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Reflection paper on the pharmaceutical development of medicines for use in the older population

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1. Introduction

According to Eurostat, the older population in the European Union (65+ years) is expected to grow from around 84 million in 2008 to approximately 141 million by 2050. The oldest old (85+ years) constitute the fastest growing subset. Older people differ from children and adults of younger or middle age with respect to an increased prevalence of gradually declining organ and body functions, commonly resulting in physical, physiological and/or cognitive impairments, multi- and co-morbidities, and/or frailty. As any such impairment may start at different chronological ages, occur in different orders, and worsen at different rates in different people, older people of the same chronological age can be quite diverse e.g. healthy, facing some minor impairments only or frail. In general, older people are the majority users of many medicines and at highest risk of encountering practical medication (usability) problems, which may increase the risk for poor adherence, medication errors and/or reduced patient or caregiver quality of life. Therefore, it is essential that the needs of older (and especially frail) people are considered in the pharmaceutical development of medicines that may be used in the older population.

According to the Q&A of the ICH E7 guideline on clinical trials in the geriatric population, older people can be divided into three age ranges (65-74; 75-84 and 85+ years). However, rather than focussing solely on chronological age, it is more important to focus on biological age, and to acknowledge that the reflections in this paper may be of relevance to people of any age suffering from similar impairments and/or with similar needs. For example, the need for an easy to open package is relevant for rheumatic patients of any age, and dysphagia can occur in conditions such as multiple sclerosis which can affect both younger and older people.

Where possible, it is therefore encouraged to take a patient-centric approach to pharmaceutical development as the model approach. In addition, companies are encouraged to seek scientific advice in order to design, from the beginning, a medicine portfolio that takes into account as much as possible, the disease, disease setting and the needs of any patient, including older people with co-morbidities and polypharmacy. Collaboration within the pharmaceutical industry may be helpful to address common practical issues, such as the user testing of containers. Interdisciplinary collaboration and research by the pharmaceutical industry, device manufacturers, academia, health care professionals and patient organisations is encouraged to foster scientific progress in developing patient-centric medicines. Further collaboration with other parties such as regulators and experts in Health Technology Assessment (HTA) could be helpful to facilitate the entry of patient centric medicines into the market and to ensure adequate patient access.

While this reflection paper is primarily targeted at the pharmaceutical industry, it is acknowledged that it may also be of interest to other stakeholders such as physicians, pharmacists and patients because of topics such as patient adherence, medication safety and practical medication problems. The paper is intended to communicate the current status of discussions on the pharmaceutical development of medicines that may be used in the older population, and to invite comments on the topics addressed. It is not intended to provide regulatory or scientific guidance, although it may contribute to any such development in the future. It is expected that the paper will be read in conjunction with the existing directives, regulations, European Commission, ICH, CHMP and EMA guidelines, Q&A documents and other documents of relevance as linked to or published on the EMA website (www.ema.europa.eu). ISO standards may be considered, where relevant. The examples in this paper should neither be understood as an exhaustive list nor as the only possible options to address a specific topic.

The reflections in this paper apply to any new application for a marketing authorisation (MA) or variation to an existing MA, and for all application types including full and abridged MAs (i.e. new medicinal products, generics, well established use). Where appropriate, the reflections may be considered during the clinical trial phases and in the post-authorisation phase as part of the product lifecycle management. To support the progression of scientific and regulatory knowledge in the development of medicines for older people / patient-centric medicines, users of this paper are encouraged to actively send feedback to EMA on the basis of their experiences applying the principles of this reflection paper.

2. Discussion

2.1. General considerations

Characteristics of older people requiring particular consideration in the pharmaceutical development of medicines for use in the older population are summarised in Annex 1. In order to facilitate a consistent understanding of the reflections in this paper across stakeholders, a glossary is included in Annex 2.

2.2. Patient acceptability

Patient acceptability can be defined as the ability and willingness of a patient to self-administer, and also of any of his/her lay or professional caregivers, to administer a medicinal product as intended. Patient acceptability is likely to have a significant impact on patient adherence, which can have an impact on the (perceived) patient and caregiver quality of life, institutional or hospital medication safety systems and/or the medicine's benefit-risk profile. Patient acceptability is mainly determined by the interplay of the multi-dimensional requirements of the medicinal product (design) and the characteristics of the patient and, where relevant, his/her caregiver (patient product interface).

The product characteristics influencing patient acceptability in older people include:

- Route of administration (e.g. oral, inhalation, rectal, vaginal, dermal)
- Type of dosage form (e.g. tablet, capsule, suppository, oral solution, oral gel, injection).
- Site of application or administration (e.g. arm, feet, back, abdomen, ocular).
- Appearance (e.g. product size, shape, colour, bossing, inner/outer packaging, labelling).
- Swallowability (e.g. tablet size, shape, coating/waxing, liquid viscosity).
- Palatability (e.g. taste, aftertaste, smell, grittiness, , texture, flavouring).
- Patient perception (e.g. anticipated swallowability and palatability by patient before taking; appreciation of the product colour, size, shape, viscosity).
- The recommended single dose (e.g. number of tablets or injections, total volume of liquid, dose tapering).
- The recommended dosing frequency, duration of treatment, instructions on moments of dosing (e.g. take in the morning and do not eat for some time afterwards).
- The authorised shelf-life (expiry date) and recommended storage conditions.
- Any handling to be conducted prior to use (e.g. opening capsules, picking up very small tablets, measuring liquids, possibility for co-administration or mixing with food or drink).
- Ease of use of the preparation, the container closure system and the selected device.
- The complexity of the dosing instructions (e.g. every day for the first five days of the first week, and then not for five additional weeks, and then to repeat this schedule for six months).
- The readability of the package leaflet (PL; text and figures) and the completeness of information.
- The need for caregiver assistance and the setting(s) where the product is intended to be used.

Adequate patient acceptability implies that a company has identified the relevant patient needs across the different subsets in the target patient population; considered if the medicine's product portfolio is covering all such needs; evaluated if each product in the portfolio is sufficiently accepted by the subset(s) for which it has been designed; and justified that the achieved level of patient acceptability commensurate with the level of risk involved. Adequate patient acceptability is an essential aspect of the pharmaceutical development of a medicinal product and its post-authorisation life cycle. Where appropriate, adequate patient acceptability may need to be (re)confirmed or measures may need to be adopted to (re)assure a sufficient level of acceptability over the product lifecycle.

Adequate patient acceptability can be demonstrated by different means (e.g. using data from clinical trials, representative simulated use studies, human factor studies with healthy volunteers or patients, market experiences, literature). As knowledge on testing a product's acceptability in the older patient population is fragmented, the selection of the method and acceptance criteria is left to the company. However, companies will need to justify their approach (e.g. design of the trial, limit(s)) with respect to the product benefit to risk considerations in each of the relevant subsets of the older population. This justification would include consideration of the risk of poor adherence, any alternative administration strategies and medication errors.

2.3. Route of administration and dosage form

Generally, the choice of the route of administration and type of dosage form are determined by the characteristics of the active substance, the intended mode and site of action, the patient and caregiver characteristics and the setting where the product is intended to be used.

The advantages and disadvantages associated with the selection of a particular administration route and dosage form for a (specific subset of the) target patient population need to be clearly discussed in the development pharmaceuticals (CTD Module 3.2.P.2) together with the advantages and disadvantages of the selected formulation, excipients, container closure system, device and user instructions. Attention should be paid to the fact that older people may be at increased risk of non-adherence and/or medication errors.

Where appropriate, instructions or warnings in the Summary of Product Characteristics (SmPC) or Package Leaflet (PL) to ensure the safe and correct use of a specific dosage form through a specific route of administration should be considered. Any differences in instructions or warnings between the SmPC and PL are to be avoided.

An integrated approach to the design of the medicine is encouraged, including an evaluation of the risk for medication errors due to off-label use (intentional or unintentional), the advantages and disadvantages of the most relevant alternative approaches, and the rationale for the selected approach. For example, while the acceptability of fixed dose combination (FDCs) is mainly determined by clinical considerations, practical medication issues with respect to the dosage form, route of administration, formulation, packaging and user instruction also need to be considered.

Relevant aspects of the different types of dosage forms and routes of administration including those of specific importance for older patients are further elaborated below. Unless otherwise indicated, the advantages and disadvantages of particular dosage forms and routes of administration in the older population are considered to be similar to those in other age ranges.

2.3.1. Preparations for oral use

Oral administration is generally accepted as the preferred route of administration across ages. It is also the route that is most commonly used. In the older population, the patient acceptability of oral preparations and the complexity of self-administration and medication management require particular attention.

Oral liquid preparations can be manufactured in a variety of dosage forms e.g. oral solutions, emulsions, suspensions, dispersions, syrups, drops. The main advantages of these preparations are similar across ages (e.g. easy swallowing, dosing flexibility, potential for administration through feeding tubes). However, in the older population, the disadvantages are generally of more importance (e.g. choking, aspiration, difficulties opening the container closure system, risk for errors when measuring the dose or counting the number of drops, risk for excipient overload, spillage upon intake). Older people may also have greater difficulties shaking suspensions, dispersions or emulsions to attain homogeneity. For frail people or people with dysphagia, there is an increased risk that the entire recommended volume of liquid may not be swallowed, or may hamper any subsequent intake of food or drink. In some cases, thickeners may be needed to ensure safe swallowing and/or avoid choking. Large volumes may be a problem for older people on a fluid restricted diet.

Oral semi-solid preparations. Semi-solid preparations like oral gels can overcome some of the disadvantages associated with the use of oral liquid preparations. Generally, they can be taken in small volumes, can be safely swallowed, and can be packed in packages that are easy to handle and transport.

Powders, granules (including other multi-particulates). For ease of swallowing and/or to increase the overall patient acceptability, these preparations may be co-administered or mixed with food or drink rather than water in clinical practice, even if not authorised. Powders, granules and multi-particulates are commonly packed in sachets (including sticks), but in exceptional cases they may also be packed in capsules if these can be opened without problems and deliver accurate doses.

Uncoated tablets, soft capsules and hard capsules. These preparations may adhere to the mucosal surfaces in patients with dehydration, hyposalivation or xerostomia. Moreover, these preparations cannot be used in dysphagic patients. Large tablets and capsules might be problematic to swallow even in non dysphagic older patients. The ease, accuracy and acceptability of manipulation by younger adults (e.g. breaking or crushing a tablet, or opening a hard capsule) may not be predictive for older people.

Immediate and modified release tablets. There is no fixed posology or dosing frequency for these different tablet types (e.g. some immediate release tablets only need to be taken once daily; some modified release tablets need to be taken several times a day). Although immediate and modified release tablets are intended to be taken intact, immediate release tablets may be crumbled or chewed to ease swallowing, unless otherwise indicated in the SmPC/PL, whereas modified release tablets may not be handled likewise, unless recommended in the SmPC/PL.

Older people in need of lower doses or having difficulties swallowing tablets intact may (be advised to) revert to coping strategies such as tablet breaking, splitting, crumbling, chewing or even crushing. All such handling may have an effect on the patient acceptability, efficacy and safety of the medicine. Therefore, the tablet size, shape, coating and breakability require attention for products that are likely to be used in the older population.

Chewable tablets. The disadvantages of chewable tablets are of particular importance to older people. For example, chewable tablets typically contain large amounts of sugar alcohols (e.g. sorbitol, mannitol), which increase the risk for excipient overload in case of multiple medication use. Swallowability and disintegration of chewable tablets may also be negatively affected in patients suffering from e.g. dehydration, hyposalivation or impaired mastication.

Orodispersible tablets (including oral lyophilisates; ODTs). ODTs need to be protected from moisture and humidity by storage in tightly closed containers, blisters or strips. Therefore, they can normally not be stored outside their recommended package in a Multi-compartment Compliance Aid or Multi-dose Drug Dispensing System (MCA/MDD). ODTs are also often very porous and generally have limited tablet strength, which may result in further special packaging requirements. All this may result in the ODT packaging becoming difficult to open by older people.

Effervescent and dispersible tablets possess some advantages and disadvantages that are especially important at older age (e.g. easy swallowing, adequate portability, risk for sodium overload, risk for under-dosing when the resultant liquid is not fully swallowed).

Small tablets (also referred to as mini-tablets if ≤ 5 mm) are increasingly accepted as a suitable dosage form for children. The advantages may be equally relevant to the older population (e.g. dosing flexibility, easy swallowing, reduced or no risk for choking, adequate portability, alternative to oral liquid formulation). However, the disadvantage (e.g. that the tablets may be difficult to pick up) may be more relevant in older people than children.

Small (mini-) tablets can be packed in a container or blister, but also in appropriate size capsules, sachets or a dedicated dose dispenser when several tablets are needed as a single dose. A dedicated dose dispenser may also be helpful when the tablet size and shape cause handling issues (e.g. pushing small tablets through the blister, or picking up). Emerging evidence from paediatrics, vitamin supplements and newly marketed product(s) suggest that small (mini-)tablets may be well accepted in the older population. Nevertheless, patient acceptability of medicated small (mini-) tablets requires confirmation in the older population as scientific evidence in this population is scarce and fragmented.

Capsules (hard, soft). The disadvantages of capsules may be of more importance to the older population (e.g. difficulties swallowing larger capsules intact, picking up smaller capsules softening of capsules when stored outside their primary packaging (e.g. MCA)). Although capsules are normally intended to be taken intact, in justified cases they may also be opened and their contents taken as such. Soft capsules may be somewhat easier to swallow than hard capsules; however, they cannot be opened. Scientific evidence on the patient acceptability of hard or soft capsules of different sizes in the older population is fragmented and requires further confirmation.

Fixed dose combinations. From a patient perspective, the main advantage of oral fixed dose combinations relates to the reduction of the pill burden and the consequential reduction in excipient load and the complexity of medication management. The main disadvantage relates to the risk for swallowing problems if the tablet or capsule size are increased or to adapt the dose of the individual substances.

2.3.2. Preparations for dental, gingival, sublingual, buccal, oropharyngeal, oromucosal use

In the older population, the complexity of administration and the risk for accidental swallowing of these dosage forms requires particular attention (e.g. due to impaired cognition, reduced physical

capabilities). Correct use may require a certain degree of training of patients and caregivers. Accidental swallowing may be prevented by the use of dedicated administration strategies which commonly would need caregiver assistance. The absorption and distribution of these preparations may be altered by hyposalivation. Therefore, the dissolution characteristics of the solid forms may require testing in patients with normal and impaired salivation.

2.3.3. Preparations for use in the eye or ear

Older people may have greater difficulties with the correct use of these products (e.g. handling small containers, difficulties opening and holding the container, contamination of the bottle tip, difficulties to obtain enough pressure to release a drop, lifting the arm high enough to enable dropping, scratching the cornea with the bottle tip or nails). Occasionally, semi-solid ocular preparations, inserts and strips may cause prolonged blurred vision, which may increase the risk of accidents (e.g. falling).

Older people may benefit from devices supporting self-administration. These may be recommended in the SmPC/PL if found adequate. The need for unpreserved products that are commonly packed in containers which are difficult to use by older people needs to be carefully balanced against the need for containers that may be easier in use, but would need product preservation. Both types of products may need to be developed.

2.3.4. Preparations for nasal administration, inhalation and nebulisation

In general, the same technical considerations apply as to those for use in the eye or ear. A disadvantage of products for nasal administration is that older people may encounter increased difficulty in the product handling (e.g. squeezing the bottle or holding it in the correct position).

Preparations for inhalation and nebulisation requires more specific skills towards the handling of the product, the administration device and the inhalation method. The necessary skills are similar across ages however, ageing implies that older people are more prone to difficulties understanding the instructions for use; being physically able to inhale and/or handle the product as intended, or to remember how many doses have been taken from the container. All this underpins the need to confirm the patient acceptability of preparations for inhalation and nebulisation in the older population. Evidence indicates that the correct use of these preparations by older people benefits from training, especially on first use. The need for any such training may be recommended in the terms of the marketing authorisation. A dosing counter is preferred for those products commonly used in older age.

2.3.5. Preparations for cutaneous and transdermal use

The disadvantages of these dosage forms require increased attention in the older population (e.g. difficulties reaching the site of administration, opening the packaging, squeezing preparations from a tube without spillage, keeping the outer side clean from the preparation in order to avoid contamination of the patient's environment).

2.3.6. Preparations for rectal, vaginal and urethral use

The advantages of these preparations may be of particular relevance for older patients, for example, treatment at the site of action whilst reducing systemic exposure and administration in cases where the oral route cannot be used (e.g. nausea). Rectal preparations are also of value to achieve systemic effect without any relevant first pass hepatic effect. Generally, older people may have greater

difficulties opening the specific packages (e.g. strips) or understanding the instructions for use. Depending on patient characteristics such as age and culture, patients/caregivers may feel embarrassed using/administering these preparations. Especially in patients with cognitive impairment who are unfamiliar with these types of products, caregiver assistance may also be misinterpreted as an attempt for abuse.

2.3.7. Parenteral preparations

The self-administration of parenteral products by older people requires specific attention as they may have difficulty following the administration instructions correctly (e.g. impaired dexterity or cognition could impact on their ability to prepare the product or site for injection, administration of correct dose and the safe disposal of waste, used needles etc..).

For parenteral products intended to be administered by healthcare professionals and/or in hospital or other institutional settings, the user instructions in the SmPC/PL require specific attention with respect to correct product storage, handling, administration and safe disposal. Where concurrent administration of multiple parenteral products is likely, the risk of electrolyte and excipient overload requires careful attention.

2.3.8. Administration through enteral feeding tubes

Ageing increases the probability that medicines need to be administered through a feeding tube. Whereas (reconstituted) oral liquid preparations may be administered on their own and oral powders and granules with some water, other solid preparations may need to be modified and subsequently dispersed in a suitable liquid. In exceptional cases, some non-oral preparations can be given through a feeding tube (e.g. parenterals). Where the administration of a medicine through a feeding tube is a reasonable possibility in the older population given the authorised indication, it is encouraged that the feasibility of the administration of the different preparations in the medicine's portfolio through the tube is discussed in the development pharmaceuticals.

Where administration of a preparation through a feeding tube is considered to be very likely, companies will need to define and verify the instructions for the procedure for administering one of the preparations in the medicine's portfolio through a feeding tube, including any modifications of the intact dosage form. These instructions need to be added to the SmPC/PL. Inclusion of additional information in the SmPC/PL is encouraged, for example, on dissolving or dispersing a solid preparation prior to administration using a syringe, possible types of tube materials (e.g. silicone, polyvinylchloride, polyurethane, silicone), suitable tube constructions (e.g. length, diameter), compatibility of tube material with the formulation and the possibility to administer the product with enteral nutrition preparations. Information on known incompatibilities would be helpful.

Aspects to be considered in the verification of enteral administration of a preparation are generally similar across ages and may include dose and volumes for administration; possible effect of administration through the tube on bioavailability; particle size of oral powders, granules or other solid products following modification; impact of any crushing, dispersion, dissolving of solid preparations on stability and/or bio-availability; viscosity of the preparation as administered through the tube; compatibility of the (modified) preparation with the tube material and risk of physical tube blockage; normal and minimum rinsing volumes relevant to older people; dose recovery after extrusion;

2.3.9. Modifications to facilitate intake or to lower the dose

General aspects. Where a “ready to use” product addressing the needs of an older adult is not commercially available, there may be no other option than to modify one of the authorised products prior to use, e.g. mixing medicines with food or drink, breaking, crumbling or even crushing tablets. The likelihood for and risks associated with any such modifications in the older population need to be discussed in the development pharmaceuticals (CTD Module 3.2.P.2). This would include any impact on patient acceptability (including patient and caregiver quality of life) and medication safety systems.

Co-administering or mixing medicines with food or drink (including herbal products and other supplements) may be employed to ease swallowing, or to improve palatability. For orally administered products intended for use in the older population, it is encouraged that the compatibility with food or drink (food interactions) is verified, and the relevant instructions and/or warnings are included in the SmPC/PL. If the medicine’s portfolio does not include an easy to swallow preparation in the doses relevant to older people, it is envisaged that the relevant doses could be co-administered or mixed with one or several preparations for which it has been verified that they can be taken with a specific type of food or drink. The relevant instructions for the verified administration strategy need to be included in the SmPC/PL.

In case of co-administration, the compatibility with food or drink may be verified by a scientific evaluation of the characteristics of the preparation, food or drink whilst taking into consideration the short contact time, small contact area, and any instructions or contra-indications on the moments of dosing. For preparations that are mixed with food or drink, appropriate compatibility studies are normally needed. Mixing with food or drink is generally discouraged for medicines containing substances with a narrow therapeutic window, unless it has been specifically studied, as the potential variability of the delivered dose may have a more pronounced clinical impact (e.g. an unknown portion of the medicated food or drink may not be ingested or may be lost).

It is acknowledged that food and drinks are usually not standardised products and that the whole range of variability cannot be considered. Therefore, the company’s choice of food and drink requires due consideration in relation to patient acceptability, product stability and bio-availability, taking into account if the product has been administered in the clinical trials following mixing with the similar type of food or drink. Where appropriate, bio-equivalence studies could be considered.

Break-marks. Regardless of age, the presence of a break-mark needs to be considered first in relation to its potential impact on drug product stability, bio-availability and/or accidental exposure of health care professionals or the environment to a potentially harmful active substance. If a break-mark can be accepted, adequate patient acceptability (taste, texture, no sharp ridges) needs to be ensured. Break-marks may be intended to facilitate breaking for ease of swallowing or to lower the dose. Although current guidance indicates that the intended function of a break-mark should be stated in the SmPC/PL (and supported by data in the dossier where relevant), tablets are commonly marketed with an older SmPC/PL that fails to provide such information. Also, some older SmPC/PLs clearly state that the tablet may not be broken, although there is a line on the tablet suggesting breakability. Moreover, the function of the break-mark may differ between trademarks of otherwise similar products, and health care professionals may instruct patients to break tablets off-label when there are no better options available. All this may cause confusion for patients, caregivers, and health care professionals. In order to acknowledge current clinical practices and avoid medication errors, it is encouraged that all tablets with a break-mark can be subdivided into equal parts along the break-mark(either by hand or with an appropriate tablet splitter) and that lines suggesting breaking are removed from the tablet

where the tablet cannot be broken. Companies may consider adding such technical information to the SmPC/PL regardless of the function of the break-mark (i.e. for dose adjustment or ease of swallowing).

In order to avoid poor adherence and/or caregiver burden home dwelling older people should ideally be able to break tablets by hand without requiring caregiver assistance and without any relevant pain or discomfort. The implications of the disease for impaired dexterity, likelihood for comorbidities affecting dexterity and the risk of non-adherence to treatment should be considered. Given the lack of a harmonised methodology on the ease of tablet breaking in a variety of patient populations, companies may use their own justified approaches and acceptance criteria for testing the ease of hand-breaking tablets. Such justification should include details on the main characteristics of the volunteers or patients that would support adequate ease of breaking (e.g. gender, age, grip strength). When results indicate that older people with sufficient hand function find it difficult to break a tablet by hand the tablet breakability may need to be improved or an alternative tablet strength or flexible dosage form may need to be developed. Tablets that do not have a break-mark are not developed to be broken.

2.4. Dosing frequency

The dosing frequency is determined by the characteristics of the active substance, possible formulation approaches, patient characteristics, and setting. Generally, increased dosing frequencies are associated with an increase in patient burden, and reduced patient adherence.

The patient burden of more than once daily dosing is exacerbated in case of multiple medication use (especially when different preparations need to be taken at different moments of dosing e.g. before breakfast, during meals, not with other types of medicines); when specific handlings prior to administration are needed (e.g. subdivision into tablet fragments, opening capsules, measuring a liquid dose) and/or when there is a need to be take the products through different routes of administration (oral, dermal, eye).

Frequent dosing may result in impaired patient adherence. For example, home-dwelling older people may forget to take their medication or they may not have access to assisted care at each of the required moments of dosing. In hospitals and institutions, dosing may be delayed due to a lack of human resources or the need for other interventions at the recommended moments. In achieving the desired dosing frequency, fundamental changes in the product design may be considered where appropriate (e.g. modified release formulations). Assistive device technologies may be helpful to remind patients when to take medicines.

2.5. Excipients in the formulation

Generally, the suitability of excipients in the older population needs to be considered in relation to:

- the risk for altered safety profiles in case of impaired organ and body functions;
- conditions associated with ageing that might be more pronounced and/or important in the older population (e.g. coconut oil may increase cholesterol levels; sugars may increase blood glucose levels, cause dental caries and further reduce oral health).
- the likelihood of, and risk associated with, any excipient overload due to multiple medication use (e.g. sorbitol or mannitol overload may result in altered gastric transit times, laxative effect).

Besides safety considerations, the potential utility of excipients in preparations for older people also need to be considered (e.g. certain polymers and other excipients in a coating can enhance

swallowability, colours may improve medication recognition and reduce the risk of unintentional swapping and preservatives may avoid the need for storage in the refrigerator).

2.6. Container closure systems

Ease of opening. The use of the container closure system by older people may be associated with a variety of practical medication problems, e.g. difficulties opening the container due to lack of strength and difficulties with understanding the necessary handling). A diversity of coping strategies may be adopted (e.g. to refrain from administration at all or at some specific moments of dosing; to change the dosing frequency in a way that fits into caregiver visits; to ask somebody else to open the container once and to keep it open from then on or to remove all contents from the container and store these differently). All such strategies may affect the product (photo)stability, alter the medicine's efficacy and safety and increase the risk for harm to the patient and/or his/her environment (e.g. accidental child poisoning or contamination with a harmful substance).

For medicinal products that are likely to be used in the older population, the ease of administering the product through its container (e.g. ear/eye drops) or the ease of opening the container prior to administration, needs to be confirmed in justified subset(s) of the older population. Companies need to acknowledge that older people may have limited vision and health literacy and thus encounter difficulties reading and/or understanding instructions on the use of the container closure system in the package leaflet. Additional instructions on the product label may be necessary, especially when the container is used in an unfamiliar way (e.g. peel off blister).

Companies are reminded that child resistant containers should be suitable for opening by older people according to ISO standards. Where it becomes evident that home-dwelling older people with adequate hand function cannot open a child resistant container despite the ISO norm, it is encouraged that companies address this problem.

Multi-compartment Compliance Aids (MCAs) and Multi-dose Dispensing systems (MDDs) are commonly used to support medication management in special patient populations such as chronic and poly-medicated patients. Health care professionals and/or patients may not realise that the stability of a medicinal product in such packages may not be ensured if the product is taken from its authorised packaging for subsequent storage in the MCA or MDD. Although it is expected that pharmacists will carefully consider whether products can be stored in a specific MCA or MDD, and where relevant in the canisters of an automated dose dispensing (ADD) system, such evaluations are difficult to make when scientific information is scarce and fragmented. Moreover, pharmacists (and medical doctors) may be unaware that an MCA is being used by the patient. It is important to note that in some cases the need for use of MCAs and MDDs may be avoided by simple measures such as a day to day indication on a blister, or the ability for patients to write short day to day indications on blisters or strips themselves.

To ensure the stability of products in a diversity of ADDs, MCAs and MDDs, companies are encouraged to study the stability of products that are likely to be used in the older population outside the authorised container closure systems (open dish study) for short periods of time (e.g. 1-3 month) at appropriate conditions. Open dish studies are preferably conducted at 40 °C/75 % RH and repeated at 30 °C/65 % RH where the results indicate that the product is not stable. All results should be clearly reflected in the SmPC/PL. When the stability can be inferred from existing stability data, this can replace open dish studies.

Where products cannot be stored in an MCA or MDD for at least a week or in the canisters for an ADD for 1 month, it is important that this information is available in the SmPC/PL to adequately inform users of any risks. It is recommended that in such cases, companies will otherwise assist patients and health care professionals in adequate medication management, for example by the development of another type of dosage form, unit dose blisters or strips, or a day to day indication on the packaging. Warnings in the SmPC/PL that are based on a lack of data are to be avoided.

2.7. Devices and technologies

Devices. Older people may use products that need to be administered with the help of a device. Such devices can be an integral part of the medicinal product, co-packed with the product, recommended in the SmPC/PL or implicit to the type of dosage form (e.g. liquid formulations). The usability of any such devices with the product by older people requires particular attention. Where appropriate, human factor studies can be conducted.

Dosing devices. Older people may encounter difficulties measuring the correct dose. Therefore, the designs of devices that are likely to be used in the older population require particular consideration. Aspects to be considered include ease of administration by the older patient or any caregiver and the robustness of the device in daily practice e.g. to ensure that the device does not need to be filled up to the edge to account for some tremor; to ensure the appropriate size and contrast of the graduation and to avoid the risk for multi- (e.g. 10-fold) accidental dosing errors. Alternative administration strategies are expected for subsets where difficulties in handling devices are clearly recognised (e.g. Parkinson's disease).

It is expected that devices are dispensed with the product unless the device is commercially available in the region where the product is marketed. If a product requires a dosing device for administration and no device is co-packed or specified in the SmPC/PL, it is encouraged that companies demonstrate accurate dosing with the relevant types of devices that are available in the regions where the product will be marketed, and by the relevant subsets of the target patient population. If a dosing device is specifically designed for use with a particular product by the older population, then the font size and readability of the product name on the device is important.

New(er) manufacturing technologies. As a result of the anticipated increase in interdisciplinary collaboration, it is expected that the value of new(er) manufacturing technologies such as continuous or additive manufacturing (3D printing) to the development of medicines will be explored at an early stage for any special patient population. Early communication with the regulatory authorities is envisaged to consider any necessary actions in the regulatory domain.

New(er) technology related to the correct use of medicines. Newer technologies such as dose dispensers, apps, technologies to record the intake of the medication etc., may be helpful in ensuring adequate patient adherence. However, the familiarity of older people to these (assistive device) technologies is likely to vary. Also, older people may have greater difficulties in learning to handle and use these technologies as intended. A (written or visual) step-by-step user instruction in the SmPC/PL may be helpful. In addition, the need for appropriate training may be recommended. Human factor studies to evaluate the learnability and appropriateness of such a technology may be needed.

2.8. Product information

User instructions. The correct use of a medicinal product (e.g. the method to administer the product, the use of the product within its shelf-life, adhering to the correct storage condition cleaning of devices etc.) is essential to its anticipated benefit-risk profile. Taking into account different levels of health literacy, a wide variety of measures may be adopted to transfer the essential information among health care professionals, caregivers or patients (e.g. verbal, written, pictorial, videos). This reflection paper only addresses the authorised information in the SmPC/PL or on the product label.

Older people are more likely to have difficulties administering preparations themselves, or as intended. They may also have greater difficulties or even not be able to read the instructions due to the (small) font size. Therefore, the suitability of any instruction in the SmPC/PL/label needs to be considered for the different subsets in the target patient population and in the settings where the product is intended to be used. The robustness of the user instruction needs to be verified in the subset where the administration of the product is most likely to cause problems. Any alternative strategies for self-administration are highly welcomed, if verified, and should be stated in the SmPC/PL. Acknowledging that older people may need caregiver assistance, it should be considered whether there is a need to include specific instructions for assisted care.

Health literacy. Health care professionals, older people and/or caregivers may have limited knowledge on regulatory principles. Users may misinterpret the information in SmPC/PL if it is ambiguous. They may also not know what to do if the SmPC/PL do not contain the necessary practical user information. For example, they may consider that the lack of information on certain handling in the SmPC/PL implies that such handling would be acceptable (e.g. crumbling tablets or mixing medicines with food); that instructions or warnings in the SmPC/PL are identical among trademarks or that formulations with the same active substance, dosage form and strength can always be substituted. As these understandings are not correct, it is encouraged that the SmPC/PL/labelling provides either clear instructions or alternatively warnings on authorised as well as non-authorised (but commonly conducted), handling that may be associated with an important risk. Where appropriate, it is encouraged that the reason(s) for the warning is explained in the SmPC/PL. If a warning is based on lack of data, this should be clearly indicated.

User perspective. Evidence from stakeholders/scientific literature indicates that the information in the SmPC/PL and labelling of marketed products does not always meet user expectations. This may be for a number of reasons: the SmPC/PL and labelling of the marketed products do not meet current guidance; inadequate consideration of patients of different ages and/or with specific needs in the company consultation with patient groups, and regulatory provisions taking insufficient account of regional clinical practices (e.g. generic substitution, drug shortages). Therefore, companies are encouraged to review the information in the SmPC/PL and labelling of any product on the market that may be used in the older population, and to evaluate the suitability of the information for use in older people in practice. It is encouraged that the SmPC/PL and labelling of all products on the market at least meet the requirements of the current Guideline on the SmPC/PL and labelling and consider the reflections of this paper. Where companies consider that updating the SmPC/PL/labelling is not a reasonable possibility for a marketed product, they are expected to assist users in obtaining the missing information otherwise in a timely manner (e.g. additional information from compatibility or stability studies may be published and/or provided to healthcare professionals on request).

2.9. Medication management

Multiple medication use and polypharmacy. Older people are commonly on multiple medications or exposed to polypharmacy. Both imply an increased risk for prescription cascades, drug-drug interactions, drug-food interactions, the overload of salts (e.g. sodium) and/or potentially harmful excipients (e.g. sorbitol), suboptimal patient adherence, off-label handlings and delays in taking meals, drink or certain types of food i.e. sufficient and healthy eating. Thus, multiple medication use and polypharmacy may place limitations on the use of some preparations in the pharmaceutical care of older people, even if the use of such preparations in older people would be adequate on their own.

Multiple medication use and polypharmacy commonly result in complex medication regimens. Methods of tackling such complex regimens may require strategies such as standardised dosing frequencies and moments of dosing, the use of prolonged release products, application of MCAs/MDDs and medication review etc. All such strategies may cause other problems which may differ among settings. It is important that the added burden of another medicinal product on the complexity of the overall therapy in an older person is carefully considered by all of the relevant stakeholder parties. Understanding of the considerations of other parties and working practices is likely to assist in deciding on measures to ease medication management e.g. by use of medication reviews and error reporting systems in pharmacy.

Medication recognition. Patients commonly recognise oral solid preparations by their size, shape, colour, bossing or other markings rather than by reading the product label, whereas oral liquid preparations or preparations for other routes of administration may be recognized by their immediate container closure system. This practice is more likely in the older population due to the prevalence of multiple medication use and difficulties in reading. In community, hospital and institutional care, caregivers are also likely to administer medicinal products to older patients by a visual verification of the product appearance. Any confusion due to similarities in the appearance or packaging of products with a different active substance (look-alikes), or alternatively, differences in the appearance or packaging of otherwise similar products, may increase the risk for medication errors. Therefore, the appearance of the formulation (and dosage form) and the appearance and type of container closure system needs to be considered from a user perspective, taking into account the different settings where the product may be used and the likelihood for any transitions in care.

Colouring of the product preparation and colours on the product package may be helpful to differentiate among strengths. For some types of active substances or family of medicines, an EU/global colour coding system may be helpful and considered in the future. Specific sizes, shapes and colours on the outer packages may be helpful to indicate a particular (type of) product within the portfolio of a company. Harmonisation of approaches between MA holders may be needed to avoid confusion in case patients are inter-changing between products (e.g. due to generic substitution).

Switching between medicines. In order to avoid medication errors in a variety of settings, companies are encouraged to carefully compare the appearance and user instruction of their own product (preparation, device, packaging) versus others on the market (e.g. sound- or look-alikes, differences in the user instructions of otherwise similar products). Where relevant, appropriate measures in the product characteristics such as the formulation, outer packaging or product information are introduced to mitigate risk. It is encouraged that innovator and generic products have the same key visual appearance (i.e. colour, size etc.) and user instruction to the degree (legally) possible and that these instructions are up to date addressing older people's specific needs.

Stability. Older people may not remember when they opened a container. If the product has a limited shelf-life after first opening, a location on the container for the patient to write down the date of opening could be helpful.

3. Conclusions

Ageing comes with an increased prevalence of gradually declining human organ and body functions resulting in a wide variety of impairments and subsequently an increased risk of practical medication problems. In view of relevant differences in any such impairments at a certain chronological age, older people constitute a very heterogeneous group that may be better classified according to their specific needs rather than chronological age. Any such needs may require specific measures in the pharmaceutical design of the medicine (i.e. in the selection of the route of administration, type(s) of dosage form(s), formulation characteristics, strength/volume, dosing frequency, container closure system, device and user instructions in the SmPC, PL and/or labelling). The aspects associated with older age may also be of relevance to adults of middle or younger age as well as children (e.g. juvenile idiopathic arthritis). Therefore, a patient-centric approach to the medicine's pharmaceutical development is encouraged.

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Annex 1: General considerations in the development of medicines for older people

General / Cognition

- Reduced or gradually impaired cognition, mental capabilities and forgetfulness (e.g. resulting in difficulties remembering when and how to take a medicine, managing sequential procedures, swallowing oral preparations, understanding instructions, overall confusion, resisting help from others)
- Reduced health literacy

Sensory functions

- Impaired near visual acuity and/or overall vision (e.g. resulting in difficulties reading the product label or package leaflet (PL), difficulties handling preparations or opening containers).
- Impaired or altered sense of smell or taste (e.g. resulting in altered patient acceptability).
- Impaired hearing (e.g. missing instructions or explanations).
- Impaired tactile sense

Motor functions

- Dysphagia (e.g. resulting in increased risk for choking and off-label coping strategies).
- Reduced control of mouth and throat muscles (may cause swallowing difficulties).
- Impaired manual and finger dexterity, grip strength, key pinch and/or loss of finger top feel (e.g. resulting in difficulties in picking tablets from the container, pushing tablets through a blister).
- Trembling hands (e.g. resulting in difficulties measuring liquids without spillage).
- Reduced suppleness/flexibility of the arms causing difficulties reaching specific parts of the body (e.g. for administering of medicines to the ear, eye, feet or back).
- Reduced hand-eye coordination causing difficulties handling medicines (e.g. when instilling eye drops).
- Impairments in fine and gross motor skills (e.g. causing difficulties travelling to health care providers, lying prostrate may affect gastrointestinal motility, dizziness).
- Overall stiffness

Physiology and pathophysiology

- Hyposalivation, xerostomia (dry mouth), impaired mastication (chewing) (e.g. causing swallowing problems).
- Taste bud atrophy and impaired smelling (e.g. resulting in altered taste experiences).
- Altered liver and/or renal function, altered pH values in the stomach, altered gastro-intestinal motility, changes in the ratio of human body surface area to body weight and altered human body composition and functions (these may all result in changes in the pharmacokinetic pharmacodynamics (PKPD) profile of the drug, implying a need for dose adjustments; ; also

multiple pathophysiological changes of different organ systems could result in more pronounced PKPD changes).

- Reduced inspirational force and tidal volume and altered transcutaneous absorption (e.g. resulting in altered systemic effect).

Generally, older people experience greater difficulty in self-administering medicines than adults of younger or middle age, implying an increased need for caregiver assistance. Such assistance may not be readily available to older people as they commonly live alone or with an older person who faces the same difficulties. All this may result in poor adherence, specific coping strategies and/or medication errors, which may subsequently result in lack of efficacy and an increased risk for multi- and co-morbidities. Even if the medicine is administered adequately, the coping strategies may have a high impact on the patient's and/or caregiver's quality of life. Older people may also be bed ridden due to e.g. frailty or severe disease status. This may affect the passage of products through the gastrointestinal tract and the product's safety and efficacy.

Applicants and/or MA holders (i.e. pharmaceutical companies) are encouraged to develop a portfolio of medicinal products that addresses the needs of older people in the different settings where the medicine may be used (e.g. at home, in hospital, in an institution, in different countries and regions, and in different cultures). MA holders are encouraged to monitor the market and in case of changes in the availability of other products, to re-evaluate their own marketing and development strategies and take appropriate action to address the needs of older people.

Annex 2: Glossary

The following definitions have been employed in this paper.

Age ranges

- Children (paediatrics): people between birth and 18 years of age
- Adults of younger age: adults between 18 and 45 years of age
- Adults of middle age: adults between 45 and 65 years of age
- Older people (older population): adults from 65 years of age. Older people can be divided in three groups: 65-74 years (younger old), 75-84 years (middle old) and 85+ years (oldest old) (note ICH E7 Q&A).

Alternative (industry verified) administration strategy

The administration of a medicinal product other than by the usual method. Alternative administration strategies may either be industry verified and included in the SmPC and PL or they may be conducted off-label (either intentional or unintentional). Industry verification refers to the process of providing any type of adequate evidence in the marketing authorisation dossier (e.g. new (bio)analytical data, data from the literature or references to existing practices to support that the proposed administration strategy will not change the pharmaceutical characteristics of the original preparation in a way that will affect the benefit to risk profile of the medicinal product to a relevant extent).

Caregiver

A person who is e.g. assisting a patient with the management and/or administration of his/her medication. Caregivers can either be professionals (e.g. nurses, homeworkers) or lay people (e.g. family, friends). Caregivers can be of different ages, from an older child to an old person his/herself.

Co-administration or mixing with food and/or drink

The administration of a medicinal product to a patient by combining (parts of the) dose with a small portion of the food or drink (usually one spoon) and to administer the medicated food to the patient immediately afterwards. In all other cases the term mixing should be employed (e.g. dividing (parts of the) dose through a larger portion of the food or drink (usually the full meal or glass) and to administer it to the patient bite by bite or slug by slug over a longer period of time after the medicine was combined with the food or drink).

Device

Umbrella term for 1) medical device such as an oral syringe, or an inhalation spacer; 2) part of an integrated medicinal product that is intended to facilitate administration (e.g. the pen part of a prefilled-pen); 3) household tools clearly intended for the use with a medicinal product (e.g. a tablet splitter); 4) any other tool recommended for use with a medicinal product in the SmPC or PL (e.g. to cut a tablet with scissors).

Moment of dosing

Instruction on the administration of a medicinal product which implies intake at a certain moment on the day, but not necessarily exactly the same time. In case of multiple medication use, twice daily dosing of three products may result in up to six moments of dosing depending on the user instructions. For example, first product take with food, second product do not take with food, third product do not use with any other product.

Medicinal product

A preparation from a specific company in its container closure system, together with any measuring and administration device and the user instruction in the medicinal product information.

Formulation

A dosage form with a particular composition and with specific product characteristics (e.g. tablet size, shape, colour, bossing, break-mark). Formulations are not considered similar when they differ towards relevant manufacturing aspects such as dissolution, hardness and friability.

Frailty

Frailty is a dynamic process with several phases. It represents a reduction in resistance to stressors leading to increased clinical vulnerability and adverse health outcomes, whereas frail people are also vulnerable to clinically important adverse drug reactions. In older people, frailty can be preceded by multi-morbidity and followed by the development of disability. However, multi-morbidity and disability often co-exist and overlap at least in part. The prevalence of frailty increases with age, with a non-linear pattern. Frailty is more common in women than in men, but frail women have a better survival rate than frail men.

Medication management

Medication management can be defined as the facilitation and optimisation of safe, effective and appropriate use of one or all of the prescribed medicinal products by a particular patient. It is usually achieved through collaboration between the patient, their caregivers and health care professionals and determined by the characteristics of the patient, the product, and setting. Adequate medication management may require a range of measures to address practical problems (e.g. associated with medication recognition, opening of container closure system, switching). Medication management differs from the usability of a medicinal product by its focus on the complete patient's medication regimen and the adopted coping strategies.

Medicine (medication)

A general reference to all medicinal products containing a particular active substance, or, in case of a fixed dose combination product, active substances.

Medicinal product portfolio

The medicinal products marketed in a certain region that contain a particular active substance.

Mini-tablet

Small tablets ≤ 5 mm diameter, width or length, whichever is the longest.

Multiple compartment compliance aid (MCA)

An MCA normally constitutes of a box divided in smaller compartments that clearly state the name of the day and/or moment of dosing. The compartments are intended to be filled by the patient or their caregiver with all of the oral solid preparations to be taken at the indicated day and moment of dosing. MCAs are normally filled with tablets and capsules that have been taken from their packaging, but where the compartment is large enough, they may be filled with tablets or capsules still in their original blister pocket. In exceptional cases, an MCA may have been developed for use with one specific medicinal product only.

Multi-dose drug dispensing system (MDDs)

An MDD constitutes of a number of plastic bags or sealed blisters that clearly state the name of the day and/or moment of dosing. They are each mechanically filled by a pharmacy or dedicated company with all the preparations intended to be taken at the same moment of dosing. MDDs are normally used only for oral solid preparations, although some novel MDDs claim to be suitable for use with oral liquid preparations also. Oral solid preparations need to be taken from their authorised package before they can be re-packed in an MDD.

Multiple medication use and polypharmacy

The concurrent use of two or more preparations for the same or different diseases or conditions. In case of five or more preparations, the term polypharmacy may be used.

Palatability

The patient appreciation of a medicinal product following administration or entry into the oral cavity. Palatability includes the taste, aftertaste, smell, flavouring, grittiness and texture of a medicinal product.

Patient acceptability

The ability and willingness of a patient to use, and of his/her caregiver to administer, an (authorised) medicinal product as intended.

Patient-centric (centred) pharmaceutical development / product design

The pharmaceutical development of a medicine taking the specific needs of the individual patients or distinct subsets of the overall target patient population into consideration in a real world setting. This would include the patient's physiological, physical, psychological and social characteristics. A patient-centric approach could result in the selection of one or a range of medicinal products addressing specific needs across multiple subsets of the population (i.e. possibly from birth into end of life) rather than an approach directed at the development of a specific product for each subset of the population (i.e. children, adults, and older people with specific impairments). The approach may also consider issues that are currently not (fully) considered in regulatory affairs (e.g. medication management and product cost).

Patient perception

The patient anticipated swallowability and palatability of a product based on its appearance and physical properties.

Pharmaceutical design of a medicine/medicinal product

The route of administration, type of dosage form, formulation, strength/volume, dosing frequency, container closure system, measuring or administration device and the user instructions in the product information of a medicine/medicinal product (including any industry verified modifications).

Preparation

A formulation in a particular strength (e.g. tablets 5 mg, solution for injections 5 mg/ml), and, where relevant, the labelled contents of a container for single use (e.g. solution for injection 5 mg/ml, 1 ml = 5 mg or 2 ml = 10 mg).

Prescription cascade

A prescription cascade occurs when signs and symptoms of a patient are inaccurately assessed and an adverse drug reaction (ADR) is misinterpreted as a new condition, resulting in a new medication being prescribed.

Product information

The Summary of product characteristics (SmPC) and/or the Package Leaflet (PL) and the product label.

Setting

The type of patient environment where a medicinal product may be used and that may affect the use of the product by the patient and/or his/her caregiver (e.g. home, hospital, institution, country, rural or urban environment and culture).

Subdivision

General term for dividing a tablet into fragments (by hand i.e. breaking; with the help of a tablet splitter i.e. splitting or by any other tool).

Swallowability

A measure of the capacity (ability) of a patient to ingest an oral medicinal product upon administration into the oral cavity.

User

The user involves any person who is involved in the prescription, dispensing, administration or intake of a medicinal product by a patient, including any necessary product handling, modification, storage and transport.

Usability

The level to which a medicinal product can be handled in accordance with the product information in the different settings where it may be used, taking into account the variety of patient characteristics, the risk for medication errors and the burden to the patient and caregiver's quality of life.