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Analysis of the variability of the pharmacokinetics of multiple drugs in young adult and elderly subjects and its implications for acceptable daily exposures and cleaning validation limits

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ABSTRACT

The elderly constitute a significant, potentially sensitive, subpopulation within the general population, which must be taken into account when performing risk assessments including determining an acceptable daily exposure (ADE) for the purpose of a cleaning validation. Known differences in the pharmacokinetics of drugs between young adults (who are typically the subjects recruited into clinical trials) and the elderly are potential contributors affecting the interindividual uncertainty factor (UF_H) component of the ADE calculation. The UF_H values were calculated for 206 drugs for young adult and elderly groups separately and combined (with the elderly assumed to be a sensitive subpopulation) from published studies where the pharmacokinetics of the young adult and elderly groups were directly compared. Based on the analysis presented here, it is recommended to use a default UF_H value of 10 for worker populations (which are assumed to be approximately equivalent to the young adult groups) where no supporting pharmacokinetic data exist, while it is recommended to use a default UF_H value of 15 for the general population, to take the elderly into consideration when calculating ADE values. The underlying reasons for the large differences between the exposures in the young adult and elderly subjects for the 10 compounds which show the greatest separation are different in almost every case, involving the OCT2 transporter, glucuronidation, hydrolysis, CYP1A2, CYP2A6, CYP2C19, CYP2D6, CYP3A4 or CYP3A5. Therefore, there is no consistent underlying mechanism which appears responsible for the largest differences in pharmacokinetic parameters between young adult and elderly subjects.

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1. Introduction

When more than one drug is manufactured at a shared site, it is necessary to clean the equipment that is used for subsequent drugs, between each manufacturing process, down to a level where contamination of the second drug by the first would not result in the

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exposure of a patient treated with the second drug to biologically relevant doses of the first drug. An acceptable daily exposure (ADE), in support of calculating maximum carry-over (MACO) values for cleaning, is a necessary calculation for all drugs manufactured in non-dedicated (shared) facilities. Recently, the European Medicines Agency (2014) defined for the same purpose the similar term "permitted daily exposure" (PDE) derived from the following equation:

$$PDE = \frac{NOAEL \times Weight \quad Adjustment}{F1 \times F2 \times F3 \times F4 \times F5}$$

where: *NOAEL* is the no observed adverse effect level and F1 to F5 are addressing various different forms of uncertainty.

ADE and PDE can be considered as synonymous terms, however, while the EMA guidance does suggest that certain pharmacokinetic factors might also be included in the calculation, they are not explicitly included in the PDE equation. Therefore, nomenclature relating to the ADE calculation, which does specifically include several pharmacokinetic factors, will be used in this article. An ADE can be derived from the following formula (Naumann and Weideman 1995; Sargent et al., 2013; Reichard et al., 2016):

$$ADE = \frac{NOAEL(mg/kg/day) \times BW(kg)}{UF_C \times MF \times S \times \alpha}$$

where: *NOAEL* is the no observed adverse effect level, *BW* is body weight, UF_C is the composite uncertainty factor, *MF* is the modifying factor, *S* is the accumulation factor, and α is the bioavailability factor.

The composite uncertainty factor can have several contributing parts, including that for extrapolating from animal species to humans, but one of the most important is an uncertainty factor to account for inter-individual variability (UF_H) which has traditionally been set at a default value of 10 (Krasovskii 1976; Dourson and Stara 1983; Calabrese 1985; Hattis et al., 1987; International Society for Pharmaceutical Engineering, 2010; International Conference on Harmonisation, 2011). However, even early on, it was recognized that this default factor of 10 might not always be sufficient to protect against the inter-individual variability in the elderly and other sensitive human subpopulations (Krasovskii 1976; Hattis et al., 1987). The UF_H from the ADE equation is essentially the same as the F2 from the PDE equation which is defined as "a factor of 10 to account for variability between individuals" (European Medicines Agency 2014). Despite the wide acceptance of the value of 10 as a default for the inter-individual variability factor for Occupational Exposure Level (OEL) calculations in pharmaceutical worker populations (Dankovic et al., 2015) and more recently ADE calculations in the general population (Sargent et al., 2013; Sussman et al., 2016), the European Chemicals Agency (2012) has recently recommended the use of a default UF_H value of 5 for workers, and a default UF_H value of 10 for the general population (which would include the elderly). The scientific basis for these latter, apparently inconsistent, recommendations is not clear.

The component parts that constitute inter-individual variability in the generation of an adverse event are delivery of the compound to the site of its toxicity (pharmacokinetics) and the activity of that compound after it reaches the site (pharmacodynamics). Upon more detailed consideration of its component parts, the UF_H factor has been further divided to account for the inter-individual variability in pharmacokinetics and pharmacodynamics (Renwick 1991, 1993). The International Programme on Chemical Safety (2005) has recommended that it be divided into two equal default factors of 3.16 ($10^{0.5}$) for pharmacokinetics ($UF_{H,PK}$) and pharmacodynamics ($UF_{H,PD}$), respectively.

However, where clinical data exist for pharmacokinetics and/or pharmacodynamics, calculated values should be used in place of the default factors. Naumann et al. (1997) proposed a methodology to calculate numerical values for the $UF_{H,PK}$ and $UF_{H,PD}$ from experimentally-derived pharmacokinetic and pharmacodynamic data, when available, an approach later endorsed by the International Programme on Chemical Safety (2005). This method involves dividing the upper 95% confidence limit for a set of data by the mean, and the resulting value can be substituted for the default value of 3.16 in the calculation of either an occupational exposure limit calculated to protect workers (OEL) or ADE. Such calculations are appropriate for a pharmacokinetic parameter which demonstrates a unimodal normal distribution, but also for a parameter which displays a bimodal distribution because of the presence in the population of a sensitive subpopulation. In the latter case, the upper 95% confidence limit of the sensitive subpopulation is divided by the mean of the non-sensitive population (see Methods section).

The U.S. Census Bureau (2012) reported that one in seven U.S. residents was aged 65 or older in 2012 and that the number would increase to one in five by 2060. A recent survey by Qato et al. (2008) of U.S. residents aged 65 or older indicated that only 6% or less took no medications on a regular basis, and 29% used at least five prescription medications concurrently. Clearly, the elderly are a significant portion of the population that should be considered as a potentially sensitive subpopulation. A few examples where the pharmacokinetic portion of the $UF_{H,PK}$ value has been calculated, assuming the elderly subjects to be a sensitive subpopulation, have been reported in the literature for the following compounds: benazeprilat, captopril, enalaprilat, fluvastatin, lisinopril, lovastatin, perindoprilat, simvastatin (Naumann et al., 2001), famotidine (Silverman et al., 1999), desipramine (Riyad et al., 2002), bumetanide, furosemide, metoprolol, atenolol, naproxen, ibuprofen (Skowronski and Abdel-Rahman 2001), mivacurium, atracurium, rocuronium, vecuronium, doxacurium, pancuronium, and pipecuronium (Suh and Abdel-Rahman 2002). Of these, only desipramine (males but not females), bumetanide, captopril, enalaprilat, and perindoprilat had calculated $UF_{H,PK}$ values greater than the default of 3.16, with the largest value being 7.22 for the AUC of perindoprilat. Therefore, assuming the default value of 3.16 for $UF_{H,PD}$, the calculated UF_H would be 22.8 for perindoprilat (i.e., $3.16 \times 7.22 = 22.8$). The corresponding values for desipramine (renal clearance), bumetanide (AUC), captopril (C_{max}) and enalaprilat (AUC) would be 13.2, 12.6, 12.2 and 19.5, respectively.

The publically available data set of 23 compounds is too small of a sample for meaningful conclusions and two of the compounds that exceed the default (enalaprilat and perindoprilat) are active metabolites of prodrugs, giving an extra metabolic step to add more variability. However, there are indications (3 out of 21 parent drugs or 14%) that there may be a significant number of drugs that will have a calculated UF_H value that is greater than the default of 10 in the general population. Over the years, there have been a large number of literature reports on the pharmacokinetics of numerous drugs in elderly versus young adult subjects, primarily to address the potential need for dose adjustments. Since there are few publications where both pharmacokinetics and pharmacodynamics have both been determined at the same time in young adult and elderly populations, only pharmacokinetic data will be considered here. Therefore, the objectives of this article were to analyze in a systematic way the pharmacokinetic parameters of 206 drugs (204 small molecules and 2 large molecules) from published studies (Table 1) where young adult and elderly subjects were directly compared, and to see whether the proposed default values for the pharmaceutical workers (who may be roughly equivalent to young adults) and the general population (with its elderly sensitive subpopulation) are adequate.