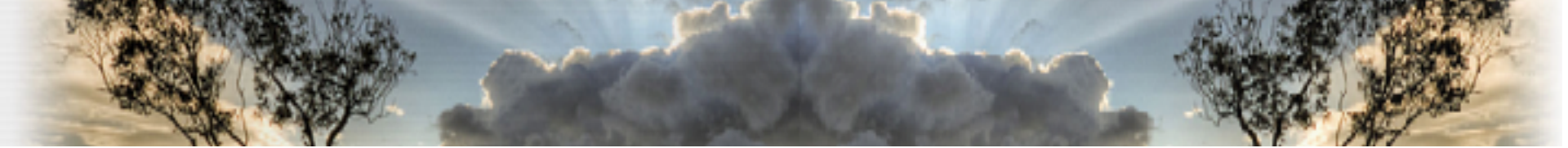


Did the FDA BMV change our view of biomarker assay validations?

Robert Nelson, on behalf of the EBF

12th EBF Open Symposium
Imagine! A new bioanalytical Earthrise

http://www.e-b-f..eu

Overview

- Biomarkers in bioanalytical method validation (BMV) guidance
- Biomarker work should start from the end
- How are we approaching biomarker assay validation?
- The journey continues

Biomarkers in Bioanalytical Guidance

- FDA BMV 2001
  - No mention of biomarkers
- EMA BMV 2012
  - Methods used for determining quantitative concentrations of biomarkers used in assessing pharmacodynamic endpoints are out of scope of this guidance.

Biomarkers in Bioanalytical Guidance

- FDA BMV 2018 (& 2013 Draft)
  - The recommendations in this guidance only pertain to the validation of assays to measure in vivo biomarker concentrations in **biological matrices such as blood or urine**.
  - Because of the important roles biomarkers can play in evaluating the safety, activity, or effectiveness of a new medical product, it is critical to **ensure the integrity of the data** generated by assays used to measure them.
  - Biomarkers can be used for a wide variety of purposes during drug development; therefore, **a FFP (fit-for-purpose) approach** should be used when determining the appropriate **extent of method validation**.

Biomarkers in Bioanalytical Guidance

- FDA BMV 2018
  - When biomarker data will be used to support a regulatory decision making, such as the **pivotal determination of safety** and/or **effectiveness** or to **support dosing instructions in product labeling**, ***the assay should be fully validated***.
  - For assays intended to support early drug development (e.g., candidate selection, go-no-go decisions, proof-of-concept), the sponsor should **incorporate the extent of method validation they deem appropriate**.

Biomarkers in Bioanalytical Guidance

- FDA BMV 2018
  - The ***accuracy***, **precision**, **sensitivity**, **selectivity**, **parallelism**, **range**, **reproducibility**, and **stability** of a biomarker assay are important characteristics that define the method.
  - The ***approach used for drug assays should be the starting point for validation of biomarker assays***, although the FDA realizes that some characteristics may not apply or that different considerations may need to be addressed.

How some people *may* read the FDA BMV 2018

- The FDA recognize the importance of biomarkers in drug development
- The FDA recognize that biomarker assays will be different to PK assays
- If you are using biomarker data to support a claim of safety and/or efficacy, or to support dosing instructions in the labeling, the FDA expect to see a **validation that demonstrates that the assay is fit for that purpose**.

How other people *may* read the FDA BMV 2018

- The FDA recognize the importance of biomarkers in drug development
- ***If you are measuring biomarkers you must validate the assay according to your PK SOP***

Fit-for-purpose - which are the best shoes?

- It depends…
  - We need ‘context of use’

Credit: Lauren Stevenson

Start from the end

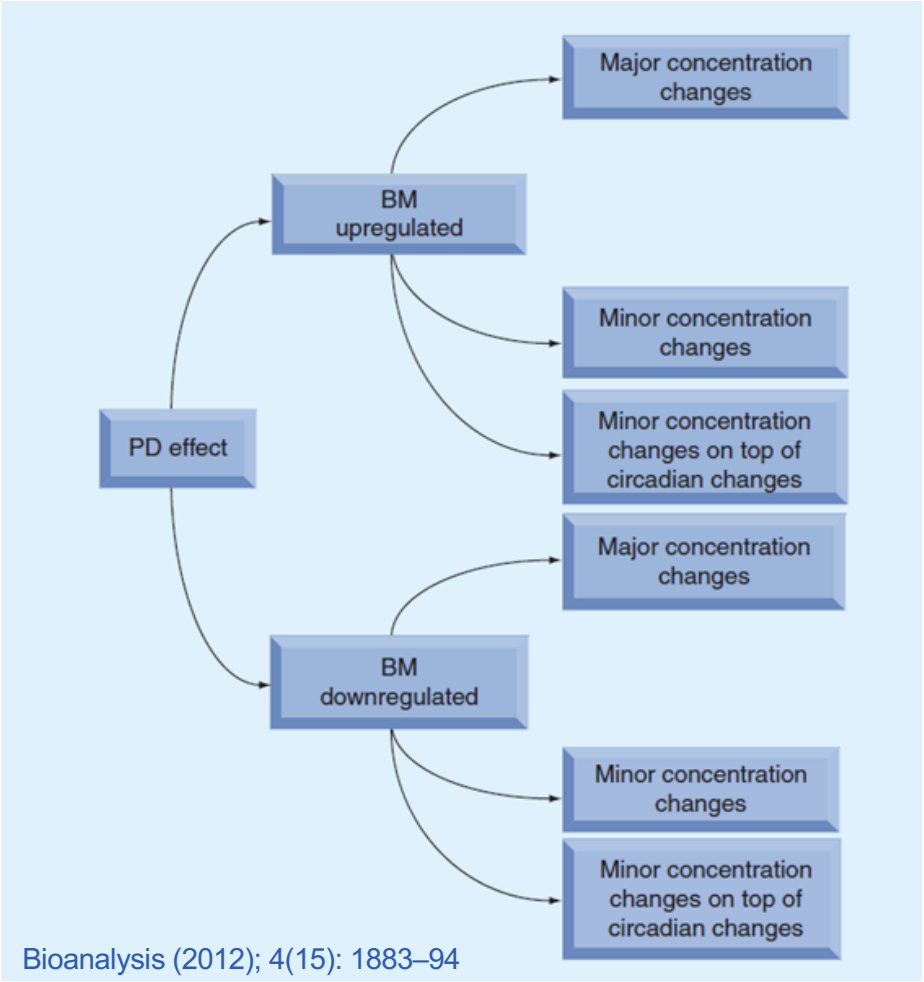
- A biomarker assay cannot be developed and validated in isolation

Start from the end

How will the BM data be used?

+

Understand the biology



Bioanalysis (2012); 4(15): 1883–94

Start from the end

How will the BM data be used?

+

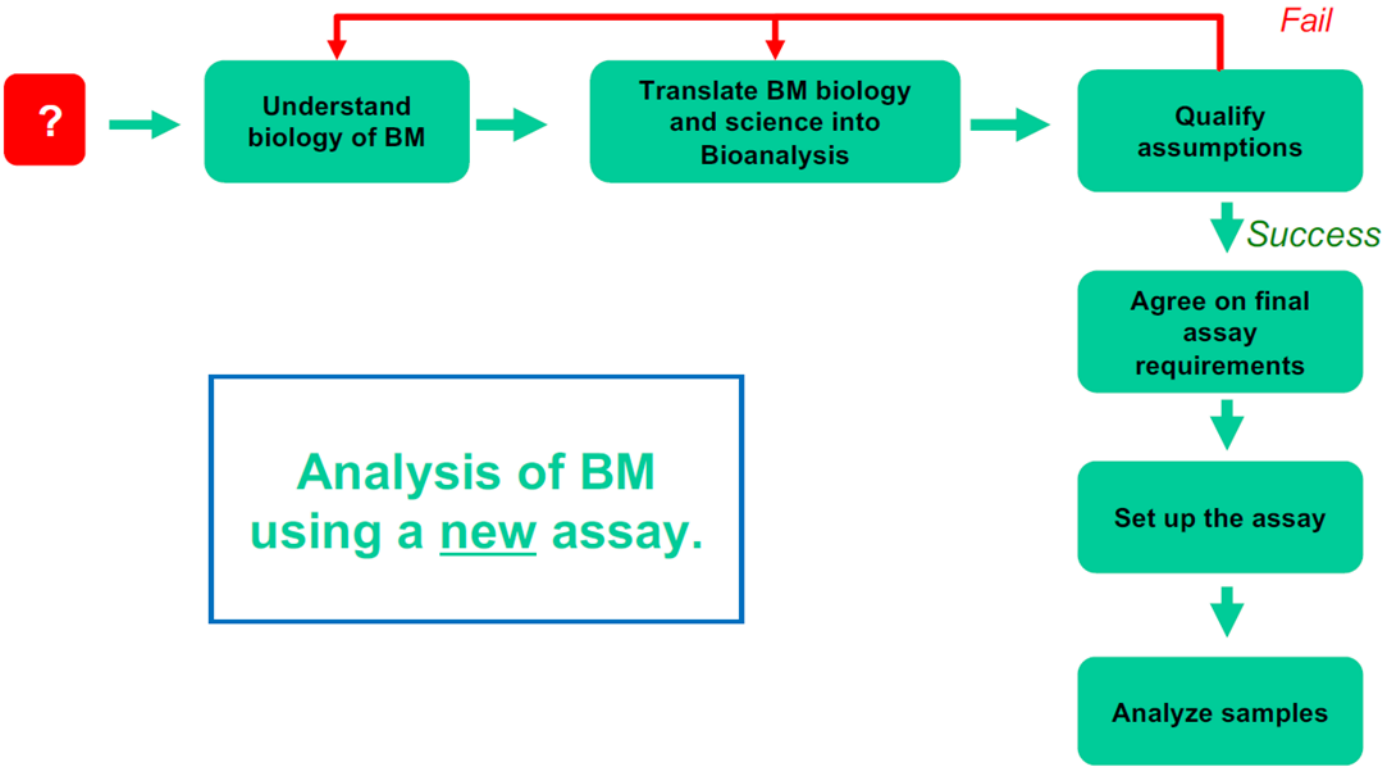
Understand the biology

Translate into BM assay performance requirements

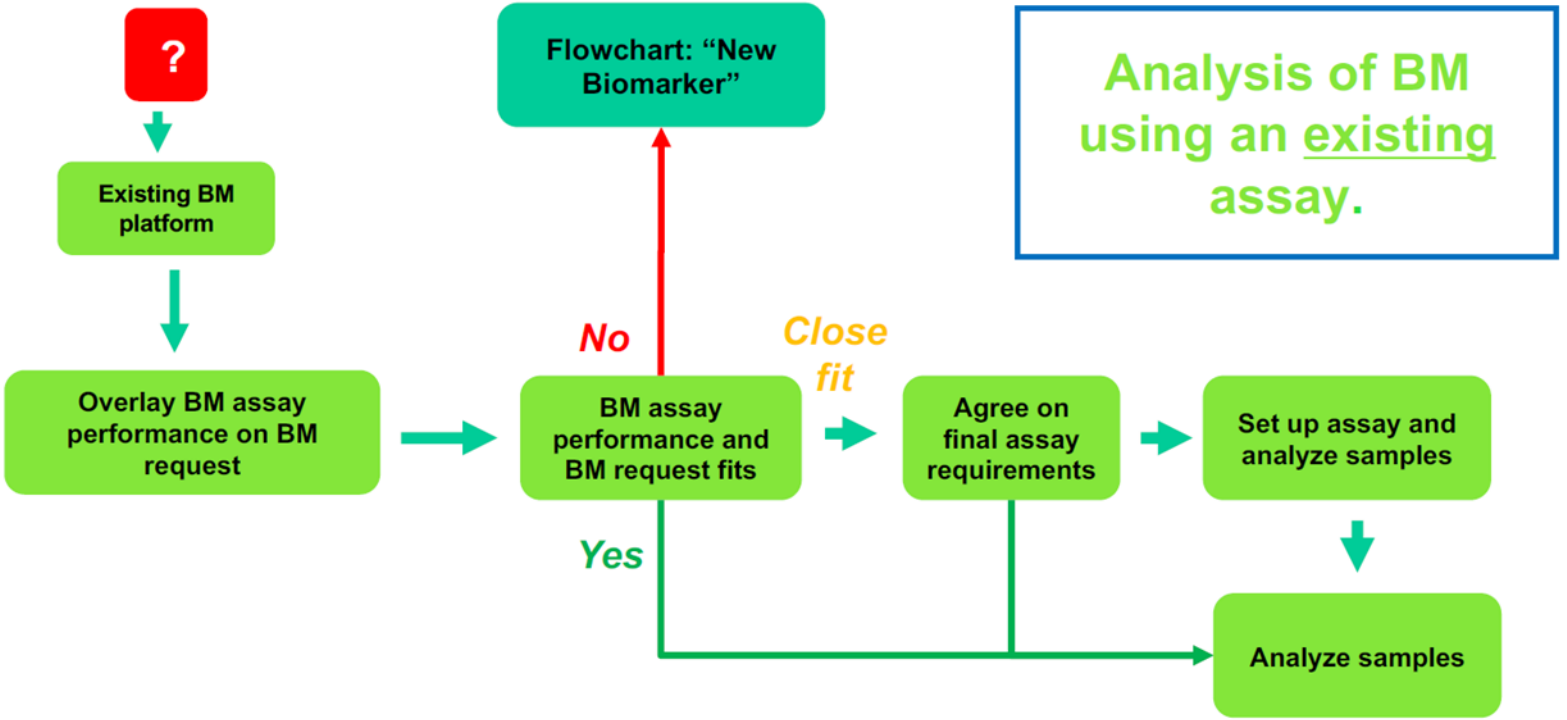
A flowchart proposed in the EBF recommendation paper

Bioanalysis (2012); 4(15): 1883–94

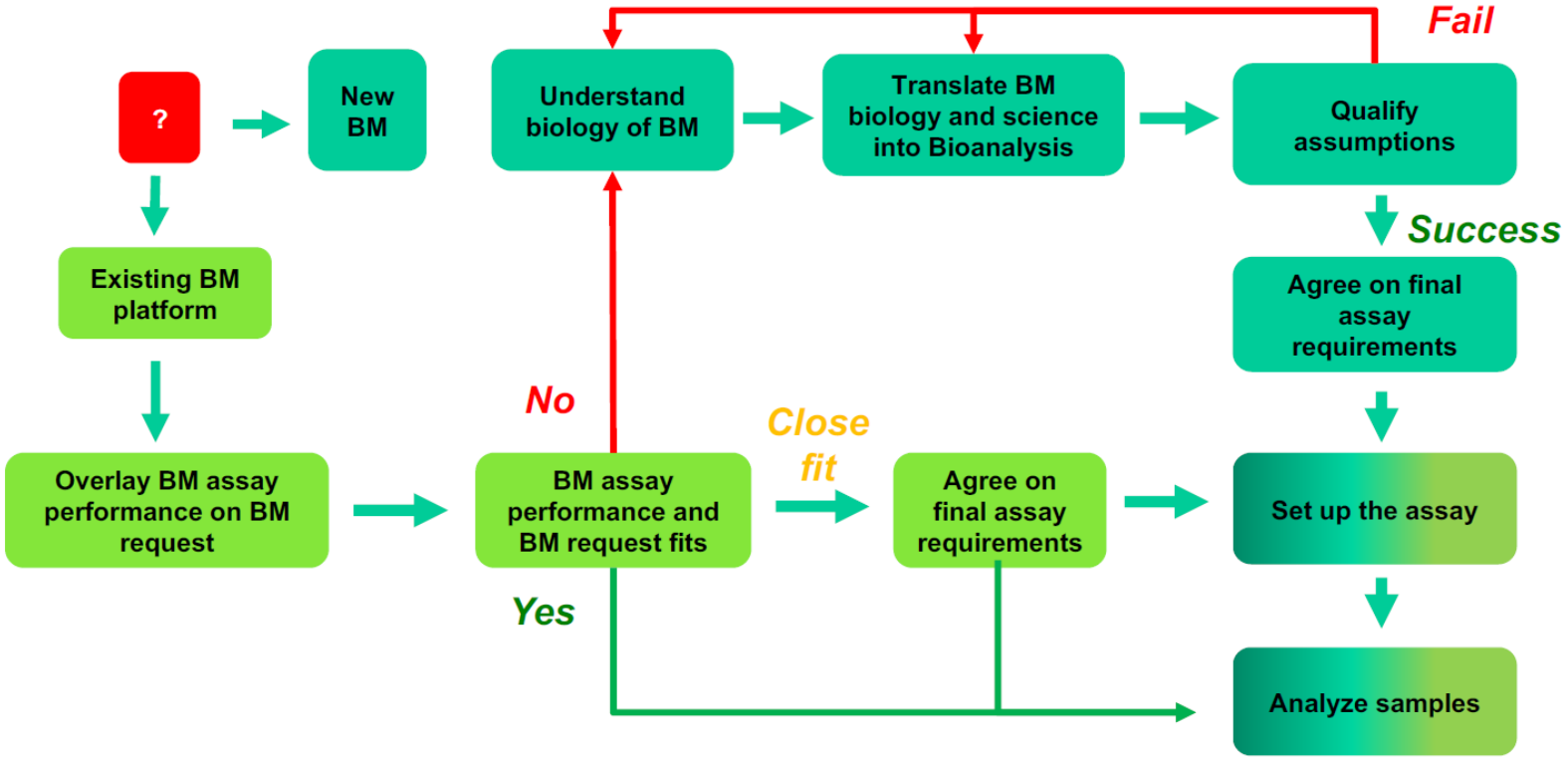
Analysis of biomarkers with a new assay



Analysis of biomarkers with an existing assay



Analysis of biomarkers with an existing assay



So, how are we approaching biomarker assays?

EBF Focus Workshop

Biomarker Assay Validation – Bringing Context of Use into Practice

Malaga, 18-19 September 2019

We did a little survey…

Q1: Prior to setting up the assay, I have reached out to the end user of the data to discuss the assay requirements and/or be informed on the "biology"

- o Yes =
- o No =

Q2: Prior to setting up the assay, the end user provided me the precision required for the assay

- o Yes =
- o No =

Yes

- Precision requested was tighter than "4-6-15/20"
- Precision requested was as for "PK assays, i.e. 4-6-15/20
- Precision was looser than 4-6-15/20

Required precision:

No

I validated the assay towards "4-6-15/20" as per PK SOP applicable in my lab

- Yes:
- No:

Required precision:

We did a little survey…

Q1: Prior to setting up the assay, I have reached out to the end user of the data to discuss the assay requirements and/or be informed on the "biology"

- Yes = 51
- No = 49

Q2: Prior to setting up the assay, the end user provided me the precision required for the assay

- Yes = 23
- No = 78

Yes

- Precision requested was tighter than "4-6-15/20 4
- Precision requested was as for "PK assays, i.e. 4-6-15/20 12
- Precision was looser than 4-6-15/20 7

Required precision:

Typically adding 5 or 10% imprecision, but still in the 4-6-xx paradigm

No

I validated the assay towards "4-6-15/20" as per PK SOP applicable in my lab

- Yes: 47
- No: 23

Required precision:

Typically adding 5 or 10% imprecision, but still in the 4-6-xx paradigm

Digging deeper…

Q1: Prior to setting up the assay, I have reached out to the end user of the data to discuss the assay requirements and/or be informed on the "biology"

- Yes = 51
  - Pharma = 30
  - CRO = 21
- No = 49
  - Pharma = 12
  - CRO = 37

Majority of Pharma (30:12 ratio) speak to the "end user of the data"

Majority of CRO (21:37 ratio) say they don't

We did a little survey…

Q1: Prior to setting up the assay, I have reached out to the end user of the data to discuss the assay requirements and/or be informed on the "biology"

- Yes = 51

Q2: Prior to setting up the assay, the end user provided me the precision required for the assay

- Yes = 23

Yes

- Precision requested was tighter than "4-6-15/20 4
- Precision requested was as for "PK assays, i.e. 4-6-15/20 12
- Precision was looser than 4-6-15/20 7

Required precision:

Typically adding 5 or 10% imprecision, but still in the 4-6-xx paradigm

Talking to the end user, doesn't always result in them providing assay requirements

Deeper still…

Q1: prior to setting up the assay, I have reached out to the end user of the data to discuss the assay requirements and/or be informed on the “biology”

- No = 49

Q2: prior to setting up the assay, the end user provided me the precision required for the assay

- No = 78

Many are on their own, and sucked into what the are familiar with

PK
SOP

No

I validated the assay towards “4-6-15/20” as per PK SOP applicable in my lab

- Yes: 47
- No: 23

Required precision:

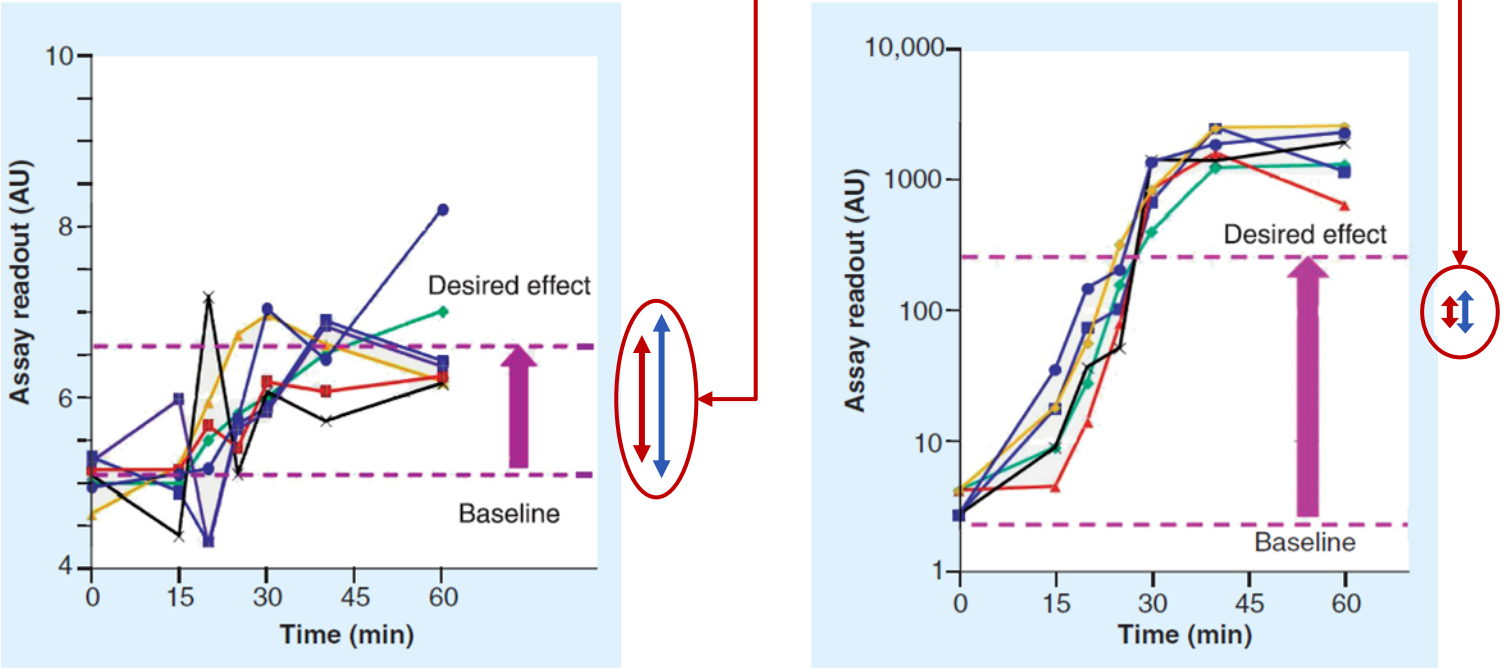
Typically adding 5 or 10% imprecision, but still in the 4-6-xx paradigm

What if we don’t get it right?

- We will produce the ‘wrong’ numbers
  - Scientifically
    - Data not fit for its intended use
  - Economically
    - Impact our mission to ensure that safe, effective, and high quality medicines are developed and registered in the *most resource-efficient manner*

What if we don't get it right?

PK Criteria : 4-6-15/20



- In both cases PK A&P is *inappropriate*

Bioanalysis (2012); 4(15): 1883–94

Biomarkers: The challenges we face today

- Analytical:
  - Progress in technology opens a new world of options for analysis
  - New and/or multiple assays platform for 1 biomarker
  - Biomarker assays run by PK assay scientists
- Scientific:
  - Understanding the PD / biology, i.e. the context
- Communication:
  - Who talks, who listens? Who understands and who translates?
- Regulatory:
  - HA in learning mode too….
  - Expectations may not reflect the best science
  - Unrealistic analytical requirements for the assay

Acknowledgment

- EBF Community and Workshop attendee for providing input
- EBF Autumn Focus Workshop 2019 Team
  - Agenda: www.e-b-f.eu/wp-content/uploads/2019/10/Autumn-FW-Agenda.pdf
  - Slides: www.e-b-f.eu/fw201909-slides/

EBF

Biomarkers in Pharma R&D

A roadmap from Context of Use to Using the data

NH Málaga Centro
Málaga, Spain
12 May 2020 (Training Day)
13-14 May 2020 (Workshop)

REGISTER NOW

Contact Information

Questions: info@e-b-f.eu

European Bioanalysis Forum vzw

www.e-b-f.eu