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Ask an Expert

Addressing the needs of the geriatric population

Q: What role can excipients and dosage forms play in addressing the challenges of treating geriatric patients?

A: Alen Guy, IMCD Group says:

We're all getting older, of course, but worldwide the percentage of people aged 65 and older will grow from 528 million in 2010 to about 1.47 billion in 2050 [1]. Furthermore, people in that age cohort, who now use 30 to 50 percent of prescriptions, will use 60 to 90 percent of them by 2050 [1]. That makes sense when you consider that someone 55 years old has, on average, 2.68 chronic conditions [2]. By the time this person is older than 65, the average reaches 5 chronic conditions [3]. In addition, nearly 40 percent of the elderly suffer from arthritis and another serious health condition, such as cardiovascular disease or diabetes [4].

The elderly also face cognitive, visual, motor, and swallowing limitations and likely consume numerous drug products, known as polypharmacy. Of the approximately 40 percent of American adults who have experienced difficulty swallowing tablets or capsules, the vast majority are the elderly [5].

Preston and Morris and Anderson et al have estimated that 35 to 68 percent of the elderly have some degree of swallowing dysfunction, including dysphagia [6, 7]. In one survey of patients and care-givers in England, 477 patients reported difficulty. Of those, 68 percent opened the capsule or crushed the tablet, and 64 percent simply didn't take their medicine as prescribed if it was too difficult to swallow [8].

Physiological changes in elderly patients can lead to numerous challenges. For instance, it's common for their total body fat to increase while total body water decreases, and the change in their fat-to-water ratio can affect the distribution of hydrophilic and lipophilic active pharmaceutical ingredients (APIs). Other common changes include a higher gastric pH, less hepatic mass and blood flow, reduced kidney function, altered plasma protein binding, and reduced drug metabolism. Stegemann and Reo noted that those changes can lead to serious adverse drug reactions [1].

Those authors also noted that approximately 35 percent of polypharmacy patients experienced adverse drug reactions, and that, upon review:

- 95 percent of the adverse reactions were predictable;
- 63 percent of patients required a physician;
- 10 percent required emergency-room treatment; and
- 11 percent required hospitalization.

In short, these outcomes required expensive interventions.

Yet despite its special needs, the geriatric population isn't normally considered in clinical trials. More often, trials focus on younger adults and now, increasingly, the pediatric population.

What can be done for the elderly: The challenge of dose administration
To be considered elderly, a patient is usually 65 or more years old, but the definition can and should be extended downward to 55+ years, given that long-term care environments are not just for the elderly. Conditions such as Parkinson's disease, for example, are frequent in people younger than 50. That disease is also associated with difficulty in swallowing.

As with very young patients, the elderly often require caregivers to administer or help them self-administer drug products. But unlike children, the elderly often must self-medicate, and that leads to

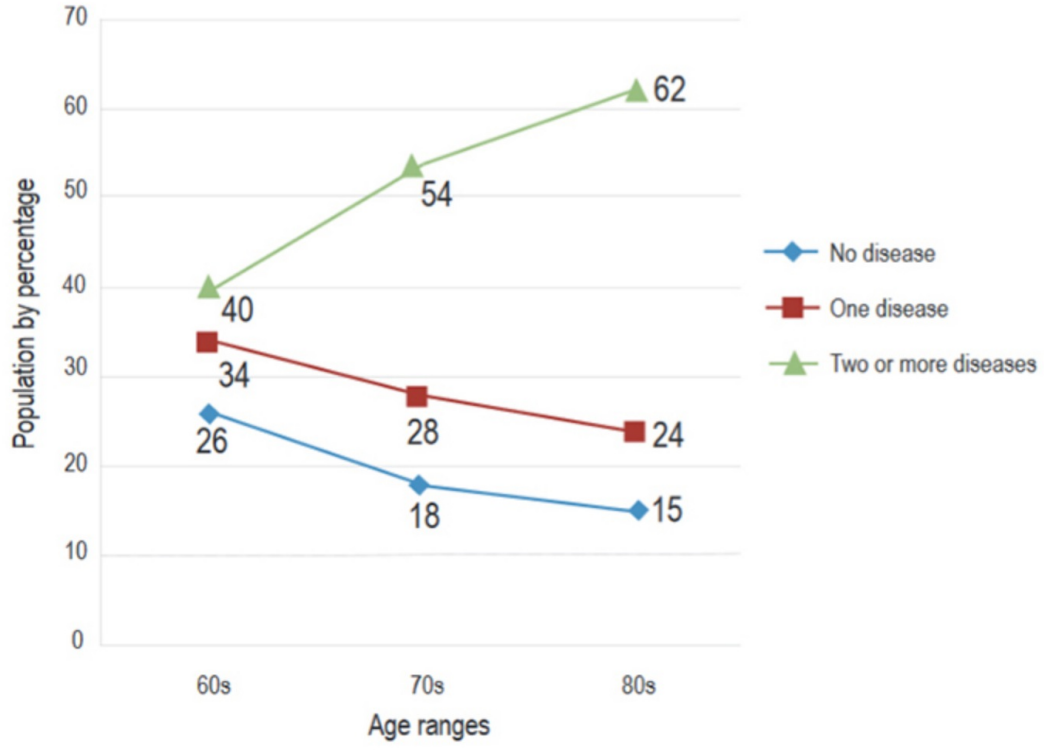
challenges in packaging and identifying drug products to make administration as easy and accurate as possible. Even when patients remove tablets and capsules from their original packaging and organize them in a Sunday-to-Saturday holder, the patient may still need to differentiate a white caplet from a white capsule. For many elderly patients, that's not easy.

Most pharmaceutical manufacturers default to the tablet form when possible, and most offer two or three dose strengths. Manufacturers also score some tablets to allow them to be split to reduce dose strength further if required. When patients have difficulty swallowing a tablet, they or their caregivers often resort to crushing the tablet or opening the capsule and sprinkling the contents into a drink or food. Solid dosage forms are also sometimes added to an enteral feeding tube. The implications of such actions have been addressed elsewhere. They are considerable and formulators, brand managers, and business development professionals involved in drug delivery should address them.

The problems that the elderly face are troubling and worthy of much greater consideration than pharmaceutical companies have given them until very recently. If you're a formulator, consider the challenge of drug delivery to elderly patients as an opportunity. What is the appropriate dosage form? How should formulators identify it? How can formulators simplify delivery to improve compliance and thus the therapeutic benefit? To these already difficult-to-answer questions, add another: What's the cost of developing drug products that cater to the elderly population and how will they be paid for? Consider for example, the cost of a 5-day supply of dipyridamole. In tablet form, the cost is about $1.80. Delivered in an oral-suspension equivalent, it's $66.00. Furthermore, costs can increase significantly as people age and physicians add prescriptions to address co-morbidity. See Figure 1.

Figure 1

Co-morbidity increases with age [9]



In pediatric medicine, age groups are clearly defined and adequately divided into manageable sub-

groups. Such is not the case for the elderly, a large and growing population that the pharmaceutical industry considers—erroneously—to be homogeneous. It may make sense to group the elderly population by generation, or at least by decade, instead of the 0-to-21-years-old scale that an FDA Guidance on pediatric sub-populations recommends [10]. On the other hand, when I was 18 years old, I had long stopped considering myself in need of kids' medicine. For other people in other places, the age of adulthood could be 16 or 21. It's unclear how exactly regulators should define pediatric populations.

Naturally, the success of any pharmaceutical product is measured in terms of its therapeutic benefit, but success also depends on its meeting a need and its availability in age-appropriate formulations. It should also depend on the product's value for money. Value is particularly relevant when discussing the elderly population, an ever-increasing group of patients that is and will continue to strain medical-care budgets. One way to reduce that strain is to prevent waste, which is common for a variety of reasons. Some waste occurs when physicians change existing prescriptions, rendering the products already in hand of little or no use. Waste can also stem from inappropriate formulations, which can lead to non-compliance with the prescribed regimen. If that's the case, manufacturers should investigate whether they can improve the formulation.

Route of administration, dose level, excipient load, palatability, and stability
In a previous contribution to *Tablets & Capsules,* "Eye on Excipients: Pediatric formulations", which addressed pediatric medicines, I discussed excipient loads, dosage form design, and ways to reduce the potential for adverse reactions. Some of these same issues arise in the geriatric population and others figure less. For instance, with pediatric medicines, many reasons exist to avoid certain excipients, usually because of their effects on an immature and developing body. For elderly patients—with proportionally greater chances of having life-threatening conditions—the benefits of treatment in many cases outweigh the potential side effects of certain excipients.

However, our knowledge of the pharmacology of older patients is considerably behind that of other age groups, and co-morbidity issues further complicate the challenge of addressing their needs. The lack of relevant, fit-for-purpose clinical trials has also allowed a large knowledge gap to remain. Even so, formulators can and should use some groups of excipients extensively to deliver needed drug products.

Taste. Among the excipients and technologies that I believe to be suitable are ion-exchange resins (vinyl- and divinylbenzene and polystyrene copolymers); betacyclodextrins; and pore-forming barrier coatings, such as ethylcellulose and hydroxypropyl methylcellulose (HPMC).

Flavorings are clearly required, but I accept only their general utility as a flavor or a taste-masker in rare cases. That's because the majority of adult doses are larger than pediatric doses and are considerably more difficult to taste-mask. In addition, adult taste preferences differ wildly from those of small children and/or juveniles. Tutti-frutti and sticky grape flavors will not win the geriatric compliance game. It's rather more likely that the warmer flavors—vanilla, apple-cinnamon—will improve compliance since they will more likely instill a positive memory and be associated with taking the needed drug products.

Color. Pharmaceutical manufacturers can achieve identification of any orodispersible dosage form in numerous ways with respect to packaging for liquid and stickpack forms. However, in standard blister-pack forms, the use of color should be a factor worthy of high consideration. Notwithstanding the possibilities of color-blindness as aging progresses, the use of color can be beneficial in aiding drug-product identification for both the patient and the caregiver.

ODTs, for example, are typically not coated and present, typically, as a white product in the end-dosage form. However, a carefully selected color could significantly aid compliance with correct medicine, specifically when co-morbidity occurs, and the patient requires polypharmacy. Formulators can use two approaches. The first is to add a coloring agent directly to the powder blend. Alternatively, formulators could directly color ODT binder products, providing a more-consistent, homogeneous color distribution through the powder bed and ultimately the tablet. From a regulatory perspective, it is important to know the maximum daily intake of a colorant.

Mouthfeel and binders. Mannitol and other polyols still have some utility in geriatric formulations. Given

the dose loading and the frequency of doses, however, be aware that diarrhea is a potential side effect, which could inflict discomfort, lead to dehydration, and thus lead to additional therapy to rehydrate and/or replace electrolytes. The preferred method may be use of isomalt and the careful use of sugars.

Diabetes and issues related to glycemia may play a part in how or whether formulators use certain binders. But in a managed environment, these are less of a concern because physicians are aware, as are well-managed diabetic patients, that sugar per se is not an issue, but rather uncontrolled or ignored sugar.

Disintegrants and lubricants. These are not considered challenging excipients for many people, and because their use levels are generally low, they are of limited concern in terms of therapeutic impact.

Excipients for suspensions and syrups. Much care is required here. Suspensions are typically aqueous, and it's important to know how much liquid the patient is ingesting. The viscosity of the suspensions and syrups must also be well managed and formulated to ensure they are easy to self-administer accurately. Once those factors are addressed, the range of excipients tends to revolve around suspending agents, such as colloidal microcrystalline cellulose (MCC), including FMC's Avicel RC 591 and CL611, and sodium alginate. Also important are viscosifiers (hydroxyethylcellulose) and preservatives (sodium benzoate). Syrups are an altogether different challenge. Liquid sorbitol and glycerine are popular syrup ingredients, and they, as noted regarding polyols, may cause diarrhea.

Overall, suspensions and syrups are considered useful in combination therapies. In the case of geriatric patients residing in care facilities, they can ensure nutritional balance, and suspensions or low-viscosity syrups are especially useful if patients suffer from dry mouth.

Conventional dosage forms

A great many elderly patients are still able to consume oral medicines in a solid form, but it is vitally important that pharmaceutical companies formulate them properly. Where possible, formulate modified-release tablets to minimize dose frequency and prevent *tablet fatigue.* The range of possibilities in this realm is nearly endless, and multiparticulate dosage forms (pellets in capsules) are often a good option because they reduce the chances of dose dumping compared to other forms. Therefore, ethylcellulosic dispersions—with or without pore-formers—would be an appropriate excipient technology to use. A potentially very important safeguard is also available for use in painkilling products, both opioids and non-opioids, which are often prescribed alongside other treatments. The technology—FMC's Aquacoat ARC is but one example—ensures that the function of drug products remains robust even when alcohol is present.

In the tableting arena, the latest development for matrix-based controlled-release tablets is direct-compression grades of high-molecular-weight HPMC, such as those offered from Dow and Ashland. These grades provide significant functional performance, especially for flowability during tableting, which may lower the cost of producing inexpensive medicines for the geriatric and other populations. Improving excipient functionality is another way of doing this. It ensures that the dose is delivered reliably while minimizing waste in the manufacturing process and offering the potential to reduce tablet size and improve compliance.

Conclusions

The excipients, technology, and formulation innovation required to significantly improve the treatment of geriatric and long-term care patients are available. The challenge is to understand the specific pharmaceutical needs of each patient. By delivering single-API or combination products to patients, either as standard tablets or orally disintegrating versions, formulators can help patients while potentially reducing the cost of care. Let's focus on combining the best elements of each excipient to deliver broad-purpose products while ensuring that individuals are well treated and little is wasted. Let's think long-term about long-term care.

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This article is an update to Guy's previous article, "Eye on Excipients: Addressing the needs of the geriatric population," in the March 2014 issue of *Tablets & Capsules.*

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