Inclusion of Subjects with Obesity in Drug Development: Current Status and Opportunities

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Disclaimer

- This presentation represents the views of the speaker and may not necessarily represent official FDA policy.
- Conflicts of interest: None

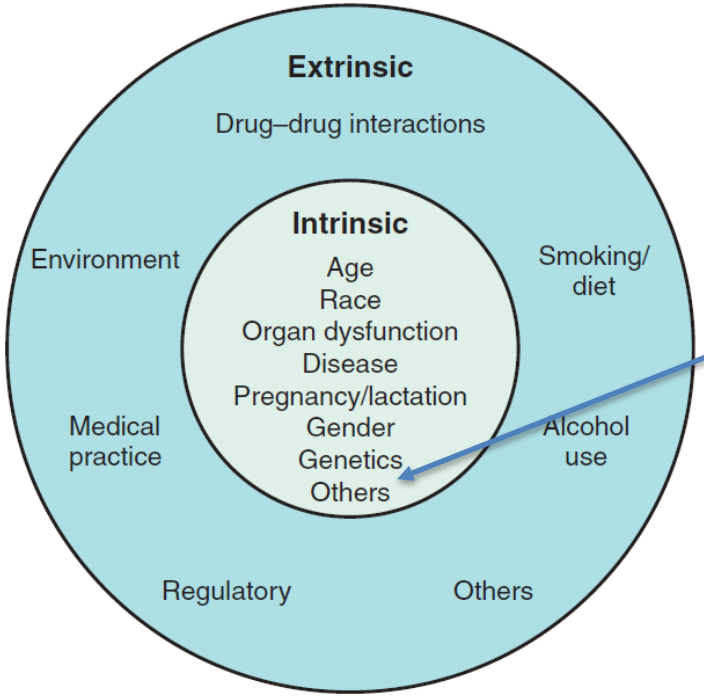
Outline

- Clinical trials
- Current state and challenges
- Inclusion of subjects with obesity and regulatory considerations
- Drug labeling examples
- Summary

Clinical Trial Population

- Diverse US population
- Intended patient population
  - Better understanding of benefit-risk profile
- Randomized clinical trials pre-approval
  - Limits treatment heterogeneity
  - Homogeneous population
  - Gaps (e.g., obesity)

Clinical Pharmacology



Body weight

Huang S-M, Temple R, Clin Pharmacol Ther. 84: 287-294, September 2008

Clinical Trials

- Pharmacokinetics (PK) and pharmacodynamics (PD) characterization – single dose, multiple dosing
- Drug-drug interactions
- Intrinsic factors– organ impairment, pediatrics, pregnancy, age, sex, race, body weight, etc.
- Dose finding studies
- Pivotal efficacy and safety trials

Effect of Covariates/Sub-groups

- Dedicated PK studies
  - Typically, single dose and in healthy subjects; include different categories (e.g., mild, moderate severe; male vs. female)
  - Intense blood sampling for PK analysis
  - Ideally conducted early to decide dosing in Phase 3
- Population PK and exposure-response
  - Effect of intrinsic factors
- Other modeling approaches
  - E.g., Physiologically based PK models (PBPK)

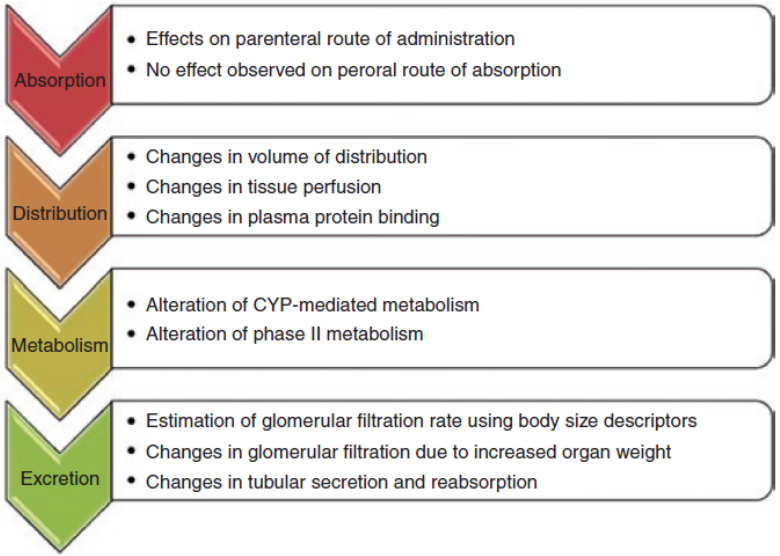
Clinical Trials – Regulatory Review

- Investigational product review
  - Continuous assessment; critical stages
  - End of Phase 2/Phase 3 planning – Adequacy of data evaluated in EOP2 stage; inclusion/exclusion criteria
- New drug application submitted
  - Good review practice document
    - Policies and procedure for documenting clinical review of NDA/BLA
  - Review templates
    - Clinical pharmacology review, integrated review template
    - Includes focus on therapeutic optimization and individualization

https://www.fda.gov/files/about fda/published/Good-Review-Practice--Clinical-Review-Template.pdf

https://www.fda.gov/media/71709/download https://www.fda.gov/media/87621/download

Obesity Related Changes in Pharmacokinetics



R Jain et al., https://doi.org/10.1038/clpt.2011.104

Current State of Dosing Information for Patients with Obesity

- Jain et al (survey 2004 – 2010)
  - 5 drugs with impact on PK/PD
  - Only 1 drug with specific dosing instructions in obesity
- Recent survey (until Sept 2022)
  - Heterogeneity in type and amount of information
- Vaughns et al (pediatric drug product labels 2007-2016)
  - Only 4 drug labels noted the effect of BMI on the PK of the drug
- Samuels et al (pediatric drug product labels 2016 – 2021)
  - No specific drug dosage recommendations for use in pediatric patients (except liraglutide)
  - Most data originated from adults (e.g., risk of adverse events, comorbidity)

https://doi.org/10.1038/clpt.2011.104 DOI: 10.1002/jcph.2305 https://doi.org/10.1002/jcph.1054 https://cersi.umd.edu/bridging-drug-efficacy-and-safety-obese-considerations-and-scientific-approaches

Challenges

- Paucity of data regarding use of drugs in subjects with obesity
- Lack of dosing information
- Lack of studies obese vs. non obese
- Lack of best practices or regulatory guideline

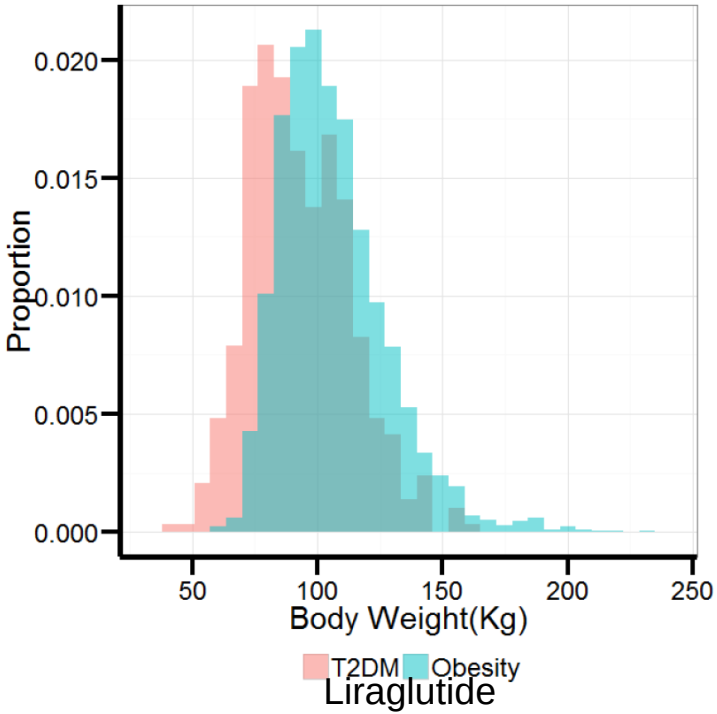
Challenges

- Although enrollment criteria did not exclude participants based on BMI
  - Did not enroll enough patients in the higher BMI range
  - Poor representation of racial or ethnic minorities in whom obesity is more prevalent
  - Reluctance to enroll patients if outcome could be poor in this subpopulation
  - Clinical site locations in regions where obesity prevalence is lower
- Potential exclusion of patients with comorbidities or those at high risk of disease
- Limitations to extrapolating dosage adjustments from adult to adolescents with obesity

DOI: 10.1002/jcph.2327
https://doi.org/10.1007/s40615-022-01487-0
https://doi.org/10.1200/JCO.2013.52.6962
https://doi.org/10.1038/clpt.2011.104
https://doi.org/10.1093/annonc/mdy138

Inclusion of Subjects with Obesity

- No specific regulatory requirement
- Inclusion in certain drug development programs with high frequency of obesity (e.g., type 2 diabetes)



re 1: Body weight distribution in the T2DM and obesity programs

http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm413316.htm

Perspective on Inclusion of Subjects with Obesity

- Several initiatives to promote diversity in clinical trials
  - Engaging stakeholders
    - FDA, M-CERSI workshop Nov 2022
  - Regulatory research
    - JCP obesity themed issue 63(S2), 2023
  - Regulatory review
  - Guidance documents

A Ramamoorthy et.al.,, Clin Pharmacol Ther. 2023,113(3);528-535
J Vaidyanathan et.al.,, J Clin Pharm. 2023,163(S2): S10-S17

Regulatory Guidances with Recommendations on Obesity Concepts

- Provides recommendation for inclusion of participants who have obesity
  - During drug development
  - As a prespecified subgroup with prospective analysis plan
  - Evaluation of impact of obesity on PK, dose, efficacy
  - Development of new drug products for weight management
  - Exclusion of such patients when warranted for safety perspective
  - Presentation of relevant information in package insert with relevant labeling recommendations for health care providers

J Vaidyanathan et.al.,, J Clin Pharm. 2023,163(S2): S10-S17

Regulatory Guidances

- Enhancing the diversity of clinical trial populations – Eligibility criteria, enrollment practices, and trial design (Final, 2020)
- General clinical pharmacology considerations for pediatric studies of drugs, including biological products (Draft, 2022)

Regulatory Guidances

- Establishing effectiveness and safety for hormonal drug products intended to prevent pregnancy (Draft, 2019)
- Noncirrhotic, nonalcoholic steatohepatitis with liver fibrosis: Developing drugs for treatment (Draft, 2018)

Regulatory Guidances

Guidance	Key obesity-related concept
Developing products for weight management (Draft, 2007)	This guidance provides recommendations to industry regarding the development of drugs and therapeutic biologics for the indication of chronic weight management
Coronary Drug-Eluting Stents – Nonclinical and Clinical Studies Companion Document (Draft, 2008)	Factors affecting the poolability of US and non-US studies: patient demographics/clinical characteristics (obesity and others)
Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format (Final, 2016)	Additional subheadings representing other specific populations (eg, smokers, patients who are obese, or patients with low body weight) may be included if informative for clinical use of the drug. A description of the studies and the results should be included under these subheadings
Anthrax: Developing Drugs for Prophylaxis of Inhalational Anthrax (Final, 2018)	Obtaining PK data for specific populations (eg, geriatrics, pregnant women, patients who are obese/morbidly obese, patients with renal or hepatic impairment, and pediatrics, if possible (see section III.C.1., Pediatrics)) is recommended, as well as conducting studies to investigate the potential for drug–drug interactions with medicinal products likely to be co-administered in the clinical scenario
Development of Anti-Infective Drug Products for the Pediatric Population (Final, 2021)	Cohorts based on age, body weight or body surface area. The sponsor should consider the need to assess the effect of obesity on dose selection

Obesity Information in Labeling

- Oral contraceptives

Drospirenone/estetrol	Limitations of use: may be less effective in females with a BMI of $\geq$30 kg/m^2. In females with BMI $\geq$ 30 kg/m^2, decreasing effectiveness may be associated with increasing BMI. The safety and efficacy of NEXTSTELLIS in females with a BMI of $\geq$35 kg/m^2 have not been adequately evaluated.
Estradiol valerate/dienogest	The efficacy in women with a BMI of $>$30 kg/m^2 has not been evaluated
Etonogestrel	The effectiveness of the etonogestrel implant in women who weighed more than 130% of their IBW has not been defined because such women were not studied in clinical trials. Serum concentrations of etonogestrel are inversely related to body weight and decrease with time after implant insertion. It is therefore possible that NEXPLANON may be less effective in overweight women, especially in the presence of other factors that decrease serum etonogestrel concentrations, such as the concomitant use of hepatic enzyme inducers
Levonorgestrel/ethinyl estradiol	Contraindication: in women with a BMI of $\geq$30 kg/m^2 – reduced effectiveness and may have a higher risk for venous thromboembolic events Limitations of use: consider reduced effectiveness in women with a BMI of $\geq$25 to $<$30 kg/m^2 before prescribing
Norethindrone acetate/ethinyl estradiol	Efficacy in women with a BMI of $>$35 kg/m^2 has not been evaluated
Progesterone	The safety and efficacy in women with a BMI of $>$38 kg/m^2 has not been studied
Segesterone acetate/ethinyl estradiol	Limitations of use: has not been adequately studied in females with a BMI of $>$29 kg/m^2

Obesity Information in Labeling

- Dosing

Digoxin	Reduce the dose in patients whose LBW is an abnormally small fraction of their TBW because of obesity or edema
Doxorubicin	Consider use of the lower dose in the recommended dosage range or longer intervals between cycles for heavily pretreated patients, elderly patients, or obese patients
Somatropin	Weight-based dosing is not recommended for obese patients as they are more likely to experience adverse reactions with this regimen
Vancomycin	Other patient factors, such as age or obesity, may call for modification of the usual intravenous daily dose
Tecovirimat	Dosing based on body weight cut off 40 kg to 120 kg and 120 kg or more

Obesity Information in Labeling

- Close monitoring in patients with obesity
  - Goserelin, Enoxaparin
- Considerations of using longer needle lengths
  - Cabotegravir, triamcinolone
- Dose modifications
  - Digoxin, vancomycin
- Impact on PK
  - Either changes or indicating no change

Opportunities

- Model informed drug development (MIDD)
  - Application of quantitative models to facilitate drug development and decision making
  - Regulatory tool to promote early interaction with FDA on key issues
  - Enhance therapeutic individualization

Example: MIDD Approach for Dose Capping

MIDD used to assess appropriateness for enfortumab vedotin-ejfv (Padcev)
Dose cap of 125 mg for patients with obesity weighing 100 kg or greater

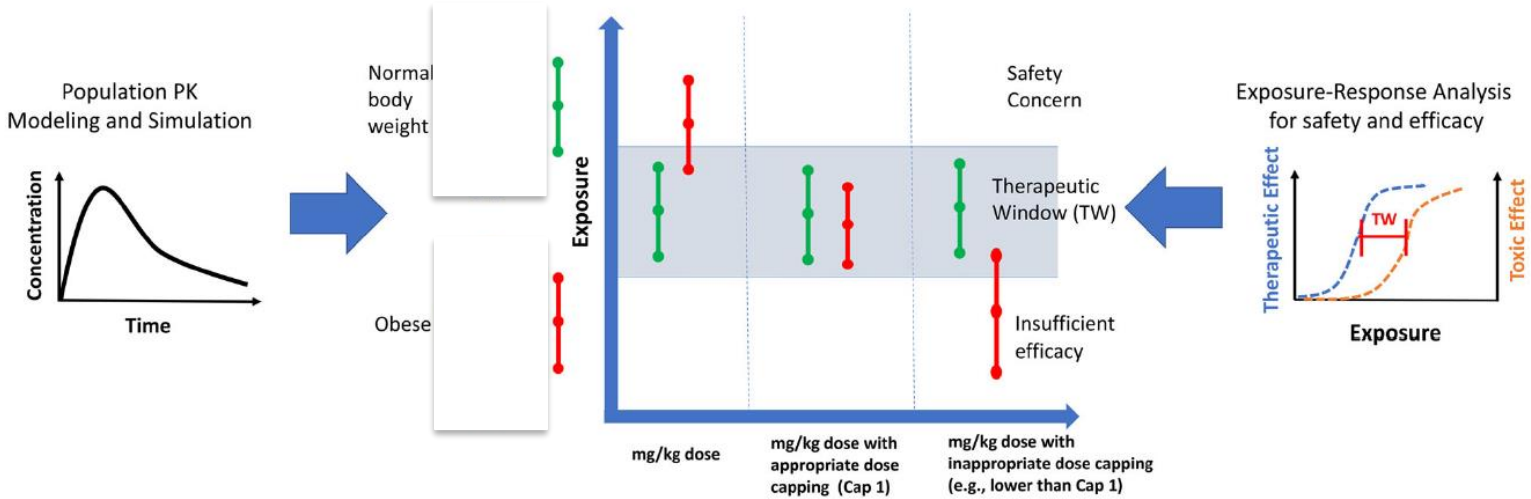
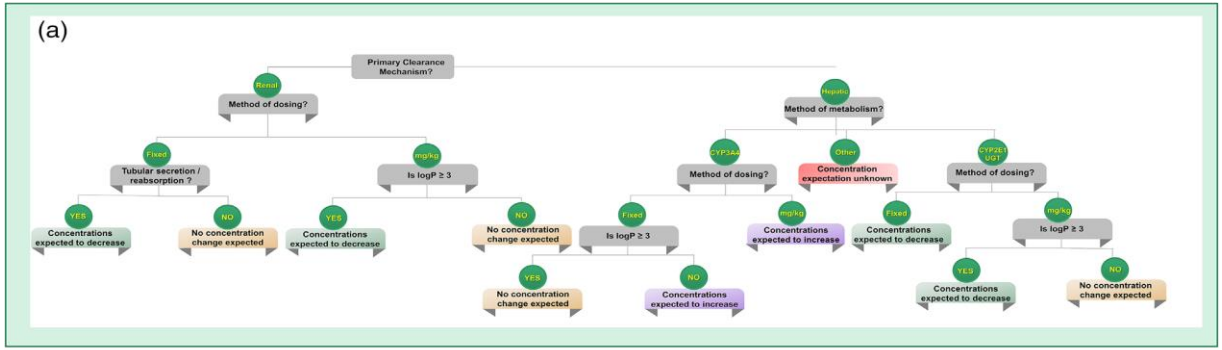


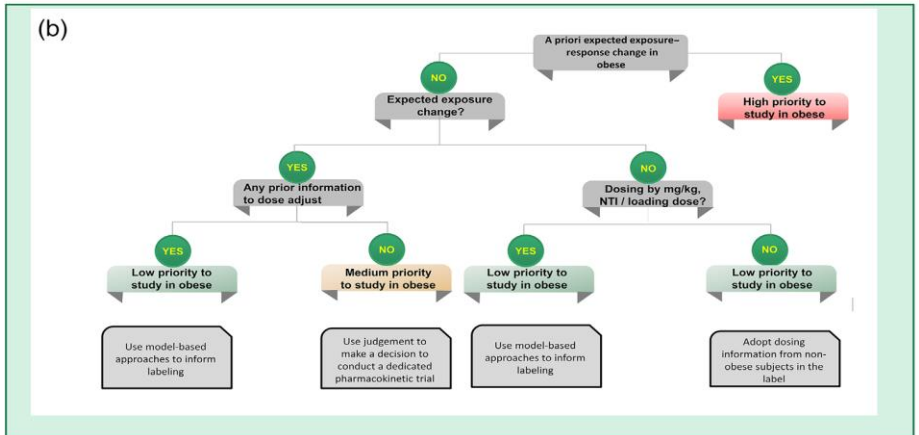
Figure 1. MIDD approaches supporting regulatory decision making of dosing capping for patients with obesity. PK, pharmacokinetics.

Pan et al: DOI: 10.1002/jcph.2349

Opportunities

- Decision tree using modeling





DOI: 10.1002/jcph.2304

Summary

- Inclusion of subjects with obesity is important considering the prevalence of obesity in the US.
- Sponsors should address drug disposition and impact of obesity early in drug development
  - Modeling tools can help
  - Determine need to enroll in phase 2/3 clinical trials
- FDA guidances highlight the need for inclusion
- Stakeholder engagement
  - Collective efforts is needed from all stakeholders

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