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CASE STUDY

When a Contract Manufacturer Receives a 483

As is the case for many of our clients, regulatory agency observations create an environment of stress as stakeholders assemble to act urgently with the appropriate actions / next steps identified. With contract manufacturers, customers are quick to insert themselves into the remediation process to mitigate risk to their product as well, creating a need for a thorough, robust remediation plan with efficient timelines identified to reduce as much manufacturing downtime as possible.

The Quality & Compliance service within ProPharma is built for supporting clients faced with this situation and are prepared to act / mobilize quickly in all phases of the response lifecycle. An example of a recent response / remediation effort is detailed below which highlights ProPharma's internal diverse expertise and scalable response effort.

Initial intake

A small contract manufacturer received an FDA 483 Observation notice ahead of a holiday weekend. They turned to a law firm specializing in FDA enforcement situations who, in turn, recommended their client reach out to ProPharma based on years of experience working together on similar cases. Initial meetings between the client and internal FDA compliance SME were held within 24 hours of the outreach to formalize a plan for the response.

Over the next three days, the engagement was well organized with daily progress meetings, ongoing response letter edits and a site visit by ProPharma's designated Remediation Lead, which was considered the Phase 2 effort being initiated concurrently with the FDA 483 Observation response submittal.

All of these were collaborative efforts between the client, ProPharma and external legal firm. Based on these swift actions and ability to mobilize an experienced and skilled team familiar with the observations, the team delivered a comprehensive response to the FDA 483 prior to the deadline, setting the tone for the remediation phase to act on the corrective actions established in the response letter.

Remediation

The observations identified in the Form 483 included several system-wide concerns which required a holistic remediation plan to act upon immediately. Systems affected included:

- Incomplete validations, including cleaning and water systems
- Inadequate document control processes, including GDP documentation and document storage
- Deviation management, including incomplete investigations and CAPAs

The remediation plan focused on two discipline leaders: Quality Management Systems and Validation. With experienced and skilled leaders engaged and working together with the client stakeholders, teams were assembled to deliver on the tasks associated with the remediation plan. The client's resources were constrained by day-to-day tasks and limited experience with remediation, so ProPharma led and managed the resource loading associated with the work breakdown structure of the remediation plan. A breakdown of the remediation efforts is summarized below.

1. FDA Updates / Quality Management System (QMS)

ProPharma provided the onsite Remediation Lead to coordinate remediation efforts and timely FDA updates. They assigned skilled resources to complete overdue investigations / CAPAs associated with response actions and document control activities while streamlining and revising QMS programs to ensure alignment with current guidelines.

Additionally, the Remediation Lead identified risks with the current Deviation Management Program and supported identification / implementation of compliant electronic system which encompasses the entire QMS today.

The training program received updates that included:

- GDP training and written assessments to all staff, including job aids for line staff who have English as a second language
- Deviation Management training for Quality and Production personnel
- Mentor Training Coordinator regarding guidance on curriculum and training documentation

2. Cleaning Validation

Numerous GMP production lines were shut down to remediate inadequate cleaning validations identified in the Form 483. The ProPharma Validation Lead deployed a team of cleaning validation consultants, focused on analytical methods and cleaning practices, to assess and mitigate risks associated with each line. Additionally, they worked with client stakeholders on a plan to bring each production line on-line in a phased approach.

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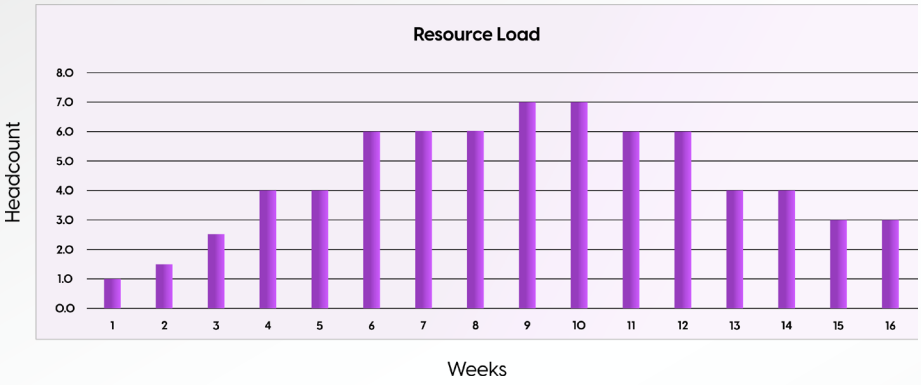
The team utilized Six Sigma DMAIC methodology for the remediation efforts and provided daily updates as part of the ongoing stakeholder meetings, including:

- Defining the cleaning solution and supplier to be used going forward based on assessment and evaluation of current cleaning practices and analytical capabilities
- Product dissolution challenges performed to confirm line cleaning failures with different solutions / temperatures based on identified product contact materials and matrix
- Collaborating with cleaning agent supplier and analytical laboratory to assess analyze data and perform a cleaning program assessment
- Cleaning program improvements made using analytical dissolution data and component assessments

Additionally, GMP Production lines were brought back on-line based on priority using the new cleaning validation strategy / program with continued improvement plans identified as strategic initiatives for the site.

The Results

Over the course of sixteen weeks, the site went through its first Form 483 response and remediation plan / action. ProPharma scaled efforts to ensure cost efficiency by ramping effort up to a peak load at weeks six to 10 and controlled ramp down through weeks 11 to 16.



This cost efficiency was maintained while providing timely and phase appropriate actions according to schedule to ensure production was not down for extended periods of time.

The site has received an Establishment Inspection Report (EIR) from the FDA, completed the response action plan and tasks associated within it and is awaiting routine inspection on a regular cycle. ProPharma continues to support ongoing validation efforts related to process improvements and maintains an open line of communication to ensure the plan is maintained.

ProPharma's ability to utilize in-house expertise across multiple disciplines to deliver a timely response, holistic remediation plan and corrective actions illustrates a highly scalable and flexible approach. Collaboration and transparency between project management and subject matter experts allow for seamless integration with the client stakeholders. ProPharma's project management acts to ensure proper communication channels, robust scheduling and planning and resource loading to achieve maximum efficiency.

Need help remediating a Form 483 or Warning Letter? Learn how our experienced team can help ensure compliance with a tailored remediation and correct action plans. Speak with an expert today.