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Reflection paper on investigation of pharmacokinetics and pharmacodynamics in the obese population

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Reflection paper on investigations of pharmacokinetics and pharmacodynamics in the obese population

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1. Introduction

Obesity affects a large sub-set of the general population covering all ages and will continue to increase based on observed trends. The alteration of body composition and physiology as well as steatosis and a chronic state of inflammation (1) can potentially lead to important changes in the disposition of a given drug in obese as compared to non-obese subjects. Thus, the need for adequate pharmacokinetic (PK) characterisation in obese subjects should be considered in drug development to ensure their effective and safe use in this subgroup and to inform on possible dose adjustments required in these patients. Note, the term 'non-obese' includes both normal/lean subjects and underweight subjects.

The World Health Organisation (WHO) defines overweight and obesity as abnormal or excessive fat accumulation that presents a risk to health. Body Mass Index (BMI = body weight (kg)/height $(m)^2$) is still the most widely used metric for overweight and obesity gradation in adults and is independent of gender. According to the WHO, BMI between 25 and 29.9 kg/m^2 represents overweight, while obesity is defined as BMI ≥ 30 kg/m^2. The WHO further defines different classes of obesity as class I (moderately obese) with BMI 30-34.9 kg/m^2, class II (severely obese) with BMI 35 -39.9 kg/m^2 and class III (very severely obese) with BMI ≥ 40 kg/m^2. In addition to BMI, other body size descriptors can also be used to grade patients/subjects with regard to obesity (see appendix).

While generally the impact of body weight, BMI and Body Surface Area (BSA) on PK is investigated, more specific PK investigations targeting obese subjects are usually left unaddressed. This is considered a shortcoming that is potentially compounded by obese patients often being poorly represented not just in early but also later phase studies. Furthermore, effects may only be possible to estimate in a limited obesity range. An exception is studies investigating therapies for populations with a particularly high frequency of overweight and obese patients e.g. weight loss, type-2 diabetes, where obesity is more common in the clinical studies.

Obese subjects have larger absolute fat tissue mass but also more lean body mass (LBM) than non-obese of the same age, gender and height (2). However, in obesity the ratio of fat mass to total body weight is increased, therefore differentiation based on weight only might not be helpful and a dose by weight adjustment may be insufficient.

There is currently no specific Committee for Medicinal Products for Human Use (CHMP) guidance on how and when to investigate PK and/or pharmacokinetic/pharmacodynamic (PK/PD) relationships in obese subjects. However, a number of CHMP guidelines are relevant in the context of defining approaches and strategies that can be used for such investigations (3, 4, 5).

The specific aims of this reflection paper are to:

- describe how the effects of obesity can be investigated during clinical drug development;
- provide recommendations on when investigations of the effect of obesity on the PK of a drug should be considered;
- provide information on specific important considerations for these investigations and
- discuss how to reflect PK findings in weight/size based dosing recommendations.

2. Scientific background: effects of obesity on pharmacokinetics and pharmacodynamics

2.1. Absorption

It is possible that the bioavailability of drugs from the site of administration may be altered in obese patients. Reduced rate of absorption is reported for the subcutaneous and transdermal routes. This is plausibly linked to locally reduced blood flow. Increases in perfusion of the gut and accelerated gastric emptying with subsequent enhancement of drug bioavailability have been reported for the oral route (6).

2.2. Distribution

The distribution of drugs is driven by body composition, regional blood flow and binding to tissue and plasma proteins.

Obese subjects have a larger absolute lean body weight as well as fat mass. While the lean mass accounts for 20-40% of the excess of weight, fat mass is significantly enhanced in obese subjects and the lean mass per kg body weight is reduced (7, 8).

The physicochemical properties of a drug (lipophilicity, polarity, molecular size and degree of ionization) influence its distribution into the body. A higher distribution volume in obese subjects is reported for lipophilic drugs such as steroids, benzodiazepines and tricyclic anti-depressants, which can lead to prolonged half-life. Conversely, polar molecules appear to have no marked differences in distribution between obese and non-obese subjects.

Under normal body-weight conditions, the blood flow in fat tissue is poor and accounts for only 5% of the cardiac output compared to 73% in the viscera and 22% in lean tissue. In BMI class III obese subjects, the blood flow per gram of fat is significantly lower than that observed in class I obese or lean subjects (2). This can alter the distribution to and from a target in fatty tissue (9), but also from the fat compartment in case of e.g. sub-cutaneous administration.

An increased amount of alpha-1-acid-glycoprotein (AAG), linked to a chronic inflammatory state, is reported in obese individuals. Therefore alteration of protein binding is possible, indicating a particular need to determine unbound exposure for basic drugs particularly with concentration-dependent protein binding exhibiting high affinity to AAG.

2.3. Elimination

There are many physio-pathological changes that may impact the elimination of drugs in obese subjects:

- increased cardiac output and hepatic blood flow;
- fatty infiltrates occurring in the liver (extent is proportional to the degree of obesity);
- low grade inflammation affecting the liver function;
- glomerular hyperfiltration (glomerular filtration rate (GFR) is approximately 60 % higher in obese subjects (10)).

The consequences of these changes on the elimination (metabolism and excretion) of drugs are reviewed below.

2.3.1. Metabolism

The effect of obesity on drug metabolism is dependent on:

- which major enzymes are involved in a drug's elimination;
- whether the hepatic extraction ratio is high or low;
- the route of administration.

For drugs of high and moderate hepatic extraction, an increase in hepatic blood flow gives rise to increased first-pass extraction in the liver as well as increased hepatic clearance. No change is expected for drugs with low hepatic extraction.

Histologically proven liver abnormalities of fatty infiltrations are present in 90% of obese subjects. It is estimated that up to 20% of the obese population and up to 50% of morbidly obese patients have NASH (non-alcoholic steato-hepatitis), where steatosis is combined with inflammation and fibrosis (9) and its incidence correlates with increasing BMI.

In general, inflammation is known to cause decreased activity of metabolic enzymes resulting from the production of cytokines and the modulation of the transcription factors that control the expression of specific CYP forms (11).

The effect of obesity may vary between enzymes. For example, CYP3A4 is very commonly involved in the metabolism of drugs. Weight normalised and absolute CYP3A mediated clearance has been observed to be significantly lower in obese patients (12). Effects on other CYP enzymes have also been observed, but data are sparse. Available data regarding the impact of obesity on non-CYP enzymes are also limited.

Obesity could also influence metabolism through effects on hepatic uptake and efflux transporters (see below).

2.3.2. Biliary and renal excretion

BMI class III obesity is associated with a state of glomerular hyperfiltration, irrespective of the presence of hypertension, due to an increase of renal blood flow (10). The influence of obesity on renal transporters involved in reabsorption and tubular secretion and on the hepatic uptake and efflux transporters is presently not well known.

Obesity may also affect biliary and renal secretion though effects on renal and hepatic uptake and efflux transporters. Based on presently available data, it has been suggested that uptake transporters are downregulated while efflux transporters may be upregulated (13). More investigations are needed in these areas.

2.4. Effect of bariatric surgery

Bariatric surgery, with gastric bypass as the most commonly used procedure, is used to manage obesity by altering the anatomy of the gastrointestinal tract. Significant changes in the absorption and metabolism of drugs have been observed after bariatric surgery (14, 15). The properties of the drug, the type of surgical procedure and the time after surgery may impact on whether an increase or decrease in exposure will manifest itself. Where relevant, the potential alterations of absorption linked to gastric intervention should be investigated.

2.5. Pharmacokinetic/pharmacodynamic (PK/PD) correlation

Besides the PK differences between normal weight and obese patients reported above, PD changes may also occur in obese patients. A decreased sensitivity for effects on certain receptors, especially acetylcholine, and increased psychomotor response to benzodiazepines has been reported (16). The cytokine tumour necrosis factor alpha (TNFα) is reported to be produced in excessive amounts, which further perpetuates insulin resistance (17). In addition adipose tissue has greater intrinsic insulin cleaving activity. However, currently available data regarding the impact of obesity on PK/PD is limited.

2.6. Conclusions on effects of obesity on PK, PD and PK/PD

The knowledge on the effects of obesity on PK and PD processes is limited, but emerging. The applicant is recommended to investigate the scientific literature for information on effects of obesity on PK processes and on potential differences in PK/PD in obese subjects, to enable consideration of such data when deciding on the need for investigations in obese patients.

3. When to investigate effects of obesity

The need for adequate PK characterisation in obese subjects should be considered in drug development to ensure their effective and safe use in this subgroup. Since the PK/PD relationship may be different in obese subjects comparatively to normal weight subjects, it is encouraged that through the whole development program the population in the trials should be representative for the population to be treated including in terms of aspects such as obesity.

Some examples of where evaluation of PK in obese patients, and thus inclusion of a sufficient number of obese patients of different BMI classes in the clinical studies, is particularly recommended are:

1. obese patients are a reasonably large part of the target patient population;
2. there are reasons to believe based on the scientific literature that obesity may lead to a marked effect on drug elimination and/or distribution or on the PK/PD relationship;
3. body weight has a large effect on PK based on population pharmacokinetic (Pop-PK) analysis;
4. body weight based dosing is applied;
5. the drug has a relatively narrow therapeutic range.

If obese patients are a reasonably large proportion of the patient population and there is reason to expect an effect on PK, the need for early investigations of the effect of obesity on PK should be considered to aid dose-finding in this population.

If obese subjects are a significant proportion of the population and dosing is body weight based, the suitability of the dose recommendation in obese patients (preferably for different BMI classes of obesity) needs to be addressed and whether the descriptor used for dosing is optimal in all patients regardless of obesity. If there is a risk of increased exposure in the obese, a cap on the maximal dose could be applied to “normalise” drug exposure, if it can be assumed that the target concentration range is similar in obese and non-obese individuals.

To provide appropriate dosing recommendations for studies in late phase clinical development, additional dedicated PK studies in (morbidly) obese subjects may be needed if insufficient PK data are available from the earliest clinical studies.

If the drug has a narrow therapeutic window and assuming that the target concentration range is similar in obese and non-obese individuals, pharmacokinetics should be investigated in obese patients for different BMI classes of obesity to guide on the dosing strategy i.e. use of loading dose, dosing using total body weight / lean body weight, dose capping, etc.

4. Investigation of the effect of obesity on PK

4.1. Population pharmacokinetic (PopPK) analysis

In applications for new marketing authorisations (MA) and/or new indications (including paediatrics) for an existing MA, the effect of intrinsic factors, including body weight, on the PK of the substance is usually investigated by PopPK analysis. This uses non-linear mixed effects models, on rich and sparse plasma drug concentration data from clinical studies. A pre-requisite for a successful analysis is inclusion of a sufficient number of patients having the required targeted characteristics

PopPK can therefore be an appropriate methodology to explore the effects of obesity, when a sufficient number of obese subjects have been included in the clinical studies. However, focus or emphasis on obese patients is rarely made. Sufficient data should, if possible, be collected in all categories of obesity: pre-obese and BMI I, II, and III classes.

Testing body weight as a covariate in PopPK development is a common, general approach. If an effect of body weight is found, the analysis should attempt to separate the effect of obesity from the effect of body weight/size. Many approaches could potentially be used in order to obtain an understanding on the influence of obesity on PK. Covariates such as Total Body Weight (TBW), BMI, BSA, LBM or Ideal Body Weight (IBW) could all be tested as covariates in model development. The selected descriptors tested as covariates in the PopPK model should be clearly justified. The most relevant covariates should be included in models for further simulation of dosing scenario and posology adaptation if needed. The final choice of covariate is based on the criteria to define significance, the reduced residual variability and the clinical impact of the improved precision as well as the practicality of the covariate during clinical use. The body size metrics should be tested as both continuous and categorical variables (obesity estimators - see appendix), although it is important to consider that all body size covariates are highly correlated and a testing procedure must take this into account. If the parameters are likely to change within individuals during the studies, repeated measurements over time may be necessary and the model should account for changes over time. Note that fluid retention, comorbidities and bariatric surgery can be confounding factors.

Presentation of the analysis should follow the recommendations outlined in the relevant CHMP guidance (4).

4.2. Non-compartmental analysis (NCA)

Another possible but less common approach is to conduct a formal PK study with full sampling in parallel groups of healthy volunteers/patients classified as ‘normal weight’ and as ‘obese’ (matched with respect to other factors expected to influence the PK). This type of study could be performed early in drug development to support dosing in obese subjects in phase III clinical trials.

Optimally, such a study should be sufficiently powered to detect and quantify relevant PK differences between obesity classes. A PK study in obese subjects may have a “full-range design” or be a reduced or staged study. When using a NCA approach, at least the following parameters should be estimated and compared: AUC_t, AUC_{inf}, C_{max}, CL or CL/F, Vd or Vd/F, and $T_{1/2}$. Statistical analysis of the parameters versus size and obesity descriptors could be considered and correlations visualized.

4.3. Physiologically based pharmacokinetic (PBPK) modelling

PBPK models in obese populations are being developed in PBPK platforms. However, more scientific information on the physio-pathological changes needs to be gained before this approach can be qualified for use to reliably simulate exposure in obese subjects. The qualification requirements depend on the regulatory impact of the simulation but will require clinical data sets, demonstrating effects of obesity (18).

5. Presentation and discussion of data

The aim is to develop treatment recommendations to ensure that obese patients will obtain a treatment that is considered to be as effective and safe as for the general target population. This should be based on information available on exposure effect relationships gained in the clinical studies or conventional documentation of exposure vs efficacy and safety in the reference group and obese population. Target criteria (the concentration for which satisfactory efficacy and safety has been shown) should specify what change in exposure would justify a posology adjustment based on the main concern (adverse events or lack of efficacy) for the specific medicinal product.

As background for the decision on adequate treatment recommendations, simulations of the predicted exposure during treatment should be provided and should include a graphical description of concentration over time and the predicted variability in the population. The choice of dosing strategy i.e. use of loading dose, TBW, lean body weight (LBW), IBW, dose capping, etc. should be carefully considered. If needed, different descriptors may be needed to optimise the loading and maintenance dose. The dose optimisation should include discussions of the risk of under- or over-dosing in each BMI grade of obese patients, as well as practical applicability and risk of dosing errors. Graphical and numerical presentations may aid this discussion. If dose titration is applied, the suitability of the titration for obese patients should be supported.

It is recommended that the numbers of subjects studied in the clinical development programme categorised according to their BMI are presented in tabular format as follows:

BMI (WHO classification)	Pre-obesity (25.0-29.9)	Obesity class I (30.0-34.9)	Obesity class II (35.0-39.9)	Obesity class III (Above 40)
Clinical Trial				

Identification of the sub-population for which the posology adjustments are to be recommended should be clearly described under section 4.2 (Posology) of the Summary of Product Characteristics (SmPC). Other types of treatment recommendations should be similarly supported and addressed in relevant SmPC sections. The recommendations should be as practically applicable as possible.

A description of the PK data in obese patients should be presented in section 5.2 (pharmacokinetic properties) of the SmPC together with existing information on the effects of covariates on the PK of the drug.

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7. Appendix: obesity estimators

Many methods are used for the measurement of body fat composition and the gradation of obesity:

The most commonly used obesity estimators are:

A. Body Mass Index (BMI):

BMI (kg/m^2) = Body Weight (kg)/Height $(m)^2$. This metric is still the most widely used for overweight and obesity classification in adults due to its practicality. The WHO recommendation is presented in Table 1.

Table 1 - WHO underweight, overweight and obesity classification for adults

Weight Status	Underweight	Normal range	Overweight	Pre-obese	Obese, class I	Obese, class II	Obese, class III
Kg/m^2	< 18.50	18.50-24.99	≥25.00	25.00-29.99	30.00-34.99	35.00-39.99	≥40.00

However, in children the situation is more complex as the BMI changes as they mature. BMI cut-offs based on pooled international data that link the accepted adult cut-off points to cut-off points related to age for children should be used to define overweight and obesity in the paediatric population. WHO currently suggest a set of thresholds based on single standard deviation (SD) spacing above or below the standard median for children aged 5 – 19 years:

Table 2 - WHO SD thresholds for children aged 5 – 19 years

Thinness	Overweight	Obese
<-2SD	Between +1SD and <+2SD	>+2SD

Obesity is defined for children aged less than 5 years as having weight-for-height greater than 3 SD above the WHO Child Growth Standards median.

B. Body Surface Area (BSA):

The body surface area (BSA) is the measured or calculated surface area of a human body. Direct measurement of BSA could not be easily performed. Similarly to BMI, BSA is derived from the assumption that BSA depends upon weight and height and also does not take the subject's gender into account.

Various formulas are proposed for BSA estimation. A simplified formula to estimate BSA is used in oncology:

BSA (m^2) = $[TBW\ (kg) \times Height\ (cm)\ /3600]^{½}$.

The classification of overweight and obesity based on BSA has the same limitations as BMI and BSA is more difficult to estimate, increasing the risk of dosing errors. The utility of BSA for obesity classification needs to be further supported.

C. Fat mass calculated from Total Body Weight (TBW) and Lean Body Weight (LBW):

The amount of body fat is defined as the difference between the TBW and the Fat-Free Mass (FFM). There are many different methods to estimate the fraction of body fat to TBW, which are described in the literature, such as hydrodensitometry, skin fold-thickness, bioelectrical impedance analysis (BIA) and dual-energy X-ray absorptiometry. Presently, mainly indirect indexes, based on weight and height are used, as these are considered easily accessible and measurable parameters. Failure to distinguish between the lean and adipose tissues are among the major drawbacks of using these metrics.

Estimation of the body fat mass is also a useful approach to describe obesity. By subtracting LBW (extracellular fluid, muscle, bone and vital organs) from TBW, the adipose tissue mass can then be estimated as well as the ratio adipose tissue to TBW.