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Review

Current strategies to streamline pharmacotherapy for older adults

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ABSTRACT

Although the term “personalized medicine” has been associated in many cases with pharmacogenomics, its definition embraces the use of specific biomarkers and covariates to help in the selection of medical treatments and procedures which are best for each patient. While several efforts have been performed for the tailored selection of therapies and dosing regimens in the general population, developing personalized medicine initiatives for elderly patients remains understudied. The personalized drug therapy for older patients requires the consideration of anatomical, physiological and functional alterations in a multimorbid setting requiring multiple medications. The present review focuses on currently employed qualitative and quantitative precision medicine approaches for elderly patients and discusses some of the associated challenges and limitations. Furthermore, the use of and confidence in physiologically-based approaches for optimal dose selection in this understudied yet clinically important patient population will be highlighted and discussed.

1. Introduction

Evidence of efficacy and safety of new drug products is based primarily on results of one or more randomized, placebo-controlled clinical trials, which generally derive “one-size-fits all” dosing regimens for new drug products (Lesko and Schmidt, 2012). However, patients respond differently to medications due to many reasons, which can either be intrinsic (e.g., age, weight, metabolic capacity, genetic constitution etc.) or extrinsic (e.g., comedications, comorbidities, etc.). Flat dosing regimens can consequently have serious consequences for efficacy and safety. In contrast, the purpose of “personalizing” drug therapy is to optimize the benefit and minimize the harm of medication interventions on a patient-by-patient basis (Lesko and Schmidt, 2012). Although personalized treatment regimen should be the first choice, initial drug labels often lack useful and explicit label information for special population groups (Jadhav et al., 2015). Individualization is then left to the physician, using the “art of medicine” based on experience, clinical judgment, and unique and frequently intangible factors relating to a given patient. The situation becomes even more complex in the case of elderly patients due to the lack of actual data from dedicated clinical trials in this heterogeneous population. Highly variable organ functions, comorbidities, high drug-drug interaction (DDI) potential, and lack of compliance are additional factors contributing to suboptimal pharmacotherapy.

Provided that the typical western society is growing increasingly older, there is a need for well controlled treatment strategies to improve the efficiency and safety of drug therapies in older adults. In particular, the impact of changes in bodily functions in elderly patients compared to healthy subjects needs to be understood in order to provide optimal pharmacotherapy in this special patient population. For example, aging is associated with changes in cellular, tissue, and organ function as well as increased probability of suffering from multiple illnesses. This can lead to an un-recoverable loss of physiological capacity, such as a continuous decrease in the metabolic capacity of the liver over time (Patki et al., 2004).

The International Conference on Harmonization (ICH) Efficacy Guideline E7 defines the elderly patient as a person of the standard retirement age 65 years or older (ICH, 1993). In order to account for inter-individual variability in this large age group, the ICH purposes a further split of the elderly population into ‘young old’ (65 to 74 years),

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the 'old' (75 to 84 years), and the 'oldest old' (≥ 85 years). Within this framework, the classification of geriatric patients by age groups becomes important to account for differences related to physiological and functional changes observed in these patients with age (Swanlund, 2010).

However, a chronological age (years since birth) classification is often not applicable for the elderly patient because it may or may not appropriately reflect the patient's actual "biological age". Age-related changes are highly heterogeneous due to the dynamic interplay between multiple, complex and poorly understood genetic, environmental, and disease-related risk factors. As a consequence, flat dosing regimens that fail to take the biological age into account are unlikely to appropriately meet the medication needs of the individual elderly patient (de Onis and Habicht, 1996).

The primary objectives of this review are: *i*) to summarize current challenges for an age-appropriate design of clinical trials, *ii*) to provide a brief overview on consensus-based criteria for the pharmacotherapy for elderly, *iii*) to review currently employed quantitative precision medicine approaches for older patients and to discuss some of the associated challenges and limitations, and *iv*) to outline how innovative, physiologically-based approaches can be used for optimal dose selection in this understudied yet clinically important patient population involving the use of genome-based approaches and quantitative clinical pharmacology applications for single and multiple drug therapies.

2. Current status and need for clinical studies in elderly

To account for the increasing number of older adults and their special pharmacotherapeutic needs, the ICH E7 guideline recommends the inclusion of a meaningful number of geriatric patients (age 65 years of age and older) in phase 3 or phase 2/3, but ideally in exclusive dedicated geriatric trials in order to appropriately account for comorbidities and investigate the influence of polymedications in the elderly patient. In particular, the guideline arbitrarily recommends the inclusion of at least 100 geriatric patients to identify clinically relevant differences (ICH, 1993). This allows for an assessment of deviating dose response and varying degrees of effectiveness with increasing age. Based on this framework, the U.S. Food and Drug Administration (FDA) proposes to include data for elderly patients of all subgroups mentioned in ICH E7 for the marketing application of new drugs (FDA, 2012). These subgroups should be considerable in size and comparable in patient numbers for the respective disease (EMA, 2010).

However, even if the intent behind present regulations is the inclusion of different groups of elderly patients in clinical trials, these recommendations are frequently not fully implemented. For example, in the phase II and III type 2 diabetes mellitus trials, only 1% of the study population is older than 75 years of age (Beers et al., 2013). In addition, the outcome of a typical trial may not accurately reflect clinical reality because elderly subjects included in clinical trials are typically young, healthy older adults who have fewer and less severe comorbidities (Masoudi et al., 2003). A similar case is shown in Fig. 1 for simvastatin, where the clinical trial population (Martin et al., 2004) was compared to the actual target patient population (Schaufler and Telschow, 2016). It can be seen from this figure that the distributions of these two populations clearly differ.

Older adults that are generally underrepresented in clinical trial settings include patients with dementia, non-native speakers, functionally dependent (nursing home or homebound) and those who are unable to consent to participate in a research study (Golden et al., 2010). These patients are often geographically isolated from studies conducted at large medical centers. Similarly, patients with advanced co-morbid illnesses are also often excluded. It is not surprising that 61% of new cancers are diagnosed in the elderly, whereas only 25% of oncology trial participants can be assigned to this age group (Lewis et al., 2003). As a consequence, insufficient data is often available from geriatric clinical trials intended to develop geriatric-specific dosing information (Herrera et al., 2010). Therefore, 'start low, go slow' recommendations are common. These empirical dosing approaches may lead to an increase in mortality as evident from over-treating hypertension and diabetes mellitus in older adults (Cherubini et al., 2010).

3. Precision medicine approaches in the elderly

This need for more precise dosing recommendations for older adults has been addressed at various levels of complexity ranging from expert consensus-based to physiologically-based personalized medicine approaches. While quantitative methods are less established in older adults, we will attempt to outline their potential for the development of tailored elderly pharmacotherapy. First, we shall briefly summarize the routinely applied and trusted methods though.

3.1. Expert consensus-based personalized medicine approaches

Expert consensus-based personalized medicine approaches are intended to optimize medication use by guiding the avoidance of medications that place older adults at an increased risk of adverse events and for which safer alternatives exist.

3.1.1. Beers criteria

The Beers Criteria for inappropriate medications were developed by expert consensus in 1991 and have subsequently been updated in 1997, 2003, 2012, and 2015 (Beers, 1997; Beers et al., 1991; Fick et al., 2003; Fick and Semla, 2012; Radcliff et al., 2015). These criteria identify medications with risks that may be greater than their benefits for people 65 or older, and were developed to "guide" health care professionals prescribe for older adult patients. Although they have been used as a quality of care measure by many health care systems, these criteria were not intended to imply that these medications are absolutely "contraindicated". In addition, many newer medications are not included in the criteria and issues of inappropriate drug interactions or drug class duplications are not captured (Golden et al., 2005). Studies to date have struggled to demonstrate a clear correlation between compliance with Beers Criteria recommendations and improved clinical outcomes.

3.1.2. STOPP/START criteria

The Screening Tool of Older People's Prescriptions (STOPP) and the Screening Tool to Alert to Right Treatment (START) originated in 2008 (Gallagher and O'Mahony, 2008) and were updated in 2015 (O'Mahony et al., 2015). Like the Beers Criteria, STOPP Criteria were developed through expert review using Delphi consensus methodology and are intended to identify medications to be avoided in older adults. The START Criteria were developed through a similar methodology to identify medication prescribing omissions. A comparison between the STOPP and the 2003 Beers Criteria found that patients taking a medication on STOPP list were 85% more likely to have an adverse drug event than those without a STOPP list drug. No association was found with the 2003 Beers criteria (Hamilton et al., 2011).

One of the major concerns about using a "hit list" approach includes lack of allowance for exceptions (e.g., palliative care). On the other hand, drugs that are considered beneficial may still present a high risk for adverse drug events in medically complex older adults. Budnitz et al. investigated hospital admissions due to adverse drug events (ADEs) and pointed out that only a few drugs cause the majority of hospitalizations (Budnitz et al., 2011). Warfarin and insulins are the primary suspects for ADEs. However, the retrospective review of emergency room and hospital claims data may underestimate the true risk of adverse events in older adults as many medication side-effects (i.e. dry mouth, incontinence, anorexia, confusion) are not captured in electronic health records (Golden et al., 2008).

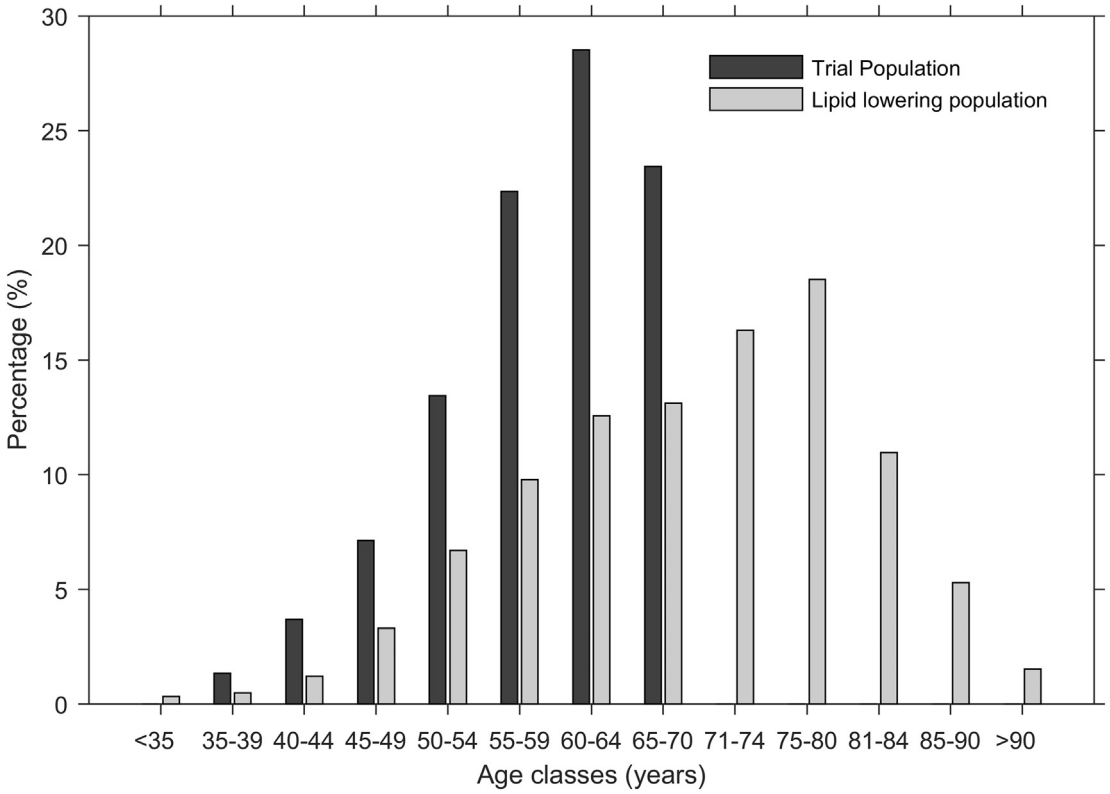

Fig. 1. Simvastatin clinical trials population adopted from Martin et al. (Martin et al., 2004) shown in *dark grey bars* compared to the prescription pattern for lipid-lowering medication for publicly insured patients in Germany stratified by age visualized in *light grey bars* (Schaufler and Telschow, 2016).

3.2. Genome-based personalization approaches for the elderly

During the past two decades, the quest for identifying the genetic basis for aging has sparked an entire field of research that focuses on cellular aging processes. The study of nutrient signaling pathways, reactive oxygen species (i.e. “free radicals”), telomere length, DNA repair mechanisms, and mitochondrial dysfunction have been of particular interest because they represent cellular mechanisms for senescence and apoptosis (Golden and Troen, 2010). Studies in centenarians (age ≥ 100 years) have gained prominence in evaluating the genetic basis for extreme longevity and the delay of frailty (Butler et al., 2004). Several genes, such as APOE and FOXO3A, have been associated with aging (Brooks-Wilson, 2013) during Genome Wide Association Studies (GWAS). GWAS studies determine statistical correlations between the genomic variability among individuals and the phenotypic variability among the same individuals (Miles and Wayne, 2008). The impact of the genomic variability of these “aging genes” on the pharmacokinetics (PK) and pharmacodynamics (PD) of medications in older adults remains unknown.

3.2.1. Genotype guided dosing in the elderly

Genotype guided dosing regimens are available for many drugs (FDA, 2015; Mallal et al., 2008; Oztaner et al., 2015). They are intended to enable safer and more effective drug treatment by identifying genetic sources of inter-individual variability which is needed to optimize dosing strategies by reducing toxicity and increasing efficacy of a given drug treatment. Regardless of the genotype, elderly patients may present higher drug blood levels than younger patients when the same dose is administered to both patient populations due to age-related reduction of intrinsic clearance capacity. In addition, the variance in Cytochrome P-450 (CYP) functionality with age may result in a multiplicative effect on metabolism (Winner, 2014). As an example, venlafaxine plasma concentrations are 18-fold higher in elderly CYP2D6 poor metabolizers than in non-elderly poor metabolizers (Waade et al., 2014; Winner, 2014). In spite of the limited number of elderly poor metabolizers included in this study, an important observation was that all of them had serum venlafaxine and *O*-desmethylvenlafaxine (pharmacologically active compound) above the upper recommended therapeutic limit (Waade et al., 2014).

Warfarin is another prominent example for genotype-guided (CYP2C9 and VKORC1) dosing regimen. Although age was not identified as the most significant covariate, a reduction of dose requirement of 0.2 mg per day per decade, independent of genotype and weight, was observed (Miao et al., 2007). Because the impact on the PK of the CYP variation may be more pronounced and clinically meaningful in older adults, still all possible covariates including age and genotype should be considered to develop a comprehensive dosing strategy regardless of its time-consuming and costly nature (Gage et al., 2008; Sconce et al., 2005).

3.2.2. The genome-based disease risk assessment

Certain diseases are associated with age or have an increased prevalence in the elderly. Based on genomic testing, estimates can conceptually be made for the incidence and/or prognosis of these diseases. However, the genetic basis for most diseases remain poorly understood. For example, the efforts invested to develop clinically useful genomic tests that can predict a higher risk for Alzheimer's disease in individual patients have not yet come to fruition and currently available results still remain elusive.

While pharmacogenomic considerations for drug usage might not vary with increasing age, the value for a timely diagnosis will become more important for the elderly population. Similarly, understanding a patient's genetic variation is needed in order to optimize dosing strategies to reduce toxicity and increase efficacy of a particular drug treatment.

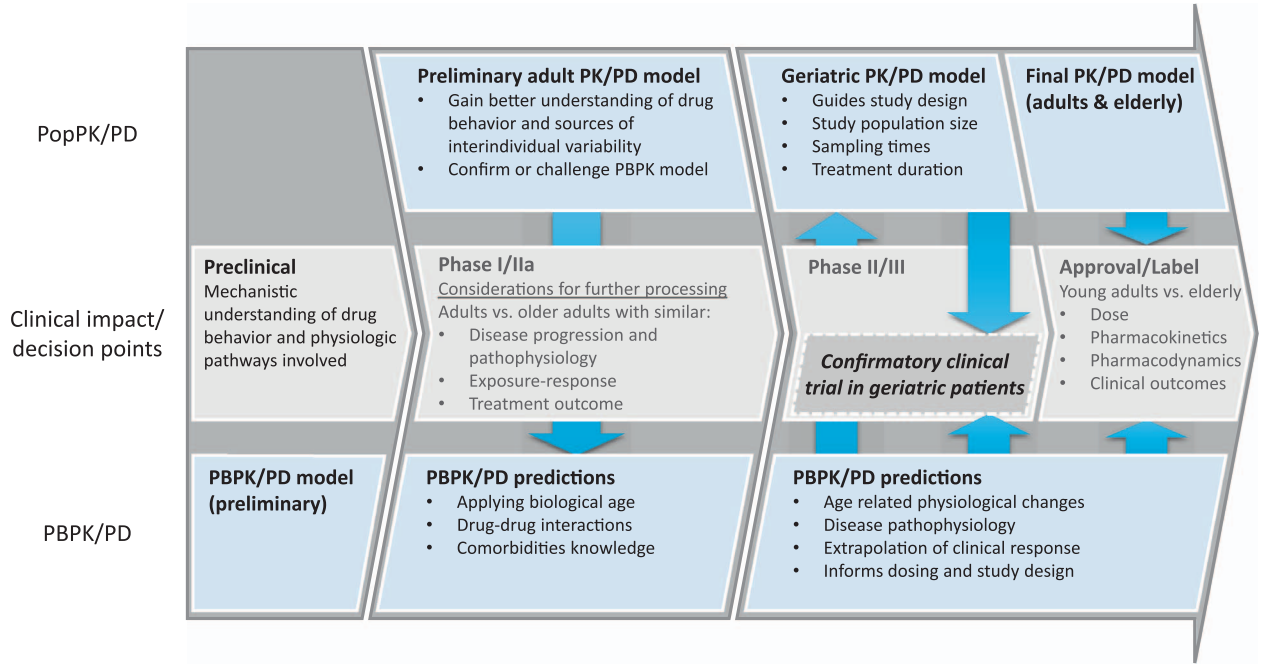

Fig. 2. Interplay of qualitative pharmacokinetic approaches inform and confirm geriatric dosing strategies during drug development. PBPK (*lower stream*) and PopPK (*upper stream*) model development run in parallel during early clinical development, the interplay can gain importance after certain decision points (*main development stream*) in order to inform and streamline subsequent trials (*dashed box*) or clinical decisions for older adults.

3.3. Biomarkers

The development of drug treatments in the elderly is limited by the lack of reliable biomarkers in this special patient population. Current efforts for developing effective medications for the prevention and treatment of Alzheimer's disease are hampered by the lack of established biomarkers, both for preclinical detection and for monitoring treatment response in the clinic (Bor, 2014).

Given that many body functions either change or loose physiologic capacity as subjects become older, it is currently unclear which of the identified biomarkers in healthy adults are equally applicable to the elderly patient. In addition, elderly patient may have different disease progression, lifestyle, comorbidities and poly-medication which may deem necessary the combination of different biomarkers or scores to obtain more specific measures of the drug response in this population. Ideally, the dynamic interplay between all above factors should be quantified to establish appropriate dosing regimens and support precision medicine approaches in the elderly.

Type II diabetes mellitus (T2DM) is a good example for the complexity of factors involved in the identification of appropriate biomarkers in the older adults. The general guidelines for controlling T2DM in elderly patients recommend higher target levels of glycosylated hemoglobin (HbA_{1C}) than in younger adults (Du et al., 2014). This recommendation is in part the result of the ACCORD trial, where even if a premature termination was required after a median duration of 3.5 years because of higher mortality in the group targeting lower HbA_{1C} levels, it provided the first evidences that hypoglycemia and other adverse effects are more frequent in older patients (Du et al., 2014; Kirkman et al., 2012). Hypoglycemia is related with serious morbid outcomes in the elderly population, such as falls, cognitive decline, autonomic dysfunction, depression, recurrent hypoglycemia, poor compliance, and possible cardiac ischemia or arrhythmia, which may contribute to poor function and poor prognosis (Bonaventura et al., 2015; Du et al., 2014). In addition, the regulatory feedback mechanisms involved in the maintenance of glucose homeostasis are defective in older people, which lead to an increased risk of hypoglycemia. Antidiabetic drugs with lower glycemic variability should, therefore, be part of the first line treatments of T2DM in older adults. In addition, aging is related with a progressive impairment in carbohydrate tolerance (possibly due to disorderly insulin release), reduced insulin production and reduced glucagon-like peptide 1 (GLP-1) secretion, increased adiposity, sarcopenia, and physical inactivity (Du et al., 2014; Geloneze et al., 2014; Kirkman et al., 2012; Meneilly et al., 1997). In the case of elderly patients, the relative contribution of postprandial glucose is higher than that of fasting glucose. Therefore, selecting antidiabetic therapies that are more efficacious in postprandial glucose control for older adults may also be considered for these patients (Du et al., 2014).

3.4. Quantitative personalized medicine approaches

Mathematical and statistical approaches that integrate information on the drugs' PK and PD as well as the disease at the population and the individual patient level have been increasingly used in drug development and regulatory decision making since the 1990s. Compared to the expert consensus-based approaches introduced earlier in this review, quantitative approaches typically use information on the dynamic interplay between drug(s), pharmacology, disease pathogenesis, and intrinsic as well as extrinsic patient factors to characterize and predict age-dependent changes in elderly patients and to personalize drug treatments in this population. The highly variable organ function(s) in the elderly population and the resulting variability in absorption, distribution, metabolism and elimination (ADME) as well as in the PD processes need to be considered to develop appropriate dose-exposure-response relationships. The establishment of these relationship is typically more problematic in elderly patients, which has a bearing on optimal dose selection for this population (Leong et al., 2012). This challenge may be met by the combined use of quantitative approaches (e.g., population pharmacokinetic (PopPK) or physiologically based PK (PBPK) models) and prospective clinical trials. This combined approach is intended to identify a trial design and treatment regimen with the highest probability of maximizing desired effects while minimizing undesired side effects and may thus help to reduce cost and burden to the elderly patient.

Fig. 2 shows an example of how a combination of quantitative

clinical pharmacology approaches and clinical trials can serve as a tool for establishing safe and effective dosing regimens for older adults. Both models complement each other and are adapted gradually. In a first stage, the preclinical information is used to facilitate the mechanistic understanding of the drug's PK/PD behavior and to develop a preliminary PBPK/PD model including the physiological pathways identified to play a major role. Model predictions can then be used to guide the design of the clinical studies in an iterative manner (learning and confirming cycles that are used to inform both modeling approaches) and used to assist dosing decision making. Once the PK/PD data from the clinical trials are available, popPK/PD analysis can then be used to validate the predictions and to further confirm the PBPK/PD model assumptions. This step will allow a better understanding of the drug's behavior in humans together with its associated interindividual variability, and can also be used as supportive evidence for drug labelling. The updated PBPK/PD model can then be used to bridge the PK/PD to the elderly population (geriatric PK/PD model) by informing the model on age related physiological changes, alterations in the pathophysiology and to extrapolate the clinical response to streamline the design of a confirmatory trial in the population of older adults. Again at this stage, the PK or PK/PD data arising from a confirmatory trial can be used to evaluate the effects of age on the geriatric PK/PD parameters when data from different age populations are available, also confirming the PBPK/PD modeling outcomes, and allowing a selection of the most appropriate dosing regimens in different categories of older adults.

It should be noted, however, that in isolation, information on PK is of limited clinical utility and needs to be linked to the corresponding PD response. While the impact of age on a drug's PK is typically easier to assess, respective changes in PD remain understudied. Therefore, a robust understanding about the mode of action coupled with reliable appropriate measures is essential for the age-related PD assessment. Drug-effects are most often based on a complex molecular cascade (Hammerlein et al., 1998). For example, the density of receptors can be reduce with increasing age as shown for α-adrenergic (Borst and Scarpace, 1990) or μ receptors (Morley et al., 1990). It also seems that there is increased sensitivity to various central nervous system drugs, including benzodiazepines, halothane, metoclopramide, and narcotic analgesics, as patients become older (Kane et al., 2013). While some of these effects can be studied directly in the elderly patient, our understanding of other PD effects relies on extrapolated animal data (Van Dam and De Deyn, 2006).

This approach has been extensively used in clinical drug development for children (FDA, 2014) and could also be used for extrapolation of adult dosing regimens to older adults.

3.4.1. Population pharmacokinetic/pharmacodynamic approaches

The majority of the currently employed population approaches are descriptive (non-mechanistic or empirical) in nature and use statistically robust criteria to characterize the data. These methods, however, can be optimized by the inclusion of physiology related processes to improve their predictive performance and further increase their applicability (Encinas et al., 2013; Vozmediano et al., 2014). As an example, PK scaling approaches are intended to extrapolate the dose-exposure relationship from a well characterized population to the special population of interest by defining specific physiological processes in the model. While exposure matching using allometric scaling is most commonly employed in pediatrics (Samant et al., 2015), age- or organ function-based (e.g. creatinine clearance) scaling approaches are frequently employed in geriatrics (Lagishetty, 2013). For example, the FDA label for the anticoagulant apixaban (BMS-Pfizer, 2013) recommends age-, weight-, and serum creatinine-based dosing. The normal dose is 5 mg twice daily except for patients with two of the three factors: age ≥ 80 years, bodyweight ≤ 60 kg and serum creatinine ≥ 1.5 mg/dL. Under these circumstances the dose is reduced to half of the normal dose. “Scaling by size only” (i.e. allometric scaling) approaches typically face limitations in the presence of non-linearity. For pediatrics, non-linearity is typically the result of enzyme ontogeny, whereas other factors, such as changes in body composition, play a bigger role among older adults. Ideal body weight based on age do not exist for geriatric patients and hypervolemic states from congestive heart failure, cirrhosis, and nephrotic syndrome are common. Even accurate height and weight measures may be unattainable in patients who are bedridden or have amputations, contractures or kyphosis. Therefore, it would seem that a frail, medically complex 79 year-old would be more appropriate for the reduced dose of apixaban than a healthy 80 year old.

Although population approaches are typically descriptive and drug-centric in nature, they are routinely employed for dose selection and clinical trial design. They further allow for evaluation of covariates, both genetic and non-genetic, in order to account for inter-individual differences in patients' dose-concentration-response relationships (Mueck et al., 2014). Once established and qualified, population models can be used to address specific questions, either during drug development or in clinical practice (Saeed et al., 2015). During drug development, they can be applied to address specific questions on e.g. the dose-concentration-response (PK/PD) relationship of a drug or combination of drugs in a given patient population, which can then be prospectively qualified in a clinical trial setting. If linked to epidemiological, biological, clinical or real world patient data, these methods can be used to simulate a virtual elderly patient population, which can be used to assess benefit-risk relationship of a given treatment in a given patient population. One prominent example for the application of this innovative approach is the Alzheimer's disease progression simulator. This simulator integrates patient-level data with information from the neuroimaging initiative database and pooled literature data in a drug-disease trial model (Rogers et al., 2012). This model then allows to simultaneously evaluate multiple factors that contribute to the heterogeneity of the disease and its manifestation, which can then be used to project an individual patient's disease progression. These approaches have gained popularity for characterizing the progression of highly heterogeneous diseases in the absence of distinct information on the onset and trajectory of an individual's disease. As such, this simulator provides a powerful approach for enriching our knowledge on patient cohorts with small sample sizes, i.e., chronically understudied elderly patients.

Given the practical limitations outlined earlier in this review, this approach can be applied to optimize the clinical development of drugs in older adults, thus reducing the number of subject to include in the study, as well as the number of samples per patient and the number of studies required to characterize drug PK/PD behavior. Combining these innovative simulation approaches with prospective clinical trials may therefore be helpful to establish respective geriatric dosing recommendations, while reducing cost and burden to the elderly patient. The use of sparse sampling designs may be a solution to improve the recruitment of the oldest study patients overcoming some of the barriers to participation (as time in the center by the accommodation of blood withdrawals in more flexible sampling windows, or the number of days required for participation).

Once in the clinic, especially for those drugs with narrow therapeutic index and high variability (i.e. difficult to be managed in clinical settings), population models can be applied in combination with posterior Bayesian estimations to integrate the underlying PK or PK/PD mechanism of a drug along with patient specific covariates (characteristics) to aid in the prediction of the right dose for each individual patient (Hennig et al., 2008; Karafoulidou et al., 2009; Krauss et al., 2013; Krauss et al., 2015; Oteo et al., 2011; Oteo et al., 2013; Sanchez et al., 2011; Valdivieso et al., 2013). Ideally these individualization methods for complicated drugs should be applied during drug development to find the right dose for the right patient prior to it entering the market. However, such pharmaco-statistical methods have found limited application at the bedside to date. This is primarily due to a lack of practitioner-friendly decision support tool

interfaces, which are needed to facilitate the translation of biomarker data and other patient-specific information into actionable treatment recommendations, without burdening practitioners with the underlying technical details (Zineh and Huang, 2011).

3.4.2. Physiologically-based approaches

PBPK models are set up to characterize and predict drug exposure at different target sites by dividing the biological system into a number of compartments, each representing a different organ or tissue. These organs or tissues are connected through arterial and venous blood flow. PBPK models consist of three distinct parts: 1) a drug-specific component that characterizes the physicochemical properties of the drug (e.g., pKa, molecular weight, logP), which can be predicted on the basis of in vitro assays, 2) a system-specific component that describes the functioning of the underlying physiological system, which can differ between and within species, e.g. between adult and elderly patients, and 3) a trial design component that characterizes the impact of intrinsic (e.g. disease state, genetic constitution) and extrinsic (e.g. diet, smoking, drug-drug interactions) factors on the drug's PK as well as the trial design (Kuepfer et al., 2016; Samant et al., 2015). Although PBPK models have been especially used in regulatory applications to characterize and predict the impact of DDIs they are also gaining popularity for testing and understanding the PK in specific populations, such as pediatrics, but also to perform in vitro–in vivo extrapolations, to translate the PK cross-species and within-species as well as for pharmacogenomics purposes, evaluation of organ impairment on drug elimination, investigation drug absorption, and combinations thereof (Huang et al., 2013). They may also serve as screening tools during early stages of drug development to facilitate strategic decision-making to select those compounds with a more favorable PK and formulation properties (Jones et al., 2012).

Although PBPK approaches are uniquely positioned for evaluating the dose-exposure relationship or efficacy/safety assessments in clinically understudied populations, such as pediatrics, this approach has found little application for elderly patients thus far (Marsousi et al., 2017). There are some ongoing initiatives that are attempting to expand PBPK modeling and simulation platforms to geriatrics by accounting for changes in the underlying physiology and for the age-related decline in the organ function, as well as for the influence of pathophysiological conditions (Polasek et al., 2013; Schlender et al., 2016). Once established and qualified, these expanded PBPK models may also serve as a platform to evaluate the impact of other clinically relevant factors, such as DDIs in elderly patients in the absence of actual clinical trial data, ideally as a basis for future confirmatory prospective studies.

The use of PBPK/PD models is the subsequent next step for integrating relevant information on PK (e.g., changes in metabolic capacity, or transporter expression) and PD (e.g., changes in receptor expression and activity) in order to select an optimal treatment and dosing regimen (De Buck et al., 2007; Sinha et al., 2012). Once established and qualified, these PBPK/PD models can be used for the individualization of drug and dosing regimens in the elderly by accounting for differences in e.g. organ function, genetic make-up, or general physiology (Schaller et al., 2013). However, it should be noted that both, implementation and predictive performance of these approaches, will rely on the use of clinically relevant biomarkers for the elderly patient. However, it should be noted that both, implementation and predictive performance of these approaches, will rely on the use of clinically relevant biomarkers for the elderly patient as well as on the adequacy of the physiological database used for model development.

3.4.2.1. Development and qualification of an elderly PBPK database. An elderly PBPK platform combined with age-related information on pathway or target abundance changes can be applied to develop novel treatment strategies. However, a comprehensive qualification upfront is essential in order to build confidence towards any PBPK application. Similar to pediatrics or the adult age range, a verified and/or qualified elderly PBPK database can be considered as the foundation for further disease implementation in the elderly PBPK approach. Such a database allows a diversification of age- and/or disease-related physiological alterations. Although multimorbidity hampers a clear disease-related pathophysiological distinction, changes due to healthy aging can clearly be separated with an elderly patient PBPK approach. Once the PK alterations with increasing age are physiologically informed, shifts in PD patterns can be explained by the plain exposure-response relationship.

The integrated use of PBPK & PD and their predictive performance relies on the concerted use of physiological, demographic, and genetic information. These PBPK & PD models consequently require the use of highly curated databases, which summarize our knowledge on human anatomy and (patho-) physiology as well as changes thereof with age. Jadhav et al. outlined the steps necessary to developed and qualify a model that appropriately characterizes the fate of a given drug in a particular patient population (Jadhav et al., 2015). In addition to the fate of the drug, changes in the biological systems with age need to be considered in order to appropriately characterize and predict the dynamic changes in the interplay between drug, patient and potentially disease. The established database by Thompson et al. comprises (patho-)physiological changes of healthy and diseased older adults based on a thorough literature search (Thompson et al., 2009). Intended to inform a PBPK framework towards aging by their raw data summary, the authors also analyze data density and point out knowledge gaps. As a next step, Schlender et al. developed, verified and qualified a PBPK framework with an underlying database that summarizes changes in human physiology with age (Schlender et al., 2016). These include changes in body and organ composition, organ blood flow as well as functional changes as the result of e.g. changes in plasma proteins or glomerular filtration rate (GFR).

The establishment of databases for older adults is hampered by the fact that changes in the underlying physiology may or may not correlate well with chronological age and heavily depend on extrinsic and intrinsic factors. These factors are typically not normally distributed and can be significantly affected by comorbidities and co-medication. For example, acute medical illness and hospitalization can profoundly affect biological aging, while therapeutic or lifestyle interventions may lead to partial regeneration (Vidal et al., 2015). The rate at which anatomical, physical and cognitive impairment progresses with age differs in pace, which results in pharmacological heterogeneity in elderly patients. Finally, there are gender-specific differences in aging that need to be considered. While menopause represents a distinct event in women's lives, which is associated with distinct biological changes in the female body, aging is a much more heterogeneous process in men (Schlender et al., 2016; Turnheim, 1998). The World Health Organization (WHO) consequently recommends ten-year age bins for aging studies to capture the various degrees of physiological and biological changes in this patient group (de Onis and Habicht, 1996).

While functional, physical or cognitive age-related changes are frequently monitored in sizeable study cohorts, anatomical and (patho-) physiological changes are primarily investigated in cross-sectional studies (Thompson et al., 2009). The general lack of longitudinal data also poses a challenge for our ability to compare results from different studies. This becomes particularly apparent when today's humans are compared to their age-matched counterparts from previous decades, who tended to be smaller and less obese than today's average adult (Kawamura, 2012). The comorbidities and medication profiles are also different. This phenomenon is also referred to as ‘secular trend’ and needs to be considered when developing a database that includes data from previous decades.

3.4.2.2. Database qualification steps. Once a physiological database that accounts for age-related changes in physiology has been established, a rigorous qualification process is needed to ensure its broader validity and applicability. There has been a lot of controversy in the recent years

on what is the best approach for qualifying PBPK platforms and models, highlighting the need for well-defined model development and qualification criteria (Shepard et al., 2015). However, this is not a new challenge and solutions are offered in the US Environmental Protection Agency (EPA) guideline (EPA, 2010), the European Medicines Agency (EMA) guideline (EMA, 2016), and the FDA guidance (FDA, 2016).

External model qualification is an overarching theme in all of the current best practices for PBPK model development and qualification. It refers to the use of one or more data sets that have not been used for model development to test the model's descriptive and predictive performance and, thus, the assumptions made during model development. The same concept also applies for associated model parameters (Kuepfer et al., 2016). A major advantage of PBPK models and associated databases is that this verification step does not have to be performed on a one off basis, i.e. for each drug, because the underlying anatomy and physiology of the biological system does not change with each drug. As a consequence, a distinction between biological system specific and drug specific model components can be made. While biological system specific model components characterize the functioning of the underlying biological system, drug specific model components characterize the physicochemical properties of the drug.

Both model components can be qualified independently from one another. In other words, once a biological system has been characterized by biological system specific model components, the PBPK model's setup is completed through the integration of system-independent, drug specific parameters (Rowland and Tozer, 2005). Of course, this concept also applies the other way around, e.g. by acknowledging changes in the biological system with age via the use of time-varying functions, while keeping the drug specific model components constant. These time-dependent changes in the biological system are typically “mapped out” through the use of probe compounds. Changes in the probe compounds' clearance and distribution patterns serve as indirect measures of changes in e.g. metabolic capacity, perfusion or tissue composition.

Hence, PBPK models for selected probe drugs should be built for healthy young adults first and subsequently be scaled to the age-range of interest (see Fig. 3). An appropriate step-by-step ADME process-driven qualification should consider the following elements and exclude subsequent characteristics when selecting the paradigm compounds:

1) The first test compounds should be characteristic for the extracellular space (e.g. aminoglycosides, ibuprofen). This property allows for a description and concomitant qualification of changes in blood volume and interstitial space with age. Preferably, the test compounds for this step should freely distribute in the absence of tissue binding.
2) Once this first task has been accomplished, the impact of plasma protein binding and changes therein with age can be verified in a second step through the use of probe compounds that show extensive plasma protein binding in the absence of tissue distribution. The latter will also provide an estimate of age-related changes in extracellular body water.
3) As tissue concentrations and biopsy studies in elderly are rarely performed, changes in drug tissue distribution need to be qualified by informing the age-related changes of the accountable process. Here, the changes of the volume of distribution can be evaluated as a measure for altered tissue distribution. Turnheim et al. gathered literature information on the volume of distribution shifts between adults and elderly which can be used as a test set for these steps (Turnheim, 1998). When the reported elderly to young ratio of volume of distribution was related to the compounds octanol/water partition-coefficient (LogP value), a tendency to a gradual increase of volume of distribution in elderly was observed towards compounds with a LogP > 2 (McLean and Le Couteur, 2004). The reversed tendency was inferred for more hydrophilic compounds. Volume of distribution qualification steps as parametrized for young adults will be governed by the age-related changes in organ size and blood flow.
4) Thereafter, the impact of age on clearance pathways can be qualified within an elderly PBPK approach. Firstly, characteristic single elimination pathway compounds should be selected for qualification to assess in a later stage the shifting extraction ratios of drugs with multiple elimination pathways.
   a) Renal clearance (CL_R) mediated by a descending GFR needs to be qualified by testing hydrophilic drugs solely eliminated by filtration without subsequent reabsorption or secretion processes.
   b) Hepatic elimination can be governed by the hepatic perfusion in case of high extraction drugs (propranolol, metoprolol, morphine) or by the intrinsic clearance mediated by a certain enzymatic process besides shifts in the unbound fraction for low extraction drugs (CYP-paradigm substrates). Qualification should proceed via single-elimination pathway compounds. Multiple pathway elimination compounds can serve for additional assessments.
5) Once the major systemic processes driving distribution, metabolism and elimination have been qualified, the following step is to assess factors influencing the oral absorption. Gastric emptying and transit time or passive absorption due to alterations of the surface area may be qualified using relatively small, Biopharmaceutics Drug Disposition Classification System (BDDCS) class I molecules such as paracetamol or caffeine (Benet et al., 2011). In addition first pass effects, especially intestinal metabolism can be characterized.

The choice of probe compounds and sequence described above is certainly idealistic. It is consequently possible that not all steps are applicable to all/other specific populations, e.g., due to the lack of appropriate data. However, both a general physiology verification and specific ADME process-driven qualification procedure should be aspired once a new specific population PBPK database is established, and prior to its use for modeling purposes. Qualification for intended use is especially important, when considering high impact applications (EMA, 2016). Fig. 3 depicts the database, as the backbone of a platform, qualification and verification steps. The described procedure defines criteria towards a fit-for-purpose characterization of a PBPK specific population database requiring a reliable standard PBPK framework. However, the qualification of the specific model for each compound should be predefined and considered with strong criteria mainly for drugs with narrow therapeutic index. For such purpose, the best practice of model assessment proposed by the WHO (2010) is frequently applied. A recent investigation revealed a lack of consensus in the model qualification and verification practices for the majority of peer-reviewed PBPK models published between 2008 and 2015, where 56% of the articles did not pre-define the criteria to evaluate the successful performance of the model for it specific purpose. Importantly, for narrow therapeutic index drugs, a 30% or 2-fold deviation in the prediction of plasma concentrations or PK parameters were applied as qualification criteria but only in less than half of the studies while the other half had no criteria (Sager et al., 2015). These results highlight the need for consensus to decide on best practices to qualify PBPK models. In addition, the criteria actually used for model evaluation might be too soft for narrow therapeutic index drugs for which failures in the selection of the optimal dose can have fatal consequences. Finally, it is important to remark that the level of qualification determines the confidence into the extrapolative performance, especially, when the prediction requires increased prior system knowledge. Sensitivity

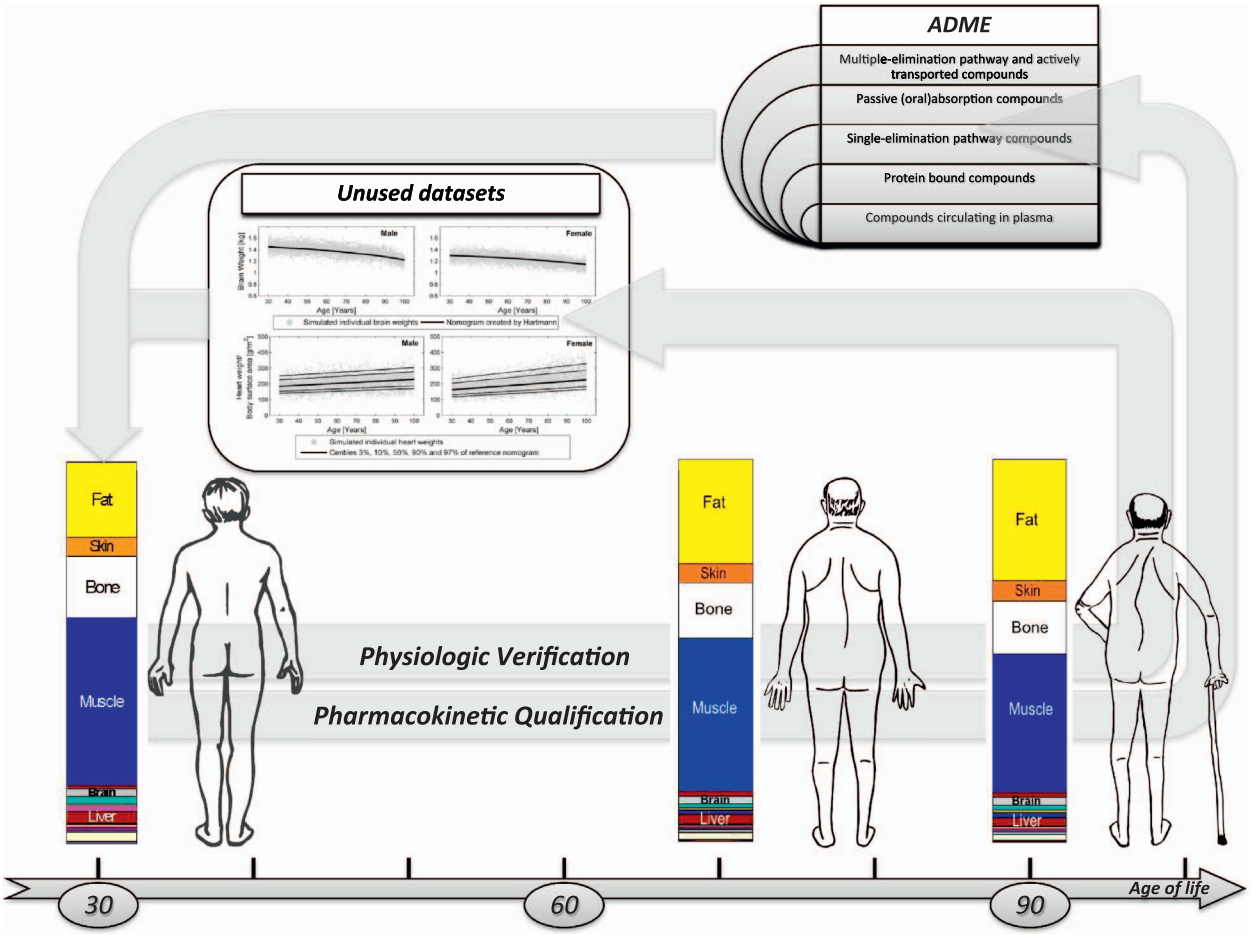

Fig. 3. Database qualification and verification steps. Bars represent the body composition of a 30 year old individual, a septuagenarian, and a nonagenarian male with their relative organ volumes as part of the total body weight.

analysis can serve as a powerful tool in this regard because it can aid the identification of the most influential parameters that represent the impact of age on PK and associated PK parameters such as AUC or the maximum plasma concentration (C_{max}). Investigating the impact of changes in the system's input on the output also allows investigating how uncertainties influence model behavior and can thereby serve as an indicator for model performance, reliability, and significance of results achieved (Zhang et al., 2015).

Moreover, when the model is going to be used to impact drug labelling, as for example to decide the dose recommendation for older adults, it is very important to ensure its adequate performance for this purpose, as the model based decision taken will directly impact the clinical practice and will have direct consequences on the patient.

Once established and qualified, a major advantage of PBPK models is their ability to characterize and predict the dynamic interplay between multiple biological processes, such as the interplay between multiple metabolic enzymes. This ability can also be used to evaluate the impact of aging on a drug's hepatic clearance. Clearance of drugs which are eliminated to > 70% from blood or plasma upon passage through the liver (i.e., high extraction drugs) is mainly restricted by the liver blood flow, whereas clearance of low extraction drugs (cleared to < 30%) is dependent on the metabolic capacity of the eliminating organ, in this case, the liver. As summarized in Table 1, the majority of studies do not report a significant impact of age on enzyme-mediated processes, but reporting a heterogeneous situation for clearance via phase 1 and 2 metabolization (Le Couteur and McLean, 1998). It should be noted that, compared to children, where metabolites that are different from those in adults, can be formed, this does not seem to be the case in the elderly (Benedetti et al., 2007).

4. Challenges and opportunities to streamline dosing regimens in the elderly

4.1. What are the current challenges?

The inclusion of older patients in the testing of new medications as outlined in the ICH E7 guidelines is not mandatory for pharmaceutical industry as long as reasonable justification for not doing so is provided. In addition, a comprehensive representation of the elderly in clinical trials remains hindered by the complex nature of this patient population including the heterogeneity in comorbidities, poly-medication, socio-economic backgrounds, and in physiological state. It also disqualifies a direct comparison of the elderly population in its entirety to healthy adults. The situation is particularly challenging for narrow therapeutic index drugs, where small changes in PK and/or PD have the potential to change the benefit/risk profile of the drug, consequently warranting close assessment in older adults. In addition, adherence to medication and off-label use due to poly-medication, complex dosing regimen, cognitive and functional disabilities are major challenges in geriatric pharmacotherapy in general and individualization in particular. As discussed in greater detail in the previous sections of this manuscript, the lack of geriatric information can be supplemented by the application of informative pharmacometric modeling and simulation methods.

Table 1
Summary of activity changes of selected phase I and II metabolizing enzymes in elderly compared to adults based on Benedetti et al. (2007).

Metabolizing enzyme	Probe drug	Indication	Activity change	Reference
CYP1A2	Caffeine	CNS stimulant	↔	Bebia et al. (2004)
CYP2C19	Mephenytoin	Epilepsy	↓	Bebia et al. (2004)
	Omeprazole	Heartburn		Ishizawa et al. (2005)
CYP2D6	Debrisoquin	Hypertension	↔	Bebia et al. (2004)
CYP3A4	Midazolam	Sedation	↓	Greenblatt et al. (1984)
	Triazolam	Insomnia	↔	Smith et al. (1983)
UGT	Paracetamol	Pain, fever	↔	Herd et al. (1991)
	Oxazepam	Anxiety	↓	Sonne et al. (1991)
	Ezogabine	Epilepsy		Hermann et al. (2003)
Sulfotransferase	Dehydroepiandrosterone	Hormone supplement	↔	Aksoy et al. (1993)
	Paracetamol	Pain, fever		Herd et al. (1991)

↓ indicates decrease; ↑ indicates increase; ↔indicates no effect.

4.2. What are the opportunities?

Personalization of drug therapy holds tremendous potential to change the way drug therapies could be used in elderly patients to better care for the patients. Over the past decade, FDA and other regulatory authorities are on the forefront of establishing approaches that increase the benefit of drug therapies while minimizing their risk in this vulnerable patient population. While pediatric guidances have been frequently updated over the past decade (EP, 2006; FDA, 2013), respective regulatory documents are not yet available for the elderly even when the concepts outlined for pediatrics may be used as reference point for geriatrics as well.

Whenever possible, clinical trials should include elderly subjects in order to establish appropriate dosing regimen for this special patient population. The conduct of these trials can be supported through the use of modeling and simulation approaches that account for the dynamic interplay between genetic and non-genetic factors in older adults as well as their impact on the drug's PK/PD as a function of age. These quantitate approaches can be used to optimize study designs based on sparse sampling strategies to overcome some of the practical limitations of performing clinical trials in older adults. The success and failure of these approaches are closely linked to the identification of reliable biomarkers of aging. While the identification of age-appropriate biomarkers is currently primarily subject to academic research (Lagishetty, 2013), an increase in research efforts can be expected over the next decade given the importance of this growing patient population. In addition, to these “hard” endpoints, the impact of socioeconomic factors and patient behavior on drug therapy needs to be better understood when attempting to optimize treatment on a patient-by-patient basis. To that end, a promising approach was recently promoted by Novartis in order to personalize clinical development in the field of oncology. The program was for a couple of compounds associated with certain mutations independent from the affected tissue (Kang et al., 2015). Based on a hierarchical Bayesian approach, information gained in one subgroup can verify the potency of a compound in another subgroup (Berry et al., 2013). This approach can, for example, be used in elderly cancer patients who are highly variable in their tumor set of mutations. This approach is already feasible with small study groups and, thus, could facilitate and personalize geriatric clinical development. The development of large databases and big data management that integrate prescription payment and medical claims information provide an opportunity for post-marketing geriatric pharmacovigilance. Database analysis allows for pharmacovigilance of older generic mediations that may no longer be under active investigation. The data mining of these large health care databases does not prove a medication-related side-effect but shows association that provides the hypotheses generation for future studies.

Therapeutic drug monitoring (TDM) approaches are nowadays a useful tool to individualize the dose of compounds with a narrow therapeutic window in the clinical settings. While this approach is usually based on popPK knowledge, PBPK applications in patient care will help to individualize dosing for a starting drug treatment once the approach is clinically robust. Knowledge of exposure and response under a certain medication can be translated and used for an introduced treatment in this patient or individually help to balance the potential hazard against the possible benefit.

The selection of the best quantitative approach to optimize and/or personalize drug therapies in the elderly should be evaluated in a case by case basis. The success depends on the available knowledge on the drug and biological systems, as well on the drug development stage. While PBPK models can be useful to establish dosing regimens in population subgroups based on specific physio-pathological conditions during drug development, Bayesian approaches are usually aimed to individualize the dose at the patient level in the clinical environment. Both approaches can be used in combination to understand the underlying mechanism of age-related physiology and their impact on drug PK/PD and to stablish the most appropriate dosing regimens for each population subgroup since the early drug development phases. In any case, the development and application of these approaches is complex and requires high level training for its successful application. Additionally, for those drugs that require a more precise selection of the dose due to its narrow therapeutic index and high variability, the development of practitioner-friendly decision support tool interfaces is needed to simplify its clinical application (Zineh and Huang, 2011).

Key messages

- Personalization of drug therapy can maximize benefit and minimize side-effects in the elderly.
- Current inclusion criteria often do not represent the entire age spectrum of the elderly for a particular geriatric clinical trial.
- The International Conference on Harmonization (ICH) Efficacy Guideline E7 defines various groups for the elderly patients in order to enable the sponsors to conduct geriatric clinical research effectively.
- Genotype guided and genome based risk assessment techniques can be employed for advanced screening and pharmacotherapy.
- ADME processes are highly variable in the elderly and should be considered accurately to drive informed decision making for guiding dose recommendations.
- Quantitative tools such as pharmacometric and physiologically-based approaches can be used for dose personalization in the elderly.
- Key challenges include adherence to medication, poly-medication, complex dosing regimens, cognitive and functional disabilities in geriatric pharmacotherapy.
- Key opportunities rely on determination and validation of reliable biomarkers of aging, accurate determination dynamic interplay between genetic and non-genetic factors along with PK/PD consideration in the elderly.

Declaration of conflicting interests

J.F.S.: employee of Bayer AG.
V.V.: employee of Dynakin SL.
A.G.G.: Pharmacy and Therapeutics Committee, Magellen Rx.
M.R.: employee of Dynakin SL.
T.S.S.: employee and shareholder of Novartis.
C.V.L.: employee and shareholder of GlaxoSmithKline.
T.E.: employee and shareholder of Bayer AG.
S.S.: none.

References

Aksoy, I.A., Sochorova, V., Weinshilboum, R.M., 1993. Human liver dehydroepiandrosterone sulfotransferase: nature and extent of individual variation. Clin. Pharmacol. Ther. 54, 498–506.

Bebia, Z., Buch, S.C., Wilson, J.W., Frye, R.F., Romkes, M., Cecchetti, A., Chaves-Gnecco, D., Branch, R.A., 2004. Bioequivalence revisited: influence of age and sex on CYP enzymes. Clin. Pharmacol. Ther. 76, 618–627.

Beers, M.H., 1997. Explicit criteria for determining potentially inappropriate medication use by the elderly. An update. Arch. Intern. Med. 157, 1531–1536.

Beers, M.H., Ouslander, J.G., Rollingher, I., Reuben, D.B., Brooks, J., Beck, J.C., 1991. Explicit criteria for determining inappropriate medication use in nursing home residents. UCLA Division of Geriatric Medicine. Arch. Intern. Med. 151, 1825–1832.

Beers, E., Egberts, T.C., Leufkens, H.G., Jansen, P.A., 2013. Information for adequate prescribing to older patients: an evaluation of the product information of 53 recently approved medicines. Drugs Aging 30, 255–262.

Benedetti, M.S., Whomsley, R., Canning, M., 2007. Drug metabolism in the paediatric population and in the elderly. Drug Discov. Today 12, 599–610.

Benet, L.Z., Broccatelli, F., Oprea, T.I., 2011. BDDCS applied to over 900 drugs. AAPS J. 13, 519–547.

Berry, S.M., Broglio, K.R., Groshen, S., Berry, D.A., 2013. Bayesian hierarchical modeling of patient subpopulations: efficient designs of phase II oncology clinical trials. Clin. Trials 10, 720–734.

Bonaventura, A., Montecucco, F., Dallegri, F., 2015. Update on strategies limiting iatrogenic hypoglycemia. Endocr. Connect. 4, R37–45.

Bor, J.S., 2014. The search for effective Alzheimer's therapies: a work in progress. Health Aff. (Millwood) 33, 527–533.

Borst, S.E., Scarpace, P.J., 1990. Reduced high-affinity alpha 1-adrenoceptors in liver of senescent rats: implications of assessment at various temperatures. Br. J. Pharmacol. 101, 650–654.

Bristol-Myers Squibb (BMS) Pfizer EEIG, 2013. Eliquis (Apixaban) — Summary of Product Characteristics. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002148/WC500107728.pdf, Accessed date: 1 June 2017.

Brooks-Wilson, A.R., 2013. Genetics of healthy aging and longevity. Hum. Genet. 132, 1323–1338.

Budnitz, D.S., Lovegrove, M.C., Shehab, N., Richards, C.L., 2011. Emergency hospitalizations for adverse drug events in older Americans. N. Engl. J. Med. 365, 2002–2012.

Butler, R.N., Sprott, R., Warner, H., Bland, J., Feuers, R., Forster, M., Fillit, H., Harman, S.M., Hewitt, M., Hyman, M., Johnson, K., Kligman, E., McClearn, G., Nelson, J., Richardson, A., Sonntag, W., Weindruch, R., Wolf, N., 2004. Biomarkers of aging: from primitive organisms to humans. J. Gerontol. A Biol. Sci. Med. Sci. 59, B560–567.

Cherubini, A., Del Signore, S., Ouslander, J., Semla, T., Michel, J.P., 2010. Fighting against age discrimination in clinical trials. J. Am. Geriatr. Soc. 58, 1791–1796.

De Buck, S.S., Sinha, V.K., Fenu, L.A., Nijsen, M.J., Mackie, C.E., Gilissen, R.A., 2007. Prediction of human pharmacokinetics using physiologically based modeling: a retrospective analysis of 26 clinically tested drugs. Drug Metab. Dispos. 35, 1766–1780.

de Onis, M., Habicht, J.P., 1996. Anthropometric reference data for international use: recommendations from a World Health Organization Expert Committee. Am. J. Clin. Nutr. 64, 650–658.

Du, Y.F., Ou, H.Y., Beverly, E.A., Chiu, C.J., 2014. Achieving glycemic control in elderly patients with type 2 diabetes: a critical comparison of current options. Clin. Interv. Aging 9, 1963–1980.

Encinas, E., Calvo, R., Lukas, J.C., Vozmediano, V., Rodriguez, M., Suarez, E., 2013. A predictive pharmacokinetic/pharmacodynamic model of fentanyl for analgesia/sedation in neonates based on a semi-physiologic approach. Paediat. drugs 15, 247–257.

European Medicines Agency (EMA), 2010. Studies in Support of Special Populations: Geriatrics, Questions and Answers. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500005218.pdf, Accessed date: 1 June 2017.

European Medicines Agency (EMA), 2016. Draft guideline on the qualification and reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/07/WC500211315.pdf, Accessed date: 1 June 2017.

European Parliament (EP) and of the Council EEC, 2006. Regulation (EC) No 1901/2006 of the European Parliament and of the Council on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004. http://ec.europa.eu/health/files/eudralex/vol-1/reg_2006_1901/reg_2006_1901_en.pdf, Accessed date: 1 June 2017.

Fick, D.M., Semla, T.P., 2012. 2012 American Geriatrics Society Beers Criteria: new year, new criteria, new perspective. J. Am. Geriatr. Soc. 60, 614–615.

Fick, D.M., Cooper, J.W., Wade, W.E., Waller, J.L., Maclean, J.R., Beers, M.H., 2003. Updating the Beers criteria for potentially inappropriate medication use in older adults: results of a US consensus panel of experts. Arch. Intern. Med. 163, 2716–2724.

Gage, B.F., Eby, C., Johnson, J.A., Deych, E., Rieder, M.J., Ridker, P.M., Milligan, P.E., Grice, G., Lenzini, P., Rettie, A.E., Aquilante, C.L., Grosso, L., Marsh, S., Langaee, T., Farnett, L.E., Voora, D., Veenstra, D.L., Glynn, R.J., Barrett, A., McLeod, H.L., 2008. Use of pharmacogenetic and clinical factors to predict the therapeutic dose of warfarin. Clin. Pharmacol. Ther. 84, 326–331.

Gallagher, P., O'Mahony, D., 2008. STOPP (Screening Tool of Older Persons' potentially inappropriate Prescriptions): application to acutely ill elderly patients and comparison with Beers' criteria. Age Ageing 37, 673–679.

Geloneze, B., de Oliveira Mda, S., Vasques, A.C., Novaes, F.S., Pareja, J.C., Tambascia, M.A., 2014. Impaired incretin secretion and pancreatic dysfunction with older age and diabetes. Metabolism 63, 922–929.

Golden, A., Troen, B., 2010. Biology of aging. In: Hirth, V., Wieland, D., Dever-Bumba, M. (Eds.), Case-based Geriatrics. McGraw Hill, New York.

Golden, A., Silverman, M., Daiello, L., Llorente, M., 2005. Inappropriate medication prescribing: going beyond the Beer's criteria. Long-Term Care Interface Mag. 6, 31–34.

Golden, A., Beers, M.H., Fick, D.M., 2008. Is it safe to conclude that Beers criteria medications led to few adverse events? Ann. Intern. Med. 148, 628–629 (author reply 629).

Golden, A.G., Tewary, S., Dang, S., Roos, B.A., 2010. Care management's challenges and opportunities to reduce the rapid rehospitalization of frail community-dwelling older adults. Gerontologist 50, 451–458.

Greenblatt, D.J., Abernethy, D.R., Locniskar, A., Harmatz, J.S., Limjuco, R.A., Shader, R.I., 1984. Effect of age, gender, and obesity on midazolam kinetics. Anesthesiology 61, 27–35.

Hamilton, H., Gallagher, P., Ryan, C., Byrne, S., O'Mahony, D., 2011. Potentially inappropriate medications defined by STOPP criteria and the risk of adverse drug events in older hospitalized patients. Arch. Intern. Med. 171, 1013–1019.

Hammerlein, A., Derendorf, H., Lowenthal, D.T., 1998. Pharmacokinetic and pharmacodynamic changes in the elderly. Clinical implications. Clin. Pharmacokinet. 35, 49–64.

Hennig, S., Norris, R., Kirkpatrick, C.M., 2008. Target concentration intervention is needed for tobramycin dosing in paediatric patients with cystic fibrosis—a population pharmacokinetic study. Br. J. Clin. Pharmacol. 65, 502–510.

Herd, B., Wynne, H., Wright, P., James, O., Woodhouse, K., 1991. The effect of age on glucuronidation and sulphation of paracetamol by human liver fractions. Br. J. Clin. Pharmacol. 32, 768–770.

Hermann, R., Ferron, G.M., Erb, K., Knebel, N., Ruus, P., Paul, J., Richards, L., Cnota, H.P., Troy, S., 2003. Effects of age and sex on the disposition of retigabine. Clin. Pharmacol. Ther. 73, 61–70.

Herrera, A.P., Snipes, S.A., King, D.W., Torres-Vigil, I., Goldberg, D.S., Weinberg, A.D., 2010. Disparate inclusion of older adults in clinical trials: priorities and opportunities for policy and practice change. Am. J. Public Health 100 (Suppl. 1), S105–112.

Huang, S.M., Abernethy, D.R., Wang, Y., Zhao, P., Zineh, I., 2013. The utility of modeling and simulation in drug development and regulatory review. J. Pharm. Sci. 102, 2912–2923.

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), 1993. E7 studies in support of special populations: geriatrics. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E7/Step4/E7_Guideline.pdf, Accessed date: 1 June 2017.

Ishizawa, Y., Yasui-Furukori, N., Takahata, T., Sasaki, M., Tateishi, T., 2005. The effect of aging on the relationship between the cytochrome P450 2C19 genotype and omeprazole pharmacokinetics. Clin. Pharmacokinet. 44, 1179–1189.

Jadhav, P.R., Cook, J., Sinha, V., Zhao, P., Rostami-Hodjegan, A., Sahasrabudhe, V., Stockbridge, N., Powell, J.R., 2015. A proposal for scientific framework enabling specific population drug dosing recommendations. J. Clin. Pharmacol. 55, 1073–1078.

Jones, H.M., Dickins, M., Youdim, K., Gosset, J.R., Attkins, N.J., Hay, T.L., Gurrell, I.K., Logan, Y.R., Bungay, P.J., Jones, B.C., Gardner, I.B., 2012. Application of PBPK modelling in drug discovery and development at Pfizer. Xenobiotica 42, 94–106.

Kane, R., Ouslander, J., Abrass, I., Resnick, B., 2013. Essentials of Clinical Geriatrics, 7th ed. McGraw-Hill, New York.

Kang, B.P., Slosberg, E., Snodgrass, S., Lebedinsky, C., Berry, D.A., Corless, C.L., Stein, S., Salvado, A., 2015. The signature program: bringing the protocol to the patient. Clin. Pharmacol. Ther. 98, 124–126.

Karafoulidou, A., Suarez, E., Anastasopoulou, I., Katsarou, O., Kouramba, A., Kotsi, P., Zografidis, A., Lukas, J.C., 2009. Population pharmacokinetics of recombinant factor VIII:C (ReFacto) in adult HIV-negative and HIV-positive haemophilia patients. Eur. J. Clin. Pharmacol. 65, 1121–1130.

Kawamura, H., 2012. Development of the Japanese reference man model for age-specific phantoms. Radiat. Prot. Dosim. 149, 28–34.

Kirkman, M.S., Briscoe, V.J., Clark, N., Florez, H., Haas, L.B., Halter, J.B., Huang, E.S., Korytkowski, M.T., Munshi, M.N., Odegard, P.S., Pratley, R.E., Swift, C.S., 2012. Consensus Development Conference on Diabetes and Older Adults, 2012. Diabetes in older adults: a consensus report. J. Am. Geriatr. Soc. 60, 2342–2356.

Krauss, M., Burghaus, R., Lippert, J., Niemi, M., Neuvonen, P., Schuppert, A., Willmann, S., Kuepfer, L., Gorlitz, L., 2013. Using Bayesian-PBPK modeling for assessment of inter-individual variability and subgroup stratification. In: In Silico Pharmacology. Vol. 1. pp. 6.

Krauss, M., Tappe, K., Schuppert, A., Kuepfer, L., Goerlitz, L., 2015. Bayesian population physiologically-based pharmacokinetic (PBPK) approach for a physiologically realistic characterization of interindividual variability in clinically relevant populations. PLoS One 10, e0139423.

Kuepfer, L., Niederalt, C., Wendl, T., Schlender, J.F., Willmann, S., Lippert, J., Block, M., Eissing, T., Teutonico, D., 2016. Applied concepts in PBPK modeling: how to build a PBPK/PD model. CPT Pharmacometrics Syst. Pharmacol. 5, 516–531.

Lagishetty, C., 2013. Chapter 1. In: Covariates in Pharmacometrics [PhD thesis]. University of Otago, pp. 26–27. https://otago.ourarchive.ac.nz/handle/10523/4520, Accessed date: 1 June 2017.

Le Couteur, D.G., McLean, A.J., 1998. The aging liver. Drug clearance and an oxygen

diffusion barrier hypothesis. Clin. Pharmacokinet. 34, 359–373.
Leong, R., Vieira, M.L., Zhao, P., Mulugeta, Y., Lee, C.S., Huang, S.M., Burckart, G.J., 2012. Regulatory experience with physiologically based pharmacokinetic modeling for pediatric drug trials. Clin. Pharmacol. Ther. 91, 926–931.
Lesko, L.J., Schmidt, S., 2012. Individualization of drug therapy: history, present state, and opportunities for the future. Clin. Pharmacol. Ther. 92, 458–466.
Lewis, J.H., Kilgore, M.L., Goldman, D.P., Trimble, E.L., Kaplan, R., Montello, M.J., Housman, M.G., Escarce, J.J., 2003. Participation of patients 65 years of age or older in cancer clinical trials. J. Clin. Oncol. 21, 1383–1389.
Mallal, S., Phillips, E., Carosi, G., Molina, J.M., Workman, C., Tomazic, J., Jagel-Guedes, E., Rugina, S., Kozyrev, O., Cid, J.F., Hay, P., Nolan, D., Hughes, S., Hughes, A., Ryan, S., Fitch, N., Thorborn, D., Benbow, A., 2008. HLA-B*5701 screening for hypersensitivity to abacavir. N. Engl. J. Med. 358, 568–579.
Marsousi, N., Desmeules, J.A., Rudaz, S., Daali, Y., 2017. Usefulness of PBPK modeling in incorporation of clinical conditions in personalized medicine. J. Pharm. Sci. 106, 2380–2391.
Martin, K., Begaud, B., Latry, P., Miremont-Salame, G., Fourrier, A., Moore, N., 2004. Differences between clinical trials and postmarketing use. Br. J. Clin. Pharmacol. 57, 86–92.
Masoudi, F.A., Havranek, E.P., Wolfe, P., Gross, C.P., Rathore, S.S., Steiner, J.F., Ordin, D.L., Krumholz, H.M., 2003. Most hospitalized older persons do not meet the enrollment criteria for clinical trials in heart failure. Am. Heart J. 146, 250–257.
McLean, A.J., Le Couteur, D.G., 2004. Aging biology and geriatric clinical pharmacology. Pharmacol. Rev. 56, 163–184.
Meneilly, G.S., Ryan, A.S., Veldhuis, J.D., Elahi, D., 1997. Increased disorderliness of basal insulin release, attenuated insulin secretory burst mass, and reduced ultradian rhythmicity of insulin secretion in older individuals. J. Clin. Endocrinol. Metab. 82, 4088–4093.
Miao, L., Yang, J., Huang, C., Shen, Z., 2007. Contribution of age, body weight, and CYP2C9 and VKORC1 genotype to the anticoagulant response to warfarin: proposal for a new dosing regimen in Chinese patients. Eur. J. Clin. Pharmacol. 63, 1135–1141.
Miles, C., Wayne, M., 2008. Quantitative trait locus (QTL) analysis. Nature Education 1, 208.
Morley, J.E., Flood, J.F., Silver, A.J., 1990. Opioid peptides and aging. Ann. N. Y. Acad. Sci. 579, 123–132.
Mueck, W., Stampfuss, J., Kubitza, D., Becka, M., 2014. Clinical pharmacokinetic and pharmacodynamic profile of rivaroxaban. Clin. Pharmacokinet. 53, 1–16.
O'Mahony, D., O'Sullivan, D., Byrne, S., O'Connor, M.N., Ryan, C., Gallagher, P., 2015. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. Age Ageing 44, 213–218.
Oteo, I., Lukas, J.C., Leal, N., Suarez, E., Valdivieso, A., Gastaca, M., de Urbina, J.O., Calvo, R., 2011. Pathophysiological idiosyncrasies and pharmacokinetic realities may interfere with tacrolimus dose titration in liver transplantation. Eur. J. Clin. Pharmacol. 67, 671–679.
Oteo, I., Lukas, J.C., Leal, N., Suarez, E., Valdivieso, A., Gastaca, M., Ortiz de Urbina, J., Calvo, R., 2013. Tacrolimus pharmacokinetics in the early post-liver transplantation period and clinical applicability via Bayesian prediction. Eur. J. Clin. Pharmacol. 69, 65–74.
Oztaner, S.M., Taskaya Temizel, T., Erdem, S.R., Ozer, M., 2015. A Bayesian estimation framework for pharmacogenomics driven warfarin dosing: a comparative study. IEEE J. Biomed. Health Inform. 19, 1724–1733.
Patki, K.C., von Moltke, L.L., Harmatz, J.S., Hesse, L.M., Court, M.H., Greenblatt, D.J., 2004. Effect of age on in vitro triazolam biotransformation in male human liver microsomes. J. Pharmacol. Exp. Ther. 308, 874–879.
Polasek, T.M., Patel, F., Jensen, B.P., Sorich, M.J., Wiese, M.D., Doogue, M.P., 2013. Predicted metabolic drug clearance with increasing adult age. Br. J. Clin. Pharmacol. 75, 1019–1028.
Radcliff, S., Yue, J., Rocco, G., Aiello, S.E., Ickowicz, E., Hurd, Z., Samuel, M.J., Beers, M.H., 2015. American Geriatrics Society 2015 updated Beers criteria for potentially inappropriate medication use in older adults. J. Am. Geriatr. Soc. 63, 2227–2246.
Rogers, J.A., Polhamus, D., Gillespie, W.R., Ito, K., Romero, K., Qiu, R., Stephenson, D., Gastonguay, M.R., Corrigan, B., 2012. Combining patient-level and summary-level data for Alzheimer's disease modeling and simulation: a beta regression meta-analysis. J. Pharmacokinet. Pharmacodyn. 39, 479–498.
Rowland, M., Tozer, T.N., 2005. Clinical Pharmacokinetics/Pharmacodynamics, 4th ed. Lippincott Williams and Wilkins, Philadelphia.
Saeed, M.A., Vlasakakis, G., Della Pasqua, O., 2015. Rational use of medicines in older adults: can we do better during clinical development? Clin. Pharmacol. Ther. 97, 440–443.
Sager, J.E., Yu, J., Ragueneau-Majlessi, I., Isoherranen, N., 2015. Physiologically based pharmacokinetic (PBPK) modeling and simulation approaches: a systematic review of published models, applications, and model verification. Drug Metab. Dispos. 43, 1823–1837.
Samant, T.S., Mangal, N., Lukacova, V., Schmidt, S., 2015. Quantitative clinical pharmacology for size and age scaling in pediatric drug development: a systematic review. J. Clin. Pharmacol. 55 (11), 1207–1217.
Sanchez, A., Cabrera, S., Santos, D., Valverde, M.P., Fuertes, A., Dominguez-Gil, A., Garcia, M.J., Tormes, G., 2011. Population pharmacokinetic/pharmacogenetic model for optimization of efavirenz therapy in Caucasian HIV-infected patients. Antimicrob. Agents Chemother. 55, 5314–5324.
Schaller, S., Willmann, S., Lippert, J., Schaupp, L., Pieber, T.R., Schuppert, A., Eissing, T., 2013. A generic integrated physiologically based whole-body model of the glucose-insulin-glucagon regulatory system. CPT: Pharmacometrics Syst. Pharmacol. 2, e65.
Schaufler, J., Telschow, C., 2016. Arzneimittelverordnungen nach Alter und Geschlecht. German In: Schwabe, U., Paffrath, D. (Eds.), Arzneiverordnungs-Report 2016: Aktuelle Daten, Kosten, Trends und Kommentare. Springer Berlin Heidelberg, Berlin, Heidelberg, pp. 763–773.
Schlender, J.F., Meyer, M., Thelen, K., Krauss, M., Willmann, S., Eissing, T., Jaehde, U., 2016. Development of a whole-body physiologically based pharmacokinetic approach to assess the pharmacokinetics of drugs in elderly individuals. Clin. Pharmacokinet. 55, 1573–1589.
Sconce, E.A., Khan, T.I., Wynne, H.A., Avery, P., Monkhouse, L., King, B.P., Wood, P., Kesteven, P., Daly, A.K., Kamali, F., 2005. The impact of CYP2C9 and VKORC1 genetic polymorphism and patient characteristics upon warfarin dose requirements: proposal for a new dosing regimen. Blood 106, 2329–2333.
Shepard, T., Scott, G., Cole, S., Nordmark, A., Bouzom, F., 2015. Physiologically based models in regulatory submissions: output from the ABPI/MHRA forum on physiologically based modeling and simulation. CPT: Pharmacometrics Syst. Pharmacol. 4, 221.
Sinha, V.K., Snoeys, J., Osselaer, N.V., Peer, A.V., Mackie, C., Heald, D., 2012. From preclinical to human—prediction of oral absorption and drug-drug interaction potential using physiologically based pharmacokinetic (PBPK) modeling approach in an industrial setting: a workflow by using case example. Biopharm. Drug Dispos. 33, 111–121.
Smith, R.B., Divoll, M., Gillespie, W.R., Greenblatt, D.J., 1983. Effect of subject age and gender on the pharmacokinetics of oral triazolam and temazepam. J. Clin. Psychopharmacol. 3, 172–176.
Sonne, J., Loft, S., Dossing, M., Boesgaard, S., Andreasen, F., 1991. Single dose pharmacokinetics and pharmacodynamics of oral oxazepam in very elderly institutionalised subjects. Br. J. Clin. Pharmacol. 31, 719–722.
Swanlund, S.L., 2010. Successful cardiovascular medication management processes as perceived by community-dwelling adults over age 74. Appl. Nurs. Res. 23, 22–29.
Thompson, C.M., Johns, D.O., Sonawane, B., Barton, H.A., Hattis, D., Tardif, R., Krishnan, K., 2009. Database for physiologically based pharmacokinetic (PBPK) modeling: physiological data for healthy and health-impaired elderly. J. Toxicol. Environ. Health B Crit. Rev. 12, 1–24.
Turnheim, K., 1998. Drug dosage in the elderly. Is it rational? Drugs Aging 13, 357–379.
U.S. Department of Health and Human Services Food and Drug Administration (FDA), 2012. E7 Studies in Support of Special Populations: Geriatrics Guidance for Industry. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm189544.pdf, Accessed date: 1 June 2017.
U.S. Department of Health and Human Services Food and Drug Administration (FDA), 2013. Pediatric Study Plans. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm360507.pdf, Accessed date: 1 June 2017.
U.S. Department of Health and Human Services Food and Drug Administration (FDA), 2014. General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425885.pdf.%202014, Accessed date: 1 June 2017.
U.S. Department of Health and Human Services Food and Drug Administration (FDA), 2015. Table of Pharmacogenomic Biomarkers in Drug Labeling. http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm, Accessed date: 1 June 2017.
U.S. Department of Health and Human Services Food and Drug Administration (FDA), 2016. Physiologically Based Pharmacokinetic Analyses — Format and Content. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM531207.pdf, Accessed date: 1 June 2017.
US Environmental Protection Agency (EPA), 2010. Physiologically-Based Pharmacokinetic (PBPK) Modeling White Paper: Addressing the Use of PBPK Models to Support Derivation of Acute Exposure Guideline Levels. https://www.epa.gov/sites/production/files/2015-07/documents/aegl_pbpk_whitepaper_final_volume9_2010.pdf#page=25, Accessed date: 1 June 2017.
Valdivieso, N., Oteo, I., Valdivieso, A., Lukas, J.C., Leal, N., Gastaca, M., de Urbina, J.O., Calvo, R., Suarez, E., 2013. Tacrolimus dose individualization in “de novo” patients after 10 years of experience in liver transplantation: pharmacokinetic considerations and patient pathophysiology. Int. J. Clin. Pharmacol. Ther. 51, 606–614.
Van Dam, D., De Deyn, P.P., 2006. Drug discovery in dementia: the role of rodent models. Nat. Rev. Drug Discov. 5, 956–970.
Vidal, E.I., Mayoral, V.F., Villas Boas, P.J., Jacinto, A.F., Fukushima, F.B., 2015. Physical frailty as a clinical marker of biological age and aging. J. Am. Geriatr. Soc. 63, 837–838.
Vozmediano, V., Ortega, I., Lukas, J.C., Gonzalo, A., Rodriguez, M., Lucero, M.L., 2014. Integration of preclinical and clinical knowledge to predict intravenous PK in human: bilastine case study. Eur. J. Drug Metab. Pharmacokinet. 39, 33–41.
Waade, R.B., Hermann, M., Moe, H.L., Molden, E., 2014. Impact of age on serum concentrations of venlafaxine and escitalopram in different CYP2D6 and CYP2C19 genotype subgroups. Eur. J. Clin. Pharmacol. 70, 933–940.
Winner, J., 2014. Pharmacogenomic treatment support. Geriatr. Med. Today 4 (20). http://www.todaysgeriatricmedicine.com/archive/0714p20.shtml, Accessed date: 1 June 2017 (July/August).
World Health Organization (WHO), 2010. International Programme on Chemical Safety Harmonization Project. Characterization and application of physiologically based pharmacokinetic models in risk assessment. Harmonization Project Document No. 9. http://www.inchem.org/documents/harmproj/harmproj/harmproj9.pdf, Accessed date: 1 June 2017.
Zhang, X.Y., Trame, M.N., Lesko, L.J., Schmidt, S., 2015. Sobol sensitivity analysis: a tool to guide the development and evaluation of systems pharmacology models. CPT: Pharmacometrics Syst. Pharmacol. 4, 69–79.
Zineh, I., Huang, S.M., 2011. Biomarkers in drug development and regulation: a paradigm for clinical implementation of personalized medicine. Biomark. Med 5, 705–713.