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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: Response in Opposition to Eli Lilly's Nomination of Tirzepatide to Drug Products that Present Demonstrable Difficulties for Compounding Under Sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act
Docket No. FDA-2017-N-2562

To Whom It May Concern:

This law firm and the undersigned represent the Alliance for Pharmacy Compounding ("APC") and its members. APC is a national trade association advocating on behalf of millions of patients who benefit from compounded medications. APC's more than 5,000 members, located in all 50 states, include compounding pharmacists, pharmacy technicians, educators, students, researchers, and suppliers. APC further represents the interests of physicians, veterinarians, nurse practitioners, and other medical professionals who prescribe compounded medications to their patients.

APC is the voice for state-licensed compounding pharmacies ("503A pharmacies") and FDA-registered outsourcing facilities ("503B outsourcing facilities") throughout the country and works to ensure the availability of—and access to—customized medications for patients for whom manufactured drugs are not suited. Its mission is to preserve the rights of physicians to prescribe, pharmacists to prepare, and patients to take personalized medication solutions to meet their unique healthcare needs for a range of issues, including women's health, autism, oncology, dermatology, ophthalmology, pediatrics, and others. As such, APC not only represents the interests of compounders but just as importantly, it also represents the interests of patients who rely upon their services for access to life-saving and life-improving medications they cannot obtain from any other source.

This letter is written in response to commercial drugmaker Eli Lilly's self-serving request that tirzepatide injection be added to the FDA's lists of drug products that present demonstrable difficulties for compounding under 21 USC § 353a(b)(3)(A) and 21 USC § 353b(a)(6) of the Federal Food, Drug, and Cosmetic Act ("FDCA") (the "DDC Lists"). The drugmaker appears to contend that because the tirzepatide molecule is so complex for drugmakers to manufacture, the FDA should immediately prohibit 503A pharmacies from compounding with it by placing tirzepatide injection on the 503A DDC List without convening and consulting an advisory committee on compounding or undergoing the notice-and-comment rulemaking process, as required by 21 USC § 353a(c)(1). Yet, the drugmaker's nomination letter has been so heavily redacted that it is impossible for compounders to evaluate and respond to the drugmaker's complexity claim. How can the drugmaker's nomination to the DDC Lists be reviewed by compounders, much less by an advisory committee and undergo notice-and-comment rulemaking as required by the FDCA, if the entire basis for the drugmaker's complexity claim has been redacted?

Even assuming that the process of *creating* the tirzepatide molecule may be complex for Eli Lilly, *compounding* finished drug products using that active pharmaceutical ingredient (API) after it has been manufactured is not complex. 503A pharmacies and 503B outsourcing facilities regularly compound drug preparations whose compounding processes are more complex than preparing tirzepatide injection. Moreover, the drugmaker's contention that the API used by 503A pharmacies and 503B outsourcing facilities is somehow substandard simply is not true. By statute, 503A pharmacies and 503B outsourcing facilities may only use API that are supplied by FDA-registered manufacturers and that are accompanied by valid certificates of analysis.[1] Tirzepatide injection is not demonstrably difficult to compound, it is not prepared from inferior API, and it should not be placed on the FDA's DDC Lists.

As noted by the FDA, approximately 70% of American adults have obesity or are overweight, and many of those who are overweight have a weight-related condition.[2] Losing 5% to 10% of body weight through diet and exercise has been associated with a reduced risk of cardiovascular disease in adults with obesity or overweight. *Id.* Tirzepatide is a critical tool in the fight against the national obesity epidemic, which is a contributing factor to countless other medical issues afflicting tens of millions of Americans. Tirzepatide has been so successful at treating Type 2 diabetes and other weight-related conditions that Eli Lilly quickly became unable to satisfy the growing demand. As a result, on December 15, 2022, the FDA added tirzepatide

[1] See 21 USC § 353a(b)(1)(A)(ii) and (iii); 21 USC § 353b(a)(2)(C) and (D)
[2] See https://www.fda.gov/news-events/press-announcements/fda-approves-new-medication-chronic-weight-management#:~:text=Today%2C%20the%20U.S.%20Food%20and,weight%2Drelated%20condition%20(such%20as

injection to its Drug Shortage List where it remained until October 2, 2024.[3] 503A pharmacies and 503B outsourcing facilities have been instrumental in providing patients with access to tirzepatide therapies during the nationwide shortage.

While the FDA listed tirzepatide injection as "currently in shortage," 503A pharmacies and 503B outsourcing facilities dispensed millions of doses of compounded tirzepatide injections to patients throughout the United States. Yet, after nearly two years and millions of doses dispensed, the drugmaker is suddenly urging the FDA to quickly declare that tirzepatide injection is too difficult to compound. The drugmaker's nomination of tirzepatide injection to the DDC Lists does not arise out of a sincere concern for patient safety. Rather, it is merely one of several transparent attempts the drugmaker has recently taken to stifle what it improperly perceives as competition. However, 503A pharmacies and 503B outsourcing facilities are not competitors with commercial manufacturers. Adding tirzepatide injection to the DDC Lists would do nothing more than prevent countless patients from obtaining access to compounded versions of this life-enhancing drug while Eli Lilly remains unable to meet current and projected demands.

In support of its contention that tirzepatide injection is demonstrably difficult to compound, the drugmaker claims that "compounded tirzepatide places patients at risk and has already led to significant adverse events including death." To support this claim, the drugmaker references data posted on the FDA's Adverse Events Reporting System (FAERS) Public Dashboard, claiming that compounded tirzepatide injection is unsafe because "over 150 adverse events" have been reported.[4]

We would point out that Eli Lilly's nomination letter fails to provide important context regarding its own FDA-approved drug products' adverse event records. According to the FAERS public dashboard, from 2022 through September 30, 2024, there were **47,484** reported adverse events related to Eli Lilly's commercially manufactured drug products.[5] This includes **40,643**

[3] We note that FDA relied solely upon similarly self-serving representations by Eli Lilly in determining that the nationwide drug shortage was resolved. APC applauds the FDA's recent decision to re-evaluate the credibility of Eli Lilly's representation and to gather and consider drug availability data from other sources. We ask that the FDA similarly consider information from a variety of sources and not merely rely upon the self-serving nomination of Eli Lilly before declaring that tirzepatide injection is demonstrably difficult to compound.

[4] APC acknowledges that 503A pharmacies are not required by federal law to report adverse events to FDA. APC has proposed implementing in law the mandatory reporting of serious adverse events by 503A pharmacies – and a framework for that reporting – but the FDA has yet to respond to that proposal.

[5] See.https://fis.fda.gov/sense/app/95239e26-e0be-42d9-a960-9a5f7f1c25ee/sheet/45beeb74-30ab-46be-8267-5756582633b4/state/analysis

adverse events related to Eli Lilly's FDA-approved Mounjaro, and **6,841** adverse events reported for Eli Lilly's FDA-approved Zepbound. *Id.* Of those 47,484 adverse events, there have been **1,834 hospitalizations** and **165 deaths** reported. *Id.*

While these numbers might initially appear alarming, the FAERS public dashboard, itself, specifically states that a report in the database does *not* mean that the drug *caused* the adverse event:

> [W]hile FAERS contains reports on a particular drug or biologic, this does not mean that the drug or biologic caused the adverse event. Importantly, the FAERS data by themselves are not an indicator of the safety profile of the drug or biologic. Some additional limitations to note include: . . . **Existence of a report does not establish causation**: For any given report, there is no certainty that a suspected drug caused the event. While consumers and healthcare professionals are encouraged to report adverse events, the event may have been related to the underlying disease being treated, or caused by some other drug being taken concurrently, or occurred for other reasons. The information in these reports reflects only the reporter's observations and opinions.[6] (Emphasis in original).

The difficulty of establishing a causal link between a drug and a reported adverse event is highlighted by the fact that, although Eli Lilly's Mounjaro and Zepbound are the same drug and are presumably manufactured in the same manner, six-times as many adverse events have been reported for Mounjaro than for Zepbound. This disparity is not surprising given the differences in the patient populations those drugs are prescribed to treat. Mounjaro is FDA approved to treat patients with Type 2 diabetes, whereas Zepbound is FDA approved to treat obesity and other weight-related conditions. Certainly Eli Lilly would not agree that Mounjaro is six-times riskier for patients than its identically formulated Zepbound product, simply because six-times as many adverse events have been reported for Mounjaro than for Zepbound.

Moreover, attempting to draw conclusions from FDA's FAERS public dashboard is also problematic because the database includes reports related to the *known* side effects of the drug. As noted on Eli Lilly's web site, its FDA-approved tirzepatide products are known to cause "serious side effects," including severe stomach problems, kidney failure, gallbladder problems, pancreatitis, serious allergic reactions, hypoglycemia, changes in vision in patients with Type 2 diabetes, and depression or thoughts of suicide.[7] The most common side effects include, but are

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[6] See https://www.fda.gov/drugs/fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard

[7] See https://tirzepatide.lilly.com/?utm_id=go_cmp-20875812395_adg-157966203058_ad-685137166943_kwd-2269523762821_dev-c_ext-_prd-_mca-_sig-

not limited to, nausea, diarrhea, vomiting, constipation, stomach (abdominal) pain, indigestion, injection site reactions, feeling tired, allergic reactions, belching, hair loss, and heartburn. *Id.* Each of these known side effects are inherent in the drug itself, and they have no relationship to whether the drug is manufactured or compounded. Moreover, the adverse events reported to FAERS for compounded tirzepatide injection are largely the same known side effects as are reported for the drugmaker's FDA-approved tirzepatide products. As such, the FAERS data would indicate that the reported adverse events have more to do with the patients' comorbidities or the known side effects of the drug itself, than with whether the drug is manufactured versus compounded.

On behalf of the many 503A pharmacies and 503B outsourcing facilities across the country that have successfully compounded millions of doses of tirzepatide injection since the manufactured drugs were placed on the FDA's Drug Shortage List in 2022, APC strongly opposes Eli Lilly's nomination of tirzepatide injection for addition to the FDA's DDC Lists. Compounded tirzepatide injections have provided a life-enhancing therapy for patients who otherwise would have no access to tirzepatide therapies during the prolonged shortage.

Hundreds of thousands, if not millions, of patients rely upon tirzepatide to treat their Type 2 diabetes and other conditions related to weight management. GIP and GLP-1 treatment protocols are making a significant impact on the country's obesity epidemic and are improving the overall health and well-being of countless Americans. 503A pharmacies and 503B outsourcing facilities have played a critical role in making this life-changing drug available to patients while the commercially manufactured versions have been in shortage. There is no medical, scientific, or statistical basis for placing tirzepatide injection on the FDA's DDC Lists.

Thank you for your consideration of this matter. If you would like to discuss this matter further, APC welcomes the opportunity to do so.

Sincerely,

Stephen T. Snow

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