Inclusion of Obese Participants in Drug Development: Reflections on the Current Landscape and a Call for Action

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Obesity is a national health issue, with a prevalence that has increased from 30% to 43% in adults in the United States during the past 20 years.[1] Importantly, obesity is also associated with increased risks for other comorbid diseases such as diabetes, hypertension, cardiovascular disease, respiratory failure, and cancer.[2–4] As such, the American College of Clinical Pharmacology (ACCP) is issuing a call for action aimed toward the timely inclusion of obese participants in clinical trials during the drug development process. A road map is proposed to recommend the inclusion of obese participants within clinical trials with the consideration of disease epidemiology, comorbidities, pharmacokinetics (PK), pharmacodynamics (PD), efficacy, and safety of the investigational agent, and encourages evidence synthesis through model-informed data integration to optimize the posology of therapeutics and maximize benefit versus risk in the intended patient population.

With the increasing prevalence of obesity in the United States, it would be ideal to have a greater representation of this population in both Phase 1 studies conducted in otherwise healthy volunteers and late-stage Phase 2/3 clinical trials in patients. Typical Phase 1 clinical pharmacology trials conducted in healthy volunteers tend to have inclusion and exclusion criteria that limit participation by those that have a body size, weight, or body mass index (BMI) that falls outside a particular "healthy" range. These typical trial designs fail to appreciate that there can be important differences in the distribution of body size/weight/BMI in the actual target patient population assessed later during clinical development. The understanding of such differences, coupled with an assessment of expected sensitivity of the investigational agent's clinical pharmacology profile to physiological changes associated with increased body weight can better inform the Phase 1 strategy for assessing the PK, PD, and safety parameters and optimize any guidance for their inclusion in Phase 2/3 trials.

To gain a better understanding of the current regulatory environment in which these patients are represented in late phase 2/3 clinical trials, we performed a US Food and Drug Administration (FDA) label search of approved New Drug Applications/Biologics Licensing Applications (https://nctr-crs.fda.gov/fdalabel/ui/search). The key words used for searching label sections were "obese," "overweight," or "BMI". A total of 97 approved labels for New Drug Applications/Biologics Licensing Applications were retrieved using these search words. Dosing recommendations for overweight or obese patients based on BMI were provided in 14 of 97 labels (approximately 14%) indicating that evidence in support of dosing such patients was generated during the clinical development programs for these drugs. It should be emphasized that 7 of these 14 labels were for either weight loss or obesity management indications, thereby necessitating inclusion of this study population and label considerations. Taken together, this suggests that, despite the overall steadily increasing prevalence of obesity in the US population, dosing recommendations for obese patients are typically not provided in the majority of the current FDA-approved labels. This may be due to a lack of inclusion of a sufficient number of these patients in clinical studies, likely resulting from safety concerns associated with higher comorbidities and lack of safety data in such patients. Even when the inclusion/exclusion

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criteria of a clinical study allow obese participants to enroll, insufficient participation may still exist for a variety of reasons such as recruitment challenges due to lack of awareness and logistical challenges for these patients.

Epidemiological Context

Clinically, obesity is defined as a BMI (body weight [kg]/height $(m)^2$) of 30 kg/m^2 or greater, although the need to move beyond BMI in its definition has now been acknowledged.[5] Obesity is often further subdivided into 3 classes: Class 1: BMI of 30 to less than 35 kg/m^2; Class 2: BMI of 35 to less than 40 kg/m^2; and Class 3: BMI of 40 kg/m^2 or greater, which is commonly termed as "severe" or "extreme" obesity.[3] According to the World Health Organization's Obesity and Overweight Key Facts, the prevalence of obesity has nearly tripled since 1975. Based on 2016 statistics, more than 1.9 billion adults worldwide were considered overweight, of which 650 million were considered obese.[1] In the United States alone, according to the National Health and Nutrition Examination Survey 2021 report, the prevalence of obesity in the United States was 41.9% of the population as of 2017. This is a greater than 10% increase from the previous 1999/2000 report, which cited a prevalence of 30.5%.[2] The cause of obesity is multifactorial and can include genetic, environmental, socioeconomic, and behavioral influences. However, in most cases it is associated with behaviors that are considered modifiable, such as a sedentary lifestyle and increased caloric intake.

Potential Impact of Obesity on the Clinical Pharmacology of Drugs

Obesity leads to a myriad of physiological modifications that can affect the disposition of commonly prescribed drugs. Physiological changes due to obesity that affect oral drug absorption generally include increases in gastrointestinal blood perfusion, higher cardiac output, increased splanchnic blood flow, changes in enterohepatic recirculation, accelerated gastric emptying, and increased gut permeability, all of which can alter both the rate and extent of drug absorption.[6–9] Since obesity is associated with a significant increase in subcutaneous fat, subcutaneous, transdermal, and intramuscular administrations may all be affected by changes in the quantity of fat tissue and associated changes in blood flow to the skin, subcutaneous fat, and muscle.[7,9]

Changes in drug distribution associated with obesity can be a result of the physiological changes observed with increased body weight (ie, increases in adipose tissue, changes in protein binding, and reduced tissue perfusion) and are additionally dependent on the intrinsic physiochemical properties of the drug, such as protein binding and tissue penetration.[6] As an example, adequate tissue penetration is particularly important for antibiotics used for localized infections or perioperative prophylaxis, where minimum inhibitory concentrations need to be achieved. Microdialysis studies with cefuroxime and ciprofloxacin have shown that tissue penetrations in obese patients were significantly reduced.[7] Furthermore, highly lipophilic drugs can show a dramatic increase in volume of distribution translating to prolonged accumulation as demonstrated in a seminal PK study of the benzodiazepine diazepam in obese subjects.[10]

In obese individuals, liver pathologies are common. Chronic low-grade inflammation in the liver may result in decreased enzyme expression of certain cytochrome P450 enzymes.[7] For example, obesity-associated decrease in cytochrome P450 3A4-mediated metabolism has been reported for the corticosteroid methylprednisolone, where the absolute clearance was decreased by approximately 40% in obese individuals.[11] There is also some evidence that obesity is related to a state of glomerular hyperfiltration with an increase in glomerular filtration rate (GFR). This increase in GFR mimics what is observed in early-stage diabetic nephropathy or end-stage renal disease, both of which are commonly observed in obese individuals. The observed increase in GFR may also be secondary to increased kidney size and renal blood flow, which are generally associated with obesity.[6,12]

Current Dosing Paradigms in Obese Populations

Medications are commonly administered on the basis of either fixed, weight-based, or body surface area (BSA)-based dosing approaches. The basic assumption for these approaches is that drug clearance and/or volume of distribution increases in proportion to weight or BSA. This is generally applicable for nonobese patients (BMI less than 25 kg/m^2) and where linear PK is observed with increasing dose. However, the above approaches may lead to an over- or underestimation in individuals who are overweight (BMI = 25-29.99 kg/m^2) or obese since the assumption that clearance and/or volume of distribution increases in proportion to weight or BSA often needs to be altered with increases in total body fat, organ mass, blood volume, and cardiac output in obese patients. Therefore, other alternative methods using body size descriptors such as adjusted body weight, lean body weight, and ideal body weight, which rely on physical attributes of individuals such as height, weight, sex, and, more importantly, body proportions, may be needed to guide dosing in these individuals.[13] While some of these descriptors

take distribution of total body fat into consideration, others do not and thus are not ideal for dose determination. Other considerations in evaluating body size descriptors include sex differences in body composition (lean body mass vs fat mass) that are further compounded by differences in average weight between male and female populations. Therefore, scientifically guided and data-driven approaches for developing posology recommendations in obese patient populations is critically important.

Clinical Pharmacology Tools to Evaluate Impact of Obesity on Dosage Requirements

Population pharmacokinetic (PopPK) modeling remains the preferred method of analysis of pharmacological data from clinical studies, as it can accommodate sparse plasma drug concentration data and assess general trends as well as interindividual variabilities in PK and/or PD due to intrinsic factors, including body weight. A prerequisite for a successful PopPK analysis is the inclusion of a sufficient number of patients who have the required targeted characteristics to explore the effects of obesity. Thus, an adequately sized study in the population of interest, with an informative PK sampling strategy to identify clinically relevant covariates, is required to generate a PopPK model with sufficient resolution, especially for drugs with complex disposition.

High-fidelity physiologically based pharmacokinetic (PBPK) models based on mechanistic resolution and quantitative understanding of in vivo human clearance routes (eg, biliary, renal, metabolic) and physicochemical properties of the drug can be valuable for assessing the impact of obesity on PK during drug development.[14] While it is recognized that this approach also requires a large amount of quantitative and longitudinal information related to the population of interest, data on anatomical, physiological, and biological changes induced by obesity in a population with a BMI of 18.5-60 kg/m^2 were published recently.[15] The continuous physiological changes and their variabilities for each system parameter can be used to inform a PBPK framework. Application of these models in an obese population has received increasing attention over the past few years due to their mechanistic nature. However, until sufficient verification of PBPK modeling in obese subjects has been performed and confidence is sufficiently high in prospective predictions, PBPK modeling could be used to support initial dose estimates for clinical trials and also systematically elucidate the impact of key parameters among the (patho)physiological changes, drug properties, and longitudinal changes, which all interact with each other.[16,17]

Any translational or clinical characterization of the effects of obesity on the PK of an investigational agent in development should be coupled with an assessment of anticipated clinical impact. This reinforces the critical importance of characterizing the exposure-response relationships for efficacy and safety throughout drug development. In one recent example, a comprehensive characterization of PopPK and exposure-response relationships for efficacy and safety of an investigational progesterone receptor modulator vilaprisan based on Phase 1 and Phase 2 trials enabled the conclusion of limited clinical relevance of exposure alterations in obesity, supporting a common dosage in the Phase 3 clinical program in patients with uterine fibroids.[18] Depending on the drug's properties, the peak concentration, trough concentration, and total systemic exposure may not be equally altered by obesity. Knowledge of the PK driver for drug effects (which may be different for efficacy versus safety and different for different safety outcomes) and the associated exposure-response relationships is therefore vital in deciding whether an alteration in exposure or shape of the PK profile is potentially clinically relevant to warrant dosage adjustments, lead-in designs for confirmation of safety, or specific monitoring for risk management when including obese patients in clinical trials. While some of this knowledge will be based on clinical characterization of exposure-response relationships, it is possible that such complete understanding is not available at midstage drug development before pivotal trials have been initiated. To this end, the decision to include obese patients in late-stage trials based on PK characterized in earlier stages of development should be based on a totality-of-evidence approach. Such an approach should aim to quantitatively integrate all relevant preclinical, translational, and clinical prior knowledge on the investigational agent as well as clinical and real-world data on the benefit-risk profile of drugs with similar mechanisms of action, physicochemical properties, or other features in obese patient populations.

Regulatory Considerations

While focusing specifically on racial and ethnic demographics, the FDA 2022 draft guidance on plans to make clinical trials more diverse[19] indicates that sponsors should include other underrepresented populations such as those with comorbidities. In the guidance, the FDA also encourages sponsors to submit diversity plans early during drug development to ensure adequate participation of relevant and underrepresented populations and analyses of data collected from clinically relevant subpopulations. Just recently, the FDA, in collaboration with the University of Maryland Center of Excellence in Regulatory Science and Innovation,

hosted a 1-day virtual public workshop entitled "Bridging Efficacy and Safety to the Obese: Considerations and Scientific Approaches" in 2022.[20] The aim of this workshop was to discuss the impact of obesity on drug exposures in adult and pediatric populations in terms of safety and efficacy. Application of model-informed drug development (MIDD), including PopPK, PK/PD, and PBPK approaches to support dose optimization, clinical trial design, and efficacy in obese patients, was encouraged and clearly emphasized. Sponsors were encouraged to request an MIDD Paired Meeting Program with the FDA to discuss strategies relating to the conduct of appropriate modeling analyses in obese patients for drugs in development.

Another example of the importance of this focus can be seen within the professional medical associations, most recently with the American Society of Clinical Oncology. After conducting a systematic review of the literature regarding dosing of chemotherapy, immunotherapy, and targeted therapies in obese adults with cancer, the American Society of Clinical Oncology convened an expert panel to review the evidence and formulate recommendations. In addition to the recommendation that full, weight-based cytotoxic chemotherapy doses be used to treat obese adults with cancer (already in place), the panel also recommended that full, approved doses of immunotherapy and targeted therapies be offered to these patients. This example further indicates the need to carefully consider expansion of enrollment of obese patients to support benefit-risk assessment in drug development.

A Call for Action and Proposed Road Map to Expand Inclusion of Obese Participants in Drug Development

Epidemiological data indicate a growing prevalence of obesity in the general population worldwide and in the United States. Ideally, label recommendations for drugs are meant to reflect both the population studied and provide generalizable knowledge that can be applied to a broader population who will use the therapy.[21] Therefore, the inclusion of obese participants in clinical studies during drug development should be considered and actively discussed among clinicians, sponsors, and regulators in the context of the prevalence of obesity and related comorbidities in the target patient population. The assessment of expanding or actively enabling inclusion of obese participants in a clinical drug development program requires careful evaluation of potential effects of obesity on PK, PD, efficacy, and safety of the specific investigational agent. The assessment needs to consider the physicochemical properties, mechanisms of disposition, mechanism of action, efficacy and safety profiles, and anticipated therapeutic index of the investigational agent in relation to the anticipated comorbidities and sensitivity to potential adverse events in the obese population. These considerations and their quantitative integration are essential to determine the initial dosage, safety monitoring, and risk management/mitigation strategy to enable safe evaluation of the investigational agent in this specific population. A suggested good practice for clinical development is to incorporate inclusion of a subset of overweight or obese participants in early Phase 1 studies to specifically determine PK parameters as a function of body size descriptors. This should set the stage for inclusion of obese patients in proof-of-concept (ie, Phase 2a) trials, and subsequently in the pivotal Phase 2/3 program, with appropriate dosing and risk management in these trials to ensure safe evaluations. Taken together, sufficient data should be available in obese patients and assessed on the basis of body size descriptors. These data, when integrated using population PK and exposure-response model-based analyses, will help determine if the dose should be adjusted on the basis of body size descriptors of individual obese patients. The practice of actively but carefully and responsibly including obese patients in clinical studies during drug development will enhance the understanding of the benefit-risk profile of new drugs in the intended patient population. This will eventually help clinicians make informed dosing decisions for new drugs entering the market. Going beyond the evidence generation phase in drug development, enabling the safe and effective use of drugs in obese patients in practice settings will require education and training of health care providers, including but not limited to pharmacists.

The ACCP proposes the following roadmap in support of a call for action to promote the safe inclusion of obese participants throughout the drug development cycle to optimize dosage and maximize benefit versus risk of medicines in obese patients (Figure 1):

1. Learn and characterize the effect of obesity on the PK, PD, efficacy, and safety of drugs through all phases of the clinical development program, leveraging applicable MIDD tools.
2. Expand the inclusion and exclusion criteria of clinical studies to enable inclusion of obese participants when data are available to support doing so safely.
3. Include dosing information in relation to body size descriptors in drug labels when appropriate to guide their safe use in obese patients.

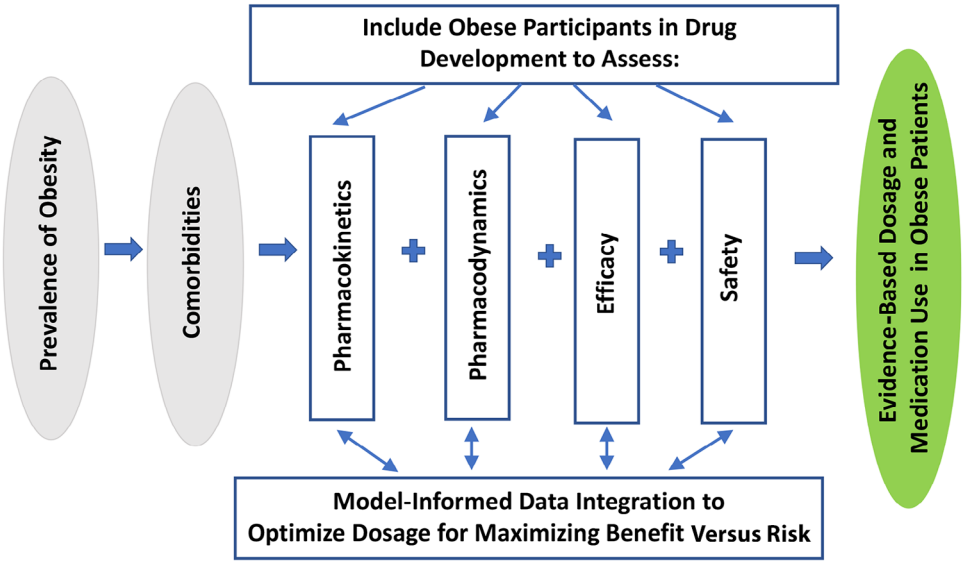

Figure 1. Roadmap to include obese participants in drug development.

Conflicts of Interest

The authors declare no conflicts of interest.

Disclaimer

The opinions expressed in this article are those of the authors on behalf of the American College of Clinical Pharmacology and should not be interpreted as the position of the entities or institutions at which the authors are employed.

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References

1. Center for Disease Control and Prevention. Prevalence of Overweight, Obesity, and Severe Obesity Among Adults Aged 20 and Over: United States, 1960–1962 Through 2017–2018. Accessed May 20, 2023. https://www.cdc.gov/nchs/data/hestat/obesity-adult-17-18/obesity-adult.htm
2. Jensen MD, Ryan DH, Apovian CM, et al. AHA/ACC/TOS Guideline for the management of overweight and obesity in adults. *Circulation*. 2014;129(25 suppl 2):S102-S138.
3. Garvey WT, Mechanick JI, Brett EM, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Comprehensive Clinical Practice Guidelines for medical care of patients with obesity. *Endocr Pract*. 2016;22(suppl 3): 1-203.
4. Center for Disease Control and Prevention. Obesity and Cancer. Accessed August 13, 2023. https://www.cdc.gov/cancer/obesity/index.htm
5. Flegal KM. Use and misuse of BMI categories. *AMA J Ethics*. 2023;5(7):E550-E558.
6. Knibbe CA, Brill MJ. van Rongen A, et al. Drug disposition in obesity: toward evidence-based dosing. *Annu Rev Pharmacol Toxicol*. 2015;55:149-167.
7. Smit C, De Hoogd S, Brüggemann RJM, Knibbe CAJ. Obesity and drug pharmacology: a review of the influence of obesity on pharmacokinetic and pharmacodynamic parameters. *Expert Opin Drug Metab Toxicol*. 2018;14(3):275-285.
8. Shank BR, Zimmerman DE. *Demystifying Drug Dosing in Obese Patients*. American Society of Health System Pharmacists; 2015.
9. Cheymol G. Effects of obesity on pharmacokinetics implications for drug therapy. *Clin Pharmacokinet*. 2000;39(3):215-231.
10. Abernethy DR, Greenblatt DJ, Divoll M, Shader R. Prolonged accumulation of diazepam in obesity. *J Clin Pharmacol*. 1983;23(8-9):369-376.
11. Dunn TE, Ludwig EA, Slaughter RL, Camara DS, Jusko WJ. Pharmacokinetics and pharmacodynamics of methylprednisolone in obesity. *Clin Pharmacol Ther*. 1991;49(5):536-549.
12. Brill MJ, Diepstraten J, van Rongen A, van Kralingen S, van den Anker JN, Knibbe CA. Impact of obesity on drug metabolism and elimination in adults and children. *Clin Pharmacokinet*. 2012;51(5):277-304.
13. Pai MP. Drug dosing based on weight and body surface area: mathematical assumptions and limitations in obese adults. *Pharmacotherapy*. 2012;32(9):856-868.
14. Rowland Yeo K, Venkatakrishnan K. Physiologically-based pharmacokinetic models as enablers of precision dosing in drug development: pivotal role of the human mass balance study. *Clin Pharmacol Ther*. 2021;109(1):51-54.
15. Berton M, Bettonte S, Stader F. et al. Repository describing the anatomical, physiological, and biological changes in an obese population to inform physiologically based pharmacokinetic models. *Clin Pharmacokinet*. 2022;61:1251-1270.
16. Gerhart JG, Balevic S, Sinha J, et al. Characterizing pharmacokinetics in children with obesity-physiological, drug, patient, and methodological considerations. *Front Pharmacol*. 2022;13:818726.
17. Zhang T, Krekels EHJ, Smit C, Knibbe CAJ. Drug pharmacokinetics in the obese population: challenging common

assumptions on predictors of obesity-related parameter changes. *Expert Opin Drug Metab Toxicol*. 2022;18(10):657-674.
18. Wegler C, Wiśniewski JR, Robertsen I, et al. Drug disposition protein quantification in matched human jejunum and liver from donors with obesity. *Clin Pharmacol Ther*. 2022;111(5):1142-1154.
19. Bell LN, Temm CJ, Saxena R, et al. Bariatric surgery-induced weight loss reduces hepatic lipid peroxidation levels and affects hepatic cytochrome P-450 protein content. *Ann Surg*. 2010;251(6):1041-1048.
20. The Center of Excellence in Regulatory Science and Innovation (M-CERSI), University of Maryland. Accessed August 13, 2023. https://cersi.umd.edu/bridging-drug-efficacy-and-safety-obese-considerations-and-scientific-approaches
21. Burckart GJ, Greenblatt DJ. Addressing the knowledge gaps for providing optimal drug pharmacotherapy for the obese. *J Clin Pharmacol*. 2023. https://doi.org/10.1002/jcph.2264. Online ahead of print.