Paper SA03

Health Authorities Inspections: What to Expect? A Statistical Programmer Experience

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ABSTRACT

A crucial aspect of clinical trials is the submission to the regulatory authorities, not only for the pharmaceutical companies manufacturing the compounds, but also for the Clinical Research Organizations involved in the projects. It's imperative that when submitting data analyzed in clinical trials we follow all necessary regulations, such as GCP or guidance developed by the regulatory body themselves, as well as our company processes. It's likely once a project is submitted to the appropriate regulatory authority, as a programmer, you will be expected to respond to queries/feedback and potentially take part in an inspection.

The purpose of this presentation is to share Cytel's unique experience of being involved in a simultaneous EMA/FDA inspection and highlight the different approaches and expectations of the regulatory bodies. We will discuss the preparation and training, the extent of our input during the inspection, common challenges we faced, and the outcome/feedback of the inspection.

INTRODUCTION

The purpose of this paper is to discuss Cytel's experience from actively taking part in a regulatory inspection of a sponsor who submitted an application with the EMA (European Medicines Agency) and FDA (Food and Drug Administration), specifically from a statistical programmer's perspective. Of course, there are many participants usually involved in regulatory inspections, ranging from the sponsor themselves, to external vendors and CROs (Clinical Research Organizations), but covering the roles and responsibilities of such participants belongs to a larger, more extensive paper, and thus, is not considered within the scope of this document.

Secondly, an additional subject which is not thoroughly discussed in this paper, is general maintenance of audit readiness in preparation for any internal/external inspection as a prerequisite for a larger scale regulatory inspection performed by a health authority. Obviously, this is still a hugely important aspect, which directly overlaps with the requirements and responsibilities of any participant or entity who's involved in a health authority inspection.

WHAT IS A REGULATORY INSPECTION

Health authorities routinely will conduct inspections and assessments to determine if a company is compliant with any regulations or applicable legal requirements. The inspection process is an integral step to ensure safety and efficacy in any products manufactured for widespread use. There are several different types of inspections that can occur during different periods (prior, during or after) a clinical trial, but typically the most common type of inspection that a statistical programmer is likely to be involved in is a pre-approval inspection. A pre-approval inspection essentially verifies if the manufacturer who submitted the application to market a drug is capable of doing so as described, and if the data included in the submission is accurate and reliable.

HOW TO PREPARE FOR REGULATORY INSPECTION

COMPANY PROCESS COMPLIANCE

Once an inspection is confirmed, the first step is to adequately prepare and undertake any training necessary to ensure a successful outcome. Notably, it will mean the revisiting of any pertinent SOPs (Standard Operating Procedures) to confirm that all the work completed on the project has been compliant and follows all company defined process, both for the CRO and the sponsor, and all the necessary documentation is in place. To prepare for Cytel's involvement in this particular inspection, we luckily already had some internal training courses to complete specifically for inspection readiness, followed by several external training sessions hosted by the sponsor. If all project work carried out followed SOPs, Wis (Work Instructions), and applicable audit readiness training, this step should be relatively brief and straightforward.

MOCK INSPECTIONS

Another useful practice is to undertake a mock audit/inspection (i.e., a simulated inspection with people role playing as inspectors), preferably led by someone who has experience with regulatory body inspections and/or even formerly worked for them. In our case, the "lead investigator" role was undertaken by someone who had directly worked for the FDA as an inspector in the field, conducting real clinical investigations and having been involved in numerous inspections. The mock inspection was scheduled to take part over the course of one working week, on site for the

sponsor with Cytel team members dialing in via teleconference. Much of the internal preparation leading up to the mock inspection simulated the steps we'd have to follow for the actual event, and thanks to the practical experience and insight of the "lead investigator" it certainly provided an element of realism. As discussed in the training, we received a proposed inspection agenda the week before and had scheduled times for interviews with the inspector. This gave us time to prepare, and a rough idea of topics may be brought up during the mock inspection. We also received numerous requests during the mock inspection, intending to mirror the pace and intensity of a real inspection. This process proved to be very beneficial for all those involved and provided a great opportunity to put all the aforementioned training into practice.

STORYBOARDS

A great way of preparing for a regulatory inspection is to create storyboards for the submitted projects. You certainly need to know all the key events that happened during a project and why particular decisions were made, as you will most certainly be asked about them. For example, for this particular project we experienced a fairly unique situation where the datasets, TFLs and CSR were considered final, until Cytel were informed of an external file that we needed to incorporate into our SDTMs, to use as part of the analysis. This meant that we had to re-run everything that was previously considered final, and essentially had two final versions of the same CSR which we knew would be a point of particular interest to any regulatory authority. Prior to the commencement of the mock inspection, all the Cytel representatives listed all the milestones and dates of particular importance and created a centralized file which contained all this information. This document included certain delivery dates, any significant updates made to datasets/documentation, and the dates when any noteworthy issues were raised by Cytel and/or the sponsor. From the inspector's point of view, if you're able to demonstrate and conduct a knowledgeable and professional interview, it will improve your reliability and credibility during the inspection process.

STUDY SPECIFIC DOCUMENTATION

If necessary, it's also a good idea to document all possible process deviations relevant to your line function and be sure to know the ins and outs of a given issue, as it's highly likely these will be discussed. Even if these were client requests that deviated from a standard process, it's always good to have the supporting documentation to prove the proactiveness of the CRO in recording such scenarios. For example, receiving an external file from the sponsor to include additional flags/comments that were not present in the CRF or external database to present in the listings. If the decision and rationale for this action is well documented somewhere (e.g., the SAP or a note to file), then it's much easier to explain for the inspector to understand.

In most cases, non-conformity to a non-crucial process can be considered normal, assuming there was a documented response or reasoning why this might have happened, in addition to a CAPA (corrective and preventive action) which implements a process improvement to avoid repeating the same situation in the future if required. As the old saying goes, if it is not documented, it did not happen!

INTERVIEW PREPARATION

Regulatory interviews can sometimes have the reputation of feeling more like interrogations, but this isn't necessarily the case. Unfortunately, however, if you don't answer their questions adequately, it may not be far from the truth! Be sure to answer as clearly and succinctly as possible, and don't be afraid to say you don't know, or can't offer a valid answer, as this is much better than guessing/speculating. It's usually acceptable to mention you will investigate this point and come back to this request before the end of inspection (they certainly will not forget). If you're asked a particular question, it's important to only answer that question without offering further information beyond what is required. Another point to consider is to not be afraid of any awkward silence. During an inspection, the interviewers will often use techniques to keep people talking to extract as much information as possible. An example of this is being subjected to a long pause after you finish answering a question to encourage the interviewee to continue speaking. If you have nothing more to say and have answered their question to the best of your ability, then resist the urge to continue talking! Interviewers will also pick up on imprecise language (such as "I think" or "I believe") and dig deeper into any potentially vague answers you give, so be confident and prudent with your choice of words. It's also likely they will ask the same/similar questions to different line functions to check for any inconsistent responses, so be sure everyone is prepared for expected questions if possible.

REGULATORY INSPECTION OVERVIEW

COMBINED INSPECTIONS

With the ever-increasing scale of the pharmaceutical industry continuing to trend upwards, regulatory collaboration is also becoming more and more important. The EMA and FDA have formally been collaborating for almost 20 years, but in 2017 they signed a mutual recognition agreement meaning official collaboration on inspections will only become more common. Lucky enough for us at Cytel, we found out that the upcoming inspection was set to be a joint investigation by the EMA and the FDA. Whilst this was certainly a daunting prospect, it offered a unique experience, and something Cytel had not been involved in before.

Whilst the EMA and FDA are completely different organizations, and a comparison of their standards, regulations and expectations belongs to an entirely separate paper, from a statistical programmer's perspective they do have some identifiable differences. Of course, this is only based on Cytel's observations and anecdotal experience with this joint inspection process, requests, and interview questions. In a nutshell, our impression was that the EMA mainly focused on process conformance and documentation whilst the FDA predominantly concentrated on data, data transformation and statistical methodology.

As most programmer's know, the FDA standards are generally more stringent particularly for programming for data submissions (we've also all likely read a lot of FDA guidance throughout implementation guides and typical methods/responses when handling Pinnacle 21 findings). Although the sponsor submitted all outputs and datasets to both the EMA and FDA, it was the FDA who had more compliance focused requirements, and some requests received were related to this (we will discuss the requests in subsequent sections).

Since submission activities had been completely externalized to Cytel for this particular project, this meant we handled all operational Biometric aspects of the submitted studies. This of course was a huge responsibility for Cytel to act professionally and absorb the pressure throughout the inspection.

PROCESS OF THE INSPECTION

From the sponsor's side, obviously the inspection process is a lot more long winded, but since this paper details the experience from a Statistical Programmer's point of view, I will only discuss a portion of the procedure. After all the preparation and training is complete, then hopefully everyone involved should be ready for the real thing! The first thing you should be made aware of is the date(s) and duration of the inspection, which of course the sponsor is informed and responsible to communicate to all relevant parties. The inspection agenda is usually communicated in advance, although you may only receive a detailed schedule one week before the inspection is due to commence. However, don't become too familiar with the agenda, as it's very likely it will change throughout the inspection. Not only is this another technique to keep everyone involved on their toes, but it also depends on how the inspection tends to evolve. For example, the investigators may focus more on a particular area of a study, whether it be related to the clinical side, manufacturing, data management or statistics and programming. It could also be specific to a set of key data, perhaps of particular importance to the primary endpoint. Obviously, all studies are different and have different circumstances, but if you think it's probable one area of a project could be of interest and investigated deeper then there's a very good chance you'll be correct!

You will also need to identify key people to be involved in the inspection and interviews. Usually, for simplicity purposes, this should be limited to one person per function to represent their respective department and expertise. For example, from Cytel, we had the lead Data Manager, lead Statistical Programmer (myself), lead Biostatistician, Project Manager, and a QA Representative. It is possible to have other people available who could offer additional insight if required, but this is typically limited to specific requests that could come from the inspectors. From the detailed agenda, you can anticipate when you will be required, and have a good idea of what you'll need to discuss.

Per the agenda, one of the first sessions involving Cytel was to provide an overview of our services, processes, and responsibilities a few days prior to the first scheduled interviews. However, don't let your guard down, as in our case the inspectors politely interrupted and asked many questions and sought clarifications. For example, whilst presenting slides explaining the responsibilities of statistical programmers, what was originally planned to be a high-level overview programming processes, turned out to be quite an in-depth Q&A session with the inspectors.

INSPECTION REQUESTS AND EXPECTATIONS

As previously discussed, it's now common practice for different health regulatory bodies to work closely together on an NDA (New Drug Application), so we anticipated that we may receive requests about certain topics, from the perspectives of both the FDA and EMA. By the time the scheduled interview portions of the inspection commenced, our instincts proved to be correct, and it was clear which data were the focal point of their requests. The requests would come from both organizations simultaneously, with the EMA generally requesting documentation and process related information, whereas the FDA requested mainly additional data, subset datasets and ad hoc outputs. It became quickly evident that we didn't have much time to query, prepare and deliver any requests, so acting quickly and efficiently is crucial. Although, it wasn't uncommon for the first question from the inspectors to be: "when can we expect to receive this?", they were open to discuss and agree to realistic timelines.

Per our training and preparation, it's recommended to have specific roles for all people involved. For example, one person's role could mainly focus on documenting all requests received (trust me, there will be a lot), whereas someone else would actively respond to questions and fulfil requests (typically the functional leads). It was incredibly useful to refer to the internal centralized request tracker we had in place to keep on top of what was being asked of us, and I strongly recommend having someone take up this role.

A lot of the requests centered around providing different pieces of documentation or any other documents of interest. For example, a key focus of the statistical programming session was to provide all proof of QC (Quality Control) documentation for certain deliverables and even in one case to show examples of our internal issue logs, where we store QC comments. These requests were mainly from the EMA, but at times it was difficult to identify the origin of

the request, as it was obvious the regulatory bodies had planned and orchestrated a lot of these in advance. From the FDA inspectors, we had numerous requests to provide additional datasets (mostly subsets of SDTMs, ADaMs already submitted, focusing on one parameter for example), programs (not including those already submitted) and ad-hoc outputs on some topics that had come up during the interviews. Initially for some of these requests, we tried to create ad-hoc SAPs and TFL Shells to outline the basic requirements where possible, but for a significant portion of the tasks this wasn't feasible, due to the time constraints. This presented obvious difficulties, as we'd need to produce datasets/outputs without much/if any reference documentation – a programmer's nightmare!

One unexpected request from the EMA was to provide a live demonstration of Cytel's programming processes, including study area set up, creation and running of programs, internal QC processes, version control and our delivery system. We briefly touched on a point during our training that it's becoming more of a common occurrence to include screen sharing and live presentations explaining briefly how some activities are performed, but we did not prepare for this specific circumstance. I created several outputs during the live demo, and orchestrated some QC scenarios, and how our processes work for proc compare mismatches, outputs passing QC and the subsequent statistician review. Apart from the obvious anxiety inducing side effects of explaining all the above during a live demonstration to a room full of experts, it was also important to maintain complete confidentiality of other clients of Cytel, strategically navigating our servers to only show information. If required to present a live demonstration to the inspectors, it is recommended to do this on a "clean computer" which contains virtually nothing but the items to be presented. Due to the limited time to prepare the presentation in our case, it wasn't possible to put this into place prior to the follow-up slot on the agenda. Similarly to the initial presentations of the Cytel services to the EMA and FDA inspectors, this live demonstration was subject to many questions from the inspectors.

CHALLENGES FACED

During the entire process, there were of course many challenges and difficulties as a statistical programmer being directly involved in the inspection. First and foremost, one of the primary focus points was adequately answering and handling all the requests from the inspectors within the specified timeline. As discussed in the previous section, the requests could be drastically different, and often it was not obvious which should take precedence (for example the EMA requesting QC documentation for a certain delivery, whilst the FDA have simultaneously asked for some additional tables). In such situations, the inspectors are usually happy to negotiate within reason. Additionally, the duration of a typical FDA inspection is in the region of 3-6 consecutive days, however in this case, the inspection lasted a grueling 2+ weeks (the majority of which was in person, with the final stages performed remotely). During this time, it was obvious the agenda was a flexible and living document, with interviewers' questions branching into separate topics which were not initially considered in the plan. As a result, at any moment your presence could be requested to attend an unplanned interview about a particular matter, oftentimes leaving little time to prepare.

Although the mock inspection and preparatory trainings were extremely useful, many events transpired in a completely different way during the real inspection. Obviously, it's not possible to predict everything for a regulatory inspection, and naturally the investigation will evolve based on the information the inspectors collect. On a personal note, it was my first time directly taking part in a regulatory inspection, so it was certainly a nerve-racking but valuable experience.

In parallel to the EMA and FDA inspection, the FDA Reviewers were also in the process of assessing all the documentation (SAP, CSRs), datasets, TLFs, define.xmls and reviewer's guides as part of the submission package. As a result of the FDA's Reviewer's evaluation, independent of the ongoing inspection, the sponsor received a formal Information Request (IR) letter which consisted of additional analyses and outputs required to be created by Cytel. From our perspective, this was not expected and something we didn't account for during our training and preparation for the inspection. We had to quickly assess the IR and coordinate the additional work to fulfil the demands, whilst still negotiating the ongoing requirements of the inspection. This situation proposed resourcing constraints and a necessity to prioritize accordingly.

Finally, we faced an unexpected internal challenge which was not related to the inspection itself. Indeed, the Russian invasion of Ukraine started at the same time of this inspection and impacted this particular project as a number of programmers were based in Ukraine and unable to work full time during this period, meaning a limited number of staff with working knowledge of the submitted studies were available to support any requests.

OUTCOME AND CONCLUSION

At the conclusion of the joint inspection, the inspectors raised all preliminary findings, and often categorized as minor or major, depending on all the items submitted and interviews conducted during the preceding 2-3 weeks. The findings raised at this point can be subject to change and are dependent on any outstanding and open request and also once the inspectors have had more time to review all feedback received. Luckily for Cytel, the outcome of the inspection was very positive and resulted in no findings, and as a result strengthened our relationship with the sponsor.

This experience was valuable for Cytel and offered several items for future learning. It also identified several areas for procedural improvement, baseline inspection readiness, which in combination will help prepare for future regulatory inspections. It also demonstrated how in-depth the regulatory authorities' investigations are, leaving no stone unturned during the meticulous reviews they perform. In turn, this should remind us of the importance of our processes and work as statistical programmers, meaning we unfortunately cannot simply bury our heads in SAS and hope our programming skills will speak for themselves!

On a personal level, this was also the first time being directly involved in a regulatory inspection, aside from internal/external audits. It provided a great learning experience and I gained a new insight into the process of being involved in a data submission and an associated inspection.

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RECOMMENDED READING

"What auditors want": Cedric Marchand and Angelo Tinazzi, Cytel Inc., PhUSE 2016, Paper RG04.

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