

BioBenchmarkSM Biopharmaceutical Operations Benchmarking Study

QUALITY ASSURANCE

The focus of the quality assurance (QA) portion of the benchmark study was on those aspects of the business that tend to be the largest problem areas for an organization. Typically, these are activities that limit a company's ability to release product to the market;

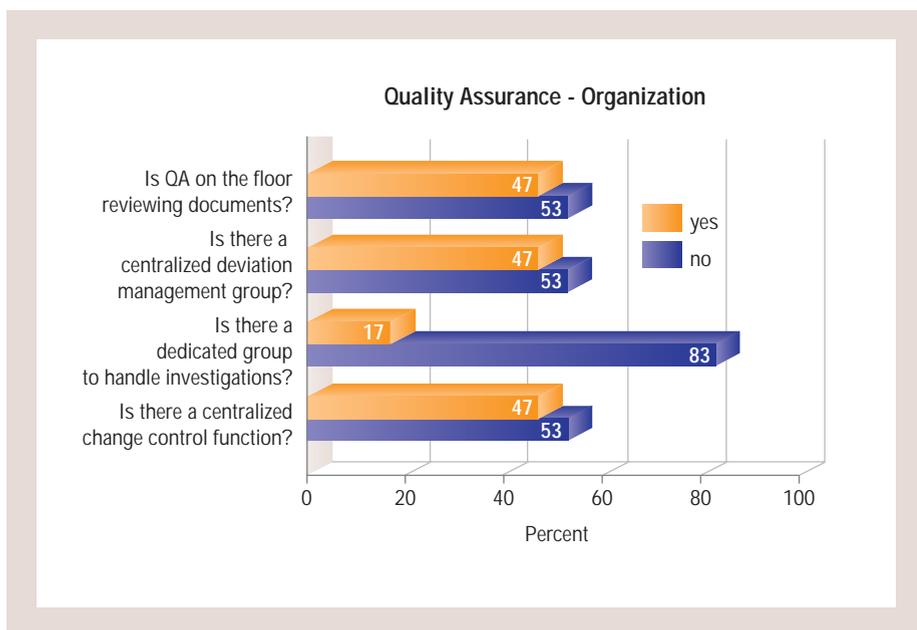
place severe demands on key resources; or expose the company to regulatory enforcement.

OVERALL IMPRESSIONS

More than any other area observed in the study, QA processes are undergoing significant reengineering in most of the participating companies. Either through regulatory guidance (21 CFR Part 11), corporate initiatives (development of global regulations), or recognition of inefficiencies, biopharmaceutical companies are placing a strong, primary focus on improving deviation management and change control processes.

QA processes are most challenging because of their cross-functional nature. The closure of a deviation requires review and actions from manufacturing, quality control (QC), QA, maintenance, and engineering groups. Similarly, change control in many companies is a distributed function, depending on the type of change initiated. This typically results in a process that lacks visibility into the overall number of process changes, along with their monitoring and closure.

As companies grow and mature, many are improving QA processes and gaining further visibility by adopting automated systems. Additionally, companies are restructuring to better focus not just on quality, but also on efficiency. Eventually, overall cycle times in the industry will shorten, and the biopharmaceutical companies will look more like traditional pharmaceutical companies in their ability to produce product and release it quickly and cleanly.



Automation of CAPA Management – What Drives Its Success in the Industry?

The purpose of corrective action and preventive action (CAPA) is to ensure the root cause of any problem is addressed to alleviate current or future problems. Nearly 50% of all 483 citations issued by the U.S. Food & Drug Administration over the past year are related to CAPA management, according to a recent AMR Research analysis.

Overall, CAPA processes require a high level of workflow management, accuracy, and flexibility due to their critical and dynamic nature and are thereby the main drivers of automation. CAPAs are a required quality measure outlined in the CFR 820.100 regulation.

What, then, has been the success of automating CAPA processes? A recent study by Tefen indicated that the CAPA Code measurements for the biopharmaceutical industry – after automation – revealed there were still gaps to close.

The gaps are primarily in the areas of trending – to detect recurring problems – and effectiveness verification of the action taken. Considering these are the two most challenging areas, it is evident there is still much for the industry to do to fully integrate automation into its processes.

ORGANIZATION

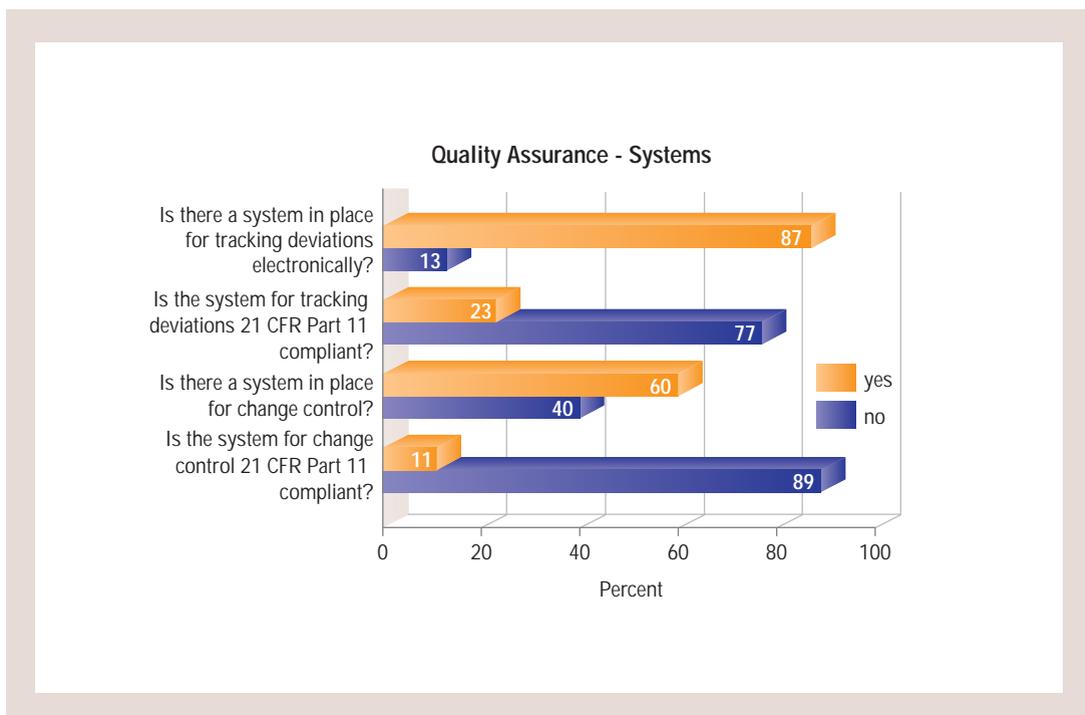
QA's role within the organization has experienced some recent changes. More companies now experiment with locating key QA resources either near production or on the floor, reviewing documents in real-time, and resolving issues quickly. Slightly less than one-half of the participating companies currently post QA members on the production floor, with many more planning to break down the cultural "wall" that has traditionally separated these two groups.

Deviation management is one particularly challenging area for companies today. Many unforeseen deviations occur during complex biopharmaceutical processes, and each needs to undergo a formal investigation to determine the event's impact on product safety, purity, and efficacy. This can be a time-consuming process requiring significant support from engineering and laboratory resources already burdened with their normal day-to-day tasks. More than one-half of

CAPA Code Report Card for the Biopharmaceutical Industry

The CAPA Code is based on a scale of 1-5, where “1” signifies low compliance and “5” signifies high compliance. The biopharmaceutical industry received the following evaluation, according to a recent study by Tefen:

- Analyze all sources of quality data to identify existing and potential causes of nonconformance (3)
- Apply appropriate statistical methodology to detect recurring quality problems (2)
- Investigate the cause (3)
- Identify the actions needed to correct and prevent recurrence of nonconformance (3)
- Verify or validate the actions to ensure such action is effective and does not adversely affect the finished product (2)
- Implement and record changes in methods and procedures (3)
- Ensure information related to quality problems and nonconformance is disseminated to the relevant people (3)
- Submit relevant information for management review (4)
- Document all activities required under this section and their results (4)



the organizations in the study assign a group to focus on deviation management. Although they are not dedicated investigators, these specialists are members of the quality unit who track deviations and facilitate their closure.

Few of the surveyed companies identify a dedicated pool of investigators to handle investigations. When there is such a team, it is within QC environments to assist with laboratory-related deviations. Additionally, companies have, in some cases, put together “tiger teams” of investigators

to work through a particularly large backlog of open issues, but they were disbanded once the deviation backlog reached an acceptable level.

Organizationally, change control is a challenge. Tracking all the open items that might impact the line, and controlling those changes, are distributed functions in most companies. In fact, many study participants had a very limited business review or formal approval process for change control. A best practice from other industries that has yet to cross over into life science is

Key Measures of Quality Systems Performance

	Average	Minimum	Maximum
Bulk Release Cycle Time (days)	89	50	196
Average minor deviation closure time (days)	46	27	90
Average major deviation closure time (days)	56	29	93
Deviations in-process (weeks)	9	3	30

the creation of controls for the process of minimizing change as much as possible, and the requirement within change requests to define not just the quality but also the *business* justification for each change.

SYSTEMS

Having critical, real-time information offers clear visibility into an organization's operating performance and supports the subsequent decision-making process. In quality assurance, a growing number of companies are replacing paper processes with electronic systems well before electronic batch records even reach the production floor. Systems that support deviation management and change control are now used with more frequency. Newer products in the marketplace offer easily configurable, 21 CFR Part 11-compliant software that provides a company with the ability to build business process flows quickly. Some profess to almost completely automate a company's key quality processes, although companies with these systems have only attempted implementation for one or two key processes.

The acceptance of these systems is still not complete. Although many companies already manage deviations in some type of electronic system, most still use home-built databases that typically only manage product tracking – but do not replace existing paper processes. Change control, because of its distributed nature in many companies, is electronically tracked 60% of the time, with only 11% of the participating companies using a 21 CFR Part 11-compliant system to replace the paper process.

Disposition Time

Disposition time, as a single measure, offers a fairly good estimate of a company's overall operational performance. Disposition times can be delayed due to a variety of reasons, including slow laboratory testing processes, production deviations, environmental monitoring issues, and doc-

ument quality. Deviation management, by itself, is often the largest contributor to long disposition times – more than any other process – and so this process is broken out for further analysis.

An 89-day cycle is the industry average for lot disposition – from the time the lot leaves manufacturing to when the final approval is given. As a whole, the industry's biggest opportunity, performance-wise, is in driving this number lower. The cycle time is more than double that of laboratory testing and other release requirements, demonstrating the inefficiencies in this very important process.

Deviations

As for deviations, most companies in the study declared a 30-day closure time in their procedures. However, even the simplest of deviations requires an average of 46 days to close. As a result, deviations are often the limiting component of lot release. Deviation closure issues occur because there is poor visibility of open deviations; investigators are not solely dedicated to the task and have other demands on their time; lengthy laboratory retesting requirements are time consuming, and ownership of the closure process is poorly defined. In many cases, study participants claim that 30 days as a target is an unreasonable expectation, considering the degree of required testing that is necessary to properly investigate an event.

Another contributor to this lengthy cycle time is the overall number of open deviations. Through poor process execution or limited resources, many companies accumulate a significant number of open deviations and expedite those connected to the most "releasable" lots. The remaining open deviations in the backlog are then dropped to the bottom of the priority list until their lot must be released, at which time they become the priority. This constant expediting results in overall higher average closure times and a constant firefighting mode.