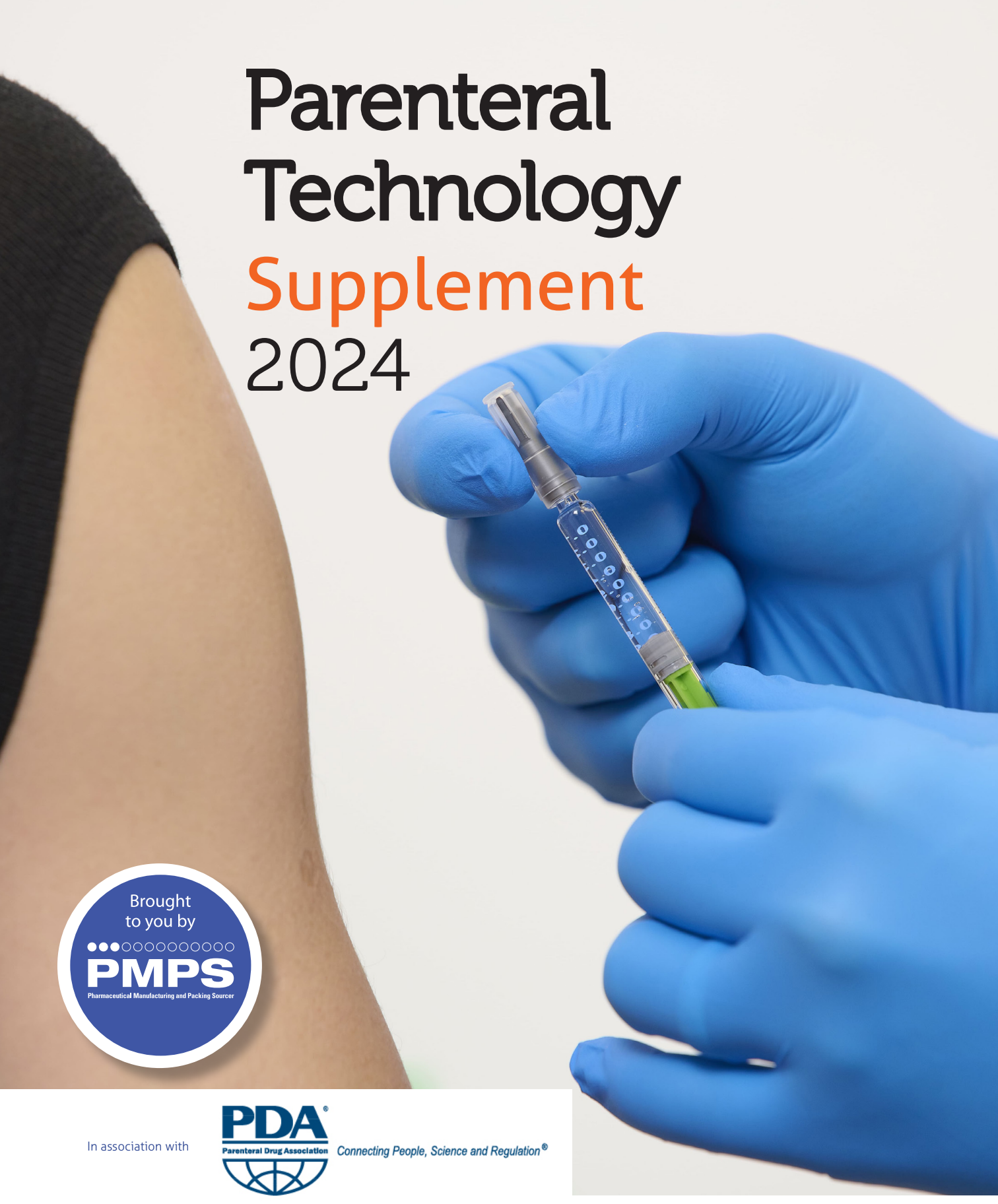
Parenteral Technology Supplement 2024



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SPOTLIGHT

Primary packaging in the wake of Annex 1

Estelle Verger at Aptar Pharma Injectables explores the recent revisions to EMA GMP Annex 1, the impact that this will have on the primary packaging landscape, and how Aptar Pharma's solutions can help manufacturers adapt to these changes

***PMPS*: What were the recent updates to the European Medicines Agency's Good Manufacturing Practice (EMA GMP) Annex 1, and how do they impact pharmaceutical manufacturers worldwide?**

Estelle Verger (EV): In the pharmaceutical industry, it is of paramount importance that the end-product is both safe and efficient. GMP guidelines exist as means for regulatory bodies to ensure this is the case, as they offer guidance to drug manufacturers and their suppliers so that they are consistent in their quality and remain adherent to their marketing or clinical trial authorisation requirements.[1]

Translating a development from initial research through to a drug, and then getting that drug product to market, is an intense and involved process, requiring a significant investment of resources.

As such, pharma manufacturers must be aware of any changes related to this process as these could have significant impacts across their development pipeline. The recent revision of EMA GMP Annex 1 is an example of such a change – the guidelines explore in more depth the importance of contamination control and sterility assurance throughout the process, with increased emphasis put on suppliers and drug packaging.[2]

While patient safety will increase as a result, introducing such regulation does have the effect of increasing the pressure on pharma manufacturers, who have to adapt their practices to adhere to these new standards. This can be a costly endeavour, especially if new manufacturing infrastructure and logistics are required.

***PMPS*: Why are primary packaging containers now so important especially after these updates, and why is there more emphasis on the role of suppliers?**

EV: Primary packaging refers to the packaging that directly contacts the drug such as the glass container or rubber closure components. As such, it is a prime source of potential contamination and ensuring that the primary packaging itself remains free of contaminants and sterile from storage through to drug manufacturing and patient administration is key. This is specifically the concerns that Annex 1 revision is addressing.

Beyond Annex 1, the changing nature of the pharma landscape – more specifically, the rise in popularity in biotech therapeutics and biosimilars – has also increased the emphasis on the role of primary packaging suppliers. These new therapeutics, such as monoclonal antibodies or recombinant proteins, can be very sensitive, so extra care is needed when packaging and transporting them. Primary packaging is therefore an integral element in ensuring the safety and efficacy of these therapeutics, and must adhere to the strictest quality standards in terms of cleanliness and sterility until it reaches patients.

***PMPS*: What are the best practices that pharma manufacturers can adopt to limit the risk of contamination linked to the use of primary packaging?**

EV: One way that pharma companies can ensure that drugs get to market

and patients successfully is through engaging in partnerships with the right drug delivery experts. At Aptar Pharma, we have experience across the pharmaceutical drug development journey, in supporting drug developers from formulation to patient. When it comes to injectable drug delivery, and whether it is for handling changes related to the new GMP Annex 1 or accelerating the development of sensitive drug products, our partners rely on decades of expertise in developing and validating advanced parenteral closure solutions.

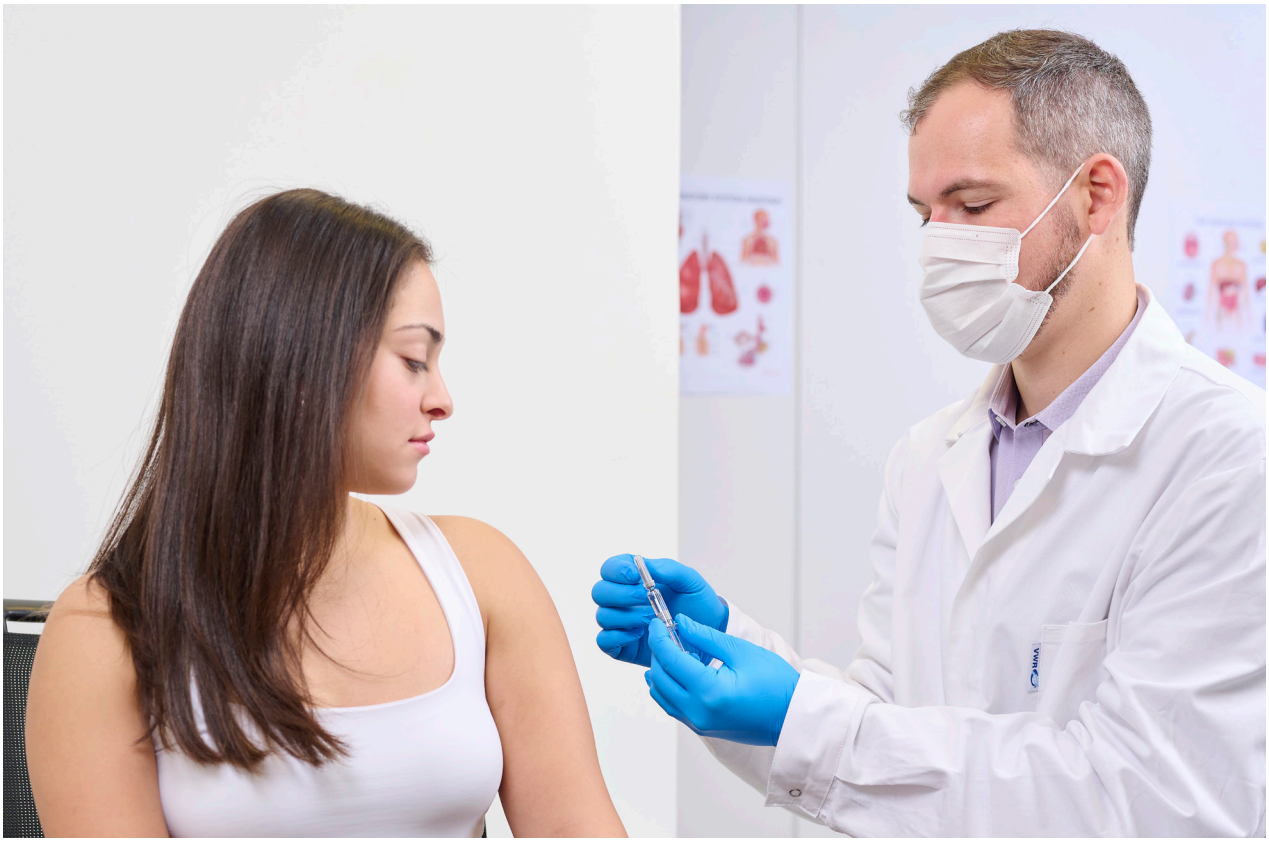
As part of Annex 1 revision, sterile drug manufacturers now need to ensure they have pharmaceutical quality systems in place that address specific requirements for product manufacturing. This includes limiting contamination across the product's life cycle, whether it is from microbial, biological or particulated origin, which are the main causes for FDA recalls.[3,4] Drug manufacturers must establish a contamination control strategy (CCS) to identify, document and mitigate all risks of contamination throughout their manufacturing process. This extends across the entire supply chain, and the sterile primary packaging manufacturers now have to implement their own CCS, supporting the CCS of the sterile drug manufacturers.

Consequently, sterile drug manufacturers are encouraged to select higher quality solutions in their supply chain. Aptar Pharma's PremiumFill® vial stoppers and Pre-Filled Syringe plungers are among the solutions that can support contamination reduction and improve fill-finish operational efficiency. By performing the rubber moulding and trimming steps within an ISO 7 cleanroom, while leveraging advanced robotisation, PremiumFill® delivers tightened specifications on key contamination criteria, as defined by Annex 1, and other defects of injectables primary packaging components.

A case study performed at a customer's facility demonstrated that swapping from a standard Aptar Pharma vial stopper to the corresponding PremiumFill® vial stopper led to over 20% reduction in its scrap rate over nine months, while also reporting no quality complaints related to the PremiumFill® stoppers.

The main defect reductions that were reported were for fibres and stains, both of which being included in PremiumFill® specifications. In addition to supporting compliance with Annex 1, this can support increased profitability by reducing costs linked to scraps and product rejection – therefore, reducing the total ownership costs associated with closure components. Most importantly, at Aptar Pharma, we evaluated that upgrading to PremiumFill® does not require regulatory re-approval or process adaptation.

The rubber formulation, product design and finishing process remain strictly identical to standard vial stoppers, allowing PremiumFill® products to be seamlessly implemented with no impact on extractables and leachables and on machinability with existing filling lines.



***PMPS*: What role does primary packaging play in ensuring that pharmaceutical products remain sterile until point-of-use?**

EV: Pharmaceutical products need to remain sterile until they reach the patient. Because not all drug combination products can undergo terminal sterilisation, the onus of sterility lies on ensuring that fill-finish operations are performed under sterile conditions. Primary packaging must therefore be sterile when entering the filling line, to preserve the sterility of the drug.

To help ensure that this is the case, Aptar Pharma offers ready-to-use (RTU) gamma sterilised components that are guaranteed to be sterile at the time of use on the fill-finish line. This guarantee is ensured through multiple factors.

For one, Aptar Pharma's sterilisation process has been fully validated, and continues to be periodically assessed and validated. All upstream manufacturing steps involved in the production of primary packaging have been optimised to limit the risk of introducing microbial contaminants early on. All Aptar Pharma sterile elastomeric components are provided with a certificate of gamma sterilisation and carry a gamma irradiation indicator to demonstrate that the products have been irradiated, and therefore sterilised. Our RTU components are packaged in specifically designed bags that allow operators to easily check their integrity, and therefore that the sterility has been preserved after gamma irradiation, until the time of use.

Additionally, our RTU bags do not use Tyvek, which can be source of particles or fibres, thus helping with particle contamination control.[5]

Taken together, these elements allow customers to have the utmost confidence in our products for preserving the sterility of their fill-finish operations but also ensure compliance with Annex 1 guidelines, which require demonstration of sterility and packaging integrity at the time of use.

***PMPS*: What do pharma companies need to do to address aseptic transfer questions on their filling lines?**

EV: All primary packaging components need to be clean when they are being used and the transfer of these components onto the fill-finish must not introduce any further microbial or particulate contamination.

To address this issue, section 4.3 of the Annex 1 revision recommends isolators and restricted access barrier system (RABS) systems be used alongside rapid transfer port (RTP) bags to minimise the risk of contamination during aseptic transfer. This is done through the direct attachment of the RTP bags onto the isolator/RABS, without any contact of the component or fill-finish environment with the outside environment.

As of today, this is the most efficient method for transferring sterile components onto a fill-finish line. Within the scope of the revised Annex 1, using any alternative method would require drug manufacturers to specifically justify and document how sterility is ensured during the transfer of components onto the filling lines.

References:

1. *Visit: ema.europa.eu/en/human-regulatory-overview/research-development/compliance-research-development/good-manufacturing-practice*
2. *Visit: gmp-compliance.org/files/guidemgr/20220825_gmp-an1_en_0.pdf*
3. *Tawde S (2015), 'Particulate Matter in Injectables: Main cause for Recalls', J Pharmacovigil, 03, 01*
4. *US FDA (2020), Recalls, Market Withdrawals, & Safety Alerts*
5. *Berggren J, Deuthschlet G (2020), 'Winning combination: reducing particles in RTU packaging by aligning lid material, adhesive and sealing parameters in a holistic approach', A3P, Jul 2020.*

Estelle Verger is the business development senior manager for Advanced Parenteral Closure Solutions for **Aptar Pharma**'s Injectables division and is responsible for the growth of those solutions in the global injectable market. A graduate from ESSEC Business School, France, and Fachhochschule Dortmund, Germany, with a Masters' degree in international business management, she joined Aptar Pharma in 2011 as a sales manager, Injectables. Ms Verger then moved to Aptar Pharma's Consumer Healthcare division as a product manager, where she was responsible for airless dispensing solutions for pharmaceutical applications for several years, before returning to the Aptar Pharma Injectables division in 2020.

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