EBF

16th Open Symposium

Science Winning the Race

Context-of-Use Strategy

Biomarkers and Beyond…

Kyra Cowan, Merck KGaA, on behalf of the EBF

15-17 November 2023, Barcelona

Our Session:

Day 2: 16 November 2023

9:00	**10:40**	**Session 8: CoU Strategy - Biomarkers and beyond… - Auditorium**
		Session Chair: Kyra Cowan, Merck KGaA, on behalf of the EBF
9:00	9:20	***EBF team presentation - BM, qPCR, ADA…CoU is everywhere...***
		Kyra Cowan, on behalf of the EBF
9:20	9:40	***Nanda Gruben, ICON***
		Case studies for testing stabilities for biomarker assays
9:40	10:00	***Heike Wiese, Nuvisan***
		Metabolomics screening kits for use in clinical trials – fit for purpose?
10:00	10:20	***Liz Hickford, UCB-Biopharma***
		A biomarker assay validation approach tailored to the context of use and bioanalytical platform
10:20	10:40	***Richard Hughes, Resolian***
		If the shoe doesn't fit, must we change the shoe? Managing expectations around using 'off the shelf' biomarker validations.

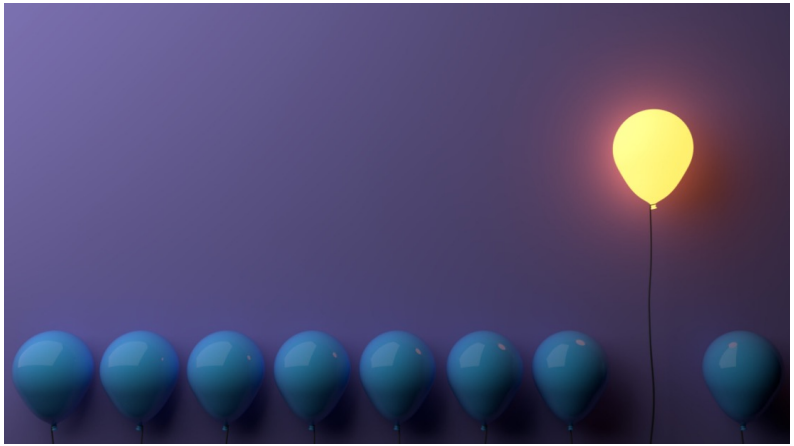
Later today:

16:20	**18:00**	**Pitlane 4: Context of Use - (Parallel)** **In Jin Mao/Petronals/Liberty** **Session Chair: Kyra Cowan, Merck KGaA, on behalf of the EBF** In this workshop, we will share and discuss the progress and challenges related to implementing the principles of Context to Use for BM assay validation and sample analysis. At the Pitlane-Workshop, which is being prepared by the EBF BM/CoU team, we will engage the audience on the value of a CoU statement as a starting point for CoU discussions between the BA team and the stakeholders/end users of the BM concentration data.
18:00	**19:00**	**Complementary Cocktail Reception**
19:00		**End of day 2**

Content

- CoU and the rationale
- Recent deliverables from the EBF Biomarker Teams
- Takeaways from recent BM CoU Roadshows
- CoU is needed for more than just BM assays
  - ADA
  - qPCR
- Today‘s presentations

Optimal BM Strategies are key to successful Drug Development: Our opportunity to impact success of molecule teams



Optimised Drug Development

- **The biomarker strategy is as important as the drug development strategy**
  - Given attrition rates
  - Given need for quantitative predictions, translatability of preclinical and clinical data, and holistic data interpretation

First:

- Need to ask the right questions.
- Need to know the biology.
- Need to understand the impact of molecule design.

Then:

- Need to know how each biomarker can be measured appropriately.

Biomarker Assay CoU: The Game-Changer for Many

- **Understand what it is**
- **Understand why it is critical**
- **Understand how to implement it, considering the many challenges:**
  - Scientific
  - Analytical
  - Strategic:
    - communication, stakeholder management, operational

We know the history:
Over a decade of debate, discussion, and scientific rationale through case studies:

Future Science Ltd
Bioanalysis
Volume 4, Issue 15, August 2012, Pages 1883-1894
https://doi.org/10.4155/bio.12.164

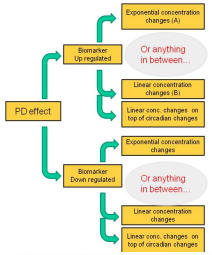
Bioanalysis

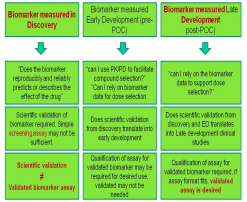
General content - White Paper

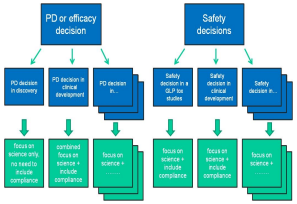
European Bioanalysis Forum recommendation on method establishment and bioanalysis of biomarkers in support of drug development

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] & Ulrich Kunz[11]

EBF recommendation paper (2012) – 4 pillars







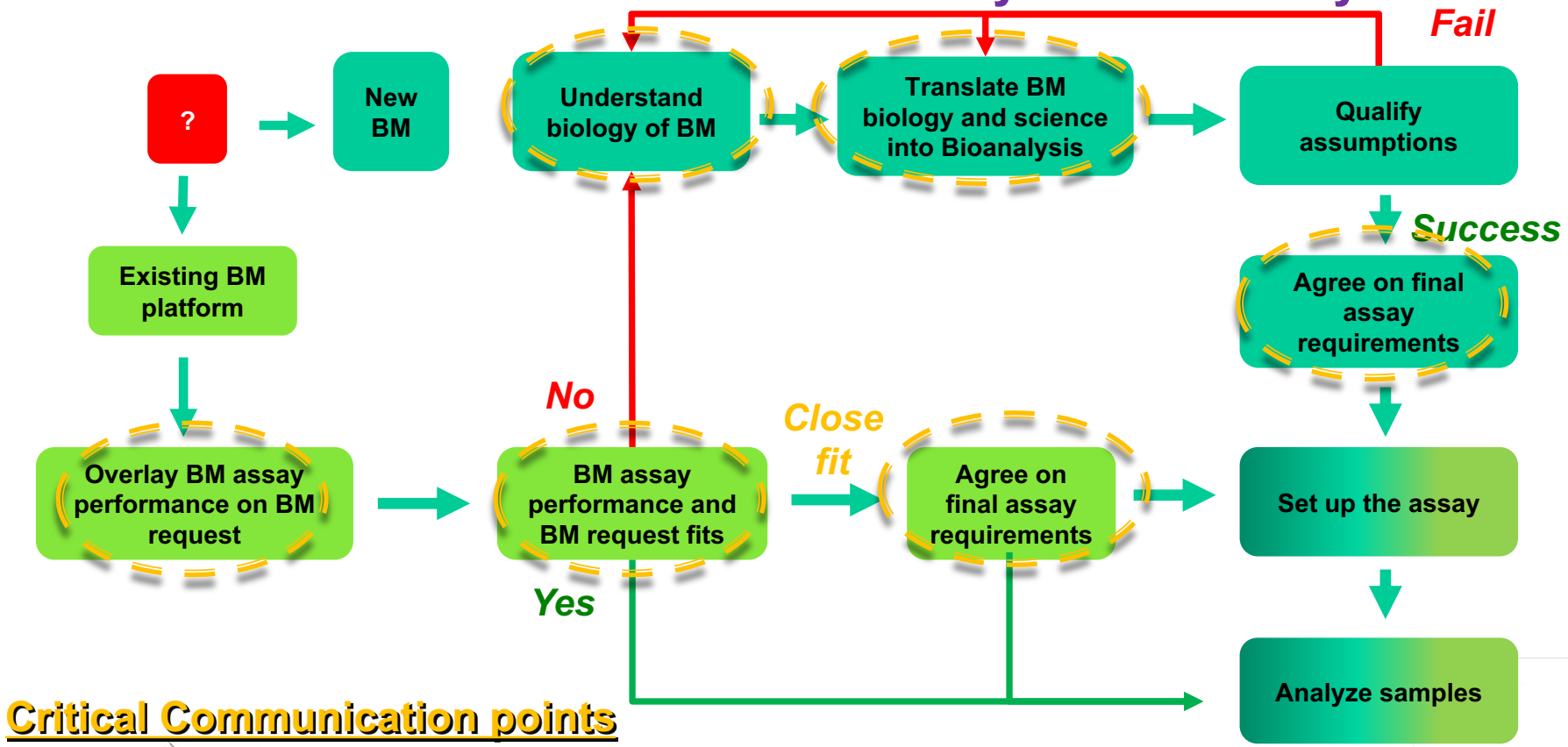
Biology

Phase of Molecule

Molecule Team Decisions

Guidances?

Lack of Communication –
Can lead to downfall of any success story



Critical Communication points

The 5th pillar - COMMUNICATION:

- To understand the biology, effect of the therapeutic on the biomarker
- To understand what the data will be used for
  - Scientific decisions taken
  - Safety decisions taken
  - Other?
- To share what is possible and what is not realistic from a Bioanalytical perspective

- **To ensure optimal drug development for patients…**

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

EBF Recommendations on BM Assay Characterisation

(1) CoU must first be defined and agreed upon by <u>all stakeholders</u>:

- **EBF recommends** this to fully understand what question(s) the biomarker data will address.
- **Every assay begins with a question: Why?**
  - What is the scientific rationale to measure this, i.e. The purpose??
  - Followed by: Full, documented definition of the purpose (context of use) of the biomarker in question

(2) CoU can then serve to identify: How?

1) Type of assay required (e.g. free or total, in-house assay, commercial kit, single analyte, multiplex, research use, diagnostic)
2) Format of the assay and critical reagents
3) Technology choice, with pros and cons
4) Appropriate biomarker samples

EBF Biomarker Teams 2021-2022 (Parts I & II)

Overarching Question:

- **What is slowing the implementation of CoU for Biomarkers?**
  - Issues with understanding/alignment within BA space of what CoU is
  - Issues with how to get the CoU information right
  - Issues with how CoU directly affects what is done in the lab
  - Issues with stakeholder management.

- **We need to keep the momentum going for clarity and alignment across industry.**
- **Beginning of several missions…**

BM Team Part I: CoU Statement for BM Assays

- A few sentences, detailed enough to define the purpose of the assay for each analyte

Eg. the biology, pharmacological effect, what the data will be used for, eg. scientific or safety decisions taken, and to understand the biological, the analytical variability, etc.

- **Understood and agreed upon by all stakeholders**
- **Documented in method summaries, validation plans, validation reports**

- Then consider what is possible from a BA perspective:

This leads to the appropriate assay, characterisation, and acceptance criteria.

IMPACT: ensure the appropriate interpretation of data for the best drug development strategy, ultimately to serve patients.

Implementing CoU: What WORKS

- Clear, documented BM strategy and integrated BM approach.
- Clearly defined, centralised BM group that covers BM assay, operational, and BM strategy expertise.
- Ideally, operational separation of decision-making and processes of BM assays from PK/ADA.
- Close collaboration between BA and BM leads, if separate functions, and with stakeholders
- Implementation and documentation of Purpose (CoU) for each set of BM data
- High-functioning matrix work environment with clear R&Rs and close collaborations.

(Biomarker Team Part I, 2021)

CoU: From a CRO Perspective, how it could work

1. Request a proposal/service estimate (Biomarker Team Part I, 2021)
2. Request to fill in CRO's BM questionnaire
3. Selection of possible method (already clear or discussed)
4. Proposal of fit-for purpose validation parameters
5. Agreement on fit-for purpose validation parameters
6. Prep of proposal/service estimate for the client

Need to insist on a documented, scientifically sound CoU statement for each analyte.
Then the assay chosen can be validated for its purpose. Only when the CoU is clear can the data be fit-for-purpose.

2021: Biomarker Team Part I

Newlands Press Ltd
Bioanalysis
Volume 14, Issue 13, July 2022, Pages 911-917
https://doi.org/10.4155/bio-2022-0143

Bioanalysis

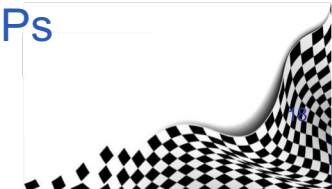
White Paper

Biomarker context-of-use: how organizational design can impact the implementation of the appropriate biomarker assay strategy

Kyra J Cowan[1], Michaela Golob[2], Joanne Goodman[3], Anna Laurén[4], Lene Andersen[5], Philip De Decker[6], Lien Dejager[7], Marianne Scheel Fjording[8], Peter Groenen[9], Renaud Jasnowski[10], Nicole Justies[11], Matti Kimberg[12,‡], Ulrich Kunz[13], James Lawrence[14], Mario Richter[15], Laetitia Sordé[16], Radboud van Trigt[17], Laurent Vermet[18], Alessandra Vitaliti[19], Michael Wright[20] & Philip Timmerman[21,*]

2022 BM Team Part II:
CoU Focus Workshop: Case Studies

- Cross-industry workshop in September 2022
- Pharma, biotech, and CROs, plus stakeholders included
- 14 Case Studies showing the implementation of CoU on Biomarkers
  - CROs, Biotech, Pharma; BA community, BA stakeholers
  - Technology agnostic
- **Take-Home Messages:**
  - All BM assay should have: The What, The Why
    - And then The How
  - Acceptance criteria: depends on CoU! Choose appropriately
  - Stakeholder management key, need to understand BM biology
  - Push back if no CoU, or ask clarifying questions
  - CROs – more challenging – often no formal process for CoU
  - CROs: require culture change, tend towards templates and SOPs



Where we are now: EBF Biomarker Team Next Steps

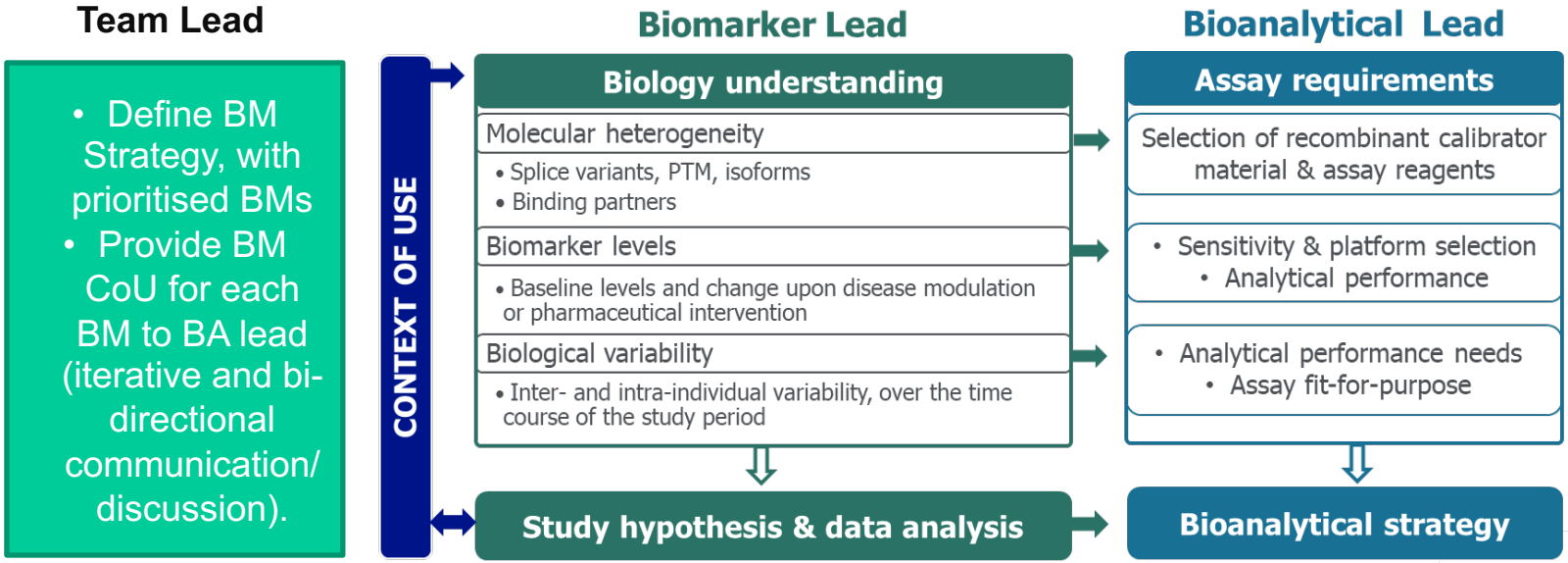
- **Continuing the momentum**
  - Cyberevent „Roadshows“ (**BM Team Part III**)
  - Brussels, Basel this last October 2023
  - Next Year: UK, Denmark/Sweden-region, more places to come...
  - Focus on: the empowerment of CROs, the benefit of a CRO saying „No“
  - Focus on case studies, and the „what ifs“, suggestions for hypothetical situations

CoU Roadshows: Basel and Brussels takeaways

- **BA scientist not ultimately reponsible, should receive the CoU by default from crossfunctional team leadership**:
  - Clinicians, Medical Affairs, Team Leads, BM Leads, all should DRIVE getting the CoU statement to the BA scientist
  - **Recommendation: BM or Project lead needs to ultimately provide CoU by default.**
  - Need to include a BA expert in the analysis of published data, eg. not just clinician.
    - Do you know how the BM assay described was characterised?
  - Worth discussing with team any changes with variabiltiy due to eg. increase in patient populations – **variability, expected changes are so critical to know**.
- **WE (EBF) need to publish our case studies**, with „What ifs“, and CoU statement and implementation examples.
- Stakeholders: will the clinical scientists now drive this?
  - How do we get away from BA scientists asking for it (as in our recent bandaid efforts), and being provided from their team leads with the CoU as a requirement for BM analytes?

From COU to Assay requirements: UCB

Assay specification document, modified from Hickford (UCB) 2023 paper:



Based on figure from Hickford et al. 2023

Rationale for Documenting CoU for BM Assays

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…

…Leading to incorrect data and decisions, negatively impacting patients

Institutional knowledge may change: people leaving, new team members...

Bottom Line: Bioanalytical scientist takes ownership of ensuring Assay CoU:

- **Align with team stakeholders**
- **Update CoU over time per analyte.**

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<u>Bottom Line:</u> (BM) Team Lead ensures delivery of CoU Statement to BA scientist per study per analyte:

- **Aligned with team stakeholders including BA scientist**
- **Update CoU over time per analyte.**

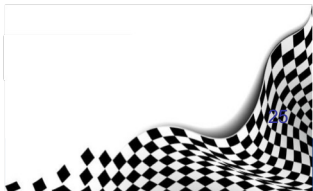
Additional takeaways

- **CoU statement examples** needed for community
- **More roadshows**, more interactions with stakeholders, beyond the multipliers that are present so far.
- Who leads the CoU, who ensures it discussion? **Team Lead!**
- **Need more „What if“ examples**
- CoU statements should be **essential part of every early BM Strategy**
- Define BM Strategies (not all companies do this)
- **Publish CoU Case Studies**, including „what ifs“
- **Publish CoU statements**

EBF Biomarker Team Next Steps

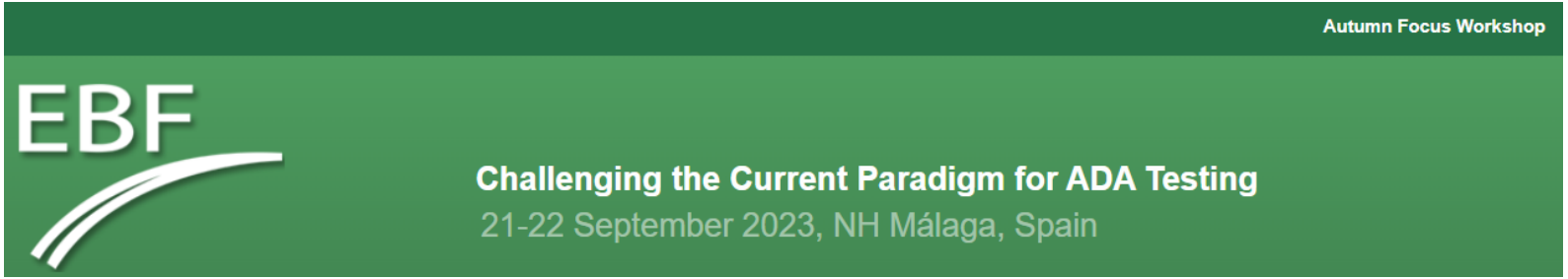
- Continuing the momentum
  - Cyberevent „Roadshows“ (BM Team Part III)
  - Brussels, Basel in October 2023
  - **Next Year: UK, Denmark/Sweden-region, more places to come...**
  - Focus on: the empowerment of CROs, the benefit of a CRO saying „No“
  - Focus on case studies, and the „what ifs“, suggestions for hypothetical situations

  - **BM CoU Statement Team (BM Team Part IV)**
  - Approaches for implementation and examples of CoU statement(s) that can be used by our community
  - **Discussion this afternoon, Pitlane 4 (1620-1800)**



EBF Discussions on Immunogenicity focus on CoU

Challenging the Current Paradigm for ADA Testing



21-22 September 2023 – Malaga, Spain

Topics Presented and Discussed at FW

- Challenging the tiered paradigm
- S:N as an alternative for titer
- Characterization (e.g. multi-domain, nAb etc.)
- Regarding singlicate analysis – we perform one sample preparation – are we just testing pipetting?
- Drug tolerance
- Measurement of placebo samples in clinical testing

All immunogenicity assays need a context of use as well

- **Purpose of the assay and the decisions being made with the data**
  - CoU requires stakeholder management
  - CoU statement impacted by stage of development (nonclinical, clinical, Ph1 versus Ph3)
  - CoU affects which tier of immunogenicity assessment is utilized (which assay(s) are appropriate)
  - CoU requires understanding the ability and limitation of the assay(s)

- Even if an assay follows current regulatory guidance, the science may be flawed, and this will not guarantee a successful submission
  - Particularly considering new modalities

- **Key Questions apply to all Immunogenicity Assays:**
  - What is the scientific rationale behind the analysis?
  - How data will be used?
  - Will anything change based on data?
  - Every assay must have a CoU

EBF Discussions on qPCR focus on CoU as well

Newlands Press Ltd
Bioanalysis
Volume 13, Issue 23, December 2021, Pages 1723-1729
https://doi.org/10.4155/bio-2021-0218

Bioanalysis

White Paper

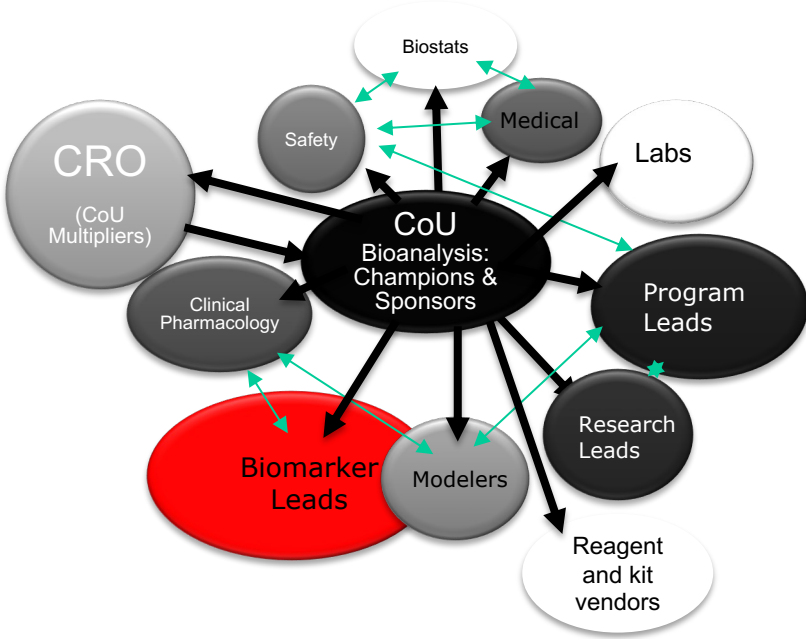
Applying context of use to quantitative polymerase chain reaction method validation and analysis: a recommendation from the European Bioanalysis Forum

Anna Laurén[1], Manuela Braun[2], Paul Byrne[3], Chiara Cazzin[4], Kelly Colletti[5], Chris Cox[6], Lisa Dietz[7], Thomas Emrich[8], Kristin Geddes[9], Kate Herr[10], Tracy Iles[3], Alexandra Rogue[11], Yvan Verlinden[12] & Philip Timmerman[13,*]

- There are **many different CoU for the various qPCR applications**;
- Each COU has its own performance requirements for the qPCR method;
- There is a desire for the harmonisation of bioanalytical qPCR approaches;
- **Most importantly:** existing regulatory BMV guidance/guidelines written for PK assays using chromatographic and ligand binding assay technologies are generally not suitable for PCR technologies.

For All Assays:

We should expect cross-Industry Implementation of CoU



Stakeholder Management

- **Do not omit CoU for Assays**
  - None/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 and acceptance criteria**.
  - Decisions need to be driven by the science.

- Do not default to the misapplication of any existing guidance
- Encourage the crucial conversations needed for defining the CoU, the “purpose” in fit-for-purpose.

Later today:

16:20	18:00	**Pitlane 4: Context of Use - (Parallel)** **In Jin Mao/Petronals/Liberty** **Session Chair: Kyra Cowan, Merck KGaA, on behalf of the EBF** In this workshop, we will share and discuss the progress and challenges related to implementing the principles of Context to Use for BM assay validation and sample analysis. At the Pitlane-Workshop, which is being prepared by the EBF BM/CoU team, we will engage the audience on the value of a CoU statement as a starting point for CoU discussions between the BA team and the stakeholders/end users of the BM concentration data.
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Today‘s Pitlane: Actual CoU Statements

- Uli Kunz (Boehringer Ingelheim): CS1
- Richard Hughes (Resolian): CS2
- Prat Gulati (Roche): CS3
- Danny Thwaite (LabCorp): CS4

- Frazer Lambert (CRL): note-taker

Acknowledgements

EBF Biomarker Team Parts I, II, III, and IV!
...And from previous EBF BM teams from 2012

EBF Steering Committee
EBF Organising Committees, including
Jo Goodman, AstraZeneca
Michaela Golob, Nuvisan
Rob Nelson, BioAgilytix
Anna Lauren, Novo Nordisk
Philip Timmerman, EBF

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Contact Information

Questions: info@e-b-f.eu

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