THE OBESITY SOCIETY
Professionals Collaborating to Overcome Obesity

Food and Drug Administration
Dockets Management Staff (HFA–305)
5630 Fishers Lane, Room 1061
Rockville, MD 20852

June 30, 2026

Re: Docket No. FDA–2026–N–3499 – Obesity and Drug Dosing: Clinical Pharmacology Considerations

Dear Sir or Madam:

The Obesity Society appreciates the Food and Drug Administration's decision to establish this public docket on obesity and drug dosing. This request for information recognizes an important and longstanding gap in drug development and clinical pharmacology. As obesity has become one of the most prevalent chronic diseases in the United States, ensuring that medications are appropriately evaluated in people with obesity has become an essential component of safe, effective, and equitable drug development.[1]

The Obesity Society (TOS) is the leading scientific organization dedicated to the study, prevention, and treatment of obesity. TOS represents a diverse membership of researchers, clinicians, and public health professionals committed to advancing evidence-based approaches to obesity care and improving the lives of people affected by obesity. Through research, education, and advocacy, TOS works to ensure that clinical and policy decisions reflect scientific rigor and promote equitable, effective healthcare.

These comments are also informed by the 2023 joint statement issued by leading clinical, scientific, and patient advocacy organizations—including TOS, the Obesity Action Coalition, STOP Obesity Alliance, Obesity Medicine Association, and the American Society for Metabolic and Bariatric Surgery—which called for closing gaps in drug approval and labeling for people with obesity.[2]

Use of People-First Language

TOS also encourages the FDA to adopt and consistently use people-first, non-stigmatizing language in future communications, guidance documents, workshops, and regulatory materials addressing obesity. The docket and associated materials include terminology that is not fully consistent with current people-first language recommendations, including references to "obese patients." People-first language—such as "people with obesity"—recognizes the individual before the disease and is consistent with current scientific and clinical recommendations. [1,19]

Research and policy guidance have emphasized that weight bias and stigmatizing language can adversely affect healthcare experiences, patient engagement, clinical decision-making, and public understanding of obesity. As the FDA continues its leadership in advancing evidence-

based approaches to obesity and drug development, the Agency has an opportunity to model language that reflects both scientific accuracy and respect for people living with obesity.[19]

TOS recently published *Speaking the Language of Obesity: Guidance for Obesity-Related Conversations, Research, Education, and Publications*, which provides practical recommendations for policymakers, regulators, clinicians, researchers, advocates, media professionals, and the public. We encourage FDA to review this resource and consider incorporating its recommendations into future obesity-related communications and guidance documents.[19]

Obesity and Drug Dosing: Clinical Pharmacology Considerations

Both the FDA and external experts have recognized the importance of obesity and drug dosing. During the FDA workshop *Bridging Efficacy and Safety to the Obese: Considerations and Scientific Approaches*, FDA Commissioner Robert Califf acknowledged that "there are generally no FDA regulatory requirements at present to evaluate weight as a specific issue." Subsequent publications have highlighted the potential risks associated with limited obesity-specific pharmacokinetic and pharmacodynamic data and the implications for patient safety, treatment effectiveness, and appropriate dosing recommendations. These concerns underscore the need for a more systematic approach to evaluating obesity as an intrinsic factor in drug development and regulatory review.[3,4]

Historically, people with obesity have frequently been excluded from clinical trials or have been substantially underrepresented, particularly individuals with severe obesity. As a result, clinicians are often left without reliable information regarding the pharmacokinetics (PK), pharmacodynamics (PD), efficacy, or safety of medications in a population representing approximately 40% of U.S. adults. The resulting uncertainty can adversely affect therapeutic decision-making, increase the risk of treatment failure or toxicity, and undermine confidence in prescribing information.[5,6]

Obesity produces numerous physiological changes that can influence drug disposition. Alterations in body composition, hepatic metabolism, renal function, gastrointestinal physiology, plasma protein binding, inflammation, and expression of drug-metabolizing enzymes may significantly affect absorption, distribution, metabolism, elimination, and pharmacodynamic response. These effects are drug-specific, but they are sufficiently well documented that obesity should no longer be viewed as an exceptional circumstance requiring special justification for study. Rather, it should be recognized as an increasingly common clinical characteristic that warrants prospective evaluation whenever drugs are likely to be used in this population.[7]

The Society therefore offers three principal recommendations:

Drug development programs should routinely evaluate pharmacokinetics and pharmacodynamics in participants with obesity whenever the drug is reasonably expected to be used in this population.

The FDA's recent initiatives encouraging broader representation of patient populations in clinical trials provide an important foundation. We encourage the FDA to extend these principles explicitly to obesity. For medications intended for widespread clinical use—or for diseases whose prevalence is increased among people with obesity—development programs should prospectively include adequate numbers of participants across the spectrum of obesity. Inclusion should encompass sufficient representation of individuals with class II and class III obesity whenever scientifically appropriate.[8–10]

The specific approach should remain flexible and risk-based. Depending upon the drug and therapeutic area, useful information may be generated through dedicated phase 1 studies, population PK analyses, model-informed drug development approaches, exposure-response analyses, or integrated analyses across development programs. FDA appropriately identifies these options in its request for comments. However, the critical principle is that clinically meaningful PK and PD data cannot be generated if people with obesity are absent from development programs. Historically, this has too often been the case. [1]

As the American College of Clinical Pharmacology recently concluded, obesity should be considered a routinely evaluated intrinsic factor during drug development whenever scientifically appropriate. Given high rates of obesity in the United States, inclusion of people with obesity in pharmacodynamic studies should be considered a default principle rather than an exceptional case. [5]

FDA-approved labeling should communicate clinically relevant pharmacokinetic findings in people with obesity.

Generating evidence is only the first step. The information must also be communicated effectively to clinicians. The FDA-approved prescribing information remains the primary authoritative source clinicians use when making prescribing decisions. Yet obesity-related PK information is absent from the overwhelming majority of current labels, even when published evidence demonstrates clinically meaningful differences. Current labeling frequently provides detailed guidance regarding renal impairment, hepatic impairment, age, sex, pharmacogenomics, and drug-drug interactions. Similar transparency should exist when obesity significantly alters pharmacokinetics or pharmacodynamics.[4]

When clinically meaningful differences are identified, labeling should clearly describe:

- observed PK and PD differences;
- populations studied;
- effects on exposure, clearance, half-life, or distribution;
- implications for dosing, monitoring, or washout intervals; and
- limitations of available evidence where uncertainty remains.

Such information allows clinicians to individualize treatment while remaining consistent with the FDA's long-standing principles for communicating intrinsic factors that influence drug disposition. Importantly, labels should also acknowledge when clinically relevant obesity-

specific data are unavailable. Absence of evidence should not be mistaken for evidence of no effect.

FDA should encourage updating existing labeling when scientifically reliable obesity-related pharmacokinetic evidence becomes available.

The need to improve labeling extends beyond newly approved products. Many medications currently in widespread clinical use entered the market before obesity became as prevalent as it is today or before the modern understanding of obesity-related pharmacology had developed. Consequently, labels often omit information now supported by peer-reviewed literature.[4]

Examples described in the published literature illustrate why these omissions matter. Altered elimination of posaconazole in people with obesity may prolong clinically significant CYP3A4 inhibition and extend the duration of important drug-drug interactions.[11–13] Modeling studies suggest delayed attainment of therapeutic concentrations for brexpiprazole in patients with obesity, with potential implications for treatment effectiveness.[14] Similar obesity-related PK differences have been reported for multiple antimicrobial medications, psychotropic medications, immunosuppressants, and contraceptives.[15–18]

These examples are not presented to suggest that every existing medication requires relabeling. Rather, they demonstrate that scientifically credible evidence already exists for selected products where updated prescribing information could improve patient care. The FDA has long maintained mechanisms for updating labeling as new safety or pharmacology information emerges. Obesity-related PK findings should be treated no differently. When reliable evidence demonstrates clinically meaningful effects on exposure, efficacy, safety, or dosing, the FDA should encourage appropriate revisions to product labeling.

Responses to FDA's Questions

Adequacy of BMI and Alternative Measures

BMI alone is unlikely to capture the biological complexity relevant to pharmacokinetics. BMI remains a practical and widely accepted screening measure and should continue to serve as an initial classification tool. However, whenever feasible, analyses should also consider additional factors that influence drug disposition, including total body weight, lean body mass, body composition, body surface area, visceral adiposity, hepatic steatosis, renal function, inflammatory biomarkers, and obesity-related comorbidities. Model-informed approaches integrating these variables may ultimately provide more informative dosing recommendations than BMI alone.[7]

Drug-Specific and Therapeutic Considerations

Assessment should be prioritized for drugs with narrow therapeutic indices, lipophilic compounds, medications extensively metabolized through hepatic pathways, drugs dependent

upon renal clearance, therapies requiring rapid attainment of therapeutic concentrations, and medications intended for conditions that commonly coexist with obesity.[4,7]

Assessment Across Drug Development

TOS supports a flexible scientific framework rather than a single required study design. Dedicated PK studies, population analyses, physiologically based pharmacokinetic modeling, exposure-response analyses, and postmarketing evidence each have important roles depending upon the characteristics of the drug and available evidence. The goal should be the generation of sufficiently robust evidence to inform clinically meaningful labeling and dosing recommendations. [1,5]

Conclusion

The increasing prevalence of obesity requires corresponding advances in clinical pharmacology and regulatory science. FDA's decision to seek public input represents an important opportunity to improve drug development and prescribing for millions of patients.

The Obesity Society respectfully recommends that the FDA:

- Encourage routine inclusion of people with obesity in drug development programs whenever the medication is likely to be used in this population. The default design of programs should include people with obesity, given its prevalence;
- Ensure that clinically meaningful obesity-related pharmacokinetic and pharmacodynamic findings are communicated clearly in FDA-approved labeling; and
- Encourage timely updates to existing product labeling when reliable scientific evidence demonstrates clinically important obesity-related effects.

These recommendations are consistent with sound clinical pharmacology, patient safety, scientific transparency, equitable access to evidence-based prescribing information, and respectful communication about obesity. They will help ensure that people living with obesity receive the same evidence-informed care that the FDA seeks to provide for every population affected by intrinsic factors that influence drug disposition. Please direct any questions regarding this submission to Jeanne Blankenship, MS RDN, at jblankenship@obesity.org.

Sincerely,



Jacqueline M. Stephens, PhD, FTOS
President
The Obesity Society

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