Writing bioanalytical reports

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Abstract

Bioanalytical reports are usually written by bioanalysts. Medical writers offer a valuable contribution to bioanalytical reporting, increasing the efficiency of document development and improving the quality of data presentation. This article covers essential aspects of reporting bioanalytical results, including the key parameters of bioanalysis, regulatory requirements, and the content and structure of bioanalytical reports. It will also be of interest to medical writers who deal with bioequivalence and other pharmacokinetic trials.

Keywords: Bioanalysis, Bioanalytical reports, Regulatory requirements

Bioanalysis serves the determination of drug concentrations in biological samples and thus provides the primary data for toxicokinetic and pharmacokinetic evaluations. The validity of such evaluations depends directly on the validity of the underlying bioanalytical measurements. Accordingly, bioanalytical studies should be properly documented and reported, with bioanalytical reports presenting evidence of the quality of the obtained data. Moreover, bioanalytical reports should be closely aligned with the respective non-clinical studies or clinical trials and should be seen in the context of the regulatory submission as a whole. These considerations pose a great challenge to bioanalytical laboratories, which usually produce study reports on their own.

Medical writers can greatly assist in the preparation of bioanalytical reports, providing expertise in presenting data and in the management of complex documents. With their good overview of the drug development process, medical writers are able to place those reports into the perspective of a clinical trial or a submission package. A good insight into bioanalysis allows medical writers to consider bioanalytical issues while developing a clinical trial protocol and to coordinate clinical and bioanalytical reporting at the end of a clinical trial. This integrative approach is especially beneficial for trials that depend heavily on bioanalysis, such as bioequivalence trials.

However, medical writers rarely contribute to bioanalytical reports. With this article, I am challenging this tradition, as I am convinced from my experience that the quality of bioanalytical reporting considerably improves upon the involvement of medical writers. Nevertheless, getting started with bioanalytical reports can be difficult. For this reason, I do not provide a comprehensive guide here (in any case impossible within the article format), but rather concentrate on the most important background information and the essential features of the three key documents for regulated bioanalysis:[1] the method validation report, the sample analysis (analytical) report, and the bioanalytical part of the Common Technical Document.

Bioanalysis

Broadly speaking, the very task of any bioanalytical investigation is providing concentration data. A great deal of scientific effort, however, focuses on ensuring the quality of these data. Before sample analysis, validation experiments need to demonstrate the validity of the bioanalytical method. During sample analysis, the performance of the method needs to be constantly monitored to confirm the acceptability of the obtained concentration results. Regulatory guidelines[2,3] systematically describe parameters of a bioanalytical method that need to be validated and monitored. To avoid repetition, I elaborate here on only a few important points.

Accuracy and precision represent the key parameters of a bioanalytical method. They are assessed by measuring samples with known concentrations of the analyte, so-called quality control (QC) samples. Accuracy (the closeness of the determined value to the accepted true value) is calculated by comparing the measured concentration of a QC sample to its nominal concentration, whereas precision (the degree of scatter between measurements) is evaluated from repeated measurements of the same QC sample. Both values determine the

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acceptability of a single bioanalytical experiment (analytical run) and the overall validity of the bioanalytical study results.[4]

The method performance during sample analysis is additionally controlled by reanalysis of incurred samples (study samples from dosed animals/subjects). Deviations between originally measured concentrations and those determined in incurred sample reanalysis (ISR) are evaluated according to predefined criteria.[3,5] ISR failure implies lack of reliability of the obtained data and requires laboratory investigation.[3,6] ISR should not be confused with study sample reanalysis: the results of ISR are not used to generate concentration data but solely to control the reproducibility of the obtained results.

Importantly, the accuracy and precision of the method refer to the specific range of concentrations for which they were established. A concentration outside this range can still be determined, but with uncertainty regarding the accuracy and precision of the measurement. High concentrations do not pose a significant problem because such samples can be analysed after dilution down to the validated range. Low concentrations, however, cannot be brought up to the validated range. Therefore, bioanalytical laboratories do not report quantitative data for concentrations below the lower end of the validated range (the lower limit of quantitation, LLOQ), with such values being set to 'missing', zero, or $\frac{1}{2}$ LLOQ in pharmacokinetic models. Thus, the LLOQ is an important parameter of a bioanalytical assay that directly influences the validity of pharmacokinetic evaluations. For this reason, it should be clearly stated in both bioanalytical and clinical reports.

Historical background

The development of regulated bioanalysis is a good example of the successful interaction between industry and regulatory bodies. Intensive dialogue has led to clearly written and widely accepted guidelines and ensured a high degree of harmonisation between regulatory requirements. The harmonisation of the method validation procedures started in 1990 at the first bioanalytical method validation workshop cosponsored by the American Association of Pharmaceutical Scientists, the FDA, and others and continued at the second workshop in 2000.[7] The results of both workshops were implemented in the FDA guidance[2] published in 2001, which was the first regulatory guideline on bioanalysis.[8] The FDA guidance was followed in 2003 by the detailed guide[9] of the Brazilian Health Surveillance Agency.

The rapid advance of bioanalytical methods in the 2000s necessitated further regulations to address methodological developments. Two more workshops held in 2006[4] and 2008[10] dealt with these issues, preparing the ground for the new EMA guideline on bioanalytical method validation. This guideline,[3] issued in 2011, was well accepted by the bioanalytical community.[8] It introduced new developments, such as ISR, and had an elaborated description of ligand-binding assays, but was otherwise considered to be in line with the FDA regulations.[8] In May 2012, the Brazilian agency updated its guide on bioanalysis and, lastly, the FDA published the draft revision of its guidance,[5] which mostly implemented methodological advances but also covered new topics, including the analysis of biomarkers and examples of report tables.

Regulatory framework

Bioanalytical guidelines

The comprehensive guidelines[2,3,5,9] define the regulatory framework for bioanalytical method validation and sample analysis in non-clinical studies and clinical trials. As outlined above, they are largely compatible, with the differences reflecting technical advances rather than differences in regulatory views. The bulk of these guidelines describes experimental conduct; however, they also set forth requirements for bioanalytical documentation and the content of final reports. Any writer engaged in the preparation of bioanalytical reports should be familiar with these guidelines and know the definitions provided therein.

In addition, regulated bioanalysis can also come within many other regulations.[11,12] Some of them cover trial-specific requirements, whereas others, most notably Good Laboratory Practice (GLP), apply, at least partially, to the majority of bioanalytical studies. Commonly encountered trial-specific regulations are bioequivalence guidelines,[13,14] which set additional (stricter) requirements on conducting and reporting bioanalytical studies in support of bioequivalence claims. Another example is the bioanalytical specifications for therapeutic proteins.[15] General principles to be considered in regulated bioanalysis include GLP and Good Clinical Practice (GCP), although the application (and applicability) of these principles is not always straightforward. It is therefore worthwhile to discuss the role of these principles in bioanalytical studies at some length.

Good Laboratory Practice and Good Clinical Practice

GLP is a quality system designed for non-clinical studies.[16,17] Although most bioanalytical

laboratories run under GLP conditions, it remains somewhat uncertain, to what extent GLP is applicable to bioanalysis.[1,8,16] Sample analysis in non-clinical studies clearly requires GLP compliance;[2,3,5] method validation experiments and clinical sample analysis may, however, fall outside the scope of GLP.[1,16] It may also be difficult to fully apply the principles of GLP to clinical bioanalysis,[16,17] even if following the principles of GLP is clearly required by the regulator (e.g. bioequivalence trials[14]). The European Bioanalysis Forum recommends, therefore, to use GLP for all bioanalytical studies and to claim GLP compliance for non-clinical sample analysis.[8] Claiming GLP compliance presumes verification (monitoring) by the GLP authority,[18] which, under the European Union legislation, does not cover clinical sample analysis.[19]

Being a non-clinical standard, GLP does not address the safety and rights of the trial subjects. Although bioanalysis of human samples is subjected to the same ethical provisions as the clinical part of a trial, GCP lacks clear guidelines for the processes at bioanalytical laboratories and thus cannot be easily applied to bioanalysis (of note, some regulators' positions can be found in the GCP inspection procedures for the bioanalytical part of bioequivalence trials[20]). Therefore, so-called Good Clinical Laboratory Practice guidelines[17,21,22] have been issued, which combine the principles of GLP and GCP, thereby providing a framework for the analysis of clinical trial samples under GLP conditions.

Requirements for bioanalytical reports

The bioanalytical guidelines[2,3,5,9] specify regulatory standards for the content of the final report. They do not, however, provide any guidance on the report structure. Lack of a dedicated guideline leads to a wide variety of bioanalytical report formats, which results in inefficiency at many stages, including report writing, preparation of submission summaries, and, not least, regulatory review. Aiming to standardise the presentation of bioanalytical reports, the Global Bioanalysis Consortium has been developing a high-level report structure, with the first recommendations being recently published.[1]

Common Technical Document

The presentation of bioanalysis in the Common Technical Document has been criticised by the Global Bioanalysis Consortium due to a lack of standardisation and uniformity that hinders efficient review.[1] Currently, summaries of bioanalytical methods are contained in Sections 2.6.4.2 and 2.6.5 for non-clinical studies and Section 2.7.1 for clinical studies. Section 2.7.1, however, covers bioanalysis performed in biopharmaceutical trials (e.g. bioequivalence[14]) and thus may not be suitable for bioanalytical information from other pharmacokinetic trials.[1] The Global Bioanalysis Consortium, therefore, proposes[1] a separate section 'summary of bioanalytical methods' with tables showing method validation parameters and links between clinical trials and respective bioanalytical studies (validation and sample analysis). The EMA,[23] and more recently the FDA,[5] have provided templates for such summary tables, which should be considered in the preparation of bioanalytical study reports.

Bioanalytical reports

Bioanalytical laboratories issue two types of reports: the method validation report and the analytical report. These reports can be prepared separately or be combined. For example, a method validation report can be appended to an analytical report, especially if a per-study validation was performed. In any case, the analytical report must contain a reference to the applicable validation report(s).[3]

I discuss here some specific features of bioanalytical reports; given the limited scope of this article, I refer the reader to the cited guidelines and publications for detailed information.

Title page

It is advisable to provide on the title page the identifier of the non-clinical study or the clinical trial whose samples were analysed (bioanalytical studies often have different identifiers). This eases attribution of the bioanalytical report and creation of summary tables for regulatory submissions.

Within GLP, regulators sometimes require more than one signed report.[24] The identification (original 1 or 2) must be present in such reports and can be placed on the title page.

GLP compliance and quality assurance statements

A GLP compliance statement must be included in the final reports of studies performed under GLP. This, however, may not be applicable to the bioanalysis of clinical samples, as discussed above. For such studies, the bioanalytical community proposed a more general regulatory statement that avoids claiming GLP compliance and should contain reference to Good Clinical Laboratory Practice guidelines.[1,8] Huntsinger[18] provides examples of GLP compliance statements.

In addition, the final report of GLP-compliant studies must be inspected by quality assurance

and a quality assurance statement must be included in the report.

Study summary table

A summary table containing key parameters of the study can substantially facilitate preparation and review of higher-level summaries, submission packages, and clinical trial reports. The table can be designed from templates provided in the guidelines[5,23] and may be further aligned to specific regulatory requirements (e.g. bioequivalence summary for Health Canada[25]).

Method description

The validation report should provide detailed information on the bioanalytical method, whereas the sample analysis report may contain a short description of the assay procedure with a reference to validation reports.[3,5] The Global Bioanalysis Consortium suggests including a brief method description in the text and putting detailed information in the appendices.[1]

Compounds

Reference items and internal standards should be listed in the report along with the data required by the regulators (e.g. origin, purity). Certificates of analysis can be included in the appendices, if available.

Preparation of calibration standards and QC samples

The report should describe the preparation of calibration standards and QC samples, including storage conditions. Regulatory requirements,[2,3,5,25] however, differ in the level of detail required in this section. The bioanalytical community favours a very general description, with specific information being stored in the raw data.[1]

Sample receipt and storage

This section is present, by definition, in the analytical report only (except for some validation experiments that require subject samples too). Its goal is to show that the storage conditions and period are fully covered by the validation (stability) experiments. At minimum, it should contain a table with the longest storage period and conditions, although, again, the extent of the required information varies between guidelines[2,3,5,25] and even between recommendations of bioanalytical societies.[1,4,8] This section can also contain a brief statement that the laboratory was informed in a timely manner if a subject withdrew informed consent (as required by Good Clinical Laboratory Practice guidelines).

Experimental phase

Analytical experiments should be sufficiently described in the report, including, in particular, the acceptance criteria for an analytical run.[1,3,4] Criteria for sample reanalysis should be predefined (e.g. in a standard operating procedure) and clearly stated in the report[2,3,5,8] (regulators are very sensitive to this issue). As with the method description, the text in the report can be brief, with detailed information given in the appendices. Experimental starting and completion dates must be indicated in GLP studies.

Results

This section contains a description of the study results with references to data tables in the 'Tables' section at the end of the report. The basic results to be presented in both types of reports include the number of analytical runs (all versus valid), experimental dates, precision and accuracy of calibration standards and QC samples, and, if applicable, assay linearity (clearly, validation reports contain more elaborated presentation).

The analytical report should include a summary of the sample analysis (number of analysed and reanalysed samples, reasons for reanalysis, number of samples with valid results) and, if applicable, a summary of ISR.

Appendices

The report appendices can include the study plan, standard operating procedures, representative chromatograms (validation reports) or serial chromatograms of sample analysis (analytical reports), certificates of analysis, method validation reports (if not provided as standalone reports), and any other supportive documents (e.g. laboratory investigation reports).

Conclusion

The notion of medical writers preparing bioanalytical reports may seem unorthodox at first glance, for these reports are usually, if not exclusively, written by bioanalysts. But think of clinical trials – you would hardly find anyone in the industry who would insist on clinical reports being written by investigators. Medical writers provide valuable contributions to clinical reports and they surely can do the same for bioanalytical reporting.

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Conflicts of interest

The author is an employee of CRS Clinical Research Services Mannheim GmbH. The information

provided in the article should not be used to make decisions regarding bioanalysis, such as which guidelines to follow or what kind of quality system to use. Such responsibility rests solely with bioanalysts, laboratory management, and sponsors, and involves many other considerations.

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