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Reflection paper on investigation of pharmacokinetics in the obese population

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1. Introduction

Obesity affects a large sub-set of the general population. It affects all ages and will continue to increase based on observed trends. The alteration of body composition and physiology and a chronic state of inflammation (1) linked to obesity can potentially lead to significant changes in the disposition of a given medicinal product in obese subjects as compared to non-obese subjects. Thus, the need for adequate pharmacokinetic (PK) characterisation in obese subjects should be considered in medicinal product development to ensure effective and safe use in this subgroup and to inform on dose adjustments that might be required. Note, the term 'non-obese' as applied here 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 classification in adults and is independent of gender. According to the WHO, for adults, BMI between 25 and 29.9 kg/m2 represents overweight, while obesity is defined as BMI ≥ 30 kg/m^2. The WHO further defines different classes of obesity as class I with BMI 30-34.9 kg/m^2, class II with BMI 35 -39.9 kg/m^2 and class III with BMI ≥ 40 kg/m^2.

However, in children the situation is more complex as BMI changes as they mature. WHO currently suggest a set of thresholds based on standard deviation (SD) spacing above or below the standard median for children aged 5 – 19 years (z-scores) with overweight defined as between +1SD and <+2SD from the standard median and obese defined as >+2SD from the standard median.

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.

In general, PK investigations in obese subjects are limited to the impact of body weight, BMI, and Body Surface Area (BSA) that are routinely considered in medicinal product development. This is considered a shortcoming that is potentially compounded by obese patients often being poorly represented in clinical studies. Furthermore, effects may only be possible to estimate in a limited obesity range. Yet in studies investigating therapies for populations with a particularly high frequency of overweight and obese patients e.g. weight loss, type-2 diabetes, cardiovascular disease, and several cancers (colon, endometrial and breast) (2, 3), obese subjects are more commonly included

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 (4). However, in obesity the ratio of fat mass to total body weight (TBW) 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 (5, 6, 7).

The specific aims of this reflection paper are to:

- describe how the effects of obesity can be investigated during clinical medicinal product development.
- provide recommendations on when investigations of the effect of obesity on the PK of a medicinal product should be particularly considered.
- provide information on specific important considerations for these investigations.

- discuss how to reflect PK (and/or PK/PD) findings in weight/weight-based dosing recommendations.

2. Scientific background: effects of obesity on PK

2.1. Absorption

Reduced rate of absorption linked to locally reduced blood flow (8) is reported for the subcutaneous and transdermal routes in obese subjects. For therapeutic protein medicinal products like peptides and antibodies that are administered subcutaneously and are absorbed predominantly through the lymph, lymph flow can be an important determinant.

Increases in perfusion and permeability (9, 10) of the gut and accelerated gastric emptying with subsequent enhancement of medicinal product bioavailability have been reported for the oral route (11) in obese subjects.

The impact of obesity on the PK of oral medicines may also be related to other aspects of transit conditions along the gastro-intestinal tract, including mechanistic conditions such as timing, kinetics, and intensity of physiological events of transport, fortitude of the mechanical agitation and total duration in the gastro-intestinal transit.

2.2. Distribution

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

Obese subjects have a larger absolute lean body weight (LBW) as well as fat mass. While the lean mass accounts for 20-40% of the excess weight, fat mass is significantly enhanced in obese subjects and the lean mass per kg body weight is reduced (12, 13, 14).

The physicochemical properties of a medicinal product (lipophilicity, polarity, molecular size, and degree of ionization) influence its distribution in the body. Despite higher volume of distribution (Vd) in obese subjects being reported for some lipophilic medicinal products such as most steroids, benzodiazepines, antiepileptics and tricyclic anti-depressants, which can lead to a prolonged half-life, this is not a general rule. Indeed, for lipophilic medicinal products, the values for Vd normalised for body weight may be increased, unchanged, or reduced (15, 16), suggesting that factors other than lipid solubility influence tissue distribution. Therefore, changes in Vd cannot be predicted on the basis of lipophilicity alone.

In general, polar molecules (such as therapeutic proteins) are expected to have no marked differences in distribution between obese and non-obese subjects; indeed, for hydrophilic medicinal products unchanged or decreased ratios of Vd normalized with body weight were observed, but the magnitude of the effect of obesity was smaller than for lipophilic medicinal products (15).

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 (4). This can alter the distribution to and from a target in fatty tissue (17), 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 medicinal products particularly with concentration-dependent protein binding exhibiting high affinity to AAG. In addition, hypoalbuminemia associated with obesity may influence protein binding (18, 19).

2.3. Elimination

There are many physio-pathological changes connected with obesity that may impact the elimination (metabolism and excretion) of medicinal products in obese subjects:

- increased cardiac output and hepatic blood flow.
- fatty infiltrates occurring in the liver.
- low grade inflammation affecting liver function.
- glomerular hyperfiltration.

The consequences of these changes on the metabolism and excretion of medicinal products are reviewed below.

2.3.1. Metabolism

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

Fatty infiltrations are present in the liver for 90% of obese subjects, with the extent of the infiltrations being proportional to the degree of obesity. Chronic liver disease is a potential source of significant interindividual variation in medicinal product metabolism (20). This may be mediated by the effects of inflammation, which might 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 (21, 22).

The effects of obesity may vary between the major enzymes involved in the elimination of a particular medicinal product. In some cases, in particular for CYP3A4 metabolized medicinal products, bodyweight normalized clearance can be lower in obese patients (23). In contrast to CYP3A4, clearance of medicinal products primarily metabolized by CYP2E1 has been reported to be higher in obese subjects [24, 25, 26, 27]. Effects on other CYP enzymes have also been observed (such as an increased activity of CYP1A2, CYP2C9, CYP2C19 and CYP2D6), but data are sparse (27). Available data regarding the impact of obesity on non-CYP enzymes are also limited.

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 in renal blood flow (28, 29, 30). The influence of obesity on renal transporters involved in reabsorption and tubular secretion is presently not well known.

Obesity may also affect biliary and renal secretion through 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 (31). More investigations are needed in these areas.

2.4. Effect of bariatric surgery

In general, GI surgery has an impact on the oral bioavailability of medicinal products (32). Bariatric surgery, with gastric bypass or gastric sleeve as the most commonly used procedures, is used to manage obesity by altering the anatomy of the GI tract. Significant changes in the absorption and metabolism of medicinal products have been observed after bariatric surgery (33, 34), and potential alterations of volume of distribution and elimination may also be expected (35, 36). The properties of the medicinal product, the type of surgical procedure and the time after surgery may impact on whether an increase or decrease in exposure will manifest itself. Several alterations in relation to the absorption and distribution of medications could be responsible, such as an effect on gastric emptying time, an increase of gastric pH, ionisation of the medicinal product, or decrease of the volume of distribution of lipophilic medicinal products (37, 38). Where relevant, the potential alterations of absorption linked to gastric intervention should be investigated. It may be impractical or difficult to conduct trials for these situations and alternative methods, such as modelling approaches (39), may be considered.

2.5. Pharmacology considerations

Pharmacodynamic (PD) changes may also occur in obese patients (40). A decreased sensitivity for effects on certain receptors, especially acetylcholine, and increased psychomotor response to benzodiazepines has been reported (15). The cytokine tumour necrosis factor alpha (TNFα) is reported to be produced in excessive amounts, which further perpetuates insulin resistance (41). In addition, adipose tissue has greater intrinsic insulin cleaving activity. Platelet hyper-reactivity is also observed, which can impair the response to anti-platelet medicinal products in obese patients (42, 43). More evidence shows that PD changes, i.e. a difference in medicinal product efficacy or toxicity even when corrected for PK differences, also play a key role e.g. adipocytes secrete adipokines such as leptin, which reduces macrophage and T-cell differentiation and activity. However, overall currently available data regarding the impact of obesity on PK/PD is limited.

3. When to investigate effects of obesity

The need for adequate PK characterisation in obese subjects should be considered for all medicinal products that are known to be impacted by body weight 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 the population in the trials conducted after the first-in-human and early clinical studies in healthy volunteers or patients (Phase 1) should take into account the population to be treated in terms of obesity.

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 where one or more of the following criteria apply:

1. when obese patients constitute a larger proportion of the target patient population as compared to the general population.
2. in case of subcutaneous/dermal drug administration.

3. the medicinal product properties and scientific literature indicate that obesity may lead to a marked effect on elimination and/or distribution or on the PK/PD relationship.
4. body weight has a large effect on PK, based on population pharmacokinetic (PopPK) analysis.
5. body weight-based dosing is applied.
6. the medicinal product has a narrow therapeutic range.

If obese patients are a significant proportion of the target 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.

If obese subjects represent a significant proportion of the target 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. If there is a risk of increased exposure in obese subjects, a cap on the maximal dose could be applied to "normalise" medicinal product 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 (very severely) obese subjects (BMI ≥ 40 kg/m^2) may be needed. This should be considered on a case-by-case basis and early dialogue with the Agency is recommended.

If the medicinal product has a narrow therapeutic range 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 TBW/LBW, dose capping, etc.

4. Investigation of the effect of obesity

4.1. Population pharmacokinetic (PopPK) analysis

The effect of intrinsic factors, including body weight, on the PK of a medicinal product is usually investigated by PopPK analysis. This uses non-linear mixed effects models, on rich and sparse medicinal product concentration data from clinical studies. A prerequisite for a successful PopPK analysis is inclusion of a sufficient number of patients having the required targeted characteristics.

PopPK (7) 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 and, if possible, in all categories of overweight and obese. This is to enable the effect of obesity to be estimated with sufficient precision to justify a posology adjustment.

Testing body weight as a covariate in PopPK development is a general approach. If an effect of body weight is found, the analysis should attempt to further define an effect of obesity. Covariates such as TBW, BMI, BSA, LBM or Ideal Body Weight (IBW) could all be tested as covariates in model development. The selected covariates in the PopPK model should be clearly justified. The most relevant covariates should be included in models for further simulation of dosing scenarios and posology adaptation if needed. The final choice of covariate is based on the criteria to define clinical significance and statistical significance with respect to null covariate effect, the reduced between-subject and residual variability, and the clinical impact of the reduced uncertainty of predicted exposure and/or PD due to inclusion of a covariate, as well as the practicality of the covariate during clinical use. The body

weight metrics should be tested as continuous variables, when available, although it is important to consider that all body weight covariates are highly correlated, and a testing procedure must take this into account. If no continuous variables are available, the clinical utility of categorised obesity metrics should be investigated in a simulation of PopPK and/or PK/PD models. 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 (7).

4.2. Dedicated PK study

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'. This type of study could be performed early in medicinal product development to support dosing in obese subjects in phase III clinical trials.

Ideally, such a study should be adequately 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 non-compartmental analysis (NCA) approach, at least the following parameters should be estimated and compared: $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ (or $AUC_{(0-72h)}$ if appropriate), C_{max}, CL or CL/F, Vd or Vd/F, and $t_{1/2}$. Statistical analysis of the parameters versus weight and obesity descriptors could be considered.

4.3. Use of modelling approaches

Physiologically based pharmacokinetic (PBPK) models in obese populations are being developed in PBPK platforms. If PBPK modelling is used to simulate exposure in obese subjects to support a regulatory decision, the PBPK platform needs to be qualified for this intended use (44).

PK/PD and quantitative systems pharmacology models can be developed to describe the effect of physiological changes in obesity on PD and biomarkers of medicinal product safety and efficacy. These models may aid in extrapolating the known efficacy and safety in the non-obese population to the obese population. Paediatric medicinal product development is an example of a field where such approaches are frequently used (45).

The use of modelling approaches is encouraged, particularly for situations where clinical studies in the obese population are challenging. The evaluation and qualification requirements depend on the regulatory impact of the modelling and simulation approach(es).

5. Presentation and discussion of data

The aim of studying PK in obese subjects is to develop treatment recommendations that can be considered to be as effective and safe as for the general target population while considering specific needs. This should be based on information available on exposure effect relationships gained in the clinical studies of exposure versus 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. The impact of changes in the exposure-response relationship on dose selection should also be discussed.

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, LBW, IBW, dose capping, etc., should be carefully considered. 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.

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). Consideration may also be given on the need for dose adjustment on a dynamic basis e.g., it may entail checking the patient's weight/BMI at regular intervals.

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 medicinal product.

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