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Keeping Up with a Shifting Regulatory Landscape:

Understanding Quality by Design and its Impact on Total Cost of Ownership

Patient safety is at the forefront of considerations in the pharmaceutical industry, with high expectations from patients and care providers for quality in injectable medicines. But it is about more than just manufacturing quality drugs. Also contributing significantly to patient safety is the production of high-quality packaging components and delivery systems.

As a result, the US Food and Drug Administration (FDA) and other regulatory agencies around the world are requiring drug makers to develop and institute quality processes in the manufacturing of drug products and their container closure and delivery systems. It goes without saying that pharmaceutical companies and their packaging and delivery system providers should be ever-diligent in ensuring that quality and compliance are top priorities, but there must also be a balance that allows for appropriate cost management to maintain affordability for the patient and profitability for the drug maker, which will ensure continued investment in bringing needed therapies to market.

Biologics and Increased Regulatory Focus on Quality

There continues to be a steady rise in new biologic and biosimilar drugs coming onto the market to treat chronic conditions such as multiple sclerosis and certain autoimmune diseases. Additionally, biologic therapies show promise for helping acute conditions, such as certain types of cancer, become manageable chronic conditions by targeting specific components of a disease in ways never thought possible before.

This trend isn't going away. In fact, the QuintilesIMS Institute predicts that spending on biologic treatments for autoimmune diseases and a range of related disorders will reach $75–90 billion by 2021. In addition, biosimilars will be available for several of the leading autoimmune products in the same timeframe, potentially allowing wider use of these medicines.[1]

Quality is particularly at the forefront with the influx of new biologic and biosimilar drugs, which often have very specialised needs around containment and delivery. For example, biologics can have sensitive compositions that pose the potential for interaction with materials traditionally used for packaging and delivery systems. In particular, the fact that many sensitive biologics are coming on the market as combination products is spurring regulatory agencies to more closely scrutinise the compatibility of packaging components with injectable drugs and their delivery systems. Regulatory guidances such as ICH 8, 9 and 10 are also contributing to the increased focus on quality within the biopharmaceutical industry.

These factors are ushering in new considerations for biopharmaceutical companies and their packaging and delivery system partners around drug delivery and risk mitigation. In this new era, the adoption of quality by design (QbD) principles in the design and manufacturing of packaging and delivery system components for injectable drugs products helps to ensure that how the therapy is contained and delivered is engineered with these stringent and specialised needs in mind.

The adoption of QbD principles delivers an improved, data-driven output, providing manufacturers with superior product and process understanding that minimises risk, emphasises patient-critical quality requirements and supports drug product effectiveness in an industry where patient-centricity is paramount and quality must be top of mind from the very beginning.

QbD principles were designed to promote an understanding of the drug product and manufacturing process, starting with product development. During the design and development process, a QbD-driven approach requires manufacturers to define desired product performance goals and identify critical quality attributes (CQAs). The product and process can then be designed to meet those attributes, potentially improving understanding of how material attributes and process parameters impact CQAs and enabling manufacturers to mitigate variability.

QbD has helped facilitate more expedient and efficient introduction of high-quality biologics to market because stakeholders are now armed with critical data that allows them to control potential risk factors. It also allows drug, packaging and delivery manufacturers to continually monitor and adjust their manufacturing processes to ensure consistent quality throughout a drug product's lifecycle.

The scientific, risk-mitigation-based QbD approach is fast becoming an essential strategy for bringing high-quality biologics to market quickly and efficiently, while identifying and controlling potential quality concerns. High-quality components designed using QbD principles and processes can help optimise the performance of drug delivery systems and protect sensitive drug products with exceptional cleanliness and barrier properties, while helping to ensure patient safety.

While pharmaceutical companies are working to ensure that new quality and compliance paradigms for a drug and its packaging are met, a balance must be achieved between the realities of managing costs in an effort to provide a product that meets the requirements of payers along with facilitating profitability to support adequate business

reinvestment. The adoption of QbD concepts over recent years has helped pharmaceutical companies and their packaging and delivery partners balance these priorities effectively.

However, some manufacturers have been slow to integrate QbD for one very clear reason: cost. Instituting QbD processes in manufacturing requires a significant up-front investment, which can understandably lead some in the industry to initially shy away. That said, the benefits of incorporating QbD principles into manufacturing can go a long way in reducing the total cost of ownership (TCO) for a given product.

QbD's Impact on Total Cost of Ownership

To ensure that the QbD return on investment is maximised, it is important to understand the total cost of ownership – i.e., the analysis of price, risk, quality, service and delivery performance – in evaluating the overall cost of a product versus its benefit. Reducing end-of-line rejections is an example of how the pharmaceutical manufacturer can clearly recognise benefits from TCO. QbD can often drastically lower end-of-line rejections to very minimal rates and generate significant cost savings by enabling more products to go to market for patient use. This, in turn, reduces the probability of product shortage and helps to manage capital expenditures more effectively. The end result? More revenue is generated for the pharmaceutical or biotech company.

Container closure systems represent another area where a TCO model can support QbD initiatives. While drug packaging is often the final consideration in the drug development process, the selection of appropriate, high-quality primary packaging components is critical to drug stability and the effectiveness and compliance of a commercial manufacturing process. For example, selecting a vial made from a cyclic olefin polymer, such as the Daikyo Crystal Zenith® polymer, and a high-quality, ready-to-use component that has been through optimised washing, sterilisation and automated vision verification processes can combat issues from particulate and extractables.

Instituting a QbD Approach for Components

As industry demands for high-quality components have evolved, there is growing need for packaging components developed using QbD processes. A QbD approach promotes a holistic understanding of the drug product, its integrated delivery system and the manufacturing process. Employing a QbD strategy for packaging components starts with product development. When designing and developing a product using QbD principles, manufacturers must first define desired product performance goals and identify CQAs. The product and process can then be designed to meet those attributes, potentially improving understanding of how material attributes and process parameters impact CQAs and enabling manufacturers to mitigate variability. As a result of this knowledge, a company can continually monitor and update its manufacturing process to ensure consistent product quality.

The design and manufacturing of high-quality components should follow a development lifecycle programme that uses a quality target product profile (QTPP) to establish CQAs for control of breakloose and glide forces. The QTPP can serve as a guideline throughout the development process – which should include risk-based design inputs, finite element analysis modelling, data generation on multiple concepts and final product performance verification with barrels from multiple suppliers – to ensure that targeted specification values for breakloose and glide force are met.

By applying a holistic, QbD approach to the design and development of

prefillable syringe components, packaging manufacturers can gain a thorough understanding of both the product and the process. This, in turn, enables multiple benefits for manufacturers and end users:

- **Improved Functionality** – High-quality components, such as plungers, can enhance the functionality of prefillable syringes and self-injection systems. Using QbD principles can help to optimise breakloose and glide forces – aspects that are very important when syringes are used in combination with an injection system. By optimising a delivery system's functional and dimensional performance, it is possible to improve the consistency of injections and the rate of injection times.

- **Patient Confidence** – A self-injection system needs to function consistently and reliably in order for patients to have confidence that it will work. QbD-designed components allow for larger-size delivery systems and greater dosing volumes which may enable home administration, and encourage device use and more accurate dosing – all of which can help boost a patient's confidence in their use of a self-injection system.

- **Efficient Manufacturing** – Employing a QbD approach in the manufacturing process can significantly reduce variation from part to part. This can help facilitate more efficient manufacturing processes and support a reliable supply of drug products.

Use of QbD principles ensures that components are developed using science-based and data-driven decisions, and that they meet critical specification for defects, visible and sub-visible particulate and extractables consistently. The knowledge gained throughout the QbD process can be used on an ongoing basis to maintain continuous improvement by the manufacturer.

Partnering to Enhance Quality

Efficiency in manufacturing and the ability to meet critical compliance standards are a must to compete in today's market. Effective packaging selection early in the development process can be key for pharmaceutical manufacturers. Early partnerships between pharmaceutical companies and drug delivery device companies help pharmaceutical manufacturers select consistent components that can be used throughout the drug product's lifecycle and potentially mitigate risk associated with issues such as particles. Additionally, as delivery systems are utilised to a greater extent with many speciality pharmaceuticals, the ability to ensure the packaging and delivery system work together effectively minimises risk and total cost.

The best way to maximise a drug product's safety and efficacy is for pharmaceutical companies and their drug packaging and delivery partners to collaborate at the onset of the entire manufacturing process, from design and development to commercialisation and administration. This will ensure that they build new quality principles into the product from the very beginning.

Choosing a packaging partner that employs a QbD philosophy, pharmaceutical manufacturers can employ high-quality packaging components that can help lower their total cost of ownership through reduced compliance risk, filling rejection rate and process costs. Full return on investment can be realised once a drug product is commercialised and has gained patient loyalty through ease of use and therapeutic benefit.

The collaboration and use of QbD principles to design high-quality components ensures the highest levels of reliability, which ultimately helps the pharmaceutical industry achieve its most critical goal: providing safe and effective drug products for their patients.

REFERENCES

1. QuintilesIMS Institute. Outlook for Global Medicines through 2021: Balancing Cost and Value. December 2016.

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Fran DeGrazio has been in the pharmaceutical packaging industry for over 30 years with extensive expertise in the area of delivery of injectable drug products, such as vial/closure combinations, prefillable syringe systems and injectable combination products.

Throughout her tenure at West, Fran has served in various functions within the analytical laboratory and research and development areas. Thirteen years were spent in the Technical Customer Service and Contract Laboratories areas with responsibility for strategic planning and implementation for both organizations.

Fran was promoted to Vice President, Quality Assurance, Americas, in 2002 with responsibility for quality assurance and quality control for nine manufacturing facilities, the corporate analytical laboratories and the regulatory organization. In May 2006 she transitioned into the role of Vice President of Marketing and Strategic Business Development leading initiatives such as the concept of applying Quality by Design to closure development. As of 2012, Fran assumed a role as Global Vice President, Research and Development, Strategic Program Management and Technical Customer Support leading all packaging new product activities. As of February 2016, Fran was asked to develop a new organization for West. In this role, she leads the Scientific Affairs and Technical Services organization for the enterprise. This role is focused on assuring West's scientific industry leadership as we innovate new products and services for the et.

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