Quality Management Paradigm Shift

Risk-Centric Practices Come Center Stage

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Data-driven, pro-innovation strategies advance new-era therapies.

This is the eighth of a nine-part series of articles addressing pharmaceutical outsourcing industry trends.

Disruptive technologies fuel the transformation of quality management practices by contract development and manufacturing organizations (CDMOs) as groundbreaking new-era medicines emerge into manufacturing.

Advanced therapy medicinal products (ATMPs) along with cell and gene therapy products (CGTs) are today's fastest-growing business segment and increasingly, pharma is shifting the focus to personalized therapies and biologics.

More than two and a half dozen CGT products have already been approved by the U.S. FDA and many products are in development. At the same time CDMOs are aggressively expanding their capabilities into the high-growth ATMP/CGT space.

For novel advanced therapeutics, standards frequently change. Regulators update guidelines as new information about the drug product classes becomes available.

Considering the novelty and increasing complexity of these products, experts say the evolving regulatory climate is shifting towards risk management and health authority approval based

on the given risk profile.

The risk-based, quality-first approach, which focuses on critical data and processes to ensure trial subject or patient safety, marks a departure from the traditional approach favoring extensive and often indiscriminate documentation, vetting, and validation of every small detail against a list of requirements.

RISK-BASED QM BECOMES INTEGRAL

"Risk-based quality management (RBQM) has become a cornerstone of modern quality management," says Mike McCormick, senior vice president of quality and compliance at Center for Breakthrough Medicines (CBM), a cell and gene therapy CDMO, based in King of Prussia, PA.

According to McCormick, RBQM provides assurance that regulatory requirements are achieved while navigating the demands of manufacturing operations. It prioritizes resources and efforts based on the potential risks to product quality, ensuring that the most critical areas receive the most attention.

In this approach, case-by-case risk assessment evaluation takes center stage as de-risking plans may vary between advanced therapies.

CBM's manufacturing facility near Philadelphia has more than 20 suites for viral vector production and over 20 dedicated to cell therapy.

Oliver Schlaefli, senior vice president and global head of quality at Lonza, also affirms that advances are being made in applying risk-based approaches in quality management by implementing the principles in relevant ICH guidelines.

While presenting great opportunities, each of the key modalities in CGT brings unique challenges to manufacturing, notes Schlaefli.

From a quality standpoint, a high degree of variability resulting from both new starting as well as raw materials and the manufacturing process conditions is one of the major challenges that ATMP/CGT products continue to face.

In general, there is a lack of industrialized manufacturing processes and platform technologies. The diversity of the underlying technology and the actual product platforms is also an issue.

Different asset requirements result from the implementation of different technologies and processes.

A leading CDMO in CGT, Lonza joined hands with Vertex Pharmaceuticals in August to build a more than 130,000 square foot manufacturing facility in Portsmouth, NH to support the commercial production of the latter's type 1 diabetes cell therapy portfolio.

Lonza's approach to developing a commercially viable process, according to Schlaefli, is based on de-risking development that includes establishing the baseline process, identifying the major manufacturability gaps, process optimization based on design specifications and critical quality attributes (CQAs), and all necessary steps for successful process performance qualification (PPQ), and, ultimately, product commercialization.

CLOUD LEADS THE WAY

The application of risk-based quality management, which calls for highly integrated and digitalized processes, is being powered by a CDMO industry that is fast becoming data-driven.

There's a push, says McCormick, towards adopting state-of-the-art technologies to meet and exceed regulatory standards. For instance, CDMOs are integrating advanced data analytics, artificial intelligence, manufacturing enterprise systems, and machine learning into their quality management systems to predict and prevent potential quality issues.

Surveys show that industry-leading CDMOs are fast-evolving their processes by leveraging on cloud-based applications, and digital quality systems from relying on legacy systems. For CDMOs, the cloud offers a way to aggregate data to gain insights into the root cause of quality issues such as deviations and out-of-specification (OOS) events.

Cloud-based systems not only enhance efficiency, observes McCormick, but also ensure that CBM can scale its operations seamlessly to meet the dynamic needs of its clients.

It also improves the management of quality metrics and key performance indicators, particularly when used with IoT-enabled devices. These capabilities, along with assured data integrity, are crucial to reducing quality risks.

In addition to scalability, the advantages of cloud solutions include fast setup and deployment, and the ability to transform business processes, says Schlaefli of Lonza.

In terms of systems used to manage quality processes, CDMOs observe a high adaptation rate of cloud solutions that support quality assurance processes. However, "traditional on-premises systems still outweigh in labs for quality control purposes," he hastens to add.

TRACKING QUALITY REAL-TIME

Basel-headquartered Lonza, which offers services across biologics and small molecules in addition to CGTs has developed solutions to digitalize quality and manufacturing. The company's proprietary MODA platform aims to bridge the gap between manufacturing and quality control, providing a mechanism to produce a single electronic batch record.

Digitalized processes enhance visibility across production lines besides making manufacturing more dynamic through automatic alerts, reminders, and prompts. As a result, the manufacturer gets the opportunity to track quality in real time and flag issues.

CDMOs can deploy from a vast array of tools and systems that are available today to capture all the data for preventive action. This helps them embed quality management much more within real-time processes and ensure that any patterns in deviations do not occur again and satisfy regulators and auditors.

"One of the standout features of digital systems is the ability to monitor processes in real-time," says McCormick. Coupled with advanced analytics, CBM can predict potential quality issues before they arise, allowing it to take a proactive rather

than reactive approach.

The more the systems and processes are interlinked the greater the scope of improvement, say domain experts. Manufacturers can use digitalized workflow management and apply intelligent process automation to go that extra mile to avert every possible risk.

HUMAN CAPABILITIES AUGMENTED

Covid-19 and the associated wider lockdowns took a decisive turn in the digitization efforts of CDMOs.

Many CDMOs are now evaluating quality management practices adopted during the pandemic for continued use under normal operating conditions. Digital technology is being adapted to support these new practices, observes Schlaefli, such as performing internal audits remotely, supporting health authority audits that are performed remotely, and customer-requested remote audits.

The application of virtual reality (VR) as part of quality management practices to provide standardized training is also on the rise. VR training modules, for example, can be used for training on aseptic practices. This can enhance new operator training and deliver real-time results such as speed in the cleanroom and breaking first air.

Similarly, by using augmented reality (AR) glasses, standard operating procedures (SOPs) or images can be projected in front of the operator, removing the need to have a computer or tablet nearby to refer to their work instructions.

AI, another striking advance impacting CDMO practices, can enhance the ability to automate tasks and improve efficiency by augmenting human capabilities. The use of AI can enhance the identification and assessment of quality issues and evaluate trends.

STAYING AHEAD OF THE CURVE

The increasingly stringent regulatory requirements are having a profound impact on quality management practices within the manufacturing landscape, say CDMOs.

With stricter regulations, there is a heightened emphasis on maintaining comprehensive documentation and data integrity for every step of the manufacturing process.

For example, the implementation of revised EMA Requirements for the Manufacturing of Sterile Products (Annex 1), which went into effect on August 25, 2023, is having a widespread impact on the industry.

The new version of Annex 1 has been expanded considerably and now contains a stronger focus on risk management and the implementation of a contamination control strategy.

"Alignment with the revised guidance requires changes in quality management practices for manufacturing sterile products," points out Schlaefli.

Schlaefli opines that CDMOs must have robust regulatory intelligence processes to identify changes in regulatory requirements in a timely manner. This helps them to remain ahead of the curve in anticipating regulatory shifts, understanding the impact on the customers, and adapting CDMOs' standards, policies, and site documentation to align with requirements.

As manufacturing becomes more complex, quality assurance becomes an enabler of operational excellence and a source of competitive advantage.

SHORTENING LEAD TIMES

Many CDMOs find "fit-for-purpose" quality management strategies come to their aid to accelerate timelines—one of the foremost challenges faced by CDMOs.

Customers mostly demand the quickest possible route to get the therapeutic to the clinic or patient. So, it becomes critical to manufacture a product at a pace demanded while ensuring quality that is compliant with industry regulators.

For many novel products, where the processes are not well-established, CDMOs prefer phase-appropriate practices to the traditional one-size-fits-all approach. In this approach, the control strategy is further refined with "process understanding gathered along the way." This contrasts with the standardized and rigid formats where any deviation can necessitate extensive investigation. Costly time delays in the remedial action could prove harmful to the interests of sponsors looking for shorter lead times.

Extensive experience and knowledge working on different molecules and processes enable CDMOs to support the sponsor in designing a phase-appropriate quality by design (QbD) strategy—a holistic approach that emphasizes product and process understanding and process control, based on sound science and quality risk management.

"Even for early-stage development, more and more clients are now asking for the QbD approach and they are willing to pay extra for the effort. This was not the case until three years back," comments a senior quality official from an India-headquartered CDMO, referring to the increasing popularity of the strategy.

He can also discern a clear shift in today's regulatory focus, saying, "Unlike a decade ago, today the regulators are open to hearing your rationale if your development process is robust. If you can demonstrate it, they will support it. They want you to know the molecule better. Then come up with the strategy." **CP**

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