EBF Cyberconnect Meeting

Biomarkers: Setting the Stage

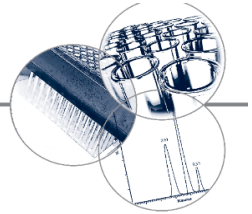
Context of Use, removing the appetite for PK-criteria and practice for BM: The Basics Revisited

Kyra Cowan - On behalf of the EBF

2012: EBF Recommendation Paper

WHITE PAPER

For reprint orders, please contact reprints@future-science.com



European Bioanalysis Forum recommendation on method establishment and bioanalysis of biomarkers in support of drug development

Biomarkers have become increasingly important in drug development and many bioanalysts are getting involved. Consequently, different views on how to approach the bioanalysis of biomarkers have been published or are being developed. The European Bioanalysis Forum has intensively discussed this topic since 2010 and is ready with their recommendation on method establishment and bioanalysis of biomarkers. Acknowledging that the challenges step outside the bioanalytical laboratory is a cornerstone of our recommendation. The importance of integrating all scientific aspects, from purely analytical aspects, all the way to understanding the biology and effects of the biomarker, prior to embarking on method establishment or sample analysis, cannot be underestimated. Close and iterative interactions with the teams requesting the data is imperative to develop a bioanalytical strategy that combines science, analytical performance and regulations. The European Bioanalysis Forum developed a straightforward decision tree to help the scientific community in developing a bioanalytical strategy for any biomarker in drug development.

1. Introduction & scope

In this manuscript, the European Bioanalysis Forum (EBF) reports back from their internal discussions on the method establishment and bioanalysis of biomarkers in support of drug development performed in the regulated bioanalytical environment. Initially, these discussions were an integral part of an EBF subteam assigned to provide a recommendation on the (bio)analytical community's approach to biomarker bioanalysis [3]. Nevertheless, although the latter paper provides excellent insight into the science of how to approach biomarker bioanalysis, the EBF experienced that the industry was moving forward too often to analyze biomarkers using existing regulated bioanalysis standards [4,103–105] or remained confused on fully embracing the opportunities and tiered

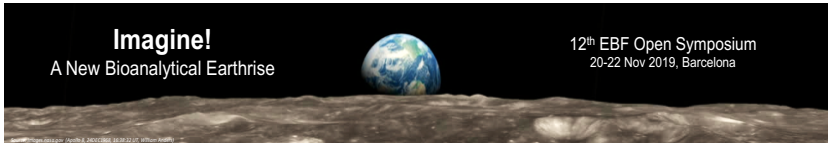
Philip Timmerman*[1], Christian Herling[2], Daniela Stoellner[3], Birgit Jaitner[3], Susanne Pihl[4], Karen Elsby[5], Neil Henderson[5], Begona Barroso[6], Stephanie Fischmann[7], Arjen Companjen[8], Amanda Versteilen[8], Stewart Bates[9], Clare Kingsley[10]

Bioanalysis (2012); 4(15): 1883–94

2019: Autumn Focus & 12th EBF OS

Autumn Focus Workshop
Biomarker Assay Validation
Bringing *Context of Use* into practice

NH Málaga Centro - Málaga, Spain
18-19 September 2019



12th EBF Open Symposium
Hesperia Tower, Barcelona, Spain

Imagine!
A New Bioanalytical Earthrise

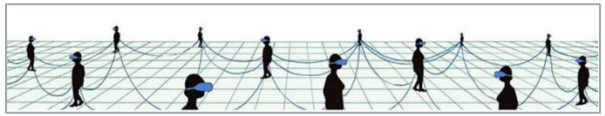
Where can EBF be of help?

1. Publish recommendation
2. Interact with authorities @ EBF level
3. Provide Training
4. Continue regular meetings as this one
5. Continue to connect with other cross industry groups

Launchpad session

2020

1. Publish recommendation
2. Interact with authorities @ EBF level ? → in cross industry collaborations
3. Provide Training
4. **Continue regular meetings as this one**
5. **Continue to connect with other cross industry groups**



aaps
American Association of Pharmaceutical Scientists

EBF

Autumn Focus Workshop

The FW is organised in collaboration with the Biomarker and Precision Medicine Community (AAPS), CBF and JBF

aaps

Biomarkers in Pharma R&D

A roadmap from *Context of Use* to *Using the data*

In CYBERSPACE

15-17 September 2020

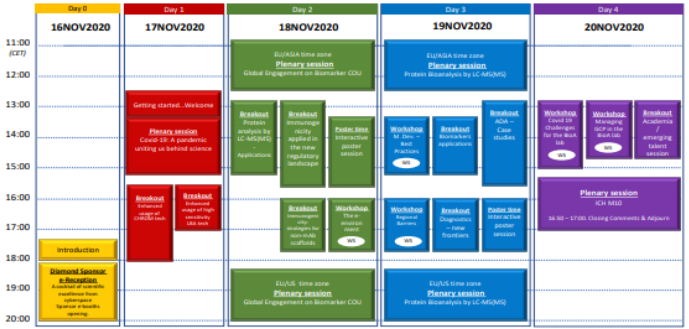
EBF

EBF Open Symposium

17 – 20 November 2020

N° 13 From Cyberspace - Staying Connected

13th EBF Open Symposium – Agenda outline



1. **Publish recommendation**
2. Interact with authorities @ EBF level ? → in cross industry collaborations
3. Provide Training
4. Continue regular meetings as this one
5. Continue to connect with other cross industry groups

2020

White Paper

For reprint orders, please contact: reprints@future-science.com

Bioanalysis

Update to the European Bioanalysis Forum recommendation on biomarkers assays; bringing context of use into practice

Joanne Goodman[1], Kyra J Cowan[2], Michaela Golob[3], Lars Karlsson[4], Ulrich Kunz[5], Robert Nelson[6], Hans Ulrichts[7], Lauren Stevenson[8], Linda Terry[9] & Philip Timmerman*,[10]

Bioanalysis (2020) 12(20), 1427–1437

Learnings from 2019 and 2020 again:

- 2020-FW workshop reconfirmed the community struggles to apply CoU
- Hurdles didn't change
  - Difficult to identify or get stakeholder/end-user engaged
  - Fear for 483
  - Fear to leave the PK SOP-comfort zone

2021 bioanalytical community poll: still struggling…

1. **No proper guidance available** to understand what is expected for the various use cases
2. **Convincing stakeholders of applying CoU** process and receiving correct feedback from stakeholders
3. Sponsors tend to think in terms of **broad categories** (exploratory & primary and secondary end point).
4. The expectation is that an **off the shelf commercial kit or prior validated method will meet** the requirements of the biomarker measurement.

Game-changer: recommendation highlights, what we can do…

What is Context of Use for BM Assays?

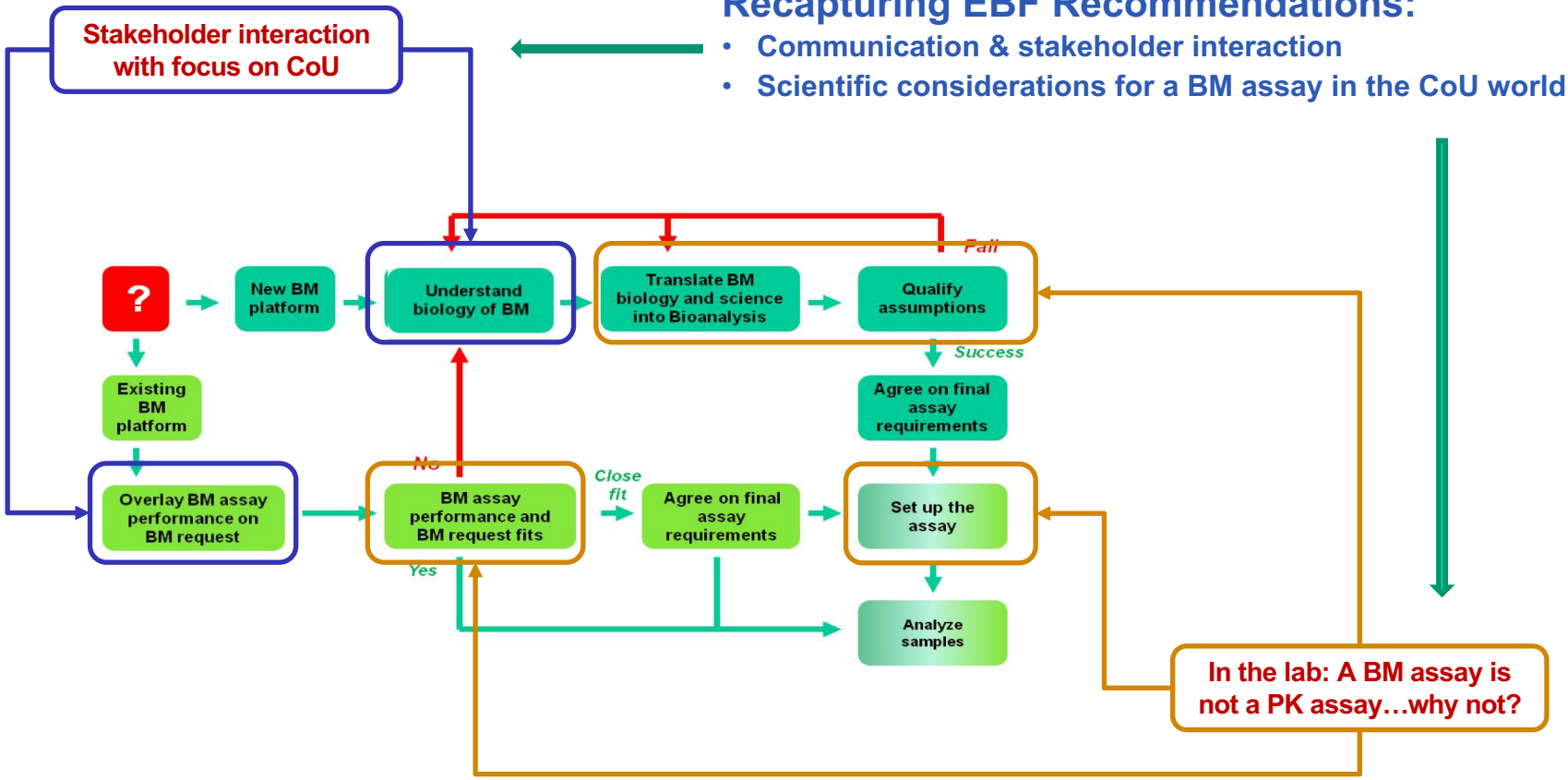
- Detailed definition of the purpose of the assay for each analyte
  - Understood and agreed upon by all stakeholders
  - Documented in method summaries, validation plans, validation reports

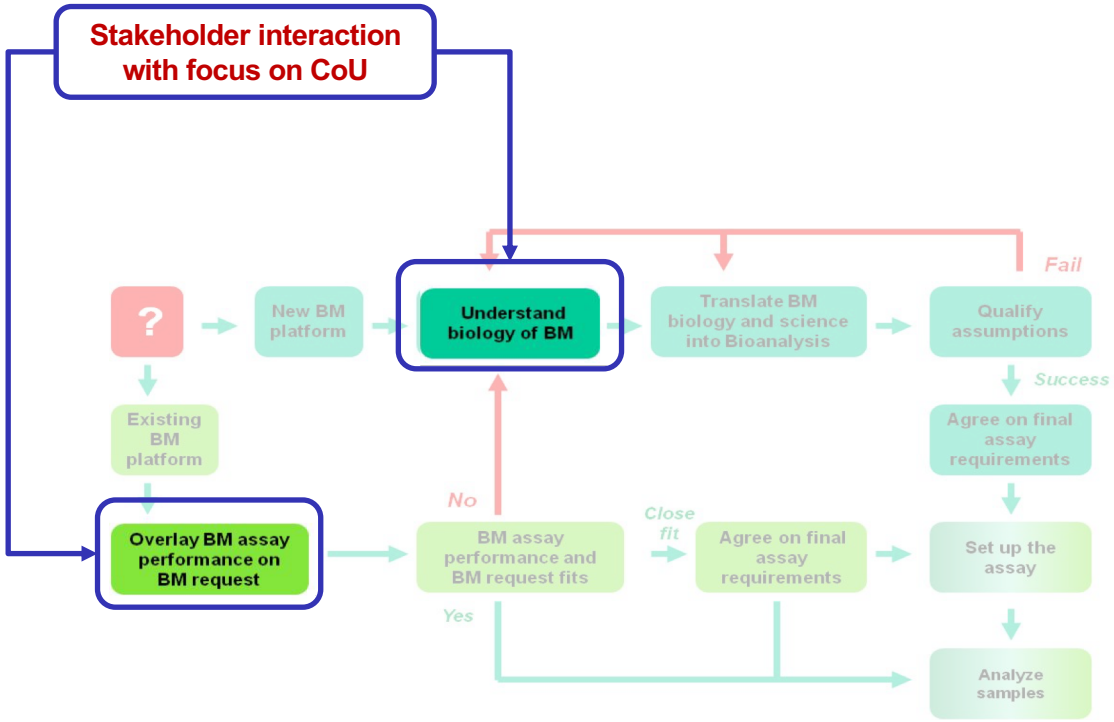
- What does it look like?:
  - Examples and case studies provided during this workshop
- Key thoughts: To understand the biology, pharmacological effect; to understand what the data will be used for, e.g. scientific or safety decisions taken, to then consider what is possible from a BA perspective; to understand biological, analytical variability…
- Ultimately: To ensure the appropriate interpretation of data to serve patients.

- What does it not look like?:
  - „To quantify the analyte“

Recapturing EBF Recommendations:

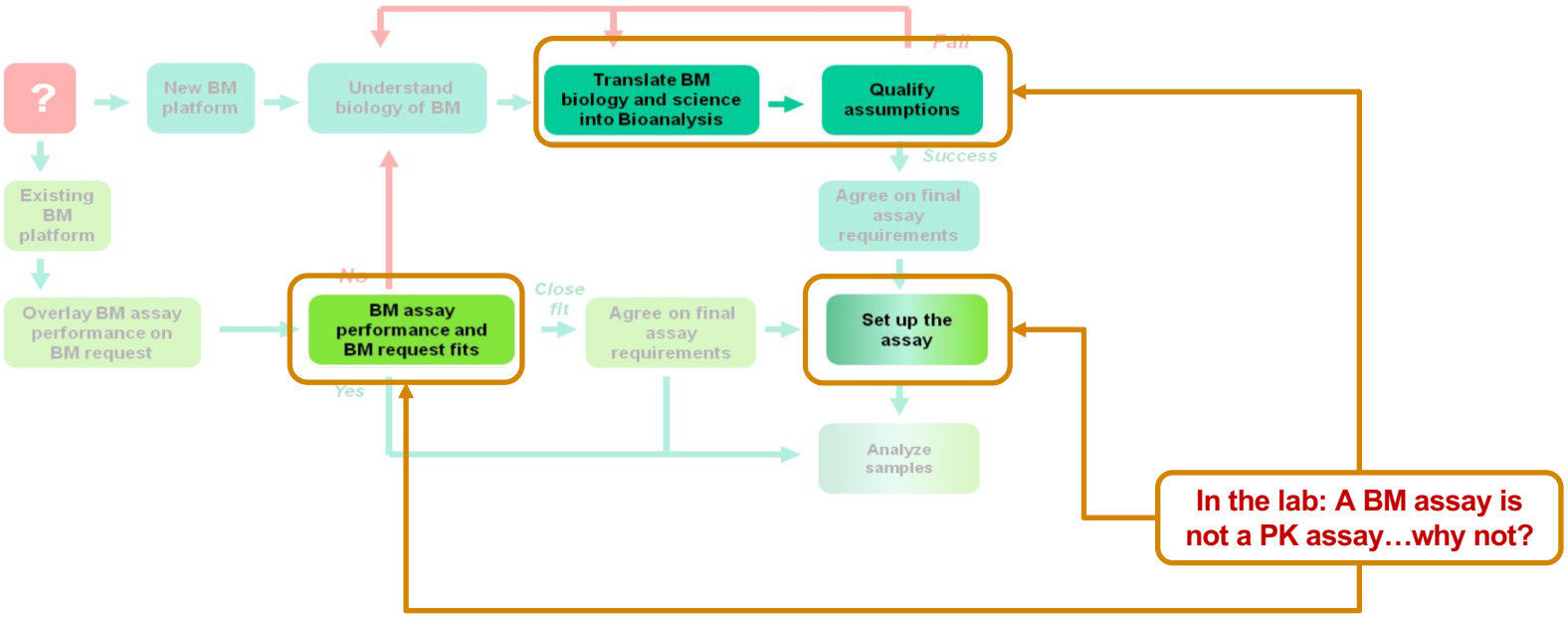
- Communication & stakeholder interaction
- Scientific considerations for a BM assay in the CoU world




Stakeholder interaction with focus on CoU
?
New BM platform
Understand biology of BM
Translate BM biology and science into Bioanalysis
Qualify assumptions
Fail
Success
Existing BM platform
Agree on final assay requirements
Overlay BM assay performance on BM request
No
BM assay performance and BM request fits
Close fit
Agree on final assay requirements
Set up the assay
Yes
Analyze samples

1/2: Highlights from the EBF 2020 Recommendations

- **Communication is KEY, and must be sustained.**
  - Major challenge, given organizational structures and perceptions
- **Know your stakeholders and involve them.**
  - Understanding the complexity of matrix environment, mapping is critical
  - Program Leads, Project Managers, Safety, Pharmacologists, Modelers, etc.
- **Agree on and document the COU.**
  - Implement the right assay for the right data and the right decisions
  - May require some high level, appropriate training to gain common ground


?
New BM platform
Understand biology of BM
Translate BM biology and science into Bioanalysis
Qualify assumptions
Fail
Success
Existing BM platform
Agree on final assay requirements
Overlay BM assay performance on BM request
No
BM assay performance and BM request fits
Close fit
Agree on final assay requirements
Set up the assay
Yes
Analyze samples
In the lab: A BM assay is not a PK assay…why not?

2/2: Highlights from the EBF 2020 Recommendations

- **A BM Assay is NOT a PK Assay: Why Not?**
  - Challenges, both scientific and analytical
  - Scientific: expression levels, endogenous forms, variability, sample collection
  - Analytical: Technological advances, platforms available, kits or de novo, PK or biomarker assay expertise or

  Plus: Analytical variability and the achievable precision for an assay will be affected by assay platform and reagent choices.

- **Differences from PK assays**
  - Infinite COU‘s
  - Starting material (Endogenous vs. Recombinant, Platforms, reagents, kit);
  - Development and Validation: Parameters, Acceptance criteria
  - Regulatory Guidances: Limited

Bottom Line: Agreement across the team and documentation of the COU

A BM Assay is NOT a PK Assay: Development & Validation?

The context is ever-changing… **…but key ingredients stay the same:**

- **Development (new assay), Characterization (existing assay), Feasibility (testing with known COU)**: more or less constant experiments (depending on analytical technique), independent of COU:
  - Parallelism (Selectivity, MRD, LLOQ)
  - Specificity
  - Detectability in target matrix

- **Validation:** a “rubber stamp”, based on previous assay characterization, and not equal to development.
  - Validation purely confirms, in a controlled environment, what is already known from the experiments conducted in method development.

EBF Recommendations on BM Assay Characterisation

- **COU must first be defined and agreed upon by all stakeholders:**
  - **EBF recommends** that the requirements for assay characterization occurs, and is agreed upon, as part of the COU conversation with the relevant stakeholders.

- **Key Topics to include:**
  - Type of assay required (e.g. free or total, in-house assay, commercial kit, single analyte, multiplex, research use, diagnostic)
  - Format of the assay and critical reagents
  - Technology choice, with pros and cons
  - Do you have access to biomarker samples that are reflective of the subjects (e.g. commercial or samples from other trials, biobank)?

EBF Recommendations on BM Assay Characterisation

- **Several BM assay-specific parameters should be evaluated early on:**
  - Precision: one aspect - biological variability in population, as well as analytical variability present within the assay.
  - Parallelism, selectivity, specificity, stability and sample processing must be equally evaluated.

- **EBF does not recommend definitive terms for dividing up into differing purposes, which may result in inappropriate regulatory hurdles being created around biomarker validation.**
  - Avoid categories or buckets for BM assays when starting with method development:

- The term “fit for purpose” or “qualified” rather than “fully validated” can create a perspective that the quality of the assay is somehow inferior. However, in practice this is not the case.

Why is Documenting CoU for BM Assays Important?

- **The purpose of the assay may change from one study to the next**
  - The types of decisions being made based on the results may vary and should be communicated each time
  - Without an agreed COU there is a risk of implementing the wrong assay, with inappropriate characterizations and therefore validation
  - Leads to incorrect data and decisions, negatively impacting patients

- **Institutional knowledge may change:** new team members, people may leave

Bottom Line: Bioanalytical scientist takes ownership and accountability to communicate with their stakeholders and provide adequate education.

We Hear You

COU Communication

1. Getting from fluffy terms to a working document that can be shared with different areas
2. No proper guidance available to understand what is expected for the various use cases
3. Convincing stakeholders of applying the CoU process and receiving the correct feedback from stakeholders
4. Internal pressures (**fear of 483**)
5. Communication, roles and responsibilities in R&D
6. Getting the detail for COU from the sponsor at the contracting stage to understand the purpose of the biomarker measurements
7. Convincing that FFP validation = Full validation
8. Sponsors are still having a PK mindset for both assay validation and sample analysis

COU Analytical

1. Choosing the validation parameters and the acceptance criteria
2. Deciding the level and extent of validation of assays that are already implemented in laboratories.
3. Making sure the correct species is detected and having a proper validation guidance for the various potential uses of a biomarker
4. Understanding regulators expectations, especially for late phase/critical data
5. Making sure everyone (internally, externally) does not automatically fall back into doing PK validation experiments and using PK acceptance criteria
6. Still ticking boxes according to BMV guidelines for BM
7. Lack of understanding of the biology of the biomarker.and the limits of the analytical platforms

We Asked and We Are Listening

Pharma

1. Understanding how the use of a biomarker influences the validation and why validation is not a set number of parameters (as for PK)
2. That non-GxP status does not mean invalid data
3. Understanding the need for defining CoU when assays are available (for instance at central labs)
4. How and when to initiate the CoU discussion
5. SOP's and QA too ridged to allow flexibility
6. Communication, roles and responsibilities in organisations
7. We've heard comments that they fear the regulators will not be on board when reviewing study data at audit.
8. Very reserved on the whole idea of FFP or whatever phrase is chosen

CRO

1. Understanding their role in the CoU application
2. All struggle with understanding of validation & reg. requirements for biomarker validation/analysis.
3. Sponsors tend to think in terms of broad categories (exploratory & primary and secondary end point).
4. Internal and external GLP-QA and BD still equate FFP with lower quality validation.
5. The expectation is that an off the shelf commercial kit or prior validated method will meet requirements of the biomarker measurement. Need to perform feasibility tests, including selectivity, stability and parallelism.
6. Since in the FDA BMV guidance, study directors in bioanalysis to argue with customers/consultants about the need or not of validation or qualification for the assay method

Recognizing why we are all here: Game-changer

Cross-Industry Implementation of COU for patients

- Omission of COU for Biomarker Assays is Dangerous
  - Wrong COU: inappropriate acceptance criteria, poor use of resources and time, wrong decisions, failed drug development.
  - COU must be re-evaluated as the „purpose“ changes, will dictate assay characterization and much later validation.
    - Decisions need to be driven by the science, not a framework or categories.
- COU is everything, and may change over time
  - Diversity and complexity of biomarker assays is wide, a framework may stifle the crucial conversations that are needed for defining the assay purpose.

Therefore: default to the misapplication of PK approaches and criteria is wrong.

Biomarker Assay COU: The Game-Changer

- Understand what it is
- Understand why it is critical
- Understand how to implement it, considering the many challenges
  - Scientific
  - Analytical
  - Stakeholder management

Contact Information

Questions: info@e-b-f.eu

European Bioanalysis Forum vzw

www.e-b-f.eu