CO-PACKAGED COMPONENTS IMPROVE PATIENT EXPERIENCE AND ENSURE CONSISTENT DRUG DELIVERY

In this article, Chris Franzese, Clinical Leader, and Amy Rinaldi, Insights Associate, both of Matchstick, explore the challenges and benefits of co-packaging for manufacturers, healthcare workers and patients.

A growing combination-product market and regulatory focus on patient-centred drug development has brought human factors engineering to the forefront of the pharmaceutical industry. Whereas the term "delivery device" previously signified traditional needle and syringe systems, today significant resources are allocated to ensuring drug delivery devices reflect user-centred design principles and can be used safely and effectively.

The prefilled syringe (PFS) developed to deliver UCB's Cimzia (certolizumab pegol) was one of the first devices to exemplify this change, leveraging usability principles adapted from OXO's kitchen utensils. Since then, many PFS devices, autoinjectors (AIs), on-body injectors (OBIs) and inhalation devices have been purposefully developed with the user in mind. Connected delivery devices that communicate with the user's smartphone or other technology represent the next horizon for improving usability and patient-centricity.

While device usability has made a step-change in recent years, device packaging has not always followed suit. With few exceptions, parenteral medications – even those that are delivered with complex devices – are typically supplied in standard cartons with no additional design features or affordances. This is somewhat understandable, given the stringent labelling and child-resistance requirements for pharma packaging.

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In lieu of altering the packaging design itself, some manufacturers of oral medications have adopted co-packaging strategies to improve the user experience. One of the most prominent examples is the Kisqali (ribociclib) and Femara (letrozole) co-pack from Novartis, which supplies one 28-day cycle of both medications in a single box for the treatment of metastatic breast cancer – Kisqali is supplied in weekly blister packs alongside Femara, which is supplied in a bulk bottle.

Novel packaging configurations, such as those that employ "poka-yoke"[1] or "stepwise reveal" design elements, have been shown to improve usability,[2] but these approaches often face substantial manufacturing hurdles. In other cases, "smart packaging" that incorporates video instruction and/or audiovisual feedback has been conceptualised.

Still another strategy is to use more commonplace packaging designs and supplement this approach with co-packing, whereby delivery devices are provided alongside ideal (and tested) supplies to facilitate a drug's proper and intended use. Unlike other packaging strategies, co-packaging has the potential to impact medication administration directly, as opposed to strictly improving usability.

Including simple disposable devices (needles, syringes, transfer

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devices, vial adapters and closed-system transfer devices) in drug product packaging may confer several benefits, some of which are specific to the user and others to the manufacturer. Users may benefit most from co-packed supplies when their drug product requires some degree of manipulation (e.g. reconstitution, volume pooling or multiple transfers) before it can be administered. In these cases, several and/or specific types of supplies may be needed to facilitate the manipulation.

Some of the most well-known examples of this are found in haematologic conditions – such as haemophilia and hereditary angioedema – where many of the approved medications require reconstitution prior to administration.[3-8] As a result, these drug products are often co-packed with supplies such as diluent vials, vial adapters, transfer needles and/or injection needles to aid in reconstitution and administration.[9]

When co-packaged supplies are not available, similar populations have been shown to require significantly more time and steps to reconstitute their medications, and deviate from the product's instructions for use (IFU) more often.[10] In addition, these populations may need to procure the appropriate supplies on their own, which not only increases the probability for error but can also create a burdensome supply excess, as they must often buy these items in bulk. In some cases, dispensing pharmacies (e.g. specialty pharmacies) may provide the components they deem necessary but these supplies may not be designed for non-healthcare provider user groups and/or may not have undergone human factors or compatibility testing with the drug product.

For manufacturers, co-packing offers a means to direct users to supplies that have already been vetted for physical and chemical compatibility with a specific drug product and primary container. This is not only relevant for patient- or caregiver-administered medications but also particularly important in the acute care setting. In practice, drug products and primary containers are subject to an enormous variety of ancillary supplies, ranging from standard steel blunt and sharp needles of different lengths and gauges to large-bore plastic dispensing pins, plastic cannulae, stopcocks, vented needles and closed-system transfer devices (CSTDs).

Such variety can be problematic – a 2018 study found that variation in chemotherapy vial spike characteristics (e.g. dimensions and design) and user practices (e.g. off-centre stopper puncture) produced unpredictable stopper collapse when spikes were tested with different stoppers.[11] This finding will be increasingly relevant as the regulations and recommendations for management of hazardous drugs (e.g. NIOSH, USP Chapter <800>) are enforced. For example, the prescribing information for some chemotherapy products specifically advises against the use of chemotherapy dispensing pins or similar devices, which is at odds with USP <800> recommendations for the use of CSTDs.

Moreover, dead space is not consistent amongst supplies commonly used in the hospital environment and may result in persistently inaccurate drug dosing, depending on the product used and any adjustments made by clinicians to account for lost volume. While it is probably unnecessary and unreasonable to co-package supplies with every manufactured drug distributed to a hospital, drugs with high physicochemical sensitivities, those packaged in primary containers with stoppers prone to collapse or particulate generation, or those that require very precise dosing for therapeutic effect may be at risk when ancillary supplies cannot be controlled. This may be particularly relevant during investigational studies, where standardisation is critical to preserve internal validity.

In addition, there is a some evidence to suggest that use of CSTDs may reduce microbial ingress into primary containers and yield extended microbial stability.[12,13] Although this has not yet been reflected in standards such as USP <800>, co-packing with CSTDs to increase in-use time without the need for antimicrobial preservatives or complex formulation changes may represent a competitive advantage in the future.

Although co-packing offers tangible benefits to users and manufacturers, some manufacturers may be hesitant to employ a co-packing strategy, as it could present an incremental variable and potential risk in the drug development process that would need to be managed. While this is certainly a valid concern, new risks have emerged in recent years that may swing the balance in favour of co-packing.

In addition to the usability/convenience benefits to users and compatibility/consistency benefits to manufactures mentioned previously, increasing human factors scrutiny may make co-packing a requirement for some products in the future. This is largely dependent on the clinical situation in which the product will be used and the reliability of safe and effective use with the supplies available in the use environment.

Examples include medications used in emergency situations, where access to appropriate supplies may be limited and delayed treatment would be deleterious, medications with narrow therapeutic indices that require precise and consistent dose preparation and administration, and medications that may present a high risk for the healthcare provider or patient harm if a specific supply is not used (e.g. a particular type of infusion set or a CSTD).

One such product is the Emergency Gynecologic Methotrexate Kit (EmGyn

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Kit), compounded and sold by Edge Pharma (Colchester, VT, US), a US FDA-registered 503B outsourcing facility. This system employs a CSTD to allow for closed transfer and disposal of unused methotrexate (after an appropriate body surface area-based dose has been set) in facilities without access to a USP <800>-compliant compounding area (e.g. obstetrics and gynaecology clinics).

CONCLUSION

All strategies to enhance patient and healthcare provider experience and usability inherently involve risk/benefit analyses, as well as time, cost, manufacturing and supply chain trade-offs. Overall, it will be interesting to see how this topic evolves moving forward, although it will not be surprising if more products begin to launch with co-packed supplies in the near future, especially as medical care continues to transition to the home, medication regimens become increasingly complex and the marketplace becomes more crowded.

ABOUT THE COMPANY

Matchstick is a specialty consultancy focused on pre-concept and concept stage development of combination products, including devices, patient support and engagement programmes, training and lifecycle strategies. Matchstick helps firms understand unmet patient and caregiver needs, invent useful and relevant product and service solutions, and deliver compelling business cases to drive programmes forward within their organisations.

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Chris Franzese is Clinical Leader at Matchstick. He manages a team of clinicians supporting client projects related to combination product development and usability testing, leads the company's clinical training and is accountable for making clinical knowledge accessible and relevant to client projects. An experienced clinical trial researcher, Mr Franzese has numerous peer-reviewed publications related to usability research for connected drug delivery devices, devices for medication preparation, biomarkers and antiplatelet therapies in coronary artery disease, and clinical laboratory and diagnostic testing. He earned a BS in Biology from Loyola University (MD, US) and a concurrent PharmD and MHS in Health Informatics from Fairleigh Dickinson University School of Pharmacy and Health Sciences (NJ, US). He is a practising pharmacist in New Jersey.

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