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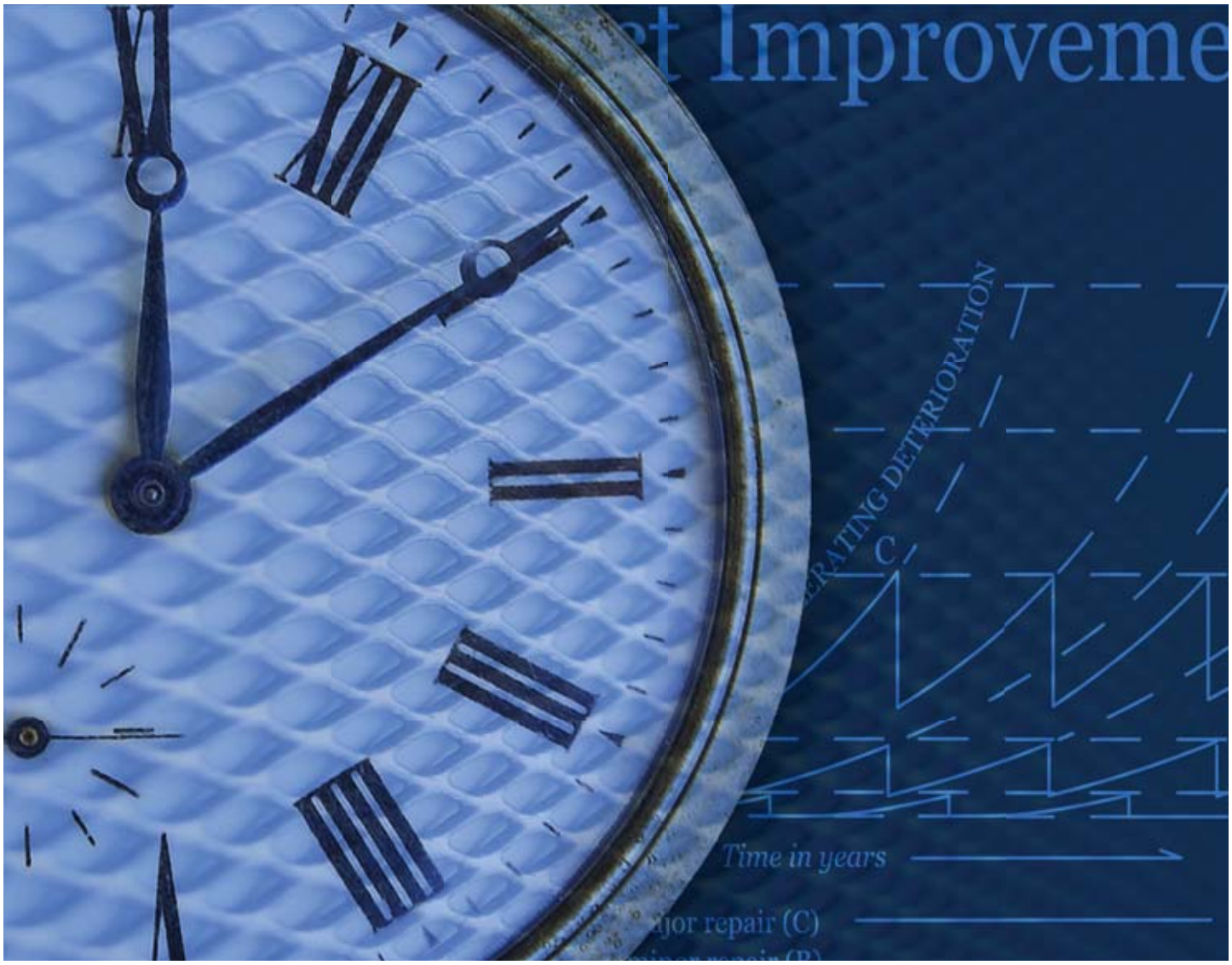
COMPLIANCE SOLUTIONS




# Compliance Under Pressure

## Rapidly reducing deviations and increasing right-first-time – and sustaining the improvements

A global pharmaceutical manufacturer had been unable to correct multiple problems cited in an FDA warning letter for a key vaccine manufacturing facility. In imminent danger of an FDA consent decree, the company turned to Tunnell. Within weeks, Tunnell analyzed the challenge, put subject matter experts on the shop floor in every critical area of compliance and partnered with client personnel to change the plant's way of working.

### The Result:

A new culture of technical, process and leadership skills that rapidly brought the plant into compliance and continues to generate exceptional results.

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**Tunnell rapidly identified three major objectives that would bring the facility into compliance and enable it to sustain improved performance.**

The company faced compliance challenges in two key areas of its operations: bulk manufacturing and capping/inspection. Due to the importance of the vaccines to public health, the FDA required biweekly meetings with the company for progress reports, increasing the pressure for rapid success of the remediation. Working with all deliberate speed, the initial Tunnell team was on-site within one week and comprehensively assessed the situation and identified improvement targets in three weeks. In concert with the client, the project was planned and launched with three key objectives:

- Reduce human-error-caused deviations by 50 percent within six months
- Increase right-first-time performance in batch records by an incremental 30 percent within six months
- Increase collaboration and partnership between Operations and Quality

Tunnell was able to quickly staff the project with 24 subject matter experts in all phases of bulk manufacturing and capping/ inspection. On the plant floor for every shift and working at every level from the union workforce to supervisors to senior directors of Operations, the Tunnell team helped the organization identify the causes of technical and process problems, establish new ways of addressing them, and develop the ability to sustain the improvements for the future.

**Tunnell's ability to manage change proved to be as important as providing technical expertise.**

In addition to technical and subject matter expertise, the Tunnell team brought the extensive experience in change management required to overcome considerable cultural obstacles. Many client personnel, having never worked anywhere else, were entrenched in ways of working far from industry norms. Operations and Quality were rigidly siloed, with Quality people rarely appearing on the plant floor. Friction between the union work force and supervisory personnel hindered cooperation.

Through mentoring, coaching, and improved training, the team helped key personnel develop the leadership skills required to over come resistance to change that occurs when new ways of working push people out of their comfort zones. Working with Tunnell, they were able to break down the walls between functional silos and overcome the resistance of the workforce. Tunnell also provided the context of industry norms of performance in these critical areas, which helped motivate client personnel to make necessary behavioral, process, and policy changes.

**Dedicated teams systematically addressed critical issues in key compliance processes.**

To reduce human-error-caused deviations, the team redesigned deviation management to bring it into line with best practices in the industry, CFR 21, and the corporation's standards. Instead of handing off deviation management to another department, as before, Operations took over responsibility for managing alerts and deviations in real time on the shop floor when the trail is still warm. Deviations are now investigated in a matter of hours, not weeks, and closed faster. Deviation reports, each of which is owned by a single investigator with specific analytical and investigation reporting skills, are succinct and focused on bridging the event from its root cause to the corrective and preventive action (CAPA), all of which helps make recurring deviations rare.

To improve the rate of right-first-time documentation, the team improved cooperation between Quality and Operations. Working with the site's Quality leadership, from supervisor to V.P., Tunnell helped create new roles designed to partner with Operations to deliver quality and compliance in real time, in-process, on the shop floor. A Quality Coordinator was assigned to the area with sole responsibility for compliance there. Compliance Specialists were created to rotate through the Operations area and to spend 80 percent of their time on the shop floor. They now provide real-time, in-process batch record documentation review, and they mentor Operations personnel on compliance issues and decision-making when deviations occur.

Because the site's environmental monitoring (EM) and aseptic practices were thought by the client to be in good working order, Tunnell was not asked to include those areas in the project's scope. However, Tunnell's analysis indicated that EM results showing potential contamination in bulk manufacturing were segregated in the tracking system. Consequently, bulk manufacturing was unaware of the real impact on deviations, 42 percent of which were in fact EM-related. At Tunnell's request, the area was included in the project. Missed EM tests, which were responsible for much of the problem, were then reduced by addressing a key informatics interface and by moving routine testing out of Operations and into EM to improve oversight. Because a significant amount of deviations were also related to positive EM test results, Tunnell worked closely with the shop floor, Qualty and Site Sterility Assurance to improve aseptic practices.

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The goal of reducing deviations caused by human error was reached within one month and within five months the number dropped to zero.

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**In every project in both areas, improvement exceeded 200 percent in every target metric in just six months, and that level of performance is being sustained today.**

In capping/inspection at the beginning of the project, right-first-time performance in batch records stood at only 32 percent (Figure 1). The one-year goal of raising that figure to just under 60 percent was, in fact, achieved within four months of Tunnell's first appearance at the site and exceeded the stretch goal for second quarter of year two shortly thereafter.

Similar results were achieved with batch records in bulk manufacturing. Within five months, the number of errors per page dropped from a high of 3.4 to 0.9, well below the year-one goal, where it has stayed since. The result not only exceeded the project goal, but also surpassed the target of one error per page that the company had previously established as a desired best practice.

**The number of human-error-caused deviations in both capping/inspection and bulk manufacturing has been reduced to zero.**

In capping/inspection, the initial project goal of reducing deviations caused by human error was reached within one month and within five months the number dropped to zero, where it has remained since Tunnell left.

In bulk manufacturing the goal of reducing such errors by 50 percent was reached in three months - well ahead of schedule and in a remarkably short time given the issue - and such errors dropped sharply thereafter (Figure 2). Since Tunnell left, the figure has fallen to zero.

Although only human-error-caused deviations were within the scope of the project, Tunnell's improvements in EM and aseptic practices resulted in a reduction in total deviations in bulk manufacturing (Figure 3).

**The true return on investment (ROI) has been significant and could be extended even further.**

Labor savings from this project are estimated to be 4.3 effort-years of investigating and writing deviations, based on client-supplied labor effort-hours. That means that as a result of this project the client could easily free up the time of four people to do other, more important things. If the project were rolled out to the rest of the site, the number could be expected to climb to as much as 250 effort-years of time freed.

**Results:** Capping / Inspection Right-First-Time (RFT)

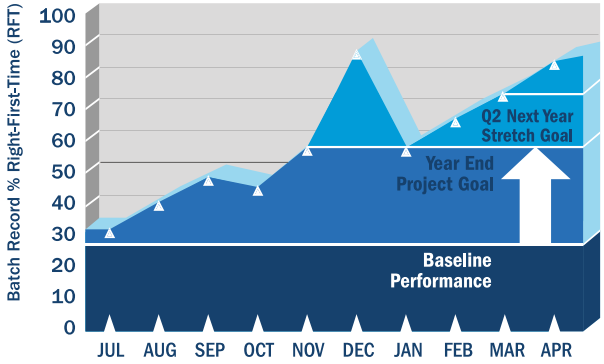


*Fig 1*

**Results:** Bulk Manufacturing Human Error Deviations

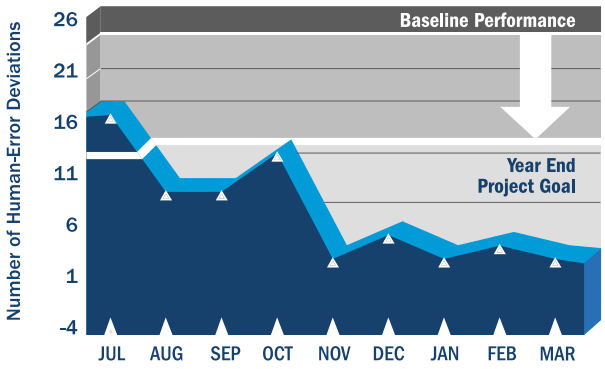


*Fig 2*

**Results:** Bulk Manufacturing Total Deviations

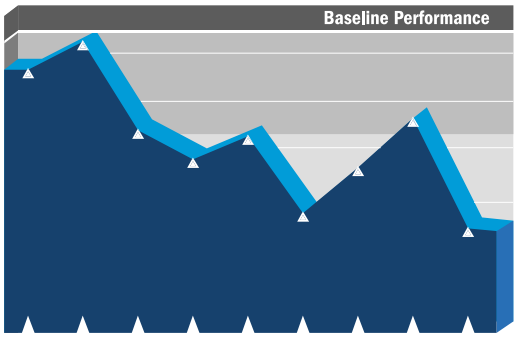


*Fig 3*

In addition to labor savings, other factors that should be considered to calculate the true ROI for a deviation reduction project include: the total cost of minor and major deviations, including labor involved beyond investigation and authoring (meetings, studies, change controls, etc.) and the cost of destroying materials and products.

For this project, the estimated annual true cost avoidance was in excess of $8 million, which equates to a nearly four-fold ROI in one year. If the project were extended to the rest of the site, this figure could be expected to climb to over $40 million. Further, extending the effort beyond human-error deviations into more critical issues could provide even greater savings opportunities. Eliminating critical deviations would avoid distribution center withdrawals and product recalls where hundreds of millions of dollars are lost every year by pharmaceutical companies.

The client more than satisfied the FDA and continues to sustain improved performance. With Tunnell's assistance, the client was able to demonstrate to the FDA that the site could deliver what it needed to do in terms of compliance. As a result, the FDA lifted the warning letter just three months into the project. A month later the agency moved to less frequent meetings with the client because they saw that the company was consistently meeting project deliverables and dramatically improving relevant metrics.

In addition, the client has continued to sustain its improved performance, indicating that the new ways of working have become part of the site's culture, which now sets its sights beyond compliance to a focus on excellence and the business and operational benefits it brings.

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For over 60 years, Tunnell has provided both expert talent and consulting services to clients including Biopharmas, CDMOs, the US Government, incubators, investors and NGOs. We have experience across multiple platforms – including large molecule, vaccines, cell and gene therapy and small molecule – and our subject matter expertise focuses on regulatory, quality, GxP, pre-clinical/clinical, supply chain, manufacturing, CMC and product launch. To learn more, visit us online at http://www.tunnellconsulting.com.

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