Guidance for Industry

E7 Studies in Support of Special Populations: Geriatrics

Questions and Answers

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

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ICH

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I. INTRODUCTION

The ICH guidance *E7 Studies in Support of Special Populations: Geriatrics* provides recommendations on special considerations that apply in the design and conduct of clinical trials of medicines that are likely to have significant use in the elderly. Since the E7 guidance was made final, experiences implementing the guidance in the ICH regions have given rise to requests for clarification. This question and answer (Q&A) document is intended to clarify key issues.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[1] This guidance was developed within the Efficacy Working Group of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. The Q&As in this document have been endorsed by the ICH Steering Committee at *Step 4* of the ICH process, July 2010. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan, and the United States.

II. QUESTIONS AND ANSWERS

Q1: Why do we need an adequate representation of geriatric patients in the clinical database?

A1: Geriatric patients can respond differently from younger patients to drug therapy in a number of ways, and such differences can be greater in patients 75 years and older:

(a) The geriatric population has age-related physiological changes that can affect the pharmacokinetics of the drug and the pharmacodynamic response to the drug, both of which can influence the drug-response and the dose response relationship.

(b) Geriatric patients are more prone to adverse effects since they often have co-morbidities and are taking concomitant therapies that could interact with the investigational drug. The adverse effects can be more severe, or less tolerated, and have more serious consequences than in the nongeriatric population.

With the increasing size of the geriatric population (including patients 75 and older) and in view of the recent advances in pharmacokinetics and pharmacodynamics since the ICH E7 guidance was established in 1993, the importance of geriatric data (from the entire spectrum of the geriatric patient population) in a drug evaluation program has increased.

Not all potential differences in pharmacokinetics, pharmacodynamics, disease-drug interactions, drug-drug interactions, and clinical response that can occur in the geriatric population can be predicted from nongeriatric populations, as the geriatric patients are far more likely to have multiple illnesses and to be receiving multiple drugs. Therefore, to assess the benefit/risk balance of a drug that will be used in the geriatric population, these patients should be appropriately represented in clinical trials.

Q2: What should be taken into account when estimating an adequate representation of geriatric patients to be included in the clinical database?

A2: It is very important to ensure, to the extent possible, that the population included in the clinical development program is representative of the target patient population. As stated in the current ICH E7 guidance, estimates of the prevalence of the disease to be treated by age or examination of the age distribution of usage for other drugs of the same class or for the same indication should be provided by the applicant. This will indicate the expected use of the drug and should influence the number of geriatric patients to be included in the marketing application.

The current guidance states, “for drugs used in diseases not unique to, but present in, the elderly, a minimum of 100 patients would usually allow detection of clinically important differences.” Given the increasing prevalence and the growing recognition of the

complexity of the geriatric population, including concomitant therapies and co-morbidities, it would usually be appropriate to include more than 100 geriatric patients in the phase 2 and 3 databases and include patients over the entire spectrum of the geriatric patient population.

In the marketing application, depending on the numbers of patients, data should be presented for various age groups (for example <65, 65-74, 75-84, and ≥ 85) to assess the consistency of the treatment effect and safety profile in these patients with the nongeriatric patient population.

As single trials may not have sufficient numbers of geriatric patients to allow such analyses, these will often need to be carried out on pooled data. Any such analyses will need to consider consistency across studies.

Q3: Are there any special patient populations or characteristics that are particularly important to address in the planning of the clinical development program?

A3: Geriatric patients often have co-morbidities and concomitant therapies that could interact with the investigational drug and make patients more likely to have undesirable effects and interactions. Therefore, it is important to assess the safety and efficacy of a drug in such patients and to design a study with inclusion/exclusion criteria that allow their participation. There may exist a reluctance to include vulnerable geriatric patients at high risk of adverse outcomes (so-called "frail" geriatric patients). However, care in randomization should allow the appropriate attribution of findings either to the investigational drug or to other factors.

This applies both to drugs intended for the geriatric patient population and for drugs used in diseases present in, but not unique to, the geriatric population.

Q4: What should be considered for the clinical development program to adequately characterize the safety and efficacy of a drug for a marketing application?

A4: An appropriate representation of the geriatric population (including patients with concomitant therapies and co-morbidities) should be enrolled in the clinical development program to adequately characterize efficacy and safety in the geriatric population and allow for comparisons with the nongeriatric population. This information would ordinarily be expected in a marketing application.

In general, it is preferable to include both nongeriatric and geriatric patients in the same study(ies), which can facilitate observation of age-related differences. In some cases, a separate study in the geriatric population can be preferable.

Every effort should be made to include geriatric patients using concomitant therapies and with co-morbidities in the premarketing clinical development program. In some

cases, enrollment of these patients can be challenging and it could be appropriate to collect data postmarketing. However, the adequacy of, and the need for, data in these patients should be considered during drug development and discussed in the marketing application submission. Where enrollment of geriatric patients has been insufficient despite the efforts of the applicant, a specific plan to collect data postmarketing should be discussed during development and presented in the marketing application.

Information relevant to the geriatric patient population, including any limitations, should be reflected in the product labeling.

Q5: Are there concerns related to the data specific to the geriatric population that could be considered in the planning of the clinical studies?

A5: Depending on the mechanism of action of the drug and/or the characteristics of the disease, certain specific adverse events and age-related efficacy endpoints should be actively sought in the geriatric population, e.g., effects on cognitive function, balance and falls, urinary incontinence or retention, weight loss, and sarcopenia. This may require specific testing, e.g., for cognitive function. Applicants should also refer to disease specific guidances for specific recommendations concerning the evaluation of both efficacy and safety in geriatric patients.

Q6: In light of recent advances in the field of pharmacokinetics and assessment of drug-drug interactions since the ICH E7 guidance was established, what studies should be considered when developing a drug that will be used in geriatric patients?

A6: The pharmacokinetics in geriatric patients (over the entire spectrum of the geriatric patient population) should be evaluated to identify age-related differences that are not explained by other factors such as reduced renal function or weight differences. The potential influence of impaired renal/hepatic function, as well as potential drug interactions, is often assessed in studies with nongeriatric subjects.

Population pharmacokinetic analysis could provide the requested data if a sufficient number of patients in different age ranges (including patients $\geq$65 and $\geq$75 years) are included in the clinical trials. The applicability of population pharmacokinetics is dependent on several factors, e.g. the representation of the target population, the pharmacokinetics of the drug, dosing regimens, and analytical requirements.

A specific pharmacokinetic study comparing nongeriatric and geriatric subjects in the same study (matched for relevant covariates, e.g., weight, sex) could achieve the same goals.

More details on the pharmacokinetic approach (population pharmacokinetics, the appropriate design of a specific pharmacokinetic study) and assessment of drug-drug interactions can be discussed with the regulatory agencies.