CLINICAL INVESTIGATION

Development of a generic laboratory manual for biological sample logistics in clinical pharmacokinetic studies

Richard W Abbott*[1], Rebecca Sleigh[2], Jeff Long[3], Carina Ekstrom[4], Bernd Matthes[5] & José Groenboom-Nieuwenhuijzen[6]

[1]Bayer Pharma AG, Aprather Weg 18a, 42096 Wuppertal, Germany
[2]LGC, Newmarket Road, Fordham, Cambridgeshire, CB7 5WW, UK
[3]UCB Pharma, 208 Bath Road, Slough, SL1 3WE, UK
[4]Ferring Pharmaceuticals A/S, Kay Fiskers Plads 11, DK– 2300 Copenhagen S, Denmark
[5]Celerion Switzerland AG, Allmendstrasse 32, 8320 Fehraltorf/Zürich, Switzerland
[6]Westerbrink 3, 9405 BJ Assen, The Netherlands (From 28 September 2015 onwards: Amerikaweg 18, 9407 TK Assen, The Netherlands)
*Author for correspondence:
Tel.: +49 202 36 8442
richard.abbott@bayer.com

The European Bioanalysis Forum (EBF) has been organizing 'Topic Teams' on issues of importance to the bioanalytical community for several years [1]. Many of these teams focus on internal bioanalytical issues of importance to bioanalysts such as technological innovation, regulatory questions and novel assay validation approaches [2]. However, there is an increasing recognition that we do need to pay more attention to external factors such as interactions and communication regarding clinical, toxicology and project team participation [3]. Topic Team 12, a virtual team of ten EBF member companies and meeting every 2 to 3 weeks by teleconference, focused on topics of interest associated with clinical trial support. Following a member survey and extended team discussion it was felt that the generation of a generic laboratory manual for use in clinical pharmacokinetic studies would offer a potential solution to the common problems created by poor logistical sample management and communication in single and multicentre trials [4]. Such a document would create a single platform to which clinical sites, central laboratories and bioanalytical groups could all relate. The benefits could be significant since a harmonized document should stimulate a consistent way of working and would be a first step in the elimination of many current issues.

Bioanalytical draft process

Individual company laboratory manuals were shared with the team, with permission, from ten pharmaceutical companies and CROs. A subteam from Topic Team 12, including Rebecca Sleigh (LGC), Jeff Long (Shire [now at UCB]) and Carina Ekstrom (Ferring) and facilitated by Richard Abbott (for EBF) convened to brainstorm a process to consolidate these ten documents into a single document describing best practice. The concept document, at that time with input from bioanalytical experts only, was presented at the EBF meeting in Barcelona (November 2013), where it was well received [5].

Clinical Focus Workshop

To give the document more credibility with all stakeholders involved in clinical trial management, the EBF decide to broaden the input into the concept document by hosting a Focus Workshop [6], inviting input from the identified stakeholders: clinical colleagues in clinical trial management, sample logistics, professionals involved in sample shipment, clinical sites, trial nurses, central laboratories, clinical pharmacokinetics and QA/regulatory groups. The workshop was held in Brussels on 05–06 February 2014 and attracted around 60 attendees with good representation from all aforementioned stakeholders. Short presentations in which stakeholders gave an introduction based on their expertise preceded each workshop discussion session. Hence, throughout the program we allowed for extended debate and focused discussion. The workshop was very interactive and the degree of passion and engagement was very encouraging.

The seven sessions were led by experts in their fields and included:

- Clinical PK perspective: Donna Smith (Cancer Research, UK) and Bart Remmerie (Janssen R&D, Belgium)
- Sample Logistics: Scott Vincent (A4PBio, UK) and Jean-Guy de Gruben, (World Courier, Belgium)

FUTURE SCIENCE part of fsg

- Clinical Study Monitor: Tammy Harter (Covance, UK), Hanneke van Asche and Peter van Amsterdam (Abbott Healthcare Products)
- Clinical Operations: Julia Gall (CRS, Germany) and Martin Harbers (PRA Health Sciences, The Netherlands)
- Phase I unit: Els Jacob (Janssen R&D, Belgium) and Berry Everts (QPS, The Netherlands)
- Central Labs: Gerrit Schönicke (LKF, Germany) and Natalia Rossignol (Covance, Switzerland)
- Quality Assurance (David Butler, RQA, UK).

Full details of the presentations can be found at: http://labman.europeanbioanalysisforum.eu/Slides

Discussion points from these sessions included:

- Production of training videos regarding sample logistics for clinical site personnel
- On-site visits of bioanalytical scientists to the clinical site
- Use of investigator meetings to convey the message about the importance of compliance to the documented laboratory manual procedures
- Bioanalytical personnel to routinely attend study start-up meeting
- Standardized sample labeling
- Data logging in sample shipments
- Freezer temperature ranges
- How often are backup samples needed?

Chapter headings from finalized generic laboratory manual.

1. Document History
2. Purpose and Scope
3. Contacts/key personnel/responsible staff
4. Documents/Information
5. Supplies
6. Equipment
7. Labeling
8. Sample Handling and Collection Procedures
9. Storage and Stability
10. Shipping
11. Sample disposal
12. Signatures
13. Appendix
    - Example Sample Inventory List
    - Sample Receipt Form
    - Example Urine Handling Sheet
    - Centrifuge Adjustment Conversion Table

- Earlier sharing of information for the clinical protocol and laboratory manual would be welcomed, currently this often happens too late
- Suggestion to perform sample reconciliation before the samples reach the bioanalytical laboratory (queries resolved before they are on the critical path)

Final revision process

At the end of the workshop it was agreed to revise the draft laboratory manual to incorporate not only the perspective from the workshop but to continue the interaction with representatives from the stakeholders in dedicated teleconferences in the months after the workshop to ensure the final document considered every aspect in great detail. At the same time, it strengthened our belief that multidisciplinary input into the document will enhance the credibility and will encourage widespread adoption. So, using a similar approach to the one used in the drafting of the original document, a number of sub teams were established to revise the entire manual with a final review by the entire topic team. We were able to secure appropriate stakeholder input in those sections where their input was essential. The result is a final document of which we can be justifiably proud: the Generic Laboratory Manual for Biological Sample Logistics in Clinical Pharmacokinetic Studies [7]. Wherever possible, tabulation has been used to make the document more 'user-friendly' for the end user. In summary, the contents of the document are summarized in Box 1 under the following headings:

Summary

We would like to encourage all readers to take a look at the document and to implement and gradually stimulate the use of it in their companies. We are aware that for some organizations the added value from their individual company perspective may be limited since the EBF lab manual may be 90% similar to their own company document. But, as in all areas of harmonization, it is the remaining 10% that creates confusion, source errors and extra work.

We should emphasize that there is no regulatory requirement to use the manual but we know that standardization of the procedures involved in the laboratory manual will help everyone.

We are convinced that you will find it useful.

Acknowledgement

This document involved the combined thoughts and opinions of many individuals and companies and we would like to acknowledge their contribution. Special thanks to the EBF Steering Committee for sponsoring EBF Topic Team 12 and to the contributors as follows:

EBF Topic Team 12

José Groenboom-Nieuwenhuijzen, PRA Health Sciences (lead)
*Richard Abbott, Bayer Pharma AG
Carolyn Mailer, Covance
Rene Megens, Quintiles
Bernd Matthes, Celerion
Iris Vanwelkenhuysen, Janssen R&D
Marianne Scheel Fjording, Novo Nordisk
*Rebecca Sleigh, LGC
*Carina Ekström, Ferring
*Jeff Long, UCB
Morten A Kall, Lundbeck
Steve White, GlaxoSmithKline
Philip Timmerman, Janssen R&D
*Lab Manual Subteam

Clinical Focus Workshop Review Team

Ingeborg Detzel, Boehringer-Ingelheim (Clinical)
Johanna Beekman, Bayer Pharma AG (Clinical Sample Management)
Berthold Lausecker, CRS (Bioanalytical)
Berry Everts, QPS (Clinical)
Olivia Daignières, Sanofi (Clinical and Non-Clinical Sample Management)
Marten Harbers, PRA Health Sciences (Clinical)
Natalia Rossignol, Covance (Central Laboratory)
Peter Pruim, PRA Health Sciences (Bioanalytical)
Suzanne Sweet, LGC (Clinical)
David Wilkinson, Quintiles (Central Laboratory)
Els Jacob, Janssen R&D (Clinical)
Bärbel Wilke, LKF (Central Laboratory)
Debbie Sisco, Janssen R&D (Clinical)
Birgit Felden de Neumann, Merck Serono (Bioanalytical)
Melloney Dröge, ABL (Bioanalytical)
Philip Timmerman, Janssen R&D (Bioanalytical)
Finally, multiple clinical colleagues participating at Focus Workshop

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

1 The European Bioanalysis Forum (EBF). www.europeanbioanalysisforum.eu/home_membership.php

2 Timmermann P, Luedtke S, van Amsterdam P, Brudny-Kloeppel M, Lausecker B. Incurred sample reproducibility: views and recommendations by the European Bioanalysis Forum. *Bioanalysis* 1(6), 1049–56 (2009).

3 Dudal S, Staack RF, Stoellner D *et al.* How the bioanalytical scientist plays a key role in interdisciplinary project teams in the development of biotherapeutics – a reflection of the European Bioanalysis Forum. *Bioanalysis* 6(10), 1339–1348 (2014).

4 Sample logistics: problems and solutions in multi-center clinical trials. http://bcn2013.europeanbioanalysisforum.eu/slides/PDF/P3-Log-1%20Jose%20Groenboom%20TT-12%20final%2005Nov13.pdf

5 Sample logistics: problems and solutions in multi-center clinical trials. Proposed Generic EBF Lab Manual. http://bcn2013.europeanbioanalysisforum.eu/slides/PDF/P3-Log-2%20Rebecca%20Sleigh%20Lab%20Manual%20BCN2013%20subteam%20Fin.pdf

6 EBF lab manual. http://labman.europeanbioanalysisforum.eu/General

7 EBF proposed lab manual template. http://labman.europeanbioana-lysisforum.eu/site/ebf_bru2014/assets/documents/Lab%20manual%20final%2012Aug14.pdf