Final Concept Paper
E7(R1): Studies in Support of Special Populations: Geriatrics
(Revision of the ICH E7 Guideline)
23 October 2008
Endorsed by the Steering Committee on 24 September 2008*

Type of Harmonisation Action Proposed

Establishment of Implementation Working Group to create new questions and answers (Q&A document).

Statement of the Perceived Problem

The increasing prevalence in the general population of elderly and very elderly persons generates important therapeutic needs that are characteristic of these age *strata* and that in turn require optimal characterisation of safety and efficacy of medicines in the geriatric population. For example, elderly patients, especially the very elderly, may differ from younger patients in their response to drugs for a variety of reasons including a greater likelihood of concomitant illnesses and multiple concomitant therapies.

The essential elements for inclusion of elderly patients in clinical studies are outlined in the current ICH E7 guidance document. ICH E7 notes that for drugs with significant use in the elderly, the inclusion in clinical trials of a minimum of 100 patients aged 65 years or older "*would usually allow detection of clinically important differences*" in drug responses compared with younger patients.

However, with the increasing prevalence of elderly and very elderly in the society and in view of the recent advances in clinical science and clinical trials experience build over the last 15 years, this number may no longer be adequate. More systematic acquisition of controlled data and data from additional activities conducted after the initial product approval may be needed to better address the benefit/risk balance in this special population.

Therefore requirements of clinical database in terms of design/methodology should be better specified.

A positive impact on public health associated with an earlier and optimised access of elderly patients to relevant innovative drugs is anticipated.

Issues to be Resolved

Therefore, several additional issues should be taken into consideration by the guidance:

- ***Elderly patients representation in clinical development***

  Study design and methodology and the size of clinical database should be adequate in order to properly characterise the benefits and risks in this special population.

- ***Age cut-offs***

  ICH E7: Special Populations: Geriatrics defines its scope as patients aged 65 years (standard retirement age) or older. Although this inclusive definition of the elderly

* Endorsed by the Steering Committee on 24 September 2008, subject to amendments which have been included in this version dated 23 October 2008.

population may be appropriate, specific age-classes such as “very elderly” should be taken into account.

- ***Requirement for specific safety data***

Adequate characterisation of the safety profile in the geriatric population is necessary and should include sufficient data from prospective studies.

- ***Endpoints***

Age-specific efficacy endpoints may be appropriate for diseases prevalent in the elderly. The quality of life and maintenance of functional abilities are often the major concerns of patients, their families and their physicians, rather than solely prolongation of life.

The use of adapted/specific endpoints should be considered when measuring the clinical benefits in this special population.

- ***Heterogeneity***

Very elderly patients represent a heterogeneous population. Concomitant illnesses and treatments make extrapolation from a given sample less accurate. On the other hand, the inclusion of only otherwise healthy elderly subjects may yield results of limited applicability to the more heterogeneous population.

- ***Access to clinical trials***

Cultural, economic and logistics barriers can limit the participation of elderly and very elderly patients in controlled clinical trials. Some of these barriers may be overcome and feasibility of elderly participation should be considered when designing clinical development of new medicinal products.

This point is however outside the scope of the ICH E7.

- ***Frailty***

Frailty has a complex pathophysiology, and the concept of frailty is still evolving in the scientific field. Although chronic conditions, co-morbidity and physical dependency contribute to frailty, they do not encompass or define “frailty.” To date, there is no agreed operational definition for the subgroup of frail patients within the elderly population. The subgroup of frail elderly patients should be acknowledged in the guidance but it seems unfeasible to set specific requirements for frail patients in the frame of a general development program. However, a reliable estimation of their number included in clinical trials would be useful. A consensus will be sought within the international scientific community for both the definition of ‘frailty’ and for representation in clinical trials of this subgroup.

- ***Specific indications***

Extended life expectancy is associated with age related conditions that may represent a more substantial therapeutic need than in other age classes: e.g. urinary incontinence, chronic malnutrition, sarcopenia, balance and falls, etc.; or may assume specific features in the elderly, such as depression, anxiety, apathy, insomnia, behavioural abnormalities, etc.

- ***Population pharmacokinetics***

Currently population pharmacokinetics appear as the most adequate and informative tool to be used across the heterogeneous population of elderly patients. Even if specific

pharmacokinetic studies are needed, this aspect should be conveniently addressed during phase III studies.

- ***Adapted formulations and dosages***

Both the physiological changes of ageing and the presence of concomitant illnesses in the elderly lead to variable pharmacokinetic and pharmacodynamic responses to substances. Poly-medication, disability, dependence on carers and social isolation may affect compliance. It may be useful to assess problems with pill ingestion and compliance.

In this respect the development of galenical formulations that facilitate the dose adjustment and enable both the patients and the carers to reduce the risk of medication errors and to improve compliance could also be considered.

Although ICH E7 covers most of the previous issues in general terms, the following three recommendations should be specified to Applicants:

A. To discuss the number and age distribution of expected elderly participants in a given indication development and the criteria on which these figures are based. *Priority 1*

- Age distribution should generally reflect that of the target disease (e.g. in Parkinson's disease meaningful *strata* over 75 and over 85 years should be enrolled).
- Efforts to include the "very elderly" should be specifically addressed. For issues regarding gender in clinical trials (e.g. possible gender imbalance secondary to late onset of cardiovascular diseases in women, and osteoporosis in men) see Gender Considerations in the Conduct of Clinical Trails)

B. To plan a development approach that will ensure exposure of a sufficient number of elderly and very elderly patients, with appropriate testing to adequately characterise the safety in that population. This information would ordinarily be expected in a marketing application, but whether in some circumstances it could be obtained post-marketing should be discussed. *Priority 1*

C. To describe specific elements in clinical studies that will be evaluated in the assessment of the risks and benefits of the drug in the elderly, including in the context of common co-morbidities and concomitant therapies.

In the discussion of above points, the following two points may be included or discussed, if necessary:

d. To discuss and justify the opportunity for specific endpoints in the elderly population (elderly-relevant outcomes to be pre-defined and assessed in the planned subsets);

e. In relation to the specific pharmacokinetic considerations, defining the usefulness of specific pharmacokinetic studies versus population pharmacokinetics.

Some of these points could be addressed post-authorisation in the frame of risk management plans, to be considered on a case by case basis, because the fulfilment of all these recommendations may lead to multiple, long and expensive studies that may not all be feasible before authorisation.

In any case the actual content of clinical database will be reflected in the Summary of Product Characteristics.

Background to the Proposal

In December 2006 following the request of a scientific opinion by the European Commission, the European Medicines Agency (EMEA) reviewed the body of existing European guidance documents and a sample of recent European Marketing Authorisations (1)

A reasonable fulfilment of ICH E7 requirements of representation of the elderly patients in clinical trials was found. All reviewed dossiers included more than 100 patients aged over 65 in the clinical development. However further analysis would be needed to see whether sufficient patients in the higher age range were included. When the proportion of patients over 65 was rather low, either specific studies (pharmacokinetic studies) or independent analysis for dose-response, safety and efficacy were performed for this age group. If not, an acknowledgement was included in the Summary of Product Characteristics or the Marketing Application Holder was required to provide further data in the Periodic Safety Update Reports.

However, when taking into account the current demographic data and trends, this approach should be further developed.

In general terms, the number of elderly patients in the clinical development programmes and the requirements for data in geriatric population needs to be based on the therapeutic indication. For instance, schizophrenia *per se* is not typically a disorder of the elderly. On the other hand, macular degeneration is common in the elderly whereas Parkinson's disease spreads across the end of adulthood and elderhood. This was reflected in the development programmes of the various approved medicinal products in Europe and is also discussed in the relevant efficacy guidelines. One area to be discussed more in depth is the extent to which existing efficacy and/or safety data may be extrapolated from the younger age group to the older one and whether specific safety concerns apply to elderly patients.

At the same time of the European Commission request, the EMEA has started a consultation phase with learned societies and other interested parties on the representation of the elderly population in clinical developments of new medical products.

Type of Expert Working Group

The IWG should include representatives from the six ICH Parties, plus ICH Observers and WSMI. The IWG will provide preparatory work *via* regular teleconferences. Q&A draft documents will be subsequently discussed during two face-to-face meetings.

Discussion of the draft will require a time frame of approximately 1 year.

References

1) EMEA/498920/2006 COMMITTEE FOR HUMAN MEDICINAL PRODUCTS (CHMP) Adequacy of Guidance on the Elderly Regarding Medicinal Products for human use. London. 14 December 2006