Feedback from the EBF Focus Workshop on Biomarker Assay validation and analysis

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on behalf of the EBF

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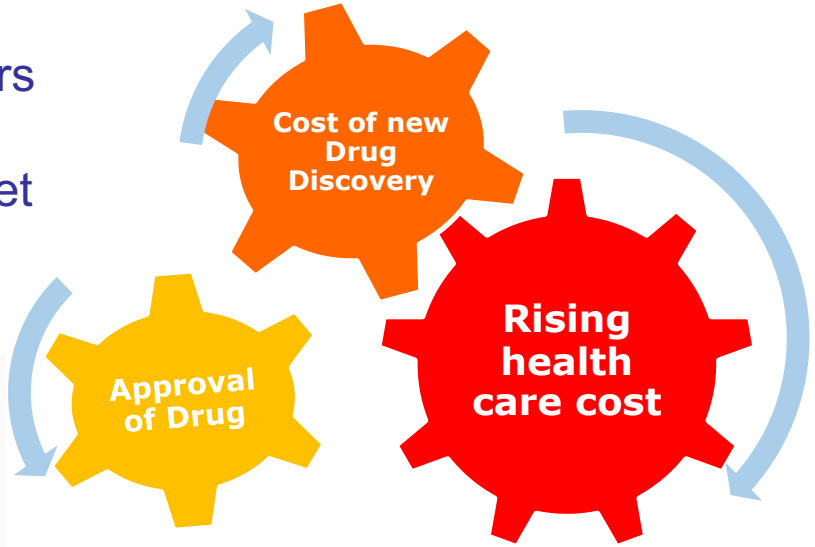
Barcelona

Outline

- What is a biomarker?
- Introduction the EBF recommendation paper
  - The 4 pillars
- The Lisbon Focus Workshop
  - Aim of workshop
- The 5th Pillar
- Where are we now?

Why a need for biomarkers?

Drug development rely more on biomarkers
to assess efficacy, safety and MoA
in order to be get a new drug on the market



Lead selection — **Safety** — **Dose-escalation Exclusion/inclusion criteria** — **Change following treatment; - safety or prediction of benefit**

Discovery → Non-clinical → Phase 1 → Phase 2 → Phase 3 → Phase 4

What is a Biomarker?

Biomarkers Definitions Working Group (2001), NIH

a biomarker is defined as

'a characteristic that is objective measured and evaluated as an indicator of a biological response to a therapeutic intervention'

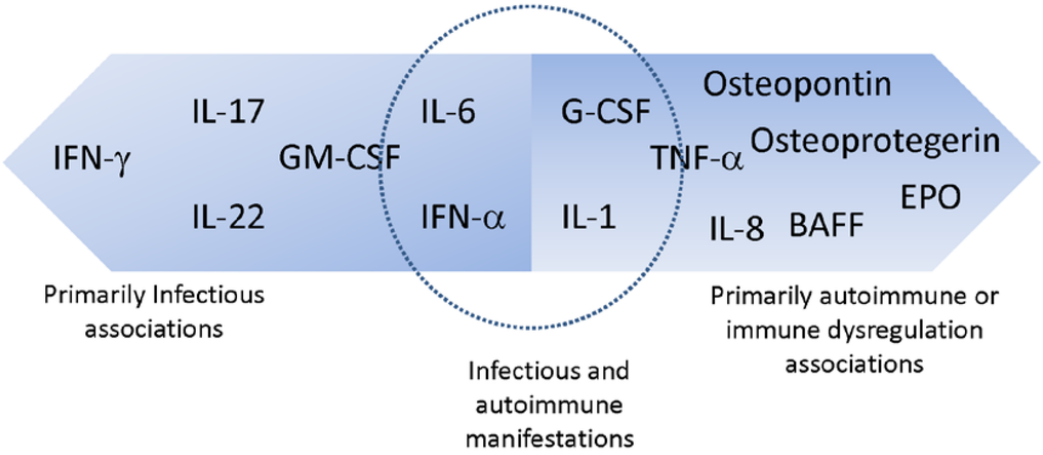
Or in other words

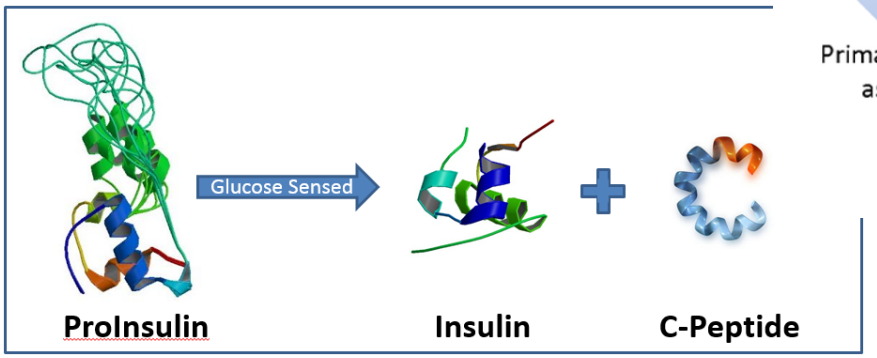
A Biomarker or biological marker:

Generally refers to a measurable

- indicator of a disease
- or the effects of treatment

Examples of biomarkers used in clinical practice

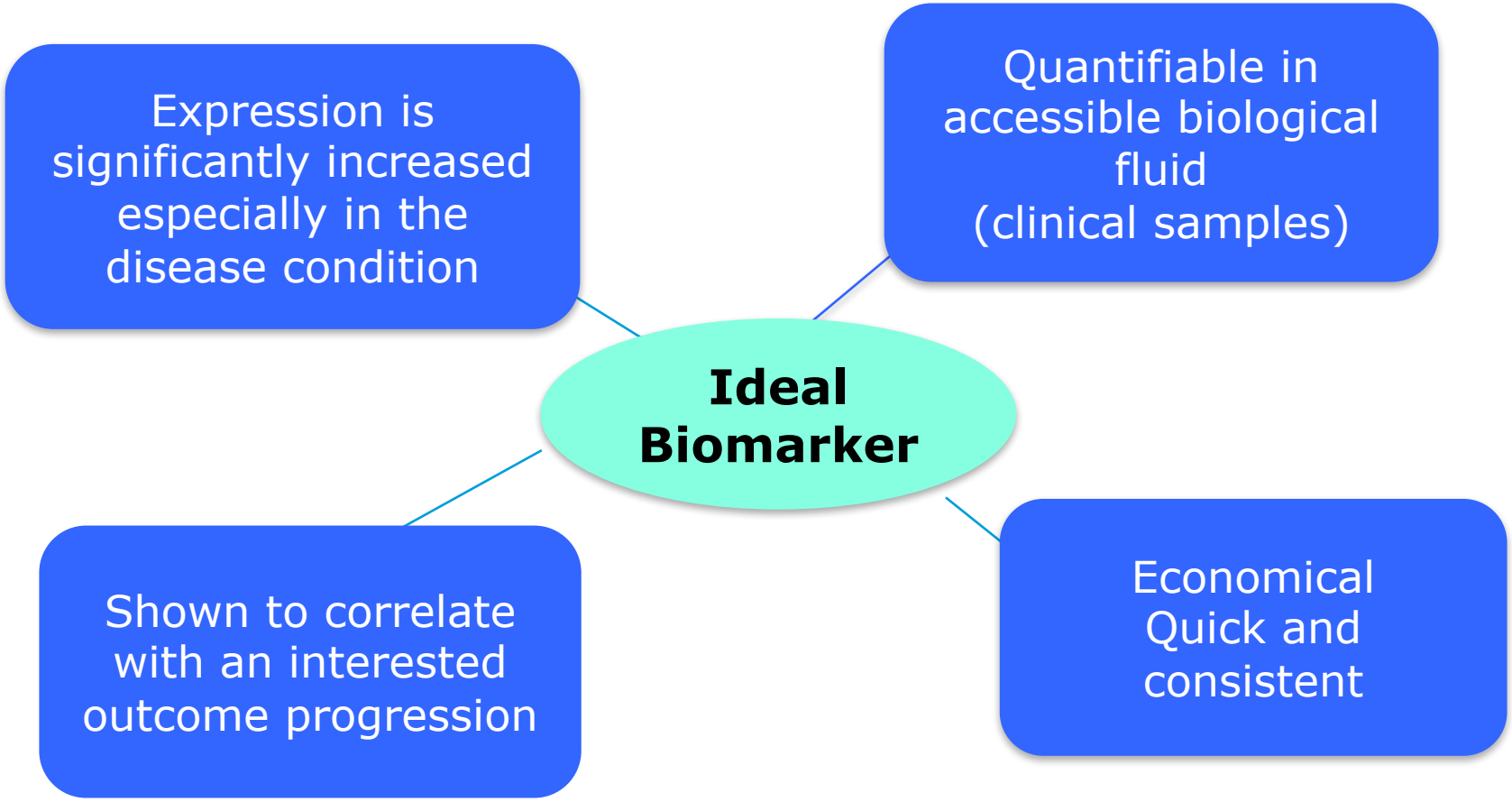




hs-CRP Value	Cardiovascular Disease Risk Level*
< 1 mg/L	**low** risk
1-3 mg/L	**average** risk
> 3 mg/L	**high** risk

* Risk levels published in 2003. American Heart Association / Centers for Disease Control and Prevention Scientific Statement

What is an ideal biomarker?



Biomarker met in Clinical protocols

Primary & Secondary endpoint

Prognostic
- Prediction of future disease

Diagnostic
- diagnosis of disease

Exclusion/Inclusion Biomarker

Predictive
- Identification of patients
- Who will benefit from the treatment

Safety Biomarker

Efficacy Biomarker

Stratification Biomarker

Disease Biomarker

Pharmacogenomics Biomarker

Exploratory Biomarker

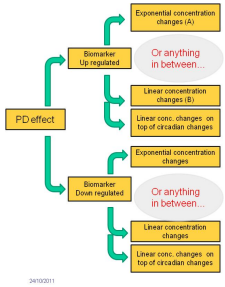
Why all this?

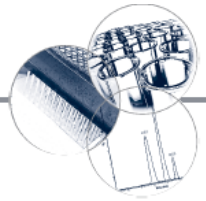
- Crystal City VI meeting with Industry and FDA

Sept-2015

- Do you know what you are measuring?
- **What is the purpose of the assay?**
- Assay design – reagents?
- What are the limitations of the assay?
- What is the precision of the measurement?
- How do sample handling conditions affect the measurement?

EBF recommendation on Biomarkers 2012





WHITE PAPER

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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 practical implementation of the tiered approach principles. This subteam started their activities in 2008, following up on the publication of the Crystal City III proceedings [1] and have already reported back on a first deliverable: application of the tiered approach applied in the quantification of metabolites in relation to the Metabolites in Safety Testing guideline [2]. In 2010, the EBF wanted to give priority to a recommendation in light of the ongoing Metabolites in Safety Testing discussions after the publication of the related regulatory guidances [101,102].

From 2010 onwards, an EBF biomarker team was formed out of the aforementioned tiered approach team to further investigate how the EBF can contribute to the already intense discussions on biomarker bioanalysis within the global bioanalytical community. We acknowledged the many interesting and important technical papers and White Papers already published on the bioanalysis of biomarkers. Certainly, articles such as the 'fit-for-purpose' paper impacted 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 approach of these 'fit-for-purpose' principles. Consequently, the EBF Biomarker team, consisting of bioanalytical experts from both pharmaceutical companies and CROs, identified the need to contribute to this discussion by integrating the internal EBF knowledge and reflections on the tiered approach with the already existing practices applied for the bioanalysis of a biomarker into an EBF recommendation.

As part of our recommendation and publication strategy, preludes of the insights in this manuscript were already shared for input and socializing at the 4th Open Symposium in Barcelona, Spain [5].

Although all our discussions intended to refer to biomarker analysis requests entering the traditional regulated bioanalysis laboratory, irrespective of size of the molecule of analytical technique involved, the principles of the recommendations we propose in this manuscript may also apply for other areas such as diagnostics or commercial immunoassay kits or similar. We did

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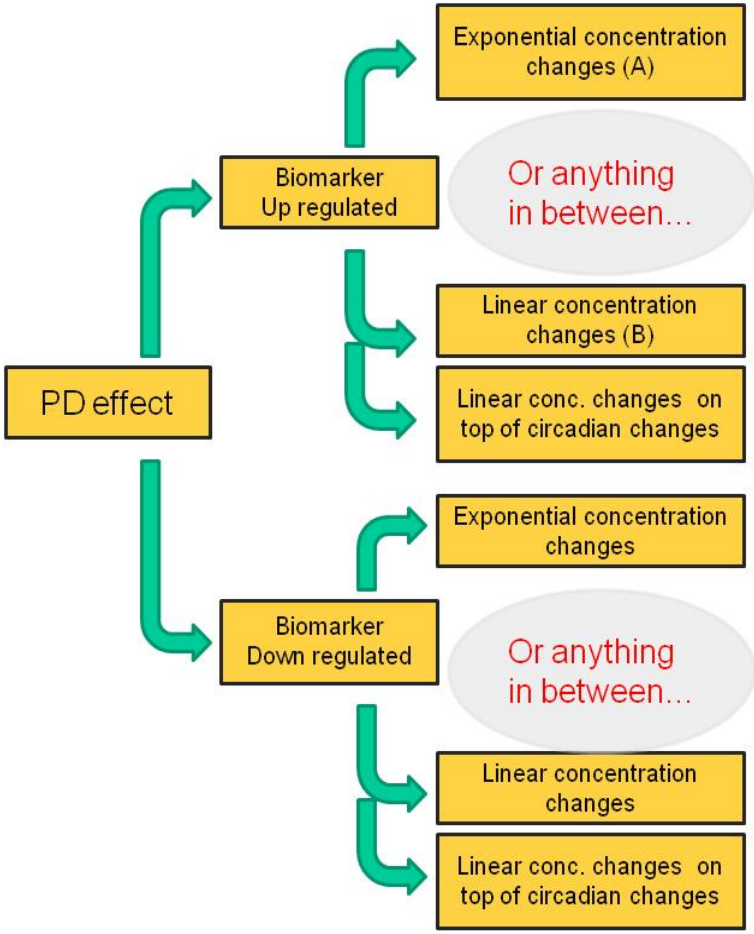
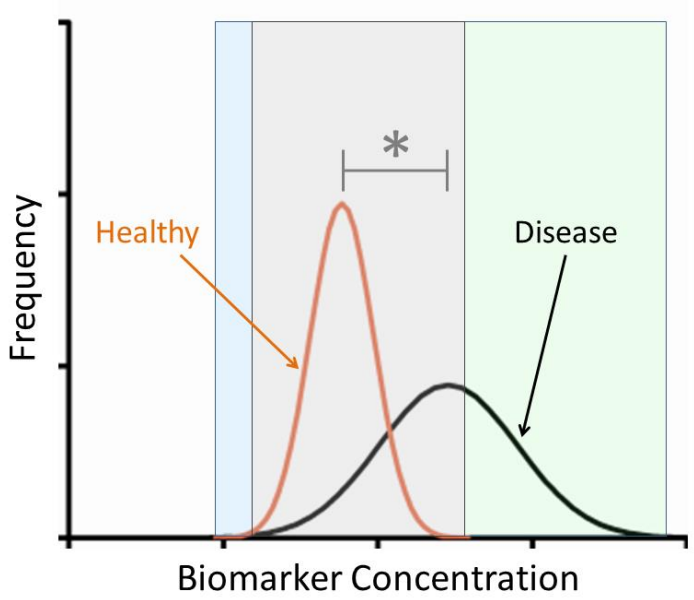
4 pillars
Drivers for BM assay validation

1. Observed or anticipated biomarker level changes





4 pillars
Drivers for BM assay validation

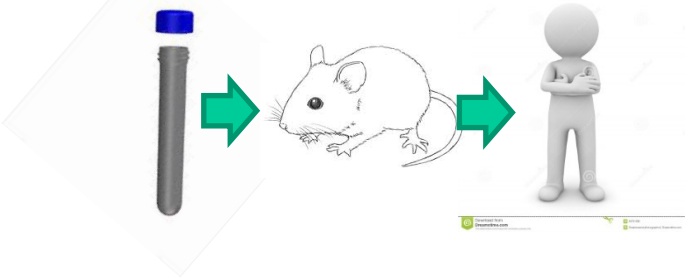
2. Development Phase in which a biomarker is measured

Discovery → Non-clinical → Phase I → Phase 2 → Phase 3 → Phase 4

Biomarker measured in Discovery	Biomarker measured Early Development (pre-POC)	**Biomarker measured** Late **Development** post-POC)
"Does the biomarker reproducibly and reliably predicts or describes the effect of the drug"	"can I use PK/PD to facilitate compound selection?" "Can I rely on biomarker data for dose selection	"can I rely on the biomarker data to support dose selection?"
Scientific validation of biomarker required. Simple screening assay may not be sufficient.	Does scientific validation from discovery translate into early development	Does scientific validation from discovery and ED translates into Late development clinical studies
Scientific validation ≠ Validated biomarker assay	Qualification of assay for validated biomarker may be required for desired use, validated may not be needed	Qualification of assay for validated biomarker required, if assay format fits, validated assay is desired

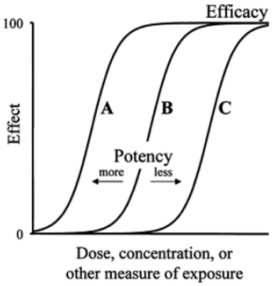
Translational

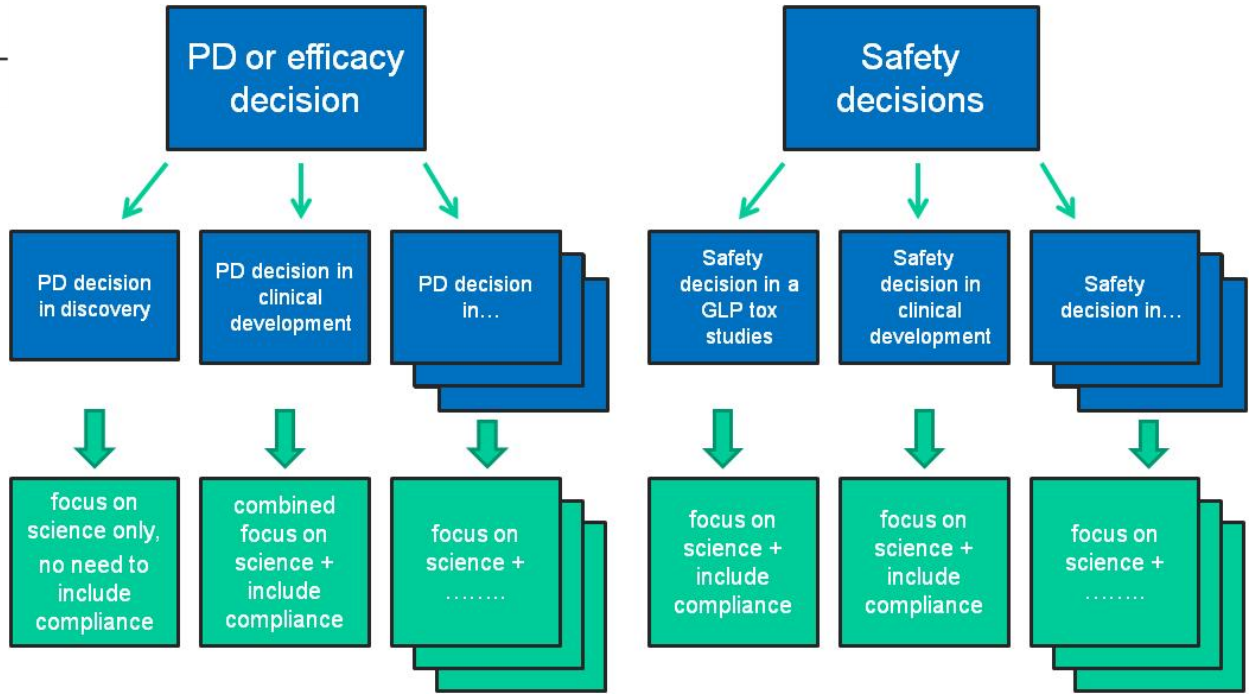
In vitro *In vivo* In man



4 pillars
Drivers for BM assay validation

3. Decisions taken from the biomarker data
   - efficacy decisions
   - safety decisions



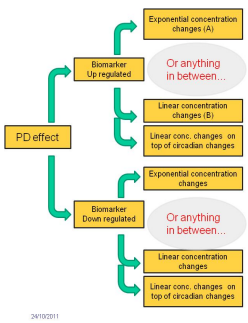


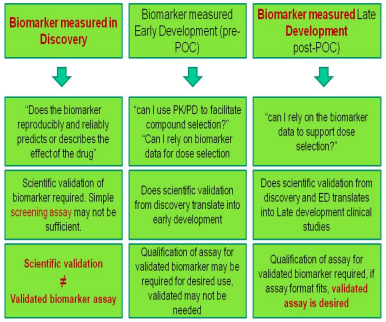
4 pillars
Drivers for BM assay validation

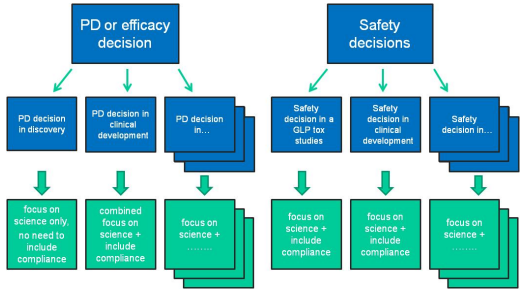
4. Fit of assay with Regulated Bioanalysis Guidelines

4 pillars
Drivers for BM assay validation

1 2 3 4

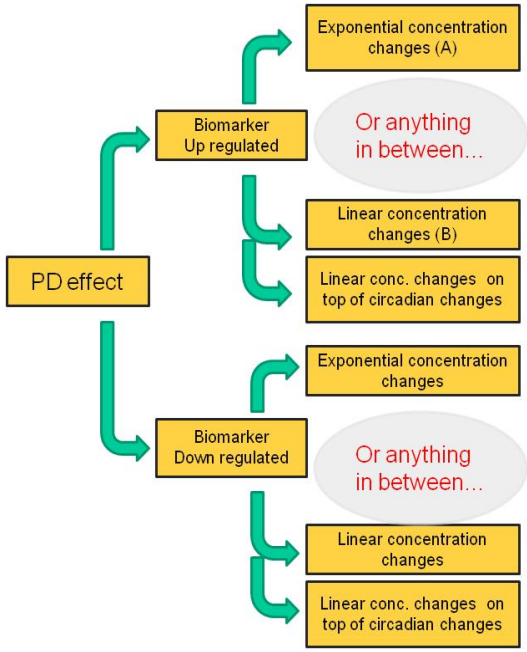






1. Observed or anticipated biomarker level changes
2. Development Phase in which a biomarker is measured
3. Decisions taken from the biomarker data
   - efficacy decisions
   - safety decisions
4. Fit of assay with Regulated Bioanalysis Guidelines

Above classification are superimposable - should be applied in concert to tailor an bioanalytical strategy in support of a Biomarker



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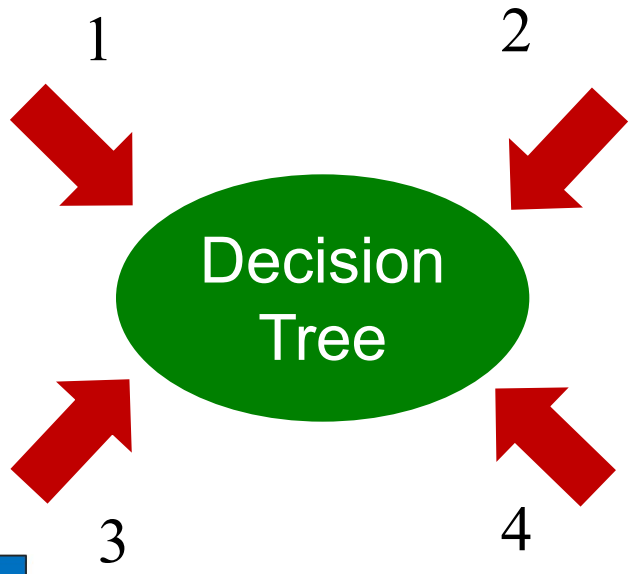
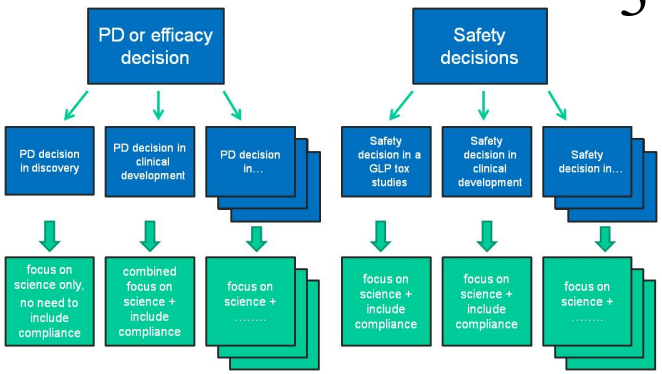
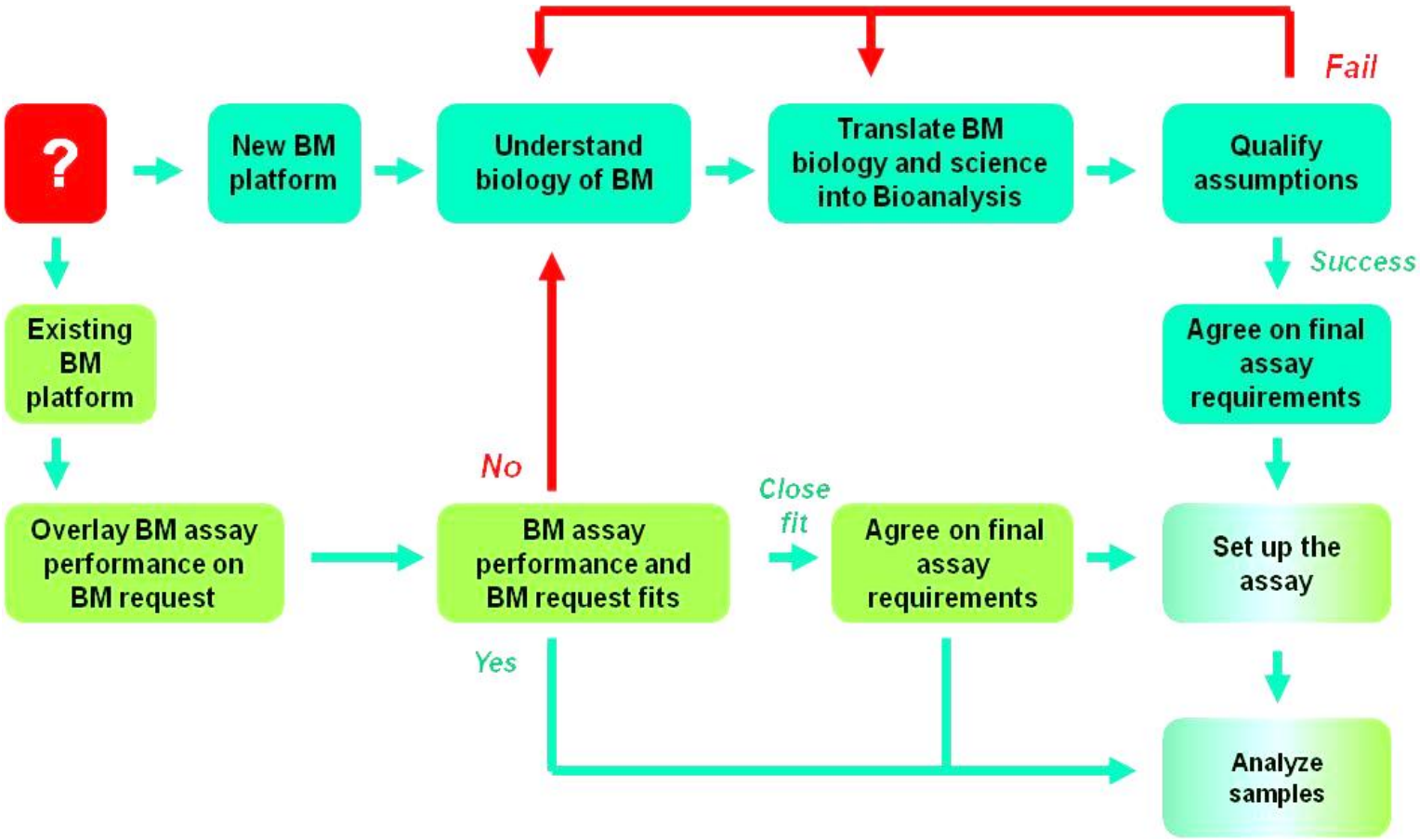




2012: EBF recommendation
Combined flowchart



So how to bring this into practice?

EBF Biomarker Focus Workshop
(Lisbon June-2016)

Biomarker Focus Workshop
(Lisbon June-2016)

Aim of the workshop: Bring assay validation and analysis into practise

- Regulatory environment
  - Crystal City VI meeting
    - Biomarker Assays ≠ PK assays
- Case studies
  - Exploratory biomarker in Discovery
  - Safety biomarker in a GLP tox study
  - An exploratory biomarker in FHD
  - Diagnostic biomarker in Drug-drug interaction
  - Efficacy biomarker for dose setting
- Panel discussion
  - Focus on communication
  - GLP and biomarker analysis

Take home messages from CC-VI

Consensus

Sept-2015

- **Category 1** = most Biomarkers we analyse today
  - Internal decision making
  - Extent of assay validation is up to you!

- **Category 2**
  - Biomarker to support pivotal decision & label claim
  - Assay validation in scope of FDA review

Biomarker Assays ≠ PK assays

- How do Biomarker assays differ from PK assays?
  - Reference material do not resemble endogenous counter part => Relative accuracy
  - Parallelism is the key analytical validation experiment
  - Matrix contain endogenous analyte => surrogate matrix
  - Stability of spiked Ref Mat ≠ endogenous stability (ISS)
  - Understand the biology!

ISS= Incurred sample stability

EBF Focus Workshop
Panel Discussion Communication

Key questions

- What is missing to bring the EBF recommendation paper into daily practice and how do we get there?
  - focus on internal BA experts
  - focus on our stakeholders
- What is missing to bring the PK bioanalyst more informed to understand the questions asked?

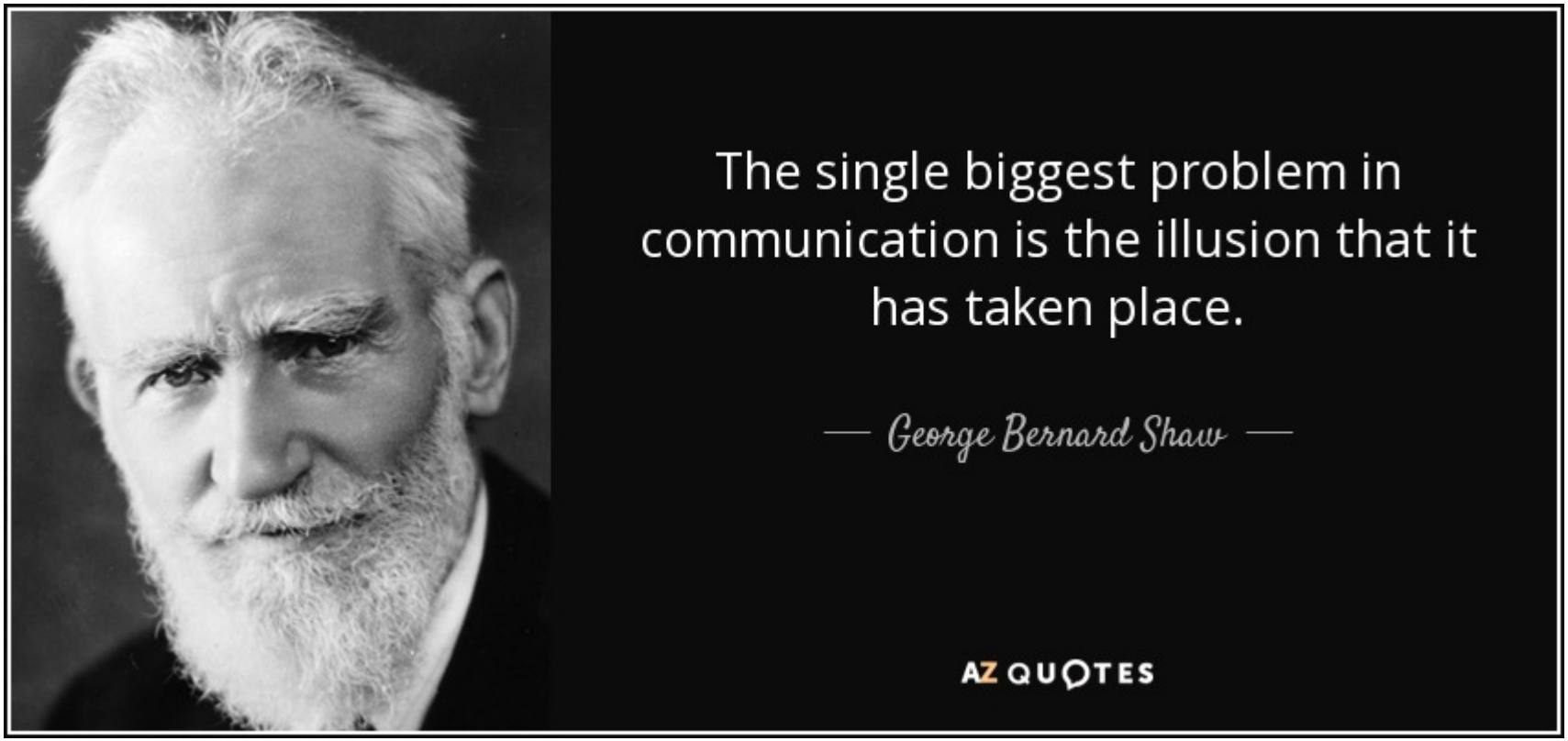
BA Scientist are passionate about accuracy

And we also want to have guidelines

GLP

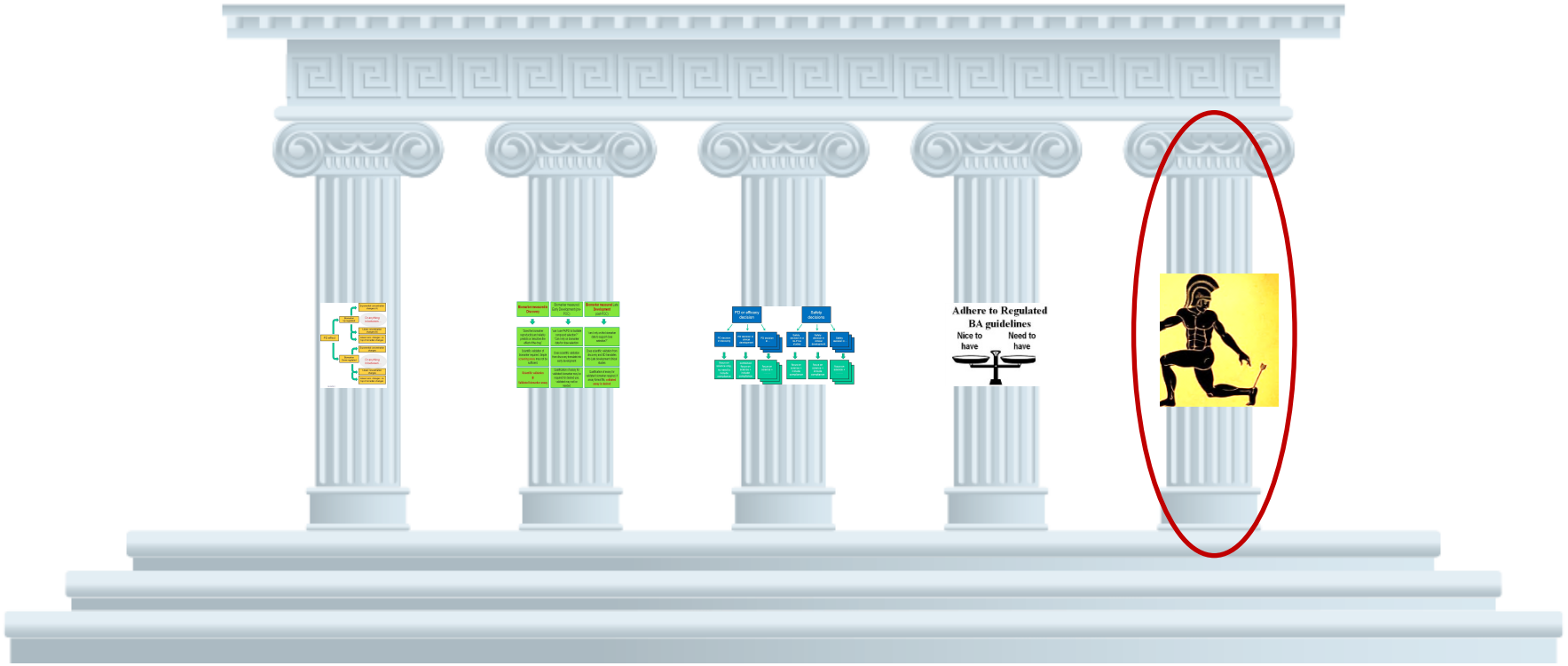
compliant

Guidelines


The single biggest problem in communication is the illusion that it has taken place.
— George Bernard Shaw —
AZ QUOTES

(Lack of) Communication – the Achilles heel of any success story

Communication
The 5th Pillar in EBF recommendation

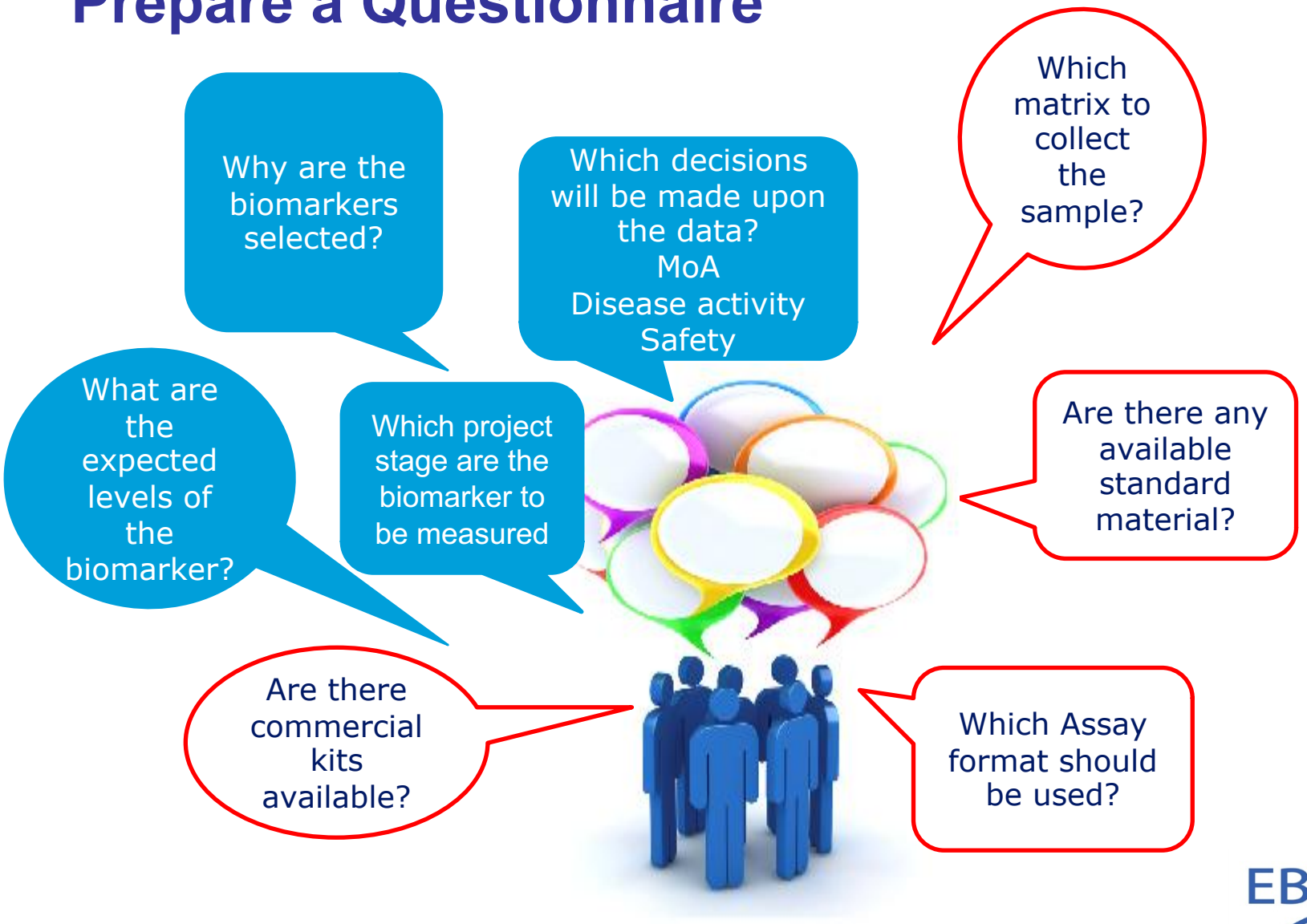


Communication internal BA experts

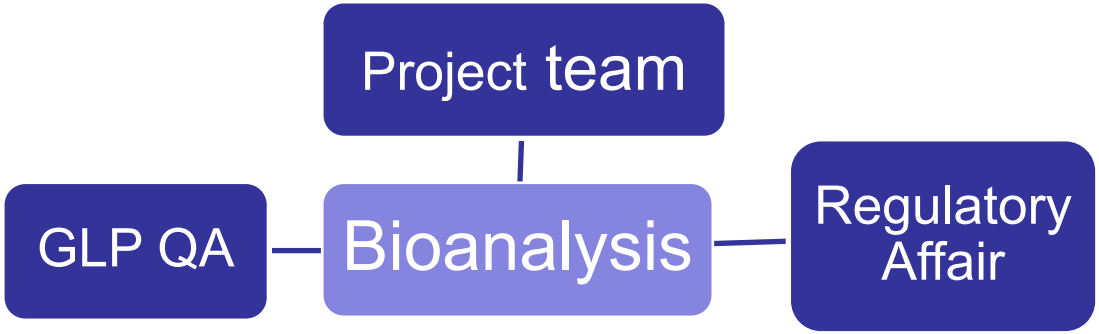
Assay must be reliable in order to be confident in decisions taken for the biomarker data

- Do you know what you are measuring?
- What is the purpose of the assay?
- Assay design – reagents?
- What are the limitations of the assay?
- What is the precision of the measurement?
- How do sample handling conditions affect the measurement?

Communication with stakeholders Prepare a Questionnaire



Communication with our stakeholders



- BA Fear: Do not use data outside the intended scope
- Stakeholders have a general fear for regulators when reviewing Biomarker data
  - Biomarker Assays ≠ PK assays
- GLP claim for biomarker assay validation and analysis → more in a minute

Communication
PK scientist to become a BM scientist

- Biomarker Assays ≠ PK assays

- How much assay characterisation is needed for a biomarker assay validation?

> The challenge for biomarker scientists is to develop a validation strategy that covers both the analytical and the biology process and to understand what is the intended use of data
>
> *Crystal City VI white paper*

- Understanding the data & the biology
- BM scientist to be part of the project team

Take home messages

- Generic acceptance criteria are difficult for all BM assay
- Communication is the key and should include all stakeholders
- Assay validation requirements can change
- GLP and compliance status
- Look for global consensus

BM= Biomarker

EBF

Acknowledgment

- EBF community

- All of you

EBF

Thank you and…….