EU GMP ANNEX 1 AND PARENTERAL PACKAGING: A QUALITY BY DESIGN APPROACH TO STERILE MANUFACTURING

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DATWYLER

INTRODUCTION

The pharmaceutical industry is, by its very nature, in a constant state of flux as innovation and regulation advance without pause. Currently, the market is driven by three clear trends that are shaping the needs of pharma companies and their suppliers, causing all stakeholders to focus on improving quality, efficiency and compliance procedures.

Firstly, the market is shaped by the ongoing development of innovative and complex drugs, which are often increasingly sensitive to physical conditions, microbial contamination and other influences. Secondly, this development process is happening under increasingly stringent scrutiny from regulatory authorities.

Finally, the pursuit of innovation and regulatory compliance must go hand-in-hand with the unstoppable tide of globalisation and the ongoing need for supply chain optimisation, as the industry strives to meet demands for ever-higher levels of quality.

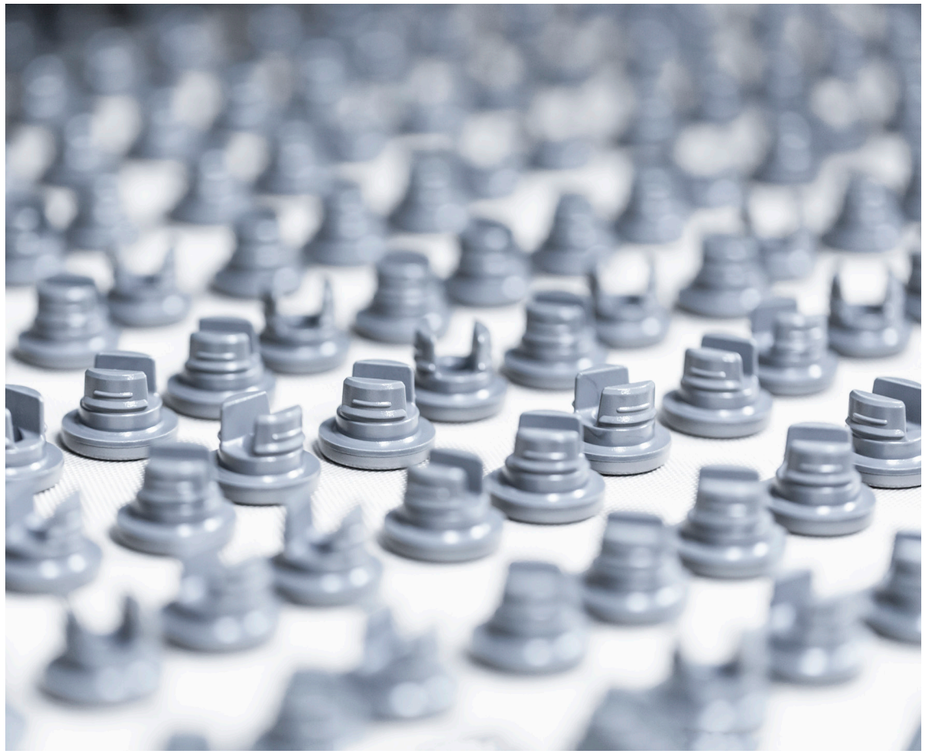
These trends clearly present some challenges, as illustrated by the number of warning letters sent by the US Food and Drug Administration (FDA) over the years, which are linked not only to issues with the final product, but in certain cases, also the quality of components.

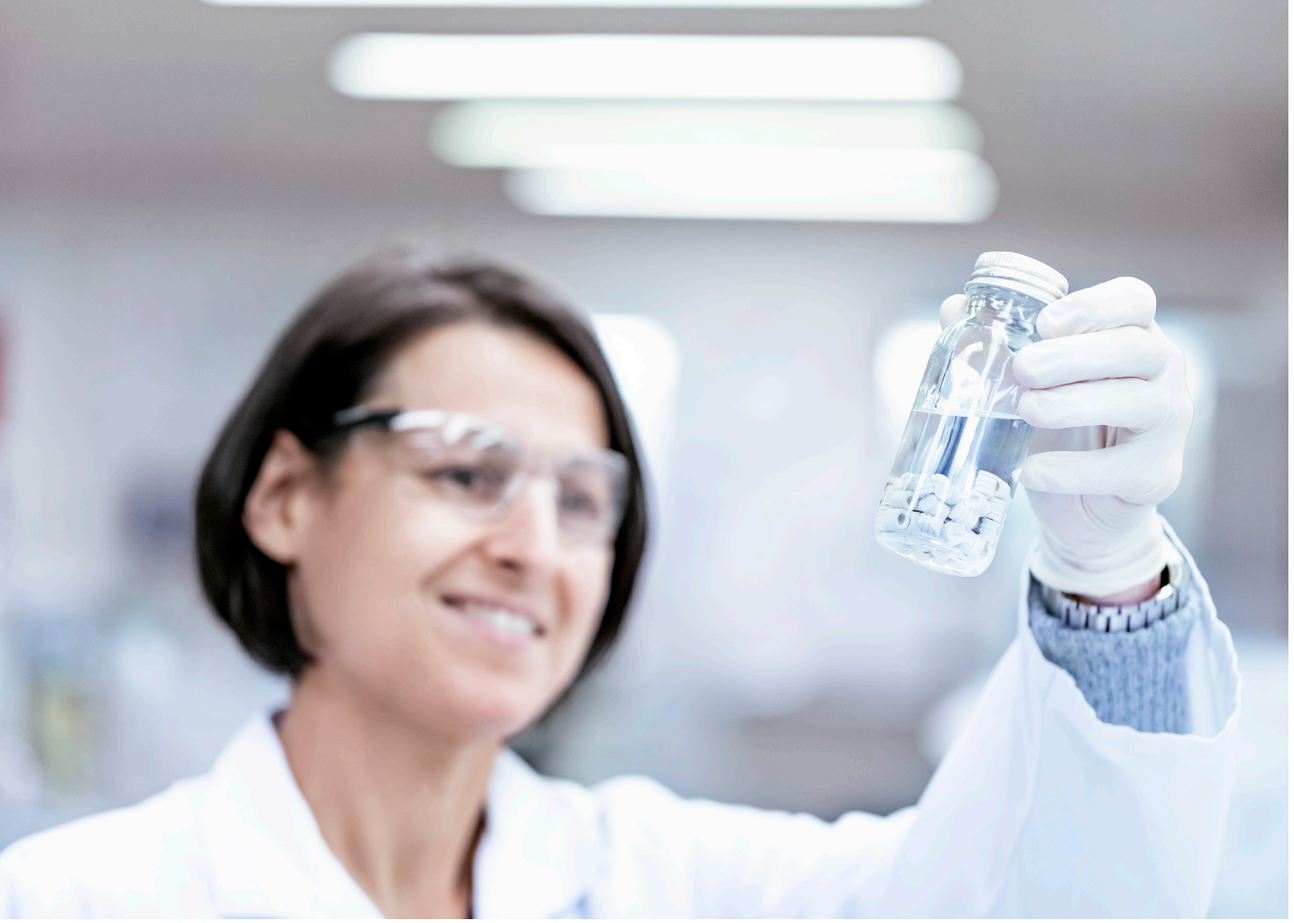
In 2018, the FDA issued 442 such letters, which climbed to 686 in 2022. Particulate contamination (cellulose, silicone, hair, etc.) is a frequent problem, and this turns the spotlight on suppliers of pharmaceutical packaging components, as well as the pharma companies themselves.

"From 2018 until 2022, approximately 34% of drug products are recalled from the USA market due to particulate contamination or lack of sterility", says Tabassam Sharif, Manager Regulatory Affairs at Datwyler.

Parenteral packaging is essential to preserve pharmaceuticals from contamination and to ensure they are administered to patients in an aseptic manner. Updates to the EU Good Manufacturing Practice (EU GMP) guidelines – particularly the release of Annex 1, which concerns the sterile manufacturing of pharmaceuticals – shows pharma companies and their parenteral packaging suppliers are compelled to focus on a Quality by Design (QbD) approach to manufacturing.

In this paper, we will explore the implications of this legislation with the help of Datwyler, a Swiss-based supplier of system critical components for drug packaging and medical devices.





UNDERSTANDING GOOD PRACTICE: THE EU GMP

The EU GMP is a comprehensive system for ensuring that drug products are produced and controlled according to strict quality standards. Its purpose is to minimise the risks involved in any pharmaceutical production process that cannot be eliminated through testing the final product.

These risks include: unexpected contamination, which can cause damage to health or even death; incorrect labelling, which can result in patients receiving the wrong medicine; and either too little or too much active ingredient, leading to ineffective treatment or adverse effects.

Clearly, these issues affect both drug developers and packaging suppliers, the latter having a key role in protecting drugs from contamination. Indeed, the EU GMP covers all aspects of production and defines the minimum standard that a medicines manufacturer must meet in their production processes. The European Medicines Agency (EMA) coordinates inspections to verify compliance with these standards as part of its role to ensure poor-quality medicines do not result in health hazards or, indeed, a waste of money for governments and consumers.

The EMA database of good manufacturing and good distribution practices (EudraGMDP) currently shows that 146 non-compliance reports were issued between the start of 2010 and the end of September this year.

“Authority expectations are becoming much more stringent and pushing our industry to reach higher quality levels,” says Ashwini Bhisikar, technical & scientific expert at Datwyler. “If we look at the FDA warning letters, there are various topics, like concerns with the stability of container closure systems, cleaning and maintenance of equipment, failure to meet final specifications, non-conformance with procedures for production and processes, and issues with microbial contamination.”

She adds: “The observations are not only linked to the final drug product, but also the quality of packaging components, which are a critical part of the discussion around challenges facing the industry. These are the driving factors for authorities to go strict on the regulation with respect to manufacturing.”

NEW RULES: ANNEX 1 COMES INTO FORCE

The key part of EU GMP that has recently come into effect is Annex 1. First published in 2022, after five years of feedback and revision from the industry, and official since August 2023, it provides guidance on the manufacture of sterile products.

“Annex 1 provides specific guidance on the manufacturing of sterile products, including primary packaging, and also provides general guidance that should be used in the design and control of facilities, equipment systems and procedures used for manufacturing of sterile products, applying the principles of quality risk management to ensure microbial particulate and endotoxin contamination is prevented in the final product,” says Bhisikar.

Sharif further added that "the basic structure of the new Annex 1 has not changed, but has become more comprehensive by adopting the holistic concept of risk management. One significant addition is the focus on a holistic Contamination Control Strategy (CCS)."

CCS appears more than 50 times throughout Annex 1 and the goal of the Contamination Control Strategy is to define critical points throughout the entire manufacturing process and assess the effectiveness of all controls (design, procedural, technical, and organisational) and monitor measures employed to prevent contamination risks (microbial, particulate, and pyrogen/endotoxin) to the products and components.

"The CCS should be actively reviewed and, where appropriate, updated to drive continuous improvement," Sharif explains. "The second most important focus is the introduction of new technologies, such as Restricted Access Barrier Systems (RABS) and isolators, which are strongly encouraged and can reduce interventions and contamination in cleanrooms."

Annex 1 specifically mentions that primary packaging containers and components should be cleaned using validated processes to control contamination, and that the washing method should demonstrate Log 3 (99.9% reduction) endotoxin reduction.

The Annex further focuses on container closure integrity (CCI) validation data, stipulating that it should consider the entire system, including transportation and shipping requirements. Furthermore, all sterilisation processes should be validated and presented in a data package, and all packaging containers should be validated to ensure they limit the risk of contamination. CCI validation must cover the whole system rather than a single component.

“The packaging should be qualified for minimising the risk of particulates, particularly microbial endotoxin or chemical contamination,” says Bhisikar. “After sterilisation, packaging has to ensure integrity until the specified retention time."

The elastomeric components are supplied to pharmaceutical manufacturers in various packaging profiles, such as Ready-for-Sterilization (RFS), Ready-to-Use (RTU), and rapid transfer port (RTP-RFS and RTP-RTU).

For RFS elastomers, washing is done through a validated washing cycle, which ensures endotoxin reduction, and further sterilisation is within the scope of the pharmaceutical company. In the case of RTU elastomers, which are being increasingly used by pharmaceutical companies, washing and sterilisation is done by the packaging provider, such as Datwyler, using validated procedures. A similar process holds true for RTP-RFS and RTP-RTU. Annex 1 affects these packaging profiles to different extents.

QUALITY BY DESIGN: WHEN TESTING IS NOT ENOUGH

A key consequence of Annex 1 is a move towards a QbD approach to manufacturing. The fundamental tenet of QbD is that quality cannot be tested into products, so should be built in by design. A QbD approach to component manufacturing can help companies adhere to the requirements of Annex 1 by addressing the issues at the heart of the new regulation.

"The key considerations for parenteral packaging components are component design and component manufacturing," Bhisikar says. "However, Annex 1 also focuses on component selection, which makes us look closely at component design, which has three key aspects: the dimensions and type of elastomeric component, which determines the fit compatibility of the entire container closure system, and thus container closure integrity; the design of the elastomer compounds, which determines extractables and leachables, and the coating required, if any; and then elastomeric processing, as the siliconization process determines functionality and machinability."

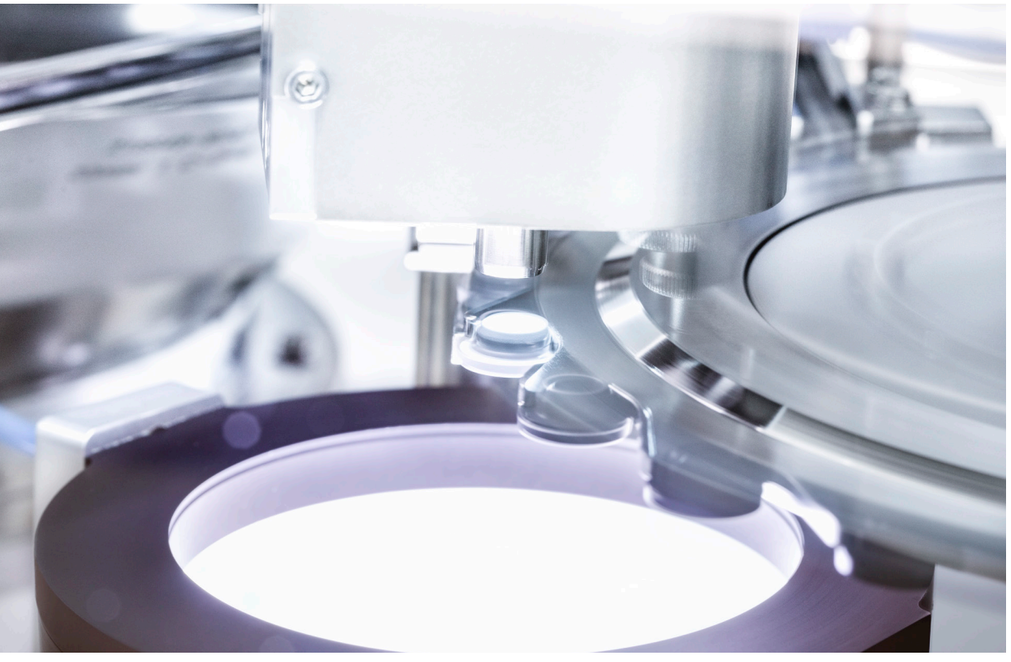
She adds: "The other consideration is component manufacturing, which focuses on the manufacturing environment. This determines the particulates, visible or subvisible. It also determines the microbial contamination in terms of bioburden and endotoxin. Manufacturing process control through automation determines defects and contamination, reliability and consistency.

Elastomeric manufacturing involves many steps. Firstly, the raw materials are weighed together before being mixed and then extruded. Then the elastomer is moulded into stoppers and trimmed. The next stage is intermediate washing and, if the stopper is to be coated, a fluoropolymer spray coating is applied before the final washing phase. Next comes camera inspection and the final packaging.

"In the high-value biotech market, particulate presence can easily lead to quality issues, authority inspections and market recalls, for example, so a manufacturing concept driven by the QbD approach, which focuses on prevention and correction, helps us to achieve industry leading specifications at all of these stages," says Bhisikar.

The focus of Annex 1 may be more on component manufacturing than design, but both are important considerations. On the design side, for example, the choice of elastomer material and its coating are key considerations, as is the type of processing that the material will undergo. The component manufacturing aspects of Annex 1 focus on contaminants in the manufacturing environment and the use of process control with automation.

"The driving factors for the QbD approach are current market trends – the development of innovative drugs, more stringent rules from market authorities and supply chain optimisation," Bhisikar notes. "Datwyler's FirstLine® manufacturing environment is designed to address all of these."



BUILT FOR THE CHALLENGE: DATWYLER'S FIRSTLINE® STEPS UP

Datwyler's most advanced manufacturing standard, FirstLine, is especially designed to manufacture pharmaceutical rubber components for high-end pharma and biotech markets in a fully integrated cleanroom environment that conforms to the highest industry standards. The manufacturing concept is based on ultra-modern cleanroom technology, automated production cells, fully automated camera inspection and a unique, validated washing process.

FirstLine helps support the development of innovative, complex and sensitive drugs by delivering best-in-class fluoropolymer coatings, rubber compounding and analytical expertise. Its fluoropolymer coatings are bonded to rubber components to form a barrier between the stopper and the drug product to reduce extractables and leachables, improve compatibility with drugs and excipients, and to avoid both adsorption on the surface of the rubber and absorption into the rubber.

These coatings can be used with all sensitive drugs that have compatibility challenges, proteins prone to oxidation in the presence of metal ions and oil-based formulations. According to Datwyler's research, spray-coated stoppers demonstrate low levels of subvisible particles, and when they have no surface silicone, they show a significant reduction in the number of particles.

"By using the QbD approach, we guarantee a perfect match for innovative drugs with our primary packaging components," says Bhisikar. "Datwyler's FirstLine aims to continue offering best-in-class knowledge and expertise in pharmaceutical elastomeric formulation."

FirstLine helps drug developers meet the more stringent expectations from authorities in many ways. It facilitates Datwyler's zero-defect philosophy, which involves the design of all facilities to prevent or correct any contamination or defect that may occur. This is achieved through full cleanroom zoning, state-of-the-art automation and camera inspection systems, and industry leading particulate level specifications.

Datwyler can support CCI validation of packaging systems, as it can perform tests for its plungers and closures, along with other components, with a range of methods, including helium leak testing, headspace analysis, and more.

"We aim to deliver the lowest possible level of defects, cross-contamination, particulates, endotoxin and bioburden load," says Bhisikar. "The enhancement in automation helps to achieve a zero-defect approach. For example, reduced operator handling reduces the risk of foreign material and biological contamination. Automatic spraying of mould release leads to a reduced risk of non-embedded defects. Automated demoulding leads to a reduced risk of tearing and rubber particle generation."

"State-of-the-art camera inspection helps to find defects, including deformations, foreign matter and damaged coating, resulting in stricter acceptable quality levels (AQL). In fact, it can reduce AQLs by a factor of ten."

When it comes to globalisation and supply chain optimisation, FirstLine provides increased global capacity through Datwyler's international network, which supports the regional sourcing necessary to guarantee supply flexibility.

Overall, Datwyler firmly believes that packaging manufacturers are directly and indirectly within the scope of Annex 1, because they have quality agreements with their customers.

"The key takeaway is that primary packaging suppliers can support pharmaceutical manufacturers to comply with Annex 1 by manufacturing elastomeric components at their manufacturing facilities through the QbD approach, and the FirstLine facility is one such manufacturing concept."

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