EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 May 2017
EMA/CHMP/QWP/292439/2017

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

Draft

Draft reflection paper agreed by QWP	February 2017
Adopted by CHMP for release for consultation	18 May 2017
Start of public consultation	01 August 2017
End of consultation (deadline for comments)	31 January 2018

Comments should be provided using this template. The completed comments form should be sent to QWP@ema.europa.eu

Keywords	pharmaceutical development, older people, elderly, ageing, frailty, age-appropriateness, medication management, medication errors, off-label, usability

Note: The CHMP would like to highlight the points below for which specific attention and feedback (either supportive or with a proposal for revision) is sought:

- The format of this document which is written as a reflection paper intended to bring together the available evidence and to support discussion on the topics raised, rather than a guideline which would be intended to provide technical and regulatory requirements.
- The target audience of the paper. Currently a wide audience is considered (e.g. drug developers in industry and academia; quality assessors in regulatory agencies; patients and patient representatives; other medicinal product experts in industry and regulatory agencies).
- The use of the term 'older patient/people/population' versus 'the elderly'.
- The reflections on the accuracy of tablet breaking (2.3.9), the minimum data in regulatory submissions on the administration of medicines through feeding tubes (2.3.8) and multiple compliance aids / multiple drug dispensing systems (2.6).

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

An agency of the European Union

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

Table of contents

1 Introduction

According to Eurostat, the older population in the European Union is expected to grow from around 84 million in 2008 to approximately 141 million by 2050. The very elderly 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 human organ and body functions, resulting in physical, physiological and/or cognitive impairments, multi- and co-morbidities, and/or frailty. As any such impairments may start at a different chronological age, occur in different orders, and worsen in different rates, older people of the same chronological age can be quite different (e.g. healthy, facing some minor impairments only, 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. Considering the above, it is essential that the needs of older (and especially frail) people are duly considered in the pharmaceutical development of medicines that may be used in the older population.

This reflection 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. The paper 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.eu). 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 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. They may also be of relevance to other age groups suffering from similar impairments and/or needs (e.g. an easy to open packaging is relevant for rheumatic patients of any age). They need to be considered in a patient centric approach to pharmaceutical development.

2 Discussion

2.1 General considerations

Characteristics on older people requiring particular consideration in the pharmaceutical development of medicines for use in the older population are summarized in Annex 1. In order to facilitate a consistent understanding of the reflections in this paper across stakeholders, a glossary is included as 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 their 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 e.g. have an impact on the patient and caregiver quality of life, institutional or hospital medication safety systems

and/or the medicine's benefit to risk profile. Patient acceptability is mainly determined by the interplay of the multi-dimensional requirements (design) of the medicinal product and the characteristics of the patient and, where relevant, its caregiver. The product characteristics influencing patient acceptability in older people include *inter alia*:

- Route of administration (e.g. oral, inhalation, rectal, vaginal, dermal).
- Site of dermal application (e.g. arm, feet, back).
- Appearance (e.g. product size, shape, colour, embossing, inner/outer packaging, labelling).
- Swallowability (e.g. related to tablet size, shape, coating/waxing, liquid viscosity, mouth feel).
- The recommended single dose (e.g. number of tablets, total volume of liquid).
- The recommended dosing frequency, duration of treatment, instructions on dosing moments.
- The characteristics of the container closure system .
- The selected (medical) device to support dosing and/or administration.
- Any handlings to be conducted prior to use (e.g. opening capsules, measuring liquids).
- The complexity of the dosing instructions (e.g. every three weeks but not the fourth).
- The need for caregiver assistance
- 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 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, human factor studies with healthy volunteers or actual patients, market experiences, literature). As knowledge on testing a product's patient acceptability in the older population is fragmented, the selection of the method and acceptance criteria is left to the company. However, companies will need to justify their approach with respect to the product benefit to risk considerations in the older population, including the risk of poor adherence and/or alternative administration strategies.

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 pharmaceutics together with the advantages and disadvantages of the consequential or selected formulation, preparation, container closure system, device and user instructions. 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 rational for the selected route and dosage form.

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 complexity of self-administration and medication management require particular attention.

Oral liquid preparations. The main advantages of oral liquid 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. difficulties opening the container closure system, risk for errors when measuring the dose, 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 hamper any subsequent intake of food or drink. In some cases thickeners may be needed to ensure swallowing and/or avoid choking. Large volumes may be a problem for older people on a fluid restricted diet.

Oral solid preparations. Uncoated tablets, soft capsules and hard capsules may adhere to the mucosal surfaces in patients with hyposalivation or xerostomia. Where appropriate, a warning in the SmPC/PL or an instruction to ensure safe intake may be considered.

Powders and granules*.* The main advantages of powders and granules are similar across ages. For ease of swallowing, they may be co-administered or mixed with food or drink rather than water, even if not authorised. Powders and granules are commonly packed in sachets, but in exceptional cases they may also be packed in capsules if these can be opened without problems and deliver accurate doses.

Immediate and modified release tablets. 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, crushing or chewing. All such handlings may have an effect on the efficacy and safety of the medicine. Therefore, the tablet size, shape, coating and breakability requires attention for products that are likely to be used in the older population. 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 are likely to suffer from conditions that may affect the efficacy and safety of modified release tablets (e.g. lying prostrate).

Chewable tablets. The advantages of chewable tablets are similar across ages (e.g. they may bring benefit to people who are unable to swallow tablets or capsules intact). However, the disadvantages 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. Also, the swallowability and disintegration of chewable tablets may be negatively affected in people suffering from hyposalivation or impaired mastication.

Orodispersible tablets (ODTs). The main advantages of ODTs are similar across ages (i.e. easy swallowing, fast onset of action, adequate patient adherence). However, ODTs need to be protected from moisture and humidity by storage in tightly closed containers or blisters, which may be difficult to open by older people. ODTs also require sufficient saliva to allow disintegrants in the formulation to take effect, which may not be the case in older people suffering from hyposalivation.

Effervescent 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) 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). A dedicated dose dispenser can be considered when several tablets are needed as a single dose, or 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 tablets may be well accepted in the older population. Nevertheless, patient acceptability of small medicated tablets requires confirmation in the older population as scientific evidence in this population is scarce and fragmented.

Capsules (hard, soft). The advantages of capsules are similar across ages, however the disadvantages may be of more importance to the older population (e.g. difficulties swallowing larger capsules intact, 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. The acceptability of fixed dose combination (FDCs) is mainly determined by clinical considerations, however practical medication issues may also need to be considered. From a practical perspective, the main advantage of fixed dose combinations relates to the reduction of the pill burden and the consequential reduction in the complexity of medication management. The main disadvantage relates to the risk for swallowing problems due to increased tablet or capsule sizes.

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

The main advantages and disadvantages of these preparations are similar across ages. However, in the older population, the risk for accidental swallowing requires particular attention (e.g. due to impaired cognition, reduced physical capabilities). Accidental swallowing may be prevented by the use of dedicated administration strategies which commonly would need caregiver assistance. The absorption and distribution of the 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

The advantages of preparations for use in the eye or ear are similar across ages. However, older people may have greater difficulties with the correct use of the product (e.g. difficulties opening 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. For eye or ear suspensions, dispersions and emulsions, the same issues apply as to those for oral use. 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

The advantages and disadvantages of preparations for nasal use are similar across ages. In general, the same technical considerations apply as to those for use in the eye or ear. The use of preparations for inhalation and nebulisation requires specific skills towards the handling of the product, device and inhalation method that are similar across ages. However, ageing implies that older people are more prone to difficulties understanding and/or being physically able to follow the instructions for use; 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 at older age.

2.3.5 Preparations for cutaneous and transdermal use

The advantages of preparations for cutaneous or transdermal use are similar across ages. However, the disadvantages 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 environment.

2.3.6 Preparations for rectal, vaginal and urethral use

The advantages of these preparations are similar across ages and include, for example, treatment at the site of action whilst reducing systemic exposure, 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, people may feel embarrassed taking these preparations, especially when caregiver assistance is needed.

2.3.7 Parenteral preparations

The advantages and disadvantages of parenteral preparations are generally similar across ages. However, in older people self-administration requires specific attention.

2.3.8 Administration through enteral feeding tubes

Ageing increases the risk 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 administration of the different preparations in the medicine's portfolio through the tube is discussed in the development pharmaceutics. It is recommended that at least one of the preparations is suitable for such use and that the relevant instructions, or alternatively warnings, are included in the SmPC/PL.

Where administration of a preparation through a feeding tube is considered to be very likely, companies will need to verify the instructions for the procedure for administering the preparation, 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, latex), suitable tube constructions (e.g. length, diameter), possibility to administer the product with enteral nutrition preparations.

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, rheology, osmolality 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; effect of the preparations on mechanical integrity of the tubing material.

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 at the present time, there may be no other option than to modify one of the authorised products prior to use. The likelihood for and risks associated with any such modifications in the older population need to be discussed in the development pharmaceutics.

Co-administering or mixing medicines with food or drink 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 is verified, and the relevant instructions and/or warnings 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, limited contact area, and any instructions or contra-indications on dosing moments. 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.

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 can be administered 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.

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 acceptability, stability, bio-availability. Where appropriate, bio-equivalence studies could be conducted. However, if the product has been administered in the clinical trials following mixing with the similar type of food or drink, no further studies are needed.

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, it 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, whereas health care professionals may instruct patients to break tablets off-label when there are no better options available. All this may cause confusion with 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. 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, it is essential that a justified portion of home dwelling older people can break tablets by hand without any relevant pain or discomfort. Given the lack of a harmonised methodology, companies may use their own justified approaches and acceptance criteria for testing the ease of tablet breaking. Such justification should include details on the main patient characteristics determining the ease of breaking (e.g. gender, age, grip strength). When results indicate that older people find it difficult to break a tablet by hand whereas their hand function is still good enough to avoid assisted care, the tablet breakability may need to be improved or an alternative administration approach may need to be considered, (e.g. small (mini-) tablets).

2.4 Dosing frequency

The dosing frequency requires particular attention in the older population as it is determined by the characteristics of the active substance, possible formulation approaches, patient characteristics, and setting. Generally, the patient burden is exacerbated in case of multiple medication use, especially when different preparations need to be taken at different moments (e.g. before breakfast, during meals, not with other types of medicines), require specific handling prior to administration (e.g. subdivision into tablet fragments, opening capsules, measuring a liquid dose) and/or need to be taken through different routes of administration (oral, dermal, eye). Whereas frequent dosing can be assured in institutional care, it may result in impaired patient adherence in case of outpatient use, e.g. because of lack of assisted care at each of the different moments. In achieving the desired dosing frequency, fundamental changes in the product design may be considered where appropriate (e.g. modified release formulations).

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 human organ and body functions;
- conditions associated with ageing (e.g. coconut oil may increase cholesterol levels; sugars may increase blood glucose levels and may 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 benefits of excipients in preparations for older people also need to be considered, (e.g. colours may improve medication recognition and reduce the risk of unintentional swapping, 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, which are commonly related to the type of dosage form. A common problem relates to difficulties opening the container. A diversity of coping strategies may be adopted (e.g. to refrain from administration at all or at some specific moments; 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; to remove all contents from the container and store these differently). All such strategies may alter the medicine's efficacy and safety and increase the risk for harm in the patient and/or its environment (e.g. accidental child poisoning, contamination with a harmful substance). For medicinal products that are likely to be used in the older population, the ease of opening the container needs to be confirmed in a justified portion of the older population.

Companies need to acknowledge that older people may have low 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.

Multi-compartment Compliance Aids (MCAs) and Multi Dose Dispensing systems (MDDs) are commonly used to ease medication management i.e. in older people. 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, such evaluations are difficult to make when scientific information is scarce and fragmented. Moreover, pharmacists may be unaware that an MCA is being used by the patient. To ensure the stability of products in a diversity of 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 at ambient conditions (e.g. 1 month at 25°C/60%RH) and to clearly reflect the results in the SmPC/PL. Where products cannot be stored in an MCA or MDD for at least a week, it is important that this information is available in the SmPC/PL to adequately inform older people and health care professionals on any risks. It is recommended that in such case companies will otherwise assist patients and health care professionals in adequate medication management, for example by the development of another type of dosage form, or a day to day indication on the packaging.

2.7 Devices and technologies

Older people are commonly using preparations 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 are conducted.

Dosing devices. Older people may encounter difficulties measuring the correct dose. Therefore, the design of devices that are likely to be used in the older population require particular consideration (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; 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).

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 Member States 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, then it is expected that the product name is displayed on the device, and in such a way it can be read by older people. It is important that it is clear to patients and health care professionals that the device should not be used with other products.

New(er) technologies such as dose dispensers, apps and smart phones may be helpful in ensuring adequate patient adherence. However, the familiarity of older people to these technologies is likely to vary. Also, they may have greater difficulties in learning to handle and use these technologies as intended. A 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 (Medicinal) product information

The correct use of a medicinal product is essential to its anticipated benefit to risk profile. 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. According to current guidance on the SmPC/PL, the target patient population of a medicinal product and its presentation should be clearly described (e.g. young children, older patients with swallowing difficulties). In some cases inclusion of a warning regarding the appropriate age range may be useful. If so, it is encouraged that the risks of using the preparation outside the target age range is explained.

Older people are more likely to have difficulties administering preparations themselves, or as intended. Therefore, the suitability of any instruction 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. For products for which adequate patient adherence and dosing is critical, the robustness of the user instruction needs to be verified in the subset where the administration is most likely to cause problems. Any alternative strategies for self-administration are highly welcomed, if verified. 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 care professionals, older people and/or caregivers may consider that the lack of information on a certain handling implies that these would be acceptable. As this understanding is not correct, it is encouraged that the SmPC/PL provides either clear instructions or alternatively warnings on non-authorised, but commonly conducted, handlings that may be associated with an important risk. Where appropriate, it is encouraged that the reason(s) for the warning is explained. Where the warning is based on lack of data, this should be clearly indicated.

2.9 Medication management

Multiple medication use and polypharmacy. Older people are commonly on multiple medication use or on polypharmacy. Both may imply an increased risk for drug-drug interactions, the overload of salts (e.g. sodium) and/or potentially harmful excipients (e.g. sorbitol), suboptimal patient adherence, off-label handlings. Thus, multiple medication use and polypharmacy may place limitations to the use of some preparations in clinical practice, even if the use of such preparations in the older population 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 standardized dosing frequencies and moments, the use of prolonged release products, application of MCAs/MDDs etc. All such strategies may cause other problems. 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.

Medication recognition. Patients commonly recognise oral preparations by their size, shape, colour, embossing, rather than by reading the product label, whereas 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 reading. In hospital and institutional care, caregivers are also likely to administer medicinal products to the mainly 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, or alternatively, differences in the appearance or packaging of otherwise similar products, may increase the risk for medication errors. Therefore, 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. Colours may be helpful to differentiate among strengths. Specific sizes and shapes and colours on the outer packages may be helpful to indicate a particular (type of) product.

Switching between medicines. In order to avoid medication errors, companies are encouraged to carefully compare the appearance and user instruction of their own product versus others on the market (e.g. sound or lookalikes, differences in the user instructions of otherwise similar products). Where relevant, appropriate measures in the product characteristics such as the formulation, 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; the latter should be up to date and address older people's specific needs.

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 of 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, 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.

4 References

Cerreta F, Eichler HG, Rasi G. Drug policy for an aging population-the European Medicines Agency's geriatric medicines strategy. N Engl J Med. 2012;367(21):1972-4.

Bredenberg S, Nyholm D, Aquilonius SM et al. An automatic dose dispenser for microtablets--a new concept for individual dosage of drugs in tablet form. Int J Pharm. 2003;261(1-2):137-46.

Burns E, Mulley G. Practical problems with eye-drops among elderly ophthalmology outpatients. Age and Ageing. 1992;21(3):168-70.

Liu, Ghaffur A, Bains J. Acceptability of oral solid medicines in older adults with and without dysphagia: A nested pilot validation questionnaire based observational study. Int J Pharm. 2016 30;512(2):374-381.

Messina R, Becker R, van Riet-Nales DA et al. Results from a preliminary review of scientific evidence for appropriateness of preparations, dosage forms and other product design elements for older adult patients. Int J Pharm. 2015;478(2):822-8.

Notenboom K, Beers E, van Riet-Nales DA. Practical problems with medication use that older people experience: a qualitative study. J Am Geriatr Soc. 2014; 62(12):2339-44.

van Riet-Nales DA, Doeve ME, Nicia AE. The accuracy, precision and sustainability of different techniques for tablet subdivision: breaking by hand and the use of tablet splitters or a kitchen knife. Int J Pharm. 2014; 466(1-2):44-51.

Sino CG, Sietzema M, Egberts TC et al. Medication management capacity in relation to cognition and self-management skills in older people on polypharmacy. J Nutr Health Aging. 2014;18(1):44-9.

de Spiegeleer B, Wynendaele E, Bracke N et al. Regulatory development of geriatric medicines: To GIP or not to GIP? Ageing Res Rev. 2016;27:23-36.

Stegemann S. Drug administration via enteral tubing: an unresolved but increasing challenge. Expert Opin Drug Deliv. 2015;12(2):159-61.

Annexes

Annex 1: General considerations on older people requiring particular consideration in the pharmaceutical development of medicines for this population

Cognition

- Reduced or gradually impaired cognition, mental capabilities and forgetfulness (e.g. resulting in difficulties remembering when and how to take a medicine, swallowing oral preparations, understanding instructions).

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 sense of smell (e.g. resulting in altered patient acceptability).
- Impaired hearing (e.g. missing instructions or explanations).

Motor functions

- Dysphagia (e.g. resulting in increased risk for choking, off-label coping strategies).
- Impaired tactile sense, 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, 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).

Physiology and pathophysiology

- Hyposalivation, xerostomia (dry mouth), impaired mastication (chewing) (e.g. causing swallowing problems).
- Hyposalivation, taste bud atrophy and impaired smelling (e.g. resulting in altered taste experiences).
- Hepatic impairment, renal impairment, 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).

Generally, older people encounter greater difficulties 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 are commonly living 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. Even if the medicine is adequately administered, the coping strategies may have a high impact on the patient and/or caregiver quality of life.

Applicants and/or MA holders (i.e. pharmaceutical companies) are encouraged to develop a portfolio of medicinal products that well 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). Companies may rely on the availability of products from other companies to address older people's needs. However, in such case, companies are encouraged to monitor the market and to re-evaluate their own marketing and development strategies in case of changes in the availability of other products. Where the development of a product / a range of products addressing the needs of older people is not feasible by any company, it is expected that at least one company will develop an instruction for modification of an authorised product.

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

Adults of very old age (very elderly): adults from 75 years of age

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 assisting a patient with the management and/or administration of its medication. Caregivers can either be professionals (e.g. nurses, homeworkers) or lay people (e.g. family, friends).

Co-administration or mixing with food and/or drink

The administration of a medicinal product to a patient by combing (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).

Dosing moment

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 product may result in two up to six dosing moments 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, embossing, 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 higher in women than in men, but frail women have a better survival 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 contains a particular active substance.

Mini-tablet

This term is commonly used in literature to refer to small, medicated tablets. However, the term has not been accepted by the EDQM as a standard term. A harmonized opinion on the cut-off size of small (mini -) tablets versus those of conventional size has not yet been established. In the draft guideline on the pharmaceutical development of medicines for paediatric use small (mini)-tablets were defined as those up to 5 mm diameter, width or length whichever was 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 dosing moment. 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. 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 dosing moment. They are each mechanically filled by a pharmacy or dedicated company with all the preparations intended to be taken at the day and dosing moment printed on the specific bag or blister pocket. 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, grittiness and texture of a medicinal product.

Patient acceptability

The ability and willingness of a patient to use, and of f its caregiver to administer, a 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 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, product cost,).

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).

(Medicinal) product information

The Summary of product characteristics (SmPC) and/or the Package Leaflet (PL) and/or 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 its caregiver (e.g. home, hospital, institution, country, rural or urban environment, culture).

Subdivision

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

Swallowability

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

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 quality of life.