Commentary

Bioanalysis

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7th GCC Insights: incurred samples use; fit-for-purpose validation, solution stability, electronic laboratory notebook and hyperlipidemic matrix testing

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Note: Due to the equality principles of Global CRO Council for Bioanalysis (GCC), the authors are presented in alphabetical order of company name, with the exception of the first author who provided a major contribution to the meeting as the chair of the whole meeting, and the second to eleventh authors who provided major contributions to topics discussed as the session chairs of the meeting (presented in alphabetical order of company name).

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The Global CRO Council for Bioanalysis (GCC), a global independent consortium bringing together many senior level CRO representatives, was created in 2010 in order to openly discuss and share opinions on scientific and regulatory issues specific to the bioanalytical field [1]. Since its formation, the GCC members have met on a regular basis to discuss various topics and challenges faced by bioanalytical CRO companies. Several conference reports of past GCC meetings were published to share the discussions held during these events [2–4]. In addition, the GCC also published several influential White Papers on topics of widespread interest in bioanalysis [5–9]. These White Papers provide unified GCC recommendations that are helpful to the global bioanalytical community.

The 7th GCC Closed Forum for Bioanalysis took place in Long Beach, CA, USA on 8 April 2013, one day before the start of the 7th Workshop on Recent Issues in Bioanalysis (WRIB). In attendance were 46 senior-level participants from six countries, representing 37 bioanalytical CRO companies/sites. This event represented a good opportunity for bioanalytical experts from CROs to share and discuss these issues of concern for the outsourcing industry.

The 7th GCC Closed Forum was chaired by Mario Rocci, who started the meeting by communicating the official admonition statement, as has been done in all previous editions [1]. Prior to initiating discussions, participants introduced themselves. As in previous GCC meetings, multiple topics of

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current interest in bioanalysis were on the agenda of this closed forum. The nine topics for this 7th GCC meeting were the following:

- Use of incurred samples for metabolite testing and method specificity assessments during method development;
- Issues in performing incurred sample stability (ISS);
- Fit-for-purpose method validation;
- Determination of the stability of stock and working solutions in relation to the EMA guideline;
- Electronic laboratory notebooks (ELN);
- Discussion of recent US FDA findings;
- Hyperlipidemic matrix testing;
- Outcome of the GCC survey regarding sponsor requests versus regulatory expectations;
- Feedback on the GCC and EBF recommendations on the validation of biomarkers.

Use of incurred samples for metabolite testing & method specificity assessments during method development

The use of incurred samples collected as part of a trial for purposes other than initial analysis and various re-assays (analytical repeats, dilution repeats and incurred sample reanalysis [ISR]) can be of value when developing bioanalytical assays. However, regulatory and ethical concerns exist in using samples beyond their intended use as specified in the study protocol. In order to gauge the views of the bioanalytical CRO community on the benefits versus the risks of using incurred samples for method development purposes, a survey was generated and circulated to GCC member companies. In addition to metabolite testing and method specificity assessments, this survey included other purposes for the use of incurred samples, such as assisting in the determination of sample collection requirements, assay calibration ranges and quality control (QC) placement, selection of appropriate internal standards (IS), provisional stability, differential testing between LC–MS and LBA methods, as well as assessment of endogenous levels in biomarker assays.

The results of this survey, which were presented during the meeting, expressed the view that there are obvious advantages to performing additional experiments with incurred samples as part of the development of robust LC–MS and LBA analytical methods for the generation of accurate and reliable data. In some situations, information obtained from experiments using these samples is critical to understanding method parameters. For instance, methods for bioequivalence (BE) studies would benefit from conducting tests on incurred samples only in some specific cases (e.g., unavailability of reference standard for metabolites), whereas for first-in-human studies, aspects such as testing for metabolites are more pertinent. It was also recognized that the information obtained from the use of incurred samples is often critical in establishing immunogenicity and biomarker assays.

Sound practices, such as the use of pooled samples with adequate documentation, were suggested to minimize the potential for incurred samples misuse. In addition and as necessary, appropriate consent of volunteers/patients should be pursued to eliminate ethical concerns. During the discussion, it was acknowledged that the benefits and the risks associated with the use of incurred samples should be evaluated on a case-by-case basis considering the type of assay, its intended use, the resources involved and the value of the information that could be acquired. It was also clear that this benefit-to-risk approach must always take into account the importance of generating quality data when applying bioanalytical methods as part of sample analysis studies.

This topic was also discussed as part of the 7th WRIB; a summary of the discussions and subsequent recommendations are presented in the 2013 White Paper in Bioanalysis [10].

Issues in performing ISS

While not a regulatory requirement, the conduct of ISS has been a topic of considerable interest in recent years and was extensively discussed as part of the 2012 and 2013 WRIB White Papers in Bioanalysis [10,11]. A portion of the GCC survey on the use of incurred samples was specifically dedicated to ISS questions, and the results of these survey questions were presented and discussed during the 7th GCC meeting. From the survey results, it was clear that most participants do not routinely conduct ISS experiments, and are in favor of performing ISS testing only in specific situations. Many respondents believe that incurred samples should be used to support ISR as part of additional ISR failure investigation experiments, and most respondents feel that ISS should not be included in regulations, but rather only a recommendation for use on a case-by-case basis. In addition to ISR failure investigations, examples of situations where ISS testing is warranted included back-conversion of unknown conjugates to analytes of interest, unstable glucuronides and other metabolites, stability in presence of co-administered compounds in oncology studies, inability to support stability with QC samples, enzymatic degradation of analytes and major matrix instability.

Further discussion of this issue focused on the type of samples collected (blood, tissues, etc.), the sample

collection/processing procedures employed and the determination of the 'time zero' concentration. Despite these potentially confounding issues, the value of investigating the stability of incurred samples was recognized under appropriate circumstances. An indirect way to assess ISS can be through the ISR evaluation, where incurred samples are re-assayed after a certain time interval has passed. While it can be valuable to perform ISR testing early to identify potential issues of concern as soon as possible, performing ISR testing later in the study can provide useful insights on the stability of incurred samples. Due to the importance of this topic, GCC decided to share its recommendations on ISS with the global bioanalytical community. A GCC White Paper on ISS was published in the September 2014 issue of *Bioanalysis* (Future Science Ltd, London, UK) [12].

Fit-for-purpose method validation

The concept of fit-for-purpose method validation, which refers to an assay that does not fully meet current regulatory specifications for method validation, is another topic that has been discussed thoroughly at bioanalytical meetings in recent years. Interesting views and recommendations have been presented in several publications [2,9–10,13–16]. In non-regulated areas, the application of a fit-for-purpose approach is commonly applied to clinical therapeutics and biomarker studies, especially when encountering challenging assays with limitations. Fit-for-purpose validations, however, can pose challenges when applied in a highly regulated environment where the methods are driven by established regulatory guidance requirements.

GCC members responded to several survey questions related to fit-for-purpose validation and associated method and validation parameters. Although there is concern that the use of a fit-for-purpose approach may have the potential to be negatively received by regulators if not applied correctly, the vast majority of survey respondents have not received regulatory deficiency findings when applying the fit-for-purpose approach. This could suggest that either the data were simply not submitted to regulatory authorities or the approach is being applied through the use of scientifically sound science, accompanied by documented justification that the approach employed was suitable for the intended purpose of the assay.

Even though fit-for-purpose is often applied for particularly challenging types of assays, it was agreed that it should not be applied solely because of difficulties faced with a given assay. Rather the approach should be reserved for demonstrating acceptable assay performance when alternatives are not available.

During the GCC meeting, the attendees were strongly in favor of a scientific and well-implemented application of a fit-for-purpose strategy, considering the end use of the bioanalytical data obtained. In other words, the quality of a quantitative assay should match the quality or importance of the decision being made based on the data generated.

Determination of the stability of stock & working solutions in relation to the EMA guideline

The stability of the analyte and IS in solution was a topic of discussion during this GCC Closed Forum. Given that solution preparation is time-consuming and costly, consideration should be given to best practices for prolonging the use of stock and working solutions while maintaining robust science.

The current EMA Guideline on bioanalytical method validation (BMV) states the following regarding solution stability: "Stability of the stock and working solutions should be tested with an appropriate dilution, taking into consideration the linearity and measuring range of the detector" [17]. It is generally agreed that the stability evaluations in solvent are considered distinct and independent for a given type of solvent. When solutions of multiple concentrations are prepared for a given solvent, a bracketing approach is typically applied, where stability is assessed at the highest and lowest concentrations only. With this approach, the shortest stability duration available for the specified solvent is applied to solutions falling within the bracketed concentration range. Another important parameter that was considered during the meeting was the container material in which the solution is stored, which should be taken into account when assessing stability.

Other aspects of solution stability discussed at the meeting were related to the acceptance criteria and the application of expiry dates. The maximum percent difference acceptance criterion applied between stability and comparison solutions appears to vary among CROs. Such criterion is not present in the FDA and EMA guidance documents. Some attendees expressed discomfort with the concept of 'daisy-chaining', which refers to expiry dating sub-stock solutions without regard to the age of the stock solution used in the preparation of the sub-stock. No clear consensus was achieved by the attendees on this 'age old' issue. Other discussion revolved around the impact of using a stock solution that was extensively used on previous occasions (retrieved many times from its storage location).

In most cases, the expiry date of a solution is set based on the stability established for such a solution

through testing. This does not systematically imply that the solution is not stable for a longer period (unless this has been established through testing). Consequently, the term 'retest date' was suggested as a more representative term than 'expiration date' for solutions where no instability has yet been demonstrated.

ELN

Traditionally, paper-based approaches have been used at bioanalytical laboratories for the documentation and recording of experiment conduct, standard operating procedures (SOPs),forms and other various documents. The emergence of ELN as an alternative to paper documentation is relatively recent in bioanalytical laboratories. Some organizations performing bioanalysis have decided to move forward in the implementation of this approach in their continuous search for quality improvement and better regulatory compliance.

In order to seek the views and current state of ELN use at CROs, survey questions specific to ELN were sent to GCC members. The results of this survey indicate that paper continues to be the most widely used format for the vast majority of respondents and that ELN implementation is limited. This is surprising, considering the fact that several years have passed since ELN systems were first developed and proposed to bioanalytical facilities. ELN can be employed for many diverse applications, such as real-time recording of manual raw data, management of SOPs and other documents, collection of instrument raw data, calculation of secondary results (derived data), training and avoiding the inadvertent use of inadequate or uncalibrated equipment/materials and so on.

Although ELN can be applied to a wide range of documentation tasks, the main reason CROs provided for not implementing an ELN system is the anticipated high cost of purchase and implementation of the system. Additional obstacles highlighted include the regulatory risk posed by novel systems that were not extensively tested yet; the difficulty in finding appropriate staff resources and time to implement, configure, customize and maintain the system; and the significant disruption to current operations.

Some respondents currently using ELN acknowledge the advantages associated with its use, such as improved quality and completeness of records, as well as regulatory compliance. On the other hand, ELN users did not see much positive impact on their productivity, and the flexibility to handle different types of contracts was found to be an issue. Thus, the CRO community appears to be divided in considering ELN as the preferred choice for data and document recording and management.

Discussion of recent FDA findings

This GCC Closed Forum provided the opportunity to discuss recent FDA citations received by CROs. More specifically, the FDA findings received as part of a first FDA inspection conducted for a clinical bioequivalence study in China were shared. One legitimate question raised was whether these findings will be covered in the new FDA Draft Guidance on BMV [18], which had not yet been issued at that time? The first finding of particular interest was the failure to present long-term stability data in the presence of co-administered compounds. Such a finding was also previously observed as part of FDA inspections. Considerable debate and effort were recently expressed by the bioanalytical industry regarding this issue, as reported in the GCC White Paper specifically dedicated to this topic, as well as in the 2010, 2011 and 2012 White Papers in Bioanalysis [8,11,15–16]. The recommendation presented in the GCC White Paper is clear: a systematic evaluation of this stability is not believed to be required when scientific justifications suggest the absence of stability issues caused by the presence of the co-administered compound. The question remains as to whether the FDA will continue to cite such findings when this issue is not specifically included in the new 2013 draft BMV FDA guidance.

Another thought-provoking FDA observation received for the study conducted in China pertained to IS response variability during sample analysis. Different approaches for IS response criteria were discussed in the past as part of the 2nd GCC Closed Forum [5]: the first approach being to establish upper and lower boundaries for IS response that would trigger a response or action should the criteria fail to be met, and the second approach consisting of a trend analysis of the IS variation of known samples to define the range of acceptability for IS variation in unknown samples. Pros and cons exist in applying either approach, as further explained in the GCC publication. It is generally agreed that acceptable performance of an assay can still be demonstrated despite the presence of IS variability. Suggested evidence that could be used to establish adequate performance may include acceptable ISR results, good accuracy of QCs prepared in pre-dosed subject matrix and low variability in relative response factors. The importance of having clear predefined criteria in SOPs and being ready to scientifically defend observations involving IS variability was also reiterated during the meeting.

Other FDA comments, not listed as findings, were also shared at the meeting; they related to the conduct of partial versus full validation at a CRO laboratory when the method had previously undergone a full validation by the sponsor or another CRO, and the

conduct of long-term stability testing at a CRO laboratory (i.e., not using existing stability data from the client or another CRO in the original full validation).

A recurring question raised regarding findings or observations from regulatory agencies in general relates to whether the findings reflect the opinion of the individual inspector or of the agency as a whole? The global bioanalytical industry can significantly benefit from a certain level of uniformity within and between agencies in the application of regulatory requirements.

Hyperlipidemic matrix testing

The need to test hyperlipidemic matrix during BMV was first introduced by ANVISA back in 2003, and is now included in current EMA and ANVISA guidelines as part of the matrix effect (EMA), and for both selectivity and matrix effect (ANVISA) [17,19]. While the EMA guideline is not particularly prescriptive on the procedural requirements for hyperlipidemic matrix testing, the ANVISA guideline provides slightly more details and defines a lipemic sample as "a high lipids degree sample, for example, coming from postprandial collection". This topic was brought to the industry's attention in the past year and was also part of the agenda of the 2013 7th WRIB, where issues were discussed and recommendations proposed [10].

The value of including hyperlipidemic matrix testing during validation was deemed justified by the attendees, considering the likelihood that laboratories will handle and analyze study samples containing a high level of lipids and the potential effects of the presence of lipids on bioanalytical method performance. It was mentioned that the context of studies should be taken into account (e.g., high-fat fed studies, type of subjects enrolled, etc.), and the conduct of this test needs to be primarily science-driven. As a general approach, in order to be scientifically meaningful, the test should be representative of the samples to be analyzed and, thus, should take into account the approximate lipemia levels in matrix expected in study samples. Another issue discussed was the type of lipids to consider in the selection of an adequate matrix to be used for the test. Should specific classes of lipids be evaluated, such as triglycerides, phospholipids, or total cholesterol? With the goal of being representative, the use of 'artificial' lipemic matrix (i.e., matrix mixed with fat emulsion) may not represent a desirable approach, as opposed to the use of 'natural' matrix from high-fat donors (from subjects with high triglycerides levels or from subjects following a high-fat meal).

Some concerns were also debated regarding the information obtained from vendors of lipemic matrix, which may pose problems as the information provided on the matrix lots is often insufficient. For instance, is the matrix supplied natural or artificial? If artificial, what is the identity and quantity of the fat emulsion used? If natural, from what type of donor? If from postprandial collection, what was the meal composition and collection time? It was concluded that several aspects need to be considered and many questions still remain unanswered regarding hyperlipidemic matrix testing during method validation.

Outcome of the GCC survey regarding sponsor requests versus regulatory expectations

It is generally understood that the global bioanalytical community is operating in a challenging environment with similar but different regulatory guidances and their interpretations, varying levels of experience within regulatory agencies, sponsors and CROs, timeline pressures, the need to reduce costs and increasing regulatory expectations. In an effort to eliminate some hurdles and improve workflows, initiatives were taken by both the industry and the regulatory agencies toward global harmonization, and specific groups were formed, such as the GCC in 2010 and the Global Bioanalysis Consortium (GBC) in 2011.

A survey was sent to the GCC member companies where various sponsor requests were presented that could put the CRO at risk of facing regulatory issues and thus being 'caught in the middle' between sponsor requests and regulatory expectations. As CROs are frequently inspected and, thus, often have fresh regulatory insights, this survey served to gather useful opinions on such situations. As part of the survey, the respondents ranked the frequency of each sponsor request and the perceived regulatory risk associated with it. The responses were grouped by their risk factor based on a combination of frequency of a particular request and the perceived risk associated with the request. Each topic was then grouped as: 1 – relatively low overall concern; 2 – relatively moderate overall concern; 3 – relatively high overall concern. For example, whereas a particular sponsor request may carry a high level of regulatory objection, if the frequency of the request was rare, that specific scenario received a ranking of low general risk to the CRO community. Those scenarios categorized as high risk were associated with both a regulatory concern as well as a relatively high level of request frequency.

For the survey results, the sponsor requests showing low general concern included:

- To change the status from GLP to non-GLP;
- To follow Sponsor's SOPs as opposed to CRO procedures/criteria;

- To use a correction factor to normalize immunoassay results when standards do not match;
- To add clarifications to archived documents;
- To run Bioequivalence/Bioavailability (BE/BA) study by period to accelerate timelines;
- To use Sponsor's spreadsheets that prevent verification of calculations;
- To select ISR samples without *a priori* criteria for selection.

The requests posing moderate concern were:

- To use a Sponsor's decision tree for reporting re-assay results that omits considering data from acceptable runs;
- To not follow CRO criteria for items not addressed in a Sponsor's SOP when a Sponsor's SOP is followed;
- To report data from failed runs if the QCs in the range of the study samples are acceptable;
- To employ contract language implying Sponsor's insertion between CRO and study director for GLP studies;
- To use the analytical assay for different regulatory purposes than validated;
- To transfer an assay validated elsewhere and only perform precision and accuracy testing as partial validation to support the transfer;
- To provide input to the bioanalytical report that draws conclusions outside the scope of the data or does not reflect a conclusion reached by the CRO;
- To not include ISRs in a regulated study (clinical study or first method application in preclinical study);
- To omit valid results for various reasons.

Finally, there were seven sponsor request scenarios where high overall concern was expressed (frequent occurrence combined with a high regulatory risk). They are listed below:

- Short sample analysis timelines for a large number of samples, leading to a high percentage of initial and ISR results being generated prior to potential problems being identified (e.g., ISR failure, placement of QCs relative to unknown samples, etc.);
- Re-assay of selected samples (PK repeats) without objective *a priori* criteria for selection;
- Claims of GLP compliance for non-GLP clinical work;
- Use of long-term stability data generated by the Sponsor or third party without details regarding SOPs used to generate the data;
- Lack of information from the clinic regarding concomitant medications administered to individual subjects during the course of the study;
- Study protocol and/or amendments not provided by the Sponsor, which may include information relevant to bioanalysis;
- Discrepancies in sample management documentation provided by the sponsor or clinic and requests to make changes to correct a discrepancy without adequate supporting documentation.

The survey results demonstrated that some areas of concern seem to stand out as areas for improvement. It was mentioned that the experiences of a CRO are likely to influence perceptions of risk and the frequency of exposure to areas of concern varies widely. As an industry, CROs should focus their efforts on areas of greatest frequency and risk, and use their expertise to find the right way to further discuss potential problems with the Sponsor that may be anticipated and the recommended approaches to be adopted.

Feedback on the GCC & EBF recommendations on the validation of biomarkers

The topic of biomarker method validation has been a source of intense discussions as part of various GCC meetings in the past years [2,4,6]. Recommendations specific to the bioanalysis of biomarker assays were presented in several publications, including two White Papers, one prepared by the GCC [9] and the other by the European Bioanalytical Forum (EBF) [14]. These documents, among others, act as practical working tools in the selection of the appropriate bioanalytical strategy for the analysis of biomarkers, considering the purpose of the data to be generated and the type of clinical application involved. During the meeting, it was expressed that the GCC White Paper on biomarkers is mainly seen as a practical tool on the specific requirements for each of the recommended three tiers of biomarker method establishment: screening/qualified/validated assays. On the other hand, the EBF White Paper was said to focus more on providing insights for appropriate decision-making when establishing a biomarker assay and in this manner is found to be more directed toward what needs to be done prior to and during the development of the assay.

It was also brought up by the attendees that parallelism acts as a major and key component of a biomarker method, as demonstrated by the presence of this requirement in all three tiers of method establishment.

Future perspective

The GCC will continue to provide recommendations on hot topics in bioanalysis of global interest and expand its membership by coordinating its activities with the regional and international meetings held by the pharmaceutical industry. Please contact the GCC [20] for the exact date and time of future meetings, and for all membership information.

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