LESSONS FROM THE PANDEMIC:
BUILDING A BETTER PREFILLED SYRINGE

Report 2022

DATWYLER

INTRODUCTION

The Covid-19 pandemic has highlighted many major challenges in the pharmaceutical supply chain and a key lesson has been that injectables and their packaging requirements are more important than ever. Given the volume of vaccines required to tackle the pandemic, as well as the growing number of high-value biologics that are either on the market or in development, finding the optimum delivery device is essential to maximizing their efficacy.

Vaccines are predominantly administered by healthcare professionals, but more and more biologics will be self-administered, so safety and ease of use are at the top of the agenda when creating delivery mechanisms. Injectable pharmaceuticals are absorbed into the bloodstream at varying speeds through intravenous, subcutaneous, or intramuscular administration, so sterility is also a must.

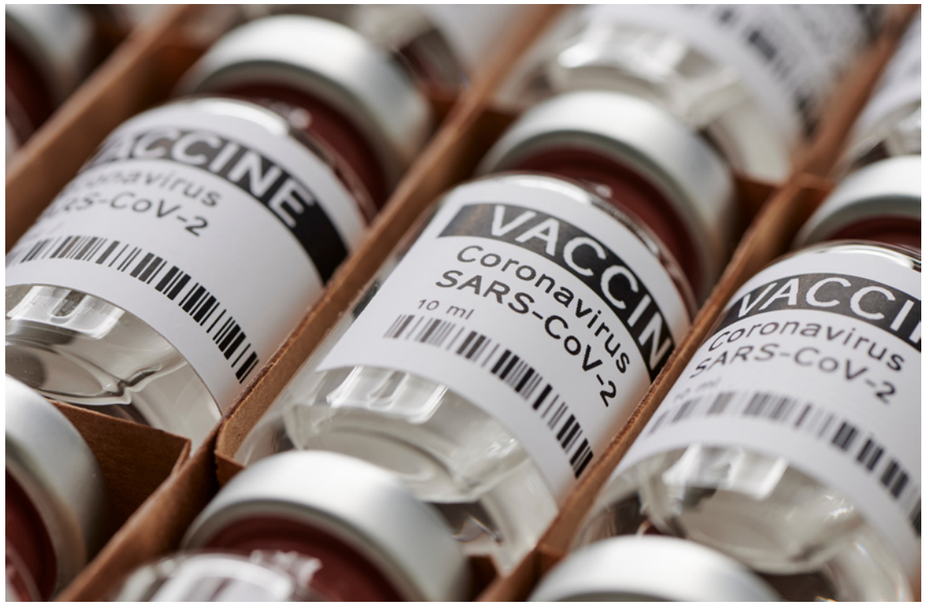
The sheer volume of injectables production that has been necessitated by the pandemic has turned the spotlight on manufacturing processes and their ability to deliver high-quality products at scale in a short timespan. Inevitably this has made manufacturers focus on the optimum design of prefilled syringes to balance performance, cost and ease of use.

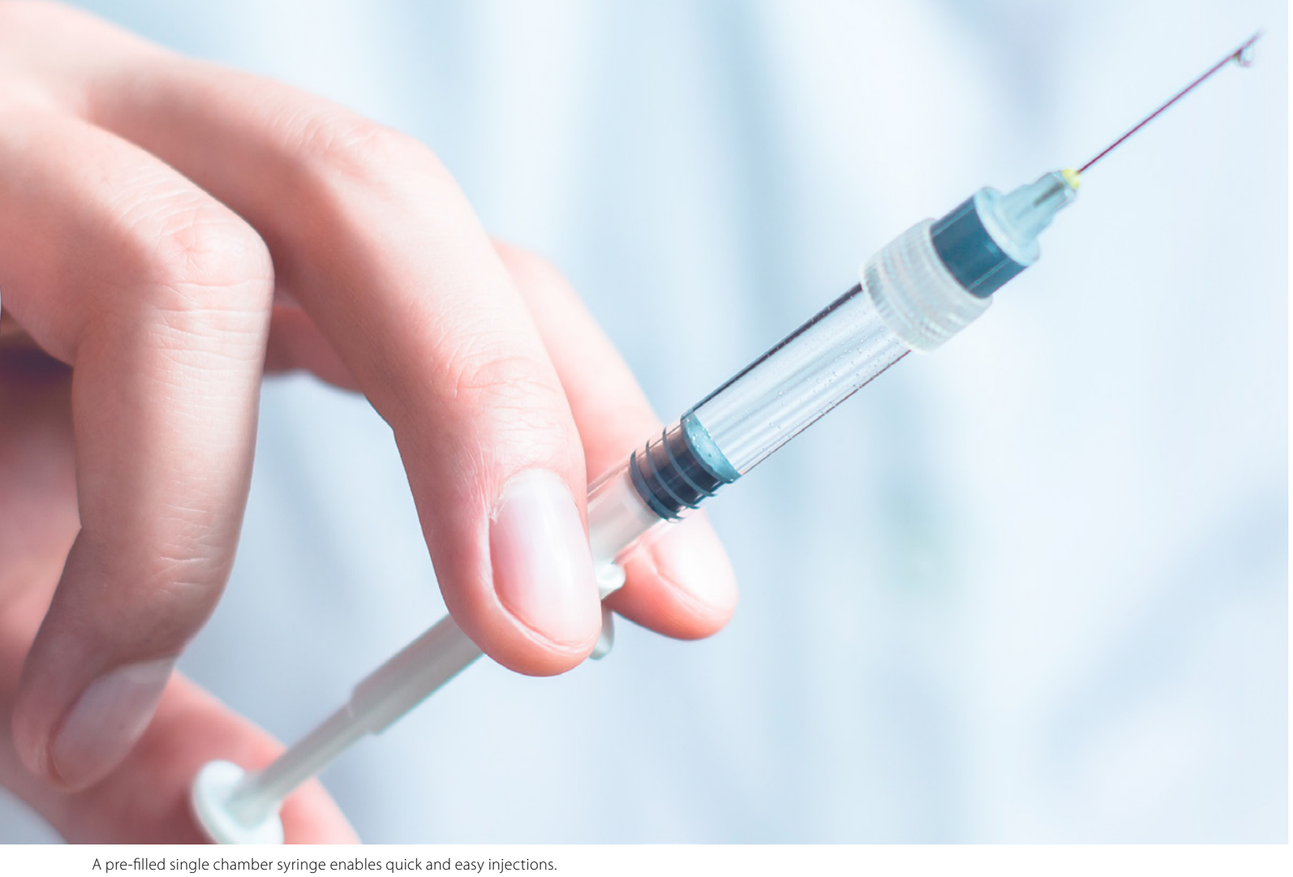
Injectable products, including vaccines, are high-value items and must be kept free from microorganisms and endotoxins in the production phase. Sterility can be achieved by terminal sterilization, aseptic filtration and aseptic formulation, which relatively few manufacturers can handle, and this tends to push up costs. It is essential, then, that they obtain the right components - the barrel that holds the drug in liquid form, the needle that is inserted into the skin or muscle, and the plunger that pushes the liquid into the skin or muscle - in a cost-efficient way that does not compromise performance.

A prefilled single-chamber syringe, which has had the drug filled into the syringe at the manufacturing site, is the preferred primary package for many self-injected drugs, like insulin or drugs for rheumatoid arthritis, and for vaccines. It allows the patient or physician to immediately inject the drug without having to extract it from a vial. Due to their popularity with patients, self-administered injectables by means of prefilled syringe and auto-injector are likely to be used far more widely in the future.

Indeed, according to GlobalData, prefilled syringes accounted for the second largest number of injectable product approvals during 2012–21. From the quality and operations perspective, prefilled syringes eliminate overfill of expensive drugs, allow for a fixed dosage form, help to reduce medical error, and lower costs due to lower material usage and easier storage and disposal. In fact, some pharma companies market customized prefilled syringes as a marketing differentiator.

Based in Switzerland, Datwyler is a leading supplier of elastomer formulations, aluminum seals and processing technologies to the global healthcare industry. Its global production footprint makes it a key component in the supply chain for many products, and in the pages that follow we will learn how it is enhancing the benefits and overcoming the challenges of building the ideal prefilled syringe for vaccines. Also, we will examine how packaging suppliers are meeting this challenge by introducing a variety of vaccine-centric components.





A pre-filled single chamber syringe enables quick and easy injections.

THE CHALLENGES
OF PACKAGING VACCINES

Bringing a high-value drug such as a vaccine or a high-value biologic to market comes with a number of key challenges. According to Carina van Eester, Global Platform Leader, Prefilled Syringes and Cartridges at Datwyler, these fall into four key categories.

"There are four key considerations that can help determine the ability of a given vaccine to be introduced within a health system," she remarks. "The first one is acceptability. The second one is accessibility. Then the affordability is a very important one, as is the availability of the vaccines."

In addressing some of these challenges, most notably accessibility and affordability, pharmaceutical companies have to make some important decisions about primary packaging. The first is to choose whether to opt for vials or prefilled syringes.

"Vials can hold more doses of the vaccine, which enables a greater number of vaccinations and a lower cost, but prefilled syringes allow for easier administration, reduced risk of contamination, minimized risk of injuries during use and improved accuracy," says Van Eester. "Vials were chosen for the first Covid-19 vaccines in the US and the EU, but if we look at China, a large amount went immediately into syringes. In general, a prefilled syringe is clearly preferred for vaccines."

Choosing the right delivery mechanism depends to some extent on the type of vaccine or biologic being administered. The decision will also be influenced by the required storage conditions of the drug, the availability of materials to create the primary packaging, and also the cost of the vaccine.

Vaccines are not homogenous, but come in many different forms. At one end of the spectrum there are whole pathogen vaccines that use the disease-causing pathogen to produce a similar immune response to that seen during natural infection. Live attenuated vaccines use whole bacteria or viruses that have been weakened (attenuated) to create a protective immune response without causing disease in healthy people.

Next come subunit vaccines, which contain one or more specific antigens from a pathogen's surface. This causes the immune response to focus on recognizing a small number of antigen targets. In recombinant vaccines, a small piece of DNA is taken from the virus or bacterium against which we want to protect and inserted into the manufacturing cells. The list goes on.

"Each vaccine has specific needs, which have to be considered when selecting the right packaging materials," says Van Eester. "Generally, it is known that larger molecules are more sensitive. As such, they can experience the negative impact of any interaction with the packaging

materials. What they could absorb through the surface could reduce the potency of the drug."

"Historically, vaccines were always packaged using uncoated rubber components," she adds. "With the new protein-based vaccines a coated rubber component is a safer solution. It is therefore imperative for a component supplier to offer customers a wide range of components in order to make sure that a stable vaccine can be developed."

In some cases, vaccines will also require specific storage conditions. For some vaccines, ultra-low temperature storage conditions are needed in order to avoid degradation. While some major approved traditional vaccines can be stored in refrigerated conditions, the new Covid-19 mRNA vaccines require much colder temperatures. For the Pfizer/BioNTech one, the range is -80°C to -60°C, and for the Moderna/AstraZeneca vaccine it is -25°C to -18°C.

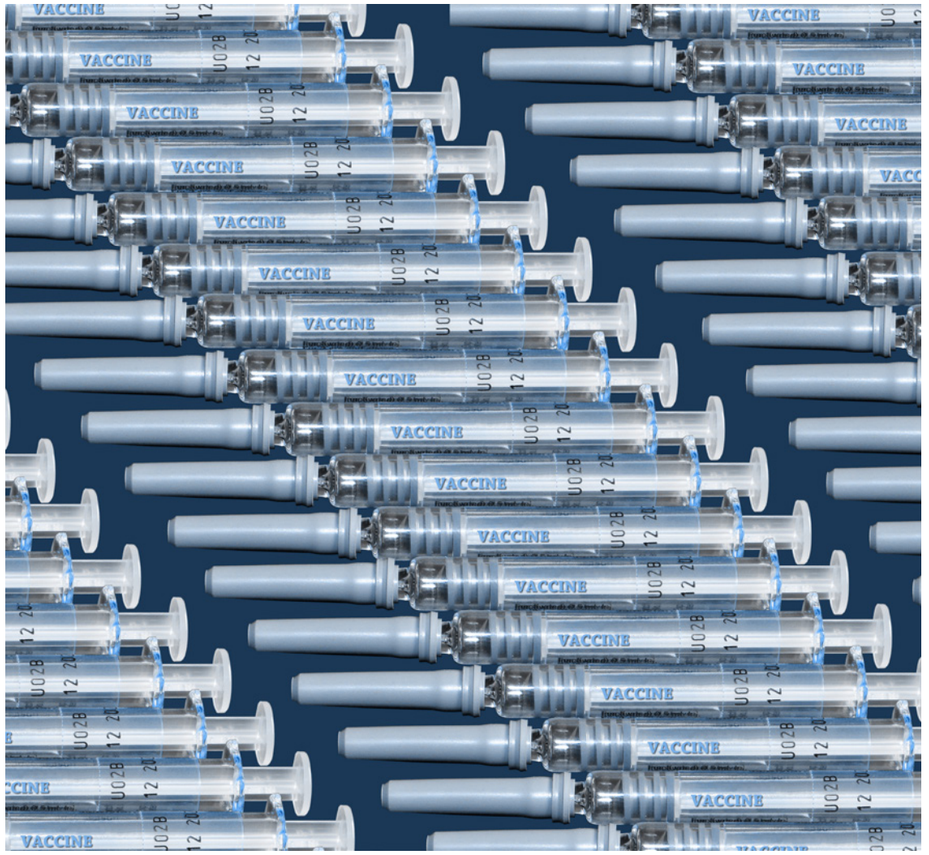
"There are shortages of many products on the market these days; this is a very important factor."

"Because the packaging industry has never been confronted with those very low temperatures, which are below freezing conditions, no data were available to support functional performance like container closure integrity, gliding performance or plunger movement when storing a prefilled syringe at these conditions," Van Eester remarks.

"Another aspect which is also important to ensure the availability of vaccines is the availability of the materials and machines to produce prefilled syringes," she adds. "We see a shortage of many products on the market these days, and this is a very important factor in making the right choice of packaging. During the Covid pandemic, for instance, we saw issues with the supply of borosilicate glass - a basic material needed to make both vials and prefilled syringes."

Similarly, sourcing rubber components has been a challenge during the pandemic. For packaging producers, it has been essential to not only source sufficient rubber to make packaging for Covid-19 vaccines, but also to ensure there was enough to continue supplying vials and prefilled syringes for all of the other drugs that are in demand globally.

"Even getting the bags to package the rubber components has been a challenge and the same is valid for machines," says Van Eester. "Last but not least, you then have the cost factor. Healthcare systems have limited budgets, and they purchase vaccines mainly through tenders. The price of a vaccine is a very important factor to make the decision of which manufacturer will be chosen. Due to this, small and mid-sized pharma companies attach a very high importance to the pricing of rubber components."



Vaccines come in many different forms, which can include whole pathogen, live attenuated, subunit, and recombinant.

OPTIMIZING THE DESIGN OF PREFILLED SYRINGES

Looking at these four major challenges - the many types of vaccines, different storage requirements, constraints on the availability of materials, and the importance of controlling costs - primary packaging manufacturers must consider how to optimize the design of prefilled syringes.

For example, in choosing the plunger material it is essential to choose the right rubber compound. Datwyler has a range of plungers available for vaccines. The FM257 is a standard halobutyl rubber component that is currently being used for the older vaccines. The FM457 compound is a very modern alternative that is known particularly for low levels of extractables. Lastly, there is the fully coated FM457 NeoFlex™ plunger platform.

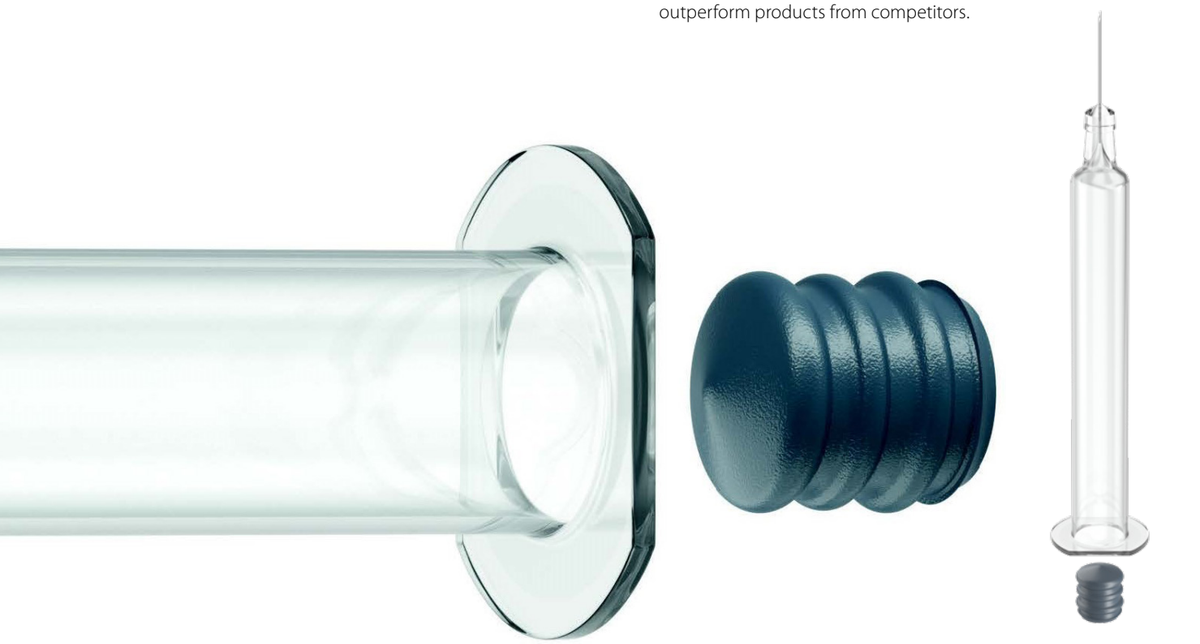
"All of them are already used in combination with vaccines," notes Van Eester. "We did extractable studies to get a better understanding of the impact on extractables once a plunger is inserted into a syringe, and we compared the three compounds. We also compared it with a coated plunger from a competitor."

"If you then compare the FM257 to the FM457 you see a significant decrease of extractable levels," she adds. "The main difference is the absence of the rubber oligomers related to the specialty elastomer used for FM457. Comparing the FM457 to the NeoFlex, the barrier effect of the coating is clearly visible. The good performance of the NeoFlex is not only related to the coating, but also to the very clean rubber substrate, which is the FM457 compound."

Datwyler has also studied the thermal expansion coefficient of its different materials to evaluate their performance at low temperature materials. The key issue is how much the materials of the plunger and the container shrink when they go from room temperature to -50°C. While there is quite a difference between the coefficients of thermal expansion from a rubber component compared to borosilicate glass, with all three Datwyler plungers there is still a high degree of interference, which means the packaging maintains its integrity even at -50°C.

"When we looked at seal integrity of closures for syringes stored for one week at -50°C in a CO_2 enriched environment, the results show that there is not too much of a difference between syringes that have been stored for one week at -50°C versus syringes that have been stored room temperature," says Van Eester. "Gliding forces are quite compatible or maybe a little bit lower, but it's not really a big difference."

The studies done by Datwyler show that its range of elastomer components is well suited to the demands of today's vaccines, including the more extreme temperatures required by some of the most popular Covid-19 vaccines. Nevertheless, the company is keen to ensure that its products continue to evolve in order to deliver prefilled syringes that outperform products from competitors.



Datwyler has a range of coated and uncoated plungers for vaccines.

Datwyler carries out performance testing with major syringe barrel manufacturers.

THE DATWYLER ADVANTAGE

Datwyler is working closely together with major barrel manufacturers. "We work together on developing and qualifying new products like the tip caps, plungers and needle shields," says Van Eester. "We also do performance testing together, and we work on continuous improvement. Samples can be obtained from Datwyler through these barrel manufacturers, which offers a great benefit for customers who have limited resources in packaging, development and purchasing of components."

This collaboration results in a one-stop-shop offering for system suppliers, which guarantees customers a lower overall cost, easier communication, quicker turnaround and clear system accountability.

In addition, Datwyler continues to innovate and has recently launched a 5/8 inch rigid needle shield (RNS) to address the rising need for prefilled syringes for vaccines for intramuscular injection.

"The pull off force, which is the force to remove the needle shield from the barrel, is influenced both by the barrel and the needle shield and eventually also by even the ethylene oxide (ETO) gas sterilization that is used," says Van Eester. "Now since barrels can slightly differ a bit and also the ETO cycle can slightly differ between the different barrel manufacturers, Datwyler has provided early during the development of this new RNS some samples to system suppliers in order to make sure that all the parameters could be finetuned at both ends before providing this new product to the market."

Although it continues to introduce new components to the market, Datwyler is aware that this can elevate costs. Consequently, the company offers several services and platform products that can help pharma companies reduce the costs that arise from packaging development. For instance, extractable reports are available for all major compounds, which provides a good starting point for selecting the right compound for a specific application.

Furthermore, functional performance data is available on parameters such as gliding behavior, container closure integrity and plunger movement in combination with different syringes available in the market. If necessary, Datwyler can also provide some laboratory services, and in some cases is open to co-development with customers to address specific needs.

"Larger molecules are more sensitive, so coated components are typically preferred."

"It is generally known that larger molecules are more sensitive and coated components are preferred, but there are also a certain costs linked to coated components," says Van Eester. "The compound FM457 is a very clean rubber compound, which in many occasions already offers good stability for larger molecules. This can reduce the component cost when filling or packaging a new drug."

Datwyler can also offer regulatory support, as it has a DMF available in the US and Canada. Also, registrations in China are available for certain components. To further control production costs, the company can offer ready-to-use components that eliminate the need to invest in sterilization equipment and cleanroom environments. It also provides camera-inspected products to avoid loss of filled syringes during final inspection.

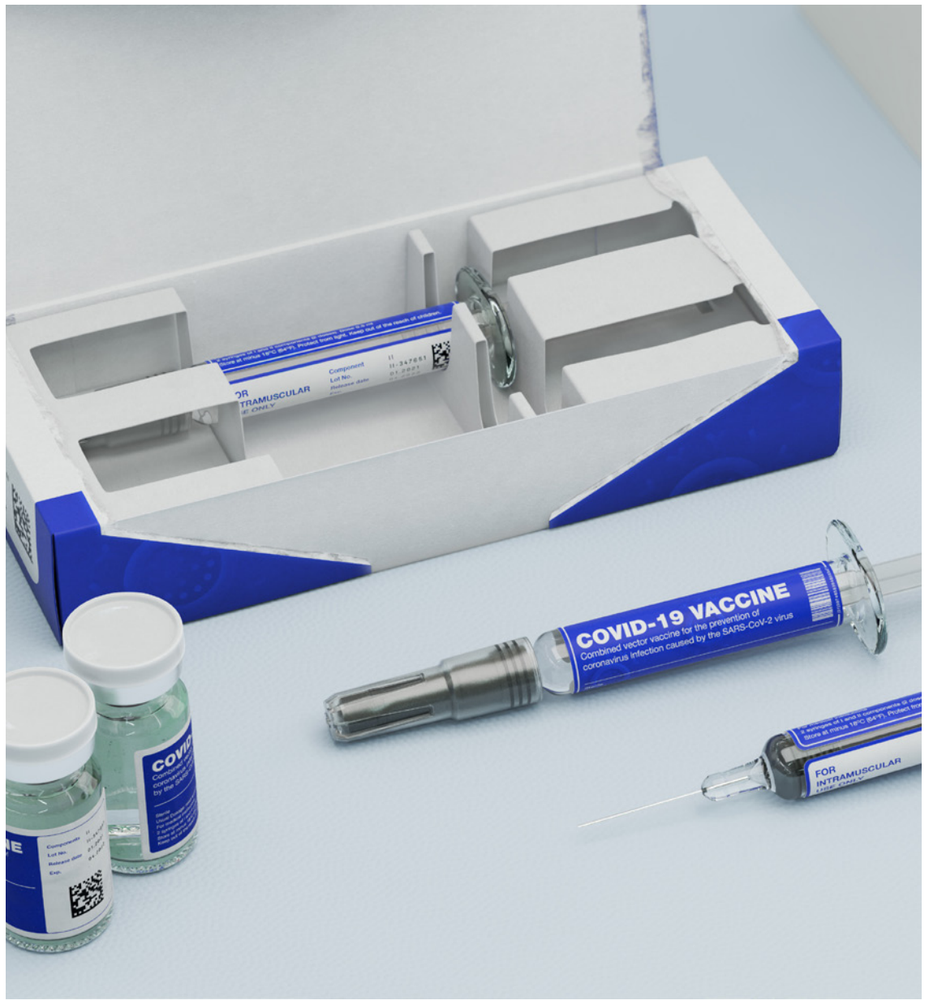
CONCLUSION

Since the start of the Covid-19 pandemic, around 67.8% of the global population has received at least one dose of the vaccine. This equates to 12.63bn doses administered globally, and 3.77m are being administered each day. To deliver the vials, prefilled syringes, rubber plungers and stoppers, and aluminum caps required for making these vaccines, the industry has made a huge effort to ensure the supply of key components in order to not delay the rollout of the vaccine.

Datwyler's global production footprint has been key to its role in this supply chain, allowing it to quickly produce billions of components at globally harmonized sites. Each production site uses the same raw materials, the same technologies, the same procedures and the same design specifications to guarantee the same product specifications.

"This makes us a very flexible part of the supply chain which can improve the time to market and also improve risk mitigation," says Van Eester. "We made significant investment in rubber and aluminum, and all sites around the world were expanded. This investment has enabled the company to provide a better, faster and more reliable level of service to our customers by ensuring that there is a lot of capacity available for the production of vaccine components."

In the midst of a crisis there is a motivation to innovate, and that is exactly what Datwyler has done in its drive to improve the design of prefilled syringes.



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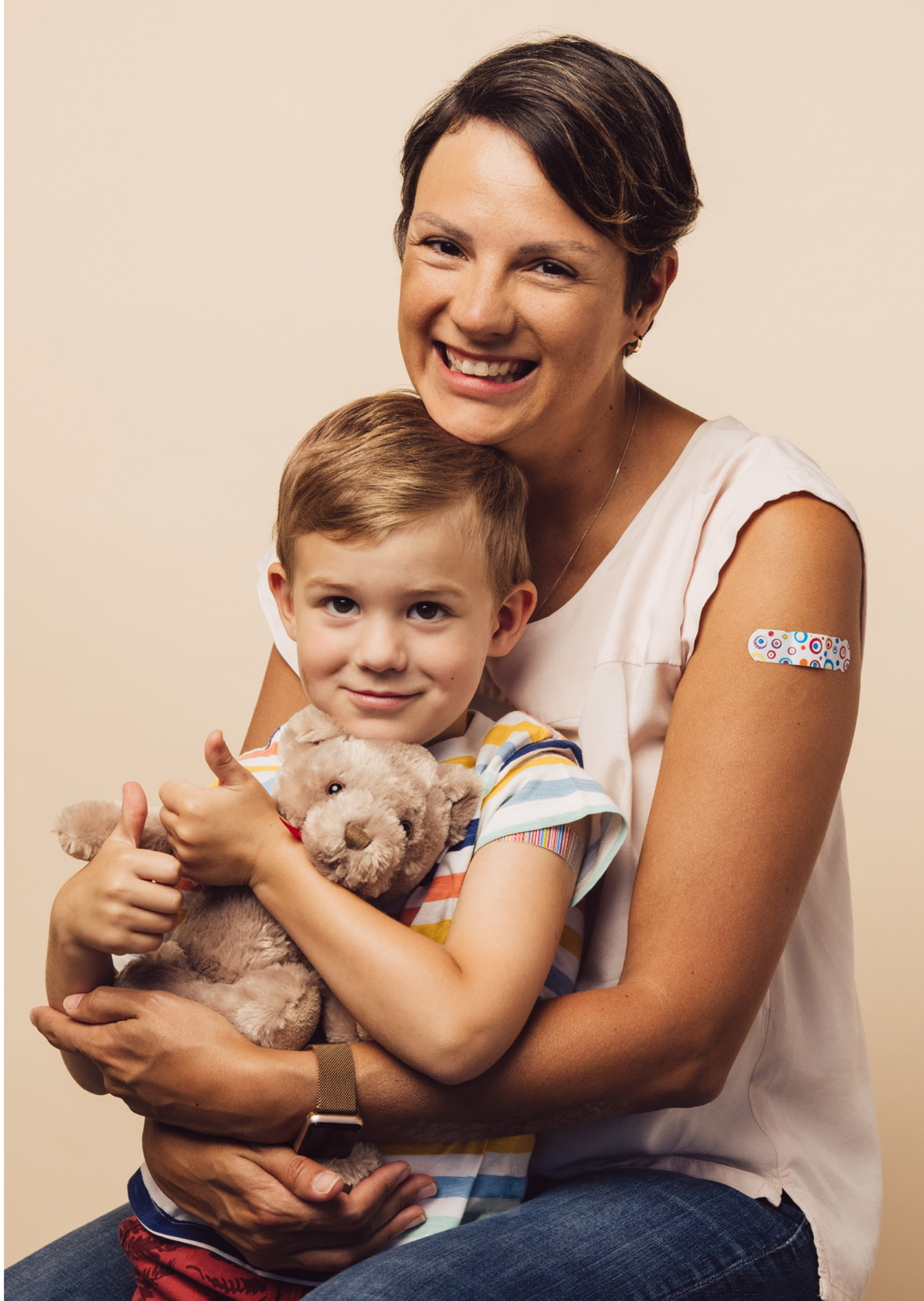

Datwyler Group
Gotthardstrasse 31, 6460 Altdorf, Switzerland
T +41 41 875 11 00, F +41 41 875 12 28
info@datwyler.com, www.datwyler.com