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Regulatory incentives to ensure better medicines for older people: From ICH E7 to the EMA reflection paper on quality aspects

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ABSTRACT

Ageing comes with an increased propensity in the alteration of human organ and body functions, which can e.g. result in multi-morbidity, frailty, polypharmacy, altered medication safety and/or efficacy, and problems with the practical use of medicines in a real world setting. Such problems may e.g. involve difficulties opening containers, swallowing large tablets, breaking tablets by hand, or correctly understanding the user instruction. This review aims to summarize the European regulatory activities towards better medicines for older people, with a main focus on formulation development and the overall drug product design. It addresses the ICH E7 guideline "Studies in support of special populations, geriatrics", the ICH Q8 guideline "Pharmaceutical development", the EMA good practice guide on "Risk minimisation and prevention of medication errors" and the forthcoming EMA CHMP QWP reflection paper on the "Quality aspects (pharmaceutical development) of medicines for older people". In addition, three key aspects to the practical use of medicines by older people are discussed in a wider context: multi-particulates including small tablets (also referred to as mini-tablets), ease of opening and storage conditions. Furthermore, attention is paid to work in progress e.g. incentives by the European national drug regulatory authorities, and patient centric drug product development.

1. Introduction

According to Eurostat, the proportion of older people in the European Union (EU) i.e. people aged 65 years or over, is expected to increase from 17% in 2008 to 30% in 2050 (EMA, 2016a). The increase results from a variety of measures, e.g. reduction in under-five mortality, a healthy environment, adequate health care systems and timely access to safe and effective medicines from birth into old age (Sadana et al., 2016; Worku and Woldesenbet, 2015). As ageing comes with gradually altering human organ and body functions, older people may differ from adults of younger or middle age in many ways. Common differences e.g. relate to limited visibility, hearing, swallowability, motor functions, hand-eye coordination, health literacy; increased susceptibility to diseases and risk for multiple medication use and polypharmacy; altered medication absorption, distribution, metabolism and elimination; difficulties with self-caring or frailty. Older people will also commonly be living alone or with a person who is just as old, meaning any possible assistance may be limited (Stegemann et al., 2010). Thus, it is essential that the special needs of older people are taken into consideration during the development, approval and use of medicines (EMA, 2016a). This review aims to summarize the European regulatory activities towards better medicines for older people, with a main focus on formulation development and the overall drug product design.

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2. From ICH E7 to Q8 and beyond

In 1994, the International Conference on Harmonisation (ICH) efficacy guideline "Studies in support of special populations: geriatrics" (E7) was adopted to address the expected increase in the proportion of older people in the ICH regions of that time (USA, Europa, Japan) as well as the impact of ageing on the human organ and body functions. The guideline concludes that the *"use of drugs in this population requires special consideration due to the frequent occurrence of underlying diseases, concomitant drug therapy and the consequent risk of drug interaction"*. Therefore, it stipulates that *"patients entering the clinical trials should be reasonably representative of the population that will be later treated with the drug"* and that *"it is also important not to exclude unnecessarily patients with concomitant illnesses"* (ICH, 1994). As a consequence, the guideline requires companies to include a representative number of older people in the phase 2 and 3 clinical trials (ICH, 1994; EMA CHMP, 2010).

The E7 guideline acknowledges the potential impact of the drug product formulation on older people's medication responsiveness towards safety/tolerability and efficacy (ICH, 1994). However, and unlike the European regulation on "Medicinal products for paediatric use" (2006), it does not specifically address the suitability of the formulation for use by older people as such (EU, 2006). For this and other reasons, the subsequent ICH Q8 guideline on "Pharmaceutical development" (2005) stipulates that *"the product should be designed to meet patients' needs and the intended product performance"* and that *"the Pharmaceutical Development section (of the Marketing Authorisation dossier) should describe the knowledge that establishes that the type of dosage form selected and the formulation proposed are suitable for the intended use"* (ICH, 2005).

It is known that older people encounter a wide variety of practical medication problems (Hennessy et al., 2011; Kairuz et al., 2008; Mehuys et al., 2012; Notenboom et al., 2014; van Geffen et al., 2010). As a consequence, health care professionals may be left with no other choice than dispensing off-label medicines, or recommending off-label instructions to authorised drug products (Jackson et al., 2012; Kwint et al., 2013; Stegemann, 2015). Such instructions may e.g. involve opening capsules and taking the contents with food or drink to ease swallowing, or the administration of a dispersion of crushed tablets through feeding tubes in patients who are seriously ill or suffering from swallowing difficulties (Cornish, 2005; Stegemann, 2015). In addition, it is known that older people may develop their own strategies to accommodate practical medication problems, such as removing tablets from the primary package for storage in a multi-compartment compliance aid to ease medication management, or using tablet splitters as an alternative to breaking tablets by hand (Elliott et al., 2016; Zedler et al., 2011). However, any off-label administration strategy can alter the medicine's safety and efficacy profile through e.g. the risk for degradation, dosing inaccuracies or altered bio-availability (Richey et al., 2012; Stegemann, 2015).

Despite the requirements of the E7 guideline, evidence indicates that an unacceptably low proportion of older people have been included in clinical trials for medicines that are not unique to older age (Beers et al., 2014; Cherubini et al., 2010). This implies that the real world practical medication problems that are associated with older age may neither have been observed by companies during the clinical trials nor by the regulatory bodies during the marketing authorisation phase. While some stakeholders have voiced the need for a Geriatric Regulation and associated Geriatric Investigation Plan, the EMA considers that older people are the main users of medicines and that their needs are better addressed by integrating the assessment of medicines for use by older people in the general framework, and to add additional targeted guidance where needed (Cerreta et al., 2012; De Spiegeleer et al., 2016). In order to better ensure the inclusion of older people in clinical trials, article 6 of the recent regulation on clinical trials stipulates that member states need to assess whether "*the groups of subjects participating in the clinical trial represent the population to be treated*" (European Commission (EC), 2014).

3. EMA geriatric expert group

The EMA is responsible for the centralised evaluation of new medicines and associated generics, post approval drug monitoring (pharmacovigilance), and guideline development (Enzmann and Schneider, 2008). In addition, the 28 EU member states (and over 28 drug regulatory authorities) are responsible for the evaluation of innovative and generic medicines through the national, mutual recognition and decentralized procedures and for providing experts to the EMA scientific committees and working parties. Moreover, most of the EMA committee members are relying on the support of the national drug regulatory authorities for the assessment of the clinical, pre-clinical and quality data (Bachmann, 2008).

In 2011, the EMA has published a Geriatric Medicines Strategy to better address the needs of older people within the existing legislative framework. The aim of the strategy is firstly to ensure that the medicines that are used by older people are of *"high quality, and appropriately researched and evaluated, throughout the lifecycle of the product, for use in this population";* and secondly, *"improving the availability of information on the use of medicines for older people, and thereby helping informed prescription"*. The EMA considers that both aims can be realized by a range of measures including the establishment of a Geriatric Expert Group (GEG) to provide scientific advice to the EMA Committee for Medicinal Products for Human use (CHMP) and the EMA secretariat; the development of (clinical) guidelines specific to older people; the inclusion of considerations on older people in other EMA documents where appropriate; the development of a dedicated EMA webpage; and the organisation of workshops (Cerreta et al., 2012; EMA, 2011).

As part of the EMA Geriatric Medicines Strategy, the CHMP has published a draft "Points to consider on frailty: evaluation instruments for baseline characterisation of clinical trials population" (EMA CHMP, 2016). Also, the Pharmacovigilance Risk Assessment Committee (PRAC) has issued a Good Practice Guide on "Risk minimisation and prevention of medication errors" including a chapter dedicated to elderly patients (EMA PRAC, 2015a). Furthermore, the EMA CHMP Quality Working Party (QWP) is developing a reflection paper on the "Quality aspects (pharmaceutical development) of medicines for older people" (EMA CHMP, 2013). The paper is intended to be read in conjunction with the existing regulatory provisions, including any other EMA document, the EU Commission guidelines and the European pharmacopoeia (Ph. Eur.) (EMA, 2016b).

Many of the current QWP guidelines, reflection papers and Question and Answers documents (Q&As) contain statements on the practical use of medicines in a real world setting. Most of these statements are related to patients of any age, yet many are particularly important to older people (EMA, 2016b). As statements that have already been published elsewhere are not intended to be repeated in QWP reflection papers, it is crucial that companies are familiar with all QWP documents. For example, the guideline on the "Quality of transdermal patches" (2014) indicates that "*the suitability of the transdermal patch in use should be fully discussed*" and that the aspects to be considered e.g. include *"the identification, markings, appearance and visibility of the transdermal patch";* the *"site of administration, and change in site per dose"; and "avoidance of cutting of the transdermal patches"*.

These statements are e.g. intended to assure that patients are more likely to self-administer patches correctly, and that they are able to control if a patch is still on their skin, accidentally attached to another person (child), or adequately removed (EMA CHMP, 2014; EMA PRAC, 2015a,b).

4. Medication errors

Medication errors can be defined as *"any unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient"* (EMA PRAC, 2015a,b). It is important to realize that such unintended failures may be due to both intentional as well as unintentional deviations from the instructions in the authorised product information i.e. in the product label, package leaflet or summary of product characteristics (SmPC) (Kwint et al., 2013; Stegemann, 2015; Urban et al., 2016). Medication errors can occur in patients of any age and at any stage of pharmacotherapy e.g. prescriptions by health care professionals; dispensing by community and hospital pharmacies; storage at pharmacies, wards, patient homes, holidays; preparing the product for administration; and the actual administration to or intake by the patient (EMA PRAC, 2015a).

As older people are the main users of medicines and have specific needs, they are particularly prone to medication errors (Elliott et al., 2016; EMA PRAC, 2015a; Urban et al., 2016). Medication errors place a high burden on health care resources. For example, Leendertse et al. showed that the main determinants for preventable medication related hospital admissions included impaired cognition, the living situation and polypharmacy. The author also estimated that the medical costs in older people was €5637 per submission (Leendertse et al., 2011). The study did not evaluate which proportion of the admissions was due to a suboptimal drug product design for patients of older age, or due to the fact that medicines had been swapped as a result of

Annex 1: Potential sources of medication error in medicinal product design

- *"Some multiple tablet strengths are available with a similar appearance in terms of colour, size and shape (or if multiple strength tablets are presented in similar packaging to each other), which may lead to incorrect dosing".*
- *"Some tablets include a score-line down the centre so that tablets can be broken into smaller doses, but the tablets may be difficult to break or not break cleanly, meaning that broken tablets may not provide the correct dose".*
- *"Blister packs may be difficult to open for patients with dexterity problems".*
- *"Non-parenteral formulations such as suppositories and pessaries may be accidentally eaten instead of being inserted, and may also be used at the wrong sites".*

Annex 2: Design features which may reduce the risk of medication errors

- *"In the case of applications for more than one tablet strength, the different tablet strengths should be distinguishable at a level sufficient to avoid mistakes between the different strengths by the final user. Distinguishing tablet strengths by colour/shape and marking/embossing is preferable. Colour conventions should be followed where these have been agreed at Member State level for a class or group of medicinal products; care should be taken in clinical trials where colours may be changed to preserve blinding"*
- *"Where reports have been received of tablets being difficult to swallow (e.g. due to size or coating), reformulation or a break mark could be considered."*
- *"The instructions for handling of tablets/capsules which are friable and prone to breaking should instruct the user to peel back the foil covering blister packs and remove the tablet from the blister".*
- *"Suppositories and pessaries should be accompanied by instructions for use which state that they should not be swallowed or placed in the mouth".*

Fig. 1. Examples from the EMA Good Practice Guide on "Risk minimisation and prevention of medication errors" which are considered to be of relevance to the drug product design of medicines for use by older people.

substitution policies or transitions in care. Nevertheless, the study underpins the need for further research into the cost or savings on national health budgets as well as improved patient health aspects by reimbursing potentially more expensive drug products that well address older people's needs, rather than those cheap(est) in class only.

The EMA Good Practice Guide on "Risk minimisation and prevention of medication errors" addresses the need to improve the current situation (EMA PRAC, 2015a). The Guide is intended to be read in conjunction with the addendum on "Risk minimization strategy for high-strength and fixed-combination insulin products" and another Good Practice Guide on "Recording, coding, reporting and assessment of medication errors" (EMA PRAC, 2015b, c). The Guide relates to medicines for people of any age, however, many aspects are of particular importance to older people. Annex 1 "Potential sources of medication error in medicinal product design" lists possible causes of medication errors. In Annex 2 "Design features which may reduce the risk of medication errors" possible risk mitigation measures are proposed (EMA PRAC, 2015a). However, there is no direct link to the issues identified in Annex 1 and Annex 2 (Fig. 1).

As the Guide is written from a pharmacovigilance perspective, it takes a retrospective view on measures in the pharmaceutical design of medicines to mitigate medication errors i.e. from real world problems to the proposed design features. We consider that a prospective strategy during pharmaceutical drug development and at the time of marketing authorisation may further add to mitigating risk. Existing, future revisions of, and new regulatory (quality) documents may serve this goal.

For products that are already on the market, pharmaceutical companies should take account of the provisions of Directive 2001/83 article 23. This article states that *"After a marketing authorisation has been granted, the marketing authorisation holder shall, in respect of the methods of manufacture and control provided for in Article 8(3)(d) and (h), take account of scientific and technical progress and introduce any changes that may be required to enable the medicinal product to be manufactured and checked by means of generally accepted scientific methods"* (EU, 2001). However, it is not yet clear if, and if so, when, drug regulatory authorities can require companies to update the quality of drug products with reference to this obligation. For example, if and when companies can be asked to add information to the package leaflet on tablet chewing or crushing; and when tablets cannot be chewed or crushed, if and when, companies can be asked to reduce the size of large tablets and/or to develop an additional easy to swallow formulation.

5. Reflections for older people: learning lessons from paediatrics

According to the "Procedure for European Union guidelines and related documents within the pharmaceutical legislative framework", the reflection paper on the "Quality aspects (pharmaceutical development) of medicines for older people" is intended to communicate the current status of discussion and to invite comments on the topics addressed. Using this approach, reflection papers can contribute to the future development of CHMP or ICH guidelines, which are then intended to reflect the current status of scientific and technical progress, and to be considered as "soft law" with a quasi-binding character (EMA, 2009). As the earlier "Reflection paper on formulations of choice for the paediatric population" was commonly used as if it would provide binding information, it is important that the reflection paper for older people will clearly note how its reflections are to be understood (EMA CHMP, 2005).

As with the drafting of the "Guideline on the pharmaceutical development of medicines for paediatric use", the development of the reflection paper on "Quality aspects (pharmaceutical development) of medicines for older people" infers that a three pillar approach will be followed (EMA CHMP and PDCO, 2013; EMA CHMP, 2013). The development of the reflection paper is therefore intended to start with an analysis of the relevant scientific literature and post-marketing data (Messina et al., 2015). Also a close interaction with stakeholders on practical issues is foreseen as well as a gap analysis of how marketed authorisations are not fully meeting the needs of older people (EMA CHMP, 2013; Notenboom et al., 2014). This information can then also be used by all stakeholders (academia, industry, regulatory authorities) to focus their research on the areas of most interest to healthy ageing. Where appropriate, it is envisaged that the quality reflections for older people will follow a similar thought process as the guidance already adopted for paediatrics.

According to the aforementioned paediatric guideline, a (paediatric) medicine/(paediatric) medicinal product can be defined as "a (paediatric) formulation in a particular strength (e.g. tablets 5 mg, solution for injections 5 mg/ml) and, in case of (paediatric) formulations for single use, the labelled container contents (e.g. solution for injection 5 mg/ml, 1 ml = 5 mg or 2 ml = 10 mg)", where a (paediatric) formulation is to be understood as "the composition (and not stated, but also meant, the appearance) of a particular dosage form of a medicine for (paediatric) use" (EMA CHMP and PDCO, 2013). This implies that companies may need to develop a range of drug products, i.e., different types of dosage forms and/or formulations and/or strengths and/or container closure systems and/or measuring and administration devices, to address the variety of special needs across the overall target patient population of a medicine.

When deciding on the portfolio of drug products in which a medicine will be put on the market, besides manufacturability and financial considerations, it is expected that companies also consider the possibility of an increased risk for medication errors due to patient confusion, e.g. when patients do not recognize that drug products that are prescribed by different health care professionals actually represent the same medicine. Thus, companies need to consider a "patient centric approach" whereby a specific design approach is intended to address a variety of needs across the target population rather than a gold standard approach for each problem and each subset specifically (Hanning et al., 2016; Sharma, 2015; Stegemann, 2016).

Although the term patient centric medicines is increasingly employed in scientific publications and an American Association of Pharmaceutical Scientists' (AAPS) focus group on patient centricity has been installed, a harmonized definition in the context of pharmaceutical product design is not yet available (AAPS, 2016; Stegemann, 2016). For the time being, the authors consider that patient centric medicines can be defined as those "that have been designed to address the variety of needs of individual patients, caregivers and health care professionals in a real world setting and across the target patient population". This definition is consistent with Hanning et al. indicating that a patient centric formulation development refers to "considering the end user from the beginning of the formulation process and right through the development to an end product", and Zucca et al. indicating that "the first step in ensuring patient-centred quality of care is to ask the patient about the care they would like" (Hanning et al., 2016; Zucca et al., 2016).

In the next paragraphs, some specific aspects relevant to the pharmaceutical development of medicines for older people will be discussed in a wider context.

6. Multi-particulates

Oral liquid formulations are known for a range of potential problems such as bad taste, need for storage in the refrigerator, limited stability, difficult portability and/or errors when measuring the dose. Oral flexible solid dosage forms (multi-particulates) have been proposed as a valuable alternative. In the past, multi-particulate formulations mainly included powders and granules. However, small sized tablets (also referred to as mini-tablets in the scientific literature) are increasingly being accepted as an oral solid flexible paediatric dosage form (van Riet-Nales et al., 2016).

Currently, a harmonized definition on the size of small (mini-) tablets is not available. In the draft version of the aforementioned paediatric guideline, they were considered as tablets up to 5 mm diameter (EMA CHMP, 2011). However, the categorization of tablets into small, medium, large and very large size was not supported by stakeholders during the public consultation as the scientific data was scarce and fragmented. Thus the definition of small (mini-)tablets is open for discussion.

Evidence suggests that the acceptability (including the risk of choking) of mini-tablets in young children relates to tablet size, shape, coating, palatability, and the time necessary to dissolve in the mouth (Liu et al., 2014). If sufficiently small (2-mm) and rapidly dissolving, they may be used from pre-term birth (Klingmann et al., 2016). In older people, the patient acceptability of mini-tablets that are to be taken on their own has hardly been investigated (Hayakawa et al., 2016; Liu et al., 2016). Nevertheless, mini-tablets may already be well known to older people due to vitamin D supplementation (Figs. 2 and 3).

We believe that the aspects to be considered in the suitability of mini-tablets for older people may be similar, but also different to children. Such differences may e.g. relate to the relationship between tablet size, shape, coating, and, where appropriate, colour, on e.g. sticking of tablets between the teeth, or sticking to the upper and back parts of the mucosal cavity; picking up tablets from the container and after dropping; visibility in and outside the primary container, in multi-compartment compliance aids or in multi-dose drug dispensing systems. In addition, the patient acceptability, preference and usability of different types and sizes of mini-tablets by older people in comparison with other types of dosage forms generally used in older age remains to be investigated. As we find it difficult to pick up 2-mm tablets by hand ourselves, we believe that it is likely that 1-mm and 2-mm mini-tablets would need to be administered to older people through a medical device. The Swedish Medical Products Agency (MPA) has already authorised 3-mm diameter tablets for use in Parkinson patients by administration through a dedicated dose dispenser (MPA (Läkemedelsverket), 2014).

7. Ease of opening

Older people may experience difficulties opening medication packages, for example because of lack of hand grip and strength, impaired hand-eye coordination, or because they were simply not aware of the peel-off rather than push-through character of a blister strip (Hennessy et al., 2011; Kairuz et al., 2008; Philbert et al., 2014; van Geffen et al., 2010). As current regulatory provisions do not foresee in testing the user friendliness of commonly applied container closure systems, older people may benefit from further attention to this topic.

Since the European legislation does not include any obligation to pack medicines in child-resistant containers, it is up to the legal provisions of the European member states and/or the opinion of the EMA or European drug regulatory authorities to decide if medicines need to be packed in child-resistant containers, and if so, when. For example, the UK Medicines & Healthcare products Regulatory Agency (MHRA) requires that products containing paracetamol, aspirin and more than 24 mg of elemental iron are

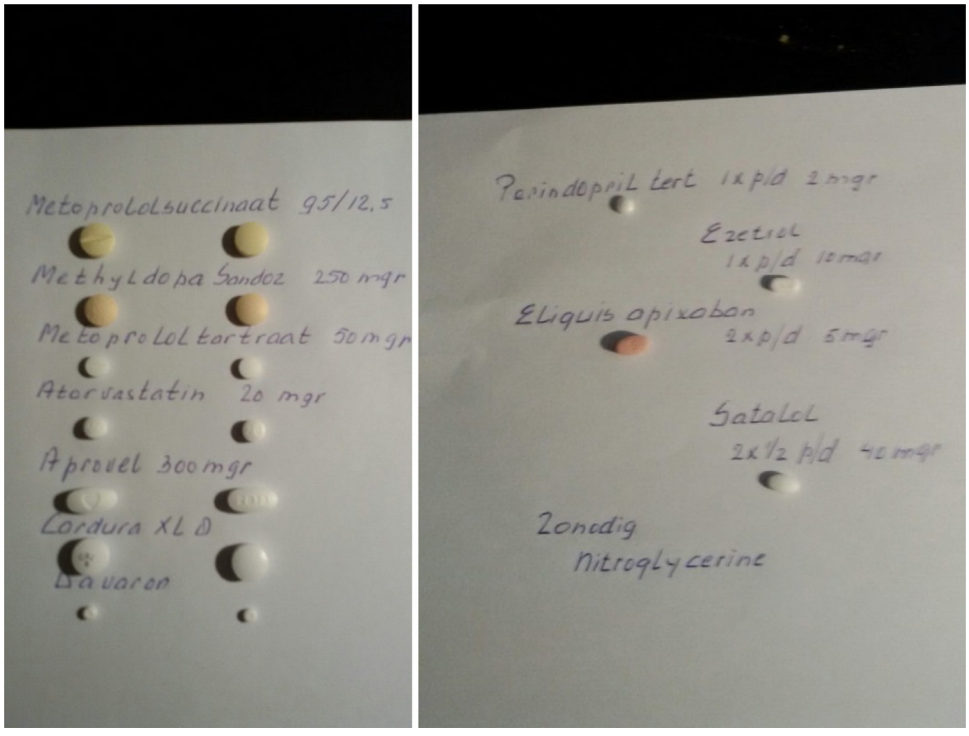

Fig. 2. Polypharmacy in an older home-dwelling couple: challenges in medication recognition and use of a small (mini-) tablet (vitamin D, davaron, left picture).

Fig. 3. Polypharmacy in an older home-dwelling couple. Medication of one of the patients two weeks later. The use of methyldopa is discontinued. The patient is given a different trademark of atorvastatin tablets with a different product appearance.

packed in child-resistant containers, but not if the formulation is effervescent or in single dose units (MHRA, 2016). In addition, it is known that other authorities have more implicit rules which are based on the consideration that drug products must be packed in child-resistant containers when the intake of a single unit may bring serious harm to the child, e.g. oxycodone, methylphenidate and apixaban. Others may rather consider that child-resistant packages may bring little benefit, as medicines must be kept out of the reach and sight of children (Fig. 4). In any case, it must be carefully assured that child-resistant containers can be adequately opened by older people, for example by showing compliance to the ISO standards for child-resistant closures (ISO 2016a; ISO 2016b).

8. Storage

Older people are likely to use more than a single medicine concurrently (Figs. 2 and 3). The concept is commonly referred to as multiple medication use or, in cases where more than 5 drug products are used, polypharmacy (Mortazavi et al., 2016). Multiple medication use and polypharmacy may necessitate the need to take specific measures to ease medication management, improve patient adherence and avoid the risk for medication errors. For example, medicines may be stored by patients at a convenient location (Fig. 4). As another example, they may be stored in multi-dose drug dispensing packages or multi-compartment compliance aids (Kwint et al., 2013; Mehuys et al., 2012; Sino et al., 2014) (Fig. 5).

Multi-morbidity in older people also implies that they may be regularly visiting different health care professionals and moving from home to hospital, institutions and back again. However, patients may be using different trademarks of the medicines in the different settings. It is known that the interchangeability of drug products containing the same active substance from different companies requires particular attention in order to ensure adequate clinical efficacy, medication recognition and adherence to potentially different user instructions (Seoane-Vazquez et al., 2016; Urban et al., 2016) (Fig. 3). It is also known that patients may gather large quantities of medicines at home when they are receiving new prescriptions upon each visit or transition of care. This may result in e.g. accidental overdosing, the use of products long after their (in-use) shelf-lives had expired, or environmental waste.

9. Work in progress

As indicated, the EMA is paying increased attention to the special needs of older people, including the drug product design (EMA, 2016a,b; EMA CHMP, 2013; EMA PRAC, 2015a,b,c). At the same time, it is known that national drug regulatory authorities and the European Pharmacopoeia are developing additional measures to support this aim. For example, the Medicines Evaluation Board in the Netherlands (MEB) has adopted a strategic business plan including a focus on the promotion of the good use of medicines, patient directed assessments and innovation (MEB, 2013). It is expected that older people will highly benefit from this strategy. Also, in collaboration with the Expertisecentre Pharmacotherapy in Old persons (EPHOR), the MEB is collecting data on older people that is less visible from the marketing authorisation approval documents. Furthermore, the MPA has, in co-operation with the National Board of Health and Welfare and other Swedish health agencies, initiated a workplan to identify problems in relation to the pharmaceutical treatment of older people in order to propose improvement measures (MPA, 2016a). Also, the MPA grants permissions for the dispensing of oral medications outside their authorised package. In order to receive an opening permission of the container closure system for automated dose dispensing, the marketing authorisation holder has to perform stability studies of the drug product in open storage. The requirements of the scope of the studies depend on the conclusions drawn from the stability data in the marketing authorisation dossier. The studies should include an analysis of stability indicating parameters such as degradation products (MPA, 2016b).

Fig. 4. Measures to ease medication management: home storage of medicines by an older home-dwelling couple on polypharmacy posing risks if young children are present in the dwelling.

Moreover, the European Directorate for the Quality of Medicines & Healthcare (EDQM) has published a proposal for revision of the European Pharmacopoeial (Ph. Eur.) test on the uniformity of mass of tablet fragments following breaking by hand (EDQM, 2015). The proposed revision is subject to multiple interpretations by stakeholders as some consider that any break-mark would need to comply with the test, whilst others consider that this is not the case. Thus, further clarification is awaited. In any case, it must be recognized that the guideline on "Summary of Product Characteristics" clearly indicates that break-marks may be present for ease of swallowing only (EU, 2009).

For break-marks that are intended to ease swallowing, it is (yet) not considered necessary that the break-mark complies with the Ph. Eur. test, as it is suggested that dosing accuracy will not be affected by taking several fragments as a single dose. However, it can be questioned if the current regulatory approach is in the interest of public health. First of all, it implies that there is no control on any loss of mass in case tablets are broken to ease swallowing. Also, there is no control as to whether breaking really eases swallowing, especially in case of fragments largely differing in mass (and thus size). Moreover, regulators are increasingly recognizing that off-label breaking for dose reductions is a common practice, and that restrictions to the use of break-marks for ease of swallowing are either not known or not practical in a real world setting. Thus, further discussion on the scope of the Ph. Eur. test is warranted.

10. Conclusion

A variety of measures has been installed over the last decades to address the specific needs of special patient populations, including older people (ICH 1994; ICH, 2005). The 2011 Geriatric Medicines Strategy will further assist addressing older people's needs within the existing legislative framework (EMA, 2011). The forthcoming EMA reflection paper on the "Quality aspects (pharmaceutical development) of medicines for older people" is expected to summarize the current status of discussion and to invite comments on the topics addressed (EMA CHMP, 2013). It is anticipated that the paper will follow a similar thought process as adopted for the "Guideline on the pharmaceutical development of medicines for paediatric use" (EMA CHMP and PRAC, 2013). Furthermore, it is envisaged that the identification of knowledge gaps will stimulate research by industry, academia and/or regulatory authorities into the domains where knowledge is still scarce and fragmented (Gispen-de Wied and Leufkens, 2013). In order to address older people needs, it must be acknowledged that any practical problems currently experienced, are related to products already on the market. Therefore, both a prospective as well as retrospective approach to adequate (patient centric) product design is warranted to better address older people's needs. A stakeholder discussion on the minimum quality standards to be met by any marketed product i.e. across the products lifecycle from early market introduction, through variations and end of sales, might be helpful.

Fig. 5. Use of multi-compartment compliance aids by an older home-dwelling couple to ease medication management and ensure adequate drug adherence for a week.

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