Citizen Petition Regarding Label Warnings and Information for Mounjaro/Zepbound and Ozempic/Wegovy

The undersigned submits this Citizen Petition under the Federal Food, Drug and Cosmetic Act to request the Commissioner of Food and Drugs with respect to the label warnings and information for Mounjaro/Zepbound and Ozempic/Wegovy to (1) require that additional clinical trails be conducted with regard to the loss of lean muscle mass, setting the ideal goal weight for patients, and maintenance of the weight loss and (2) modify and supplement the labels for these products with regard to these issues.

ACTION REQUESTED: Petitioner requests that the FDA respond to this Citizens Petition by enhancing the warnings and information on the labels for Mounjaro/Zepbound and similar products including Ozempic/Wegovy regarding: the loss of lean muscle mass (LMM); setting the ideal or goal weight; and maintaining the weight loss. **With regard to the loss of Lean Muscle Mass (LMM)** Petitioner requests that the FDA work with the pharmaceutical firms to design and conduct human clinical trials to document the nature and extent of the loss of LMM with these products. They should document the value and best practices in using body composition scans to measure the loss of LMM and fat. And recommend that all patients secure a scan before they start on these products – to give them a baseline regarding the loss of LMM. These trials should document the demographics and metrics of the loss. They should document whether the rate and extent of the loss of LMM varies depending on the dosage that the patient takes, e.g. whether the loss of LMM is slower if the patient loses weight more slowly. Is it appropriate to consider the loss of LMM a muscle wasting issue or an atrophy issue? They should focus on whether when a patient is on maintenance (more on this below), they will continue to lose LMM every time they lose a pound or two as they seek to maintain their new lower weight. In short, is the LMM loss issue a continuous problem, or just a problem when the patient is losing weight in the first place? They should focus on the elderly and their loss of LMM on top of their age-related loss of LMM. They should focus on the types of resistance exercise and protein consumption that will reduce the loss of LMM. Then this information should be incorporated in the label for these products. **With regard to setting the ideal or goal weight** Petitioner requests that the FDA work with the pharmaceutic firms to design and conduct human clinical trials to document how patients should set their ideal or goal weight. Should it focus on the patient's gender, age, and height or their A1C? Or BMI? Or some other metric? Then this information should be incorporated in the label for these products. **With regard to maintaining the weight loss** Petitioner is aware that clinical trials have shown that if a patient stops taking these products that they are likely to regain much of the weight that they have lost – and lose the health benefits of a lower BMI and lower A1C. This means that the FDA should assess and make recommendations in the label for these products on how to maintain ones weight loss over time. These actions are particularly critical because of the rampant off-label prescribing of diabetes drugs for weight loss (due in part to shortages of weight loss drugs and surging demand for them). A study of first-time prescribing of the drugs approved for treatment of type 2 diabetes mellitus (T2DM) between January 2020 and April 2023 found that the majority (56 percent) of patients who were prescribed drugs approved for T2DM did not have evidence of T2DM in their medical records. See Ozempic, Wegovy and

Mounjaro: On and Off-Label Prescribing Trends, Truveta Research, June 6, 2023. https://www.truveta.com/blog/research/ozempic-wegovy-and-mounjaro/ Many will be using them under a prescription from a doctor who is not an expert on diabetes or obesity and weight loss.

STATEMENT OF GROUNDS:

* **With regard to loss of LMM**, it has been established in a clinical trial of Ozempic/Wegovy (semaglitude) that this product could result in nearly as much loss of lean muscle as pounds of fat. Participants lost about 15 pounds of lean muscle on average, compared with 23 pounds of fat during a 68-week trial. See https://www.forbesafrica.com/health/2023/10/27/new-trial-will-test-whether-weight-loss-drugs-can-work-without-shedding-muscle-mass/ See Supplementary Table S2. Co-primary, Confirmatory and Selected Supportive Secondary Endpoints for the Trial and Supplementary Table S5. Supportive Secondary Endpoints Assessed in the DEXA Subpopulation for the Treatment Policy Estimand. See NCT03548935 – Clinical Trial

* Loss of LMM is a near pervasive health issue for elderly persons. Muscle mass decreases approximately 3–8% per decade after the age of 30 and this rate of decline is even higher after the age of 60. This involuntary loss of muscle mass, strength, and function is a fundamental cause of and contributor to disability in older people. When the elderly go on Mounjaro and similar products, they may lose LMM on top of the LMM they are losing or have already lost due to their age. Is this an adverse side effect?

* The impact of obesity is especially felt in osteoarthritis of the hip and knee joints. Every pound of body weight places four to six pounds of pressure on each knee joint. Individuals with obesity are 20 times more likely to need a knee replacement than those who are not overweight. This means that when patients, especially elderly patients, lose LMM due to Mounjaro and similar products, they might not be able to substantially increase their exercise to preserve or regain their LMM. They might become frail and at increased risk of falling. Is this an adverse side effect? Surely it is.

* In terms of preventing the loss of LMM or restoring LMM, the FDA should provide some guidance in the label. It could recommend that patients consume 100 grams of protein a day (or a formula for determining how much protein to consume), identify some of the best sources of protein (that are not so heavy in calories), and acknowledge that consuming extra protein means one is consuming more calories (5-10 calories per gram of protein). This has implications for the patient's weight loss and maintenance of the weight loss. In terms of exercise, the FDA should provide guidance in the label. Resistance training, such as power walks, wall sits, calf raises, sled pushes, leg push machines, and the like. It could recommend that patients consult a physical therapist or join a gym.

* The label for Mounjaro includes no reference either to "lean" or "muscle." The label for Zepbound (same as Mounjaro but with a focus on weight loss, rather than diabetes) does not include any mention of the word "muscle." It says only, "**Tirzepatide lowers body weight with greater fat mass loss than lean mass loss.**" (Bold in original) By not mentioning the word "muscle" this reference will not effectively alert patients and doctors to their likely loss of LMM. It will not alert the elderly to the fact that they are already losing LMM and with additional loss of LMM they might become fragile. It does nothing to recommend that all patients secure a body composition scan before they start on Mounjaro or Zepbound – so that they will have a baseline regarding their LMM and the location of their LMM. Then they can obtain additional scans to chart the loss of LMM and the location of the loss (e.g. legs vs.

arms). This label says nothing about the need for patients to undertake rigorous resistance exercise and increased consumption of protein or any of the specifics for that.
* The clinical trials should assess whether with substantial resistance training and protein consumption, patients lean muscle mass will be restored and that there will be no residual long-term weakness or shaking.
* **With regard to setting the ideal or goal weight,** the labels for Mounjaro and Zepbound contain no information on how a patient should set their idea or goal weight. The words "goal," "ideal," or "end" weight are not mentioned. It is not in the patient's interest to lose too little weight to achieve the health benefits of these products or lose too much weight and suffer adverse effects. There are a variety of ways in which this goal or ideal weight might be set. There are "ideal weight calculators" – see https://www.calculator.net/ideal-weight-calculator.html They provide readings based on gender, age and height and the work of Robinson (1983), Miller (1983), Devine (1974) and Hamwi (1964). Should the goal or ideal weight be based on one's BMI measurement? Is this a reliable measure? We have A1C and challenge glucose readings. Are they more reliable? Are there other metrics focused on other blood tests (lipids)? Is a body scan measurement of fat and LMM helpful. The FDA should set some metric in the label for this determination on when to stop losing weight.
* **With regard to maintain the weight loss,** the label for Mounjaro does not mention the word "maintenance" at all. The label for Zepbound mentions "maintenance" in ways that are not at all helpful in terms of how a patient should maintain their weight loss. Here are the references in the Zepbound label to "maintenance": "The recommended maintenance dosages of ZEPBOUND in adults are 5 mg, 10 mg, or 15 mg injected subcutaneously once weekly." "Consider treatment response and tolerability when selecting the maintenance dosage. If patients do not tolerate a maintenance dosage, consider a lower maintenance dosage." "In Study 1, the dose of ZEPBOUND or matching placebo was escalated to 5 mg, 10 mg, or 15 mg subcutaneously once weekly during a 20-week titration period followed by the maintenance period. In Study 2, the dose of ZEPBOUND or matching placebo was escalated to 10 mg or 15 mg subcutaneously once weekly during a 20-week titration period followed by the maintenance period." None of these references explains what the "maintenance period" is and how it is different from the non-maintenance period. When the patient reaches their ideal or goal weight, do they continue with weekly injections? If so, does this risk that they will continue to lose weight and lose too much weight? Do they go down to the lowest dose – 2.5? Do they maintain a regular schedule of doses – say every other week – or take doses only when they start to regain weight? These and many related questions should be answered with explanations in the label. Note: Petitioner has filed a Form 3500 B MedWatch regarding Mounjaro. And Petitioner has filed a FOIA at the FDA request regarding these issues with regard to Mounjaro.

Environmental Impact: Petitioner is not aware of any environmental impact of this proposed action or any need for the FDA to prepare and file an environmental impact statement.

Economic Impact: In terms of cost (and price) increases to industry, government and consumers, this Petition would impose additional costs on the pharmaceutical firms as they undertake the clinical trials or trials regarding lean muscle mass, the ideal goal weight and maintaining the weight loss. How much cost will be incurred by them will be determined by how many clinical trials are commissioned and the number of enrolled patients. Given the

extraordinary profitability of these products, the firms will not be raising their prices to cover these costs. These diabetes/weight loss products have been found to be cost-effective. See https://icer.org/news-insights/press-releases/semaglutide_evidence_report/ This study is attached. This study found that these products would be cost-effective if the government negotiated a price slightly lower than the current list price (a discount). If the government does negotiate that price, then the impact of these drugs on the expenditures Medicare, Medicaid and VA would be fully offset by the benefits. In terms of the impact of this petition on the productivity of wage earners, businesses, or government, if the clinical trials supplement the labels for these drugs in ways that improve the cost effectiveness of these products in improving the health of the patients, then it could improve their productivity. In terms of the impact on competition, the firms that conduct the clinical trials that provide the most insights into these three issues might gain a competitive advantage in the marketplace. Petitioner believes that there will be no impact on the supplies of important materials, products, or services and employment, or energy supply or demand.

Official Certification. Below Petitioner has signed the prescribed statement.

Identifying Information: Petitioner has supplied his contact information in the electronic form he completed in filing this Petition. Petitioners are admonished not to provide personal identifying information in the Petition itself.

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petition which are unfavorable to the petition.

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