THE PIVOTAL ROLE OF PACKAGING IN **PATIENT SAFETY**

Report 2022

DATWYLER

INTRODUCTION: PRIMARY PACKAGING AND SAFETY

The concept of patient safety cuts through every facet of the healthcare sector, from drug development and product manufacturing to hygiene protocols and the instructions for use that accompany medical devices. In an industry that is judged by patient outcomes, any risk to patient health must be mitigated, whether in clinical trials, primary care or any other setting.

While much is said about patient safety in the context of the logistics chain, the processes for care at a patient's bedside and in drug development, it is less widely discussed in the context of packaging. Nevertheless, in the primary packaging for parenteral drugs – delivered via subcutaneous, intraperitoneal, intravenous, intradermal or intramuscular routes – primary packaging is a vital factor in ensuring the integrity of the treatment and its effectiveness.

"My definition of patient safety is very simple and straightforward," remarks Katie Falcone, Scientific Support Manager at Swiss company Datwyler, which manufactures state-of-the-art solutions for parenteral drug packaging for leading pharmaceutical and biotech companies worldwide. "It's the prevention of errors and adverse events to patients associated within healthcare."

"The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) points to United States Pharmacopeia (USP) standards, which list the levels of risk associated with different packaging concerns. The two highest ones of concern are inhaled drugs and injectables."

Here, we will examine the risks to patient safety that can emerge in the parenteral packaging supply chain and the mitigating measures that can be taken to ensure manufacturing processes eliminate those risks.

Patient safety refers to the prevention of errors and adverse events in healthcare.

Countless life-saving drugs are administered in hospitals every day.

THE PATIENT SAFETY IMPLICATIONS FOR PRIMARY PACKAGING

Injections, the most common type of parenteral drug administration, are everywhere. In early May 2022, Bloomberg's COVID-19 vaccination tracker reported that approximately 11.6bn doses of vaccine had been administered across 184 countries since the start of the pandemic, with the current rate levelling out at just under 18m doses each day. And that is just one vaccination program, albeit the largest in history.

Add in multiple shots of insulin each day by the diabetic population, and countless life-saving drugs administered in hospitals every day, and the number of injections given daily is staggering. That number is only set to rise as the pharmaceutical industry continues to develop innovative injectable drug therapies. Safety, therefore, is paramount for the billions of drug delivery systems that are used around the world every year.

"Our digestive system is designed to be able to filter out contaminants," says Falcone. "When you inject something into a person, those same systems aren't in place. We don't have a stomach to first process it, break down anything that could be harmful and then excrete it. If something is harmful in an injection we're introducing that directly into a patient's bloodstream."

For this reason, preventing contamination is a vital function of primary packaging. Above all, container closure integrity (CCI) is the overriding priority. The primary packaging of the drug is the first line of defence to protect the drug against any visible or non-visible particulate matter. An effective closure also extends the shelf life of a drug, as a seamless CCI will prevent exposure to the surrounding environment, which could cause hydrolysis or oxidation. Primary packaging, therefore, is largely responsible for keeping a drug safe and viable for an extended period of time, which has major implications for both patient safety and cost.

In a healthcare facility, storage is well-controlled and potential contamination can be limited, but as the market moves increasingly towards home care solutions, the risk profile and integrity of the closure changes.

"When our elastomer products are paired with prefilled syringe systems or autoinjector systems, we are enabling our customers' missions to help bring healthcare home and allow patients to take autonomy over the administration of their medication," says Falcone.

"Especially with the onset of the pandemic, that's been a particularly important improvement for patients who would have typically gone to a hospital to get an infusion or another recurring treatment," she continues. "Right now, during COVID-19, the hospital environment could pose some risks to someone who's already ill or already has an immune deficiency."

POTENTIAL RISKS AND DEFECTS IN THE PRIMARY PACKAGING

Of the many potential contaminants that could impair the function of a drug or potentially render it dangerous to a patient, extractables and leachables (E&L) are among the most dangerous.

"Issues with extractables and leachables may not be the most common because usually there will be extensive studies done to evaluate the E&L profile of an elastomeric formulation, but extractables and leachables can affect the active concentration of the drug. They can cause the protein to denature within a biologic if it's highly sensitive to outside contaminants," remarks Falcone.

CCI is another key area of focus, and drug companies must be careful in their selection of component suppliers to ensure they use the right components for vial, syringe, or cartridge systems. A poorly designed container closure system could result in leakage in certain storage or transit environments.

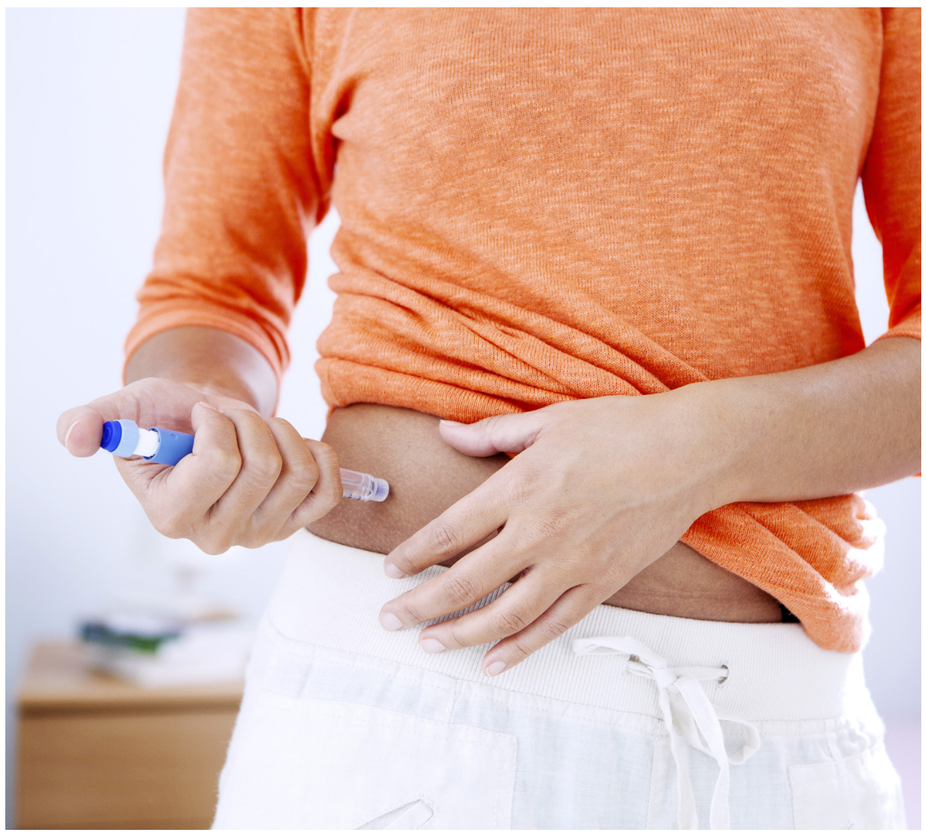
For home care solutions, for example, patients may need to carry a drug delivery device in their pocket or bag, so the container closure system must be able to withstand the resulting movement and the impacts that will cause.

"The evaluation of the self-sealing property of the elastomer is a key topic within our industry"

Loss of CCI could inactivate the drug product. The patient may not administer the correct dosage of a medication because the active ingredient could have denatured or oxidized as a result.

It is also essential to ensure that closures for multi dose products reseal properly after the initial punctures. Examples include insulin devices and multi-dose vials.

"Evaluation of the self-sealing property of the elastomer after typical use by a patient is an important topic within our industry and can cause issues if they're not properly evaluated," explains Falcone.



Autoinjectors simplify insulin administration for diabetic patients in home care settings.

RISK MITIGATION

Elastomer closures are Datwyler's area of expertise, so the company understands the intricacies of choosing the right material for a closure. A key consideration is the selection of an elastomer that works with the chosen geometry of a specific vial or syringe. It is also essential to understand whether the elastomer needs to be coated so as not to interact with the drug contained therein.

"Understanding the sterilization guidelines for your packaging is important, and that's a subject on which you should also partner with your supplier. So, is gamma sterilization the appropriate method for your particular component, or is steam sterilization better?"

"More common forms of contamination are dust, cellulose, and fibers from paper cartons."

Controlling contaminants is essential at every stage of drug manufacture, packaging and delivery. "There is a risk of introducing particulate matter to the patient's bloodstream inadvertently if there's any particulate that somehow got introduced to the drug product, whether it be through the drug's manufacturing process, the primary container, or through the elastomer closure. Whatever the particulate might be, it may cause an issue down the line," says Falcone.

"This is why silicone oil has become an issue," she adds. "When it comes to ocular injections it's been found that silicone oil can cause an inflammatory response. So that's another instance of understanding your system in its application for that target patient population when you select your packaging component."

The risk of contamination, however, is particularly severe during the manufacturing process. A major risk is from human-derived particles, which are deemed to be non-sterilizable by regulatory bodies. Even if they undergo a sterilization process, the presence of human-derived particles will prevent regulators from clearing an item for use.

As well as E&L, more common forms of contamination are exogenous particles such as dust, cellulose and fibers from paper cartons. There are also risks of endogenous particles caused by the blooming of compounds.

"It is important to remember that there's risk associated with any part of any manufacturing process," Falcone adds.

Modern treatments for diabetes enable insulin to be dosed via remote sensors.

FirstLine uses ultra-modern cleanroom technology and automated camera inspection.

FIRSTLINE®: A SAFE STANDARD FOR MANUFACTURING

Given the risks of contamination that arise during the manufacturing process, Datwyler has developed its highest manufacturing standard, FirstLine, which has been specifically designed to manufacture pharmaceutical rubber components for the high-end pharmaceutical and biotech markets.

"This is one of our best weapons in our arsenal to combat issues with patient safety," says Falcone. "It offers 100% camera-inspected pieces to ensure the quality of our products. There are multiple cameras in our FirstLine system checking products, and there are metal detectors to ensure unwanted particles are not found within our products."

"Additionally, there's a high level of cleanliness and a large use of automation within that process," she adds. "That reduces the number of people in the process, which goes back to the issue of human-generated particles. Removing that element entirely or to the best of our abilities helps with reducing particle introduction to the manufacturing environment."

FirstLine uses ultra-modern cleanroom technology, automated production cells, automated camera inspection, and a unique validated washing process. Datwyler's facilities are designed and operated under a zero-defect philosophy and rely on best-in-class processes. The technology itself relies on a zoning concept, with each separate zone equipped with material airlocks, and designed and constructed to prevent bio-contamination.

State-of-the-art pass-through washing equipment has its automatic loading side in one zone and its automatic unloading side in another zone of even higher cleanliness. The process flow, gowning protocols, personnel, and material flow, as well as cutting-edge automation processes all result in the lowest contamination and defect levels anywhere in the industry.

FirstLine is particularly well-suited for highly sensitive molecules, which is an attribute of many innovative therapies. It is also appropriate for the drugs that fall under the orphan drug designation in the US, which are produced only in small quantities.

"That makes it so much more important because the cost of manufacturing is so high," says Falcone. "One vial getting dropped or contaminated could be a financially impactful incident. Another instance is innovative therapies with high manufacturing costs for low drug yield. That's where I would recommend the FirstLine manufacturing standard because the stakes for quality become that much higher when there's such a small amount of drug being produced every year."

FirstLine's controlled environment ensures the lowest endotoxin, bioburden, and particulate defect levels possible. This is due, in part, to the ISO 5 certified clean rooms, or zones, which can each have pressure differentials between to ensure that any unwanted particles are pushed out when the doors are opened.

"Each classification of ISO control means different rules are in play, different suiting procedures, different cleanliness procedures," says Falcone. "ISO 5 means you're fully encapsulated in a whole-body suit, and usually wearing scrubs underneath, so there are no street clothes on the floor. Every possible inch of a person is covered head to toe, so there's a limited risk of introducing human particles to the entire environment, as well as the product itself."

As well as FirstLine, Datwyler also has other measures to reduce contamination, notably its fluoropolymer spray coating technology, which is used for their OmniFlex® stoppers and NeoFlex™ plungers, which offers protection against E&L. These products provide a total coating for the entirety of the surface area of the component.

CONCLUSION: THE DIFFERENCE WITH DATWYLER

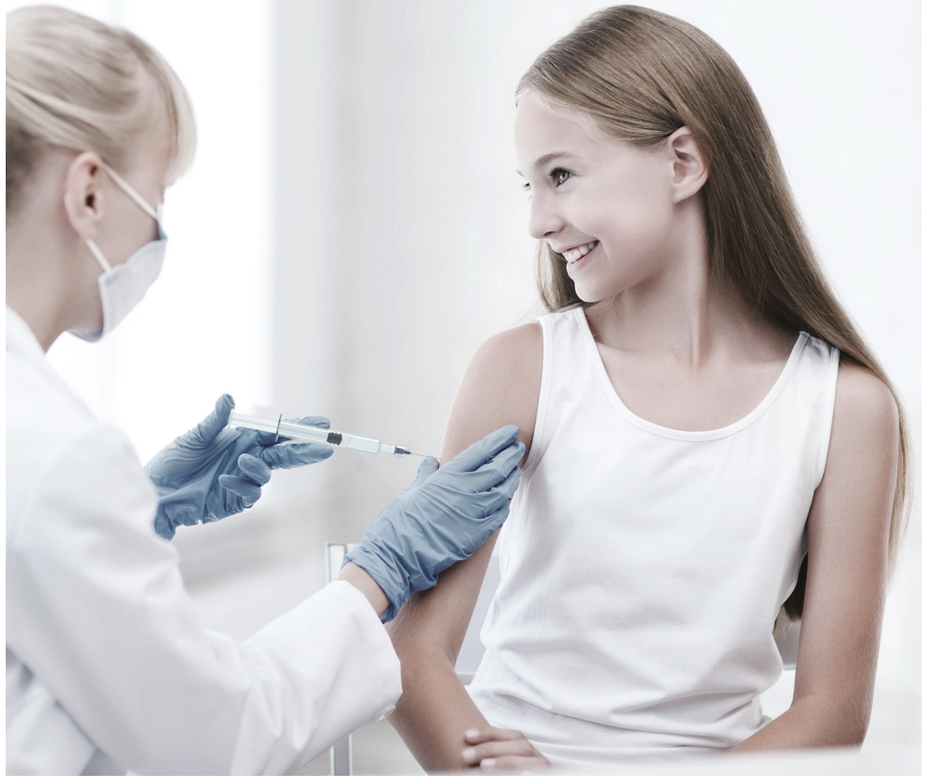
In constructing its packaging production facilities, patient safety is of paramount importance to Datwyler.

"Patients are our number one priority and helping our customers deliver life-saving medications for patients is our overall goal and mission," says Falcone. "Patient safety goes hand-in-hand with delivering those medications. It is woven into that mission and if you don't have patient safety, you don't have effectiveness."

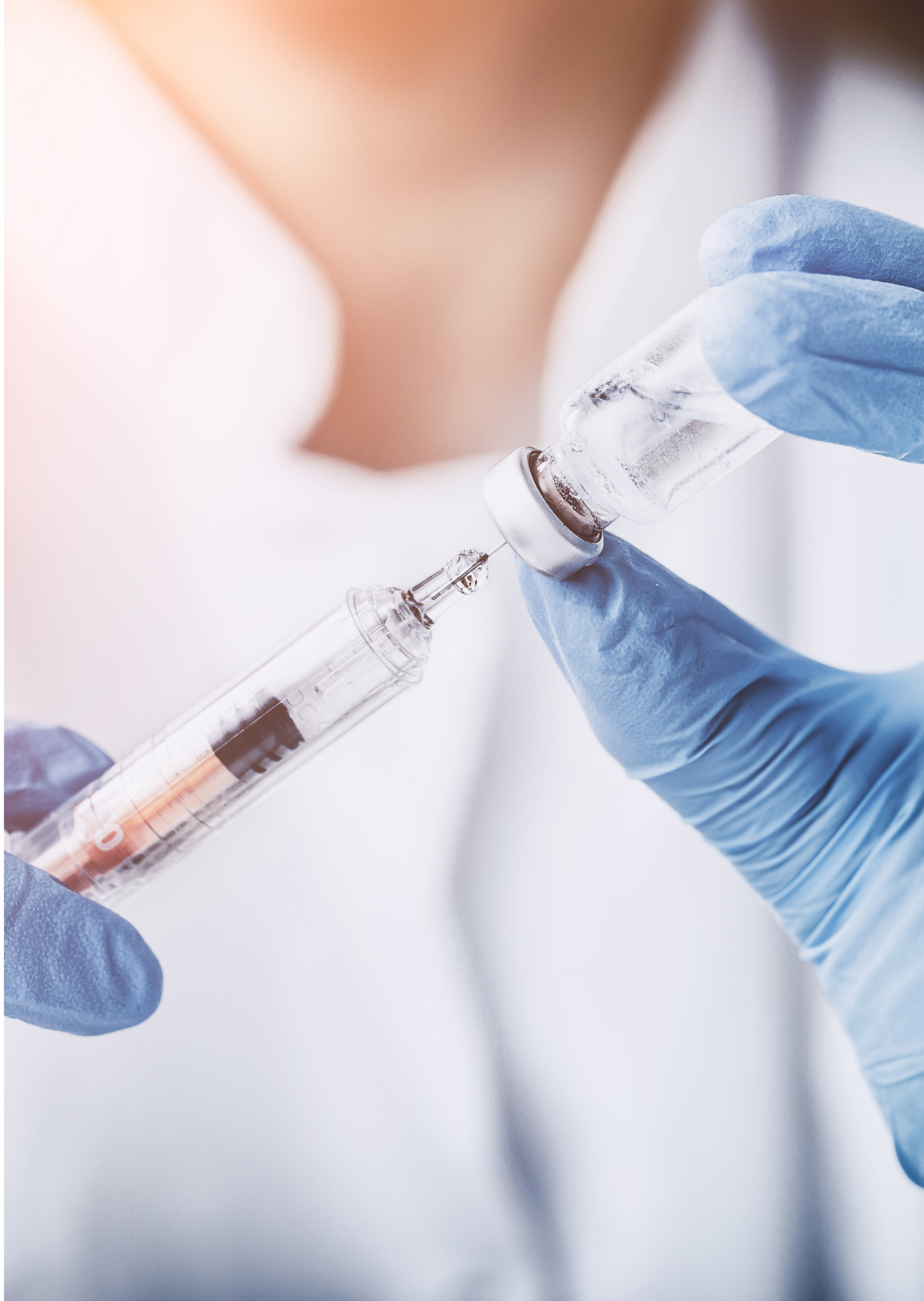
"The way the FDA works, the first phase of clinical testing revolves around safety," she adds. "Then they test the effectiveness of the drug for the intended patient population, so if you're not hitting that first pillar then you're not going to meet any of your other marks. You can't have anything else if you don't have patient safety."

The company works closely with its customers to develop specific solutions that address specific needs as part of a whole ecosystem of safety and quality. Its goal is to mitigate the risks drug manufacturers face, and its overarching mission is to deliver quality by design.

"When we are designing products, quality is at the forefront," notes Falcone. "It's a mindset, if you will, when going into designing a new process or designing a new component. You can't have a successful product without quality being at the forefront."



Datwyler's goal is to mitigate the risks faced by drug manufacturers.



Datwyler Group
Gotthardstrasse 31, 6460 Altdorf, Switzerland
T +41 41 875 11 00, F +41 41 875 12 28
info@datwyler.com, www.datwyler.com