WHITE PAPER

GMP Annex 1 Implementation

How RTU vials and cartridges can be a suitable, time-efficient and cost-effective answer to meet new regulation requirements.

Stevanato Group

Scope

Annex 1 of the European Union (EU) guidelines governing good manufacturing practice (GMP) for medicinal products (GMP Annex 1) details the requirements for the Manufacture of Sterile Medicinal Products available in the EU.[1]

The purpose of this document is to describe how the latest update to GMP Annex 1 is impacting the entire sterile medicine production supply chain and how service and packaging suppliers are supporting pharmaceutical companies in de-risking their operations throughout the process. An example of this is the presence on the market of ready-to-use containers, such as vials and cartridges, supplied to the pharmaceutical industry pre-washed and pre-sterilized. The information below will compare "traditional" pharmaceutical production processes, in which washing, depyrogenation and sterilization are carried out by the pharmaceutical industry as a preliminary step prior to filling, with leaner processes involving ready-to-use (RTU) containers. This comparison will demonstrate how these processes employing RTU components represent a more suitable, time-efficient and cost-effective solution for those who need to align their Quality Management System to the requirements of GMP Annex 1.

References
1.https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-4_en#annexes

Introduction

Sterile manufacturing has always been a very dynamic segment of the pharmaceutical industry. This point was underlined by the COVID-19 pandemic, where a resilient and well-managed sterile supply chain was fundamental to the prevention of drugs shortages.

As such, companies have intensified their focus on supporting this structure and its integrity is also a key priority for regulatory authorities. The market for sterile-manufactured drug products is forecast to remain the fastest-growing segment, registering an estimated compound annual growth rate (CAGR) of approximately 15% between 2022 and 2027.[2]

This increase is expected to be driven mainly by biologics in the form of next-generation biologics, such as single-dose finished products related to Cell Gene Therapy (CGT), Radio Ligand Therapy (RLT) and monoclonal Antibodies (mAbs), as well as increasing biosimilar launches triggered by the loss of patent protection. With market trend analysis suggesting this could lead to the sterile pharmaceuticals market expanding by more than 50 per cent over the next seven to ten years, there is a need for sterile manufacturers to create more capacity quickly to capture additional market share.

Growth in sterile production capacity must be designed with an appreciation of key market trends in mind. This includes the requirement to support innovative products with demanding characteristics, such as sensitive biologics that are prone to destabilisation. Furthermore, the continued drive to improve efficiency and quality places consequent emphasis on the need to reduce manufacturing complexity, limit component handling and avoid both breakage and wastage. Finally, pharma companies are increasingly looking to accommodate demand for small and medium-sized batches in line with the drive towards more personalised medicine, requiring a highly flexible manufacturing platform that supports diverse production requirements and rapid changeovers.

References

2.IQVIA, Alira Health; Data communicated during the Capital Markets Day, Sep. 27 2023

However, ramping up sterile capacity to meet these needs is not an easy task. Challenges here include the significant investment needed; long delivery, qualification, and validation times; and the effort required to train and qualify new employees. These conditions make it difficult for manufacturers to respond to the projected surge in demand.[3] In addition, pharma manufacturing is a closely regulated environment which requires continuous knowledge upgrades and internal process updates. Compliance with new regulations often requires the purchase, installation and validation of new equipment, such as Restricted Access Barrier Systems (RABS) and isolators. This activity can represent a significant investment in time and resources, potentially taking up to three years to complete, which limits the ability to react promptly to the changes required by the market. Cost is also an important consideration. Isolators and Restricted Access Barrier Systems (RABS) required by the updated version of GMP Annex I are equipped with advanced features and automated functions, and are therefore priced at premium rates compared with conventional systems. The average cost of isolators and RABS is around USD 4.0 million to USD 8.0 million, which is around five times that of standalone systems.[4] This increases the level of difficulty associated with compliance, especially for small companies or companies with a requirement to revamp older facilities.

References

3.https://www.mckinsey.com/industries/life-sciences/our-insights

4.Markets and Markets™ FILL FINISH MANUFACTURING MARKET report forecast to 2025 – 2020

Introduction

Sterile manufacturing is also subject to a number of well-recognized macro forces, which are influencing key trends.[5] These include:

Reduced total cost of ownership (TCO)

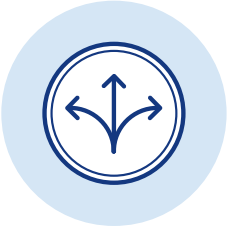
Leaner processes and better overall process yield with the ultimate purpose of reducing friction and the number of steps in customer journeys, increasing efficiency and reducing cost

Innovation in products and processes

Introducing new technologies, processes and products which improve the manufacturing, release and distribution of pharmaceutical products

Industry convergence

Collaboration between stakeholders involved in drug development and manufacturing



Competitive intensity

Small and medium-sized injectable personalized products which require flexibility in allocation of specific demand, flexibility in production lines and workforce skill, and optimization of process to avoid wasting very expensive and precious materials

References
5.Growth Opportunities in Sterile Injectable Outsourcing – Frost & Sullivan – June 2022


Courtesy of Groninger Group

Adapting to these trends and incorporating complementary values into the strategy, culture and dynamic of an organization is crucial if companies are to succeed in sterile manufacturing and deliver on the demand from patients and clients. Moreover, there is a focus on the reduction of lifecycle duration and increased pressure to demonstrate Return of Investment (ROI), both of which are accelerating project timeframes and prompting the fill-finish sector to review its approach and consider strategies that support greater agility.

From a geographic perspective, there are also factors driving sterile manufacturing growth in territories that are currently underserved. Currently, more than 80% of global manufacturing capacity is located in North America and Western Europe, but drugs shortages and patent expirations are encouraging companies to expand production capabilities in emerging countries, leveraging technologies designed to minimize costs and amortize capital investments, especially in the case of multi-product facilities. This demand for local production is further supported by improving living standards and the ambition of local governments to increase the resilience of internal supply chains. As such, economies in countries across Asia, Eastern Europe, South America and Africa represent clear short-term opportunities for growth among manufacturers serving pharmaceutical markets. However, sufficient investment will be required in the installation of new equipment and the revamping of existing lines, and sufficient time must be allowed for its qualification and validation. Market success is dependent on these barriers being overcome with innovative approaches, from both a business and technical perspective.

Indeed, in seeking to balance the pressing demand for additional flexible sterile capacity across the world with the reality of the cost and timeframes involved, it might be that players have to creatively meet this challenge by partnering with other stakeholders involved in the wider drug supply chain.

GMP Annex 1 overview

Following lengthy debate and revision involving both regulatory bodies and pharmaceutical industry associations, the updated GMP Annex 1 finally came into force on 25 August 2023. The guidance impacts significantly on the sterile manufacturing environment, making it important to understand the changes and the expectations that are introduced with this long-awaited document.

The main updates are in the Pharmaceutical Quality Systems (PQS) section, including requirements for Quality Risk Management (QRM) systems and a Contamination Control Strategy (CCS), both of which are increasingly vital to any manufacturing process within a controlled environment.

Another notable change is the expansion in coverage for new technologies, including isolators and Restricted Access Barrier Systems (RABS), which aligns the regulations with the latest developments in such areas.

Requirements for monitoring, trending, disinfection, cleaning and training have also been expanded and updated in this latest version.

Courtesy of Groninger Group

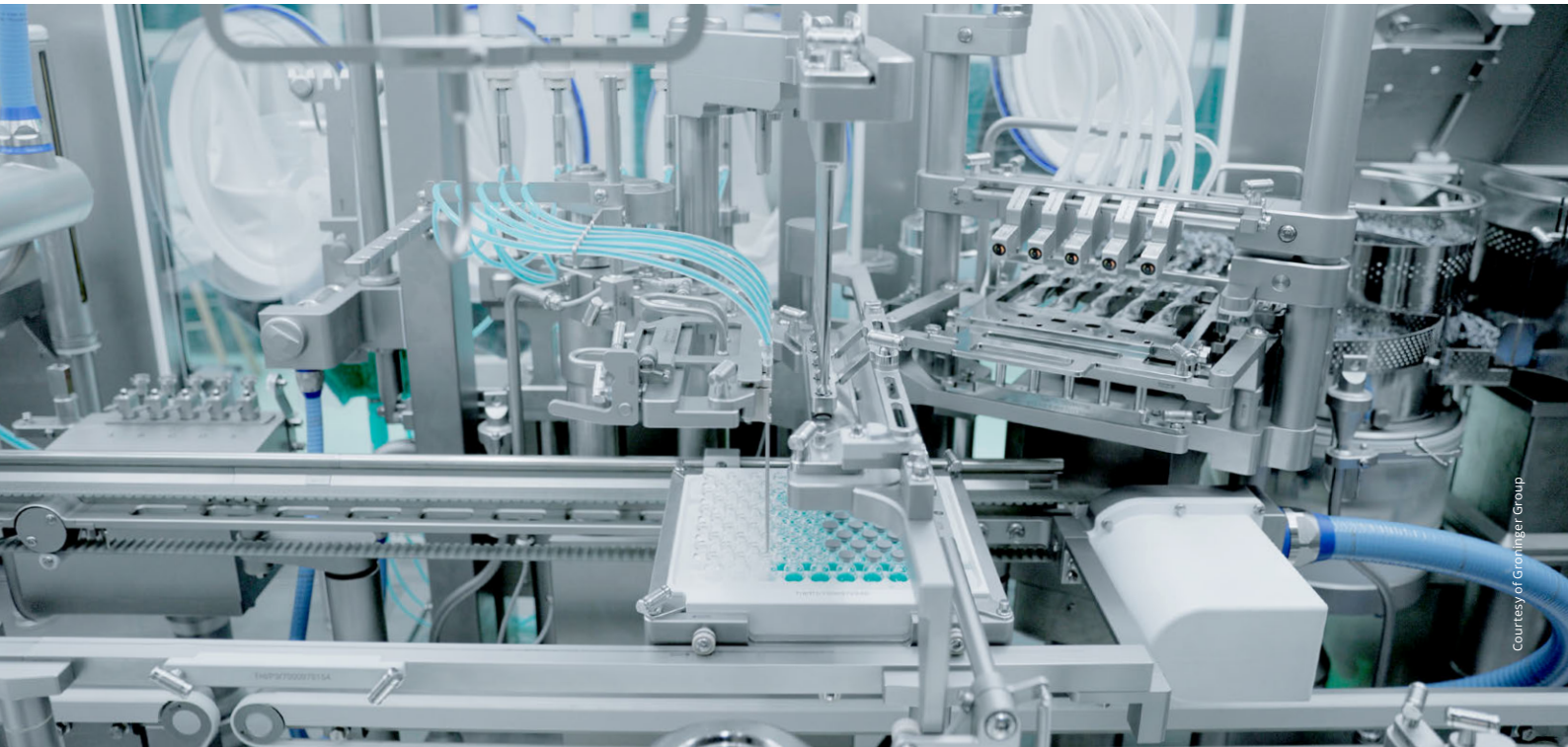
What does this mean for manufacturers?

According to the requirements set out in the updated GMP Annex 1, a sterile products manufacturer must establish a comprehensive Contamination Control Strategy (CCS), addressing its manufacturing operations to ensure the sterile product is produced under compliant conditions and, therefore, is safe for patients. The goal is to provide evidence that the identified regulatory requirements have been incorporated into the manufacturing site's operating practices and procedures with the CCS supporting document.

Based on the above, one of the objectives of the updated GMP Annex 1 is to re-emphasize the importance of implementing the elements of a modern Pharmaceutical Quality System as described in the Q10 Harmonised Guideline on Pharmaceutical Quality System from the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). Approaches should be supported by the extensive use of Quality Risk Management (QRM) principles not only for manufacturing processes but also for supporting activities, as outlined in the list of topics required for the CCS.

As such, companies should consider the tools described in the ICH Q9 QRM (R1 new version released in February 2023) and ICH Q10 PQS guidelines as mandatory to help understand the processes and aspects that should be implemented if they are to remain compliant.[6] Specifically for CCS it is necessary to ensure that the various components have been designed, monitored and evaluated to ensure that the quality of the final product meets the defined parameters. Doing so will help reduce the risk of a product being contaminated by microbial agents, endotoxins/pyrogens and particulates, thus ensuring patient safety.

References
6. https://www.ich.org/page/quality-guidelines



Courtesy of Groninger Group

GMP Annex 1 overview

How can design help manufacturers ensure compliance?

The new QRM updates mean manufacturers will need to identify the measures they will need to take to mitigate any potential risks associated with their processes.

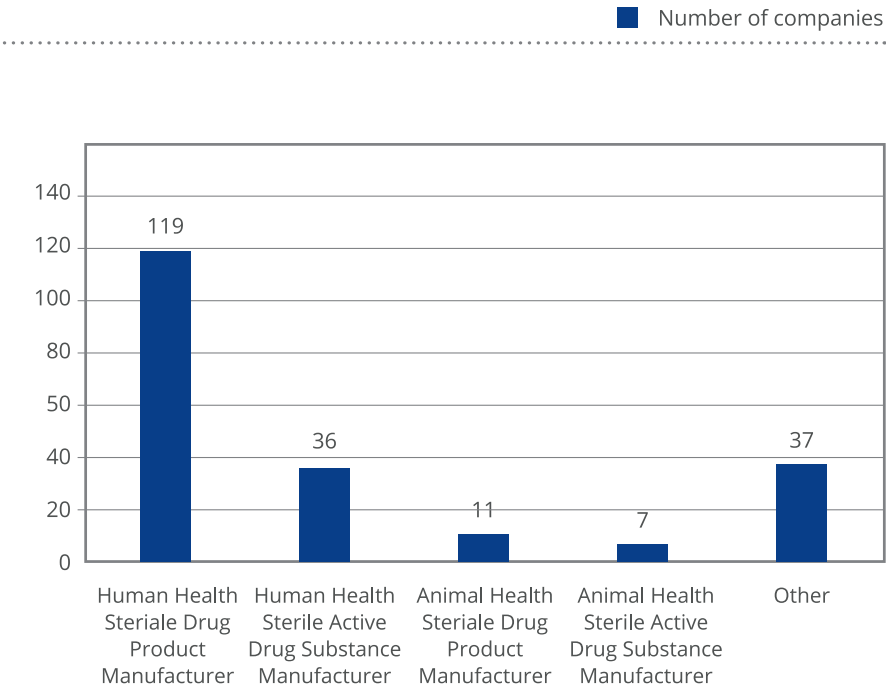
This requires a holistic evaluation of a facility's infrastructure as well as the production process, including equipment design and product components, such as primary packaging materials.

However, the updated GMP Annex 1 states under scope: the manufacture of sterile products covers a wide range of sterile product types (active substance, excipient, primary packaging material and finished dosage form).

This leads to a reduction in qualification and validation activities of equipment and related processes for the treatment of primary containers for producers of sterile products, as both particulate contamination and sterility of containers would be ensured by primary packaging producers who have implemented a quality system that manages and controls their activities in line with the requirements set out in GMP Annex 1.

The importance of GMP Annex 1 to the pharmaceutical industry has been confirmed by the high number of conferences and events dedicated to its implementation. Exploring this issue further, the Parenteral Drug Association (PDA) conducted a survey between 19 July 2023 and 11 Aug 2023 to gather information on levels of compliance as well as implementation of barrier systems.

FIG. 1 - COMPANIES' CATEGORIES THAT RESPONDED TO THE 2023 PDA SURVEY



Responses to the survey were mainly from companies manufacturing sterile drug products for human use (Fig.1). Among those manufacturers, most were located in EU (83) and North America (77) (Fig.2), with their products also mainly distributed within these markets[7] (Fig.3).

FIG. 2 - COMPANY'S LOCATIONS

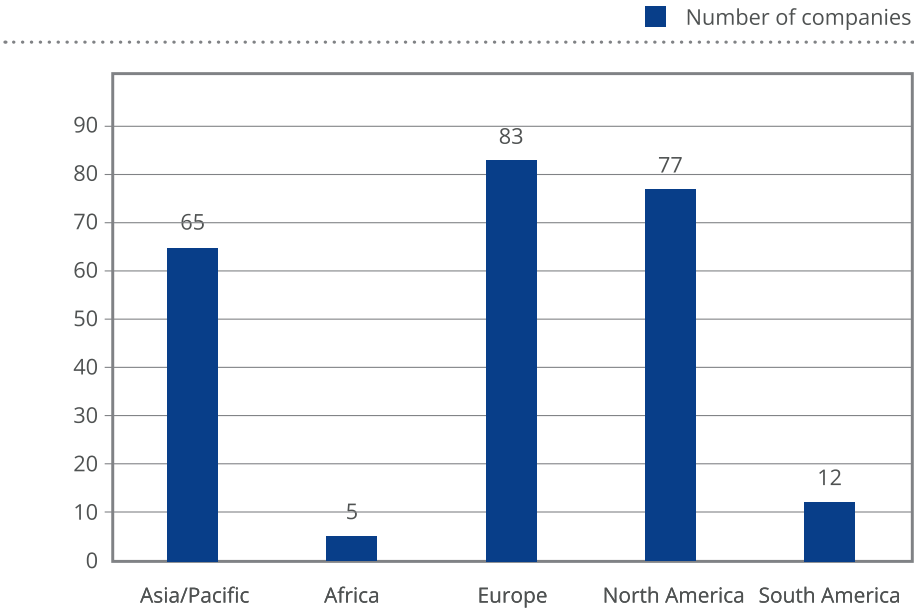
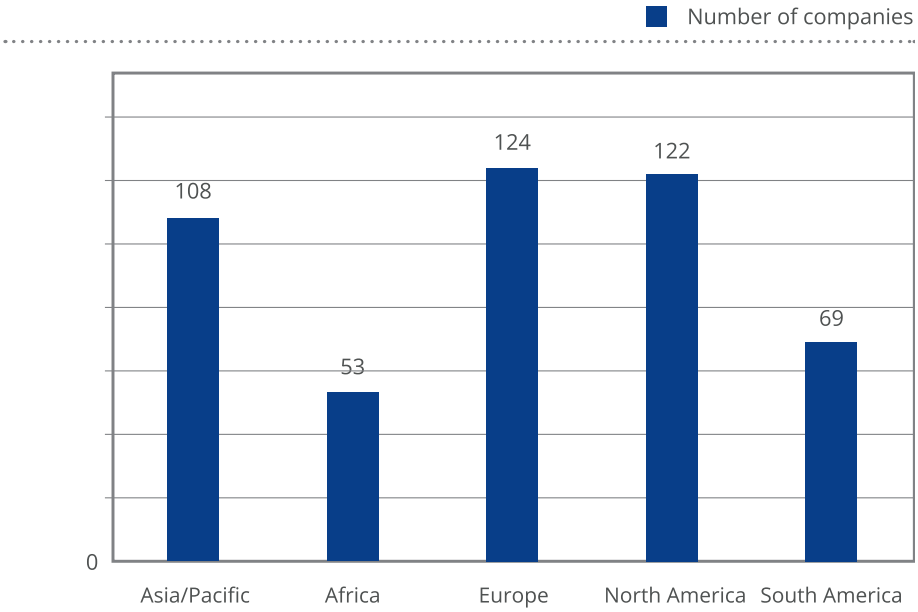


FIG.3 - COUNTRIES WHERE THEIR PRODUCTS ARE MAINLY DISTRIBUTED



References

7.Survey-report---implementation-of-new-eu-annex-1-and-implementation-of-barrier-systems-16-aug-2023.pdf (pda.org) PDA Annex I Survey August 2023 (% values removed from the graphs)

GMP Annex 1 overview

The survey also revealed that 59% of respondents are still using RABS, with 40% of the open type and 60% closed. Those using open RABS will be required to invest in the near future to comply with updated regulatory requirements, which promote the use of more restricted barriers and less human intervention. This is particularly the case in the US and EU, where the cost of labour, the tax burden and market competition is tremendously high.

Further findings from the PDA survey highlight how industries that either use traditional processes or do not provide aseptic filling intend to install an Isolator or a RABS as a consequence of the publication of the new Annex 1. Motivating factors behind this decision include:

Increase in sterility assurance

Increase in manufacturing efficiency

Reduction in manufacturing cost

It is quite clear that the main driver for such major change is to increase Sterility Assurance, knowing that any actions and changes may require significant economic investment and/or could lead to interruptions in production. Premises and equipment that are considered obsolete may therefore require revamping with the use of new technologies in order to avoid any contact with human personnel to reduce the risk of contamination.

A solution to reduce execution times and costs exists in the form of sterile and ready-to-use (RTU) packaging. This approach greatly simplifies the overall filling process, largely eliminating the need for the pharmaceutical industry to perform steps such as washing, depyrogenation, drying and sterilization, which are typical processes involved in the preparation of primary containers prior to filling.

Comparison between traditional pharmaceutical processes and those using RTU containers

Having described the sterile market, outlining the opportunities and challenges associated with a clear need to increase manufacturing capacity, we now consider how the changes introduced by Annex 1 are placing greater emphasis on higher process controls and better quality of manufacturing output.

Consider three different scenarios: manual using traditional containers, semi-automatic using traditional containers, and automatic using RTU containers. Each process consists of four steps: incoming, washing, depyrogenation and filling.

Comparing the visualisations of handling and process flows for standard and RTU containers highlights the superior efficiency of RTU components. Here, several production steps are avoided, reducing complexity and cost, optimizing time and yield, and supporting quality of output in line with market and regulatory expectations. By analysing each process step we can highlight the following key aspects.

Comparison between traditional pharmaceutical processes and those using RTU containers

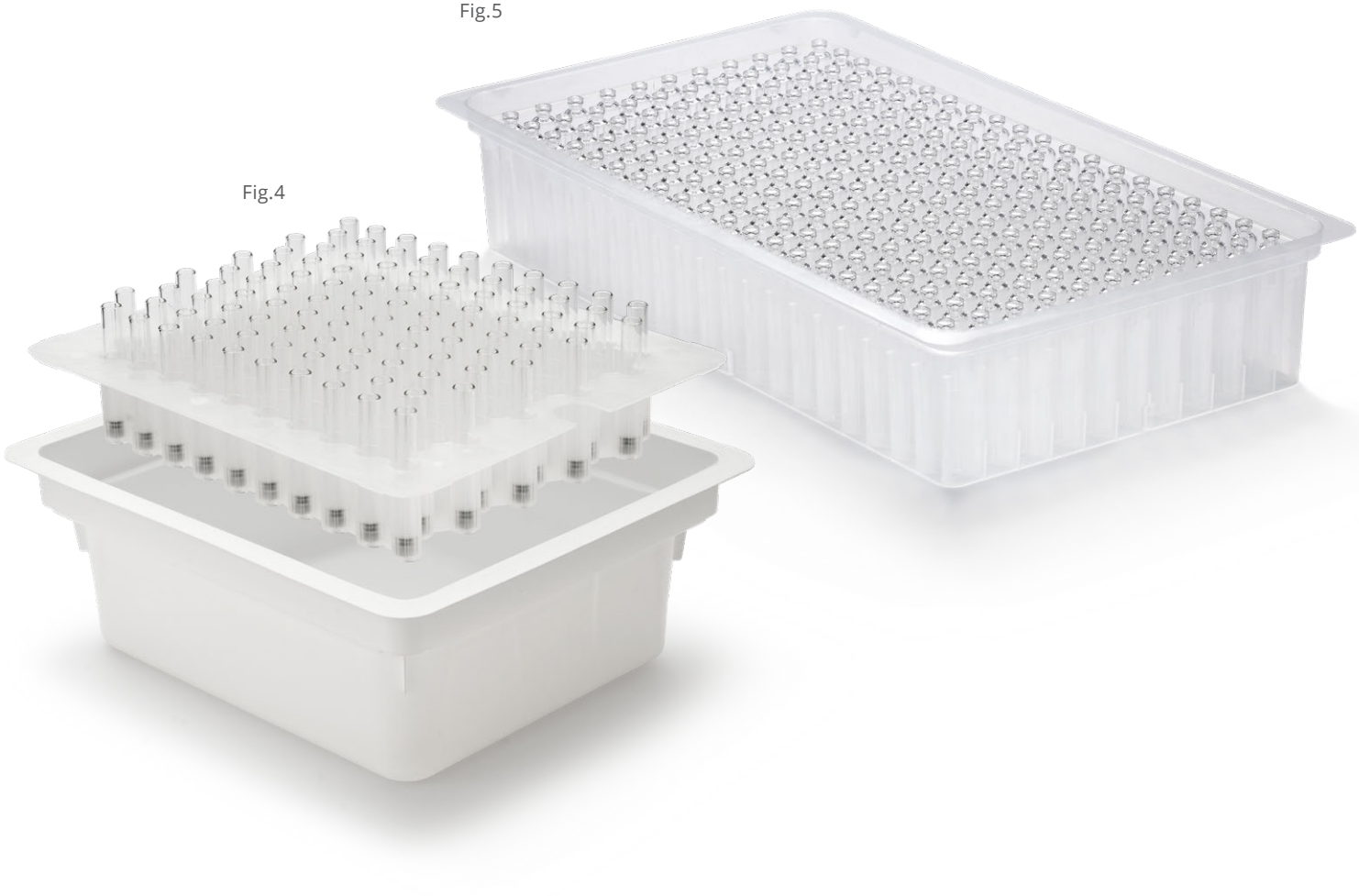
Incoming

At the incoming stage, traditional containers place a comparatively high burden on the production chain for both manual and semi-automated applications. They are subject to quality control (QC) testing and documentation review prior to their release for filling. Throughout, there is a requirement for them to be held in appropriate warehouse storage space.

In contrast, RTU containers arrive ready-washed and pre-sterilized in two available packaging solutions: nest and tub (Fig.4) or tray (Fig.5), with cartridges well separated from each other.

Fig.5

Fig.4



Packaging solutions for RTU Vials and Cartridges Nest and Tub (Fig. 4) and Tray (Fig. 5)

Even before the incoming step, the packaging of the RTU containers delivers a clear advantage from a quality and yield perspective. These packaging solutions avoid frictive sliding during transportation, eliminating the generation of particles, which could be released into the production/equipment environment as soon as the pack is open.

The no glass-to-glass contact reduces the risk of scratches that are a well-known point of weakness in the glass surface. In pharmaceutical production, the frequency of weakness points increases with the level of friction (related to pressure and time) during the handling, leading in some cases to internal particle release along the filling line. Those internal weakness points are practically impossible to identify during the filling process[8-11]. They can lead to:

1. Final products being contaminated by particles that are not inherent to the product. Particulate contamination in drug formulations is a real regulatory concern in injectable drugs and can trigger costly drug recalls. In 2008–2012, 22% of recalls for sterile injectable drugs were due to the presence of visible particles[8-11](Fig.6).

2. The release of glass particles that serve as a starting point for crystallization, impacting the integrity of the drug formulation.

3. The presence of sub-critical defects that do not instantly leading to breakage but accumulate over time. Such sub-critical defects render glass containers more vulnerable to later breakage and endanger container closure integrity, which is an important issue for keeping liquid drug products sterile.[12]

The pharmaceutical industry can avoid such problems by using RTU containers. After a complete qualification of the supplier to validate consistency and reliability, no further chemical and physical tests are necessary, which greatly reduces time-consuming quality-control activities.

Entry can be based on supplier documentation and materials released for GMP production according to current guidelines such as EudraLex Vol. 4 Part I, Chapter 5: General information and packaging material with periodic statistical control (e.g. 1 batch per year). The higher level of RTU manufacturing controls on the line (environmental and defects) is an inherently higher quality standard translated into the pharmaceutical product manufacturing process.

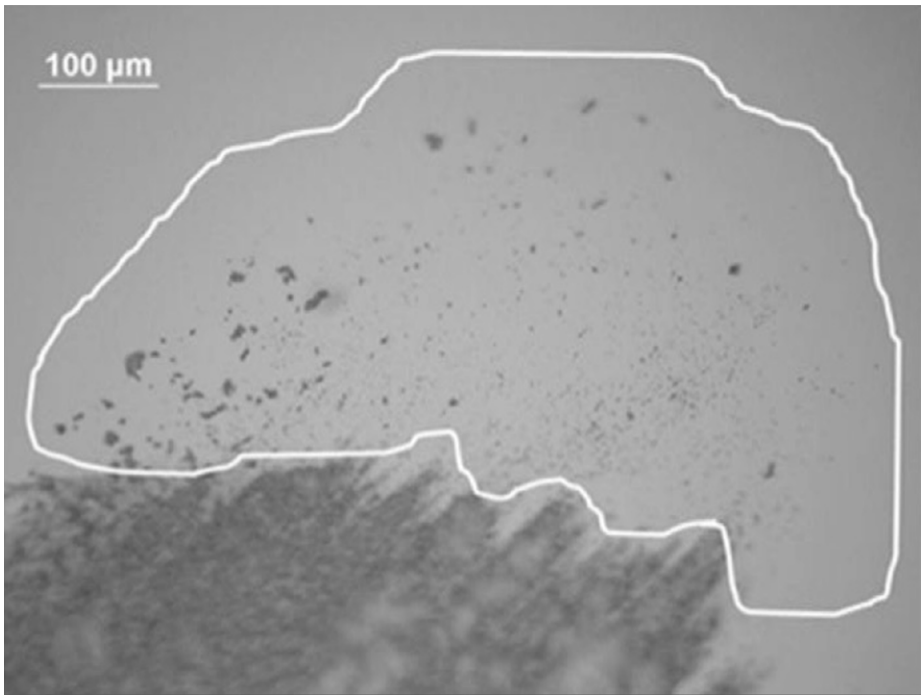


Fig. 6. Frictive sliding particle generation from glass surface

References

8.https://www.manufacturingchemistcom/news/article_page/Addressing_glass_particulates_in_injectable_drug_formulations/140216

9.Langille, S. Visual Inspection of Injectables, PDA Visual Inspection Forum. Oct. 2015

10.Tawde, S. (2014) J. Pharmacovigil. 3 (1)

11.Langille, S. (2013) PDA J. Pharma. Sci. Tech. 67 186-200

12. Bukofzer, S. et al. (2015) PDA J. Pharm. Sci. Technol. 69 123-129

Comparison between traditional pharmaceutical processes and those using RTU containers

Washing And Depyrogenation

With standard containers, the need for components to be washed and depyrogenated before feeding the filling machine equate to a higher level of handling and processing, which present increased risks to the integrity of the drug product. Washing and depyrogenation require equipment to be controlled and handled according to the GMP manufacturing guidance, including periodic maintenance and reconditioning. The washing activities are focused on removal of internal and external contamination using Purified Water (PW), Water For Injection (WFI) and pharma gases flushed out by stainless steel needles. The unit operation requires manual de-wrapping and manual feeding of the containers with related movements and transferring. Washing machines are equipped with several needles (usually >10) to guarantee high performance and output, with the needles moving up and down and entering into the containers multiple times during the process. During set up, normal process operation and maintenance, the needles can be bent or imperfectly cantered, which increases the risk that they will pinch the rim of the containers, causing chipping to its mouth and creating glass debris. All the above could be causes of breakage, scratches and sub-critical physical defects which, as seen at the beginning of this chapter, can impact process and product quality issues. Because those glass breakages or cracks can be located anywhere on the container, they are usually considered critical defects because they can enable the ingress of microbes and can be root causes of chemical degradation through diffusion of reactive gases (namely oxygen, carbon dioxide, and water) into the drug product.[13, 14]

References

13. European Journal of Pharmaceutical Sciences – 104 – 162/170 – June 2017

14. European Journal of Pharmaceutics and Biopharmaceutics - Volume 85, Issue 2, October 2013, Pages 314-326

Operational Advantages using RTU

Where they are employed, manual activities, which can form part of the washing machine set-up and normal utilization, are also a source of inconsistency in manufacturing and could lead to yield reduction or quality deviations.

The same risks also apply to the depyrogenation steps in a tunnel or oven to remove endotoxins. Depyrogenation involves exposure to a high temperature (>300°C) for a certain amount of validated time. Material in contact with containers during this step is usually Stainless Steel (SS – AISI 304 or 316 i.e., tunnel guidance or trays used in the oven) and stainless steel can be a cause of damage, particularly with reduced glass resistance at high temperature. Moreover, a documented link has been found between the fogging defect of lyophilized vials, the quality of the inner surface of the vials and the depyrogenation tunnel temperature exposure, highlighting additional concerns when standard vials need to be considered for lyophilized medicine.[15]

At Stevanato Group, the production process of RTU containers includes, in addition to glass forming, washing and depyrogenation, 100% visual inspection of the containers before gas/vapour phase sterilization, meaning the use of RTU containers by the pharmaceutical industry mitigates this type of risk while also reducing waste.

In summary, two crucial steps of the standard pharma process – washing and depyrogenation – can be removed if the tasks are performed by the packaging manufacturer, bringing several operational advantages, as listed below and quantified in the Table n.1

- Reduction in production time
- Reduction in equipment involved
- Reduction in employees resource
- Reduction in maintenance activities
- Reduction in validation and re-validation activities
- Reduction in inventory/stock of spare parts
- Reduction in environmental and process controls
- Reduction in risk of product defects generated

As referenced above, according to the updated GMP Annex 1 requirements, the main goal for a manufacturer is to put in place all possible mitigation measures to reduce the potential risks of contamination in their final products. That is the main scope of the Contamination Control Strategy (CCS) document: to identify the potential risk along the overall manufacturing and supporting processes on the site.

In this effort to keep the level of product contamination risk as low as possible, primary packaging components play an important role.

References

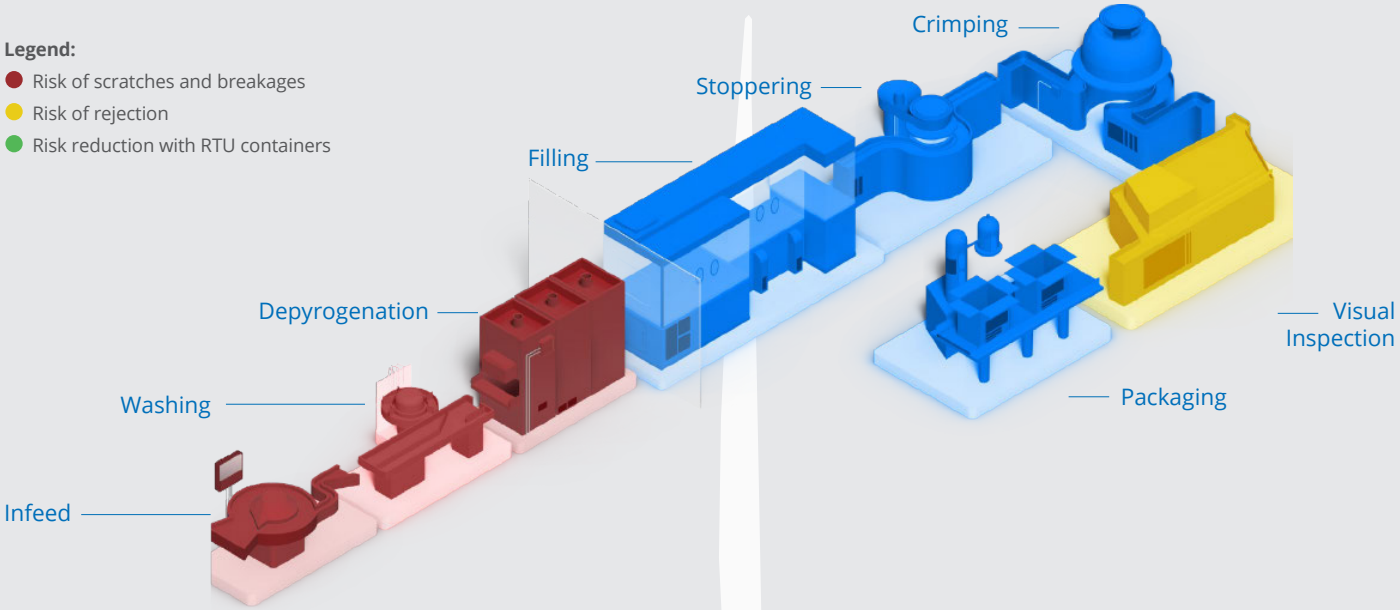
15. https://www.pharmaceuticalprocessingworld.com/advances-in-vial-processing-in-pharmaceutical-primary-packaging-to-reduce-risk-of-vial-damage-and-particle-contamination/

As required by EudraLex Vol. 4 Part I, Chapter 5, sects. 5.45-5.48. Primary Packaging Suppliers must be qualified to ensure that the material they will supply meets the required quality criteria. This supplier qualification process requires several steps according to the criticality of the involved material. For a critical material, such as primary packaging material that is in contact with the product, maximum effort is required. It starts with a request for certain documentation (paper audit) and then goes on to perform conformity to specification checks on test samples, culminating in an audit of the supplier's production site.

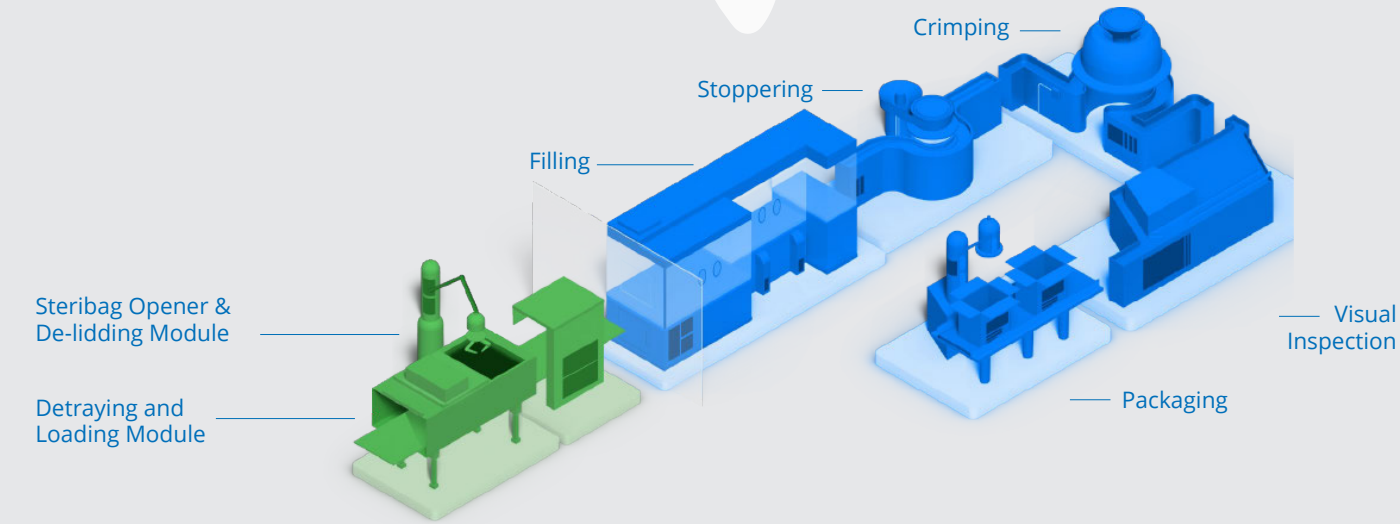
Comparing traditional and RTU containers, this qualification process requires more documentation for the latter, specifically regarding both the qualification of environments and equipment, and the validation of the washing, depyrogenation and sterilization processes performed by the supplier, since these steps are instrumental to ensure the sterility of the containers. Additionally, RTU packaging suppliers will be required to provide specific technical documentation not only about RTU manufacturing processes but also about their handling by the manufacturer.

Conventional Process

Legend:
- Risk of scratches and breakages
- Risk of rejection
- Risk reduction with RTU containers



Process with RTU containers



Operational Advantages using RTU

This will be necessary to provide knowledge and awareness about the technical characteristics of RTU components to maximize the benefit of implementing this solution in the producer manufacturing process to improve the potential contamination risks control and their mitigation.

In operations, once approved, each incoming primary packaging lot is checked (QC testing and CoA review) before it is allowed to be released and used for manufacturing purposes. This step is almost independent depending on the container type (traditional vs RTU).

Additionally, the effort to prepare a Contamination Control Strategy (CCS) will be less demanding for RTU components than for traditional containers since, as described previously, many potentially risky activities will be eliminated, such as material transfer from Grade D to Grade A due to the specific RTU protective package.

With RTU containers there is minimal or no direct human intervention due to the engineered solutions required by RTU applications and the fact that RTU containers are not in contact with each other.

Fewer activities are also required when it comes to preparing and reviewing IQ, OQ, PQ and PV protocols/reports since washing and depyrogenation steps and relevant equipment are performed by the supplier and, therefore, removed from the production process. This means there are no validation/re-validation activities for the processes used for washing and depyrogenating the RTU.

The use of RTU containers has several quality advantages listed below and quantified in the Table n.1

- Less investigation and deviation related to equipment failure or obsolescence
- Less investigation and deviation for products CQA failure linked with containers and closure system
- Fewer process controls for product, process and environment
- Fewer operational requirements and less intrusion to transfer containers from grade D to grade A compared to conventional approaches
- Less aseptic manipulation for containers since engineered solution direct human intervention inside filling line grade A linked with container movement damage since separated from each other
- Less exposure to potential risk of container contamination in grade A since no “accumulation table” is necessary
- Less effort in preparing the CCS

Stevanato Group RTU containers (EZ-fill® vials and cartridges)*

The EZ-fill® platform from Stevanato Group includes vials, cartridges and syringes that are pre-washed, pre-siliconized (where applicable), pre-sterilized and ready-to-fill. EZ-fill® vials and cartridges are available in both nested and tray configurations with either single or double steribag respectively in compliance with ISO 21882 and 21881.

The nest-and-tub configuration is compatible with multi-purpose fill-finish lines, while tray is compatible with a wide range of fill-finish processes, from manual to automatic, including high-speed lines.

Stevanato Group RTU containers (EZ-fill® vials and cartridges)*

EZ-fill® cartridges can be supplied as pre-capped or uncapped. They are available in a wide range of formats (1.5ml, 2ml, 3ml, 5ml, 10ml, 20ml) and with a choice of rubber components, including combi-seals, front stoppers and plungers. The baked-on siliconization options are set for optimal performance and low particles, and have been shown to deliver the finest gliding profile, good cosmetic appearance and 100% control in studies conducted by Stevanato Group's Technology Excellence Center.

EZ-fill® Vial systems are available in a wide range of formats (2R,4R,6R,8R,10 R,15R,20R,25R,30R,50R) in Nest & Tub format and in standard or upside-down configuration.

EZ-fill® containers employ a no glass-to-glass approach from glass forming to final packaging to minimize possible scratches or other glass defects.

EZ-fill® platform is an open platform, currently used by other primary packaging suppliers. Over the years, EZ-fill® has become the market reference platform and more than 250+ fill and finish machines have been installed using EZ-fill® packaging technology in the last 12 years.

EZ-fill® allows pharmaceutical companies to maximize flexibility in aseptic filling using a common filling platform (combi-line). As it has been developed together with the main Fill & Finish equipment manufacturers, it can therefore be integrated into the already existing pharmaceutical manufacturing filling lines.

Machine manufacturers have also been involved in the development of the packaging design and concept for the proper handling and machineability with a wide range of Fill & Finish units.

*Courtesy of Stevanato Group

Conclusion

Through our market analysis we have shown that:

1. We are playing in a fast growing but challenging environment
2. Reducing complexity to increase service will be a must
3. Innovation will be a key differentiator
4. Cooperation among supply chain stakeholders is the only way to overcome challenges and get the most out of opportunities in the market for sterile pharma products

The pharma market is regulated under a strict framework, and suppliers require resilience and the ability to quickly adapt to new guidance. Annex 1 revision has clearly set out some key rules that raise the bar in sterile applications:

1. Be knowledgeable of what you are doing
2. Be conscious of the risks along your manufacturing process from the beginning to the end, including materials and suppliers
3. Be ready to adopt any mitigations to reduce those risks and clearly formalize your approach in a document you can use as your action plan
4. Involve partners in your evaluation and mitigation to be sure you are adopting the best solution available
5. Focus on innovation and barrier technology to prevent risks linked with human intervention

The implementation of RTU primary packaging can be seen to deliver clear additional value in terms of an important upgrade to Sterility Assurance preserving quality, de-risking the operations of pharma companies throughout the process thus minimizing recalls and assuring the best results in media fill aseptic processing. Under the updated Annex 1 rules, a CCS will be the most important document for demonstrating to an inspector that, all potential risks have been identified and a mitigation strategy has been implemented to control and minimize the impact on patient safety. Among those mitigations, the use of RTU primary packaging material represents a best-in-class choice to control the contamination of the environment through the reduction of human intervention.

When we speak about the opportunity of RTU materials to support manufacturers, in the previous chapter of this document we specifically touched on the fact that CAPEX (capital expenditure) investment can be reduced by subcontracting the execution of washing and depyrogenation, and focusing on the aseptic filling process in restricted equipment (RABS or Isolator).

RTU primary packaging materials undoubtedly offer a solution to embrace the opportunity presented by a growing market while meeting expectations of the regulatory authorities.

We can summarize and quantify those advantages in two main categories as listed in the Table n.1 below.

	STANDARD CONTAINERS	RTU CONTAINERS	Δ**
Production Activities	**a.** De-dusting, de-cartooning, identification **b.** Washing step (in batch or in continuous) **c.** Depyrogenation steps (in batch or in continuous) **d.** Accumulation table in Grade A feeding the filling machine, in queue for the filling.	Loading at the beginning of the filling machine; no washing and depyrogenation in line or in batch	**1.** 50% FTE filler handling saving **2.** 30% Maintenance reduction of entire filling line (extraordinary and preventive) **3.** 25% reduction of calibration effort for the entire filling line (extraordinary and preventive/routine) **4.** 25% re-qualification effort reduction for the entire filling line **5.** 15% reduction in environmental and process controls specifically related with the washing and depyrogenation steps **6.** 5% less inventory/stock of spare parts (i.e HEPA filters for Tunnel, spare parts for washing and tunnel, etc) **7.** 15% reduction in downtime due to less stoppage of the lines linked with washing and depyrogenation (breakage removal, dropped , stuck, etc) 8. 2% reduction of defects due to sub-crack or sub-breakage in washing and tunnel equipment moved into real cracked containers to be discarded during filling or in Visual Inspection
Documentation Review associated with batch manufacturing	**a.** Full review of the manufacturing executed Batch Record including section dedicated to washing and depyrogenation and related attachments, print out and procedures	Quality Documentation review without washing and depyrogenation steps	15%-20% Batch executed documentation review effort reduction
Quality	**a.** Periodic deviations to be handled on washing and depyrogenation production steps including additional environmental controls where required **b.** Deviations related with human introduction in aseptic area at the end of the tunnel to resolve containers transport issues on the accumulation table or along the conveyor belts	No deviation due to steps removed	Approx 2 deviations/week reduction per filling line including ΔP inversion deviation from the filling room Grade A and the cooling area of the tunnel which could call for additional cleaning activities during manufacturing. No related investigations and tests/environmental and personnel controls needed

** Results of table 1 refer to the findings and conclusions derived from investigations or studies conducted by Giovanni Cosmi and Mirko Gabriele.

References
Technical report PDA n 43
Pharma glass defects Article – Matthew Hall – Sept 8, 2023 - Linkedin

For the purpose of this exercise:

• Entire filling line is the entire train of equipment from washer to crimping

• The filling occupancy has been assumed in three shifts, 44 weeks/year (excluding APS and routine bi-yearly maintenance)

• Maintenance has been assumed as routine activities done bi-yearly (2 weeks per each shutdown)

• FTE: assumed 4 FTEs for the handling of the Grade D area of the filling train (loading of the washing, washing and tunnel control, including recording of activities and data on production documentation)

• Deviation costs including – no reanalysis included is assumed approx. 7000 €/dev. Based on that assumption: 44 weeks x 2 dev / week = 88 dev / year -> 88 dev x 7,000 €/dev = 616,000 € estimated potential saving per year.

Authors

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Giovanni Cosmi has studied Chemistry at the University of Rome “La Sapienza”(I).

He has a relevant and diversified experience in Quality Operations management, developed in more than 35 years of activities with several domestic and international companies working in the pharmaceutical business area such as: Merrell Dow Pharmaceuticals, Bristol Myers-Squibb and Pfizer. During his career, he has acquired operational, strategic and organizational skills to manage processes and human resources to build and maintain a QMS in compliance with the cGMP requirements for companies working in an FDA and/or EMA environment.

Currently Senior Pharmaceutical Consultant collaborating with some important international Consulting Companies operating in the pharmaceutical business, providing to the customers, his professional assets to realize Quality, Training and Continuous Improvement projects, able to contribute to their growth and competitiveness.

Mirko Gabriele

Pharmaceutical and Innovation Consultant

Mirko is a passionate advocate of pharma and innovation, and he is currently bringing this passion in his role of health-tech advisor. He has over 20 years of experience in the Pharma industry predominantly in Technology Transfer and Operations.

As a result of his ability to successfully execute all stages of the technology transfer process, he was promoted from site roles to global roles, with the opportunity to work on Technology Transfer Policy harmonization and best practices improvement and sharing. He successfully covered several dosage forms projects, from Oral to Combination products with a strong expertise in Sterile.

Director roles in Business operations and innovation and strategy gave Mirko a full overview of the technology and pharma space, strengthen his ability to successfully lead complex team and organization (500+ reports). He is also part of the PDA (Parenteral Drug Association www.pda.org) since 2005 and is now PDA Europe Trainer for Technology Transfer. Mirko is leading the PDA Technology Transfer Interest Group (TT IG) for Europe which has the mission to define, share and implement best practices in the industry.

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Andrea holds a Pharmacy degree from the Faculty of Pharmacy, Department of Pharmaceutical Sciences, University of Padua (Italy). He is a member of ISO / TC76 / WG2-Rigid container systems and related accessories for Parenterals and Injectables.

After a long experience in Quality Assurance in the pharmaceutical industry and medical devices, he joined Stevanato Group, where he held the position of QA Manager for Pre-fillable Syringes production. He is now the Regulatory and Scientific Affairs Manager.

Founded in 1949, Stevanato Group is a leading global provider of drug containment, drug delivery and diagnostic solutions to the pharmaceutical, biotechnology and life sciences industries. The Group delivers an integrated, end-to-end portfolio of products, processes and services that address customer needs across the entire drug lifecycle at each of the development, clinical and commercial stages. Stevanato Group's core capabilities in scientific research and development, its commitment to technical innovation and its engineering excellence are central to its ability to offer value-added solutions to clients.

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WP_ANNEX1_202405