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EDITORIAL-THEMED SECTION

Demographics in the 2020s—Longevity as a challenge for pharmaceutical drug development, prescribing, dispensing, patient care and quality of life

1 | INTRODUCTION

The global increase in life expectancy is unquestionably a unique achievement of growing wealth, improved hygienic standards and advances in the provision of healthcare services realizing a declining mortality in acute and chronic diseases through diagnostics, surgery, pharmacotherapy and other interventions. However, increasing life expectancy does not come without new challenges for effective patient care, whereas these challenges in turn may provide opportunities for developing new concepts further supporting longevity and quality of life. Following a conference of experts from different disciplines in Graz (Austria) on November 7–8, 2017, entitled "Medicines for older adults: getting prepared for the scientific and regulator revolutions," this themed issue was born to provide insights to a wider audience of stakeholders into the complexity, but also the opportunity, of senior adapted, that is, senior friendly patient care. The themed issue is dedicated to an interdisciplinary review of the challenges of prescribing and dispensing medicines to older people as well as the difficulties that older and multimorbid patients may face when managing their medication regimens. It further includes a review of emerging technologies that might better serve the needs of future patient populations and is complemented by the progress in regulation on frailty and the pharmaceutical development of medicines for older people.

2 | OLD AND VERY OLD AGE

At present, patients aged 80 years and beyond are the norm rather than the exception in community and hospital care. As described by Roller-Wirnsberger et al., the increasing prevalence of acute and chronic diseases and multimorbidity with older age are important determinants for disabilities affecting older people's well-being and independence.[1] However, recent studies have shown two contradicting trends. People are living longer in better health and their quality of life conditions are better than those of earlier generations.[2] Yet at the same time, the most recent generations seem to be affected by multimorbidity at younger ages than the generations before.[3,4] Even though there is growing awareness that multimorbidity is becoming a major challenge for the future,[5–7] the complexity of treating multimorbid older patients is still underestimated because they even differ more from the single disease and young patients for whom the drug product had proven to be beneficial during the pharmaceutical and clinical development of a new drug.[8]

3 | POLYPHARMACY

In many cases, disciplinary guidelines require the simultaneous prescription of 2 and more drugs for chronic diseases. This implies that patients from two chronic diseases may already be on polypharmacy, which is defined as the use of 5 drugs or more. However, prescription guidelines are commonly based on a single disease concept and might not reflect the inter-connected factors on co-administered drugs for other chronic diseases, self-medicated drugs, nutritional products, as well as disease or age-related physiological changes.[9] This is especially true in increasingly older patients of whom more than 80% are exposed chronically or periodically to polypharmacy.[10] Strampelli et al. reviewed the top 10 prescriptions in older people by ATC level, age-subset, and gender across four representative European countries including more than 40 million prescriptions.[11] The data revealed that certain drugs or drug classes are regularly prescribed to up to every second older patient. Therefore, the use of these commonly prescribed drugs has to be considered during any prescribing, dispensing or drug development (both for new innovator as well as new generic drug products).

4 | ADVERSE DRUG REACTIONS

Adverse drug reactions (ADR) in patients aged 65 years and beyond account for up to 30% of emergency department admissions[12–14] of which the majority would be preventable.[15,16] Reasons for medication related problems in older and multimorbid patients are polypharmacy,[17] drug-drug, drug-disease, drug-food and drug-herbal medicines interactions,[18] therapeutic failures, adverse drug

withdrawal events[19] and prescribing of potentially inappropriate medications.[20] In addition, the treatment goals might change for the individual patient with increasing age which implies the need to consider the time-to-benefit[21] and deprescribing.[22] For patients in the terminal life stage, treatment objectives might shift even more to Quality-of-Life aspects and a stronger focus on the treatment of symptoms rather than the disease itself.[23] The current demographic transition inevitably leads to patients with a higher degree of clinical and therapeutic complexity, which affects the prescribing by healthcare professionals as described by Drenth-Van Maanen et al.[24] and the necessary deprescribing challenge as described by Shrestha et al.[25]

5 | DRUG PRODUCT INTERFACE AND MEDICATION ERRORS

The interface between the user (patient, lay caregiver, professional caregiver, health care professional) and the drug product is of great importance. This interface includes how the user understands the product, can handle the product in a given setting and executes its administration while taking into account the administration recommendations for other drug products that may need to be handled concurrently. Practical medication problems and even medication administration errors can thus occur at the level of professional care[26] as well as the patient or its lay caregiver. The problems and errors are often caused by product and process related factors.[27] In order to explore real-world evidence on practical medication problems and errors and the possibilities for risk mitigation through the drug product design, Karapinar-Çarkit et al. evaluated the incidents reported to a public Dutch medication incident registry.[28]

Recently, patient centric pharmaceutical drug product development has been defined as a means to reduce the risk for medication (administration) errors.[29] In order to better understand this voice, Schenk et al. investigated the typical real-world behaviour of older patients interfacing with their medications when managing complex therapeutic regimens on their own.[30]

6 | DRUG PRODUCT PREPARATION BEFORE ADMINISTRATION

The patient product interface relies on physical, sensory, and cognitive capabilities of individuals. Their suitability for the intended handling may differ among patients and is commonly most critical in older people due to impaired human and organ functions. In a study by van Riet-Nales et al., a test battery was established that intended to understand which human functions such as vision, dexterity, grip strength and coordination are most critical to tablet breaking as older people commonly reported difficulties on this handling.[31]

Sufficient function with respect to dexterity, grip strength and coordination is also required to release tablets from a product carton or blister, which is an essential handling prior to taking a tablet (part). All this was investigated by Braun-Münker et al. in a comparative study with different packaging designs. In order to administer the product according to the recommended instructions, Ecker concluded that a certain degree of planning and memory is essential.[32]

Methodologies and assessment instruments to evaluate the interface of the product and patient is an emerging science to assure that the product is acceptable and fit for use by the patient, caregiver and/or health care professional. For medical devices, human factor design principles have already been implemented in the past.[33,34] Feufel et al. provide insights into the human factor approach in the healthcare environment.[35] This approach includes several cycles of user tests to remove potential sources of errors and to optimize the ergonomics for a safe and appropriate use of devices so that adaptations can be made to support the usability of drug products.

7 | INFORMATION AND COMMUNICATION TECHNOLOGY

The development of information and communication technology (ICT) in recent years has created a new level of networking between healthcare professionals and patients and in particular the interaction between patients and physicians.[36] Eggerth et al. summarizes the actual status of progress in this emerging field of science such as diagnostic sensors connected to a smartphone in order to provide physicians with real time health parameters.[37,38] By effectively and continuously monitoring health parameters in patients, the service providers will be able to focus on preventive and proactive therapeutic measures by physicians rather than reactive measures in the event of a health crisis. Implementing ICT in healthcare provision will provide valuable manners of diagnosing, monitoring and treating older and multimorbid patients with limited mobility due to its time and location independent patient access to physicians. However, information safety requires continuous attention as unintended access to data (hacking) may result in incorrect medical decision making and/or break confidentiality.

8 | REGULATIONS ON DRUG DEVELOPMENT

Before a drug product can be put on the market by industry, regulatory authorities have thoroughly reviewed the scientific data to evaluate and judge the benefit to risk for the target patient population. Since drugs are prescribed and not purchased by patient decision, for many years, the pharmaceutical product development focused on the provision of the correct dose through a product with acceptable physico-chemical product aspects compliant with regulatory quality requirements.[39] The emerging awareness of the patient factor as an important contributor to achieve the therapeutic outcomes has gained increased awareness among regulatory bodies, including the need to reflect and discuss about the consequence for

future drug development. van Riet-Nales describes the new (draft) reflections on the pharmaceutical development of medicines for use in the older population.[40] The paper suggest that regulatory authorities will continue to increasingly request the direct involvement of target patient populations in the pharmaceutical drug development and shift their view to realizing drug products of good and consistent quality that are fit for use in real world conditions.[41,42]

9 | REGULATIONS ON FRAILTY

Clinical studies are the basis for drug approval and the labelling claims. The clinical evidence generated is often limited to randomized patient populations and exclusion of the older and multimorbid patient populations.[43] The disproportionality between the study population and the major patient population using the drug after approval remains a major limitation for the clinical evidence under real-world conditions.[8] Despite the ICH E7 guideline, van Marum et al. shows the problem remains to exist.[44] To resolve the issues with clinical trials in older patients, regulatory guidelines have been put forward[45] accompanied by practical guidance to perform such trials with older patients.[46] In this themed issue, Francesca Cerreta focused on the harmonization of evaluation instruments for the increasing population of the frail patients.

10 | VIEWS FROM INDUSTRY

While progress is being made to address the arising challenges of the demographic evolution, the implementation into new drug development programs will require substantial changes: These changes cannot be achieved by the pharmaceutical industry alone as drug development is a highly regulated and step-wise process including many stakeholders in order to mitigate the immanent risk of the unknown. Timpe et al. provide insights into the remaining challenges for industry and describe the attempts of the pharmaceutical industry to balance the benefits and risks of a new drug development program against fast access of innovative medicines to all patients and patient populations around the world.[47]

11 | CONCLUSION

Already in 1960, advances in healthcare and growing life expectancy were predicted to result in unaffordability and a crisis of the healthcare system.[48] Over the past 60 years however, the new challenges arising from demographic changes and new treatments have been managed through their improved therapeutic outcomes and innovation in healthcare provision. A recent study showed that the age-related disease burden expressed as disease adjusted life years (DALYs) is declining worldwide and that differences can be attributed to certain healthcare policies.[49] The opportunities for the healthcare system therefore lie in the continuous adaptation to the emerging patient populations and the use of new drugs as well as technologies with the aim of achieving optimal therapeutic success through the efficient use of the increasing therapeutic options. This will include intensive collaboration and synthesis of the various disciplines through expert collaboration across the different stakeholders that are supported by the common goal. In contrast to the increasing clinical complexity of the multimorbid that cannot be changed, the therapeutic complexity can be reduced by the pharmaceutical drug product development. Designing pharmaceutical drug products that do not rely on lengthy and varying administration instructions instead follow patients learned and intuitive use of, for example, an oral dosage form by a higher degree of standardization will simplify the therapy management. Performing usability studies with typical final presentations of pharmaceutical drug products based on the principles derived from human factor design and usability engineering applied in medical device development help to identify and resolve unnecessary use issues build into the product at the development stages. Emerging digital technologies offer additional opportunities in advancing patient care in the multimorbid as well as old and very old patient population. With the contributions of experts from the different disciplines, this themed issue want to provide evidence about the challenges and opportunities for pharmaceutical care providers in the aging population as well as encourage broader multidisciplinary and transdisciplinary discussions to improve the pharmaceutical care and quality of life of the old, very old and multimorbid patient population.

COMPETING INTERESTS

Diana van Riet-Nales is an EMA expert. The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of/or reflecting the position of the Medicines Evaluation Board in the Netherlands (MEB), the European Medicines Agency (EMA) or any of its committees or working parties.

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