Commentary

Theme: Best Practices for Bioanalytical Methods: Recommendations from the Global Bioanalysis Consortium

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Tiered Approaches to Chromatographic Bioanalytical Method Performance Evaluation: Recommendation for Best Practices and Harmonization from the Global Bioanalysis Consortium Harmonization Team

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ABSTRACT. The A2 harmonization team, a part of the Global Bioanalysis Consortium (GBC), focused on defining possible tiers of chromatographic-based bioanalytical method performance. The need for developing bioanalytical methods suitable for the intended use is not a new proposal and is already referenced in regulatory guidance language. However, the practical implementation of approaches that differ from the well-established full validation requirements has proven challenging. Advances in technologies, the need to progress drug development more efficiently, and emerging new drug compound classes support the use of categorized tiers of bioanalytical methods. This paper incorporated the input from an international team of experienced bioanalysts to surmise the advantages and the challenges of tiered approaches and to provide recommendations on paths forward.

KEY WORDS: bioanalysis; chromatographic; regulated; tiered approaches.

INTRODUCTION

Over the last two decades, we have steadily seen an increase in the extent of characterization of the performance

of bioanalytical assays, particularly where the data is (or may be) used to support filing of a new drug application (NDA) with a regulatory authority. This has led to bioanalysis being routinely conducted at a level that may only be needed for bioequivalence (BE) or equivalent pivotal studies. The BE study inspections, and other health authority inspections at the time of NDA regulatory review, have established the high-bar standard for bioanalytical methods. Where pharmacokinetics (PK) is a pivotal endpoint of a study, it indeed makes sense to demonstrate the highest confidence in the accuracy and precision of concentration results. Unfortunately and unintended, these “BE standards” may have become the assumed expectation of all bioanalysis used to support a regulatory filing, and in extension also increasingly for studies for internal decision making only. In effect, the BE standards are interpreted as the rules of regulated bioanalysis by the general bioanalytical community of scientists, regulators, and QA professionals.

Early in the formation of the Global Bioanalysis Consortium (GBC), the opportunity of addressing the discussion of categories or tiers of method validation was identified. A fundamental question relating to the current status of regulated bioanalysis is whether the current practice is optimum and needed for effective drug development. Based upon feedback from the bioanalytical community and in recent publications, clearly, many agree that it is not (1,2). The concept of defensible scientific flexibility is now routinely advocated, but most recognize that such flexibility should be governed by some mechanism and degree of standardization.

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Predefining what level of analytical rigor a bioanalytical method needs to achieve is, of course, not a new concept. The Crystal City 1990 workshop report (3) and, subsequently, the second Crystal City 2000 workshop resulted in the *2001 FDA Guidance for Industry: Bioanalytical Method Validation* (BMV) (4). This was almost immediately recognized globally and referred to as a definitive approach to validating a bioanalytical method. Bioanalytical methods used to support drug filing submissions increasingly deferred to this FDA BMV guidance and several associated white papers (5,6). More recently, other regions are installing their own guideline on BMV (7,8). A confounding aspect of all these BMV guidances is that they present a single approach to demonstrating method performance and establish a level of performance through fixed acceptance criteria that is not necessarily linked to the purpose of the data. It may be viewed that such fixed pass/fail criteria have served us well to date and have fostered a useful degree of standardization and consistency between laboratories. Increasingly, however, there are several driving dynamics emerging that conflict with the “one-size-fits-all” status of modern regulated bioanalysis. The need for the pharmaceutical industry to be more efficient, technology changes, new categories of therapeutics, and new applications for bioanalysis (e.g., biomarkers) call for customized approaches to establishment and use of bioanalytical methods. This encourages a review of the current paradigm of regulated bioanalysis.

The “fit-for-purpose” paper of Lee *et al.* (9) already discussed a customized bioanalytical approach, albeit with a focus on biomarkers. In addition, the Crystal City 2006 workshop III paper (5) discussed metabolite quantification performed in early stages of development to be an area qualifying for less-rigorous method performance evaluation than what is required for full-method validation per the FDA 2001 guidance. In fact, that paper can be recognized as the first pivot point in the introduction of the principles of tiered approach into regulated bioanalysis. Nevertheless, for a number of reasons, the bioanalytical community did not fully embrace these concepts and continued on a path forward of implementing the FDA BMV guidance (4) principles in earlier stages of drug development, including for metabolites analysis. From 2008/2009 onwards, the metabolites in safety testing discussion (10,11) can be seen as the second pivot point. Whereas individual scientists or companies were trying to identify how to apply the tiered approach for metabolite quantification, collectively, the European Bioanalysis Forum (EBF) took these new guidelines and proposed the consolidation of tiered approach to include three levels/tiers of quality standards: screening, qualified, and validated assays (12).

It can be reasonably assumed that at least some of the regulatory bodies governing bioanalytical data submissions are anticipating the need for flexibility in bioanalytical practice. Health authority representatives have, in recent years, referenced the appropriateness of fit-for-purpose approaches to the bioanalysis of metabolites and biomarkers (13). Also, the recently released Japanese Ministry of Health, Labour and Welfare (MHLW) draft bioanalytical method validation guideline (7) speaks to allowing “flexible adjustment and modification” of the guideline to meet the intended use of the assay, and this perspective is extended to tiered approach for metabolite quantification described in the

Annex. However, other regulatory agencies, e.g., European Medicines Agency (EMA) (8), have not clarified a stance on deviating from predefined guidance acceptance criteria and the associated experiments necessary to use a bioanalytical method for studies intended to support a regulatory filing, leaving a highway of opportunity for the bioanalytical community to propose a way forward. Recently, at the Crystal City V Workshop (14) held in Baltimore, MD (December 2013), FDA representatives did make a comment that the FDA BMV guidance is directed at late-stage clinical studies used for pivotal decision making at drug submission filing. It was added that approaches used for other studies in the drug development process are the responsibility of the sponsor of the bioanalytical work.

In view of above, it was a natural step that GBC would also concentrate on the possibilities offered by the tiered approach. A team was identified to discuss and propose best practices for tiered approaches to bioanalysis—GBC Team A2. In line with GBC goals and expectations, representation from all regions was established. The GBC Team A2 was focused on chromatographic assays and the associated recommendations applicable to small-molecule drugs. While the principles discussed can apply to chromatographic assays for biological therapeutics, it is acknowledged that endogenous analytes and biomarkers present additional bioanalytical challenges. This commentary paper does not address biomarker assays specifically, although again, the principles can be taken into consideration for addressing the fit-for-purpose needs of such bioanalytical methods.

In what follows, GBC will propose and elaborate on tiers of method performance evaluation. The objective is to provide a framework that will help rationalize the level of bioanalytical method characterization and propose a clear path for implementation and use of the tiered approaches. We are proposing a decision making process that describes the extent of bioanalytical method establishment appropriate to the intended purposes of the data generated. This is in contrast to validating all bioanalytical assays independent of their purpose to meet all aspects of current BMV regulatory guidance (and prevailing interpretations of regulator expectations) irrespective of the purpose of the generated data.

PROPOSAL OF TIERS

Validated Bioanalytical Method

We have started with the premise that an assay meeting all aspects of a current BMV regulatory guidance represents the highest tier, and for the value of consistency with the available FDA, EMA, ANVISA, MHLW, or other guidance, we have designated this as a fully “validated method.” Such a method undergoes extensive characterization for accuracy, precision, selectivity, sensitivity, stability, and reproducibility as defined in regulatory guidance and is intended to provide absolute analyte concentration with a high reliability. The globally recognized acceptance standards for a validated method are currently being addressed by two GBC teams, notably S1 (small molecule specific run acceptance) and L1 (large molecule specific run acceptance) (15). Three additional tiers of method establishment are hereby proposed as alternatives to the fully validated assay (highest tier rank) recognized to date by the bioanalytical

community and under current review by GBC teams S1 and L1. These are in the order of decreasing tier rank:

Qualified Bioanalytical Method

Undergoes limited characterization with calibration standards and QC samples prepared using an authenticated reference standard which may have incomplete documentation, but with known source, identity, and purity information. The method provides absolute analyte concentration within accuracy and precision limits determined during the qualification process. This process of method characterization is called method qualification (not partial validation or limited validation) and is thus discrete from the validated method tier.

Research Bioanalytical Method

Undergoes limited characterization with calibration standards prepared using a comparator reference material, such as an *in situ* (in solution) standard with concentration estimated by radioactivity measurement, NMR, or UV. The method provides estimated analyte concentration within broader accuracy and precision limits than the higher tiers. Such a tier can only be recommended for internal use or must be accompanied by full disclosure of the risk to accuracy associated with a relatively uncharacterized reference material.

Screening Bioanalytical Method

Undergoes limited characterization based on relative instrument analyte response, where reference material is not available. The method provides relative analyte measurement and cannot be considered quantitative but may still be suitable for decision making processes based upon the relative response data generated. For example, such an assay might be used to assess metabolic fate of an analyte in a biological matrix by comparing relative instrument response under tested, *in vitro*, conditions.

The availability of an authenticated, well-characterized reference standard or material of the analyte(s) of interest is an important influence on tier options. In the context of small-molecule chromatographic-based assays (e.g., liquid chromatography-mass spectrometry (LC/MS)), this is a practical and convenient differentiator between validated/qualified assays and research/screening assays. However, this should not override the fundamental concepts of why a particular tier is applied to the bioanalytical need. For example, it may not be appropriate to defend data submitted to support a regulatory filing with an assay designated at the research or screening tier simply because an appropriate reference standard was not available.

Use of Proposed Tiers

All the proposed tiers are intended to facilitate generation of data that supports sound scientific decision making. We believe that the key to implementation of any tiered approach is a clear road map for the decision process of what tier to use in a given circumstance. Such a process should address questions bioanalysts and other appropriate members

of the drug discovery or drug development team are likely to consider. Guiding questions include the following:

- What is the purpose or intended use of the data?
- How much risk is acceptable if the data are less accurate or less precise?
- What limitations are you bound by?
- What makes scientific sense under the drug development phase being addressed?
- Do the principles of fit-for-purpose hold for the needed assay?

The decision grid shown in Table I offers specific parameters associated with bioanalytical method correlated with the tiers being proposed. When reviewing the content the following should be considered:

1. Specific parameters have been primarily derived from the GBC team's discussion around LC/MS bioanalytical methods applied to small molecule xenobiotic drugs.
2. Overlap can be expected and discretion required by the user for all tiered levels up to the fully validated one. Users will be required to scientifically defend the tier level used. It is suggested that this is summarized in a written bioanalytical method performance evaluation plan if the method is to be used in the generation of bioanalytical data for regulatory submission.

The grid can be approached from two directions, depending on the available knowledge or information when embarking on any method establishment:

1. Prior to method establishment, one can define the tier needed to analyze the samples from the study and establish the method and extent of its characterization accordingly, based on the study type and intended decision(s) one need to make from the data. This may be the preferred approach because it complies with an important principle of good practice: *a priori* and documented decision of what constitutes acceptable method quality to support the intended use of the resulting data.
2. Alternatively, there are cases where one might not be able to define the tier needed for the study upfront, because there is so little known about the anticipated or required performance of the method, the concentration levels to be measured in actual study samples, unique human metabolites or other factors integral to establishing the method. After method establishment or (limited) study sample analysis, one can select or describe the appropriate tier that describes the method. Although at first sight it is biased or confusing to define the level of quality only after sample analysis, this approach may be needed in some situations. Of course, defining the assay tier after sample analysis would not be recommended for studies intended for inclusion in regulatory filings and in practice is likely to be more appropriate to drug discovery phases. In any case, this provides a documented approach to communicate the level of quality which the data adhere to.

Table I. Tiered method performance parameters

Requirements	Screening	Research	Qualified	Validated
Analyte concentration obtained	Relative	Estimated	Yes	
Reference standard ^a	Not required	Comparator	Authenticated reference standard	Yes with COA, as per regulatory guidance and SOP
Method development	Yes, but limited			Yes
Pre-study method performance assessment ^b	No rely on method development and in-study data		Preferred	Yes (pre-study validation) as per regulatory guidance and SOP
Calibration curve for pre-study and in-study runs	Not applicable	Yes, but fewer calibration standards allowed (>3)		Yes, as per regulatory guidance and SOP
Matrix of cal stds and QCs identical to study samples	Not applicable	Preferred		Yes, as per regulatory guidance and SOP
Independent QCs via second weighing	Not applicable	Preferred		Yes, as per regulatory guidance and SOP
Acceptance criteria (AC) for calibration curves and QCs for pre-study and in-study runs	Not applicable	Yes; AC can be broader than ±15/20%; required FFP AC may be set <i>a posteriori</i> instead <i>a priori</i>		Yes, as per regulatory guidance and SOP
Inter and intra assay accuracy and precision (CV)	Intra assay precision	Intra assay accuracy/precision (one run)		Both, as per regulatory guidance and SOP
Selectivity from the biological matrix	Yes, using one matrix batch blank (depending on the use of the method)	Yes; obtained from one matrix batch blank by in-study run		Yes, as per regulatory guidance and SOP
OTC ^a drug interference check	No	No		Yes, as per regulatory guidance and SOP
Extraction recovery	Not applicable	No		Yes, as per regulatory guidance and SOP
Internal standard (IS)	Not applicable	Preferable		Yes, as per regulatory guidance and SOP
Carry-over	Run samples in the order of sample collection time points. Include in each run a blank following a high conc sample			Yes, as per regulatory guidance and SOP
Matrix effect	Demonstrate absence of differential matrix effect between species of interest	If IS is used, check IS response across runs		Yes, as per regulatory guidance and SOP
Bench-top stability in the biological matrix	Reanalyze in the same run a couple of study samples (incurred samples) after ambient bench-top storage	Conduct spiked sample (QC) bench-top stability with consideration given to appropriate incurred sample ambient bench-top evaluation		Yes, as per regulatory guidance and SOP
F/T stability in the biological matrix	No, except for structural alert or historic data from similar compounds			Yes, as per regulatory guidance and SOP
Long-term stability in the biological matrix	Not applicable	Not require if bench-top stability is proven	Not required if bench-top stability in matrix is proven unless long-term storage is intended	Yes, as per regulatory guidance and SOP
Processed sample stability	Not required except for structural alert	Not required except for structural alert; rely on bracketing calibration stds in each run		Yes, as per regulatory guidance and SOP
Stability in whole blood	Not applicable	Not required unless unstable in plasma or structural alert		Yes, as per regulatory guidance and SOP
Stock/working solution stability	Not applicable	FFP assessment		Yes, as per regulatory guidance and SOP
Accurate recording of raw data	Yes			Yes, as per regulatory guidance and SOP
Quality control review of raw data prior to reporting	As appropriate for purpose		Yes	Yes, as per regulatory guidance and SOP
Method description/report	Description in lab notebook or report			Yes, as per regulatory guidance and SOP
Method performance description or report	Description in lab notebook or report			Yes, as per regulatory guidance and SOP
Bioanalytical study sample analysis report	Description in lab notebook or report			Yes, as per regulatory guidance and SOP

FFP a fit for purpose, OTC over the counter, AC acceptance criteria, COA certificate of analysis, SOP standard operating procedure, QC quality control, F/T freeze/thaw, CV coefficient of variation, cal stds calibration standards, IS internal standard

^a Reference standard: *Authenticated reference material* accompanied by documentation that addresses source, identity, purity, storage conditions, expiration date, and batch number as appropriate. For validated assays, this information will be provided in a COA provided by a reputable source. With *comparator material*, the documentation may be incomplete, but at least source, identity and purity indicator (e.g., HPLC-UV area %) must be known. Storage conditions and expiry or retest dates should be estimated if stability data is not available

^b Pre-study method performance assessment: establishing performance of a method, reestablishing an existing method, qualifying a new analyst, etc. prior to study sample analysis

Fig. 1. When to use a given tier—per drug development phase

In all cases, it is important to note that the grid should not be used with a “check box” mentality or to regulate what does not need to be regulated. There needs to be appropriate flexibility in the boundaries of the grid parameters, and those boundaries are the basis of important communication in the project team that extends from the bioanalysts to the users of the data and the ultimate decision makers in candidate selection or drug development. With effective communication in place, the bioanalyst should be well positioned to determine the tier applicable to the method and its use. As one thinks through the intended use of a bioanalytical method and gain insight from all parties as to what they require of the assay, defining the method establishment process becomes an intuitive process. However, it is expected that all parties may not necessarily agree on the requirements of the assay. The GBC Team A2 recognized this early in team discussions, and effort followed to help navigate the decision of what tier to use further.

An often discussed concept of tiered approaches is that of correlating the level of bioanalytical method establishment with the phase of drug development. Strategies for metabolite and biomarker assays have previously been proposed, and recently, these principles have been discussed from the context of the whole bioanalytical program for a given drug (14). Following this thought process, consideration can be given to not only the phase of drug development but also the analyte itself (e.g., drug, prodrug, metabolite) and the biological matrix to be studied. The characterization of analyte distribution in tissue matrices is another example where lower tiers may be appropriate or be the only possible approach to the bioanalytical challenge. Clearly, this level of differentiation may complicate the issue, and not every project team will necessarily view the bioanalytical strategy the same way for each drug development program. However, the thought process associated with what needs to be done to make good decisions alongside the progressive development

of the drug is crucial to the tiered approach and the realized efficiencies. Therefore, a pictorial presentation, of when to use a particular tier for a given analyte, matrix, and drug development phase, was established and is shown in Fig. 1. Following the sequence of drug development, the application of the four tiers of bioanalytical methodology is defined in this example. Starting with the discovery phase, screening, research, or qualified methods are proposed. As the drug candidate progresses through preclinical and non-clinical phases, including both non-GLP and GLP studies, assignment of the appropriate tier is driven by the analyte and the matrix in question. Here, we encounter an important deviation from what is typical today, notably some bioanalytical data intended for regulatory submission that is scientifically defensible but not generated using a fully validated method. This theme continues through the clinical drug development phases with the added consideration given to human metabolites that require quantification based upon safety testing guidance criteria (i.e., ICH M3 (R2) guidance (11)). It is expected there will be some customization of the work flow that meets the particular needs of a drug development program, but the example shown (Fig. 1) is proposed as a defensible foundation of practically applying the tiers of bioanalytical methodology described in this paper.

DISCUSSION

This paper proposes a rational and scientifically defensible approach to applying different tiers of bioanalytical methods. However, although relatively new, we recognize that this is not the first time such concepts have been proposed (9,16,17). Also, we realize and support that our contribution may only further stimulate discussion in the industry on the subject. In this context, we would support all

further discussions and make ourselves available to provide input or reflection. Undoubtedly, there has been hesitation from the industry to fully adopt such strategies to date, and the GBC team attempted to understand and then navigate a solution to the justified concerns. Lack of support from the regulatory authorities for anything other than fully validated bioanalytical methods has been the underlying concern. However, recent comments from the FDA do suggest this may be changing with consideration given to tiered strategies that do not impact drug safety, efficacy, and product labeling claims (13). The bioanalytical community also owns the responsibility to do the necessary science that helps progress safe and effective drugs to market efficiently. While the fixed criteria of a fully validated method are simple to understand and do provide a common standard, they force a “high bar” that may not be necessary or even appropriate for decision making. More so, new drug therapies do not necessarily fit with the traditional bioanalytical technologies and approaches. Therefore, again, flexibility to apply the appropriate level of bioanalytical rigor to make appropriate decisions makes sense. In contrast to the fully validated method, the broad potential of tiered approaches can introduce complexity to the bioanalytical strategy. Also, acceptance criteria and *modus operandi* are still evolving, challenging the rapid acceptance and wide deployment of tiered approaches.

With each of the concerns and opportunities, the GBC Team A2 recognized the need to provide a clear road map to implementation and use of tiered approach strategies. Emphasis was placed on tier definition while maintaining flexibility in their use. Reference material characterization is important to what accuracy a bioanalytical method is capable of and hence what options can be considered. With an authenticated and well-characterized reference standard, all tiers can be considered, as appropriate. In contrast, the options will be restricted for assays with incompletely characterized comparator material. This became a fundamental differentiator of the three new tiers proposed (i.e., screening, research, and qualified) and the validated tier. In effect, the reference material predetermines what options can be considered. If you do not have an authenticated reference standard to generate a calibration curve, then a qualified (or validated) tier is not an option.

Beyond the reference material, however, the definitive assignment of experiments to a given tier was more difficult. This was expected as it was considered by the team as another reason why tiered approaches have struggled to gain acceptance in bioanalysis. It may be argued that we are conditioned by the decades of experience with a single tier to resist the flexibility of choice and decision that comes with an appraisal of multiple tiers. Certainly, it seemed inappropriate to further breakdown each tier into subcategories. Better was to embrace the benefits of flexibility, and hence, the decision grid depicted in Table I was developed. This tool is intended to help drive the decision process of what is needed for a given bioanalytical scenario, at least in terms of the experiments required to support the resultant method. The experiments should be decided *a priori* and recommended to be documented in a plan. Predetermined or fixed acceptance criteria are established and appropriate for validated assays; however, for qualified, screening, and research tiered methods, it may be appropriate to define

these after the method performance experiments have been conducted. Minimally, it is expected that *a priori*-established acceptance criteria can be relaxed for the new tiers if such method performance still supports the intended use of the data and ultimately supports the necessary decisions that will be made.

The remaining concept that was discussed at length by the team was that of managing and accepting degrees of risk when establishing and using bioanalytical methods. That is, risk in the context of obtaining a sufficiently accurate and precise bioanalytical measurement for the intended purpose of the data. The authors wish to clarify that the proposal made here is discrete and removed from adding any risk to the patient. The past history of a single tier (fully validated assay) of bioanalysis has very much nullified discussions on how much risk as a bioanalysts we are willing to accept in our assays. The common standard of a single tier negates the discussion since it is being done to the “regulatory standard.” Of course, there still remains a risk that bioanalytical data can be inaccurate even when meeting fully validated assay requirements. With the tiered approach, risk-based decisions are integral to tier choice and how each tier is conducted (e.g., the effective acceptance criteria). This is an important consideration for the team involved in establishing the bioanalytical method and those using the resulting data. Good communication between all parties is always recommended regarding tier assignment, and risk acceptance is another factor to consider. The GBC Team recognized this throughout the dialogue, and risk profile of a given bioanalytical strategy was influential on the recommendations from the group. Following the principles outlined in this paper facilitates understanding the degree of risk associated with any method from screening to fully validated assays. Tiered approaches offer a practical means of categorizing how much risk may be incurred in using the bioanalytical method used for the subsequent sample analysis.

CONCLUSION

The GBC Team A2 hereby presents a collective consensus on how tiered approaches to bioanalytical method performance evaluation can work or help as an important basis for further discussion. It is offered to the bioanalytical community as a whole and we anticipate further publications on the topic from the said community. Integrally, there will need to be specific application examples presented and discussed by the bioanalytical community around the tiered approach concepts. The differentiation between tiers will benefit from practical examples that can be reviewed and debated. Likewise, a debate can be anticipated on how tiered levels of bioanalytical data will support the continuum of drug development from discovery phases to supporting regulatory filing. Discussion with the regulatory authorities on how and when lower tier level data can be leveraged to support the overall drug development process will be important to the practical adoption of the approaches proposed. The GBC Team A2 intends to encourage and support such open dialogue over upcoming meetings, conferences, and other bioanalytical network events.

In view of the fact the GBC assigned a team to recommend on tiered approaches and the team was populated by experts from all regions illustrates the desire of the pan-global bioanalytical community to support vigorous discussion around the topic as a scientific way forward for our industry.

REFERENCES

1. Timmerman P, Herling C, Stoellner D, *et al.* European Bioanalysis Forum recommendation on method establishment and bioanalysis of biomarkers in support of drug development. *Bioanalysis*. 2012;4(15):1883–94.
2. Viswanathan CT. Bringing new technologies into regulatory space. *Bioanalysis*. 2012;4(23):2763–4.
3. Shah VP, Midha KK, Dighe S, *et al.* Analytical methods validation: bioavailability, bioequivalence, and pharmacokinetic studies. *Pharm Res*. 1992;9:588–92.
4. Guidance for Industry Bioanalytical Method Validation U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Veterinary Medicine (CVM), May 2001
5. Viswanathan CT, Bansal S, Booth B, *et al.* Workshop/conference report—quantitative bioanalytical methods validation and implementation: best practices for chromatographic and ligand binding assays. *Work Conf Rep AAPS J*. 2007;9(1):E30–42.
6. Fast D, Kelley M, Viswanathan CT, *et al.* Workshop report and follow-up—AAPS workshop on current topics in GLP bioanalysis: assay reproducibility for incurred samples—implications of crystal city recommendations. *Work Conf Rep AAPS J*. 2009;11(2):238–41.
7. Japanese BMV guideline for chromatographic methods. Website: http://www.nihs.go.jp/drug/BMV/250913_BMV-GL_E.pdf
8. EMEA/CHMP/EWP/192217/2009, Guideline on bioanalytical method validation. Website: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/08/WC500109686.pdf
9. Lee J, Devanarayan V, Barrett Y, *et al.* Fit-for-purpose method development and validation for successful biomarker measurement. *Pharm Res*. 2006;23(2):312–28.
10. US-FDA Guidance for Industry, Safety Testing of Drug Metabolites U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Pharmacology and Toxicology, Feb. 2008
11. CPMP/ICH/286/95 - ICH Topic M 3 (R2) Non-clinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals, June 2009
12. Timmerman P, Kall M, Gordon B, *et al.* Best practices in a tiered approach to metabolite quantification: views and recommendations of the European Bioanalysis Forum. *Bioanalysis*. 2010;2(7):1185–94.
13. Booth B. When do you need a validated assay? *Bioanalysis*. 2011;3(24):2729–30.
14. Workshop/Conference Report—Crystal City V Workshop December 2013, AAPS J in press
15. GBC Website: <http://www.globalbioanalysisconsortium.org/>
16. Timmerman P. Tiered approach revisited: introducing stage-appropriate or assay-appropriate scientific validation. *Bioanalysis*. 2014;6(5):599–604.
17. Nowatzke W, Cole T, Bowsher R. Systematic analytical validation of commercial kits for the determination of novel biomarkers for clinical drug development. *Bioanalysis*. 2010;2(2):237–47.