A Quality by Design Approach toward Manufacturing of Elastomeric Components for Parenteral Packaging Applications

Introduction

Components that are used for parenteral drug packaging applications and medical devices have different requirements from a functional, regulatory, and cleanliness standpoint. As these components are held to different standards, it only makes sense to orient their manufacturing requirement to suit these needs. For instance, a plunger for a single use syringe will have different expectations as compared to a prefilled syringe plunger. Similarly, a blood collection stopper will differ in requirements from a lyophilization stopper. As these components are governed by different functionality and regulatory expectations, it is warranted that their manufacturing environments reflect the needs. Understanding these factors, Datwyler pioneered three different manufacturing standards to deliver the best value based on market requirements – Essential, Advanced, and FirstLine™. It should be noted that these are separate manufacturing facilities and not environments within the same facility.

This paper discusses the Quality by Design (QBD) approach within the FirstLine™ facilities to manufacture components that require the highest quality levels for sensitive drug applications so as to achieve patient safety.

The concept of FirstLine™ was commercially launched in 2009; although the seeds were sowed long before that. The concept stemmed from a powerful thought that the Active Pharmaceutical Ingredients (API), and drug formulations were being manufactured within clean room environments, but the packaging materials were not. Once these drugs are packaged, it is the packaging that defines the cleanliness and efficacy of these drugs. Ultimately, the manufacturing of packaging components should be considered an extension of the drug manufacturing environment and held to similar standards.

FirstLine™: Datwyler's most advanced manufacturing concept

At the time of ideation of FirstLine™, Datwyler collaborated with pharmaceutical and biotech clients to understand the needs of the market. There was clearly an unmet need to deliver the highest quality elastomeric components. Through alliances with pharma clients and surveys, we were able to distill the information into three macro trends: (1) development of complex and sensitive drugs and challenges to package and deliver these drugs in an efficacious manner, (2) more stringent expectations of the regulatory authorities, and (3) globalization and supply chain optimization to meet the requirements of the pharmaceutical companies. Let us elaborate on these three macro trends and how the FirstLine™ manufacturing concept delivers on them.

Development of complex and sensitive drugs and challenges to package and deliver these drugs in an efficacious manner

Highly sensitive drugs such as biologics, biosimilars, and some small molecules with difficult formulations, demand modern elastomer compounds with the cleanest extractable and leachables (E/L) profile. Large molecule drugs are highly sensitive to foreign contamination – cases have been

reported on protein aggregation[1], silicone sensitivity[2], loss of efficacy[3], and drug recalls[4]. To meet these product challenges, Datwyler has developed best-in-class rubber compounds such as the FM457 which is widely recognized as the cleanest elastomer in the parenteral packaging space from an E/L standpoint.

To mitigate risks against silicone sensitivity, Datwyler has developed a proprietary fluoropolymer spray coating that eliminates the need for siliconization. The spray coating has been commercially successful with several drugs on the market that benefit from this fluoropolymer technology.

Key features:

- **Proprietary, inert fluoropolymer spray coating** – offers superior chemical compatibility;
- **Total coverage,** trim edge included – no worries about the 'ring of uncertainty';
- **Covalently bound** to rubber – eliminates the risk of scraping or damaging the coating;
- **Barrier properties** – cuts down the E/L profile further;
- **Thin and flexible coating;**
- **Low coefficient of friction** – no silicone needed for machinability and plunger functionality;
- **Ultra-low visible and sub visible particle levels** – coated components are only manufactured in FirstLine™ facilities;
- **Available in FM457** – the low E/L profile of FM457 coupled with the spray coating makes this the most suitable elastomer component for highly sensitive biologics.

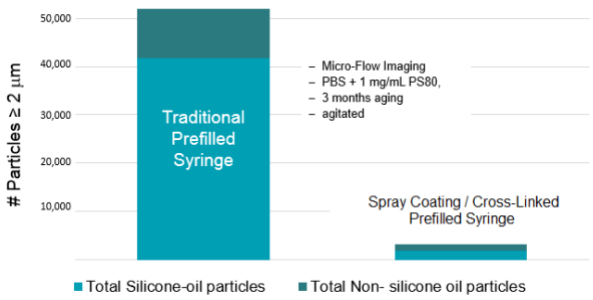

Figure 1: Visible and sub-visible particles for both coated and uncoated elastomeric plungers in traditional syringes and Gerresheimer's cross-linked syringe.

Another key advantage of the fluoropolymer spray coating process is that the process itself allows for coating of a wide variety of designs. The proprietary spray coating is well-suited for custom designs that have unique functional requirements or drug delivery needs.

CUSTOMIZATION

Why are custom design capabilities important for pharmaceutical and biotechnology companies?

- The ability to cater to unique drug delivery needs
- More innovative drug delivery devices being introduced to the market to improve upon patientexperience
- Marketing and product differentiation
- Life cycle management
- Extended patent life and exclusivity

Since coated components are needed to meet the challenges of sensitive drugs – they are only manufactured in Datwyler's FirstLine™ facilities.

Only the cleanest elastomers, designed as per modern elastomer formulation theories to have the cleanest E/L profiles are allowed to be manufactured within the FirstLine™ standard.

More stringent expectations of the regulatory authorities

[1] https://www.biopharminternational.com/view/analyzing-protein-aggregation-biopharmaceuticals-0
[2] J Pharm Sci. 2009 September ; 98(9): 3167–3181
[3] J Pharm Sci. 2009 Apr; 98(4): 1201–1205.
[4] Tawde, J Pharmacovigil 2014, 3:1

Data suggests that authorities' expectations are becoming more and more stringent, pushing our industry to reach higher quality levels. The Datwyler FirstLine™ standard has been designed to provide our customers with primary packaging solutions, meeting the most challenging expectations of the authorities.

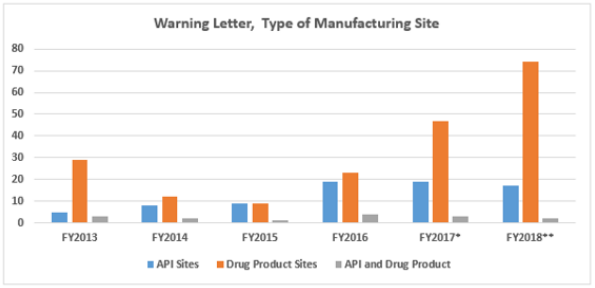

Figure 2: FDA warning letters by manufacturing site type – 2013-2018.

This will lead to a significant reduction of market recall risks and total cost of ownership for our customers. Anytime there is a market recall – it is not just a financial liability, but a risk to reputation for the pharmaceutical company.

Based on historical data, almost a quarter of drug recalls are related to visible particulate.[5] Visible particulate recall events have been on the rise. Data collected between in the past 15 years[6] suggests that there has been a consistent increase in particulate-related recall events. This increase could be attributed to:

- Implementation of improved specifications and/or stricter release criteria as mandated by regulatory bodies;
- Increased inspection;
- Improvement in analytical and inspection techniques.

It can be agreed that these trends on stricter expectations from the pharmaceutical companies as mandated by the regulatory bodies are here to stay, and will only get stricter. Lately, the FDA has been tough on big pharma companies[7] to set the bar higher for injectable drug manufacturing. It is only a matter of time until this will be the "new normal" within the industry.

To meet these challenges, Datwyler pioneered the FirstLine™ manufacturing concept much ahead of its time.

Features of the FirstLine™ Manufacturing Facility

The FirstLine™ manufacturing concept starts with a 'zero defect philosophy' in mind. To achieve zero defects while manufacturing over 1 billion components is utopian, but we strive to get as close to it as possible. To achieve this, Datwyler has implemented the following facility features:

- A smart facility design that regulates personnel flow, material flow, and waste flow to maximize efficiency and minimize defects in line with six sigma principles;
- Gowning principles in line with cGMP, with non-shedding clothing, and trained personnel only allowed on the manufacturing floor;
- Statistical process control and process FMEAs throughout the process to maximize efficiency and minimize defect rates;
- Automation in the process and minimized operator contact;
- A Pareto analysis of common defects and complaints found in injectable drugs (data collected in collaboration with pharma/biotech partners) revealed that *cellulose* was the most commonly found contaminant, therefore, the entire production floor is paperless;
- As we move downstream, closer to the finished product, there is no manual handling of the product, and the manufacturing environment is continuously improved at each step of the process, with pressure cascades in place to reduce particulate contamination

[5] Tawde, J Pharmacovigil 2014, 3:1 DOI: 10.4172/2329-6887.1000e128
[6] Shabushnig JG (2014) Detection and Control of Visible Particles in injectable products.
[7] https://www.fda.gov/drugs/warning-letters-and-notice-violation-letters-pharmaceutical-companies/warning-letters-2019

within the manufacturing area.

After putting in place a robust process and high-level automation within a clean room environment, a high-quality product that is expected of FirstLine™ is already ensured. However, to take it a step further, as a second line of defense, components can be vision inspected at a per piece level for cosmetic and dimensional defects.

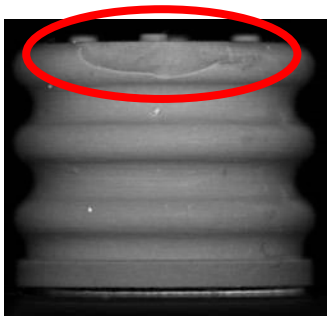

Figure 3: Each component in Datwyler's FirstLine™ facilities is 100% camera inspected. Defective or contaminated products are removed during the camera inspection process.

Strict specifications for particulate levels and continuous improvement effort are in place to move us towards our goal of zero defects. This Quality by Design approach is at the center of the FirstLine™ concept.

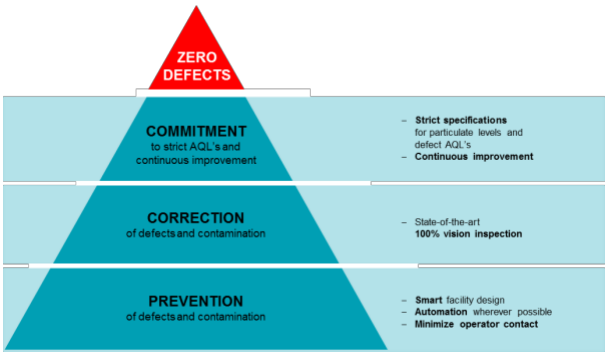

Figure 4: Datwyler's Zero Defect Philosophy is the basis for everything we do.

Globalization and supply chain optimization to meet the requirements of the pharmaceutical companies

Pharmaceutical companies maintain a global manufacturing supply chain to provide drugs into several geo-regions and varied regulatory environments. It is expected that component manufacturers are able to match that global footprint of pharma companies in order to deliver products reliably around the globe.

With FirstLine™ Belgium, FirstLine™ India and FirstLine™ USA commercially online, pharmaceutical and biotech clients have the benefit of three FirstLine™ sites on three continents, with the following advantages:

- A global manufacturing footprint;
- The same raw materials, technology, processes and products with the same specifications from all three facilities;
- Comprehensive risk mitigation strategy;
- Business continuity plans;
- A global strategic approach with local regional presence is a key success factor in the pharmaceutical market;

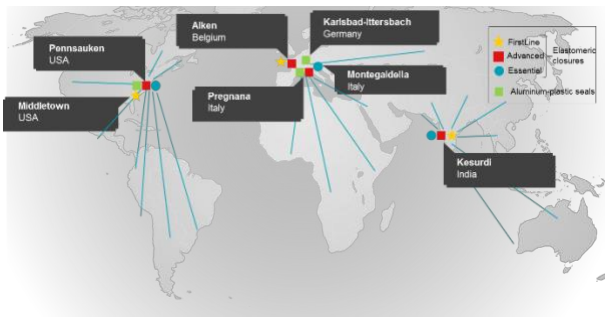

Figure 5: Datwyler's FirstLine™ manufacturing facilities are located in 3 regions, allowing us to supply the highest-quality components to pharmaceutical and biotech companies around the world.

Conclusion

In order to meet the needs of the pharmaceutical and biotech markets, Datwyler has pioneered the FirstLine™ manufacturing concept, making the goal of zero defects in parenteral packaging manufacturing a possibility. With processes in place to reduce contamination, meet stricter authority requirements, and supply products around the world, Datwyler's FirstLine™ is the most advanced manufacturing standard to meet the parenteral packaging needs for pharmaceutical and biotech companies.