Civil Aeronautics Board*, 432 F.2d 607, 612 n.9 (D.C. Cir. 1970) ("an interpretation of . . . regulations by . . . declaratory ruling . . . [is] well within the scope of the familiar power of an agency to interpret the regulations within the framework of an adjudicatory proceeding"). In addition, the temporary nature of a shortage determination is consistent with adjudication rather than rulemaking. *See Goodman v. FCC*, 182 F.3d 987, 994-5 (D.C. Cir. 1999) (upholding an order granting temporary waivers to companies who were not named parties in the proceeding, and contrasting the temporary nature of the waivers with a "general, prospective amendment" to existing rules as "a strong reason to conclude the proceeding was not a rulemaking").

The applicable statutory authorities are more consistent with adjudication than with rulemaking in part because "adjudicatory decisions are not subject to the APA's notice-and-comment requirements." *Blanca Telephone Co. v. FCC*, 743 F.3d 860 (D.C. Cir. 2014)). In rulemaking, however, the APA typically requires agencies to "give interested persons an opportunity to participate . . . through submission of written data, views, or arguments." 5 U.S.C. § 553(c). Notice to interested parties of their opportunity to do so requires the agency to "reveal[] for public evaluation" the "'technical studies and data' upon which the agency relies.'" *Chamber of Commerce v. SEC*, 443 F.3d 890, 899 (D.C. Cir. 2006) (quoting *Solite Corp. v. EPA*, 952 F.2d 473, 484 (D.C. Cir. 1991)). Under the APA, therefore, "[a]n agency commits serious procedural error when it fails to reveal portions of the technical basis for a proposed rule in time to allow for meaningful commentary." *Solite Corp.*, 952 F.2d at 484 (quoting *Connecticut Light and Power Co. v. NRC*, 673 F.2d 525, 530–31 (D.C. Cir. 1982)). Put another way, rulemaking generally requires an agency to "afford interested parties an opportunity to challenge the underlying factual data relied on by the agency." *Chemical Mfrs. Ass'n v. EPA*, 870 F.2d 177, 200 (5th Cir. 1989) (citing *Air Products & Chemicals, Inc. v. FERC*, 650 F.2d 687, 700 n.17 (5th Cir. 1981)).

These notice-and-comment requirements are impossible to reconcile with the statutory provisions governing a drug shortage determination. To begin, take the statutory section titled "public availability," 21 U.S.C. 356e(c). First, section 356e(c)(3) explicitly provides FDA with discretion not to make *the very existence of a shortage* public. It states that FDA "may choose not to make information collected under this section [356e] publicly available . . . if [FDA] determines that disclosure of such information would adversely affect the public health (such as by increasing the possibility of hoarding or other disruption of the availability of drug products to patients)." The existence of a shortage itself, as well as factual information supporting the determination of its existence, is "information collected" under section 356e, and the fact of a shortage's existence (rather than any particular factual detail supporting the determination of a shortage) is the most obvious type of information that would be likely to cause hoarding when publicly announced. Knowledge that a shortage exists may foreseeably incentivize people to, for example, hoard product for their own or others' use (thereby avoiding disruption for some patients, but at the possible expense of other patients), or for financial gain (such as by selling the product at increased prices due to scarcity). The statutory provision giving FDA discretion to choose whether to make a shortage public based on these types of concerns is impossible to reconcile with a requirement that FDA conduct notice-and-comment rulemaking. In such a circumstance there could be no notice, no comment, and no public announcement of the decision itself. By contrast, FDA could act consistently with the provision through an adjudication process in which the agency made the necessary information available only to affected entities in the product's supply chain.

Second, a large amount of the information that FDA analyzes to determine the status of a drug shortage is the drug manufacturer's trade secret and/or confidential commercial information which FDA may not publicly disclose under applicable laws and regulations. This includes detailed information about current and future production, inventory, sales, and distribution. Such information is, in most cases, closely held by the submitting company, which considers the information privileged and confidential business information. Such information is exempt from the public disclosure provisions of the Freedom of Information Act (FOIA) by exemption 4, see 5 U.S.C. 552(b)(4), and may not be disclosed by FDA because of protections in the Trade Secrets Act, see 18 U.S.C. 1905, and FDA's regulations. *See*, *e.g.*, 21 C.F.R. 20.111(d)(3) (identifying "production, sales, distribution, and similar data and information" submitted voluntarily to FDA as "not available for public disclosure" subject to certain exceptions); 10.20(j)(2)(i)(d) (similar); and 20.61 (further detailing FDA's treatment of such information). In some cases, most, or even all, of the factual materials that FDA considered, and which therefore make up the administrative record, will be subject to disclosure-law protections. The statute's "public availability" section recognizes this reality and underscores that the requirement to publish the drug shortage list does not alter or amend the disclosure restrictions in 18 U.S.C. 1905 or 5 U.S.C. 552(b)(4); *see also* 21 U.S.C. 356e(c)(2); *Food Marketing Institute v. Argus Leader Media*, 588 U.S. 427, 440 (discussing sales data, and concluding that "where commercial or financial information is both customarily and actually treated as private by its owner and provided to the government under an assurance of privacy, the information is 'confidential' within the meaning of [5 U.S.C. 552(b)(4)]"). Because, absent the drug manufacturer's consent, FDA typically cannot proactively

publish confidential information about a drug's current and future production, inventory, sales, and distribution, notice and comment rulemaking is incompatible with drug shortage decisions.

Third, section 356e(c)(1)'s directive only that the agency "shall make the information in such list publicly available" (subject to the significant exceptions discussed immediately above) is more consistent with adjudication than rulemaking. The statute does not provide that the agency must use rulemaking, or that it must publish its determination in the Federal Register. The APA requires agencies to "make available for public inspection and copying" any "final opinions, . . . as well as orders, made in the adjudication of cases," 5 U.S.C. § 552(a)(2)(A), and if an order contains "statements of general policy or interpretations of general applicability," the agency may need to publish the order in the Federal Register, 5 U.S.C. § 552(a)(1)(D). But the Federal Register publication requirement does not apply to "interpretations of general applicability [made] in the course of issuing adjudicatory opinions" in light of section 552(a)(2), which requires only "public inspection and copying" of orders. *See*, *e.g.*, *Cheshire Hosp. v. New Hampshire-Vermont Hospitalization Serv.*, 689 F.2d 1112, 1123 (1st Cir. 1982) ("Courts which have been forced to harmonize these two provisions [§ 552(a)(1)(D) and § 552(a)(2)(D)] have held that an agency may formulate interpretations of general applicability in the course of issuing adjudicatory opinions without publishing such opinions in the Federal Register. The agency need only make such opinions available to the public as provided for by 5 U.S.C. s 552(a)(2)(A).") (internal citations omitted).

Beyond the "public availability" statutory section, the requirement in 21 U.S.C. 356e(a) that the Secretary maintain an "up-to-date" drug shortage list also, at a minimum, strongly suggests that the authority is more consistent with adjudication than with rulemaking. Even if notice and comment rulemaking were done expeditiously, that procedure plus a 30-day delayed effective date, *see* 5 U.S.C. § 553(b)-(d), would not result in a drug shortage list that could fairly be characterized as "up-to-date," thereby potentially preventing the agency from fulfilling its statutory mandate. While the APA contains a "good cause" exception to the notice-and-comment and 30-day delayed effective date requirements, 5 U.S.C. § 553(b)(B), (d)(3), the exception's requirements have been stringently interpreted, which could introduce uncertainty about whether a court will agree with the agency that good cause exists in a particular circumstance. *See, e.g., State of N. J., Dep't of Env't Prot. v. U.S. Env't Prot. Agency*, 626 F.2d 1038, 1045 (D.C. Cir. 1980) ("exceptions to the notice-and-comment provisions of section 553 will be narrowly construed and only reluctantly countenanced"). And even assuming that drug shortage decisions would routinely qualify for the good cause exception, the most straightforward interpretation is that Congress did not intend such decisions to be subject to notice-and-comment requirements at all, rather than that Congress intended such decisions to be subject to, but routinely exempt from, those requirements.

For all of these reasons, FDA considers the drug shortage list authority in 21 U.S.C. 356e to be much more compatible with adjudication than rulemaking, and consistent with its approach to date, the agency continues to choose to implement this authority through adjudication.

Finally, FDA notes that this order is a product of an informal adjudication that included notice to affected parties via publication of the shortage determination on FDA's website, and an

opportunity for affected parties to be heard by submitting information to the Agency for consideration. The APA gives agencies discretion to determine the appropriate level of public participation in agency decisions. *See* 5 U.S.C. 555(b) ("So far as the orderly conduct of public business permits, an interested person may appear before an agency. . . for the . . . determination of an issue"). Multiple interested parties, including the manufacturer of the affected drug products, individual patients, pharmacy compounders, outsourcing facilities, associations representing pharmacy compounders and outsourcing facilities, and telehealth companies, did in fact submit information to the Agency, both before FDA's initial announcement that these shortages had resolved and during FDA's reevaluation of that decision. The agency considered those submissions in formulating this order. Such procedures are appropriate for the formulation of declaratory orders and avoid the problems that would be presented by notice-and-comment rulemaking, as described above. *See*, *e.g.*, *National Labor Relations Board v. Bell Aerospace*, 416 U.S. 267, 295 (1975) (no procedural error where the parties "most immediately affected" by the order were "accorded a full opportunity to be heard").

IV. Status of Compounding Following this Decision

In connection with the litigation noted above,[14] FDA stated that during the reevaluation and for a period after the Agency makes its decision, FDA does not intend to take action against compounders for violations of the FD&C Act arising from conditions that depend on tirzepatide injection products' inclusion on FDA's drug shortage list, i.e., section 503A(b)(1)(D) (compounded drugs that are essentially a copy of a commercially available drug product) or sections 503B(a)(2)(A) (bulk drug substances used in compounding) and (a)(5)) (compounded drugs that are essentially a copy of an FDA-approved drug product).

In addition to that representation, as explained further below, to avoid unnecessary disruption to patient treatment and to help facilitate an orderly transition, for the same violations described above, FDA does not intend to take action against a compounder that is not registered as an outsourcing facility for compounding, distributing, or dispensing tirzepatide injection products that are essentially a copy of a commercially available drug product[15] within 60 days of this decision. In addition, FDA does not intend to take action against an outsourcing facility for use of the bulk drug substance tirzepatide to compound, distribute, or dispense a drug product that appeared on FDA's drug shortage list,[16] or for compounding, distributing, or dispensing tirzepatide injection products that are essentially a copy of an FDA-approved drug product,[17] within 90 days of this decision.

Neither FDA's statements in the court case, the court's order, nor this order prevents FDA from taking action for violations of any other statutory or regulatory requirements, such as to address findings that a product may be of substandard quality or otherwise unsafe.

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[14] *See* Defendants' Unopposed Motion for Voluntary Remand and Stay, *Outsourcing Facilities Ass'n v. FDA*, No. 4:24-cv-953, ECF No. 27, at 3. *See also* Letter from Gail Bormel, Office Director, CDER Office of Compounding Quality and Compliance, to Scott Brunner, APC (Oct. 17, 2024), available at https://www.fda.gov/media/182948/download?attachment.

[15] See section 503A(b)(1)(D) of the FD&C Act.

[16] See section 503B(a)(2)(A) of the FD&C Act.

[17] See section 503B(a)(5) of the FD&C Act.

The enforcement discretion described here is based on the following considerations.

First, as explained in FDA's guidance documents, "Compounded Drug Products That Are Essentially Copies of a Commercially Available Drug Product Under Section 503A of the Federal Food, Drug, and Cosmetic Act" and "Compounded Drug Products That Are Essentially Copies of Approved Drug Products Under Section 503B of the Federal Food, Drug, and Cosmetic Act," the FD&C Act generally limits the compounding of drugs that are essentially copies of commercially available and approved drugs, respectively.

Although compounded drug products can provide treatment options for patients during a drug shortage, compounded drugs have not undergone FDA premarket review for safety, effectiveness, and quality, and lack a premarket inspection and finding of manufacturing quality that is part of the drug approval process. Further, drug products that meet the conditions under section 503A are not subject to CGMP requirements and are subject to less robust production standards that provide less assurance of quality. Accordingly, the statute includes restrictions on compounding drugs that are essentially copies of commercially available drugs[18] and approved drug products that are not on FDA's drug shortage list. These restrictions help reduce the risk that compounders will prepare these unapproved drug products for patients whose medical needs could be met by an approved product. This helps to protect patients from unnecessary exposure to drugs that have not been shown to be safe and effective, and that offer fewer assurances of manufacturing quality.

The copies restrictions also protect the integrity of the new drug and abbreviated new drug (ANDA) approval processes by, for example, incentivizing sponsors to invest in and seek approval of innovative, life-saving medications - by limiting the ability of compounders to, after a drug is approved, compound "substitutes" that may be less expensive because they have not had to demonstrate safety and effectiveness or be labeled with adequate directions for use, and, for drugs compounded under section 503A, are not produced in accordance with CGMP requirements.[19]

For the above reasons, an indefinite or overly long period of enforcement discretion for continued compounding of drugs that may be essentially copies of an approved drug that is no longer in shortage would not be appropriate.

FDA has also considered public health concerns and reliance interests (as discussed further below), and the enforcement discretion described here takes those concerns into account. FDA considers that the 60/90-day period described here will allow patients a reasonable amount of time to transfer their prescriptions, as needed, to different pharmacies to obtain the FDA-approved drug. Patients who used compounded tirzepatide injection products during the

[18] For purposes of section 503A, FDA does not consider a drug on FDA's drug shortage list to be "commercially available."

[19] Less directly relevant in this case, involving copies of sterile injectable products, the copies restrictions also help protect FDA's drug monograph process by limiting the ability of compounders to produce drugs without having to comply with monograph standards or CGMP requirements that apply to such products.

shortage may otherwise face gaps in their ability to access treatment.[20] The additional time will allow local pharmacies to adjust their stocking and ordering patterns to adjust to new patterns of patient demand, which should help to minimize local disruptions.[21]

FDA also recognizes that compounded versions of drugs on FDA's drug shortage list can provide an important treatment option to patients during the shortage, and that compounders who prepare such drugs may be holding finished, compounded products, or inputs to compounded drugs, when a shortage resolves and the approved drug is taken off FDA's drug shortage list. For example, the compounder may have compounded drugs that are essentially copies of the approved drug and be waiting for the results of sterility tests before releasing them. FDA is required by statute to maintain an "up-to-date list" of drugs in shortage, 21 U.S.C. § 356e(a), and does not give advance notice of its decisions to move drugs on and off the list. In recognition of this fact, FDA's guidance for outsourcing facilities has previously described a brief period of enforcement discretion at the end of a drug shortage to account for such materials to be sold off.[22]

The above considerations are particularly relevant to the tirzepatide injection products shortage. We note that the shortage was ongoing for some time,[23] and compounders and other stakeholders report that a significant amount of compounding has been occurring. Additionally, FDA's re-evaluation of the shortage decision in the context of litigation may have caused some uncertainty about whether or when compounded copies would leave the market, slowing market transition. A period of enforcement discretion should help facilitate an orderly transition, as the adjustments described above take place. Although the 60/90-day period described here is longer than the period previously described in FDA's guidance documents, we conclude that it is justified in light of the considerations described here, including the information FDA has reviewed in connection with the tirzepatide injection products shortage. That this period is relatively brief

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[20] See October 3, 2024, letter from Scott Brunner, APC, to OCQC (docket no. FDA-2015-N-0030, document ID FDA-2015-N-0030-8519), stating that a 60-day transition period "would allow for a smoother transition, giving pharmacies time to contact prescribers for updated prescriptions and to navigate insurance prior authorization processes" and "would prevent abrupt discontinuations in patient care that will undoubtedly result from the sudden unavailability of compounded copies"; and October 7, 2024, letter from Scott Brunner, APC, and Ronna Hauser, SVP, Policy and Pharmacy Affairs, National Community Pharmacists Association, to FDA, DSS, and OCQC (docket no. FDA-2015-N-0030, document ID FDA-2015-N-0030-8520), stating that during a 60-day transition period, "prescriptions can be authorized for the FDA-approved products, coverage determinations made by insurance companies, and the FDA-approved products can be obtained by pharmacies to fill the prescriptions."

[21] FDA recognizes that local and regional conditions can make it difficult for patients to get a drug through their local pharmacies, even if that drug is not in a nationwide shortage. FDA's authorities relating to drug shortages are limited to shortages that exist "in the United States," that is, at the national level. Section 506E(a) of the FD&C Act. Thus, FDA does not treat local or regional supply disruptions the same way as the Agency treats national shortages.

[22] FDA's guidance for outsourcing facilities provides a period of enforcement discretion of 60 days for orders received during a drug shortage. See Guidance for Industry: Compounded Drug Products That Are Essentially Copies of Approved Drug Products Under Section 503B of the Federal Food, Drug, and Cosmetic Act (Jan. 2018), at 8; Guidance for Industry: Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act (Jan. 2017), at 7. FDA's guidance document for section 503A compounders, Compounded Drug Products That Are Essentially Copies of a Commercially Available Drug Product Under Section 503A of the Federal Food, Drug, and Cosmetic Act (January 2018) does not address FDA's enforcement policy for this provision at the end of a drug shortage. CDER is currently re-evaluating these policies pertaining to removal of compounded drugs from the market at the end of a shortage.

[23] Since December 15, 2022.

also mitigates concerns about potential effects on patients, the integrity of the drug approval process, and any reliance interests of the approved drug manufacturer. While the approved drug manufacturer may have an interest in FDA providing only the more limited enforcement discretion stated in the Agency's existing guidances, FDA has considered any such reliance interest and concludes that it is outweighed by the reasons discussed here that otherwise support this brief additional period of enforcement discretion.

The amount of time FDA intends to exercise enforcement discretion is longer for outsourcing facilities (90 days) than for those compounding under 503A (60 days) because:

- Drugs compounded in outsourcing facilities under section 503B provide more assurances of quality than drugs compounded under section 503A because they are made in facilities registered with FDA that are subject to FDA inspection and cGMP requirements.
- FDA understands that outsourcing facilities need to invest relatively more resources and time before they can produce product during a shortage because of these quality standards.

V. Conclusion

FDA has determined that the shortage of tirzepatide injection products, which first began in December 2022, is resolved. FDA continues to monitor supply and demand for these products.

Sincerely,

Patrizia A. Cavazzoni -S

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