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An industrial perspective on the design and development of medicines for older patients

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ABSTRACT

An increasing elderly population is leading to a change in the global demographics. This presents a new challenge to society and the pharmaceutical industry. This demographic shift is providing an opportunity for the pharmaceutical industry to meet the specific needs of the changing patient population. One issue that has been identified is defining what is meant by "an older patient", since this definition cannot be simply limited to chronological age. The fundamental purpose of the design and development process is to create a product that can be used by the patient group in a safe and efficacious manner. In the pharmaceutical industry ICH Q8 is used to guide the design and development of medicines. The process leads to the definition of the Quality Target Product Profile (QTPP) for a specific drug product and patient population. One can imagine a product with various presentations described in the QTPP which suit paediatrics, adults and older patients. It is recognised that designing medicines for smaller population groups will result in multiple presentations that could lead to smaller manufacturing batch sizes. In the short to medium term; dose flexibility, easy-to-swallow formulations, and easier access packaging are all factors under consideration. Dose flexibility could be achieved with various dosage forms such as oral liquids, mini-tablets, or multi-particulates. Whilst patient dosage preferences are beginning to be understood, further investigation is needed to balance the needs of the patient, care giver, prescriber, and payer. There also remain a number of challenges with the engineering solutions and delivery device for mini-tablets and multi-particulates (aside from filled capsules) to accurately and robustly deliver the dose, and issues with handling the device and the packaging for an older patient. It is also recognised that there are numerous challenges, not least of which is the definition of the older patient and a generic QTPP for an older patients' drug product. It is likely that there will be no simple solution or 'one-size-fits-all' approach in drug product development to resolve the complex issues presented by the ageing population.

An increasing elderly population is leading to a change in the global demographics. This presents a new challenge to society and the pharmaceutical industry. In the UK alone there are 11 million people aged over 65 years and 3 million people who are aged over 80 years (Age UK, 2015). The number of those over 85 years of age has doubled in the years between 1994 and 2009 to 1.4 million and if current trends continue it is predicted to reach 3.5 million by 2035 (ONS, 2010, 2012); this change to the population age ratio is mirrored across Europe and the USA. With regard to patient care, the vast majority of medicines are used by people in this older patient population. For example in the UK alone approximately one third of over 75's living in the community are prescribed four or more medicines per day, whilst those living in nursing homes have six to eight medicines daily (Gorard, 2006).

This demographic shift is providing an opportunity for the pharmaceutical industry to meet the specific needs of the changing patient population. One issue that has been identified is defining what is meant by "an older patient", since this definition cannot be simply limited to chronological age. While it is well established that ageing impacts PK/PD, accompanied by declining renal and hepatic function (Noble, 2003), significantly slower gastric emptying, and lower gastric pH (Bai et al., 2016) there are other age-related factors which may be worthy of consideration; for example, dysphagia which can be a problem for oral administration of the drug product and can lead to non-adherence to the dosing regimen (Stegemann et al., 2012). If additional factors such as disease state, patient lifestyle, cognitive decline, visual acuity, decreasing dexterity, and lower medicine adherence are included

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then the profile of patient needs becomes increasingly diverse and difficult to define.

Often the drug product development process will focus on generating a single product and while there is usually special attention for the paediatric population (EMA, 2013) it is now becoming increasingly common that other patient populations may be considered. Patients tend to be grouped together broadly by chronological age (adult or paediatric) or by disease state. With respect to the geriatric or elderly population demographic, there is a desire to shift away from attempting to define and treat this as one specific, albeit diverse, group. Instead a patient centric approach to product design and development may now be considered; one with a focus on how the medicine will be used by the patient and/or care giver. Patient or end user definition is therefore increasingly important; when taking into account the older demographic there needs to be an understanding of whether this constitutes the majority of the patient population or is a smaller sub-set within the wider group. This in turn may influence the decision process during drug product development when seeking to establish the design of the medicine.

The fundamental purpose of the design and development process is to create a product that can be used by the patient group in a safe and efficacious manner. In the pharmaceutical industry ICH Q8 is used to guide the design and development of medicines (ICH Q8, 2009). The process essentially begins after the discovery of the active pharmaceutical ingredient (API) and the definition of the mechanism of action. Often an enabling formulation is developed to support pre- and early clinical studies, which are usually conducted in a healthy population. The next step is to define the requirements for the later clinical stages and the proposed commercial drug product; this is the ideal time in drug product development to consider patient needs including the needs of the elderly population. This process may take the form of a discussion with subject matter experts in drug product development, clinicians, marketing, regulatory specialists and patients, and often includes reaching out to specific patient advocacy groups should a drug product be targeted to say, Parkinson's disease or Alzheimer's. A simple example of this involves the design of oral dosage tablets which will look to balance the required dose against tablet size (for patients who may have difficulty swallowing or handling) and total tablet burden. Additional factors should also be investigated at this juncture, and this may include the likelihood of caregiver involvement in administration, the possibility of the dosage form being manipulated (cut, crushed, dispersed), and the consequences of non-adherence to the dosing regimen. These factors all influence dosage form design and the process leads to the definition of the Quality Target Product Profile (QTPP) for a specific drug product and patient population.

According to ICH Q8 the QTPP could include, but is not limited to, the following: 1) Intended use in clinical setting, route of administration, dosage form, delivery systems; 2) Dosage strength (s); 3) Container closure system; 4) Therapeutic moiety release or delivery and attributes affecting pharmacokinetic characteristics (e.g., dissolution, aerodynamic performance) appropriate to the drug product dosage form being developed; 5) Drug product quality criteria (e.g., sterility, purity, stability and drug release) appropriate for the intended marketed product. Taking each of these in turn, there are specific considerations for patient-centric drug product design.

1) Intended use in clinical setting, route of administration, dosage form, delivery systems. The use setting is essential to define for any drug product; will the patient self-dose at home (possibly with an equally aged carer), or in a setting such as a residential home or hospital? As mentioned previously the route of administration such as oral delivery should consider the likelihood of dysphagia. The size, shape, colour and excipient selection of the dosage form and delivery system can be evaluated with consideration of ease of swallowing and handling.

2) Dosage strength(s) are defined by the clinical need, but the required dose should again be considered along with the dosage form unit size and shape. For example, two smaller tablets or capsules might be preferable for swallowing than a single, larger, unit dose in the elderly population. Conversely it may be desirable to have one dosage unit which may be more readily remembered or easily handled.

3) The container closure system must meet the legal requirement for child-proofing (BS EN ISO 8317:2015; BS EN 14375:2003), but consideration should be given to patients who may find the typical child-proofing technologies difficult to access. During product design the container closure should be considered to balance the needs of patients that will be taking the medicine and design the packaging to be both child safe, and user acceptable.

4) Therapeutic moiety release or delivery and attributes affecting pharmacokinetic characteristics should be appropriate to the drug product dosage form being developed. For example, changes in the GI tract where lower gastric pH and higher duodenal pH (Bai et al., 2016), with renal and hepatic decline may impact the absorption of the compound. This may result in the dose needing to be administered in a flexible way, which raises formulation challenges for the drug product.

5) Drug product quality criteria (e.g., sterility, purity, stability and drug release) must be appropriate for the intended product. A single standard of quality will be met for all patient populations, and all intended markets.

Following QTPP definition the drug product is developed to meet the defined critical quality attributes and the quality manufacturing requirements of a commercial product. This process includes the required clinical, stability and regulatory steps, ahead of commercial drug product nomination.

An example of a QTPP for oral delivery could mean that consideration is given to the dosage unit size and shape to help with swallowing and handling such as oval shaped tablets, around 6–8 mm in size; and dosage unit colour to help with declining visual acuity, such as bright colours; and improved packaging to help older patients access their medicines, such as perforated blisters. Whilst the QTPP will give guidance to the design of the final drug product there may be a number of further opportunities to develop a specific age-appropriate medicine. While impact of disease state is considered with respect to formulation and handling, the age range of patients may span a considerable number of years. In certain therapeutic areas, for example, oncology, there is a strong need to get the new medicinal product to the patient quickly and the pharmaceutical industry can address this need with simple dosage forms. There could then follow a rapid development of an age-appropriate dosage form if appropriate. One can imagine a product with various presentations described in the QTPP which suit paediatrics, adults and older patients. It is recognised that designing medicines for smaller population groups will result in multiple presentations that could lead to smaller manufacturing batch sizes. To address this the industry is starting to consider the use of continuous processing; this, in theory, has the advantage of being quicker in terms of product development times and increased manufacturing flexibility, providing the option of customised production batches based on market demand (Vervaet and Remon, 2005).

The pharmaceutical industry and regulators have recognised the benefit gained from age-appropriate dosage forms for paediatrics, and during the design of new medicines population specific dosage forms are now investigated. In the short to medium term; dose flexibility, easy-to-swallow formulations, and easier access packaging are all factors under consideration. Dose flexibility could be achieved with various dosage forms such as

oral liquids, mini-tablets, or multi-particulates. The issues associated with dysphagia could also be addressed with such formulations or alternatives such as oral dispersible dosage forms. It is to be noted that the acceptability of these dosage forms to older patients, caregivers, and clinicians is still being investigated and there is some evidence that older patients have some aversion to oral liquid products (Wahlich et al., 2015). Whilst patient dosage preferences are beginning to be understood, further investigation is needed to balance the needs of the patient, care giver, prescriber, and payer. There also remain a number of challenges with the engineering solutions and delivery device for mini-tablets and multi-particulates (aside from filled capsules) to accurately and robustly deliver the dose, and issues with handling the device and the packaging for an older patient.

Beyond the drug product itself there are additional areas for investigation. Smart packaging may improve accessibility and adherence, such as counting caps or blister packs, and packs which interact with "Apps" and allow real-time E-monitoring (Vrijens et al., 2014). These could be used to provide reminders to take medications at the correct time and monitor adherence. Wearable technology could have a place in this field, with applications to improve medical education, monitor medicine usage and adherence. With regards to the immediate focus for the pharmaceutical industry, this area provides an opportunity to enhance patient education and adherence and is being expanded into clinical trial monitoring and patient feedback. It is hoped that adopting such techniques will enable the pharmaceutical industry to better understand and meet the diverse needs of diverse elderly patients.

The goal of the pharmaceutical industry is to provide new or improved treatments for a number of disease states including those relevant to ageing. In terms of tailoring treatments to a specific patient group a more nuanced approach is becoming increasingly favoured. Rather than dealing with the ageing demographic as a whole an appropriate response would be to adopt a patient centric approach, dealing with elderly care on a specific disease or treatment basis. Whilst the growing ageing population is recognised as a demographic change by the pharmaceutical industry it presents many opportunities in terms of meeting new medical needs and improved product design and monitoring to aid patient adherence. It is also recognised that there are numerous challenges, not least of which is the definition of the older patient and a generic QTPP for an older patients' drug product. It is likely that there will be no simple solution or 'one-size-fits-all' approach in drug product development to resolve the complex issues presented by the ageing population.

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