

Remediation Requires Transparency: A Process for Managing Quality and Compliance

Introducing Transparency

Standardization and alignment of the drug development and manufacturing process allow high-performing companies to globally source and efficiently produce pharmaceutical and biopharmaceutical products. Recent well-publicized quality control errors within the industry have shown that it is impossible to negate all risks involved in the design, development and manufacturing of pharmaceutical or biopharmaceutical products. However, the bulk of them can be addressed through a clear remediation plan with routine regulatory inspections intended to reveal any deficiencies related to either part, or all, of the pharmaceutical manufacturing process, so that they may be isolated and addressed. It is important for a manufacturer to also support this plan with transparency in the supply chain.

At the core, a transparent supply chain makes it easier to raise scientific, technical and regulatory issues early on in the remediation process in order to help avoid misunderstandings and reduce inconsistent (corrective) action. Furthermore, sharing the outcome of technical, regulatory and scientific issues/disputes related to the manufacturing process or supply chain management provides greater clarity about regulatory requirements. It can also facilitate the development and revision of guidance documents. Finally, dissemination of these results will help to prevent future disputes and lead to re-establishment of cGMP and approval.

What is Remediation?

The remediation process in pharmaceutical and biopharmaceutical manufacturing is based on recognizing problems, fixing them and closing the gaps where possible in order to meet required regulations. Often, the U.S. FDA and other regulatory agencies are not interested in perfecting the manufacturing facility, but rather in a pharmaceutical manufacturer's ability to fully understand their own quality processes. They are also looking for manufacturers to have a good means of storing and analyzing the relevant production data and, if necessary, the means of developing a thorough corrective action plan that gets to the root cause and remediation in a timely manner. Regulatory agencies are also interested in the manufacturer's ability to

predict any potential deviations in the production process followed by a process of required corrections before resulting in larger issues, recalls and warning letters.

Remediation for quality and regulatory compliance includes a number of predefined steps; to begin with, a manufacturer that is working with external experts to gain a thorough understanding of its overall pharmaceutical manufacturing process. This may, at times, be complicated by the fact that a manufacturer can be operating multiple facilities that differ from site to site.

The creation of an integrated data management system and manufacturing analytics process can remedy this. This approach allows manufacturers to identify all critical quality parameters involved in the process and depending on a client's needs and requirements, these services may include the evaluation of existing analytical validation. The end goal is to identify important gaps, forecast the potential for success or failure of validation against established criteria and modify existing methodologies to ensure a successful validation project.

The Benefits of Partnering with a Remediation Expert

The core benefit of enabling a transparent process is to avoid unpleasant surprises. By proactively identifying, tracking and resolving cGMP and other deficiencies, an external remediation expert (such as SAFC) can help a manufacturer lower risk and improve operational efficiencies with expertise. From initial gap-analyses and remediation planning for existing systems, to prospective assessments of new systems, their experience will help determine the regulatory relevance and associated requirements for compliance. In each of the steps involved, transparency will enhance and improve the entire operational (manufacturing) process.

The Remediation Process

1) Define Objectives and Priorities – It all starts by working with an appropriate model, such as ICH Q10. This model offers an effective pharmaceutical quality system based on ISO concepts and has been designed for the different stages of a pharmaceutical or biopharmaceutical product lifecycle. This quality system emphasizes an integrated approach to quality and risk and includes a move from regulatory to scientific guidance. The model goes beyond current cGMP requirements, which, with the exception of the manufacture of investigational medicinal products for human use, does not apply to the development part of the lifecycle.

Although optional, the content of ICH Q10 in addition to the scope of cGMP, facilitates innovation, continual improvement and strengthens the link between pharmaceutical development and manufacturing activities. The various definitions used in ICH Q10 and cGMP are critical requirements, and for both, the development of a manufacturing process (in addition to remediation) is important to focus on specific issues that are most critical in determining the quality and safety of the pharmaceutical or biopharmaceutical product.

2) Investigate Supply Chain – A critical next step in the remediation process is a thorough investigation of the supply chain. Due to the increasing number of suppliers, manufacturers and distributors around the globe, supply chain management has never been more complex than it is today. To guarantee a sound process, investigative quality assurance must be built-in early on in the manufacturing and remediation process. Quality assurance is not just limited to a back-end testing approach. To be successful, the customer needs to have a firm project description or a standard operational procedure (SOP) to manage supply chain risk. A bottleneck often occurs when customers don't stop to evaluate the financial implications that remediation may bring about (i.e., due to any unexpected changes).

3) Identify Gaps – In this phase, the external remediation partner will perform root cause analyses and develop comprehensive corrective action master (remediation) plans to satisfy regulators. An experienced remediation partner can comprehensively assess a customer's quality system and supply chain operations and identify regulatory requirement gaps and deficiencies.

4) Share Findings – Assessment of the quality of the supply chain should have included collecting and reviewing information from existing suppliers, manufacturers or distributors. The audit acts as a two-way street between the customer and the remediation expert and, as such, will only be fully beneficial if the information disclosure is completely transparent. When the information is fully disclosed, it allows the audit to reveal any flaws or regulatory deficiencies in the supply chain and can also reveal any underlying issues with the supplier's current approach to quality or any risk avoidance. This will help bring a new level of maturity to the project and demonstrates partnership with the remediation expert.

Based on the outcomes of the initial meeting and input from company representatives and (external) remediation experts, a draft plan is developed where these types of findings can

be shared. This draft plan includes an overview of critical raw materials, a quality profile and applications. A critical aspect in this phase is the customer's ability to provide application and definition for critical raw materials.

5) Formalize Plan – In this phase, the manufacturing client and an external remediation partner negotiate a quality risk management program from the draft plan. In addition to previous assessments steps, this includes:

- Development and completion of a raw material questionnaire
- On site audits in a regulated environment
- Collecting additional documentation designed to compare products (including solvents, manufacturer's process flow, cell culture tests, etc.)
- Collecting additional data and samples to support a customer's evaluation for change

Commitments from manufacturing client and the external remediation partner will secure the success of the process.

6) Monitor and Finalize – The analytical methodology and process that supports the production of a pharmaceutical or biopharmaceutical product requires a continued review throughout the product's life cycle, which is especially important for validation, efficacy and efficiency. Process validation involves establishing documented evidence that specifies a process designed to reliably and consistently produce products that meet predetermined specifications and quality. These processes can include manufacturing, filling, sterilization and packaging.

Based on a standardized development report, an external remediation partner can assist in developing scientifically justified validation plans based on a review of critical process parameters and quality assurance characteristics. This step may include updating technical agreements according to progress or single agreements per product. Customer compliance and formalization of product level and product quality support are also required in this phase.

The SAFC Approach

As a remediation expert, SAFC offers its manufacturing clients a high-quality and cost-effective compliance and validation solution. With in-depth knowledge of regulatory guidelines and working in conjunction with quality assurance (QA) to provide a complete range of remediation services, SAFC focuses on improving a manufacturing client's operations, revitalizing their facilities and staying compliant in an ever-changing and challenging regulatory environment.

To learn more about SAFC's services please visit:
safcglobal.com/EnhancedQuality.