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Ensuring Patient Adherence in Paediatric and Geriatric Populations

Pharmaceutical companies are increasingly adopting patient-centric formulation development to ensure that drug products adequately meet the needs of end-users in all target patient populations.

Adeline Siew, PhD

Pharmaceutical companies today face higher hurdles than ever before in getting products to market. The patient, as the end-user, is now a force to be reckoned with as governments, payers, and healthcare providers around the world place increasing emphasis on patient outcomes. With this new emphasis on patient centricity, the pharmaceutical industry has been quick to realize the importance of embracing the patient.

"The industry continues to move toward a system where the value of care determines a drug's market success, as can be seen with outcomes-based management programmes targeting drugs for cancer, obesity, and pulmonary diseases," observes Elizabeth Hickman, director of sales and marketing, Catalent Pharmatek. "Improving patient outcomes and patient experience is a growing trend," she says. "And companies are looking at ways to achieve this through better drug design—such as bioavailability enhancement to improve therapeutic effect at lower doses, making drugs last longer with extended-release profiles to reduce dosing frequency, delivering drugs through less invasive methods, simplifying complex regimens with combination drugs, and customized dosage forms for specific patient populations and/or indications."

Hickman cites a study by MarketWatch, which showed that patient noncompliance costs the pharmaceutical industry approximately US$330 billion annually (1). Noncompliance could be due to dose burden, size and quantity of dosage, or patient acceptance, she notes and highlights that aging and paediatric populations often present unique challenges to achieving compliance. "Dosage forms that improve swallowability, palatability, and dosing convenience, as well as reduce the pill burden can lead to better compliance, experiences, and outcomes for aging and paediatric populations," Hickman explains. "These factors can also support better product differentiation, which can lead to improved product lifecycles and sales."

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Children and the elderly

Patient-centric drug development considers the end-user from the start of the formulation process through to the selection and design of the dosage form and finished product. The evolving regulatory reforms in Europe and the United States (2–6) reflect the increasing drive toward patient-centric formulation development to ensure that drug products adequately meet the needs of end-users in all target patient populations. Developing a dosage form for geriatrics or paediatrics requires special considerations. In the elderly, factors such as age, morbidity, co-morbidity, multiple drug use, and reduced organ function have an effect on pharmacokinetics. The paediatric population, on the other hand, experience rapid and continual growth, development, and maturation; as a result, there are distinct physiological differences between neonates, infants, children, and adolescents. The most significant compliance challenge in older adults is polypharmacy and the

pill burden, whereas for children, taste is often the biggest barrier.

Geriatric. "The pharmaceutical industry acknowledges the special requirements for geriatric patients," says Ravinder Kodipyaka, senior director and head of formulation R&D, Dr. Reddy's Custom Pharmaceutical Services. However, he notes that product design and development for the elderly is complex because of the interplay of various factors. Geriatric patients often have concomitant conditions and according to Kodipyaka, pill cocktails for their multiple diseases have very limited clinical data available. "For those with cognitive problems, remembering multiple doses, multiple drugs, and their administration schedules can be a challenge. In addition, the reduced physical strength of the patient affects his/her ability to open packs, break tablets along the break-mark, or swallow tablets," he adds.

"Improving patient outcomes and patient experience is a growing trend."

—Hickman, Catalent Pharmatek

Although there are programmes and companies focusing on addressing the needs of older patients, Kodipyaka believes that there is scope to do much more. "We find that most of the drugs for chronic indications and/or that have age-related prescription potential are being developed as single-dose packs, push-pull packaging designs, and fixed-dose combination (FDC) products. Target population is a key factor that

ODTs dissolve drug administration challenges

The advantages of orally disintegrating tablets (ODTs) as a patient-centric dosage form are well recognized. "Because of their convenience and ease of administration, ODTs are ideal for paediatric, geriatric, and psychiatric patients," says Ralph Gosden, head of product development at Catalent's Swindon, United Kingdom site. "They dissolve in the mouth without water, thereby addressing the problem of difficulty in swallowing. It has been reported that 25–45% of children have swallowing difficulties and 30–40% of elderly institutionalized patients suffer from dysphagia." He adds that ODT formulations reduce the overall cost of care, citing a study that showed children receiving orally disintegrating ondansetron tablets for the treatment of gastroenteritis had less vomiting, increased oral hydration, and reduced need for intravenous hydration (1). ODTs demonstrated economic value through cost savings from reduced length of hospital stay. The authors of the study noted that the ODT was easy to administer, had few side effects, and was safe and effective, making it a useful therapy in the emergency department for children with vomiting and mild-to-moderate dehydration as a result of gastroenteritis (1).

According to Gosden, speed is an important parameter with ODTs. "The requirements for an ODT is to have fast dispersion rates," he explains. "Rapid dissolution enables effective buccal and sublingual delivery, which may enable pre-gastric absorption, rapid onset of action, and reduced side effects by avoidance of food effects and first pass metabolism." He adds that other desired critical quality attributes of ODTs include appearance, palatability, potency, physical/chemical stability, and physical strength to withstand packaging, shipping, and patient handling.

Gosden, however, notes that drawbacks of ODTs include the requirements for taste masking and the drug loading capacity. Catalent's Zydis Ultra technology was developed to address those limitations, he says. Zydis Ultra is the same basic formulation as Catalent's Zydis ODT, which is a lyophilized oral solid-dosage form that dissolves in the mouth in less than three seconds. A lyophilization process is used to make the ODT. The API is formulated into a solution or suspension, which is then filled into blisters and passed through a specially designed cryogenic freezing process to control the size of the ice crystals and subsequent pore formation during freeze drying. After the drying step, the blisters are sealed to protect the product.

Gosden explains that Zydis Ultra includes a dry coating process for taste masking. "Micronized polymer agglomerates, through the action of acoustic vibration and particle–particle interaction, are used to coat the host API. Particle collisions deform the deposited polymer to create a continuous coating layer," he says. "No solvent is involved in this process; it is a completely dry process. It has the ability to coat small particles of approximately 100 µm and the potential for much higher API potency in the coated material."

Zydis Bio offers opportunities for the sublingual or buccal delivery of biologics, such as peptides, proteins, allergens, and vaccines in an ODT formulation, Gosden highlights. He adds that there are no extreme pH exposure or proteases in the oral cavity and this route avoids the harsh environment of the gastrointestinal tract.

"For vaccines, Zydis Bio offers the potential to eliminate cold-chain storage. Zydis vaccines are suitable for mass immunization programmes and emergency response," says Gosden. For stability, he explains, Zydis Bio uses a lyophilization process with low processing temperatures, and there are formulation options to optimize in-process stability such as through matrix component selection or pH adjustment. He adds that the dried product has low water activity to ensure long-term stability. Acceptable room temperature storage has been demonstrated for multiple peptide and protein compounds, according to Gosden.

Catalent's Zydis Bio technology enabled Danish pharmaceutical company ALK-Abelló A/S to successfully launch Grazax as a patient-friendly allergen immunotherapy for the treatment of grass pollen-induced allergic rhinitis (2). Grazax is a registered trademark of ALK-Abelló A/S. Patients previously had to make monthly visits to the clinic for their subcutaneous injections. The convenience of being able to administer a daily sublingual dose of the medication at home improved patient experience and increased patient adherence.

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needs consideration in a product development programme. A holistic approach considering patient age, drug indication, and duration of therapy among others, needs to be adopted for systematic geriatric product development," he says.

Paediatric. Kodipyaka acknowledges that in terms of work that is done and being done for special populations, the paediatric population is one of the most progressive ones. "The pharmaceutical industry has actually developed and commercialized suitable products for children; for example, orodispersible dosage forms, orally disintegrating tablets, solutions, suspensions, powder for suspension, and drops for anti-retroviral, anti-tuberculosis, and anti-malarial products," he says. An important driving force, he notes, has been the focus and support of regulatory bodies, non-governmental organizations (NGO), and global agencies such as the World Health Organization (WHO), which have gathered huge data points on what is required for paediatric patients. Despite these efforts, there are still unmet needs, according to Kodipyaka, "particularly with challenges of taste masking; the risk of suboptimal dosing due to spitting/vomiting by children; high dose drugs, where administering

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Reducing medication errors

Oral drug delivery continues to be the preferred route of administration because of its convenience and patient acceptance. The vast majority of marketed products today are tablets, observes Gretchen Bedford, global market research analyst at Colorcon. "As medicine advances, so do specialized solid-dosage forms with drug combinations and layered, extended- and immediate-release tablets, as well as enteric-coated tablets and capsules," she says.

Charlotte Miller, film coatings manager, Colorcon EMEA, notes that the number and variety of medicines available are increasing. "Patients are now taking multiple medications and living longer," she says. "Administering medicines may be carried out by several healthcare professionals, and communication failures can lead to mistakes." Miller points out that medication errors are reported to harm 1.5 million people every year, some of which result in sickness, injury, and death (1). "It is estimated that between 2–14% of patients are admitted to hospitals due to medication errors, and approximately 1–2% of those patients are harmed as a result (2)," she continues, adding that these numbers are alarming considering that most, if not all medication errors could be prevented. "Further, these statistics only include those medication errors that have actually been reported," she says, but highlights that awareness and better reporting have resulted in the increased number of recorded medication errors. "Many of the regulatory authorities have issued guidance or directives (3, 4) to ensure that any errors, no matter how small, are captured, as well as to ensure learnings are made to prevent reoccurrence of incidents."

Miller notes that the United States Food and Drug Administration and EMA have published guidance for industry to minimize the risk of medication errors (5, 6). "These guidances aim to address the design of drug products to promote the safe and correct use and minimize or eliminate hazards contributing to medication errors at the product design stage," she says. "The FDA guidance conveys the current thinking about how a safety-by-design approach to new product development can be an effective tool in reducing the unintentional medication errors that result in 44,000–98,000 deaths in the US each year (7). Recommendations include, but are not limited to, the adequate distinction between immediate-release and extended-release or delayed-release products, differentiation between multiple dosage strengths, and inclusion of clear, legible imprints to help identification. The size, coating, and palatability of the tablets should also be considered to ensure tablets are easy to swallow, safeguarding patient compliance."

According to Miller, manufacturers have a duty to ensure the medicines they develop are well differentiated, especially between dosages of the same product. "Medication is more easily identified if it has a distinctive appearance, and single or multiple visual indications are a defense against swallowing the wrong tablet," she says. "For many, not just the elderly and their caregivers, colour alone can serve as that great safety net, an easy way to help reduce potential errors. For those who take multiple medications, the drugs can be safely commingled in a pill-sorting container where patients or caregivers rely on colour or other visual clues. Familiar colours, shape, and size also help patients remember proper dosing."

Miller adds that differentiating tablets does not have to be costly, but it does require the right resources at the right time. "Colorcon's unique tablet design service, BEST, enables pharmaceutical companies to explore options and evaluate tablet shapes and sizes for ease of swallowing, as well as colour for differentiation," she says. "Risk assessment studies using the proposed tablet(s) to simulate in-use testing can also be conducted with patients, pharmacists, and caregivers to identify any difficulties in identification of the product."

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large volumes of liquid medications has practical challenges for the child and the drug administrator; and dosing accuracy with liquids." The measuring cups or spoons routinely used with liquids may have residual volumes and most administrators either add overfills or the dose is administered less, he explains. Kodipyaka sees ample opportunities to develop more patient-centric, innovative drug-delivery systems and packaging systems that could address the specific needs of children.

"The pharmaceutical industry acknowledges the special requirements for geriatric patients."

—Kodipyaka, Dr. Reddy's Custom Pharmaceutical Services.

Controlled-release formulations to reduce dosing frequency

The shift to personalized medicine and an increasing focus on geriatric and paediatric applications is creating a demand for specialized dosage forms, observes Paul Spencer, head of the Oral Excipients Business at Evonik Health Care. "Controlled-release formulations, including once-daily applications, can improve patient adherence and enhance therapeutic success," he says. "In an aging society, where there is an increasing number of people with multiple morbidities, who need to administer several drug products every day, controlled-release formulations offer significant advantages. They provide constant plasma levels over a desired timeframe, optimized bioavailability, minimized side effects, and reduced dosing frequency. Such factors help to increase patient quality of life and improve compliance. There are multiple chronic conditions where controlled-release formulations are being used, for example, cardiovascular diseases, diabetes, and diseases of the central nervous system, such as Alzheimer's."

Fixed-dose combination to reduce pill burden

With polypharmacy and compliance being a huge problem, especially in geriatric patient population, Anil Kane, global head of Technical and Scientific Affairs at Patheon, part of Thermo Fisher Scientific, points out that FDCs offer the possibility of combining several drug candidates into a single pill. "FDCs could benefit patients from the potential increase in efficacy, synergistic effect, and a potentially lower dose, leading to higher convenience in administration and compliance," he says.

Kane explains that several drugs in the same category of therapeutic effectiveness have been combined for synergistic effects. "Specific examples include elvitegravir, emtricitabine, tenofovir disoproxil fumarate, cobicistat (Stribild, Gilead) for the treatment of HIV/AIDS; metformin combinations with glipizide, glimepiride, pioglitazone, rosiglitazone, and many other gliptins for diabetes; and amlodipine, valsartan, and hydrochlorothiazide (Exforge HCT, Novartis) for hypertension," he says. Citing an article (7) that listed the top 10 drugs that registered the maximum growth in global sales over 2015, Kane observes that interestingly, three of the 10 drugs are FDCs as highlighted in the following:

- Epclusa (sofosbuvir and velpatasvir), a new launch by Gilead, brought in US$1752 million in sales in 2016. Approved by the United States Food and Drug Administration in June 2016, the FDC was Gilead's third sofosbuvir-based regimen, but it marked the first and only all-oral, pan-genotypic single tablet regimen for chronic Hepatitis C virus infection.
- Genvoya (elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide) by Gilead recorded sales of US$1484 million in 2016, compared with US$45 million sales in 2015. The FDC demonstrated a better safety profile when tenofovir alafenamide was added to the combination. Genvoya has been the most successful HIV treatment launch since the introduction of the first single-tablet regimen, Atripla.
- Triumeq (abacavir, dolutegravir, and lamivudine) by GlaxoSmithKline had sales of US$2151 million in 2016 versus US$905 million in 2015. Triumeq was the company's first once-daily, single-pill FDC tablet combining dolutegravir, an integrase inhibitor, with the nucleoside reverse transcriptase inhibitors abacavir and lamivudine.

"Controlled-release formulations, including once-daily applications, can improve patient adherence and enhance therapeutic success."

— Spencer, Evonik Health Care

From a development and manufacturing perspective, Kane says that various types of drugs have been successfully combined into a single unit of a solid oral-dosage form, including low- and high-potency drugs; low- and high-dose drugs, and immediate- and controlled-release profiles for individual drugs based on the site of absorption and efficacy. "Based on the chemical and physical stability of each active drug in the FDC, the dosage form can be developed as a simple monolithic tablet or a blend of actives with some excipients in a capsule," he explains. "With molecules having stability challenges, we could develop dosage forms such as bilayer, tri-layer, tablet-in-tablet, or multi-particulates of each active in a bead/pellet form and filled into capsules. The techniques and technology have developed enough to achieve a good shelf life for a combination pill in one of these dosage form options."

Taste-masking to improve palatability

Palatability and taste are crucial parameters for oral dosage forms because they have a significant impact on patient compliance, especially for the paediatric

population. Several approaches have been used to mask the taste of bitter APIs, such as the addition of flavours and sweeteners, modification of the API to minimize its solubility in the oral cavity, complexation with cyclodextrins, or the application of a coating to form a barrier between the drug and palate.

"FDCs offer the possibility of combining several drug candidates into a single pill."
—Kane, Patheon

User-friendly dosage forms to improve patient experience and adherence

User-friendly dosage forms are increasingly popular with patients and consumers and are becoming more widely available on the market. "User-friendly dosage forms are orally administered formulations that are designed to make taking medication as convenient and trouble-free as possible for end-users," explains Martin Koeberle, head of Analytical Development and Stability Testing at Hermes Pharma. "These formulations, which include instant drinks, effervescent tablets, orally disintegrating tablets/granules (ODTs/ODGs), chewable tablets, and lozenges, overcome many of the difficulties commonly experienced with conventional tablets and capsules. As well as being easy to swallow, they can be formulated to offer a more pleasant taste and mouthfeel than traditional solid oral-dosage forms. Some forms can be taken without any liquid, enabling consumers to conveniently integrate them into their daily routines."

Koeberle notes that traditional oral dosage forms such as tablets and capsules pose a significant challenge for large number of people. A consumer survey, conducted in the US and Germany by Hermes Pharma and the Spiegel Institut Mannheim, found that more than half of the respondents from all age groups and genders experienced difficulties swallowing tablets and capsules (8). Various reasons were cited, but the most frequent were related to the pill being too large to swallow, becoming stuck in the throat, or having an unpleasant taste or odour. "As a result of these swallowing issues, some individuals reported not taking their medicine as intended (such as by crushing tablets or dissolving them in water), or worse still, not taking them at all," Koeberle says. "For patients with chronic diseases or the elderly, who may need to take multiple medicines daily, this poses a significant problem." He adds that because user-friendly dosage forms simplify administration and are more convenient to take, they can significantly improve patient compliance and treatment efficacy, as well as improve quality of life.

"User-friendly dosage forms are orally administered formulations that are designed to make taking medication as convenient and trouble-free as possible for end-users."
—Koeberle, Hermes Pharma

According to Koeberle, Hermes Pharma has developed a range of user-friendly combined calcium and vitamin D3 products for several international pharmaceutical companies. "These products are designed for osteoporosis patients, with doses ranging from 500 mg to 1200 mg calcium and 200 IU to 2000 IU vitamin D3. Our own versions are sold under the Calcimed brand, and include effervescent and chewable tablets as well as ODGs," he says. "Many aspirin products are available on the market as effervescent and chewable tablets, instant drinks, and ODG formulations. With these user-friendly formulations, aspirin is often combined with other active ingredients such as phenylephrine, caffeine, and paracetamol." Koeberle also highlights that in Germany, the most widely used formulation for mucolytic cough remedies containing acetylcysteine are effervescent tablets. "This user-friendly dosage form is more popular than other formulations, including syrups and conventional film-coated tablets," he says.

Conclusion

Kodipyaka sees a growing focus on patient-centric product developments. "In addition to safety and efficacy, patient compliance, convenience, and cost effectiveness are recognized as important elements for the commercial success of a drug product," he says. Previous misconceptions that a business model focused on putting the patient first will not generate sufficient profits to satisfy shareholders are now being reconsidered; most pharmaceutical executives are beginning to see that patient centricity holds the key to sustainable profitability.

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