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EDITORIAL

Assessing the Current Gaps Associated with Clinical Sample Bioanalysis

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ABSTRACT

Currently, the recently revised ICH E6(R3) Good Clinical Practices Guidance [1] provides no discussion pertaining to the bioanalysis of clinical trial samples. Furthermore, the harmonised published ICH M10 Bioanalytical Method Validation and Sample Analysis Guidance [2] does not refer to Good Clinical Practices (GCP) requirements and therefore the bioanalytical laboratory is left with a significant gap in guidance as to what expectations would be of the regulatory authorities associated with clinical samples in the event of an inspection. The European Bioanalysis Forum (EBF) discussions pertaining to this gap, which have gone on for 15 years, also recognize the blurred lines between the GCP and GLP (Good Laboratory Practices) in the bioanalytical laboratory [3], and even during MHRA (Medicines and Healthcare products Regulatory Agency) inspections in the United Kingdom (UK). The aim of this editorial is to assess the potential regulatory gaps in the bioanalytical laboratory when analyzing clinical samples and provide insight into how the GCPs apply to clinical sample bioanalysis.

Introduction

Currently, the recently revised ICH E6(R3) Good Clinical Practices Guidance [1] provides no discussion pertaining to the bioanalysis of clinical trial samples. Furthermore, the harmonised published ICH M10 Bioanalytical Method Validation and Sample Analysis Guidance [2] does not refer to Good Clinical Practices (GCP) requirements and therefore the bioanalytical laboratory is left with a significant gap in guidance as to what expectations would be of the regulatory authorities associated with clinical samples in the event of an inspection. The European Bioanalysis Forum discussions pertaining to this gap, which have gone on for 15 years, also recognize the blurred lines between the GCP and Good Laboratory Practices in the bioanalytical laboratory, [3] and even during MHRA inspections in the United Kingdom. The aim of this editorial is to assess the potential regulatory gaps in the bioanalytical laboratory when analyzing clinical samples and provide insight into how the GCPs apply to clinical sample bioanalysis.

Potential Gaps in Clinical Sample Bioanalysis

The ICH M10 bioanalytical guidance does reference good clinical practices in the laboratory, but only stating that, "for studies that are subject to GLP or Good Clinical Practice Requirements, the bioanalysis of study samples must conform to those requirements". [2] What those requirements are, as they apply to the bioanalytical laboratory, is not at all defined. The prior EMA bioanalytical method validation and sample analysis guidance [4] did go so far as to reference the 2012 EMA GCP Inspectors' Working Group reflection paper ('Reflection Paper for Laboratories that Perform the Analysis or Evaluation of Clinical Trial Samples') [5]. This EMA reflection paper did briefly, yet insufficiently recommend approaches to clinical sample analysis. Only the Good Clinical Laboratory Practices (GCLP), published by the British Association of Research Quality Assurance (BARQA), [6] provides a more detailed framework on clinical sample analysis; but this guidance is limited to the United Kingdom.

Below is a list of potential gaps in understanding how the GCPs apply to the bioanalytical laboratory:

- Handling informed consent and subject withdrawal
- Facilitating subject confidentiality
- Ensuring protocol adherence and that the bioanalytical laboratory receives a protocol
- Handling of and documentation associated with investigational products
- Addressing unblinding associated with sample analysis, including repeat analysis, incurred sample reanalysis (ISR), and run batching
- Reporting deviations and serious adverse events
- Sample labeling issues and chain-of-custody
- Avoiding and addressing serious breaches
- Data integrity
- GCP requirement for expedited reporting
- Applying fit-for-purpose approaches in the clinical setting

The challenge for the bioanalytical laboratory is that there is not a regulatory prescription to incorporate the processes described in the EMA reflection paper, nor is there any guidance as to what the expectations will be when the bioanalytical laboratory is inspected by a regulatory body associated with clinical trial samples. This paper presents feedback regarding the gaps in the available bioanalytical guidances and describes how GCPs apply to the bioanalytical laboratory.

Pre-Study Audits

The sponsor is responsible for implementing and maintaining quality assurance systems, including ensuring pre-study facility monitoring (pre-study inspection) is conducted and that the trial site(s) will be in compliance with the protocol, SOPs, GCPs and applicable regulatory requirements. The bioanalytical laboratory is obligated to implement the same systems and to facilitate the pre-study facility inspection. The auditor that conducts the inspection or a later audit is appointed by the sponsor and is independent of the clinical trials/systems. The sponsor must ensure that the auditor(s) is qualified by training and experience to conduct the audits properly, and these qualifications should be documented. The sponsor is also required to provide an audit plan which is required to be guided by the complexity of the trial, and the respective risks.

Informed Consent

Informed consent is the process where a subject volunteers to participate in a specific clinical trial after having been informed of all aspects of that trial that are relevant to the subject's participation as confirmed by the subject in writing. It is possible that a subject enrolled in a clinical research study may decide to withdraw from the research, or an investigator may decide to terminate a subject's participation in research regardless of whether the subject wishes to continue participating. If not already provided in writing as part of the informed consent, it will be important to know whether the withdrawal of the subject resulted from a decision by the subject or by the investigator, and whether the withdrawal was from all components of the research study or just the primary interventional component. This will be important when the sponsor informs the bioanalytical laboratory of the withdrawal of the subject's participation in the clinical trial. Under most circumstances, this would mean that the subject's samples are not analyzed, or if they were already analyzed, the results will not be reported. When a subject informs an investigator of his or her decision to withdraw from the research, or an investigator decides to terminate a subject's participation regardless of the subject's consent, the regulations do allow the investigator to retain and analyze data relating to that subject that has already been obtained and recorded by the investigator. Clear instructions must be provided to the bioanalytical laboratory in writing by the sponsor, delineating appropriate actions and ensuring compliance.

Subject Confidentiality

Confidentiality in a clinical research context refers to the researchers' corresponding duty to protect study subjects'

right to privacy. It becomes imperative that there is no data associated with the study and samples that can lead back to a clinical trial subject's personal identifying information. Bioanalytical laboratories must have written procedures describing the processes they need to follow should they receive samples from clinical trials which contain subject identifying information.

Compliance with the Protocol

Protocol adherence is vital for ensuring the safety and rights of the study participants and data integrity. Strict adherence to the protocol ensures consistency and trustworthiness of the data collected and is necessary for statistical analysis and the ultimate findings drawn from the study. Deviations can undermine the validity of the study, and non-adherence could expose participants, lead to regulatory complications, and might even invalidate the study results. The bioanalytical laboratory (investigator) is required to comply with the protocol and applicable regulatory requirements. The investigator/institution should also sign the protocol and is required to document all protocol deviations associated with the bioanalytical portion of the study.

Investigational Products

The investigational product, or treatment analyte, must be manufactured according to Good Manufacturing Practice (GMP). The sponsor is required to provide instructions on the handling of the investigational product. This includes having records with dates, quantities, batch numbers, and expiration dates. There must exist a system of retrieving investigational products and documenting this retrieval and disposition after the trial completion. Ultimately, according to the GCPs, the responsibility for investigational products at the various trial sites and laboratories rests with the investigator/institution/ bioanalytical laboratory. The investigator must ensure that the investigational products are used only in accordance with the approved protocol. For the bioanalytical laboratory, it is necessary to obtain a certificate of analysis (CofA) and the bioanalytical laboratory should not start a validation or sample analysis until it has procured an adequate CofA.

Randomization and Blinding

A fundamental part of blinded trials to have procedures to avoid accidental unblinding of patient samples. However, unblinding will be necessary under the following circumstances: (i) at the end of a trial as agreed upon and documented, (ii) for expedited reporting purposes, (iii) when there are observations of severe adverse events (emergency and safety), (iv) and during interim analysis that must be pre-planned and specified in the trial protocol. For randomization and blinding that are commonly used in clinical research, the investigator should follow the trial's randomization procedures, if any, and, in the case of an investigator-blinded trial, the investigator should ensure that the identification code is broken only in accordance with the protocol. A randomization list should be sent to an *a priori* chosen person in order to preserve any blinding and concealed allocation. The blinded investigators/research team should not see the randomization list during the running of the trial. The investigator should have ensured that a robust unblinding process has been documented and implemented, but the investigator should promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, emergency unblinding to protect trial participant, unblinding due to an observed adverse event).

When it comes to the safety of a clinical subject, unblinding of the clinical samples may become necessary, in which case the bioanalytical laboratory should have documented in a respective SOP the applicable processes for communication with the sponsor, the process of unblinding of the investigational product or clinical subject(s), and who would be responsible for that process.

Reporting Adverse Events and Deviations

An adverse event (AE), as described in the GCPs, is any unfavorable and unintended sign (including an abnormal laboratory finding) or disease temporarily associated with the investigational product [1]. Adverse events and/or laboratory abnormalities, identified in the protocol as critical to safety evaluations, should be reported to the sponsor by the bioanalytical and clinical sites, according to the reporting requirements and within the time periods specified by the sponsor in the protocol. Because the bioanalytical laboratory does not evaluate the results, for instance, for pharmacokinetics, but provides the relevant subject sample concentrations that are then analyzed outside of the scope of the bioanalytical laboratory, it is unlikely that a bioanalytical laboratory would be cognizant of an AE. It is also very unlikely in the bioanalytical space that a serious adverse event (SAE) would be apparent, where an SAE is life-threatening, requires hospitalization, or results in serious incapacity. However, the laboratory may be asked to analyze an unscheduled sample collected near the time of an event and report the result(s) in an expedited fashion.

Serious Breach

A serious breach is defined in the EMA Guideline for the notification of serious breaches of regulation (EU) No 536/2014 as "any deviation of the approved protocol version or the clinical trial regulation that is likely to affect the safety, rights of trial participants and/or data reliability and robustness to a significant degree in a clinical trial." [8] Sponsors are required to immediately report any serious breaches from the protocol within 7 calendar days of the sponsor becoming aware of a serious breach and include an assessment of the likely impact to the reliability and robustness of the trial data and/or safety of the trial subjects, as well as actions taken to prevent recurrence. Likewise, the bioanalytical laboratory is required to notify the sponsor of a serious breach upon occurrence. Any deviations in the protocol, blinding processes, informed consent, and subject confidentiality which have been described previously should be considered a suspected serious breach.

It is required that deviations from the protocol, GCPs, and the applicable regulatory requirements are reported to the sponsor and documented in the bioanalytical study report, and that appropriate actions designed to prevent recurrence of the detected deviations are taken and

documented. Important deviations should be highlighted in the report and should be the focus of remediation efforts, as appropriate.

Data and Sample Integrity

The bioanalytical laboratory should implement documented processes to ensure the integrity and confidentiality of the data, should implement measures to ensure safeguarding of the blinding, if any. The laboratory must also apply quality control to the relevant stages of the study. Quality assurance and quality control activities must focus on the review of critical data, including its relevant metadata. The sponsor is required to pre-specify the data to be collected and the method of its collection in the protocol and ensure that data acquisition tools are fit-for-purpose and designed to capture the information required by the protocol.

The bioanalytical laboratory should ensure that the investigator has access to data collected in accordance with the protocol during the course of the trial. When using computerized systems during the clinical trial, the sponsor and bioanalytical laboratory should follow the requirements for system validation and have a record of all computerized systems, including the systems' validation statuses, a description of internal and external security measures, and a record of the individuals who use the computerized systems.

The bioanalytical laboratory must document the collection, chain of custody, processing, analysis, and destruction of all biological samples. Clinical trial samples must be appropriately labeled so that there is adequate traceability throughout the study, and in such a manner that the subjects' identity cannot be identified. Note that the bioanalytical laboratory should use an unambiguous trial participant identification code that allows identification of all data reported for each subject. Just like the GLPs, the GCPs require that biological samples are maintained at the appropriate temperature throughout their entire lifecycle.

Applying Fit-for-Purpose Approaches

The ICH E6(R3) GCP guidance indicates that the quality of a clinical trial should be fit-for-purpose [1]. The quality and amount of information generated during the clinical trial should support good decision making. Strategies should be implemented to avoid, detect, and address serious non-conformances with GCPs, the trial protocol, and applicable regulatory requirements. Trial processes should be proportionate to the risk inherent in the trial and the importance of the information collected, where risk in this context includes risk to the rights, safety, and well-being of the trial subjects, as well as to the reliability of the trial results.

Clinical trial systems and processes that aid in data capture, management, and analyses, as well as those that help ensure the quality of the information generated from the trial, should also be fit-for-purpose and should capture the data required by the protocol. These should be implemented in a way that is proportionate to the risks to participants and the importance of acquired data [1]. Computerized systems used in clinical trials should be fit-for-purpose, and factors critical to their quality should be addressed in their design or adaptation for clinical trial purposes. Therefore, it is expected that such computerized systems will be validated as being fit-for-purpose.

Due to the utility of biomarkers during drug development and the desire to move towards personalized medicine, biomarker assays have become commonly employed in all phases of drug development. The context-of-use approach should be implemented, making sure that a given biomarker assay is characterized to the extent suitable for its intended use. Biomarker data that impact safety in either nonclinical or clinical studies should be derived from fully validated assays as described in the currently applicable Guidances. [9,10] Biomarker assays that have been selected to support pivotal Phase III studies, the results of which may be included in drug labeling, should also be fully validated. For exploratory biomarkers, which tend to be more common during Phase I and II clinical trials, bioanalytical laboratories use an approach that calls for a fit-for-purpose qualification.

Conclusion

Aside from aspects of the UK MHRA GCLP document [6] and the ICH reflection paper [5], there remains no specific guidance with respect to the GCPs in the bioanalytical laboratory. Without an understanding of the applicable GCPs, the bioanalytical laboratory may not be able to, or have the procedures to, identify the impacts of deviations from a clinical bioanalytical study or clinical protocol. For instance, the current bioanalytical method validation and sample analysis guidance (ICH M10) [2] does not describe considerations outside the scope of preclinical bioanalysis, such as requirements for the human test system data integrity to include patient confidentiality, informed consent, expedited reporting, *a priori* documented and protocol-driven description of all source data and locations, and sponsor communication requirements, including protocol deviations.

Clinical trials have been progressing with newer paradigms in research, sample collection, and data management, including but not limited to patient-centric sampling, electronic laboratory notebooks, increased advancements with surrogate endpoints, decentralized clinical trials, and accelerated approvals. New advances in clinical studies including immunogenicity assay approaches, target engagement, receptor occupancy, and other routine biomarkers have characteristics with data processing similar to pharmacokinetic (PK) related components, especially when it comes to statistical modeling. Processing these new data streams introduces additional risk factors of premature unblinding and also requires fit-for-purpose approaches for development and qualification.

This editorial provided feedback for the current clinical bioanalysis guidance gaps and emphasized the need for an understanding of the GCPs and how they apply to the bioanalytical laboratory so as to minimize the aforementioned risks that exist with clinical sample bioanalysis.

Conflict of Interest Statement: The author has no conflict of interest to declare

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