Innovative User-Friendly Child-Resistant Packaging Solutions

Abstract
In the European Union (EU), poisoning is the fifth leading cause of unintentional death for children and adolescents, with one of the most commonly cited causes being medicinal drugs.[1] Despite increased efforts over the last fifty years to improve parental education in child-proofing homes and developments in child-resistant packaging that have steadily decreased the number of cases, accidental poisoning remains a considerable risk in the home. This article will explore how the pharmaceutical industry faces this global medical challenge, evaluating existing and future pharma packaging trends.

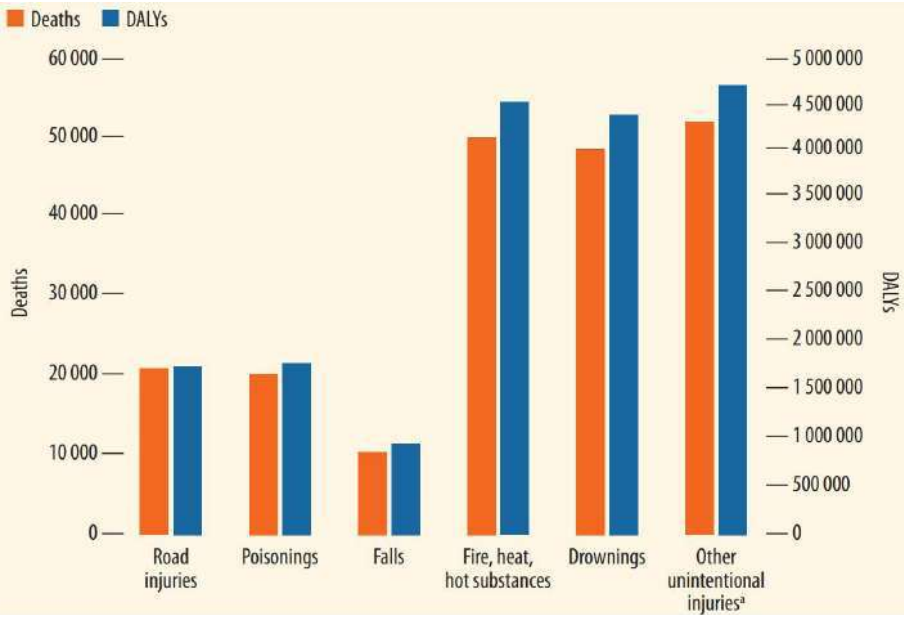

Figure 1: Burden of disease (deaths and disability-adjusted life years, DALYs) attributable to the environment globally – unintentional injuries in children ages 0–4 years, 2012. Notes: a This includes injuries from mechanical forces (tools, sports equipment, agricultural machinery), explosions, off-road transportation accidents, animal bites, venom, poisonous plants, ionizing radiation, electric currents, suffocation, natural forces (storms, extreme temperatures, earthquakes), and medical care complications. Reproduced from ref.[3] in accordance with the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 IGO licence (CC BY-NC-SA 3.0 IGO; https://creativecommons. org/licenses/by-nc-sa/3.0/igo).

Introduction

Unintentional poisoning is a relatively widespread medical emergency, with children at the highest risk of accidental intoxications that could prove fatal.[2] Cases often occur within the home when young children are exploring their surroundings and gain access to improperly stored harmful substances such as cleaning chemicals, fuels, alcohol, tobacco and, most frequently, medication. In the United States (US) and Europe, over-the-counter (OTC) and prescription medications are the leading causes of child poisoning, with analgesics being particularly common. As well as the risk to life, unintentional child poisoning has a significant socio-economic impact, with medical costs and long-lasting disability. Figure 1 shows the global burden of unintentional childhood injuries, including poisoning.

Pharmaceutical companies are therefore being increasingly called upon by patients and stakeholders to recognise the importance of child-resistant closures (CRCs) in medical packaging. When developing child-resistant packaging for pharmaceuticals, one of the greatest challenges is creating a closure design that prevents children from gaining access to harmful substances while maintaining usability by adults – particularly seniors. A growing trend of home care (intensified by the Covid-19 pandemic) as well as an increasingly aging population, is directing the focus of child-resistant packaging towards the accessibility needs of older patients. Packaging suppliers must work with pharma companies to create life-saving solutions that address this current trade-off.

Types of child-resistant packaging

Since its introduction, child-resistant

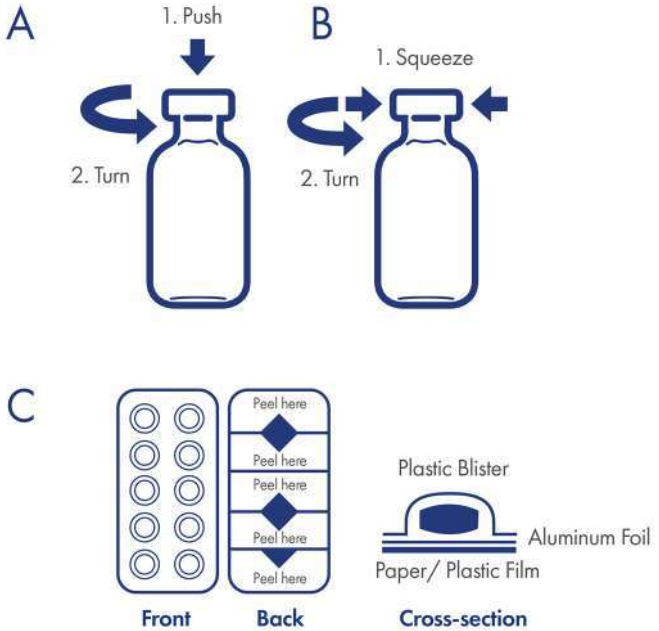

Figure 2: Different types of child-resistant packaging (a) re-closable push & turn (b) re-closable squeeze & turn [need to add], and (c) non-re-closable peel & push, where back paper/plastic film is peeled back before tablet is pushed through aluminum foil.

packaging has developed and matured into an accepted, effective product in the UK, EU, US, Canada and Australia and is gaining rapid acceptance in the Asia Pacific (APAC) region.[4] The global pharmaceutical packaging market was valued at $71 billion in 2018 and is projected to grow at a CAGR of nearly 6% during 2019–2029.[5] As well as an upward trend in contract manufacturing, an increasing focus on child-resistant packaging is driving this market growth.

Child-resistant packaging is either made out of a material that is difficult to open or relies on a particular method to open it. There is a variety of mechanisms for CRCs on medical packaging which are categorised primarily into re-closable (bottles) or non-re-closable (blister packs), these include:

Re-closable
- Push & turn caps
- Squeeze & turn caps

Non-re-closable
- Peel & push

The screw-on cap is the most well-known re-closable packaging design and can only be opened by pushing down and turning simultaneously, while the most frequently used non-reclosable design is blister packaging, containing individually wrapped pills or tablets (see figure 2).

Although the overall aim of each type of packaging is to protect children from ingesting the contents, the strategies can vary. For example, the aim of most bottle CRCs is to stop the child opening the packaging altogether, but if the cap is left off then the CRC fails to work. Another focus taken by some designs is on limiting the dose a child is exposed to if the container is opened, such as liquid flow limiters that only allow one dose to be dispensed. Blister packs offer both ease of patient use and child resistance as they have dose guards that act as more of a secondary barrier that the user must peel away to then push the oral dose through the packaging.

Testing/certification

Patient compliance influences the pharmaceutical packaging market, as it continues to be a top priority for packaging solutions, along with regulatory standards. Both are therefore important considerations in designing and manufacturing child-resistant packaging. According to the World Health Organization (WHO), "packaging must not only increase compliance through its design but must also protect the patient and indicate the integrity of the product".[6] Comprehensive regulations are in place to ensure that packaging, regardless of its CRC mechanism, complies with safety standards and meets the necessary legal requirements to identify as child-resistant.

To obtain certification, pharma companies must submit their packaging for testing by an authorised body. For packaging to be classed as child-resistant, it must meet one of the following standards:

- **International Organization for Standardization (ISO) 8317 (2015):** Child-resistant packaging – Requirements and testing procedures for recloseable packages
- **ISO 14375 (2018):** Child-resistant non-recloseable packaging for pharmaceutical products – Requirements and testing
- **US 16 CFR § 1700.20:** Testing procedure for special (Child-resistant) packaging.

An example of the testing procedure as part of ISO 8317, ISO 14375 and US 16 CFR § 1700.20 includes a panel test with 42–51 month old children and 50–70 year old adults. The packaging should be difficult for the children to open while presenting limited problems for the adults. These adults must be able to open the package twice within allocated test periods, and at least 80% of children should be unable to open during specified test periods.

As well as this standardised testing procedure, the ISO has published an internationally agreed standard test procedure for re-closable child-resistant packaging.[7] A certificate is issued by an ISO 17065 accredited organisation to offer clarity about the packaging's quality and provide legal protection to manufacturers, market participants, consumers and officials.

These standards must be adhered to for pharmaceutical and healthcare companies to claim packaging to be child resistant but are only required by law in some countries, including Austria, England, Scotland, Wales Hungary, Iceland, Israel, Italy, Poland, Spain, and Sweden (Figure 3).

Whether mandatory or not, child resistance certifications must cover the full packaging solution, including both the container and the closure. Though many pharmaceutical containers are produced with CRCs, it cannot be assumed that one combination will pass testing just because another previously has. If a container is changed or even slightly modified, the entire packaging must be re-certified. The time and cost associated with certification can be significant, so drug manufacturers can streamline the process by partnering with packaging manufacturers that can not only supply innovative, high quality packaging, but also provide the required certification.

In the early 1990s, the need for more user-friendly child-resistant packaging was recognised by the Consumer Product Safety Commission (CPSC) in the US, leading to the current protocol that trials adults between the ages of 50 and 70 who do not have "obvious or overt physical or mental disabilities".[8] Although the current procedure does attempt to ensure older patients can access their medication, it can be criticised for lacking acknowledgement of vulnerable and disabled patients who are more likely to struggle with adhering to treatment regimes in the first place.[9] By not recognising these patients in testing protocols, child-resistant packaging can remain too difficult for them to open and possibly result in them leaving the closures off their medication, increasing the risk of child-poisoning. Creating innovative, truly child resistant senior-friendly (CRSF) packaging is crucial to supporting a more patient-centered, rather than product-centred treatment approach. A strong relationship between drug manufacturers and packaging suppliers, as well as with healthcare providers and patients, will help facilitate this.

Why big pharma is changing R&D strategies to focus on child-resistant packaging

Large pharmaceutical companies are now driving awareness and innovation in child-resistant packaging, creating new advanced designs every year and redesigning their previous portfolios to meet patient needs for CRSF packaging. They have moved from a simple compliant strategy dictated by legislation to developing CRSF packaging solutions that improve and protect their patients' children's lives. For example, GSK's existing portfolio is being transitioned into CRSF packaging with 40 internal and external contract manufacturing sites now producing CRSF packaging for GSK brands. As of 2020, 200 million packs from the existing portfolio were supplied in CRSF packaging.

Pharma companies looking to implement a more robust CRSF packaging strategy should consider the following:

- Not all drug products will be suitable for development in CRSF packaging. Pharma companies should identify which products should be moved to CRSF packaging.
- Product shelf life/stability requirements.
- Changes to packaging registered details
- Markets being supplied: Possible need for patient/care giver education.

Review of recent research

The volume of research into improving child-resistant packaging for medications, as well as modernising the testing criteria for CRSF packaging, has increased significantly in recent years. The following three studies demonstrate the variety of approaches being taken to improve the effectiveness of child-resistant packaging:

1. **Multi-step mechanisms:** Researchers designed and validated the performance of a novel child-resistant packaging system for oral solid dosage forms, with a unique stepwise mechanism that showed considerable effectiveness in preventing children from opening the package.[10] The features include (i) re-closable packaging that involves a box container installed "click lock" on either side of the system, (ii) an outer packaging box of 8 cm width, which is too large for the palm width of children under 5 years of age, making it difficult to open, and (iii) a unique irritating sounding buzzer that either motivates the child to cease their attempt, or alerting an adult to the attempt. Only 6% of children succeeded in opening the packaging, while 94% of children failed to open it within 5 minutes. On the other hand, 96% of adults succeeded within 5 minutes, indicating that the mechanism does not significantly hinder patient access to medication.

2. **Visual distractors:** As well as new designs for manual CRC mechanisms, research is also being carried out to investigate other elements of packaging that could prevent or restrict child access. For example, visual distractors have been shown to effectively delay young children (24–41 months) from opening medicines, in which time adults could be more likely to notice and prevent ingestion. In this study, the visual distracter consisted of a lenticular graphic characterised by a stereoscopic, 3D perspective that yielded the illusion of movement and depth, changing colours from yellow to red when the vial was moved.[12] While it was recognised that visual distractors could potentially attract children to a container they might have otherwise ignored, the approach and consideration of targeting children's early stage processing (i.e. perception) rather than relying on late stages of information processing is an area that could be explored further.

3. **'Smart' packaging:** As packaging technology becomes more advanced, smart containers could become more commonplace in the market. Preliminary results from a recent study indicate that smart pill bottles can be used to reliably detect children trying to open pill bottles and, by emitting an aural alarm, reduce risk of child-poisoning events.[13] In this study, a prototype bottle could sense an adult opening the container with 98.16% sensitivity, and a child with 96.67% sensitivity.

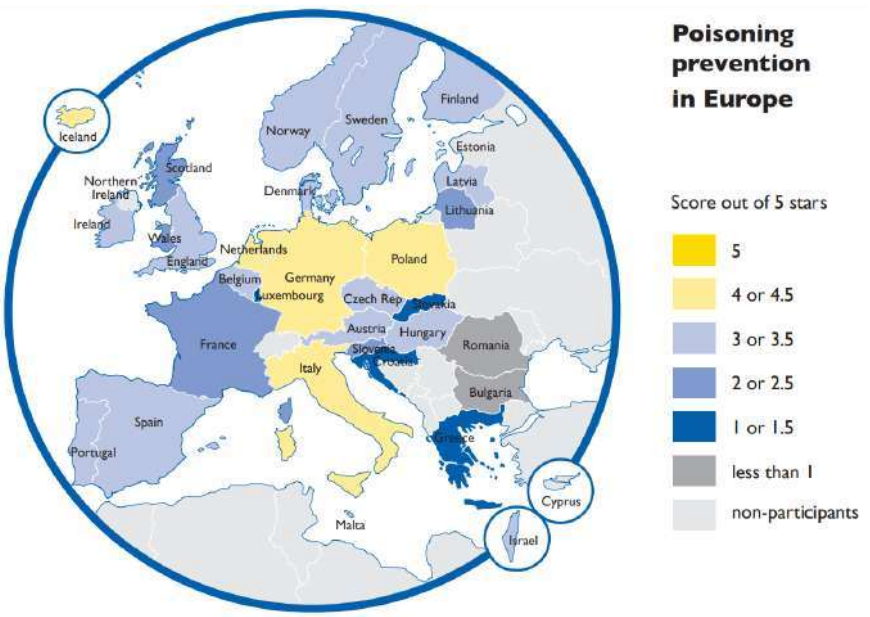

Figure 3: Map depicting the poisoning prevention scores of 31 countries in Europe, from 0-5 stars, with 5 being the highest score, based on criteria determined by the 2012 Child Safety Report Card.[11]

The following two studies indicate how some elements of child-resistant packaging testing criteria are being called into question, and whether these should be updated to reflect a wider demographic:

1. **A global divide:** Some researchers have raised the question over whether different geographical regions should be covered by the same global testing criteria for child-resistant packaging. For example, there is currently no regulation mandating the use of child-resistant packaging in Japan, but the consistently high levels of reported child drug accidents in the country have led to considerations over whether packaging that meets U.S. requirements is suitable for Japanese children. Researchers investigated paediatric characteristics such as literacy ability and finger function in Japanese subjects and examined the usefulness of child-resistant packaging technologies used in the U.S. when given to children in Japan.[14] Results suggested that the differences in the language, culture, and preschool education between Japan and the U.S. have a significant influence on paediatric characteristics.

2. **Improving understanding:** As previously mentioned, the criteria for ensuring adults can open child-resistant packaging stipulates that participants in testing must be able-bodied. Therefore, the existing test protocols for evaluation and validation of this type of package do not consider users with special needs, such as wheelchair users and people with limited range of hand movements, who are the most affected by the process of opening. Some studies have focused on better understanding the restricted movements of elderly or disabled users using devices such as movement restriction gloves, creating awareness in the hope of influencing these test protocols, as

well as informing ergonomic packaging design.[15]

Conclusion

Over the last fifty years there has been a gradual development in awareness of the risks of unintentional child-poisoning and while the incidence of poisoning events has decreased steadily over the last decade, the need for safe, compliant child-resistant packaging is receiving increasing attention. This attention has highlighted the demand to improve the safety of pharmaceutical packaging that maintains compliance with patients, particularly seniors. Child-resistant packaging that is truly senior-friendly undergoes innovation every year, and this development will be accelerated by strong relationships between drug manufacturers and packaging suppliers. Partnering with packaging manufacturers that can offer certified advanced solutions for CRSF packaging means that pharmaceutical companies can guarantee their products meet relevant regulatory requirements.

Beyond the legal requirements, child-resistant packaging makes a profound impact on pharmaceutical companies' larger goal to improve the health of people. If there is danger to the health of children, child-resistant packaging should be used and tested to establish that it works satisfactorily; as the last barrier between the child and the packaged content, it has an important part to play in solving the problem of unintentional child poisoning.

REFERENCES

1. MacKay M and Vincenten J. Child Safety Report Card 2012: Europe Summary for 31 Countries. Birmingham: European Child Safety Alliance, Eurosafe; 2012
2. Nistor N, Frăsinariu O, Rugină A, et al. (2019) 'Poisoning in the Pediatric Intensive Care Unit' in Karcioglu O, Arslan B, editors, Poisoning in the Modern World - New Tricks for an Old Dog? 1st ed. IntechOpen
3. Inheriting a sustainable world? Atlas on children's health and the environment. Geneva: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0 IGO
4. Wilkins S. Pharmaceutical packaging:child-resistant, easy opening, sustainable, European Pharmaceutical Review, 2019. https://www.europeanpharmaceuticalreview.com article/84257/pharmaceutical-packaging/
5. Pharmaceutical Packaging Market: Global Industry Analysis 2014-2018 and opportunity Assessment 2019-2029, Future Market Insights, April 2019. https://www.futuremarketinsights.com/reports/pharmaceutical-packaging-market
6. Annex 9 – Guidelines on packaging for pharmaceutical products, WHO Technical Report Series, No. 902, 2002, https://www.who.int/medicines/areas/quality_safety/quality_assurance/
7. ISO 8317:2015 – Child-resistant packaging — Requirements and testing procedures for reclosable packages, ISO, 2015. https://www.iso.org/standard/61650.html
8. US CPSC. 16 CFR Part 1700 – Requirements for the Special Packaging of Household Substances (Final Rule). Washington, DC: US Consumer Products Safety Commission, 1995.
9. Bix L, de la Fuente J, Pimple KD, et al. (2009) Is the test of senior friendly /child-resistant packaging ethical? Health Expectations, 12: 430–437.
10. Chen R, Bello NM, Becker MW, Bix L (2018) Chasing red herrings: Can visual distracters extend the time children take to open child-resistant vials? PLoS ONE 13(12): e0207738
11. MacKay M and Vincenten J. Child Safety Report Card 2012: Europe Summary for 31 Countries. Birmingham: European Child Safety Alliance, Eurosafe; 2012.
12. Talukder BMSB, Jovanov E, Schwebel DC, et al. A New Method to Prevent Unintentional Child Poisoning, 2018 40th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), Honolulu, HI, 2018: 5142-5145.
13. Mizoguchi M, Miura G and Ojimac F. Study of Child-resistant Packaging Technologies to Prevent Children from Accidental Ingestion of Drugs in Japan, Yakugaku Zasshi, 2018; 138, 1103-1110.
14. Mizoguchi M, Miura G and Ojimac F. Study of Child-resistant Packaging Technologies to Prevent Children from Accidental Ingestion of Drugs in Japan, Yakugaku Zasshi, 2018; 138, 1103-1110.
15. Bonfima GHC, Silvaa DC, Alvesa AL, et al. Hand movement restriction at the opening of child-resistant packaging: case study, Product: Management & Development, 2016; 14(2): 141-151.

Najet Mebarki

Najet Mebarki has been Senior Product Marketing Manager for oral products at SGD Pharma, since 2018. She has 15 years of experience in BtoB marketing within the packaging sector, in international companies and multicultural environments. Her role is to translate market insights into business value by developing the most suitable product & service offering. Most recently, Najet developed Ensiemo, a CRC packaging solution dedicated to the CBD oil market.

Email: najet.mebarki@sgdgroup.com

Dr. Rolf Abelmann

Dr. Rolf Abelmann is Managing Director of IVM Childsafe GmbH. Having joined in 2003 as head of testing while completing his doctorate with the University of Göttingen in 2005 he took on his current position in 2006.

Email: r.abelmann@ivm-childsafe.com