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

Draft

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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).



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# 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](http://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

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

- 43 • Route of administration (e.g. oral, inhalation, rectal, vaginal, dermal).
- 44 • Site of dermal application (e.g. arm, feet, back).
- 45 • Appearance (e.g. product size, shape, colour, embossing, inner/outer packaging, labelling).
- 46 • Swallowability (e.g. related to tablet size, shape, coating/waxing, liquid viscosity, mouth feel).
- 47 • The recommended single dose (e.g. number of tablets, total volume of liquid).
- 48 • The recommended dosing frequency, duration of treatment, instructions on dosing moments.
- 49 • The characteristics of the container closure system .
- 50 • The selected (medical) device to support dosing and/or administration.
- 51 • Any handlings to be conducted prior to use (e.g. opening capsules, measuring liquids).
- 52 • The complexity of the dosing instructions (e.g. every three weeks but not the fourth).
- 53 • The need for caregiver assistance
- 54 • The setting(s) where the product is intended to be used.

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

63 Adequate patient acceptability can be demonstrated by different means (e.g. using data from clinical  
64 trials, human factor studies with healthy volunteers or actual patients, market experiences, literature).  
65 As knowledge on testing a product's patient acceptability in the older population is fragmented, the  
66 selection of the method and acceptance criteria is left to the company. However, companies will need  
67 to justify their approach with respect to the product benefit to risk considerations in the older  
68 population, including the risk of poor adherence and/or alternative administration strategies.

## 69 **2.3 Route of administration and dosage form**

70 Generally, the choice of the route of administration and type of dosage form are determined by the  
71 characteristics of the active substance, the intended mode and site of action, the patient and caregiver  
72 characteristics and the setting where the product is intended to be used. The advantages and  
73 disadvantages associated with the selection of a particular administration route and dosage form for a  
74 (specific subset of the) target patient population need to be clearly discussed in the development  
75 pharmaceuticals together with the advantages and disadvantages of the consequential or selected  
76 formulation, preparation, container closure system, device and user instructions. An integrated  
77 approach to the design of the medicine is encouraged, including an evaluation of the risk for  
78 medication errors due to off label use (intentional or unintentional), the advantages and disadvantages  
79 of the most relevant alternative approaches, and the rationale for the selected route and dosage form.

### 80 **2.3.1 Preparations for oral use**

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

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

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

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

100 **Immediate and modified release tablets.** Older people in need of lower doses or having difficulties  
101 swallowing tablets intact, may (be advised to) revert to coping strategies such as tablet breaking,  
102 splitting, crumbling, crushing or chewing. All such handlings may have an effect on the efficacy and  
103 safety of the medicine. Therefore, the tablet size, shape, coating and breakability requires attention for  
104 products that are likely to be used in the older population. Although immediate and modified release  
105 tablets are intended to be taken intact, immediate release tablets may be crumbled or chewed to ease  
106 swallowing, unless otherwise indicated in the SmPC/PL, whereas modified release tablets may not be  
107 handled likewise, unless recommended in the SmPC/PL. Older people are likely to suffer from  
108 conditions that may affect the efficacy and safety of modified release tablets (e.g. lying prostrate).

109 **Chewable tablets.** The advantages of chewable tablets are similar across ages (e.g. they may bring  
110 benefit to people who are unable to swallow tablets or capsules intact). However, the disadvantages  
111 are of particular importance to older people. For example, chewable tablets typically contain large  
112 amounts of sugar alcohols (e.g. sorbitol, mannitol), which increase the risk for excipient overload in  
113 case of multiple medication use. Also, the swallowability and disintegration of chewable tablets may be  
114 negatively affected in people suffering from hyposalivation or impaired mastication.

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

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

123 **Small tablets** (also referred to as mini-tablets) are increasingly accepted as a suitable dosage form  
124 for children. The advantages may be equally relevant to the older population (e.g. dosing flexibility,  
125 easy swallowing, reduced or no risk for choking, adequate portability, alternative to oral liquid  
126 formulation). A dedicated dose dispenser can be considered when several tablets are needed as a  
127 single dose, or when the tablet size and shape cause handling issues (e.g. pushing small tablets  
128 through the blister, or picking up). Emerging evidence from paediatrics, vitamin supplements and  
129 newly marketed product(s) suggest that small tablets may be well accepted in the older population.  
130 Nevertheless, patient acceptability of small medicated tablets requires confirmation in the older  
131 population as scientific evidence in this population is scarce and fragmented.

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

139 **Fixed dose combinations**. The acceptability of fixed dose combination (FDCs) is mainly determined  
140 by clinical considerations, however practical medication issues may also need to be considered. From a  
141 practical perspective, the main advantage of fixed dose combinations relates to the reduction of the pill  
142 burden and the consequential reduction in the complexity of medication management. The main  
143 disadvantage relates to the risk for swallowing problems due to increased tablet or capsule sizes.

### 144 **2.3.2 Preparations for dental, gingival, sublingual, buccal, oropharyngeal,** 145 **oromucosal use**

146 The main advantages and disadvantages of these preparations are similar across ages. However, in the  
147 older population, the risk for accidental swallowing requires particular attention (e.g. due to impaired  
148 cognition, reduced physical capabilities). Accidental swallowing may be prevented by the use of  
149 dedicated administration strategies which commonly would need caregiver assistance. The absorption  
150 and distribution of the preparations may be altered by hyposalivation. Therefore, the dissolution  
151 characteristics of the solid forms may require testing in patients with normal and impaired salivation.

### 152 **2.3.3 Preparations for use in the eye or ear**

153 The advantages of preparations for use in the eye or ear are similar across ages. However, older  
154 people may have greater difficulties with the correct use of the product (e.g. difficulties opening the  
155 container, contamination of the bottle tip, difficulties to obtain enough pressure to release a drop,  
156 lifting the arm high enough to enable dropping, scratching the cornea with the bottle tip or nails).  
157 Occasionally, semi-solid ocular preparations, inserts and strips may cause prolonged blurred vision,  
158 which may increase the risk of accidents (e.g. falling). Older people may benefit from devices  
159 supporting self-administration. These may be recommended in the SmPC/PL if found adequate. For eye  
160 or ear suspensions, dispersions and emulsions, the same issues apply as to those for oral use. The  
161 need for unpreserved products that are commonly packed in containers which are difficult to use by  
162 older people needs to be carefully balanced against the need for containers that may be easier in use,  
163 but would need product preservation. Both types of products may need to be developed.

#### 164 **2.3.4 Preparations for nasal administration, inhalation and nebulisation**

165 The advantages and disadvantages of preparations for nasal use are similar across ages. In general,  
166 the same technical considerations apply as to those for use in the eye or ear. The use of preparations  
167 for inhalation and nebulisation requires specific skills towards the handling of the product, device and  
168 inhalation method that are similar across ages. However, ageing implies that older people are more  
169 prone to difficulties understanding and/or being physically able to follow the instructions for use; or to  
170 remember how many doses have been taken from the container. All this underpins the need to confirm  
171 the patient acceptability of preparations for inhalation and nebulisation in the older population.  
172 Evidence indicates that the correct use of these preparations by older people benefits from training,  
173 especially on first use. The need for any such training may be recommended in the terms of the  
174 marketing authorisation. A dosing counter is preferred for those products commonly used at older age.

#### 175 **2.3.5 Preparations for cutaneous and transdermal use**

176 The advantages of preparations for cutaneous or transdermal use are similar across ages. However,  
177 the disadvantages require increased attention in the older population (e.g. difficulties reaching the site  
178 of administration, opening the packaging, squeezing preparations from a tube without spillage, keeping  
179 the outer side clean from the preparation in order to avoid contamination of the environment.

#### 180 **2.3.6 Preparations for rectal, vaginal and urethral use**

181 The advantages of these preparations are similar across ages and include, for example, treatment at  
182 the site of action whilst reducing systemic exposure, administration in cases where the oral route  
183 cannot be used (e.g. nausea). Rectal preparations are also of value to achieve systemic effect without  
184 any relevant first pass hepatic effect. Generally, older people may have greater difficulties opening the  
185 specific packages (e.g. strips) or understanding the instructions for use. Depending on patient  
186 characteristics such as age and culture, people may feel embarrassed taking these preparations,  
187 especially when caregiver assistance is needed.

#### 188 **2.3.7 Parenteral preparations**

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

#### 191 **2.3.8 Administration through enteral feeding tubes**

192 Ageing increases the risk that medicines need to be administered through a feeding tube. Whereas  
193 (reconstituted) oral liquid preparations may be administered on their own and oral powders and  
194 granules with some water, other solid preparations may need to be modified and subsequently  
195 dispersed in a suitable liquid. In exceptional cases, some non-oral preparations can be given through a  
196 feeding tube (e.g. parenterals). Where the administration of a medicine through a feeding tube is a  
197 reasonable possibility in the older population given the authorised indication, it is encouraged that the  
198 administration of the different preparations in the medicine's portfolio through the tube is discussed in  
199 the development pharmaceuticals. It is recommended that at least one of the preparations is suitable for  
200 such use and that the relevant instructions, or alternatively warnings, are included in the SmPC/PL.



201 Where administration of a preparation through a feeding tube is considered to be very likely,  
202 companies will need to verify the instructions for the procedure for administering the preparation,  
203 including any modifications of the intact dosage form. These instructions need to be added to the  
204 SmPC/PL. Inclusion of additional information in the SmPC/PL is encouraged, for example, . on  
205 dissolving or dispersing a solid preparation prior to administration using a syringe, possible types of  
206 tube materials (e.g. silicone, polyvinylchloride, polyurethane, silicone, latex), suitable tube  
207 constructions (e.g. length, diameter), possibility to administer the product with enteral nutrition  
208 preparations.

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

### 217 **2.3.9 Modifications to facilitate intake or to lower the dose**

218 **General aspects.** Where a “ready to use” product addressing the needs of an older adult is not  
219 commercially available at the present time, there may be no other option than to modify one of the  
220 authorised products prior to use. The likelihood for and risks associated with any such modifications in  
221 the older population need to be discussed in the development pharmaceuticals.

222 **Co-administering or mixing medicines with food or drink** may be employed to ease swallowing,  
223 or to improve palatability. For orally administered products intended for use in the older population, it  
224 is encouraged that the compatibility with food or drink is verified, and the relevant instructions and/or  
225 warnings included in the SmPC/PL. In case of co-administration, the compatibility with food or drink  
226 may be verified by a scientific evaluation of the characteristics of the preparation, food or drink whilst  
227 taking into consideration the short contact time, limited contact area, and any instructions or contra-  
228 indications on dosing moments. For preparations that are mixed with food or drink, appropriate  
229 compatibility studies are normally needed. Mixing with food or drink is generally discouraged for  
230 medicines containing substances with a narrow therapeutic window.

231 If the medicine’s portfolio does not include an easy to swallow preparation in the doses relevant to  
232 older people, it is envisaged that the relevant doses can be administered with one or several  
233 preparations for which it has been verified that they can be taken with a specific type of food or drink.  
234 The relevant instructions for the verified administration strategy need to be included in the SmPC/PL.

235 It is acknowledged that food and drinks are usually not standardised products and that the whole  
236 range of variability cannot be considered. Therefore, the company’s choice of food and drink requires  
237 due consideration in relation to acceptability, stability, bio-availability. Where appropriate, bio-  
238 equivalence studies could be conducted. However, if the product has been administered in the clinical  
239 trials following mixing with the similar type of food or drink, no further studies are needed.

240 **Break marks.** Regardless of age, the presence of a break-mark needs to be considered first in relation  
241 to its potential impact on drug product stability, bio-availability and/or accidental exposure of health  
242 care professionals or the environment to a potentially harmful active substance. If a break-mark can



243 be accepted, it may be intended to facilitate breaking for ease of swallowing or to lower the dose.  
244 Although current guidance indicates that the intended function of a break-mark should be stated in the  
245 SmPC/PL (and supported by data in the dossier where relevant), tablets are commonly marketed with  
246 an older SmPC/PL that fails to provide such information. Also, some older SmPC/PLs clearly state that  
247 the tablet may not be broken, although there is a line on the tablet suggesting breakability. Moreover,  
248 the function of the break-mark may differ between trademarks of otherwise similar products, whereas  
249 health care professionals may instruct patients to break tablets off-label when there are no better  
250 options available. All this may cause confusion with patients, caregivers, and health care professionals.  
251 In order to acknowledge current clinical practices and avoid medication errors, it is encouraged that all  
252 tablets with a break-mark can be subdivided into equal parts along the break-mark, either by hand or  
253 with an appropriate tablet splitter. Companies may consider adding such technical information to the  
254 SmPC/PL regardless of the function of the break-mark (i.e. for dose adjustment or ease of swallowing).

255 In order to avoid poor adherence and/or caregiver burden, it is essential that a justified portion of  
256 home dwelling older people can break tablets by hand without any relevant pain or discomfort. Given  
257 the lack of a harmonised methodology, companies may use their own justified approaches and  
258 acceptance criteria for testing the ease of tablet breaking. Such justification should include details on  
259 the main patient characteristics determining the ease of breaking (e.g. gender, age, grip strength).  
260 When results indicate that older people find it difficult to break a tablet by hand whereas their hand  
261 function is still good enough to avoid assisted care, the tablet breakability may need to be improved or  
262 an alternative administration approach may need to be considered, (e.g. small (mini-) tablets).

## 263 **2.4 Dosing frequency**

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

## 275 **2.5 Excipients in the formulation**

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

- 277 • the risk for altered safety profiles in case of impaired human organ and body functions;
- 278 • conditions associated with ageing (e.g. coconut oil may increase cholesterol levels; sugars may  
279 increase blood glucose levels and may cause dental caries and further reduce oral health).
- 280 • the likelihood of, and risk associated with, any excipient overload due to multiple medication use  
281 (e.g. sorbitol or mannitol overload may result in altered gastric transit times, laxative effect).

282 Besides safety considerations, the potential benefits of excipients in preparations for older people also  
283 need to be considered, (e.g. colours may improve medication recognition and reduce the risk of  
284 unintentional swapping, preservatives may avoid the need for storage in the refrigerator).

## 285 **2.6 Container closure systems**

286 **Ease of opening.** The use of the container closure system by older people may be associated with a  
287 variety of practical medication problems, which are commonly related to the type of dosage form. A  
288 common problem relates to difficulties opening the container. A diversity of coping strategies may be  
289 adopted (e.g. to refrain from administration at all or at some specific moments; to change the dosing  
290 frequency in a way that fits into caregiver visits; to ask somebody else to open the container once and  
291 to keep it open from then on; to remove all contents from the container and store these differently).  
292 All such strategies may alter the medicine's efficacy and safety and increase the risk for harm in the  
293 patient and/or its environment (e.g. accidental child poisoning, contamination with a harmful  
294 substance). For medicinal products that are likely to be used in the older population, the ease of  
295 opening the container needs to be confirmed in a justified portion of the older population.

296 Companies need to acknowledge that older people may have low vision and health literacy and thus  
297 encounter difficulties reading and/or understanding instructions on the use of the container closure  
298 system in the package leaflet. Additional instructions on the product label may be necessary, especially  
299 when the container is used in an unfamiliar way (e.g. peel off blister). Companies are reminded that  
300 child resistant containers should be suitable for opening by older people according to ISO standards.

301 **Multi-compartment Compliance Aids (MCAs) and Multi Dose Dispensing systems (MDDs)** are  
302 commonly used to ease medication management i.e. in older people. Health care professionals and/or  
303 patients may not realise that the stability of a medicinal product in such packages may not be ensured  
304 if the product is taken from its authorised packaging for subsequent storage in the MCA or MDD.  
305 Although it is expected that pharmacists will carefully consider whether products can be stored in a  
306 specific MCA or MDD, such evaluations are difficult to make when scientific information is scarce and  
307 fragmented. Moreover, pharmacists may be unaware that an MCA is being used by the patient. To  
308 ensure the stability of products in a diversity of MCAs and MDDs, companies are encouraged to study  
309 the stability of products that are likely to be used in the older population outside the authorised  
310 container closure systems (open dish study) for short periods of time at ambient conditions (e.g. 1  
311 month at 25°C/60%RH) and to clearly reflect the results in the SmPC/PL. Where products cannot be  
312 stored in an MCA or MDD for at least a week, it is important that this information is available in the  
313 SmPC/PL to adequately inform older people and health care professionals on any risks. It is  
314 recommended that in such case companies will otherwise assist patients and health care professionals  
315 in adequate medication management, for example by the development of another type of dosage form,  
316 or a day to day indication on the packaging.

## 317 **2.7 Devices and technologies**

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

323 **Dosing devices.** Older people may encounter difficulties measuring the correct dose. Therefore, the  
324 design of devices that are likely to be used in the older population require particular consideration (e.g.  
325 to ensure that the device does not need to be filled up to the edge to account for some tremor; to  
326 ensure the appropriate size and contrast of the graduation; to avoid the risk for multi (e.g. 10-fold)  
327 accidental dosing errors. Alternative administration strategies are expected for subsets where  
328 difficulties in handling devices are clearly recognised (e.g. Parkinson's disease).

329 If a product requires a dosing device for administration and no device is co-packed or specified in the  
330 SmPC/PL, it is encouraged that companies demonstrate accurate dosing with the relevant types of  
331 devices that are available in the Member States where the product will be marketed, and by the  
332 relevant subsets of the target patient population. If a dosing device is specifically designed for use with  
333 a particular product, then it is expected that the product name is displayed on the device, and in such  
334 a way it can be read by older people. It is important that it is clear to patients and health care  
335 professionals that the device should not be used with other products.

336 **New(er) technologies** such as dose dispensers, apps and smart phones may be helpful in ensuring  
337 adequate patient adherence. However, the familiarity of older people to these technologies is likely to  
338 vary. Also, they may have greater difficulties in learning to handle and use these technologies as  
339 intended. A visual step by step user instruction in the SmPC/PL may be helpful. In addition, the need  
340 for appropriate training may be recommended. Human factor studies to evaluate the learnability and  
341 appropriateness of such a technology may be needed.

## 342 **2.8 (Medicinal) product information**

343 The correct use of a medicinal product is essential to its anticipated benefit to risk profile. A wide  
344 variety of measures may be adopted to transfer the essential information among health care  
345 professionals, caregivers or patients (e.g. verbal, written, pictorial, videos). This reflection paper only  
346 addresses the authorised information in the SmPC/PL or on the product label. According to current  
347 guidance on the SmPC/PL, the target patient population of a medicinal product and its presentation  
348 should be clearly described (e.g. young children, older patients with swallowing difficulties). In some  
349 cases inclusion of a warning regarding the appropriate age range may be useful. If so, it is encouraged  
350 that the risks of using the preparation outside the target age range is explained.

351 Older people are more likely to have difficulties administering preparations themselves, or as intended.  
352 Therefore, the suitability of any instruction needs to be considered for the different subsets in the  
353 target patient population and in the settings where the product is intended to be used. For products for  
354 which adequate patient adherence and dosing is critical, the robustness of the user instruction needs to  
355 be verified in the subset where the administration is most likely to cause problems. Any alternative  
356 strategies for self-administration are highly welcomed, if verified. Acknowledging that older people may  
357 need caregiver assistance, it should be considered whether there is a need to include specific  
358 instructions for assisted care.

359 Health care professionals, older people and/or caregivers may consider that the lack of information on  
360 a certain handling implies that these would be acceptable. As this understanding is not correct, it is  
361 encouraged that the SmPC/PL provides either clear instructions or alternatively warnings on non-  
362 authorised, but commonly conducted, handlings that may be associated with an important risk. Where  
363 appropriate, it is encouraged that the reason(s) for the warning is explained. Where the warning is  
364 based on lack of data, this should be clearly indicated.

## 365 2.9 Medication management

366 **Multiple medication use and polypharmacy.** Older people are commonly on multiple medication  
367 use or on polypharmacy. Both may imply an increased risk for drug-drug interactions, the overload of  
368 salts (e.g. sodium) and/or potentially harmful excipients (e.g. sorbitol), suboptimal patient adherence,  
369 off-label handlings. Thus, multiple medication use and polypharmacy may place limitations to the use  
370 of some preparations in clinical practice, even if the use of such preparations in the older population  
371 would be adequate on their own.

372 Multiple medication use and polypharmacy commonly result in complex medication regimens. Methods  
373 of tackling such complex regimens may require strategies such as standardized dosing frequencies and  
374 moments, the use of prolonged release products, application of MCAs/MDDs etc. All such strategies  
375 may cause other problems. It is important that the added burden of another medicinal product on the  
376 complexity of the overall therapy in an older person is carefully considered by all of the relevant  
377 stakeholder parties. Understanding of the considerations of other parties and working practices is likely  
378 to assist in deciding on measures to ease medication management.

379 **Medication recognition.** Patients commonly recognise oral preparations by their size, shape, colour,  
380 embossing, rather than by reading the product label, whereas preparations for other routes of  
381 administration may be recognized by their immediate container closure system. This practice is more  
382 likely in the older population due to the prevalence of multiple medication use and difficulties reading.  
383 In hospital and institutional care, caregivers are also likely to administer medicinal products to the  
384 mainly older patients by a visual verification of the product appearance. Any confusion due to  
385 similarities in the appearance or packaging of products with a different active substance, or  
386 alternatively, differences in the appearance or packaging of otherwise similar products, may increase  
387 the risk for medication errors. Therefore, the appearance and type of container closure system needs  
388 to be considered from a user perspective, taking into account the different settings where the product  
389 may be used. Colours may be helpful to differentiate among strengths. Specific sizes and shapes and  
390 colours on the outer packages may be helpful to indicate a particular (type of) product.

391 **Switching between medicines.** In order to avoid medication errors, companies are encouraged to  
392 carefully compare the appearance and user instruction of their own product versus others on the  
393 market (e.g. sound or lookalikes, differences in the user instructions of otherwise similar products).  
394 Where relevant, appropriate measures in the product characteristics such as the formulation,  
395 packaging or product information are introduced to mitigate risk. It is encouraged that innovator and  
396 generic products have the same key visual appearance (i.e. colour, size etc.) and user instruction; the  
397 latter should be up to date and address older people's specific needs.

## 398 3 Conclusions

399 Ageing comes with an increased prevalence of gradually declining human organ and body functions  
400 resulting in a wide variety of impairments and subsequently an increased risk of practical medication  
401 problems. In view of relevant differences in any of such impairments at a certain chronological age,  
402 older people constitute a very heterogeneous group that may be better classified according to their  
403 specific needs rather than chronological age. Any such needs may require specific measures in the  
404 pharmaceutical design of the medicine (i.e. in the selection of the route of administration, type(s) of  
405 dosage form(s), formulation characteristics, strength/ volume, dosing frequency, container closure  
406 system, device, user instructions in the SmPC, PL and/or labelling). The aspects associated with older

407 age may also be of relevance to adults of middle or younger age as well as children (e.g. juvenile  
408 idiopathic arthritis). Therefore, a patient centric approach to the medicine's pharmaceutical  
409 development is encouraged.

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433

## 434 **Annexes**

### 435 **Annex 1: General considerations on older people requiring particular consideration in the** 436 **pharmaceutical development of medicines for this population**

#### 437 *Cognition*

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

#### 441 *Sensory functions*

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

#### 446 *Motor functions*

- 447 • Dysphagia (e.g. resulting in increased risk for choking, off-label coping strategies).
- 448 • Impaired tactile sense, manual and finger dexterity, grip strength, key pinch and/or loss of finger  
449 top feel (e.g. resulting in difficulties in picking tablets from the container, pushing tablets through a  
450 blister).
- 451 • Trembling hands (e.g. resulting in difficulties measuring liquids without spillage).
- 452 • Reduced suppleness/flexibility of the arms causing difficulties reaching specific parts of the body  
453 (e.g. for administering of medicines to the ear, eye, feet, back).
- 454 • Reduced hand-eye coordination causing difficulties handling medicines (e.g. when instilling eye  
455 drops).
- 456 • Impairments in fine and gross motor skills (e.g. causing difficulties travelling to health care  
457 providers, lying prostrate may affect gastrointestinal motility).

#### 458 *Physiology and pathophysiology*

- 459 • Hyposalivation, xerostomia (dry mouth), impaired mastication (chewing) (e.g. causing swallowing  
460 problems).
- 461 • Hyposalivation, taste bud atrophy and impaired smelling (e.g. resulting in altered taste  
462 experiences).
- 463 • Hepatic impairment, renal impairment, altered pH values in the stomach, altered gastro-intestinal  
464 motility, changes in the ratio of human body surface area to body weight and altered human body  
465 composition and functions (these may all result in changes in the pharmacokinetic  
466 pharmacodynamics (PKPD) profile of the drug, implying a need for dose adjustments).

467 Generally, older people encounter greater difficulties in self-administering medicines than adults of  
468 younger or middle age, implying an increased need for caregiver assistance. Such assistance may not  
469 be readily available to older people as they are commonly living alone or with an older person who

470 faces the same difficulties. All this may result in poor adherence, specific coping strategies and/or  
471 medication errors. Even if the medicine is adequately administered, the coping strategies may have a  
472 high impact on the patient and/or caregiver quality of life.

473 Applicants and/or MA holders (i.e. pharmaceutical companies) are encouraged to develop a portfolio of  
474 medicinal products that well addresses the needs of older people in the different settings where the  
475 medicine may be used (e.g. at home, in hospital, in an institution, in different countries and regions,  
476 and in different cultures). Companies may rely on the availability of products from other companies to  
477 address older people's needs. However, in such case, companies are encouraged to monitor the  
478 market and to re-evaluate their own marketing and development strategies in case of changes in the  
479 availability of other products. Where the development of a product / a range of products addressing  
480 the needs of older people is not feasible by any company, it is expected that at least one company will  
481 develop an instruction for modification of an authorised product.

482



483 **Annex 2: Glossary**

484 The following definitions have been employed in this paper.

485 **Age ranges**

486 Children (paediatrics): people between birth and 18 years of age

487 Adults of younger age: adults between 18 and 45 years of age

488 Adults of middle age: adults between 45 and 65 years of age

489 Older people (older population): adults from 65 years of age

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

491 **Alternative (industry verified) administration strategy**

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

499 **Caregiver**

500 A person who is assisting a patient with the management and/or administration of its medication.

501 Caregivers can either be professionals (e.g. nurses, homeworkers) or lay people (e.g. family, friends).

502 **Co-administration or mixing with food and/or drink**

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

509 **Device**

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

515 **Dosing moment**

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

521 **Medicinal product**

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

524 **Formulation**

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

528 **Frailty**

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

536 **Medication management**

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

545 **Medicine (medication)**

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

548 **Medicinal product portfolio**

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

550 **Mini-tablet**

551 This term is commonly used in literature to refer to small, medicated tablets. However, the term has  
552 not been accepted by the EDQM as a standard term. A harmonized opinion on the cut-off size of small  
553 (mini -) tablets versus those of conventional size has not yet been established. In the draft guideline  
554 on the pharmaceutical development of medicines for paediatric use small (mini)-tablets were defined  
555 as those up to 5 mm diameter, width or length whichever was the longest.

556 **Multiple compartment compliance aid (MCA)**

557 An MCA normally constitutes of a box divided in smaller compartments that clearly state the name of  
558 the day and/or dosing moment. The compartments are intended to be filled by the patient or their  
559 caregiver with all of the oral solid preparations to be taken at the indicated day and moment. MCAs are

560 normally filled with tablets and capsules that have been taken from their packaging, but where the  
561 compartment is large enough, they may be filled with tablets or capsules still in their original blister  
562 pocket. In exceptional cases, an MCA may have been developed for use with one specific medicinal  
563 product only.

#### 564 **Multi dose drug dispensing system (MDDs)**

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

#### 571 **Multiple medication use and polypharmacy**

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

#### 574 **Palatability**

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

#### 577 **Patient acceptability**

578 The ability and willingness of a patient to use, and of f its caregiver to administer, a medicinal product  
579 as intended.

#### 580 **Patient centric (centred) pharmaceutical development / product design**

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

#### 590 **Pharmaceutical design of a medicine/medicinal product**

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

#### 594 **Preparation**

595 A formulation in a particular strength (e.g. tablets 5 mg, solution for injections 5 mg/ml), and, where  
596 relevant, the labelled contents of a container for single use (e.g. solution for injection 5 mg/ml, 1 ml =  
597 5 mg or 2 ml = 10 mg).

#### 598 **(Medicinal) product information**

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

601 **Setting**

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

605 **Subdivision**

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

608 **Swallowability**

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

611 **Usability**

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