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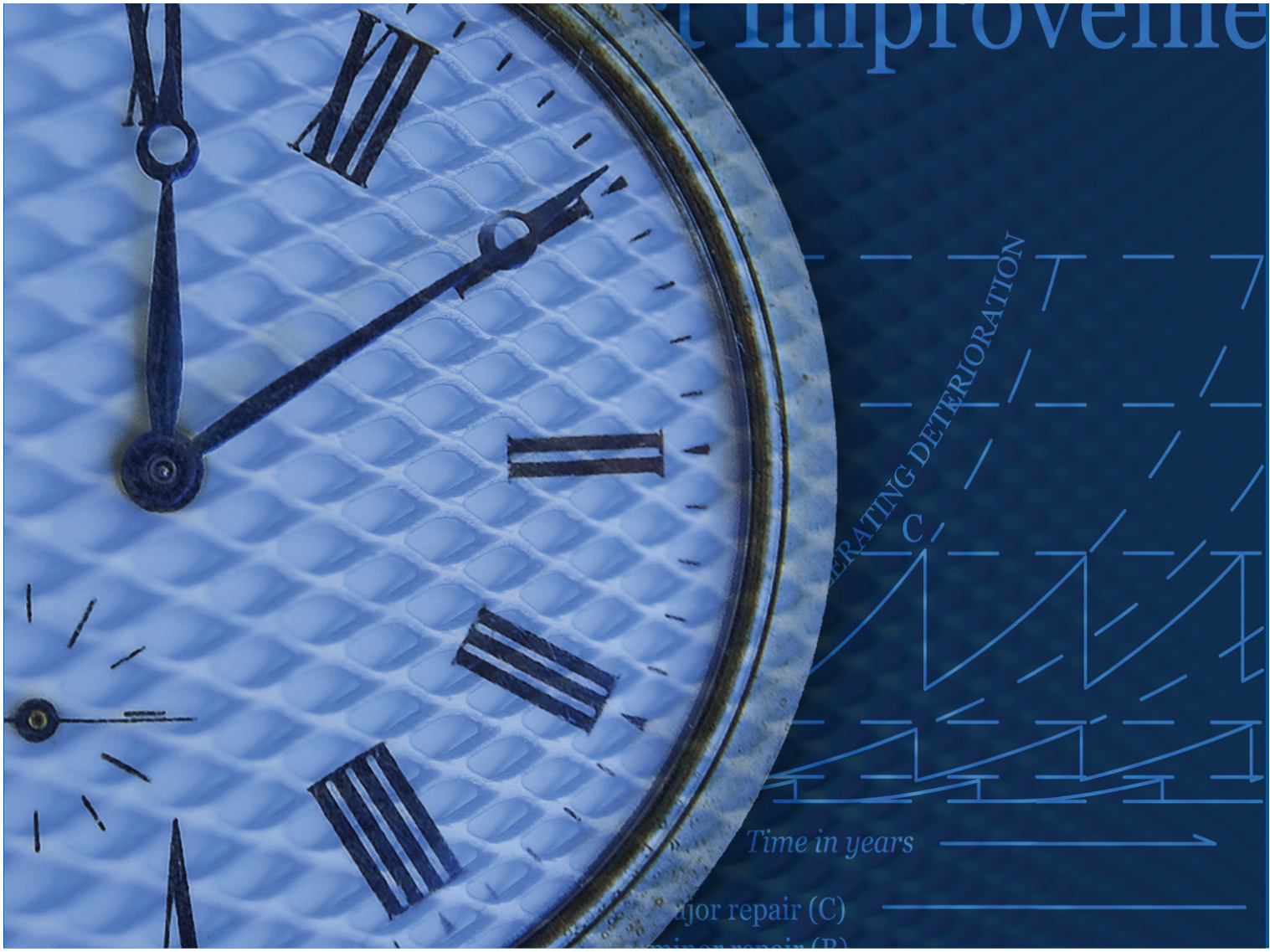

Analytical Methods Certification

Certifying Analytical Methods to Meet Regulatory Expectations

For three successive years a specialty pharmaceutical manufacturer had received FDA 483s that included numerous observations in analytical methods validation. As a result, the agency withheld approval of 11 ANDAs for products that were critical for the company's future. Facing potential closure of a manufacturing site and determined to resolve the validation problems once and for all, the company turned to Tunnell.

The Result:

Acting with a rigor that would withstand an FDA audit, Tunnell reviewed, remediated, and certifi ed 259 analytical lab validation reports, assuring the company that its analytical methods were validated to FDA/ USP/ICH standards. In a subsequent FDA inspection, including a directed audit of methods validation, all 259 reports were found to be compliant with only one minor observation. The lack of any major method validation issues cleared the way for approvals of an NDA and any ANDAs which had been held up due to analytical non-compliance issues. One NDA and one ANDA have already received final approval with 10 other ANDAs pending.

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Tunnell assembled a team that included former FDA personnel representing a combined total of more than 20 years of experience at the agency.

With 11 products stalled due to validation issues, the company faced not only significant delay to market and the possibility of more punitive FDA action, but also shareholder dissatisfaction and reputational damage. The company needed to resolve the issues in advance of a scheduled FDA re-inspection and to have full confidence that they had done so. In response, Tunnell deployed a team of subject matter experts in analytical methods validation, including one former pharmaceutical scientist and three members who had spent much of their prior careers at the FDA.

Tunnell began by carefully defi ning the criteria for providing a Certificate of Validation for Research and Development Submission and/or Quality Control Laboratory Analytical Methods.

At the outset the Tunnell team established clearly with the client the rigorous requirements that would have to be met for certification. Those criteria included:

- All required components (ICH, USP and FDA) for analytical method validation have been executed
- The approved Validation Protocol is consistent with the current best practices and regulatory requirements for analytical method validation
- All analytical validation acceptance criteria are compliant with current best practices and regulatory requirements
- All analytical validation data are within pre-defined acceptance criteria
- The method validation is in compliance with the company's existing approved SOP (Validation and Verification for Phase III and Commercial Test Methods)

To ensure FDA-level rigor, the team undertook a comprehensive review of relevant documents and processes.

The comprehensive certification process began with a review of previous method validations reports. Further, because we have found that the standard gap analysis of analytical methods validation that many companies undertake, usually with the help of a third party, is inadequate, our certification team also reviewed and assessed gap analyses previously conducted. We then reviewed and assessed a supplemental validation protocol to address any identified gaps and generate additional data to ensure the method validation was compliant with current regulatory standards. We also reviewed and assessed the supplemental validation report to ensure that all components of the supplemental validation protocol had been executed in compliance with the protocol and that all data were reported and within the pre-defined limits.

The team worked closely with the company to remediate persistent validation problems and ensure progress.

In the course of our review and assessment of existing validation processes, we uncovered numerous shortcomings, including missing documentation, inadequate QA reviews, faulty change control procedures, failure to follow the company's SOPs, and more. Instead of simply informing the company of these issues, the team helped the company remediate the problems and conducted training with key personnel to prevent recurrence. In addition, the team assisted the company in its preparation for monthly progress reports to the FDA.

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The work culminated with the certificationof 259 analytical lab reports.

Once the components of a method validation package were reviewed, assessed, and—in many cases—reviewed again after remediation, they were compared to a comprehensive checklist of certification criteria. After all certification protocol and checklist criteria had been met and found to be compliant, a certification letter was issued for the method validation package. In all, the team assessed and certifi ed 75 methods for raw materials,61 methods for excipients, and 123 methods for fi nished products and, in the process, reviewed approximately 2,000 reports and their associated data.The company reaped multiple benefits from Tunnell's work.

As a result of Tunnell's comprehensive approach:

- All 259 reports certified by Tunnell passed a subsequent FDA inspection that included a directed audit of methods validation
- The company's stalled drug applications could no longer be attributed to non-compliant analytical method validation
- The cloud of further FDA action was lifted
- The company's processes for analytical methods validation were brought up to standard; key personnel were trained to maintain that standard, and the company was able to go forward with confidence in the manufacturing site

Tunnell brought a unique combination of attributes to the engagement that delivered tangible and intangible benefi ts well beyond the immediate scope of the project.

Working collaboratively with the client but approaching the issues as an independent third party, we were able to win the confi dence of company personnel while achieving uncompromising rigor. The company was able to rest assured that it could resolve the analytical methodology issues slowing down its product applications and prevent similar problems in the future. Just as importantly, our reputation in the industry, based on more than 50 years of helping pharmaceutical companies address critical operating issues, could be relied upon to confer credibility on the company's efforts to resolve those problems once and for all.

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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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