Editorial

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

Guest Editors: Binodh DeSilva and Philip Timmerman

Introduction to the Proposals from the Global Bioanalysis Consortium Harmonization Team

Philip Timmerman,^{1,13} Mark Arnold,² Binodh DeSilva,² Fabio Garofolo,³ Michaela Golob,⁴ Peter van Amsterdam,⁵ Shinobu Kudoh,⁶ Puran Singhal,⁷ Daniel Tang,⁸ Maria Francesca Riccio,⁹ Rafael Barrientos,¹⁰ Shrinivas Savale,¹¹ and Tatsuo Kurokawa¹²

Received 20 January 2014; accepted 9 April 2014; published online 2 October 2014

INTRODUCTION

Bioanalysis in Pharmaceutical Research & Development has been at the crossroad of science, technology, and regulations from its onset [1]. The first American Association of Pharmaceutical Scientists (AAPS)/Food and Drug Administration (FDA) Bioanalytical Workshop in 1990 in Crystal City, USA (CCI) was a major landmark for the industry to agree on execution and documentation of bioanalytical experiments. And although the resulting conference report was not a regulatory guidance, it was a roadmap for bioanalysts around the world for a decade on how to validate

and apply bioanalytical methods [2]. In early 1999, the FDA promoted bioanalysis in support of pharmacokinetic evaluation in clinical and preclinical studies more formally into the regulated space by issuing a draft guidance. After broad industry consultation during an AAPS/FDA meeting again in Crystal City (CC-II) in early 2000 [3], FDA issued a guidance for Industry on Bioanalytical Method Validation in May 2001 [4]. This guidance provided the bioanalytical community the regulatory framework for bioanalytical method validation and the application of these methods. Although the guidance set clear expectations in many areas, the lack of detail on expectations in some paragraphs resulted in different interpretations in industry or by the inspectors. This, in combination with the rapid technological advancements in separation sciences, mass spectrometry, and ligand binding assay (LBA) or cell-based assay formats, resulted in individual views on how to validate bioanalytical methods and apply them to routine sample analysis. In trying to provide assistance in the interpretation of this guidance, the FDA continued to reach out to industry at conferences. In addition, some inspection findings documented in Form 483s provided a way forward.

The 2001 guidance only referred to LBAs that enabled small molecule analysis and did not address the bioanalysis of macromolecules. In support of the rapidly growing ligand binding assay scientific community, two additional white papers were published to cover LBA aspects of macromolecule bioanalysis [5, 6]. To further discuss and clarify the 2001 FDA Guidance, FDA/AAPS organized a next meeting in Crystal City (CC-III), from which a comprehensive conference report was issued [7]. Crystal City III also put Incurred Sample Reanalysis (ISR) back on the foreground, a controversial topic which was further discussed during Crystal City IV [8]. Next, as mentioned in the Kudoh paper [1], multiple other guidelines or best practices on GLPs, GCPs, computer/software, or analytical instrument validation increasingly impacted the bioanalytical laboratory. Last but not least,

¹ Janssen Research & Development, Turnhoutseweg, 30, 2340, Beerse, Belgium.

² Bristol-Myers Squibb Company, Route 206 & Province Line Road, Princeton, New Jersey 08543, USA.

³ Algorithme Pharma, 575, Armand-Frappier Blvd, Laval, Quebec, Canada.

⁴ Merck-Serono, Am Feld 32, 85567, Grafing, Germany.

⁵ Abbott Healthcare Products, CJ van Houtenlaan 36, 1381CP, Weesp, Netherlands.

⁶ Shimadzu Shimadzu Techno-Research, 1, Nishinokyo-Shimoaicho, Nakagyo-ku, Kyoto, 604-8436, Japan.

⁷ Alkem Laboratories Ltd., C-17/7, MIDC Industrial Estate, Taloja, Navi Mumbai, 410208, India.

⁸ ICON Laboratory Services, Rm 703 A-B, Chong Hing Finance Center, No 288 Nanjing West Rd, Shanghai, 200003, China.

⁹ CAEP Centro Avançado de Estudos e Pesquisas LTDA, Rua José Geraldo Cerebino Cristóforo, 245, Campinas, SP, Brazil.

¹⁰ Magabi, currently Eurofarma Laboratórios S.A, Rod. Castello Branco, km 35,6, Itapevi, SP, Brazil.

¹¹ Torrent Pharmaceuticals Ltd, Village Bhat, Gandhinagar, 382428Gujarat, India.

¹² Keio University Faculty of Pharmacy, 1-5-30, ShibakoenMinato-kuTokyo, Japan.

¹³ To whom correspondence should be addressed. (e-mail: ptimmerm@its.jnj.com)

other regions/countries besides the USA issued their own guidelines on regulated bioanalysis [9–11].

Building the Global Bioanalytical Consortium

At the initiative of four regional professional organizations from Europe (European Bioanalysis Forum (EBF)) and North America (AAPS, Applied Pharmaceutical Analysis (APA) APA and Calibration & validation group (CVG—currently represented in GBC by Canadian Forum for Analytical and Bioanalytical Sciences CFABS), a letter was sent to the FDA and the European Medicine Agency (EMA)), formally requesting the health authorities and bioanalytical community to join hands and harmonize global bioanalysis scientific best practices. The need for global harmonization of the bioanalytical guidance was also supported by publishing this letter as an open letter [12], an initiative which was supported by many [13–15]. At the same time, the authors from aforementioned open letter together with additional representatives from these organizations (currently referred to as founding members), proposed to form an organization which brings together experts from the global bioanalytical community to discuss, share, and finally propose a harmonized view on bioanalytical best practices that could lead to a guidance: the Global Bioanalysis Consortium (GBC). A consensus was reached among around 280 delegates, including five Regulatory Agencies, during the 5th Workshop on Recent Issues in Bioanalysis (5th WRIB) in April 2010 on the main characteristic of what a “harmonization and Global Bioanalytical Guidance” should be based upon the following: science driven with inclusion of a rationale behind each requirement to prevent “box checking”. In addition, it should have a global perspective (not local issues), should not be prescriptive, and finally must get buy-in from all the countries [16]. From there, the GBC founding members proposed the mission of the organization [17] and reached out into the global bioanalytical community to build the GBC ensuring balanced representation from North America, Latin America, Europe/Middle East/Africa and Asia-Pacific.

The GBC at Work

Twenty harmonization teams (HT) were formed. These HT were tasked to discuss and propose global best practices related to their team’s theme, recognizing that some overlap would exist. The teams were categorized into three major areas: practices related to all types of technologies and molecules (A, 11 teams), practices exclusively related to the bioanalysis using ligand binding assay technology (L, 6 teams) and, similarly, practices exclusively related to chromatographic (i.e., LC-MS/MS) assays (S, 3 teams).

- A1 Scope and regulations
- A2 Tiered approach
- A3 Method transfer, partial, and cross validation
- A4 Reagents and reference standards
- A5 Sample management
- A6 Stability
- A7 Repeat analysis and incurred sample reproducibility
- A8 Documentation
- A9 Analytical instrument qualification
- A10 New frontiers (initial focus on accelerator mass spectrometry, dried blood spots and inductively

coupled plasma mass spectrometry (ICP-MS)—the latter two not becoming active)

- A11 Biomarkers (halted in 2013)
- L1 Specific run acceptance criteria
- L2 Assay operation
- L3 Assay formats
- L4 Reagents stability
- 16. Automation
- L5 L6 immunogenicity (effect on pharmacokinetics)
- S1 Specific run acceptance criteria
- S2 Assay operations
- 20. S3 chromatographic run quality.

At the same time, the GBC identified communication as an important success factor: a dedicated website was built to provide regular process updates and share the draft conclusions of some teams, a LinkedIn community discussion group was set up, and Steering Committee members and/or HT leads provided continued updates to the global bioanalytical community on the status of discussions at international bioanalytical meetings in all regions. Finally, webinars were organized to provide preview and discussion opportunity to all.

The original idea of bringing the community together in a global conference hosted by the GBC was abandoned. In turn, many GBC HTs have now published their proposals under the umbrella of this manuscript [18–30] or report back on their discussions via the GBC website: <http://www.globalbioanalysisconsortium.org/Harmonizationteams/> as part of the progress and status reports given for each harmonization team.

Future Direction

“The only thing that is constant is change” (Heraclitus, 500 B.C.).....this is certainly true for regulated bioanalysis. Without any doubt, technology will evolve and insights on how to execute regulated bioanalysis will change in the years to come. Our flexibility towards these changes is important. The conclusions from the GBC should be read as current state of the art proposals for best practices identified by the HTs, complemented with community feedback, built on a desire to have a common understanding of the guidelines. Where possible and as needed, the papers will also highlight and provide contextualization of the areas of ambiguity or where the team was not able to agree on a harmonized approach.

More importantly, the take home message from discussions within the GBC and at conferences throughout the world is a strong desire of the global bioanalytical community to continue on the path of harmonization. The GBC is aware that, in addition to US FDA, Brazil Agência Nacional de Vigilância Sanitária (ANVISA), the (EMA), and Japanese Ministry of Health, Labour and Welfare (MHLW), other countries may be issuing their own guidelines on regulated bioanalysis in the near future. And although there is an inherent risk of diverging or contradicting guidance, the GBC anticipates that the conclusions from the GBC work will be considered when authorities are defining criteria for regulated bioanalysis in their countries.

In the mean time, we continue to invite the industry to openly share their experience and interpretation of the

guidance and continue to work towards a common science-based understanding of the application of this guidance in their day to day work. As recorded in the mission charter of the GBC, it is our ambition to serve as a pivot point on the continued harmonized interpretation and/or updates of globally agreed guidance. With new guidance or technologies to come, GBC may play a role in bringing scientist together, as part of existing teams or by forming new teams. And of course, the GBC will be available for any dialog with the authorities if requested.

We welcomed the growing connectivity and communication between regulators from different regions and countries, and hope this will, in absence of one global Guideline, intensify in favor of harmonized interpretation and application of the different guidance in the future.

Finally, the GBC Steering Committee wishes to thank all the scientists who contributed to the outcome of the GBC discussions for their participation, persistence, and hard work.

ACKNOWLEDGMENTS

Additional founding members: Surendra Bansal (F. Hoffmann-La Roche), Steve Lowes (Quintiles), Douglas Fast (Covance), and Eric Woolf (Merck & Co).

REFERENCES

- Kudoh S, Timmerman P, van Amsterdam P, Arnold M, Garofolo F, Savale S, *et al.* Global Harmonization on Regulated Bioanalysis and Global Bioanalysis Consortium: a historic perspective on the evolution of regulated bioanalysis since 1990 and why globalization requires harmonization. *Pharm Tech Japan*. 2012;28(3):489–99.
- Shah VP, Midha KK, Dighe S, *et al.* Analytical methods validation: bioavailability, bioequivalence, and pharmacokinetic studies. *Pharm Res*. 1992;9:588–92.
- Shah V, Midha K, Findlay J, *et al.* Bioanalytical method validation—a revisit with a decade of progress. *Pharm Res*. 2001;17(12):1551–7.
- 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
- Findlay JW, Smith WC, Lee JW, Nordblom GD, Das I, *et al.* Validation of immunoassays for bioanalysis: a pharmaceutical industry perspective. *J Pharm Biomed Anal*. 2000;21(6):1249–73.
- DeSilva B, Smith W, Weiner R, Kelley M, Smolec J, *et al.* Recommendations for the Bioanalytical Method Validation of Ligand-Binding Assays to Support Pharmacokinetic Assessments of Macromolecules Pharmaceutical Research. Nov 2003. Vol. 20, No. 11.
- Viswanathan CT *et al.* Workshop/conference report—quantitative bioanalytical methods validation and implementation: best practices for chromatographic and ligand binding assays. *AAPS J*. 2007;9(1):E117–22.
- Fast DM *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. *AAPS J*. 2009;11(2):238–41.
- Website: EMEA/CHMP/EWP/192217/2009, Guideline on bioanalytical method validation. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/08/WC500109686.pdf
- Website: MHLW Guideline (Japan). <http://bioanalysisforum.jp/images/T130918I0020.pdf#zoom=100>
- Website: Anvisa Guideline (Brazil). http://bvsms.saude.gov.br/bvs/saudelegis/anvisa/2012/rdc0027_17_05_2012.pdf
- Timmerman P, Lowes S, Fast DM, *et al.* Request for global harmonization of the guidance for bioanalytical method validation and sample analysis. *Bioanalysis*. 2010;2(4):683.
- Bansal S, Arnold M, Garofolo F. International harmonization of bioanalytical guidance. *Bioanalysis*. 2010;2(4):685–7.
- van Amsterdam P, Lausacker B, Luedtke S, *et al.* Towards harmonized regulations for bioanalysis: moving forward! *Bioanalysis*. 2010;2(4):689–90.
- van Amsterdam P, Arnold M, Bansal S, *et al.* Building the Global Bioanalysis Consortium: working towards a functional globally acceptable and harmonized guideline on bioanalytical method validation. *Bioanalysis*. 2010;2(11):1801–3.
- Savoie N, Garofolo F, van Amsterdam P, *et al.* 2010 white paper on recent issues in regulated bioanalysis & global harmonization of bioanalytical guidance. *Bioanalysis*. 2010;2(12):1945–60.
- Website: <http://www.globalbioanalysisconsortium.org/>
- Young GC, Seymour DR, Dueker SR, Timmerman P, Arjomand A, Nozawa K. New Frontiers—Accelerator Mass Spectrometry (AMS): Recommendation for Best Practices and Harmonization from Global Bioanalysis Consortium Harmonization Team. *AAPS J*. 2014;16(2).
- Bower JF, McClung JB, Watson C, Osumi T, Pastre K. Recommendations and best practices for reference standards and reagents used in bioanalytical method validation. *AAPS J*. 2014;16(2):352–6.
- Verhaeghe T, Barton HH, Hara H, Hucker R, Kelley M, Picard F, *et al.* Recommendations from the global bioanalysis consortium team a8: documentation. *AAPS J*. 2014;16(2):240–5.
- Kelley M, Beaver C, Stevenson LF, Bamford R, Gegwich P, Katsuhiko Y, *et al.* Large molecule run acceptance: recommendation for best practices and harmonization from the Global Bioanalysis Consortium Harmonization Team. *AAPS J*. 2014;16(2):221–5.
- Dudal S, Baltrukonis D, Crisino R, Goyal MJ, Joyce A, Österlund K, *et al.* Assay Formats: Recommendation for Best Practices and Harmonization from the Global Bioanalysis Consortium Harmonization Team. *AAPS J*. 2014;16(2).
- Ahene A, Calonder C, Davis S, Kowalchick J, Nakamura T, Nouri P, *et al.* Automation practices in large molecule bioanalysis: recommendations from group L5 of the global bioanalytical consortium. *AAPS J*. 2013;16(1):164–71.
- Stevenson L, Kelley M, Gorovits B, Kingsley C, Myler H, Österlund K, *et al.* Large molecule specific assay operation: recommendation for best practices and harmonization from the Global Bioanalysis Consortium Harmonization Team. *AAPS J*. 2013;16(1):83–8.
- Fluhler E, Vazvaei F, Singhal P, Vinck P, Li W, Bhatt J, *et al.* Repeat Analysis and Incurred Sample Reanalysis: Recommendation for Best Practices and Harmonization from the Global Bioanalysis Consortium Harmonization Team. *AAPS J*. 2014;16(3).
- Woolf E, McDougall S, Fast D, Andraus M, Barfield M, Blackburn M, *et al.* Small Molecule Specific Run Acceptance, Small Molecule Specific Assay Operation, and Small Molecule Chromatographic Run Quality Assessment: Recommendation for best practices and harmonization from the Global Bioanalysis Consortium Harmonization Teams. *AAPS J*. 2014;16(3).
- King LE, Farley E, Imazato M, Keefe J, Khan M, Ma M, *et al.* Ligand Binding Assay Critical Reagents and Their Stability: Recommendations and Best Practices from the Global Bioanalysis Consortium Harmonization Team. *AAPS J*. 2014;16(3).
- van de Merbel N, Savoie N, Yadav M, Ohtsu Y, White J, Riccio MF, *et al.* Stability: Recommendation for Best Practices and Harmonization from the Global Bioanalysis Consortium Harmonization Team. *AAPS J*. 2014;16(3).
- Briggs RJ, Nicholson R, Vazvaei F, Busch J, Mabuchi M, Mahesh KS, *et al.* Method Transfer, Partial Validation, and Cross Validation: Recommendations for Best Practices and Harmonization from the Global Bioanalysis Consortium Harmonization Team. *AAPS J*. 2014. doi:10.1208/s12248-014-9650-3.
- Sailstad JM, Amaravadi L, Clements-Egan A, Gorovits B, Myler HA, Pillutla RC, *et al.* White Paper—Consensus and Recommendations of a Global Harmonization Team on Assessing the Impact of Immunogenicity on Pharmacokinetic Measurements. *AAPS J*. 2014;16(3):488–98. doi:10.1208/s12248-014-9582-y.