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Ensuring safe and effective medicines for an ageing population: Workshop Proceedings

22-23 March 2012: European Medicines Agency, 7 Westferry Circus, Canary Wharf, London, UK

Executive Summary

Ensuring that medicines for use in the geriatric population are safe and effective remains one of the major challenges facing public health. Older people constitute the fastest growing segment of the population, and despite being the main users of medicines in clinical practice, they are very often underrepresented in clinical trials. In addition, older patients often present co-morbidities, are polymedicated and potentially more susceptible to adverse drug reactions, may result in a knowledge gap about the benefits and risks of medicines in this population. It is therefore essential to ensure that the needs of older patients are taken into account when developing, testing and evaluating medicines in this patient group.

Several European lead initiatives have started to address these challenges. The European Medicines Agency (EMA), acting within the remit of its mandate, has developed a Geriatric Medicines Strategy (adopted in February 2011), which aims to ensure that geriatric medicines are of high quality and appropriately tested in the elderly (evidence based medicine), as well as to help improving the availability of information on geriatric medicines (informed prescription). In the same context, the Steering Group of the European Innovation Partnership (EIP) on Active and Healthy Ageing issued a Strategic Implementation plan addressing the challenge of innovation for active and healthy ageing. This implementation plan is currently moved forward by the European Commission working closely with national governments and a wide range of stakeholders.

The EMA organised a two-day workshop focused on safe and effective medicines for an ageing population. The workshop took place on 22nd and 23rd March 2012 and brought together different stakeholders, including EU public bodies, regulators, academic researchers, patient and healthcare professional representatives as well as representatives from the pharmaceutical industry.

The workshop's objectives were: to discuss the EMA's Geriatric Medicines Strategy and related activities; to identify gaps in the strategy and the priorities for action in the area; to highlight synergy

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areas between stakeholders, as well as to obtain feed-back from stakeholders on the actions undertaken by and expected from EMA and its committees.

The workshop was divided into five sessions covering a wide range of areas, including proposals from different stakeholders to improve the development, formulation, evaluation, prescribing, provision of information and post-licensing monitoring of medicines for older patients.

The workshop presented the EC initiative on aging (EIP on Active and Healthy Ageing) which includes high priority achievable actions to improve adherence, prevent falls and address frailty. The EMA's Geriatric Medicines Strategy encompasses four key areas of work which are in line with the Agency's role in the evaluation and supervision of medicines for the benefit of public health (such as provision of scientific advice, development of guidance, etc.). In line with EMA's priority to maintain a dialogue with patients' organisations, the views of AGE Platform provided a valuable perspective on older patients' needs and expectations. Industry's views, reflected in the EFPIA survey, provided a useful insight into important issues (trial design, endpoints, definition of frailty) which are pending in the field of geriatric medicines. The EMA acknowledged the need to fine-tune the regulatory process in order to avoid unnecessary burden for companies which may delay the development of medicines for younger patients, without compromising on the quality, safety and efficacy of geriatric medicines. Stakeholders expressed their satisfaction and intention to work towards providing innovative solutions to address current challenges.

It was noted that, since older people often constitute the main users of medicines and in this optic cannot be deemed a special population, all these activities can be conducted within the existing legislative framework, however current guidelines should be revised to include specific recommendations where needed (e.g. for frail and very elderly patients). Methodology of clinical trials needs to be adapted, and initiatives such as the use of PK modelling and simulation, and subgroup analysis, should be considered. A definition of frailty as well as adequate ways for measuring it were a recognised need. In addition, specific strategies to improve patients' participation at the level of ethics committees, recruitment process and trial conduct were presented. These include patient-public involvement, the use of existing networks, and the improvement of competencies and expertise within ethics committees.

In terms of pharmacovigilance, the new legislation offers an opportunity to strengthen the system for monitoring the safety and benefit-risk balance of medicines which will also benefit older patients by improving risk management though targeted post-authorisation studies, by optimising data collection and by using information from spontaneous ADR reports to fill existing knowledge gaps.

The workshop highlighted that inappropriate formulations for older people result in poor adherence to treatment. In this area, there is no 'one-fit-all' solution, and a number of factors need to be taken into consideration by healthcare professionals and regulators, looking at the patient as a whole. Apart from formulation issues, a wide variety of therapy- or condition-related factors that can affect adherence also need to be addressed.

It was acknowledged that, in order to improve informed prescription and adherence, healthcare professionals and patients need to be provided with relevant information on geriatric medicines. Finally, the workshop highlighted the need for cooperation at an international level amongst the different stakeholders to improve medicines for elderly people.

The video recording of the workshop and the presentations are available on the EMA website.

Proceedings

22nd March 2012

Opening Remarks

Presenters: Francesca Cerreta (EMA), Guido Rasi (EMA Executive Director), Dagmar Roth-Behrendt (European Parliament)

Francesca Cerreta, organiser of the workshop, welcomed the participants.

Guido Rasi, Executive Director of the EMA, expressed his satisfaction over the workshop, an event which focuses on a priority area for the Agency. The elderly constitute in many cases the main users of medicines. Focusing on the ageing population offers a tremendous opportunity to fine-tune many regulatory activities and to address existing challenges such as the inclusion of elderly patients in clinical trials, co-morbidities and drug interactions in older people. Whereas patients with co-morbidities and concomitant medications are currently underrepresented in clinical trials drug-drug interactions may not easily be assessed in clinical trials and can also be explored through post-marketing surveillance. Here, the new pharmacovigilance legislation offers a unique opportunity to improve our knowledge. Guido Rasi identified one issue as key requiring mutual support from all stakeholders: the need to continuously adjust the therapeutic approach in the elderly due to their complex needs. Guido Rasi illustrated such complexity with a finding from the Geriatric Working Group at the Italian Medicines Agency (AIFA), as often elderly patients take medicines to treat adverse events caused by other medicines, not due to a preexisting pathology. Guido Rasi concluded by encouraging the participants to work together in order to improve geriatric medicines.

Dagmar Roth-Behrendt, member of the European Parliament, despite praising the pharmaceutical regulatory policy and the work of the EMA, admitted that the area of geriatric medicines had been neglected and requires attention. Nonetheless, Dagmar Roth-Behrendt valued current efforts to address this gap, reflected in the Agency's 'Roadmap to 2015', particularly in light of the declaration by the European Parliament of 2012, the 'European Year of Active Ageing and Solidarity between Generations'. Finally, Dagmar Roth-Behrendt noted the responsibility of all stakeholders in past shortcomings in this area and urged them to take cooperative action to try to achieve deliverable outcomes.

Session 1: Healthy Aging and Medicines

This session aimed at providing an integrated overview on the challenges posed by an ageing population and the views of the main stakeholders on the way forward.

European Innovation Partnership on Active and Healthy Ageing

Presenter: Maria Iglesia-Gomez (European Commission)

Maria Iglesia-Gomez, Head of Unit Innovation for Health and Consumers at DG SANCO European Commission (EC), explained how the European Innovation Partnership (EIP) on Active and Healthy Ageing, launched by the EC, aims to address the challenges of an ageing population.

The partnership was created to foster innovation to meet the challenges of an ageing population, in order to provide solutions for the needs of the elderly. This follows major demographic changes since the 1950s, with estimates for 2050 predicting important implications for society in terms of an increased dependency rate and healthcare costs, as well as a shrinking workforce and shortage of carers. While older people currently regarded as a burden with numerous challenges, and care is mostly passive (based on curing diseases), the Commission nonetheless views these challenges as an

opportunity to promote active ageing and to introduce a new model of pro-active, integrated care largely based on prevention and on improving functionality.

The EIP proposes a novel approach to working based on a strong collaboration among its multiple stakeholders, from both the public and private sector. The EIP's objective is to increase the lifespan of EU citizens by an average of two healthy life years by 2020. This is expected to result in several advantages for Europe: first, it will improve the health and quality of life of European citizens, including the older ones; second, it will support the long-term sustainability and efficiency of the health and social systems in Europe; finally, it will foster the growth and expansion of the European industry. As an added value, the EIP will allow a better use of resources by, for example, joining up expertise, bridging knowledge gaps and speeding up innovation.

The Strategic Implementation Plan of the EIP involves the use of current financial instruments (such as the Seventh Framework Programme, Structural Funds, etc.) in a more optimized way in the following three priority areas: 1) preventive measures, screening and early diagnosis; 2) care and cure; 3) active ageing and independent living. All three pillars will be developed under a common framework, ensuring the same standards, effective funding and regulatory conditions in order to allow the implementation of six specific actions: 1) programmes on prescription and adherence to treatment at regional level; 2) fall prevention programmes in order to identify risk factors and reduce falls in older people; 3) programme on prevention of functional decline and frailty; 4) programmes on integrated care for chronic diseases; 5) the creation of a platform of age-friendly cities/regions; 6) standardization and creation of guidelines and protocols in different industries around Europe on the topic.

In order to launch these actions, it is essential that partners and stakeholders work together and Maria Iglesia-Gomez referred to different modalities of engagement: 'Commitment': whereby all stakeholders are invited to submit proposals for specific actions; 'Reference Site': by which public healthcare sector stakeholders express their intent to become a candidate for an existing and successfully integrated example of active and healthy ageing; and 'Marketplace': an interactive online platform for networking and discussion. Finally, Maria Iglesia-Gomez noted that the Steering Group, Action Groups and the Conference of Partners will be involved in the governance to achieve an effective implementation of the plan, while the Commission will ensure monitoring and will report on the progress of the Plan's implementation to the European Parliament and the Council.

The EMA Geriatric Medicines Strategy

Presenter: Francesca Cerreta (EMA)

Francesca Cerreta, from the EMA, presented the Agency's Geriatric Medicines Strategy and highlighted the Agency's commitment to work with all stakeholders to improve medicines for older people.

The strategy aims to ensure that the needs of older people are considered when developing and evaluating medicines for their use. The need for such a strategy on geriatric medicines is supported by the fact that older people are the fastest growing population segment, major users of medicines and very often more susceptible to adverse events, while often underrepresented in clinical trials, particularly elderly above 85 years of age.

The Geriatric Strategy is based on two principles: 1) the need to ensure that geriatric medicines are of high quality, safe and effective for use in the older people and 2) the need to improve the availability of information on the use of geriatric medicines, for both patients and healthcare professionals. To achieve this, no new tools are needed but rather a better use of the existing ones is proposed. Industry is encouraged to enter into dialogue with regulators and follow existing guidelines (ICH E7), which include recommendations to appropriately study medicines in the very elderly, as well as to consider

co-morbidities and age-specific endpoints. On the other hand, regulators should better coordinate activities and improve the communication with the patient and the prescriber. Important aspects to be considered when analysing the benefit/risk balance in the elderly include: the types of studies; adherence to existing guidelines; inclusion in the dossier of relevant information on the older population; additional information useful for stakeholders (patients, prescribers and HTA bodies), as well as areas for improvement of the evaluation process.

Francesca Cerreta highlighted the work of the Agency in optimising and focusing existing regulatory tools in four key areas. First, to identify gaps in regulatory and scientific knowledge, the Agency is taking appropriate measures such as seeking input from the CHMP and PhVWP, provision of scientific advice as well as the organisation of this workshop. Second, to provide advice to the CHMP on specific issues on the elderly, the EMA is fostering and using a pool of relevant experts, e.g. establishment of the Geriatric Expert Group. Third, to ensure that the development and evaluation of new medicines for the elderly follows current guidelines, particularly ICH E7, the EMA provides scientific advice, comments on peer review of applications, revises product information to ensure adequate reflection of geriatric aspects, update of assessment report templates to focus assessors' attention on geriatric data, etc. Finally, to monitor specific pharmacovigilance issues in the elderly population, the Agency is looking at the results from the Pharmacovigilance Survey, which mentioned: lists of preferred medicines for the elderly based on safety, efficacy and cost criteria; the need for adaptations of packaging and formulations; clarity of the product information and putting in place measures to facilitate reporting of adverse reactions.

The Patients' Perspective of Ageing

Presenter: Barbro Westerholm (AGE Platform)

Barbro Westerholm, from the AGE Platform, presented an overview of the challenges and expectations of elderly patients on the issue of ageing and healthcare.

Barbro Westerholm noted that the average life expectancy has increased by 25 years in the last century and continues to increase. She also highlighted that the increasingly larger population of older people comprises a very variable group of individuals ranging from those who are healthy and fit, to those who are very ill. She stressed that it is essential for older people not to be discriminated, against especially for issues such as access to high quality care and services (such as palliative care) and not to perceive medical interventions as an assault. Geriatric healthcare often initially involves reconstructive medicine (hips, lenses) whereas at later stages patients' needs become more complex due to the frailty, often because of dementia, and co-morbidities. A proposal was made to help reduce the burden of disease by promoting health, rehabilitation and the rational use of medicines. Furthermore, Barbro Westerholm gave an overview on medication problems commonly encountered in elderly patients, based on data from the Swedish Prescription Survey 2010. They include symptomatic treatment without a proper diagnosis, polypharmacy, with more than 12% of elderly over 80 years in Sweden taking 10 or more medicines, and the contraindication of many medicines in a large percentage of this age group (over 10%). Finally, she highlighted the expectations of elderly patients such as access to healthcare personnel specialised in geriatrics and gerontology, having one physician responsible for the coordination of treatment, as well as receiving adequate information on the medications prescribed including alternative treatments such as their side effects, interactions and whether the medicines prescribed have been tested in elderly patients.

The Industry's Views on Geriatric Medicines

Presenter: Susanna Del Signore (Sanofi, EFPIA)

Susanna del Signore, Head of Global Regulatory Policy at Sanofi, and speaking on behalf of EFPIA, gave an overview of industry's orientations on geriatric medicines based on the results of a survey conducted among member companies.

On behalf of EFPIA, Susanna del Signore welcomed several initiatives initiated by the EC in the field of geriatric medicines (revision of ICH E7 guideline and Q&A, EIP on Active and Healthy Ageing and the EMA's Geriatric Medicines Strategy) and expressed EFPIA's intention to positively contribute to the debate on geriatric medicines with all stakeholders. In line with this, the EFPIA has launched a survey across members, specifically focusing on issues highlighted by the EMA's Geriatric Medicines Strategy, namely demonstration of safety and efficacy of medicines in the older population, pharmacovigilance measures, adherence and formulation and product information. While the preliminary analysis of the survey shows a positive trend in the numbers of older patients included in clinical trials in the last three years, further improvement is needed in patients above 75.

Susanna del Signore discussed the heterogeneity of the geriatric population and the implications for clinical trials. While the inclusion of older patients without significant co-morbidities would allow an understanding of the influence of normal ageing on the medicines' safety and efficacy profile (general indications), the inclusion of older patients with major co-morbidities or functional decline would be more appropriate in geriatric-specific indications like Alzheimer's disease or sarcopenia. In addition, in conditions that are associated with specific features in older patients (e.g. depression and other psychiatric conditions), *ad hoc* studies are more adequate. In general terms, unless the study is well focused, the inclusion of a geriatric group may increase the variability of endpoints, which would in turn create the need for larger and more complex studies that might delay development of new medicines.

The EFPIA survey also revealed that while guidance provided by ICH E7 Q&A is in general considered sufficient, specific guidance may be needed, for example, in case of patients above 75 years, with co-morbidities, loss of function or geriatric syndromes. Furthermore, engagement with the EMA through formal Scientific Advice seems the best way to address the specific needs of geriatric patients. Finally, Susanna del Signore expressed industry's commitment to engage in a collaborative discussion among all stakeholders to better address the unmet needs of geriatric patients.

Session 2 – Demonstrating Safety and Efficacy in the Older Population

This session aimed at discussing study requirements, design and appropriate endpoints to demonstrate safety and efficacy of medicines in older patients.

The BASE Berlin Study

Presenter: Elisabeth Steinhagen-Thiessen (EGZB)

Elisabeth Steinhagen-Thiessen, from the Evangelisches Geriatriezentrum Berlin, gave an overview of the design of the ongoing BASE Berlin study II, which analyses the health changes and ageing in young and older people.

Launched in June 2009 in Germany, the BASE Berlin II is a long-term study including 2,200 people (half of them aged 20-30 years and the other half people above 60 years). This study follows the completion in 2011 of the BASE Berlin I study which had started in the 1990s and analysed the health status of a population of 516 very old people (70-104 years).

The BASE Berlin II study aims to: 1) determine the health status of young and old people; 2) to understand the differences between both age groups; 3) to analyse the relationship of different socioeconomic parameters with physical and mental health; and 4) to compare the findings of the BASE I and BASE II study. These studies are expected to help predict age associated disease and syndromes, the consequences for potential interventions, as well as the influence of genetic parameters, biomarkers and risk factors of aging.

The study looks at a wide range of parameters including medical history, memory and cognitive abilities, socioeconomic status, genetic analysis, immune parameters, sport and leisure, diet, use of medications, quality of life and state of health. It also involves thorough medical examinations with a focus on cardiovascular and pulmonary function, hearing and vision, motor function, nutrition, metabolism etc. Elisabeth Steinhagen-Thiessen provided several examples of tests used to define musculoskeletal function and neurodegenerative disorders, such as DEXA (to measure muscle mass and bone density), electronic tapping and grooved pegbord test (to measure fine motor function) and the HU-motion belt test. Elisabeth Steinhagen-Thiessen highlighted frailty as an important topic in geriatric medicine, which should be considered as a syndrome with many contributing factors such as muscle mass, bone mass, vision, cognition, mobility, disease and neurological status, nutrition medication. She further noted that the Berlin II study, further analyses the correlation of these phenotypic factors with the genotype through a multidisciplinary approach that also takes into account socioeconomical and psychological factors. Finally, the BASE II study is also looking at sarcopenia and first results will become available in the near future.

2.1 – Pre-authorisation

ICH E7 Requirements and How They Are Translated In Practice

Presenter: Kristina Dunder (MPA, Sweden)

Kristina Dunder of the MPA, Sweden, gave an overview on the requirements and application of the overarching guideline ICH E7 and Q&A.

The ICH E7 guideline (Studies in support of special populations: Geriatrics) was adopted in 1994 by the International Conference on Harmonisation. Since then, considering an increasingly larger geriatric population (including patients over 75 years) and the recent advances in pharmacokinetics and pharmacodynamics (PK/PD), the importance of including geriatric data for the evaluation of medicines has increased. Therefore, an addendum Q&A document to update the recommendations of ICH E7 was adopted in 2010.

Kristina Dunder presented practical applications of the main issues addressed in the Q&A. First, given that the process of ageing causes physiological changes that can affect the PK/PD and older people are more prone to adverse events, the Q&A reflects the need to adequately represent the elderly in clinical trials. Although safety and efficacy for healthy elderly people is often extrapolated from PK studies included in the dossier, further clinical data are needed to confirm the PK results. Finally, for elderly with co-morbidities and concomitant medications, stand-alone data are required given that extrapolation may not be appropriate.

Second, when deciding on the number of geriatric patients to be studied, the initial ICH E7 guidance recommended to include at least 100 patients. However, the critical issue is to ensure that the population included is representative of the target population and that the entire age spectrum is reflected. It is therefore important to include patients over 75 years. Besides, it was also highlighted that the number of patients recruited need to be representative to demonstrate a benefit/risk in this population. The development plan will depend on the drug profile, and this should be discussed at scientific advice stage.

The Q&A mentions that every effort should be made to include patients with co-morbidities and comedications, and 'frail' patients, in trials in the pre-authorisation setting. However, in practical terms, in some cases the inclusion of these patients in pre-authorisation trials represents a challenge. In those cases, frail patients could be included in post-authorisation studies, but this would have to be specifically discussed in the clinical development plan of the initial MAA. The data on patients above 75 years should be clearly reflected in the product information.

While the Q&A states the need to address specific adverse effects occurring in the geriatric population and to include age-specific efficacy endpoints, in practice, this depends on the characteristics of the disease and mechanism of action of the medicine. It would be appropriate to seek guidance regarding relevant endpoints, as well as to strengthen disease specific guidelines on the expected requirements.

Finally, regarding drug-drug interactions and PK studies, while population PK studies could be used provided they include sufficient patients in the different age groups, specific PK studies comparing older and younger patients could also be performed. In practice the very elderly (over 75 years old) must be included in either type of study. In addition, other relevant PK guidelines apply as well.

Elderly Patients and Clinical Trials – EMA Notes for Guidance

Presenter: Bertil Jonssson (Vice Chair of the Scientific Advice Working Party, EMA)

Bertil Jonsson, Vice-Chair of EMA's Scientific Advice Working Party, gave an overview on the guidance available regarding clinical trials in the elderly and discussed some measures to reduce the risk of including elderly patients in trials.

Using an example, Bertil Jonsson illustrated a selection bias for the inclusion of elderly patients in trials; this is not always due the protocol design but to the physician acting as gatekeeper. A study in oncology patients carried out 15 years ago in Sweden showed the median age of patients enrolled in the trial was 10 years lower than the age of the population for which the medicine was intended.

Regarding the guidelines, it was mentioned that the 'Note for guidance on clinical investigation of medicinal products in the treatment of cardiac failure' (CPMP/EWP/235/95, Rev 1) does not include recommendations for the geriatric population, and the 'Guideline on the evaluation of anticancer medicinal products in man' (CPMP/EWP/205/95/Rev.3/Corr.2) includes very little guidance with regards to clinical development in the elderly. It does however mention that alternative endpoints can be used, however offers no further guidance on this issue. There is therefore a need to improve recommendations on this population.

Bertil Jonsson presented some statistics on the enrolment of elderly in oncology trials in the USA, which shows a reasonable involvement of old patients in trials for some types of cancers (e.g. trials for breast cancer using less aggressive agents), but this does not hold true for other types of cancer.

While Bertil Jonsson acknowledged the physician's decision to avoid including elderly in trials, in order to protect this vulnerable patient population and to reduce variability in the studies, he discussed some measures that could be followed in pre-registration trials. The main proposal focuses on the reduction of the risks for elderly and frail patients, which could be achieved by a stratified enrolment: an initial trial in the primary safety/efficacy population and then a second trial in the secondary safety/efficacy population with the patients initially excluded but who are normally treated in clinical practice. A lower starting dose with dose escalation could be used in this latter population as a strategy for risk reduction. Also, careful analysis of the results might reduce the risk of endangering the development in other age ranges.

Can PK and Modelling Help?

Presenter: Terry Shepard (MHRA, United Kingdom)

Terry Shepard, of the MHRA, presented an overview on how PK and modelling can contribute to the development of geriatric medicines.

She reminded that ageing is associated with changes in PK/PD parameters, an increase in prevalence of chronic conditions, polypharmacy as well as a higher incidence of adverse drug reactions, while older people are often underrepresented in clinical trials.

The effects the ageing process has on the PK parameters (absorption, distribution, metabolism, elimination) of a medicine can be predicted if the physicochemical properties of the medicine are well understood. Regarding renal elimination, it was mentioned that in the elderly changes in renal function occur frequently due to the effect of life-long oxidative stress on tubular function. As a consequence, a typical manifestation is an average decrease in the Glomerular Filtration Rate (GFR) by 0,75 ml/min after the age of 40, which can impact on metabolic clearance as well as on plasma and tissue binding. However, it was stressed that the decrease in GFR with age does not occur in one third of the population. Moreover, serum creatinine in elderly people who are losing muscle mass is a poor indicator of renal function.

Terry Shepard further noted that although impact of age on PK is fairly predictable, its impact on PD is less predictable. A population of elderly people with the same chronological age is very heterogeneous. Therefore, in order to prescribe the correct dose and posology it is essential that the 'frail' elderly (those with co-morbidities, comedications, functional disabilities etc.) are adequately represented in clinical trials.

If the trial population is representative, informative covariates (those that truly reflect the impact of the ageing process) are needed, since chronological age is a poor covariate. Such informative covariates would be 'physiological age', co-morbidity, frailty, a renal function estimate appropriate for the elderly (not serum creatinine) etc.

If frail elderly are not represented, however, in the trial population, tools are needed that allow the extrapolation of data in the absence of specific markers. These tools need to consider several challenges, such as an increased risk of drug-drug interactions compared with young people, and the complexity of combinations of drugs to test. As an example, Terry Shepard used a model to predict the risk of a drug-drug interaction (DDI) between codeine (which is metabolised to active metabolites linked to respiratory depression), and a metabolic inhibitor of codeine. While, for a patient with normal renal function, concomitant treatment with codeine and the metabolic inhibitor would be rather safe, the model shows high risk of respiratory depression in patients with moderate/severe renal impairment. Terry Shepard proposed that this type of modelling could be applied to determine the risk of DDI during the development of geriatric medicines. This would involve using quantitative tools such as mass balance (which quantifies the contribution of the different routes of metabolisms and elimination), physiological-based PK models, drug clearance, etc.

Modeling and simulation to evaluate Drug PK/PD in the Elderly

Presenter: Eva Bredberg (Astrazeneca, EFPIA)

Eva Bredberg, Director of Global Clinical Pharmacology at Astrazeneca and speaking on behalf of EFPIA, gave an overview of how modelling and simulation (M&S) can help optimise drug development in the elderly.

Optimising the benefit/risk balance of a drug for a safe use in the elderly is a complex challenge, due to changes in PK (e.g. renal function) or PD (e.g. increased bleeding risks with anticoagulants due to

increased sensitivity), as well as the fact that dosing cannot be guided by age as there are other confounding factors. Age is rarely an independent source of variability but confounded by other factors and may not be a significant factor or the best factor to guide dose adjustment

Because the key data for establishing the benefit/risk balance in the geriatric population, obtained in Phase II/III trials, PK/PD population modelling and simulation can help to evaluate drug PK/PD in older patients. It was also noted that an adequate assessment of the exposure-response in older patients is needed. Regarding the value of modelling and simulation for *population PK*, it can allow to identify covariate effects and variability in PK parameters, to quantify age-related effects on exposure, as well as to integrate various covariate effects on PK and exposure. In *population PK/PD*, it can help identify covariates important for the variability in response, as well as quantify age-related effects on safety and efficacy. Modelling and simulation can help dosing recommendations for older people by identifying all individual factors rather than single factor (e.g. renal clearance and weight) or considering comedications:In highly heterogeneous older patients (with diverse or wide covariate distributions) an individualized therapy, especially when the therapeutic window of a compound is narrow, should be considered.

From the EFPIA survey, it was noted that population PK/PD M&S is becoming a crucial tool to optimise trial design and operation, data integration, knowledge generation and recommendations for clinical use (such as dosing recommendations) in a wide spectrum of patients, including the elderly. The survey encouraged regulators and developers to collaborate by fostering the use of M&S.

Eva Bredberg further illustrated two cases at AstraZeneca (drug X and ximelagatran) where PK/PD M&S was used to evaluate the exposure and response in the older patients and to guide potential dose adjustments. Finally, it was concluded, that population PK/PD M&S is a powerful tool to integrate data, quantify individual effect of factors on PK and/or PD endpoints, evaluate variability and uncertainty, and then guide clinical use of drugs in different patient groups, including older patients with different combinations of contributing factors. Temporal information during the study can strengthen the information available in this subpopulation

Clinical pharmacology study results can support the M&S and be helpful if it is difficult to recruit older patients, but the population PK/PD results in the older patient population will be more informative.

2.2 – Post-authorisation

How To Get Better Data On Medicines Post Licensing

Presenter: Thomas MacDonald (Ninewells Hospital & Medical School, University of Dundee, EnCePP)

Thomas MacDonald gave a presentation on the approach and tools available to improve post-marketing data.

While data on the outcomes of exposure to medicines are essential to establish the safety profile of medicines, Thomas MacDonald discussed the hurdles to obtain adequate post-marketing data. While drugs are mostly tested in middle aged patients during clinical trials, elderly with more severe diseases often constitute the main users, and in many cases they use concomitant medications.

While several IT systems and tools exist to record and collect patient data, (e.g. the GPRD, the ENCePP network and the FDA Sentinel Network), the main challenge is, however, the bureaucracy involved in obtaining consent to use patient data for post-marketing studies. An example was given of a pilot study where patients easily provided online feedback on side effects after vaccination. These types of initiatives could alleviate the bureaucracy and data could be validated afterwards in a local health practices. Another example of an initiative to obtain consent from people involves an online platform where healthy or patients can register to provide their consent.

Thomas MacDonald proposed to carry out prospective follow-up safety studies using large consented databases. However, the first hurdle is to get a newly marketed medicine prescribed in normal care to an extent that allows a post-marketing sensible analysis. Most European States have barriers in place that delay or prevent prescribing until 'cost-effectiveness' is demonstrated. This can prevent normal care use, which then prevents normal care cost-effectiveness studies.

Thomas MacDonald discussed streamlined (or simplified) clinical trials which seek to balance the utility of the experimental design with the simplicity of prospective observation by randomising subjects within the setting of a system that can provide electronic follow-up. Randomising the prescribing policies of practices to change existing patients from standard care to new medicine care has the utility of being less bureaucratic. We need to explore new ways to get better data and the practice formulary cluster randomised design was discussed as one possible route to achieving this. Thomas MacDonald also referred to a pilot project currently ongoing in Scotland, where instead of having a randomization of patients, the medical practice and the prescription are being randomized. This allows the authorities to obtain more and better data on specific treatments in an evidence-based, effectiveness setting. The need to have a more formal approach to benefit/risk, in order to allow healthcare professionals to really understand the balance of their patients' therapies, was also defended.

2.3 – Endpoints and their relevance to older people

Cancer and Palliative Care and Work of EORTC

Presenter: Ulrich Wedding (European Organisation for Research and Treatment of Cancer)

Ulrich Wedding, of the European Organisation for Research and Treatment of Cancer (EORTC), discussed the management of older cancer patients and presented suggestions on clinical trial development and methodology in this population.

It was noted that a specific discussion on the elderly and cancer is needed. While cancer is predominantly a disease of elderly people, with the median age at diagnosis being around 70 years of age, elderly patients with cancer are rarely included in clinical trials because cancer treatment is often associated with severe side effects and elderly cancer patients experience higher rates of toxicity. Also, due to other health related changes their overall treatment benefit might be different than in younger patients. Therefore, decision making in cancer care, specifically in the elderly, is a very complex process that needs to take into account patients' characteristics such as the type of cancer and the chosen therapy. The aggressiveness of the therapy needs to be balanced in order to ensure that it is not too toxic on the one side and that it does not compromise efficacy on the other side. In addition the aim of the treatment (curative e.g., prolong survival or a non-curative e.g. palliative care) always needs to be considered when prescribing for older cancer patients.

It was mentioned that in geriatrics there are several tools to describe patients' characteristics independently of advanced age (e.g. Geriatric Depression Scale for depression). This has been transferred to the oncology field as the comprehensive geriatric assessment (CGA). Since ageing is a very heterogeneous process, Geriatric Assessment (GA) describes an individual's health situation much better than chronological age and allows detecting changes missed during routine analysis, some of which can be of prognostic importance or lead to different treatment choices. However, until now there are no clinical trial data demonstrating that care based on CGA results improves patients' outcomes. The EORTC recommends the integration of a GA into clinical trials to have a better description of older cancer elderly patients. In addition, special trials should be offered for those elderly patients with limitations in CGA, who are at high risk of toxicity and less likely to benefit from treatment.

Ulrich Wedding further presented then the main challenges and bottleneck issues in clinical trials in the elderly, including the lack of collaboration with Geriatric Medicine, poor clinical trial methodology, the

lack of infrastructure, the inadequate regulatory framework and the lack of interest from industry in studying this population. Challenges in clinical trial design in oncology were discussed, mainly in terms of endpoints and trial design. It was mentioned that classic oncology endpoints (progression free survival, overall survival) are clearly inadequate on their own and that alternative endpoints (Overall Treatment Utility, Therapeutic Success, Health Related Quality of Life (HRQoL), Quality Adjusted survival and preservation of functional capacity/independence) may be important for trials in the elderly. In terms of trial design, different options and their implications were highlighted: treatment-regimen trials (treatment A versus treatment B) or strategic trials (treatment versus no treatment). Regarding whether it would be better to have specific trials for older patients or trials with no upper age limit, it was mentioned that the optimum scenario would be a combination of both with the inclusion prospective register trial including a geriatric assessment. Ulrich Wedding mentioned the EORTC proposals of 2009 in the field of geriatric clinical research in the elderly, which include: obligatory reporting of age related subgroup analysis including the number of patients, efficacy and toxicity data and, if possible and pooled age analysis; obligatory post-marketing studies in elderly patients, with age-specific trial design if applicable; obligatory inclusion of a minimum data set for geriatric patients in registration trials and post-marketing trials. This minimum data set should include the 'G8 questions' in nutritional assessment, functional assessment of daily living, co-morbidity as well as social factors. Finally, he recommended classifying patients in three groups based on fitness and health status: 'fit' (where classical endpoints and standard treatment would apply), 'compromised' (where specific endpoints and protocols would be required) and 'frail' (where other endpoints and palliative care would apply).

Endpoints and Indications For The Older Population

Presenter: William Evans (GlaxoSmithKline, EFPIA)

William Evans, Head of the Muscle Metabolism Discovery Unit of GlaxoSmithKline, speaking on behalf of EFPIA, gave an overview of the factors which predict outcome in older people and which could be used as endpoints in clinical trials for geriatric medicines in particular sarcopenia.

Physiological changes that occur in aging patients are in most cases due to the natural aging process and are not associated with chronic disease. They include loss of skeletal muscle, changing body composition, reduced blood volume/kg weight, impaired regulation of appetite and thirst, decreased production of hormones such as Growth Hormone, IGF1, Testosterone and Estradiol. In the geriatric patients these age-related changes are associated with multiple chronic diseases, polypharmacy, frailty and inflammation.

William Evans described the functional measurement for trials in elderly people that had received the most attention in the literature: the Short Physical Performance Battery (SPPB), which measures standing balance, gait speed and the time it takes for the patient to rise from a chair. It was shown that the SPPB score is associated with prediction of mortality, nursing home admission, onset of dementia, etc, with gait speed being the most powerful predictor of survival.

William Evans further gave an overview on sarcopenia, which is a major cause of disability and increased health costs in older people. This term had been first proposed by his group to denote the loss of skeletal muscle mass and function related to ageing. He presented a consensus definition of sarcopenia, including its multifactorial causes (lack of exercise, changing endocrine function, chronic diseases, inflammation, insulin resistance and nutritional deficiencies) and, most importantly, noted the criteria for diagnosis of sarcopenia (gait speed below 1 meter/second in addition to defined levels of low muscle mass): *Sarcopenia: An undiagnosed condition in older adults. Current consensus definition JAMDA, 2011)*. Moreover, he noted sarcopenia is a key contributing factors to frailty according to Linda Fried's model.

Another factor which is emerging as a powerful predictor of disability is sarcopenic obesity: increase in weight characterised by an increase in fat mass and a decrease in muscle mass. In this population, studies show that weight loss is associated with a significant decrease in bone mineral density and contributes to the risk of hip fracture in elderly women.

William Evans further showed some data on the impact of prolonged bed stay in elderly people compared with the impact it has on younger people. Results show that after 28 days of bed rest, a young person loses 2 % of lean leg muscle mass compared with 9% of total leg mass lost after 10 days in older people. This muscle mass loss during a 10 day rest in older people is equivalent to 15 years of aging. Finally, William Evans highlighted the main unmet needs in geriatrics: the need to formally define the diagnosis criteria for frailty; the need to address sarcopenia, which is a treatable geriatric syndrome, and sarcopenic obesity, as well as other mobility limitations, anorexia of ageing and consequences of hospitalization in these patients.

2.4 – Are clinical trials in polymedicated or frail patients realistic? How can we obtain data in these patients?

Frailty: Challenges and Possible Solutions

Presenter: Niccolò Marchionni (University of Florence, Italy)

Niccolò Marchionni, Professor of Gerontology and Geriatric Medicine in the University of Florence, gave the views of the EMA Geriatric Expert Group on the definition of frailty and its possible use in trials and post-marketing surveillance of geriatric medicines.

Following a mandate from the CHMP, the GEG has been working on obtaining consensus on the definition of frailty and the possibility of using it either as a selection or a stratifying tool in randomised clinical trials in the elderly or in post-marketing studies. Frailty is defined as a multi-factorial syndrome caused by a reduction of physiological reserves and of the capability to resist stressful events (homeostatic capacity), and is associated with an increased risk of disability, hospitalisation, institutionalisation and death.

The GEG has reviewed the proposed models for this complex and dynamic condition. The main challenges for using frailty include practical ways of measuring it in a clinical setting, establishing whether it is a useful predictive measure of clinically relevant outcomes independent of co-morbidities or disability and whether frailty can be considered as a relevant measure of outcome in randomised clinical trials.

Regarding practical ways to measure frailty, Linda Fried and colleagues showed that frailty can be established by measuring strength (handgrip) in the lowest quintile, gait speed in lowest quintile, unintentional weight loss (4,5 kg during last year), increased tendency to exhaustion and usual physical activity in the lowest quartile. These measurements are used to define the Phenotype Frailty Index (PFI), which classifies the patients as frail, intermediate (pre-frail) or non-frail (robust) depending on the score. Interestingly, from the model by Fried and colleagues, frailty appears relatively independent of co-morbidities and disability. An alternative model of frailty proposed by Rockwood and colleagues was also mentioned, however in this model frailty is largely dependent on co-morbidities and disabilities. It was mentioned that in the opinion of the GEG, SBBP, which derives from the Fried model, represents a practical way of measuring frailty in a useful clinical dimension.

With respect to the usefulness of frailty measurements in predicting outcomes independently of co-morbidities or disability, Niccolò Marchionni underlined that by using SPPB, incident disability and death can be prevented in older individuals not disabled at baseline and the value of this parameter can be used to predict mortality indecently of co-morbidities and disabilities. He further illustrated the

usefulness of frailty with a study where in a multivariate analysis SPPB constitutes an independent prognostic factor of mortality in patients with chronic heart failure.

Finally, regarding whether frailty can be used as a potentially relevant outcome measure in randomised clinical trials, Niccolò Marchionni presented a study that demonstrates that SPPB correlates with an increase in walking speed in older patients when compared to a control, being then a valid outcome.

To conclude, Niccolò Marchionni listed the recommendations from the Geriatric Expert Group: 1.- Frailty, according to Fried's model, predicts clinically relevant outcomes (incident disability, death rate) in the general older population and in older people with chronic conditions such as Chronic Heart Failure; 2.- the predictive value of frailty is independent of co-morbidity, disability and disease-specific severity indexes; 3.- in RCTs, frailty proved to be either a valid selection or a valid outcome measure;4.- because of its independent prognostic power, measures of frailty could be proposed as an adjustment variable in pre- or post-registration pharmacological trials in older persons.

Evaluating the feasibility of RCTs in elderly with multimorbidity; the cluster medicine approach

Presenter: Alessandra MARENGONI (Karolinska Institute, Sweden and University of Brescia, Italy)

Alessandra Marengoni, from Karolinska Institute, gave an overview on the clustering medicine approach and provided results from several studies highlighting the feasibility of using this approach in older patients with co-morbidities.

The challenge presented by multimorbidity (the presence of two or more chronic diseases) was highlighted as a complex and heterogeneous syndrome affecting the elderly. A study was presented, which aimed at evaluating if a 'qualitative analysis' of multimorbidity, based on studying the frequency of specific patterns or clusters of disease and the distribution of co-occurring diseases, may support the feasibility of RCTs in the elderly.

Clusters are identified using statistical tools, mainly the multimorbidity coefficient (O/E), which is the ratio of the observed co-prevalence to the expected one (prevalence if the diseases are completely independent) of a set of diseases. This coefficient tells us the degree to which the co-morbid diseases exceed the chance level. The Kungsholmen Project, a population based study in Sweden, was used as an example. The study found that several pairs of chronic diseases had an O/E ratio above 1, meaning that their co-prevalence was higher than the expected one. While the association of some chronic diseases, such as heart failure & atrial fibrillation or hypertension & heart failure, was expected, this was not the case for other diseases such as depression and hip fracture or depression and cerebrovascular diseases. Next, the prevalence of disability in daily activities was calculated for each pair of diseases and it was found that the majority of disabilities in this population were explained by the coexistence, in different combinations, of only four major diseases: depression, hip fracture, cerebrovascular diseases and dementia.

However, in order to have a complete picture of how diseases distribute and co-occur in a population, there is a more informative method that can be used, called cluster analysis; clustering is simply the grouping of similar objects by using algorithms and different measures of similarity or dissimilarity in order to group variables with the highest similarity. This type of analysis allows for the generation of hypotheses rather than solving problems. A five-cluster structure was derived from the cluster analysis performed in the Kungsholmen Project. One cluster consisted of four conditions: hypertension, heart failure, chronic atrial fibrillation, and cerebrovascular disease. Three clusters consisted of three chronic conditions each. The first one included thyroid dysfunction, chronic obstructive pulmonary disease, and coronary heart disease. The second one included diabetes mellitus, visual impairments, and deafness.

The third one comprised dementia, depression, and hip fracture. The last of the five clusters consisted of two diseases: malignancy and anaemia.

Alessandra Marengoni also presented the REPOSI study which analysed the effects of co-morbidity on in-hospital death and adverse events in a large population of hospitalised, co-morbid elderly patients in Italy. The study revealed that different clusters of diseases had a distinct impact on death and adverse events in these patients. For example, co-morbid patients suffering from anaemia and chronic renal failure had an additive risk of in-hospital death, whereas co-morbid patients with heart failure and chronic renal failure had an additive risk of adverse events compared to their pairs with only one of the above diseases. Alessandra Marengoni further stated the similarities between the cluster medicine approach and the network medicine approach, whereby the linking of disease pairs by observing their coexistence allows to build up phenotypic disease networks.

In addition, several hypothetical uses of this approach were highlighted: 1) the identification of clusters at high risk of adverse drugs events may help in designing RCTs; 2) primary and secondary outcomes of RCTs may be different according to specific clusters; 3) RCTs might be carried out in groups of elderly affected by specific clusters of diseases, e.g., the most easy/difficult to treat, or the most expensive to treat, or the ones with the best cost-effectiveness ratio; 4) ideally, once the triggering event (i.e., the onset of a specific disease) that promotes the clustering with other diseases has been identified, RCTs may be designed in order to change the chain of events. Finally, the main limitations of applying this approach to the geriatric population were mentioned: 1) large numbers are required; 2) a degree of heterogeneity remains within single clusters.

Industry's Views on B/R in "Older-Old" patients

Presenters: Philippe Guillet (Sanofi, EFPIA)

Philippe Guillet, from Sanofi, speaking on behalf of EFPIA, presented the industry's views on the very old patients (above 80 years old).

The exclusion of 'older' old patients (80+ years old) from trials, mainly based on their frailty status, co-morbidities or possible polymedication, results in a lack of knowledge that leads to an increased number of adverse drug events when these medicines are prescribed in this population in real life. Frailty was highlighted as an area of unmet medical need, due to its high prevalence, increased risk of adverse outcomes in the frail population and high healthcare cost. It was also noted that frailty is potentially a reversible syndrome however the likelihood of reversion declines with the age.

Although the EFPIA Survey on Geriatrics did not specifically address the very old population, several aspects were highlighted for consideration. For example, EFPIA members identified that guidance in very elderly patients would be useful in the therapeutic guidelines, as well as guidance on overall methodologies to evaluate how medicines contribute to the overall function in this population. The number of elderly patients involved in trials should be representative of the population who will use the drug and the existence of specific adverse events in the elderly should be taken into account. The survey revealed the need for a clear definition of frailty and to avoid the use of chronological age as an indicator of frailty. Furthermore, pre-authorisation trials should take into account the specific characteristics of the very elderly: frailty status, multi-morbidity clusters and the geriatric syndromes that appear in the course of the study. Other conclusions from the survey were that only the systematic study of outcomes specific to this population will enable improvement of the Benefit/Risk of interventions needed in very old patients and that categorical classification of diseases is no longer sufficient to handle the complex therapeutic needs of the "older old" patients.

2.5 – Practical proposals on recruitment improvement

The PREDICT Study and The Need To Increase The Enrollment Of Older Adults in CTs

Presenters: Antonio Cherubini (Istituto Nazionale di Ricovero e Cura per Anziani, Italy)

Antonio Cherubini presented the results of the PREDICT study, a study sponsored by the European Commission funded by the Framework Programme 7.

The PREDICT project aimed at investigating the reasons for the exclusion of the elderly in clinical trials and to provide solutions for this problem. The first part of the study consisted of a systematic literature review of clinical trials performed in the last ten years in six common and relevant conditions for old people: heart failure, depression, Alzheimer's disease, colorectal cancer, hypertension and statin treatment. The study aimed at assessing both the extent of exclusion of older people from clinical trials and what might be done to remedy this situation. The study confirmed that there is a wide gap between the patients included in clinical trials and the patients treated in real clinical practice.

An analysis showed the lack of mandatory RCT in older people, the physician's perception of the implications of inclusion as well as the physician's view on the research topic as barriers for inclusion of elderly patients into trials. On the patients' side, the unwillingness to compromise care, dislike of randomisation and fear of trial treatment were some of the barriers identified. Several strategies to improve enrolment were proposed to be taken at different stages. These included measures at the level of the Ethics Committee (justified eligibility criteria, simplified trial design, etc.), as well as measures regarding recruitment (e.g. financial incentives, simplified informed consent, etc.). Communication was highlighted as a key aspect to promote the enrolment of these patients in the trials and to improve the adherence to the trial.

The second part of the study gathered data from ongoing trials, mainly through the analysis on ongoing trials in heart failure that were registered in the WHO database. The main conclusion is that elderly are still widely excluded from clinical trials mostly for not fulfilling eligibility criteria. As an example, 25% of ongoing trials have an upper age limit; 80% of trials exclude patients with co-morbidities, and one out of two trials had poorly justified exclusion criteria.

The third part of the project developed a questionnaire that was answered by more than 500 health care professionals belonging to 6 categories: geriatricians, primary care physicians, nurses, member of ethics committees, trialists and managers of the pharmaceutical industry. The answers showed that health professionals believe that older people are being disadvantaged because of this under-representation in clinical trials, which is mostly unjustified, and that change in the form of financial support to compensate for extra workload and introduction of a mandatory requirement to include them in trials would be required to improve this situation. In summary, professionals believe that the current situation is not satisfactory and there is a clear need for change.

The forth part of PREDICT consisted in a series of focus groups performed with older patients and their caregivers aimed at understanding their views on the inclusion of elderly in CTs. Patients and their carers believe that older people are currently excluded from research often due to ageism while they have the right to be invited to take part in clinical trials and they are willing to do so. They asked for more support and, above all, information provided by healthcare professionals before, during and after the trial. In addition, they felt that assessment of efficacy in clinical trials of new drugs should also measure any improvements in quality of life

Antonio Cherubini noted that all these findings have contributed to the elaboration of a Charter for the Rights of Older People in Clinical Trials (available at www.predicteu.org). Finally, he noted that the PREDICT study concluded that older subjects are still excluded from clinical trials, including those that

are ongoing, therefore new strategies should be developed to increase the participation of older subjects in such studies.

Involving Older People in Medical Research

Presenters: James Goodwin (AGE UK)

James Goodwin of AGE UK addressed the lack of representation of older people in research and provided suggestions for improvement.

Currently there is widespread evidence of the exclusion of older people from clinical research and their under-recruitment in clinical trials. Using an example of a cardiovascular trial, James Goodwin showed that the existing age bias in research brings uncertainty to the benefit/risk assessment of the medicines, and results in under treatment of older patients, delays in bringing new treatments to the market and a biased practice. This age bias reflects a prejudice against older people present in many areas of society including academia and healthcare professionals in general. In order to improve the quality of research, the concept of patient-public involvement has been introduced which is a model whereby patients participate at all levels of research rather than being mere “subjects”. This involvement will ensure that knowledge is transferred to the public in an interactive way, which will provide knowledge to those who need it most while gathering the data on older patients in clinical research in a dynamic way.

According to James Goodwin, a number of barriers must be overcome to facilitate the involvement of older people in research. These include: the resistance to include older people in research; the lack of good practice and resources, as well as widespread age discrimination in Europe. James Goodwin presented the golden principles to improving involvement of older patients. They include: the need to secure a climate facilitating the involvement of older people through involvement of organisations (such as AGE UK) that represent the concerns of this population; to establish good relationships with the older community and to make use of existing research networks. It is also crucial to ensure robust methodology when carrying out clinical trials. Adequate strategies need to be developed to make the involvement process of older people user-friendly. Looking at a number of scientific journals, James Goodwin showed that, albeit slow, progress has been made in including older people in research over the last three decades and the mean upper age limit has increased from the late 50s to the late 60s in all journals. Recent projects and developments in Europe leading to the recommendation of a commitment to involve patients include projects such as the PREDICT Charter, the ERA-AGE 2 Report presented to the European Commission and FUTURAGE.

Efficacy and Effectiveness Models

Presenters: Graziano Onder (Università Cattolica del Sacro Cuore, Italy)

Graziano Onder gave an overview of the current challenges facing efficacy research.

Although randomised clinical trials provide essential, high-quality evidence about the benefits and risks of medical interventions, many such trials have limited relevance to clinical practice. They often fail to address patients' and clinicians' actual questions about a given treatment. In particular, they fail to address complex older adults with multiple conditions in real settings (the ‘real world’ population), and to assess the effect of multiple interventions (pharmacological and non-pharmacological) to treat coexisting co-morbidities. These factors can however be assessed by studying effectiveness. Graziano Onder defined effectiveness research (ER) as research addressing practical questions about an intervention as it would occur in routine clinical practice preserving the “ecology” of care as opposed to efficacy research which is aimed to understand how and why an intervention works. ER is meant to include representative populations and health care providers, to examine treatment effects within various subpopulations, and to compare interventions head to head. However, heterogeneity among

patients with multiple chronic conditions complicates the analysis. In addition effectiveness research is hampered by low trial retention and treatment adherence rates.

Whereas efficacy studies are mainly conducted in a blinded and placebo controlled setting, effectiveness trials, head to head comparisons, as well as pharmacological and non-pharmacological interventions can be done in an unblinded setting. Effectiveness trials allow testing of treatments for disease clusters, interventions affecting multiple conditions simultaneously, combination of pharmacological and non-pharmacological treatments and comparison of various models of care, being thus very useful to assess real life scenarios. Effectiveness studies are therefore more informative, however the lack of blinding can increase the potential for bias and the need to combine objective and subjective outcome measures.

In terms of outcomes, efficacy research is disease-oriented using outcome tools such as rating scales, which are usually meaningless in clinical terms. Effectiveness research on the other hand allows to assess outcomes in terms of function, quality of life and other clinically useful outcomes. The CATIE-AD study is an example of a study reflecting real world practice important for shaping therapeutics. In conclusion, effectiveness trials reflect reality and are helpful to guide practitioners in real life scenarios, even though they are less perfect than efficacy studies. Effectiveness studies sacrifice internal validity to achieve external generalisability. The challenge is to keep the right balance so that the findings are correct and applicable to clinical practice. To accurately inform decision making for patients with multiple chronic conditions, ER must include large, diverse populations representative of those cared for in clinical practice, monitor harms as well as benefits, examine homogeneous subpopulations defined according to risk level, focus on broader health outcomes than clinical research generally considers, and compare interventions that have benefits for multiple health conditions or for overall health.

Proposal for Guidance On Medical Research For And With Older People In Europe

Presenters: Florian von Raison (*EFGCP*)

Florian von Raison of the EFGCP gave an overview of his organisation's involvement in drafting a proposal for improving medical research in the area of geriatrics.

Older people are currently underrepresented in clinical trials and there is no consistent ethical guidance in Europe for clinical trials in older patients. Extrapolation from clinical trials (CT) to daily life is very difficult due to poly-therapies and co-morbidities which lead to safety issues and iatrogenic disorders. The absence of proper recruitment or insufficient presence of older people in the clinical development plan of new medicinal products is a fact for products not specifically intended for an ageing population. The Geriatric Medicine Working Party from EFGCP has developed, together with various stakeholders from academia, industry and patients associations, a draft proposal for guidance on medical research with and for older people. The document provides recommendations on various ethical aspects of clinical trials performed in older people of 75 years and above, and who represent a vulnerable patient population.

One of the recommendations Florian von Raison mentioned was that informed consent should be simplified and adapted to cope with sensory impairments of older patients and consent should be obtainable from legal representatives in case of older impaired patients.

EFGCP proposes to raise the age in the definition of older patients from 65 to 80 years old and to recruit more older women into clinical trials as they are currently underrepresented. It is encouraged to include frail patients and a widely accepted definition of frailty (using tools like the SOF index) is essential. Participant guides for older people with practical information on how a medicine is taken

would be helpful. In addition, ethics committees should have geriatric competencies and expertise in order to facilitate the evaluation of research projects in older patients.

Finally, in terms of study design unnecessary data collection from older patients should be avoided and studies should be as small as possible but large enough to reflect efficacy. Uncontrolled studies should not be taken into consideration in this population and placebo should be restricted to specific studies. Assays should take into account the limitations of this populations and sampling should always be adapted to it. Benefit/risk measures should also reflect the overall patient care, the dosing, the route of administration and other variables.

This proposal is expected to contribute to the protection of all older and vulnerable patients in clinical trials and to a better inclusion rate of this population.

Practical proposals on recruitment improvement: R&D approach and focus on possible bottleneck issues

Presenters: Brigitte Stemper (Bayer, EFPIA)

Brigitte Stemper speaking on behalf of EFPIA presented the results of the survey conducted amongst EFPIA members to assess the approach but also the critical issues identified when conducting research in a geriatric population.

Fifteen pharmaceutical companies participated in the survey. The main outcome was that data from clinical randomised trials remain the preferred option. In contrast, data from *ad hoc* registries were seen as less desirable and rather as supportive evidence. How older patients should be represented in clinical trials still seems to be a topic for debate: a predefined subpopulation of older patients within a large trial was suggested as one option; another to conduct trials only in elderly patients. Testing older patients with co-morbidities was considered an additional challenge. Over-sampling or a separate analysis should be considered for frail older patients. There was broad consensus that to improve the recruitment of older patients into clinical trials, accessibility needs to be improved by making information available in an adequate way and via appropriate channels, and by ensuring that the logistics take into account the special needs of patients and also their caregivers.

In terms of endpoints, some companies agreed that the use of adapted endpoints for this population should be driven by science, and age per se was not seen as justification for less stringent endpoints. Some survey participants considered that endpoints related to quality of life or other daily living scales should be considered. When discussing the feasibility of clinical trials in frail older patients, there was general agreement that the definition of frailty needs clarification and trials should be performed only if these patients are the target population. There are however ethical challenges to be considered as older patients are a vulnerable population and maybe an open label design, or observational studies would be more appropriate as it would allow for close monitoring of these patients. Other challenges include requirements for additional resources and expertise.

Importance of geriatric population data on the benefit/risk evaluation for drug approval

Presenter: Yoshiaki Uyama (Pharmaceutical and Medical Devices Agency, Japan)

Yoshiaki Uyama of the Pharmaceutical and Medical Devices Agency, Japan stated that the PMDA is facing similar problems of underrepresentation of the geriatric population in clinical trials. There is a clear need for better scientific assessment in older patients to ensure that the benefit-risk balance of medicines continues to be positive for this population. As paediatric patients cannot be considered "young adults", geriatric patients should not be considered as "older adults" but as very complex patients with co-morbidities and specific syndromes related to ageing. A number of factors are needed to help the regulatory decision making process such as specific biomarkers for this population as well

as modelling and simulation of parameters. Forums such as the current workshop should be used to improve collaboration amongst stakeholders to improve data generation in older patients also at an international level.

23rd March 2012

Session 3 – Pharmacovigilance in the Elderly

This session aimed to discuss Pharmacovigilance in older people. It is known that older people suffer more adverse events than younger people and this session aims to understand how drug safety is currently monitored in this population in the post-authorisation period. With the new legislation pharmacovigilance is changing and new tools and opportunities will become available to improve drug safety in this population.

Medication Errors And STOPP/START Criteria

Presenter: Denis O'Mahony (University College Cork, Ireland)

Denis O'Mahony of University College of Cork, Ireland discussed the impact of inappropriate prescribing and gave an overview of the STOPP/START screening tools used to reduce and prevent inappropriate prescribing in older patients.

Inappropriate prescribing (IP) is highly prevalent in older people and is now recognised as a major public health problem throughout Europe, leading to increased risk of adverse drug reactions, with polypharmacy being the main risk factor for both, IP and adverse drug reactions. Denis O'Mahony discussed current screening tools to assist healthcare professionals to decide on a treatment, which is aimed at reducing IP in older people. The first screening tool, the Beers Criteria for Inappropriate Prescribing in Older People present several deficiencies such as the inclusion of medicines which are no longer available in Europe, the fact that they do not take into account drug-drug interactions, therapeutic duplication and under-prescribing. In addition, the criteria are not routinely used in practice and are not useful for predicting the risk of ADE's.

The deficiencies of the Beers Criteria for Inappropriate Prescribing in Older People led to the development of new criteria such as STOPP (Screening Tool of Older Persons' potentially inappropriate Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment) criteria. These criteria for IP are structured according to physiological systems and are designed to account for errors of prescribing commission and omission, to recognise specific high risk groups such as patients with dementia, to reflect current prescribing practice and can be applied in all clinical settings. STOPP criteria have been developed to help detect the prescribing of potentially inappropriate medications (PIM's) in all clinical settings; START criteria were designed to detect potential prescribing omissions (PPO's).

Denis O'Mahony explained that these criteria have been used to define and compare prevalence rates of IP in different clinical settings and in different countries. Research has been carried out to determine whether STOPP criteria can predict the risk of ADE's, improve the prescribing of appropriate medication, reduce ADE incidence or reduce the cost of pharmacotherapy. Recent research shows that STOPP criteria PIM's are significantly associated with adverse drug events (ADE's) in older people in hospital; whereas Beers criteria PIM's are not significantly associated with ADE's in the same population. A recent randomised controlled trial (RCT) shows that STOPP/START criteria applied at a single time point significantly improved medication appropriateness; and that this improvement was sustained up to the end of the 6 months' follow-up period. Another RCT is currently in progress, which is designed to examine whether STOPP/START criteria as an intervention can significantly reduce ADE incidence and healthcare cost compared to 'standard' pharmaceutical care in hospitalised older people with acute illness.

Predictors Of Outcome And Renal Clearance

Presenter: Ulf Bergman (ENCePP, Karolinska Institute, Sweden)

Ulf Bergman of the Karolinska Institute in Sweden discussed renal function in older patients, methods of assessment and its role in predicting the risk of adverse drug reactions.

Epidemiological studies show that the majority of adverse drug reactions (ADRs) are well known pharmacological reactions. They are dose dependent, predictable and often preventable (type A adverse events). Only a minority (5%) are type B adverse events, which are unpredictable based on their pharmacology or unexplained events.

Although an age-related decline in renal function (namely Glomerular Filtration Rate, GFR) from 40 years onwards has been widely reported, this is not taken into account when prescribing medicines for older people, which predisposes them to ADRs leading to hospitalisations as Swedish research has shown. The assessment of renal function based on serum/plasma creatinine (S/P-Cr) in micromol/L measurements is not accurate in older patients and renal clearance in mL/min should be used instead.

To measure renal clearance in clinical practice is cumbersome. It can be estimated using several methods such as: iohexol clearance (EMA recommendation); use of methods such as Cockgroft & Gault and MDRD4. A comparison of four methods to measure eGFR (Cockcroft Gault, MDRD4, CKD-EPI and Cystatin C) showed that all methods gave different values of renal clearance which has clinical implications in older patients.

A survey among 13 countries within the ENCePP network on the methods used for assessing renal function in older people showed that there was wide variability in the methods used and that clinical practice deviated from recommendations given by EMA. Using the example of dabigatran, a comparison of dose adjustments was made using four different equations to estimate GFR (Cockcroft & Gault, uncompensated and compensated P-creatinine (mL/min), MDRD4 (mL/min/1,73m2) and CKD-EPI (mL/min/1,73m2)). The methods provided different GFR values, which translate into different dosing recommendations depending on the method used. The differences were further highlighted when separating men and women.

Ulf Bergman finally concluded that: drug dosing should take into account renal function which should be based on pharmacokinetic studies defining drug clearance in absolute terms (mL/min) (particularly important in older women); renal clearance based on exogenous or endogenous measurements is only a surrogate marker for drug clearance; for renally excreted drugs, the determination of plasma concentrations - Therapeutic Drug Monitoring - is the most reliable method to optimise drug dosing when there is no useful effect measurement such as blood pressure, pulse etc.. Ulf Bergman further recommended an update of the 2004 guidance on pharmacokinetics in patients with renal function in clinical trials.

Considerations From a NCA And From The iPhVWP

Presenter: Dolores Montero (EMA PhVWP, AEMPS, Spain)

Dolores Montero of the Spanish Medicines Agency gave a view of a National Competent Authority on Pharmacovigilance in older patients and how it can be improved.

Pharmacokinetic (PK) and pharmacodynamic (PD) characteristics that are specific to and make older patients more vulnerable to adverse events have been widely reported. PK characteristics of this population include a higher distribution of liposoluble drugs, a decrease in hepatic metabolism and a deterioration of renal function. PD characteristics include a decrease in haemostatic response and changes in the functional and cognitive status especially in frail patients. Dolores Montero highlighted

that 35% of patients over 65 years old have three or more diseases and lack of medication review leads to duplications or inappropriate prescription of drugs.

Dolores Montero showed results from an analysis of the data from the Spanish registry. When evaluating data of patients with psoriasis, it was found that 30% would be considered ineligible for inclusion into pivotal clinical trials due to their age. When analysing the data of patients with rheumatic inflammatory diseases treated with biologicals, age was the factor that predicted discontinuation of treatment. In older patients the occurrence of adverse events are the main reason for treatment discontinuation, whereas in younger patients it is the lack of efficacy of treatment. Data from the Spanish electronic healthcare records also shows that around 25% of elderly patients over 65 years old take more than 6 different medicines on a daily basis.

Describing the current regulatory situation in Spain 30% of the clinical trials now include older patients, which compares to 14% in 1993 and 50% in 2009. In terms of specific information for older patients provided in SmPCs, an analysis of the SmpCs of the 100 most prescribed medicines in older patients showed that only a limited number contained specific information on pharmacokinetics (52%), pharmacodynamics (6%), posology (81%), warnings (46%), interactions (16%) and adverse drug events (15%) for this population. However, Dolores Montero highlighted that the new pharmacovigilance legislation provides new opportunities to improve this situation, such as direct patient reporting, additional monitoring, signal detection by EudraVigilance, risk management plans and the improvement of the information provided in the package leaflets.

Dolores Montero summarised the key points for improving the demonstration of the benefit/risk balance in older patients which were identified at the informal Pharmacovigilance Working Party Plenary in Warsaw, in 2011. These include: the need to intensify spontaneous reporting through the use of new methods and tools that simplify the reporting, but also the recording of concomitant medication. Sufficient pre-authorisation data should be gathered for indications specific for older people and if not feasible, specific post-authorisation measures should be agreed upon within the RMP. Monitoring of aspects not usually covered by trials (frailty, renal impairment), drug utilisation studies and risk minimisation measures should also be taken into account. Post-authorisation clinical effectiveness studies should be encouraged and approval documents should include clearer information on interactions, a standard SmpC text for periodic medication review in chronic conditions, information on data available in the older population.

Signal Detection and EudraVigilance

Presenter: Georgy Genov (Acting Head of Section, Signal Detection and Data Analysis, EMA)

Georgy Genov of the EMA's Signal Detection and Data Analysis Section, discussed the process of signal detection at the Agency, the impact of the new pharmacovigilance legislation on signal detection and the opportunities it provides for protecting public health by reducing burden of ADRs and optimising the use of medicines.

Adverse Drug Reactions (ADRs) are the cause of 5 % of all hospital admissions, the 5th most common cause of hospital death and account for a societal cost of up to EUR 79 Billion per year in EU. Pre-authorisation clinical trials are not large enough to detect all adverse effects of a medicinal product and results cannot be generalised to patients using the product in a real care setting. Special populations such as older people are underrepresented in pre-authorisation clinical trials and spontaneous reporting systems are an important source for safety monitoring in post authorisation "real-life" setting in these populations.

EudraVigilance is a system created ten years ago for reporting and collecting suspected adverse reactions during clinical trials and following their marketing authorisation. The database now contains

more than 5-million case reports with approximately 50,000 new reports being received each month. 25% of all case reports received post-marketing concern older patients. 85% of suspected adverse reactions reported in older patients have been serious, 14% of these leading to death and 45% to hospitalisation. Most occurred with antineoplastic and immunomodulating agents, agents affecting the nervous system, cardiovascular system and blood and blood forming organs. Most commonly reported preferred terms (PT) were “confusional state”, “dizziness”, “pruritus”, “pyrexia”, “thrombocytopenia”, “diarrhoea”, “vomiting”, “dyspnoea”, “nausea” and “rash”.

Georgy Genov explained that the new pharmacovigilance legislation will further strengthen the process of signal management through: optimising data collection; additional monitoring; reporting of overdose, abuse, misuse and medication errors, and facilitation of patient reporting. Opportunities to enhance focused signal detection in older people should also be considered such as the possibility to focus on targeted medical events, drug-drug interactions and medication errors; to check for disproportionate reporting in sub-groups; to consider possibilities for development of signal detection algorithm for drug/drug and drug/disease interactions; characterise patterns of ADR reporting in elderly and to create Standardised MedDRA queries for defined areas of interest in elderly. The Eudravigilance Access Policy aims to maximise transparency for the public and utility of spontaneous reporting data held in the Eudravigilance database. In this context, the EMA will be publishing on the web anonymised data from the Eudravigilance database for centrally authorised products during the second quarter of 2012. This will be in a searchable patient-friendly format and the website will be available in the 23 official EU languages.

Risk Management Planning In Relation To Mature Patients

Presenter: Stella Blackburn (Risk Management Coordinator, EMA)

Stella Blackburn of the EMA’s Pharmacovigilance and Risk management Sector gave a presentation on the updated EU Guidance on risk management plans (RMPs) and how data for older patients will be addressed.

Stella Blackburn explained that within the risk management plan, the safety specification has a section on “Populations not studied in clinical trials” which requires the MAH to discuss specific sections of the target population which have not been studied, or studied in limited numbers. Older people are one of these populations. In the revised guidance the MAH is asked to consider drug usage in older people, and particularly to assess if age will have a significant effect on the pharmacokinetics and, if so, the need for specific studies in older patients. The impact of multiple organ impairment and multiple medications and how to cope with the increased risk of drug-drug interactions should be considered. Adverse reactions which may be of greater significance in the more mature population should be considered and to decide whether a targeted risk minimisation approach is needed.

Pharmacovigilance in Older Patients

Presenter: Michael Richardson (Bristol-Myers Squibb, EFPIA)

Michael Richardson speaking on behalf of EFPIA discussed the position of EFPIA on safety evaluation in older patients.

Safe and effective use of medicines means that the benefits and risks of a medicine are available, accessible and understandable. This is particularly important in the geriatric population as they have specific issues which need to be addressed. Clear guidance on the use of their medicines, a holistic understanding of physiology and pharmacodynamics is therefore required. The new pharmacovigilance legislation in Europe is currently being implemented and many of its features will have an impact on the effectiveness of pharmacovigilance monitoring in the older population. Before considering further initiatives specific for the geriatric population, EFPIA recommends that the legislation be implemented

and evaluated. Specific measures to identify and evaluate hepatic, renal and drug-drug interactions, which are all exacerbated in the elderly, could be brought into drug development programs. The risk of medication error and of compliance, which is a particular problem in the geriatric population and for which there is often poor data, is also addressed in the new legislation.

Results from EFPIA's survey which also considered the impact of the new PV legislation on the collection and evaluation of geriatric safety data showed that 66% of the companies believe that the new PV system will allow for adequate collection and evaluation of geriatric safety data. For 20% the guidance provided by the new pharmacovigilance legislation is inadequate and further guidance should be provided, 14% stated that more clarity in the implementation of the new legislation is needed to correctly assess its adequacy. When asked if there is room for further streamlining, 40% of the companies stated that there is room for further improvement in legibility, clarity on post-authorisation measures in RMPs and in provide more user friendly collection tools. Concerning specific methodological issues that need to be addressed by industry and regulators, 66% believed that the new legislation provides all the methodological aspects needed and 26% had suggestions for improvement, mainly on the education of patients and healthcare professionals and on strengthening the guidance on methodologies, measurements and medication errors.

Overall, the new European pharmacovigilance legislation gives comprehensive and specific guidance to meet these challenges and evaluate safety data, and is expected to adequately handle the risks in the geriatric population.

Session 4 – Adherence and Formulation Issues in the Elderly

Chair: Alexis Nolte (Head of Sector, Quality of Medicines, EMA)

This session aimed to discuss formulation and how biopharmaceutical factors, such as the dosage performance or the pharmaceutical form can improve adherence to treatment in older people.

Formulations, Packaging and Medication Practices Considerations

Presenter: Michael Theodorakis (University of Athens) and Adalsteinn Gudmundsson (National University Hospital, Iceland)

Michael Theodorakis of the University of Athens discussed the role of medicine formulation and how it can address the requirements of older patients.

With age, the number of drugs used by an individual increases almost linearly and studies have shown that older adults use an average 2 to 6 prescribed medications and 1 to 3 non-prescribed medications. The process of ageing, the high prevalence of co-morbidities, the large numbers of drugs used and the complexities related to the use of medicines in this population, are all factors that affect the ability to take medicines and result in reduced compliance and adherence. Formulations and packaging are important because they directly affect the ability to take medications in patients with impairments or certain conditions. Formulations can also act synergistically or antagonistically with factors influencing PK and PD (dehydration, polypharmacy, co-morbidities) and thereby predispose the patient to adverse reactions. In order to improve compliance and adherence amongst older patients alternative packaging, formulations or delivery/administration options need to be considered. Providing specifically tailored formulations would increase compliance and adherence in this population. Interventions from healthcare professionals can also improve treatment adherence and compliance. They include prescribing drug combinations or long-acting drugs, use of alternative routes of administration or non pharmacological alternatives where possible to reduce the pill burden on patients, and performing routine re-evaluation of medications to avoid unnecessary medications. Medication aids should be used to help patients to take medicines correctly.

Adalsteinn Gudmundsson of the National University Hospital, Iceland discussed the relationship between altering of drug formulations and administration errors.. Splitting or crushing of tablets, mixing and even opening of capsules are a common but unsafe practice which may result in the partial administration of the medicine, destruction of extended release properties, neutralisation of medicine effects and interaction with feeding tubes used for administering the drugs . Examples of dosing error risks and ADRs associated with drug formulations were given. Several challenges for older patients were highlighted: visual impairment; swallowing difficulties; lack of dexterity; dementia and palliative care; demand for more flexibility in packaging; formulations or delivery/administration. Increased pharmacological training and interventions by healthcare professionals is needed and pharmaceutical manufacturers need to tailor to the special needs of older populations by increasing their enrolment in trials and enhance the development of alternative doses and delivery forms or "smart" novel formulations.

Geriatrics Medicines – Industry Perspective on Formulation and Packaging Considerations

Presenter: Ron Ogilvie (Pfizer, EFPIA)

Ron Ogilvie speaking on behalf of EFPIA discussed the role of dedicated formulations for older patients and to what extent paediatric formulations and packaging aspects could improve compliance in geriatric patients.

There is no 'standard' geriatric patient and a number of factors (frailty, condition, duration of treatment) need to be considered when providing medicines to these patients. There are some parallels between geriatric and paediatric patients in terms of requirements that do not usually apply to the general population (strength, dosage, formulation). However, there are significant differences between these populations. Whereas in paediatric patients, medicines may be administered by a healthy care-giver (parent / guardian) geriatric patients may be independent or be supported by a care-giver who may be aged or infirm. In addition, geriatric patients may also be treated for multiple diseases, with multiple products (both prescription and non-prescription). There are therefore additional challenges for achieving compliance in this population compared to paediatric patients. Dosage form selection is only one aspect of addressing the compliance needs for geriatric patients and a holistic approach is needed, perhaps on a case-by-case basis.

The product and its compliance needs to be seen in the widest terms of disease, patient group specific abilities, dosing parameters, the care situation of the target population, the polypharmacy status and also the complex specific geriatric limitations these patients face.

Ron Ogilvie explained that although some design criteria are similar for geriatric and paediatric medicines, there are further complicating factors for geriatric patients given the population diversity and the compliance challenges. Apart from the dosage form, physical characteristics of the product (size > taste), dosing flexibility, packaging utility and particular labelling needs may need to be considered.

A dedicated geriatric formulation may not be necessary and may not address the compliance needs of every patient. There are cases where adult formulations are suitable for older patients. In other cases paediatric formulations may be used but may not always be optimal. A holistic approach to care should be taken in these patients and solutions such as geriatric-friendly packaging or simplified dosing regimens may be considered. In terms of packaging, its role in compliance is also crucial. However in the requirements for suitable packaging are sometimes in contradiction with geriatric-friendly practices. Ron Ogilvie concluded by saying that there is no single solution to address the needs of older patients and a number of factors apart from design need to be considered on a case by case basis.

What Do We Need To Consider To Ensure Medication Adherence Of Older Adults?

Presenter: Sven Stegeman (Geriatric Medicines Society e.V., Capsugel)

Sven Stegemann of Geriatric Medicines Society e.V. gave a presentation on the adherence to treatment in older patients and the reasons for non-adherence.

Medication adherence is an important factor determining health outcomes but remains poor across the different patient populations. In order to understand a patient's medication behaviour adherence measurement systems (AMSs) have been developed as well as intervention methods to overcome adherence issues. Sven Stegemann discussed and compared the various adherence measurement systems and concluded that all AMSs have strengths and weaknesses and there is currently no gold standard AMS.

Sven Stegemann then mentioned the medication adherence in older patients. Reasons for non-adherence are multi-factorial and can include therapy-related and condition-related factors. Therapy-related factors that affect adherence include complexity of the medical regimen, co-morbidity and the involvement of multiple medical specialists in the care of the patient. Condition-related factors that negatively affect adherence include swallowing problems and dysphagia. These are often remediated by altering medication which is associated with a number of risks. Condition-related factors also include problems with handling medication and packaging issues (child-proof) are obstacles older people have to overcome when taking their medicines.

In order to increase adherence in older patients, relevant information about the reason and need for the therapy including potential ADRs should be provided, medication schedules should be simplified and healthcare providers should ensure that patients can handle the medicine and take it without alteration. Medication reviews and therapeutic adjustments should take into account relevant factors such as age and co-morbidities. Finally, practitioners should ensure that older patients are able to adhere to the treatment in cognitive and physical terms and support them in their regimens. Overall, drug adherence is the result of the entire medication process starting in the early development of the drug product and spans across all healthcare professional as well as the healthcare system working together synergistically on the individual patients.

Lessons Learnt from Paediatric formulations

Presenter: Diana van Riet-Nales (EMA QWP, MEB, The Netherlands)

Diana Van-Riet Nales of EMA's Quality Working Party shared her experience gained during the development of the guideline on the pharmaceutical development of medicines for paediatric use and any lessons learned that could be useful and applied to the geriatric population.

Although paediatric development issues are not the same as geriatric development issues similar principles apply. Experience from drafting the paediatric guideline show that when considering a geriatric population the following is needed: a clear definition of the population in question, assessment of suitability of clinical sub-groups to be further considered for quality aspects and target result of studies to confirm a specific formulation aspect for a specific group. In addition there is a need to ensure uniform categorization and taxonomy in geriatric medicines, with international collaboration, in order to allow the provision of harmonised information in approval documents and allow a more focused drug development. All parties involved need to work together from the beginning and allow for a thorough transfer of information. The development of official guidance documents such as reflection papers should be considered, to provide a framework for discussion particularly in areas where scientific knowledge is fast evolving or experience is limited. In order to supplement a reflection paper, a guideline may be needed to provide specific scientific, technical or regulatory guidance to stakeholders. Using the experience of the paediatric guideline Diana Van-Riet Nales recommended as a

first step to define the aspects important for the quality of geriatric medicines. One key aspect is the need to address the existing quality knowledge gaps in future guidelines in this population. It is important to note that not all problems (i.e. behavioural problems) related to the use of medicines can be solved though regulatory incentives. Diana Van-Riet Nales concluded that paediatric and geriatric development issues are clearly not the same i.e. paediatric guideline will not consider geriatric medicines and appropriate geriatric medicine development is a shared responsibility of industry, academia, regulators, patients. It is essential to respect good regulatory practice but assure a balanced approach between new and existing medicines.

Session 5 – Providing information to the older population

Chair: Juan Garcia Burgos (EMA)

Co-Chair: Barbro Westerholm (AGE Platform)

Understanding The Needs Of Older People

Presenter: Jean-Pierre Baeyens (EMA Healthcare Professionals Working Group)

Jean Pierre-Baeyens of the EMA Healthcare Professionals Working Group discussed the needs of older patients in terms of their medication and the problems faced by the physician when prescribing for this population.

There are clear differences in the treatment of younger and older patients: younger patients are usually treated for a single condition according to clear guidance and with medications tested in randomised clinical trials. However, older patients are treated for a number of conditions, with contradictory guidance, and with treatments that have rarely been studied in this population in an acceptable number of randomised trials with appropriate follow-up. Whereas the physician is focusing on the disease the older patient is concerned about the possible side effects, the time to an effect, the convenience and the cost. Jean Pierre-Baeyens recommended that the prescriber stop treating the disease and start treating the patient. In order to meet the needs of the older patient more data is needed, which is currently lacking due to the absence or lack of involvement of older patients in trials. In addition channels to provide information should be improved and social background, ethnicity, age discrimination and functional impairments such as loss of vision should also be taken into consideration.

A NCA Analysis Of Approval Documents

Presenter: Paul Jansen (MEB, The Netherlands)

Paul Jansen of the Medicines Evaluation Board (MEB), the Netherlands gave an overview of the results of an analysis of approval documents and their compliance with current guidelines regarding the provision of information for older patients. He also presented the results of a study determining what information should be included in the SmPC according to healthcare professionals.

A review of the approval documents of all non-generic centrally approved products was carried out assessing their compliance with the recommendations of the ICH E7 guideline that are relevant to older patients. They concerned the composition of the studied population, the clinical experience in older patients, the PK and drug-drug interaction studies. Results showed that 70 % of the information on older people recommended is present in EPARs but only 50 % in the SmPCs. Especially information on co-morbidities, age-related differences in PK, PK studies performed in older patients and studies in impaired subjects are lacking from both the SmPC and EPAR.

A recent study (Delphi Study on the Information of Medicine appropriateness in the Elderly) aimed at determining what information, according to healthcare professionals, should be part of the SmPC to

guide them in prescribing medicines to older patients. Results showed that there was a discrepancy between what regulators and geriatricians/other experts find important. Regulators found items such as information on the convenience of use for older persons, the extent of renal clearance of the active substances in older persons less important. Overall, 26 items were identified in the study that should be included such as specification on post-marketing data collection in geriatric patients , the extent of drug accumulation in older people, dosing instructions and safety specifications should be included in these documents.

How Can SmPC and EPAR Information Contribute To The Safe And Effective Use Of Medicines In Older Population?

Presenter: Laurent Brassart (Information Compliance and Consistency EMA)

Laurent Brassart of Information Compliance and Consistency Group at the EMA discussed the information for older patients contained in the SmPC and how it can contribute to the safe and effective use of medicines in this population.

Because of an increasingly ageing EU population, clear information on the safe and effective use of medicines in older population is a priority. Provision of clear information should consider the availability of data to provide evidence-based information as well as the heterogeneity of the older population with diverse health status, age-related physiological changes and co-morbidities.

The European Public Assessment Report (EPAR) presents all available data supporting the benefit-risk assessment and the information presented in the SmPC. Its template has been recently updated in 2011 to improve the presentation of geriatric data and provide clearer information on the inclusion of elderly people in the clinical trials, pharmacokinetics in older population and benefit-risk or risk management plan considerations in this population. In addition, other information already included in the EPAR could be considered for this population with high co-morbidity, such as the PK parameters in special populations (age, renal function, etc.), the secondary pharmacology (e.g. cardiovascular safety), efficacy or safety analysis in subpopulations and investigations of drug-drug interactions. Improving accessibility of the EPAR as source of available data for healthcare professionals could be further explored.

The SmPC is the basis of information for healthcare professionals on how to use the medicinal product safely and effectively. It is drawn up according to the EC guideline on SmPC which recommends that “each section of the SmPC should first deal with those issues that apply to the core population for whom the medicine is indicated followed, when necessary, by specific information for any relevant special population”. There is therefore the possibility to provide information on any clinically relevant difference in the older population but also in subpopulation with co-morbidity, e.g. in sections “4.2 Posology” or “4.4 Special Warnings and Precautions for Use”. Clear information on drug interactions is also essential for the older population, often polymedicated. It is therefore important to apply the recommendations of the EC guideline on SmPC to support healthcare professionals in making informed decision according to individual patient’s needs. Finally, clear information in the SmPC is key for preparing a clear package leaflet (often referred to as patient information leaflet) which has to be drawn up in accordance with the SmPC.

PIL Initiatives

Presenter: Alexios Skarlatos (Head of Product Information Quality, EMA)

Alexios Skarlatos of EMA’s Head of Product Information Quality discussed how information on old people is captured in the package leaflet.

The European Medicines Agency, together with its stakeholders, works at different levels within the European regulatory system to ensure that information on old people is presented in a clear, meaningful and complete way in the package leaflet of centrally authorised products.

Alexios Skarlatos explained that the translation of information on older people from the scientific assessment to the product information is straight forward when older people are the target population. However in cases where older people are not the target population there is a lack of specific data in this population and only a general warning to be cautious may be available. In other cases the population is addressed only indirectly in other sub-sets of special populations (e.g. renal impairment section) and unfortunately clear warnings and precautions based on (pre-) clinical studies are only rarely available.

Ways to ensure that information on old people is appropriately presented in the package leaflet include the review of the design and layout of the package leaflet, readability testing including older people, the availability of leaflets in formats suitable for the visually impaired, as well as the report of the European Commission on the current shortcomings in package leaflets. In parallel to this report EMA is conducting a study to analyse deviations between the PIL approved by the CHMP and the ones currently on the market.

Industry Perspective on Information to Patients and Carers

Presenter: Lisette Vromans (Merck Sharp & Dohme, EFPIA)

Lisette Vromans speaking on behalf of EFPIA presented the results of survey on the adequacy of current guidance for provision of Product Information to the geriatric population.

The results showed that although the responses were divided member companies stated that the problem is more related to the general guidance rather to the population itself and that a review of existing guidance may be needed, however responders were of the view that the guidance cannot compensate for missing information due to lack of data. Lisette Vromans recommended to also focus on the PIL not only on the SmPC. When asked if there should be a comprehensive section consolidating all the relevant aspects relating to this population in the product information, the survey response was mixed and it was noted that this approach would bring both advantages and disadvantages and that stakeholders would have an important contribution to this. It was also mentioned that this approach should be focused on the PIL, and information should be succinct and avoiding repetition, and could be delivered using alternative methods in order to personalise the information. Other recommendations included the reflection of all relevant data (efficacy and safety) in order to allow appropriate Benefit/Risk presentation, to increase prescriber knowledge on drug-specific effects of medication, to increase patient understanding on appropriate use of medicines and to develop a long-term strategy to aim for customised/personalised prescriber information.

Lisette Vromans explained that EFPIA has set up a temporary working group that is looking at new concepts to present the Product Information. The aim is to take advantage of technological and communicative advances that allow a more personalised approach towards all patients/users. General guiding principles include a single point of access for physicians and patients, easy access, fair representation of the benefit and risk balance. Specific challenges in relation to the geriatrics population on contents (differences in dosing recommendations, information on interactions in view of use of concomitant medication and differences in contraindications, specific warnings, specific AEs), and presentation (readability, clarity) and the need for and benefit of significantly faster updates of information will be taken into account. The importance of stakeholder involvement in making any changes is emphasised.

Considerations emerging from the discussion

This workshop highlighted the engagement of the EMA and its committees with the different stakeholders in order to address the challenges of evaluating and establishing the benefit/risk of medicines for use by older patients. Preliminary considerations emerging from the sessions are outlined here, together with the next steps the EMA will take to implement its Geriatric Medicines Strategy.

Ensuring the safe and effective use of medicines for an ageing population is a challenge that is not only limited to the European Union: other regulatory agencies attending the meeting, in particular the PMDA Japan, are also facing and approaching this challenge posed by the demographic shift in a similar manner. In addition, the survey conducted by EFPIA demonstrates a growing awareness and commitment from the pharmaceutical industry. To address the issue of an ageing population in a wider context the European Commission and the WHO have started in 2012 several initiatives which offer an opportunity for stakeholder synergies to extend beyond the field of medicines.

Older people are often the main users of a medicinal product, rather than a special population as opposed to the paediatric population. Nevertheless, older adults – and particularly those over 75 years of age, the fastest-growing demographic group- are often underrepresented in clinical trials, especially in conditions not exclusively affecting the elderly which generates a knowledge gap in this vulnerable population. Therefore, it was acknowledged that the risk/benefit balance in the intended population of use needs to be supported by relevant data.

This situation seems to be improving compared to a few decades ago, as there are now fewer trials with unjustified age limits. However, this has to be read in the context of a rapidly aging population: efforts in this direction need to be maintained to ensure that, in accordance with the guidance in ICH E7 and its Q&A, a representative number of patients are studied in the pre-authorisation phase. The survey conducted by EFPIA showed that most members opted for the enrolment of patients above the age of 75 years as a subgroup in clinical trials; however a separate trial might be needed in certain cases. Another problem identified was the fact that chronological age alone does not sufficiently characterise the population enrolled in a trial. It was therefore recommended to explore the possibility of reaching consensus on an operational definition of frailty and on the tools to evaluate it to be used for clinical research and to guide therapeutic decisions. The CHMP has asked its geriatric expert group (GEG) to undertake preliminary work in this respect. Industry and academia expressed the view that sarcopenia, a key contributing factor to frailty, should be recognised as a therapeutic indication, given that frailty is a predictor of clinical outcomes, and that reduction of frailty would result in a societal benefit.

The problem of a selection bias during enrolment in trials was discussed. Even when inclusion and exclusion criteria are adequately set, the clinician and the ethical review board, who act as gatekeepers in the clinical trial recruitment process, may introduce a selection bias by allowing enrolment of only some of the eligible patients. This is particularly true for very elderly and co-morbid patients. This issue has been addressed by ICH E7 Q&A which recommends that every effort should be made to gather evidence in these patients during the premarketing clinical development program.

Strategies and interventions to improve the recruitment in clinical trials were discussed: they include foreseeing adequate logistics and communication, making use of existing patient and physician networks and providing feed-back to the patient on the results at the end of the trial.

Commonly prescribed co-medications should also be studied in clinical trials. The respondents to the EFPIA survey preferred to include co-morbid patients in pivotal Phase 3 trials. However, a separate trial might show better results in terms of recruitment.

Generating data on the risk/benefit balance in the target population involves more than a discussion on absolute patients' numbers: depending on the drug profile and the target population, the product development plan requires a learning curve to acquire data and modulate risk for the patients who might be more susceptible to adverse outcomes, like frail or polymedicated patients. When setting up a strategic plan for drug development at the Scientific Advice stage, the needs and requirements of older patients should be considered in relation to the demographics of the disease. Population PK or specific PK studies including the very elderly should be performed to help informed prescription. Modelling and simulation can also offer powerful tools to quantitatively evaluate PK/PD, recommend dosing regimens, and identify patients at risk. Some of the lessons learned from paediatric development can be applied to the older population: heterogeneity could be allowable and analysed in clinical trial design both pre and post authorisation.

Both academia and patient organisations agreed that the desired outcome and the treatment choices depended on the frailty and disability status Certain adverse events, like falls and dizziness, are of greater significance in the geriatric population. The design of a clinical trial should consider age-appropriate endpoints. For older people these include functional outcomes which may be more important and also have implications for health technology assessment bodies.

Inappropriate formulations and packaging lead to low adherence to treatment, medication errors and safety and efficacy problems. Therefore several factors such as the need for ease of administration, dose reduction, visual and motor impairment, and polypharmacy, need to be considered. If appropriate, protocols to evaluate the ability of patients to manage medication should be designed.

The provision of adequate information to the patient and prescriber was another aspect discussed at the workshop. In the absence of good data, it is not possible to provide good information. However, sometimes data is available in the dossier and not adequately reflected in the approval documents, particularly for patients older than 75 years or those with co-morbidities. It was recommended to concentrate more on the package leaflet, which is the regulatory document most widely referred to by the public. Improvements could be made in explaining how to take the medicine, how age may change some of the PK and PD of a medicine and what is known about the use of concomitant medications. It was suggested that it could be useful to consolidate the information in a dedicated section.

Although a representative number of patients is expected to be included in the marketing authorisation application, postmarketing data might also be required to consolidate the knowledge in the more at-risk subpopulations. The implementation of the new pharmacovigilance legislation offers an opportunity to strengthen the system for monitoring the safety and benefit-risk balance of medicines.

Once a medicine is marketed, safety monitoring may result in safety signals. The information provided by spontaneously reports of suspected adverse reactions should be used in order to identify patterns of drug-drug and drug-disease interactions not apparent in the pre-authorisation phase. Data collection should be optimised, as ADRs are generally underreported in older patients. This could be done through facilitating the reporting of suspected side effects, use of age-adapted patient reporting tools, drug utilisation studies and optimising the use of electronic health records.

Finally the risk management plan – based on the risk profile – should be designed to fill knowledge gaps and targeted risk minimisation measures should be foreseen, if necessary.

Finally, the following steps are planned for the future:

- The recent changes of the AR template introduced in November 2011 are expected to increase transparency on the data presented in MAA and their evaluation. The EMA will continue to provide input, according to the requirements of ICH E7, on all applications at the stage of peer review.

- An analysis of the impact of the geriatric medicines strategy on the information provided in the approval documents will be conducted in one year, and compared with the current baseline.
- All guidelines currently being drafted or revised will continue to be checked for geriatric aspects, aiming to strengthen the guidance concerning elderly patients above 75 years and co-morbid patients. A consultation on a possible Q&A document on packaging formulations and adherence will be conducted.
- The work initiated by the geriatric Expert Group on an operational definition of frailty will be continued.
- Eudravigilance has already incorporated older age brackets in its reports. Data mining analysis tools for drug/drug and drug/disease interaction are currently being considered.

Annex I – Glossary

ADE – Adverse Drug Event

ADR – Adverse Drug Reaction

AE – Adverse Event

AEMPS - Agencia Española de Medicamentos y Productos Sanitarios / Spanish Medicines Agency

AIFA - Agenzia Italiana del Farmaco / Italian Medicines Agency

AMS – Adherence Measurement Systems

AR – Assessment Report

BASE - Berliner Altersstudie / Berlin Aging Study

CATIE-AD – Clinical Antipsychotic Trials of Intervention Effectiveness – Alzheimer's disease

CGA – Complementary Geriatric Assessment

CHMP – Committee for Human Medicinal Products

CKD-EPI - Chronic Kidney Disease Epidemiology Collaboration

CT – Clinical Trial

DDI – Drug-drug Interaction

DEXA - Dual-energy X-ray absorptiometry

DG SANCO – Directorate-General Health and Consumers

EC – European Commission

EFGCP – European Federation for Good Clinical Practices

EFPIA – European Federation of Pharmaceutical Industry Associations

ENCePP - European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

EGZB - Evangelisches Geriatriezentrum Berlin

EIP – European Innovation Partnership

EMA – European Medicines Agency

EORTC – European Organisation for Research and Treatment of Cancer

EPAR – European Public Assessment Report

ER – Effectiveness Research

ERA-AGE - European Research Area in Ageing

EU – European Union

EUR - Euro

FDA – Food and Drug Administration

GA – Geriatric Assessment

GEG – Geriatric Expert Group

GFR - Glomerular filtration rate

GPRD - General Practice Research Database

HRQoL – Health-related Quality of Life

HTA – Health Technology Assessment

ICH E7 – International Conference on Harmonization Guideline on Studies in Support of Special Populations: Geriatrics

IGF-1 – Insulin-like Growth Factor 1

IP – Inappropriate Prescribing

iPhVWP – Informal Pharmacovigilance Working Party

IT – Information Technology

JAMDA – Journal of the American Medical Directors Association

M&S – Modelling and Simulation

MAA – Marketing Authorization Application

MAH – Marketing Authorization Holder

MDRD4 - Modification of Diet in Renal Disease 4

MEB – Medicines Evaluation Board

MedDRA – Medical Dictionary for Regulatory Activities

MHRA – Medicines and Healthcare Products Regulatory Agency, United Kingdom

MPA - Medical Products Agency, Sweden

NCA – National Competent Authority

O/E – Multimorbidity Coefficient

PD – Pharmacodynamics

PFI – Phenotype Frailty Index

PhVWP – Pharmacovigilance Working Party

PIL – Patient Information Leaflet

PIM – Potentially Inappropriate Medication

PK – Pharmacokinetics

PMDA – Pharmaceutical and Medical Devices Agency, Japan

PPO – Potential Prescribing Omissions

PREDICT - Increasing the PaRticipation of the ElDerly In Clinical Trials

PT – Preferred Term

PV - Pharmacovigilance

Q&A – Questions and Answers

QWP – Quality Working Party

R&D – Research and Development

REPOSI - Registro Politerapie SIMI

RCT – Randomized Controlled Trials

RMP – Risk Management Plan

S/P-Cr – Serum/Plasma Creatinine

SmPC – Summary of Product Characteristics

SOF - Study of Osteoporotic Fractures

SPPB – Short Physical Performance Battery

STOPP-START - Screening Tool of Older Persons' potentially inappropriate Prescriptions - Screening Tool to Alert doctors to Right Treatment

USA – United States of America

WHO – World Health Organization