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Compliance Notes

State of Quality and Compliance in the Biopharmaceutical Industry

Have FDA initiatives improved manufacturing quality and patient safety?

The late 1990s and early 2000s witnessed a slew of enforcement actions by FDA that included multiple Form 483 observations, warning letters, and consent decrees resulting from facility inspections. The following years witnessed FDA's launching of multiple initiatives in an attempt to inspire the industry to achieve higher standards of quality and compliance. Among these initiatives are the *Pharmaceutical cGMPs for the 21st Century*, process analytical technology (PAT), quality by design (QbD), and harmonization of international standards and guidelines.

As a result of these efforts, new standards and guidelines have been published and numerous conferences held regarding quality systems, product quality, and regulatory compliance. However, after more than 10 years since the launch of these initiatives, manufacturing innovation and product quality do not appear to have improved to the extent originally envisioned. As recent years have clearly demonstrated, the industry is still struggling to attain the aspirations of *cGMPs for the 21st Century*. The industry is now in the midst of a new cycle of enforcement actions including consent decrees. So the question remains: have we, as an industry, learned from the mistakes of the past? Have we improved quality and compliance to the level expected, and if not, why?

There is no doubt that FDA has a role to play as it tries to foster positive change in our industry and, at times, has had to step up enforcement when confronted with quality and/or compliance issues. With this as background, we will attempt to explain the main drivers and potential causes of our limited success as an industry to meet the lofty goals defined earlier. Understanding these causes can hopefully lead to solutions. One thing is clear: the current state of quality is far from optimal. There must be change to address the challenges of the 21st century and remain competitive. In simple terms, the barometer of quality and compliance is skewed and is in dire need of calibration.

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The magnitude of change these initiatives would introduce may have been underestimated.

QUALITY IMPROVEMENT INITIATIVES

PAT, QbD, Quality, and *cGMPs for the 21st Century* are meant to provide increased understanding, control, and reliability of manufacturing processes, as well as consistently high product quality and regulatory flexibility. The initiatives themselves are not poor ideas. Rather, it is more likely they have not been as broadly or successfully implemented because they have been misinterpreted or incorrectly applied by both regulatory authorities and industry, only partially implemented because of competing demands on operations and staff, or not implemented at all. The magnitude of change these initiatives would introduce may have been underestimated and companies may not have been prepared to effectively manage, integrate, or sustain that change. Perhaps more time and a careful re-examination of the applications of these initiatives is what is needed for us to better understand and apply these approaches.

POTENTIAL CAUSES AND DRIVERS

The recent challenges the industry has faced regarding quality and compliance may be the result of multiple, converging factors that have caught many companies in a cycle that is difficult to break. Some of the contributing factors appear to include the following.

Lack of an effective and sustainable quality culture

While there has been considerable focus recently on the importance of attaining an effective and sustainable quality culture, as well as management's role in leading this, the industry has not been successful in accomplishing this goal. Possibly this is because the industry's attitude has been that quality and compliance are costly, do not produce profit, and require excessive time, money, and valuable resources to attain. This mindset results in a reactive approach where "fire-fighting" is sometimes all too common, but even when put out, all too frequently fires re-occur because effective measures have not been pro-actively implemented to prevent their re-occurrence. This behavior—particularly when seen as acceptable to management—then becomes the culture of the organization, and a major barrier to attaining a high and consistent level of quality and compliance.

Lack of effective quality management systems

Advances in technology have resulted in some paperless operations and the capability to communicate quickly. These systems, when not used effectively, however, can lead to inefficiencies and unnecessary complexity that impede proper system functioning. Standard operating procedures (SOPs) and batch records are sometimes so complex that they are difficult to follow, leading to human errors and deviations. The blame frequently falls on lack of effective training. The root cause, however, may be documents that are too complex. Fueling the complexity, multiple changes (e.g., addition of steps, changes to instructions) are introduced to documents, particularly batch records.

Deviation, investigation, and corrective and preventive actions (CAPA) management

These actions are crucial elements of the quality system that are the frequent focus of regulatory authorities. These systems, when not developed, implemented, and managed effectively, can lead to unnecessary 483s, warning letters, and occasionally, consent decrees. They are sometimes overly long, needlessly complex, and frequently do not provide the level of information needed to identify and resolve the root cause of the occurrence. Long scientific explanations may be written, but the primary questions are not answered. The effect of the deviation on product quality may also not be properly assessed. CAPAs may be generated without identification of the proper root cause, becoming exercises in futility. Ineffective management of these systems can result in a company getting caught in a cycle of repeated deviations and CAPAs that can result in further deviations, significantly increasing the compliance risk/exposure of the organization.

Outdated manufacturing processes and methods

There seems to be some hesitation from industry to update/improve outdated manufacturing processes and methods that pose quality risks, such as product contamination, excessive process variability, and lack of consistent product quality. Regulatory authorities approved these processes and methods several decades ago, and there is the perception that change is not needed because they have been "working fine as-is." Additionally, there is cost and time associated with having major changes approved. However, outdated processes and methods can lead to serious agency action because they may not be sufficiently in control under today's standards. It might take time to happen, but a process that is not designed appropriately to mitigate quality risks will almost certainly experience a major quality event in the future. When a quality failure happens, regulators will demand the changes and the associated time and cost to accomplish these improvements will be much higher.

Economic drivers

The recent economic crisis has not been helpful at maintaining investment in quality and compliance. There has been more pressure than ever to send batches out the door. Trained personnel have been laid off. Manufacturing campaigns tend to be smaller and there are more product changeovers. Training is frequently the first quality element to experience cuts because of economic pressure. The industry is having to do more with less, leading to increased pressures on systems and personnel.

Pipelines

The pharmaceutical industry is not producing the blockbuster drugs of the past. Stakeholders are more demanding as healthcare costs continue to skyrocket. Patients are becoming more involved and demanding about their health. Additionally, there have been several R&D disappointments in recent years that have led to dried pipelines, decreased company profitability, and lowered employee morale—each a major challenge to innovation and growth. Situations like this have led to a slew of industry mergers and acquisitions designed to foster increased profitability and growth but at the same time have significantly altered the landscape of the industry, producing new challenges.

POTENTIAL SOLUTIONS

Change is always difficult, and the transformation of quality requires time and resources. However, we see the following potential solutions.

Embrace simplicity

Common sense and simplicity sometimes appear to be lacking. More complexity does not make better science. Paperwork and bureaucracy have increased to a point where they impede proper functioning of the quality and production systems. Management must look for new ways to provide the proper support, tools, and resources to help their personnel accomplish their jobs, and strive to be more effective facilitators of needed change.

Foster individual commitment and collaboration

No one functional unit can assure high quality and compliance, not even the quality assurance department. Instead, it must be a collaborative effort across all functional areas starting with each individual employee. This is particularly true in manufacturing, where they are the experts in the technologies and processes they use—and the first line of defense to assure the uninterrupted supply of high-quality products to the market. Manufacturing can't be successful on its own. The quality unit is needed to help assure the proper systems are in place, monitor those systems, and provide guidance when needed. To do this effectively, quality needs to have a presence on the shop floor. This helps the quality unit better understand the processes and technologies being used as well as the issues and challenges that can occur.

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Getting everything done now

When people rush, mistakes happen, particularly when planning and preparation are inadequate for the task at hand. It is more difficult to correct problems after they happen than to prevent them from happening. It is better to devote the necessary time and resources in the planning phase. There needs to be a shift in thinking, attitudes, and behaviors so we don't place our companies, employees, and patients at risk when getting things done "now" is valued more than doing what is best for the situation at hand.

Use technology efficiently

Technology should introduce simplicity and efficiency, not complexity and inefficiency. Great technologies can become great impediments quickly. Unfortunately, there is no single technology that will solve all problems. Each technology must be evaluated for its benefits as a tool to improve manufacturing and product quality.

Employ effective risk management

The pharmaceutical industry must learn to assess and manage risk better. Risk management is a fundamental tool to help identify and remediate the challenges that may arise in support of attaining high and consistent quality. However, it has only recently been incorporated into the pharmaceutical quality system and has not reached its full integration and potential yet. Improvements must be made in the way risk assessment and analyses are performed and documented.

SUMMARY

The recent surge in the number of enforcement actions suggests that the current state of quality and compliance in the pharmaceutical industry is far from optimal. While some advances have been made, it appears little progress has been made in others. Advances in technology and quality initiatives have not on their own resulted in improved product quality or better-controlled manufacturing processes. The causes are varied and frequently interrelated. Let's take another look inward, as well as outward, to see how best to accomplish the goals we all aspire to with regard to quality. ◆