Paper SA03

Streamlining MHRA Inspection Preparation and Execution in CROs

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ABSTRACT

This paper delves into the meticulous process of readying for and conducting a Medicines and Healthcare products Regulatory Agency (MHRA) inspection at Cytel, focusing on logistics, personnel management, and document handling. Core elements include strategies for preparation and execution, such as preparing interviewees, staff training, managing concurrent sessions, and efficiently handling internal and inspector information flows. A robust framework with defined roles, live demonstrations, and thorough explanations fosters productive dialogue during inspections, aiming to cultivate collaborative engagement with MHRA inspectors to demonstrate regulatory readiness and integrity. Post-inspection discussions have spurred innovative solutions for ongoing enhancement. This paper offers pragmatic insights for navigating MHRA inspections adeptly, stressing the importance of thorough preparation strategies and execution precision.

INTRODUCTION

The Medicines and Healthcare products Regulatory Agency (MHRA) in the UK holds extensive powers and responsibilities to ensure the safety, quality, and efficacy of medicines and medical devices, as well as the protection of public health in general. This paper covers the MHRA's authority, inspection types, and the typical main inspection agenda, using Cytel's experience with a Statutory GCP inspection in September 2023 as a case study.

Cytel's experience with a Statutory GCP inspection involved a nine-month preparation process, culminating in a four-day inspection. The inspection process is divided into three main phases: Planning, Inspection, and Reporting. Post-inspection activities include responding to findings and implementing Corrective and Preventive Actions (CAPA).

This paper provides a comprehensive overview of the logistical challenges, workforce roles, and strategic approaches employed by Cytel to ensure a successful inspection. The insights gained from Cytel's experience offer valuable guidance for CROs and other organizations preparing for MHRA inspections.

REGULATORY FRAMEWORK

MHRA POWERS AND RESPONSABILITIES

The UK's Medicines and Healthcare products Regulatory Agency (MHRA) is responsible for ensuring the safety, quality, and efficacy of medicines and medical devices, as well as protecting public health. This involves a range of powers, including:

- Conducting routine and triggered Good Clinical Practice (GCP) inspections of clinical trial sponsors and organizations involved in the development of investigational medicinal products.
- Requiring sponsors and organizations to take preventive and corrective actions in response to inspection findings, with failure to comply potentially leading to further enforcement measures.
- Taking enforcement actions, such as issuing warnings, suspending or terminating trials, and imposing penalties, in the event of significant non-compliance with legislative requirements or GCP guidelines.

TYPES OF MHRA INSPECTIONS

Among the 2 main MHRA inspection types, Cytel underwent a Statutory GCP inspection in September 2023.

MHRA inspection types include:

- Statutory GCP Inspection ('Routine' inspection): This inspection is performed as part of **the risk-based compliance programme** and can be either systems-based or trial specific: the inspectors will select clinical trials to examine how the organization’s trial procedures are applied. The risks taken into consideration by this programme include internal information about previous inspection history, organizational changes, or intelligence from other external sources. Notification typically arrives by email within 6 months prior to the planned inspection date.
- Triggered Inspection: Triggered inspections are initiated by concerns regarding a clinical trial's conduct, often from sources like serious breach notifications, whistleblowers, or other MHRA departments. The nature of the information determines the level of notice provided, which may be short or none.

ESSENTIAL STEPS AND DOCUMENTS

The MHRA inspection process consists of three primary phases: Planning, Inspection, and Reporting (Figure 1).

- In the Planning phase, the steps include receiving an ‘Advance Notice of Statutory Inspection’ notification, preparing an Inspection Dossier, and developing an Inspection Plan.
- The Inspection phase involves the main site inspection.
- The Reporting phase comprises issuing an Inspection Report and identifying Corrective and Preventive Actions (CAPA).

POST INSPECTION ACTIVITIES

The full Inspection Report is provided by the Lead Inspector approximately 25 working days after the Main Inspection, with updates on any delays.

Upon receipt of the report, the organization has 25 working days to respond in writing and submit a Corrective and Preventive Actions (CAPA) plan addressing all findings. This response must:

- Confirm acceptance of findings
- Assess risks and impacts
- Conduct a root cause analysis
- Develop and document a CAPA plan, including corrective actions (e.g., implementation of new tools) and preventative actions

The inspectors review the organization's response and may request additional clarification. The inspection is closed by the Inspectorate only after the organization and the Lead Inspector have agreed on the CAPA plan, at which point an inspection statement is issued to the organization.

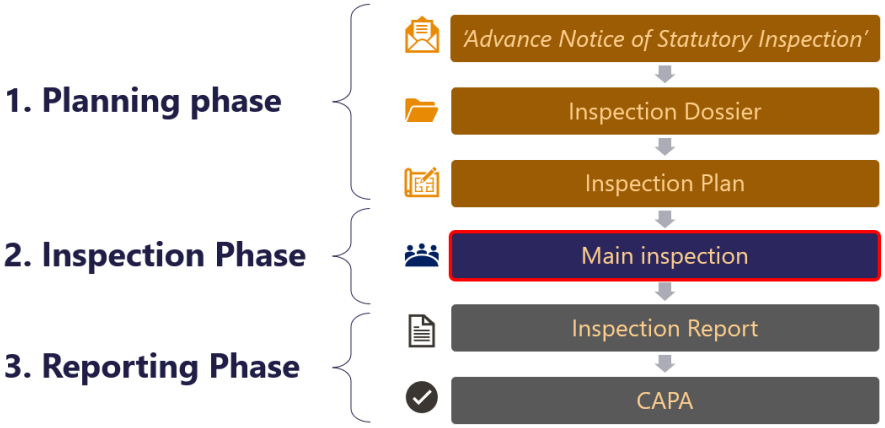

Figure 1. Key steps and documentation involved in the MHRA statutory GCP inspection process.

MHRA INSPECTION AT CYTEL

COMPLEXITIES: ADDITIONAL FACTORS TO CONSIDER

The MHRA inspection at Cytel presented several complexities due to the diverse nature of the four inspected studies, which spanned a wide time range from 2016 to recent studies. This diversity necessitated consideration of multiple factors, including:

- Multiple versions of Standard Operating Procedures (SOPs), Working Instructions (WIs), and Related Tools (RT) being used concurrently, including new, obsolete, and superseded procedures.
- Key personnel changes, such as the departure of Lead Programmers and Lead Biostatisticians.
- Significant internal changes, including systems upgrades (e.g., DMS, HR database, and Statistical Computing Environment) and infrastructure improvements.
- Implementation of electronic signatures, requiring a combination of managing wet-ink signatures/scans and accessing original documents stored centrally for earlier studies.
- Important Organizational restructuring, including the creation of a Cytel DMC Center of Excellence following the acquisition of the company AXIO, which led to significant process revisions affecting blinded data management and DMC sessions.

CHRONOLOGY OF EVENTS

The MHRA inspection process for Cytel commenced in January 2023, nine months prior to the main inspection, which unfolded over four days in September 2023. The key steps are listed hereinafter (Figure 2):

1. The initial communication began on January 12, 2023, when the MHRA issued their first notice to Cytel's Quality Assurance (QA) team. In response, by February 10, 2023, Cytel delivered an extensive batch of documentation covering approximately 300 projects, marking the start of a thorough documentation review by the authorities.
2. As the inspection timeline progressed, a second notice was issued by the MHRA on July 21, 2023, requesting additional documentation related to 12 specific projects. Cytel responded with a second delivery on August 3, 2023, providing the necessary materials.
3. The MHRA followed up with a third notice on August 10, 2023, which included pre-inspection requests for further clarification and supporting documents. Subsequently, on September 12, 2023, Cytel submitted an impressive 950 documents across 23 requests, uploaded to the MHRA website, in response to the third notice.

4. In the lead-up to the inspection, the MHRA issued a fourth notice on September 15, 2023, seeking additional information and access to Cytel's systems for a more in-depth evaluation. Cytel promptly delivered 130 files on September 17, 2023, setting the stage for the inspection itself.
5. Conducted from September 18 to 21, the main inspection involved 13 meetings held over 4 days, averaging 2 hours each, between inspectors, the QA team, and relevant stakeholders. The inspectors made 63 requests across 24 areas, demonstrating the thoroughness of their evaluation.
   Meetings included notably formal interviews, 'show and tell' sessions, and document reviews of trial documentation, SOPs, and training files.
6. Following the inspection, Cytel received the official MHRA report on October 25, 2023, detailing the findings from the inspection. In a timely manner, Cytel submitted their responses to these findings on November 29, 2023, marking the conclusion of a rigorous and comprehensive inspection process.

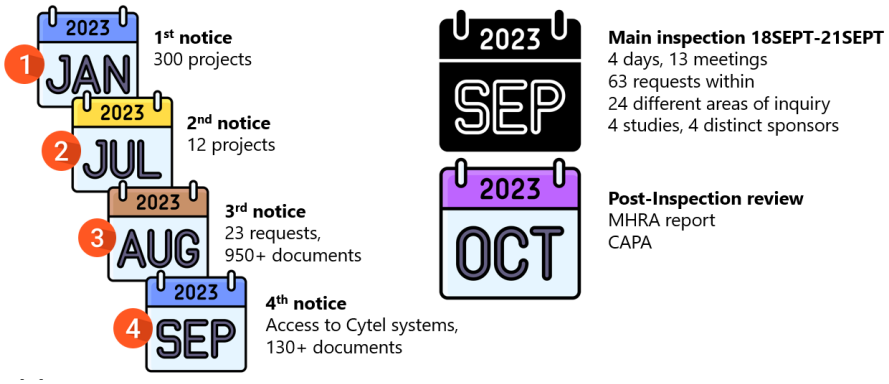

Figure 2. Essentials steps in the MHRA inspection process conducted at Cytel in 2023.

MANAGING THE INSPECTION INFORMATION FLOW

Managing the flow of information during the inspection involved a comprehensive and organized approach, with over 3,000 documents requested and provided between the MHRA and Cytel.

- This exchange was firstly facilitated via very limited and targeted email exchanges between Cytel Inspection Lead and MHRA inspectorate: detailing key inspection documents (including the inspection plan, inspection report), and notifications for document requests, reviews, and transfers, ensuring clarity and efficiency throughout the process.
- A structured preparation of the pre-inspection dossier was conducted, compiling pertinent information in response to the requests outlined in notices one through four, which was subsequently uploaded to the MHRA servers.
- Additionally, the preparation for the main inspection involved conducting internal audits and gap analyses to ensure readiness. Cytel supported requests related to four studies, by setting up within its Statistical Computing Environment (SCE), dedicated areas where access was granted to a copy of the project folders. Copies of the inspected studies were also available for "show and tell" sessions, allowing for effective demonstrations of the processes to inspectors.
- Additionally, secured access to Cytel's infrastructure was provided to the Inspectors, facilitating a seamless review process; Cytel utilized a Document Management System (DMS) that housed Standard Operating Procedures (SOPs), work instructions (Wis), and Good Clinical Practice (GCP) training materials
- A secured platform was created for internal use, enabling real-time editing and maintaining a single, accessible source of truth for authorized personnel, with privileges tailored to distinct user groups based on their roles within the inspection team. Trackers were implemented to manage internal and inspection requests, detailing ownership, request IDs, descriptions, assignments, statuses, and pathnames, ensuring meticulous oversight throughout the inspection. Notably, trial data was not included, only pathways within the Standard Clinical Environment (SCE). The exchange also included augmented versions of main inspection documents, such as inspection plans and reports, inspection notes, and supportive presentations that focused, for instance, on data integrity frameworks, critical processes, and overviews of trials with an emphasis on key topics of interest.

PHYSICAL ORGANIZATION OF THE INSPECTION SESSIONS (18-21 SEPT. 2023)

Cytel aimed to centralize part of its Core Inspection Team at a single EU location to mitigate technical risks, optimize time zone coordination with the inspectorate, and enhance real-time responsiveness. This approach allowed for direct engagement among team members and with the UK Regulation authorities and facilitated parallel sessions as outlined in the Inspection Plan.

The closed room was organized in hybrid mode, with Cytel staff on-site and inspectors attending remotely from the UK. The room was divided into two sections: the front room, where staff interacted directly with inspectors, and the backroom, where multiple team members handled tasks such as scribing, document tracking, and document reviewing.

A standby pool of selected individuals, including subject matter experts, senior management representatives, trial team members for the inspected studies and other specialized support staff (IT, HR, etc.), was also available on-demand to provide necessary assistance during the inspection, as outlined in the Inspection Plan agenda.

WORKFORCE AND ROLES

The resources required to prepare for and conduct the main inspection were substantial, involving over 80 individuals, with only a small portion of the team directly interacting with the inspectors (Figure 3).
Several key roles are essential for ensuring a smooth and effective process:

- the Inspection Host or co-host coordinates the overall inspection activities, facilitating communication between inspectors and the CRO team.
- Scribes accurately document discussions and findings throughout the inspection, facilitating internal debriefing and actions plans while Runners assist by delivering materials and information promptly between different groups.
- Document Trackers play a crucial role in managing and organizing the necessary documents for review, and Documents QC Reviewers check these materials for accuracy and completeness, further contributing to the inspection's success.
- Subject Matter Experts (SMEs) provide specialized knowledge and insights relevant to the inspection topics,
- Senior and Executive Management oversees the process, ensuring alignment with organizational objectives.

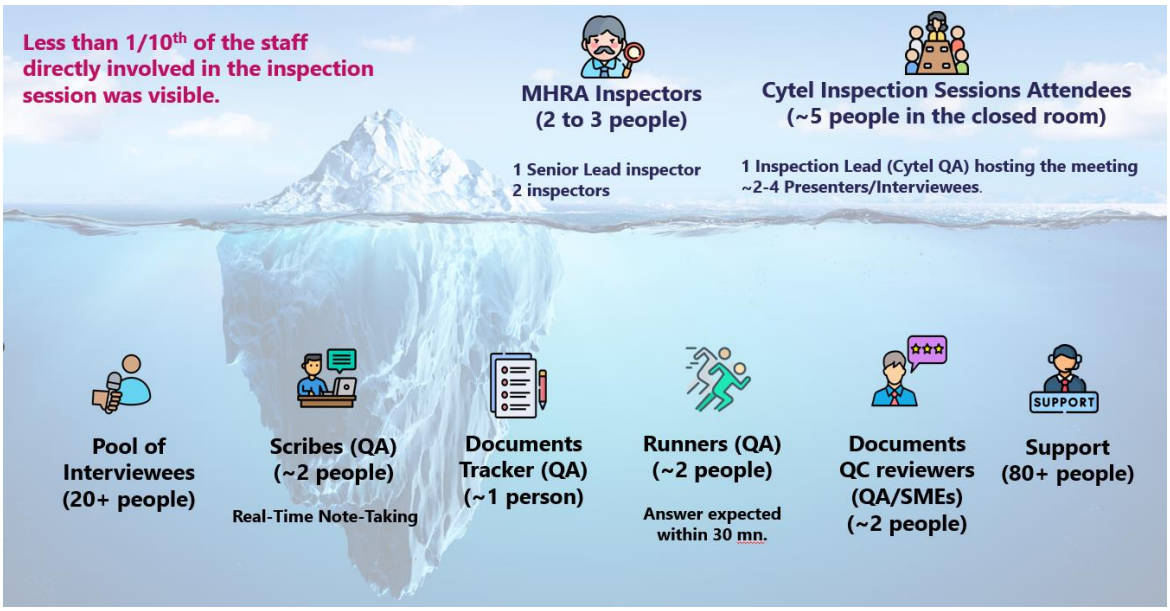

Figure 3. Roles and responsibilities of the workforce involved in the main inspection (18-21 SEPT 2023).

STRATEGIES

FRAMEWORK FOR ENGAGEMENT

We have crafted a targeted engagement framework that defines clear duties and responsibilities, emphasizes collaboration, and fosters productive dialogue. Applied with discipline, the approach based on simple principles enhanced our readiness and clarity when interacting with MHRA inspectorate.

Steering Group and Communication:

- Form a Steering Group led by Quality Assurance (QA) with input from Senior Management, defining clear roles within the inspection team.
- Designate a single point of contact: the Cytel MHRA Inspection Lead, who will notably coordinate communication with the MHRA inspection team and propose revised timelines as necessary, who will also support internal communication within Cytel inspection teams. The Cytel MHRA Inspection Lead hosts inspection sessions and designates Cytel speakers during the sessions.

Resource Management and Flexibility:

- Streamline team involvement and empowerment through an inspection training program; additionally, coaching program for the pool of interviewees. Mentoring performed by consultants being former MHRA lead inspectors.
- Limit number of personnel interacting with inspectors to ease clear, complete and consistent answers to inspectors - preferably, repeated interactions between Cytel representatives and inspectors during the multiple sessions would promote engagement and facilitate open dialogue.

- Allow flexibility in interviews to adapt to any agenda changes. Revision of supportive documents based on debriefing notes. Ability to jump on 'Show and Tell' session on-demand to help inspector to visualize a process.

Documentation:

- Prepare supportive documents to facilitate effective communication and maintain detailed notes of all discussions through designated scribes for internal debriefing with the management team and define associated actions.
- Conduct gap analysis to identify deviations and deficiencies, prioritize the Trial Master File (TMF) and essential documents, and develop corrective action plans.

Preparation and Strategic support:

- Anticipate interview directions by identifying patterns in selected studies and requests - prior and during inspection sessions and prepare slide decks to address accordingly potential questions.

PERSONNEL TRAINING

Obviously, mandatory training on current and historical versions of QA documents, including SOPs, WIs, and related tools, is required to ensure understanding of both current processes and those used at the time of production of the deliverables for each study inspected.

The scope of updates between two versions of quality documents should also be clear to any interviewee, and it is essential that this information can be presented in a way that is easily understandable to the inspectorate.

To prepare for MHRA inspections, personnel have benefited from coaching by former MHRA Lead Inspectors. Mock interviews and role-playing scenarios with former MHRA inspectors as well as with functional leads helped individuals prepare for potential questions.

Additionally, mock live demos have been conducted to simulate anticipated inspection scenarios.

As a note, here is a brief sample of quick tips which might be considered when preparing for interviews:

- Regardless of your position, prepare a one-minute bio, highlighting your role in the inspection team and stating that you are trained on GCP practices.
- Seek clarification if a question is unclear, rather than assuming an incorrect answer.
- Anticipate frequently asked questions (and prepare the appropriate responses!), such as:
    - "*Can you describe how …*" and then *"Can you show me the evidence?"*
    - *"Are you aware of any discrepancies between the documented procedures and the practices employed on the projects within the scope of this inspection?"*
    - *"Would you like to add anything?"*

PREPARATION OF SUPPORTIVE DOCUMENTS

Creating supportive documents provides essential benefits, such as enabling quick access to detailed and precise information during high-pressure situations, enhancing understanding of the procedures and trial materials under review, and preparing tools and responses for anticipated critical discussion points.

Additionally, within our engagement framework, we aim to show transparency with inspectors by addressing identified sub-optimal areas. Our goal is to engage in discussions about these gaps rather than avoiding them. We inform inspectors of these limitations and share our current plans and actions to address and correct them.

Supporting materials could include:

- Cheat sheets: single-page memos are preferred, as they can be kept entirely visible on the desk without requiring manual page-turning or searching. Their purpose is to answer promptly inspectors' requests, without disrupting the discussion flow with the inspectorate. Their content would typically cover Overviews of SOPs/WIs and guidance documents, highlighting key differences between versions of QA documents.
- Slide decks covering processes, overviews, workflows, and the Data Integrity Framework, with a focus on key processes like data unblinding, QC of statistical outputs, and locking and archiving.
- Slide decks for inspected studies include storyboards, study overviews, critical points such as note-to-file and deviation forms, and internal audit findings from inspection preparation.
- Gap-analysis reports detail deviations and proposed corrections, highlighting specific issues such as non-compliant date formats in the Programming Plan and missing signatures in the Programming Master File (PMF), referencing findings from internal audit documentation.

LIVE DEMOS, *'SHOW -AND -TELL'* SESSIONS

By helping to visualize processes, Live demos ensured the perfect understanding of our processes by the inspectorate.

Furthermore, the *'Show-and-Tell'* sessions gave inspectors the opportunity to delve into the intricate details of our practices.

A typical example of a question asked to the Statistical Programming SME by the MHRA lead inspector during those sessions was "*Can you share your screen and show me the execution of all the steps required to produce this summary table of the final analysis of this study, starting with the EDC datasets locked by the data management team?*", then immediately followed by the expected "*Please also give me the evidence and the reference of the standard procedures used for each step*.".

For Cytel, this provided a unique chance for introspection, not encountered before during any audits. Specifically,

these demonstrations enabled us to assess the risks at the intersections of various functions, as inspectors inquired about end-to-end processes involving multiple teams, all of whom participated jointly in the Live Demo sessions.
We also valued those sessions as it demonstrated that there was no disconnect between the staff performing the tasks and the process experts, as the same individuals could address both study-specific and process-related questions. This approach aligns with our strategy to limit the number of speakers, recognizing that each would face considerable pressure during the interview process.
Concretely, a restricted area has been dedicated within our SCE: the study materials from the inspected studies are copied, enabling the on-the-fly recreation of any necessary outputs.
There was an open dialogue between inspectors and Cytel speakers, making the interaction very engaging. Although inspectors are not subject matter experts of our systems and processes, they quickly formulate relevant questions, leading to dynamic and insightful discussions.

POST-INSPECTIONS ACTIVITIES AND ONGOING ENHANCEMENTS

As noted previously, the MHRA issued the Inspection Report 25 days after the main inspection, which formally initiated the CAPA preparation process. This involved notification of the authorities' findings, their classification (Critical, Major, or Others), and outlining the organization's plan for preventive and corrective actions to the MHRA.
Nevertheless, as part of our engagement strategies and framework for engagement, the process for enhancement of quality delivered is an ongoing effort.
During inspection preparation, a combination of gap analysis, internal audits conducted with high intensity, in-depth review and questioning of subject matter experts, as well as constructive dialogue across functions, helped identify potential suboptimal scenarios where improvements could be made.
Those areas of improvement aligned with the Inspectors' findings; such convergence helped to safely and promptly provide a clear resolution plan and the associated roadmap addressing these issues or risks.
To address inspection findings and suboptimal practices identified internally, we have developed innovative solutions.
Based on our experience, adding more processes can increase complexity and reduce overall robustness, leading to non-compliance. We have adopted a disciplined approach to refine our processes and eliminate root causes, aiming to streamline practices rather than adding new steps.
As an example, notably, our efforts in tool development have paid off, such as implementing Checksum algorithms to electronically ensure data integrity when generating summary outputs, thereby eliminating the need for manual steps as well as their associated required (manual) documentation that could be prone to errors; even though the original SOP itself might be satisfactory from an auditor or inspector 's point of view, this resulted in complex practices, which were favoring non-compliance or situations when practices were simply having gaps. As a side effect, this also helped to gain effectiveness.

CONCLUSION

Solid infrastructure and strategies are required to decrease unpredictability during inspections and increase the chance of success. This underlines the importance of organizational maturity. Furthermore, it highlights the logistical complexities of inspections, which cannot be left solely to external QA consultants. Overreliance on external consultants jeopardizes not only the inspection results for the company inspected but also, ultimately, for CROs, their clients' interests.
Also, a comprehensive understanding of all factors involved in the conduct of all studies is crucial, eliminating excuses about lacking information from clients or contracting partners.
Inspectors excel at integrating complex information and engaging effectively with experts in their field. At the forefront of the disciplined and rigorous approach that requires such level of scrutiny in a health authority inspection, the company seized a unique opportunity to enhance the sophistication of its engagement framework while ensuring effectiveness in its continuous improvement efforts, even considering the robust nature of its existing processes and practices.

RECOMMENDED READINGS

- MHRA Guidance *'Good clinical practice for clinical trials'* https://www.gov.uk/guidance/good-clinical-practice-for-clinical-trials
- MHRA *''GXP' Data Integrity Guidance and Definitions'*: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/687246/MHRA_GxP_data_integrity_guide_March_edited_Final.pdf

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