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Machine Readable Data Not Required for EMA… Really?

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ABSTRACT

Per current European Medicines Agency (EMA) regulations the submission of machine-readable data and related documentation is not part of a regulatory filing to EMA. To the contrary, during a routine audit as part of the review cycle for a product being considered by EMA, our organization received a number of cascading requests that, in the end, mimicked a typical electronic submission of data. This paper will discuss our experience, how we engaged with regulators and how we managed the delivery of these items under tight timelines.

INTRODUCTION

Both the US FDA and EMA utilize data provided by Sponsors during the routine audit and inspection process but their approach and involvement of the Sponsor in this process differs significantly.

For the US FDA, you prepare and submit machine readable study level data based on FDA binding guidance [1] augmented with supporting material [2] prior to and during your formal regulatory filing. In addition, you support your regulators preparing for a routine audit by preparing specific content in line with the "BIMO Guidance". [3] This guidance supports planning of bioresearch monitoring activities and facilitates the timely identification of sites for inspection. Deliverables include site level metadata, a set of defined data listings that are produced and organized by study site, and a single, integrated site level dataset that incorporates basic site metadata, safety & efficacy results & the site level and basic financial information at the site level. You typically execute BIMO packages for your pivotal studies.

EMA, currently, has a much different set of expectations for machine readable study data. At the time of submission, there simply is no requirement. The provision of data is limited to a number of ICH defined data listings provided as appendices to your CSR. Furthermore, the decision on which sites to audit is made without the provision of information by the Sponsor beyond typical deliverables such as the CSR and document provided during your regulatory filing. All of the detailed information supporting the actual site audit is requested after the sites have been identified.

Despite these different approaches to the provision of data and contribution to the identification of sites for routine GCP audit, the audit process plays out very similarly in both regions. And, as you will see, EMA eventually gets their full set of machine-readable study data, even if it wasn't provided at the time of submission…

SET THE STAGE – SCOPE OF AUDIT, INITIAL REQUEST

GSK's regulatory filing was a medication used to treat an unmet medical need and was rather urgent at the time of the filing. The program consisted of a single Phase III study and a number of Phase I/IIa studies supporting dose selection and basic safety/efficacy. The focus of this routine EMA audit was two sites from the Phase III study.

On Day 1 GSK received the Announcement of Inspection which included the boilerplate set of inspection expectations and requests for information/documentation as well as identification of the two clinical sites that would be inspected. This notification also confirmed that a routine audit of GSK as a Sponsor would also be conducted following the audit of the two clinical sites.

The identification of number of documents at the study and site level were contained in this initial request. From the set of study level documents, most notably, was a fully published CSR with appendices based on the ICH E3 guidance. What is notable about this is that these appendices provide the full set of ICH defined patient data listings for all subjects in the study. I raise it only because you will see multiple requests for similar sets of data as our experience unfolds.

The other notable request in the Announcement of Inspection was the request for an "Excel ® work book containing data listings for patients recruited at the selected site(s) (see EMA Q&A for further details – [4])." Following this link brings to a lengthy Q&A pages on a number of topics, from handling of investigational medicinal product to the role of the eTMF in the inspection to a number of GCP topics Sponsors should consider as they prepare for, participate in and react to as part of the inspection and follow-up. There was also a statement emphasizing that you should consider and prepare audit materials based on the Q&A document but should not provide any of these data driven materials until contact had been established with the Lead Inspector and that requirements for data listings had been discussed.

SORTING IT OUT

Under the GCP topics is the key topic affecting the provision of clinical data, "How should data be presented when they are sent to the inspection team prior to a GCP inspection requested by the CHMP?" This section begins with a text clarifying the theoretical reason machine readable data is requested – "The data are used by inspectors for review in order to select patients and data to inspect". [4] It also emphasizes that the details in the Q&A document exist to mitigate problems identified with data listings of sub-optimal quality that EMA has received in the past.

This section of the Q&A document is organized into three overarching sections

1. Principles of the type of data that should be present in the MS Excel data listings
2. Format and content of the MS Excel data listings
3. Content and organization of the site level patient data listings

Before I go any farther, I must provide a translation / definition in FDA/PMDA terms. What the EMA calls a data listing in MS Excel format in anything but a traditional data listing. These "data listings" are actually subject level data that, if submitted to the FDA or PMDA, would be prepared and delivered (today) as a SAS transport (XPT) file. [2,3]

Section 1 clearly defines the scope and consistency expectations for the provided data:

- EMA is looking to receive both CRF and analysis data.
- CRF data should include data that is collected in the clinic as well as data that comes from external sources, such as laboratory or pharmacokinetic data.
- **The Sponsor should provide all data for the selected sites (and if requested for all sites in the trial).**
- A statement should be provided to confirm that the data provided for this inspection matches the data used to produce the CSR.

Section 2 goes on to clarify how this data should technically be presented:

- **Names of MS Excel files, worksheets and variables should be self-evident and, if possible, be consistent with the terms used by CDISC.**
- Data should be provided in decoded format. Provision of coded data alongside the decoded data is acceptable.
- Data formats should be consistent with the types of data it is – dates should be numeric, numeric data should not be interpreted as character data in MS Excel, etc.
- Data allowing you to attribute the data to a specific date, visit or study phase, such as VISIT & VISITID, should be present in each listing where appropriate.

Section 3 highlights the details around the site level patient data listings, with a focus on organizing these listings into a number of categories to satisfy reviewer needs, including but not limited to treatment, efficacy, safety and study population.

RESPONSE TO REQUEST

When receiving an Announcement of Inspection from EMA you must prepare and act quickly. In our case the time from the Announcement to site level inspections was a little less than 10 weeks; the inspection of GSK facilities followed approximately 4 weeks later. Your top priority when receiving this Announcement of Inspection is to identify and communicate with your Lead Inspector in order to define program level specific expectations for data delivery.

Our Lead Inspector, along with supporting inspector staff covering all sites in the inspection, made themselves available within a week of the announcement and clarified their expectations and responded to our questions / clarifications, which of note included:

"Data Listings"

- We expect the full set of clinical data for the study, not just the sites being audited.
- We agree that providing the full set of typical CDISC based deliverables (SDTM – data definition file as a define.pdf, SDTM annotated CRF, Clinical Study Data Reviewer's Guide; ADaM – data definition file as a define.pdf, Analysis Data Reviewer's Guide) would be very helpful and would satisfy the need to provide both coded and decoded representations of data.
- Links that were typically active in the data definition file out to the SAS transport files did not need to be modified to open the MS Excel workbook.

"Site Level ICH Listings in PDF Format"

- We expect the site level PDF listings as referenced in the CSR with an associated category.
- Feel free to reuse listings from your CSR that might not match the ICH listings, just make sure you cross reference / categorize them in a document accompanying your provision of the listings.

These clarifications spawned two separate workstreams, one dedicated to replicating the SDTM & ADaM submission data packages in MS Excel, the other working on producing data listings subset for the sites being inspected. The latter was an academic task of first identify the existing data listings that would satisfy EMA requirements, producing these listings for each site and preparing a document that linked each listing to the EMA category it satisfied. We worked with our Lead Inspector to produce and deliver these in short order to ensure they met EMA expectations.

The data listings workstream was a bit more challenging. GSK produced a separate MS Excel file for each SDTM domain & ADaM analysis dataset and then manually assembled them into a single file as requested. The biggest challenge was engaging in non-standard QC activities to ensure that your MS Excel representation of this data accurately represented the original data and at the same time met EMA requirements as described above. Some of the QC steps involved producing the MS Excel representation of the data, then converting that back into a SAS dataset and performing a PROC COMPARE to ensure data was not compromised.

Once this data was provided to EMA it did spawn additional requests for typical data listings that would typically come from the overall review process in a FDA submission. One example was a listing of subjects and container #s of study medication when the subject received study medication from more than one batch during participation in the study. Other similar data-driven requests were made – the point is that these came as the EMA prepared for an audit, not as part of their routine submission review.

CONCLUSION

EMA has so far avoided the provision of machine-readable study data across the full set of studies in a regulatory submission, but not for long. While no one has gone on record, when speaking to a number of representatives of both the FDA & EMA, many detailed discussions and site visits between the two regulatory bodies have occurred in recent years with the goal of defining a process for preparing and providing this information much like the US FDA & Japanese PMDA require it today.

US FDA audit execution is focused on confirming principles of GCP during clinical trial preparation, execution, analysis and closeout; the heavy lifting with respect to preparing and providing data that would contribute to this process is performed at the time of regulatory filing. EMA practices make audit preparation and participation a very data centric activity and at present provide that gateway to machine readable study data that otherwise does not exist in an EMA context. Sponsors should be aware of this expectation and prepare for it based on the clear technical expectations of providing it under tight timelines at the time of routine audit.

REFERENCES

[1] "Providing Regulatory Submissions In Electronic Format — Standardized Study Data" - https://www.fda.gov/downloads/drugs/guidances/ucm292334.pdf Referenced 03 February 2019.

[2] "FDA Study Data Technical Conformance Guide, v4.2 (October 2018)" - https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM624939.pdf Referenced 03 February 2019.

[3] "Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions" - https://www.fda.gov/downloads/drugs/developmentapprovalprocess/formssubmissionrequirements/ucm332466.pdf Referenced 03 February 2019.

[4] “How should data be presented when they are sent to the inspection team prior to a GCP inspection requested by the CHMP?” – Item #7 under ‘GCP Matters’ - https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-clinical-practice/qa-good-clinical-practice-gcp Referenced 03 February 2019.

RECOMMENDED READING

All documents identified in the References section of this paper.

CONTACT INFORMATION

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