EBF

Biomarker Assay Validation – Bringing Context of Use into practice

A recap on the EBF Biomarker Recommendations

Philip Timmerman, EBF

Málaga, 18-19 September 2019

BM: 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 BM
- BM-Assays ran by PK-assay experts

Scientific:

- Understanding the PD / Biology…IOW: the context

Communication:

- Who talks, who listens? Who understands and who translates?

Regulatory:

- HA in learning mode too….
- In absence of a better idea, HA are raising the bar by off-track, sometimes irrelevant and unrealistic analytical requirements for the assay

What if we don’t get it right?

We will produce “wrong” numbers:

- Scientifically
- Economically

Biomarkers…
it’s really about the PD…

EBF Recommendation on method establishment and bioanalysis of Biomarkers in support of drug development.

Bioanalysis 4(15), August 2012)

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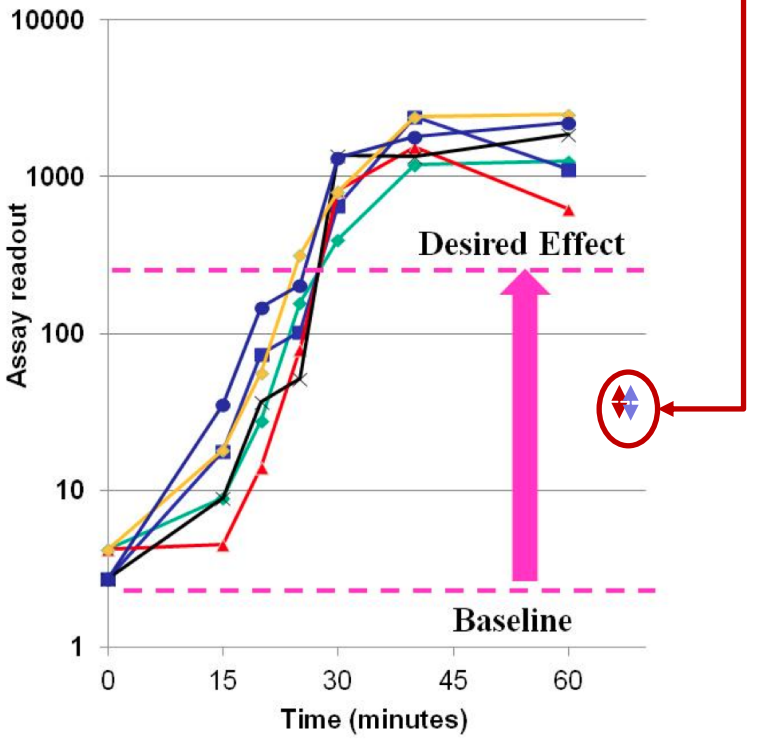
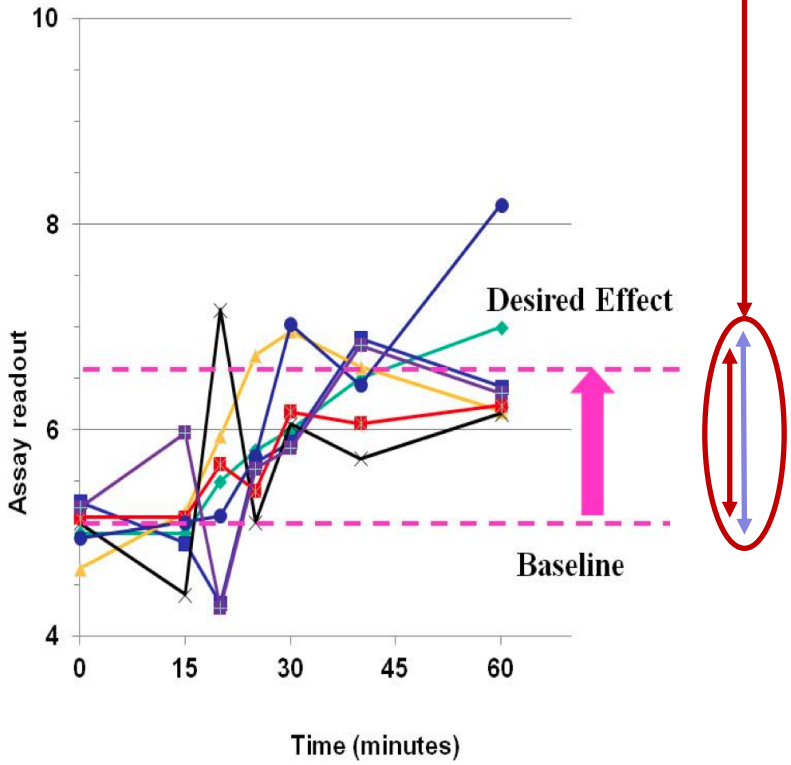
Pointer in *Biomarkers in Medicine* *to try and connect with stakeholders*
August 2012, Vol. 6, No. 4, Pages 507-509

PK criteria. 4-6-15/20

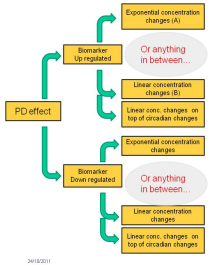


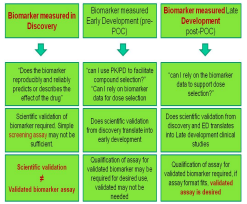


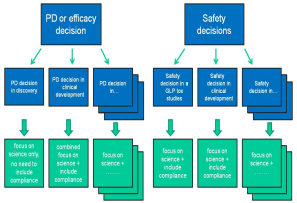
All measured using PK assay A&P. …in both cases inappropriate

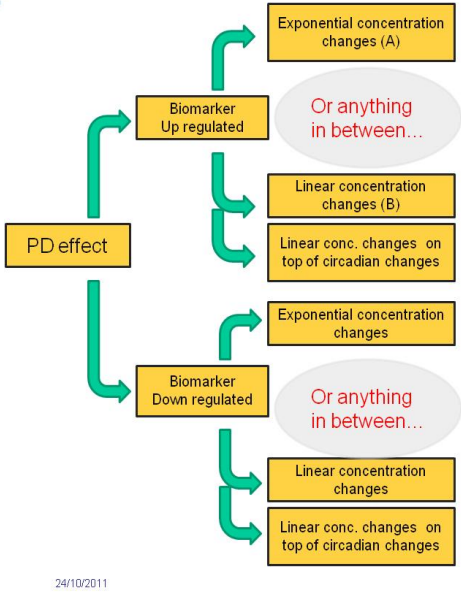
Scientific and process related considerations when setting up a biomarker assay

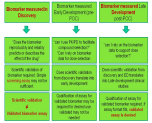
EBF recommendation – 4 pillars





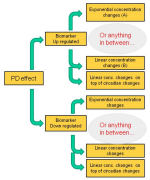




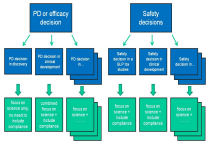


1. Observed or anticipated biomarker level changes

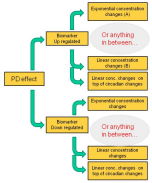
PD or PK/PD effect

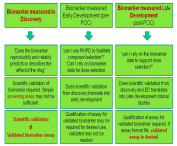


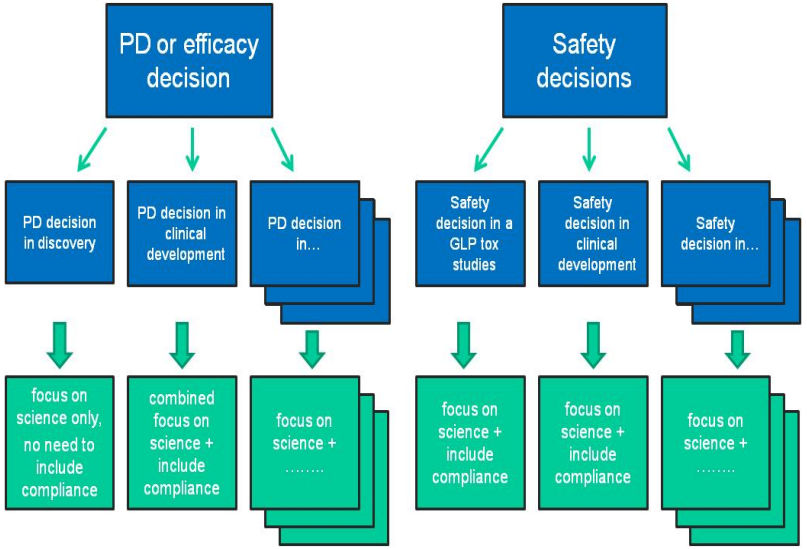
Biomarker measured in Discovery	Biomarker measured Early Development (pre-POC)	**Biomarker measured** Late **Development** post-POC)
"Does the biomarker reproducibly and reliably predicts or describes the effect of the drug"	"can I use PK/PD to facilitate compound selection?" "Can I rely on biomarker 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**



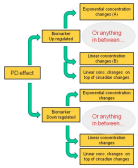
1. Observed or anticipated biomarker level changes
2. Development Phase in which a biomarker is measured

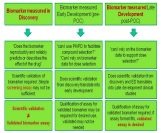


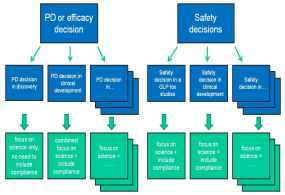




1. Observed or anticipated biomarker level changes
2. Development Phase in which a biomarker is measured
3. Decisions taken from the biomarker data
   - PD or efficacy decisions
   - Safety decisions







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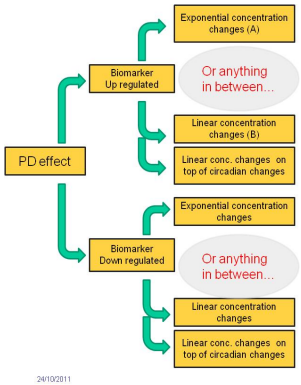
4. Fit of assay with Regulated Bioanalysis Guidelines

Four drivers should be applied in concert to tailor BA biomarkers strategies

1



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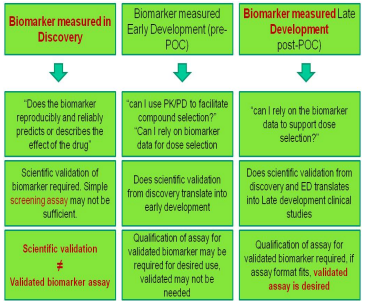

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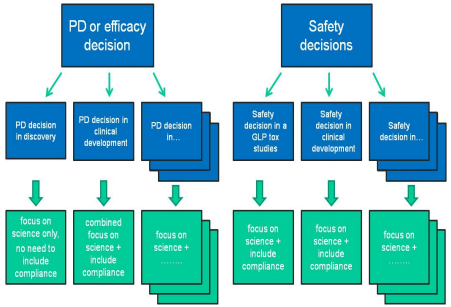

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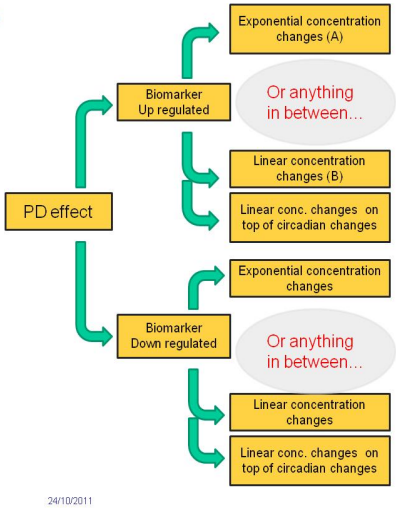

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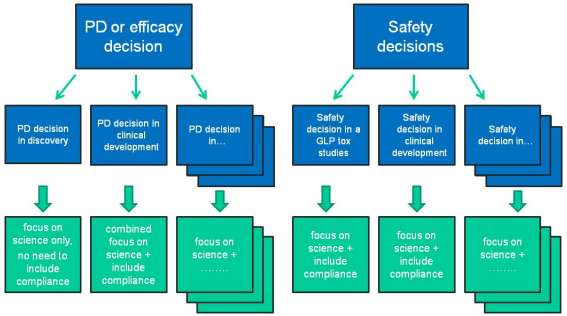

A flowchart proposed in the EBF Recommendation paper

Analysis of BM using a new assay.

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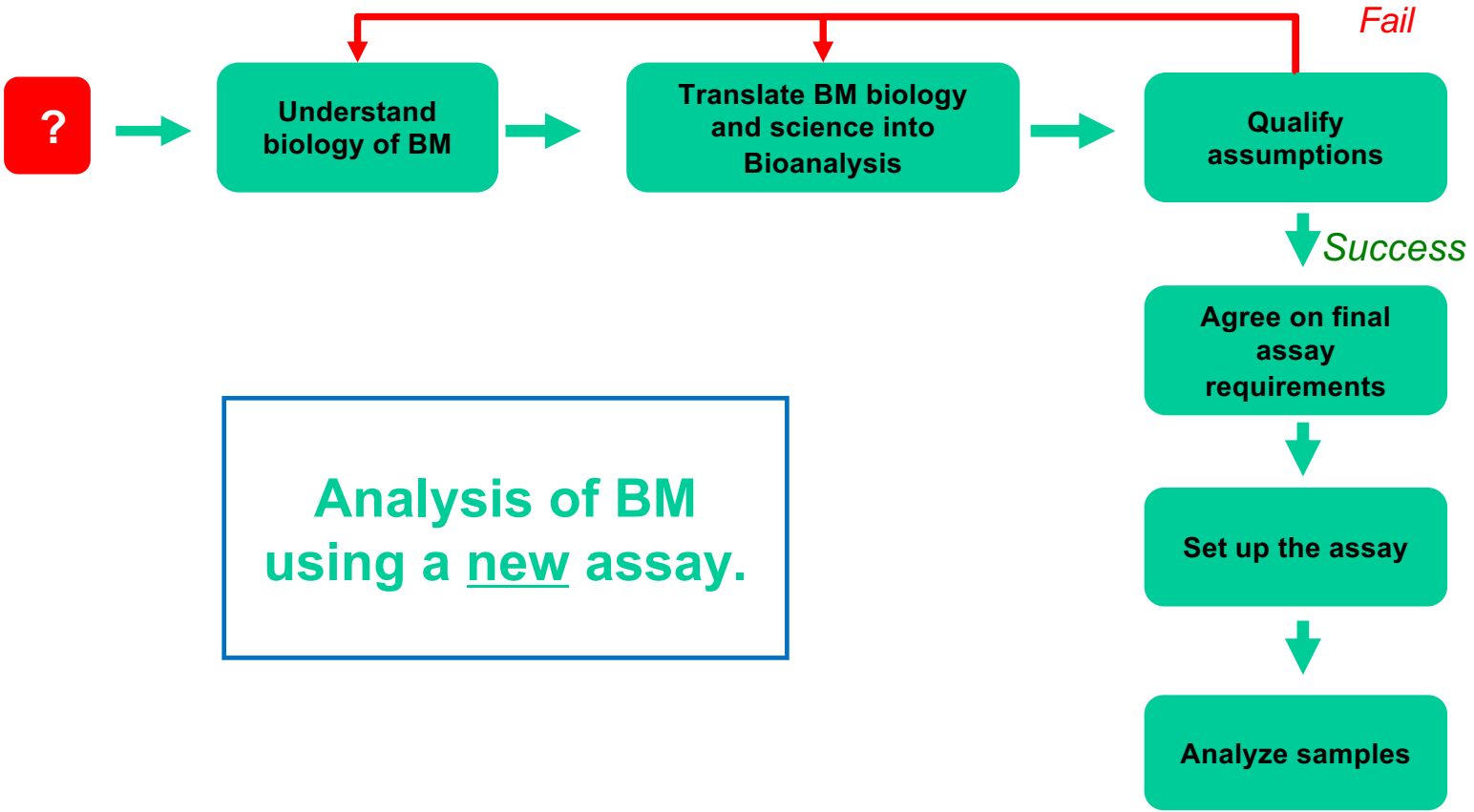
Analysis of BM using a new assay.

Analysis of BM using an existing assay.

Analysis of biomarkers using a new assay.



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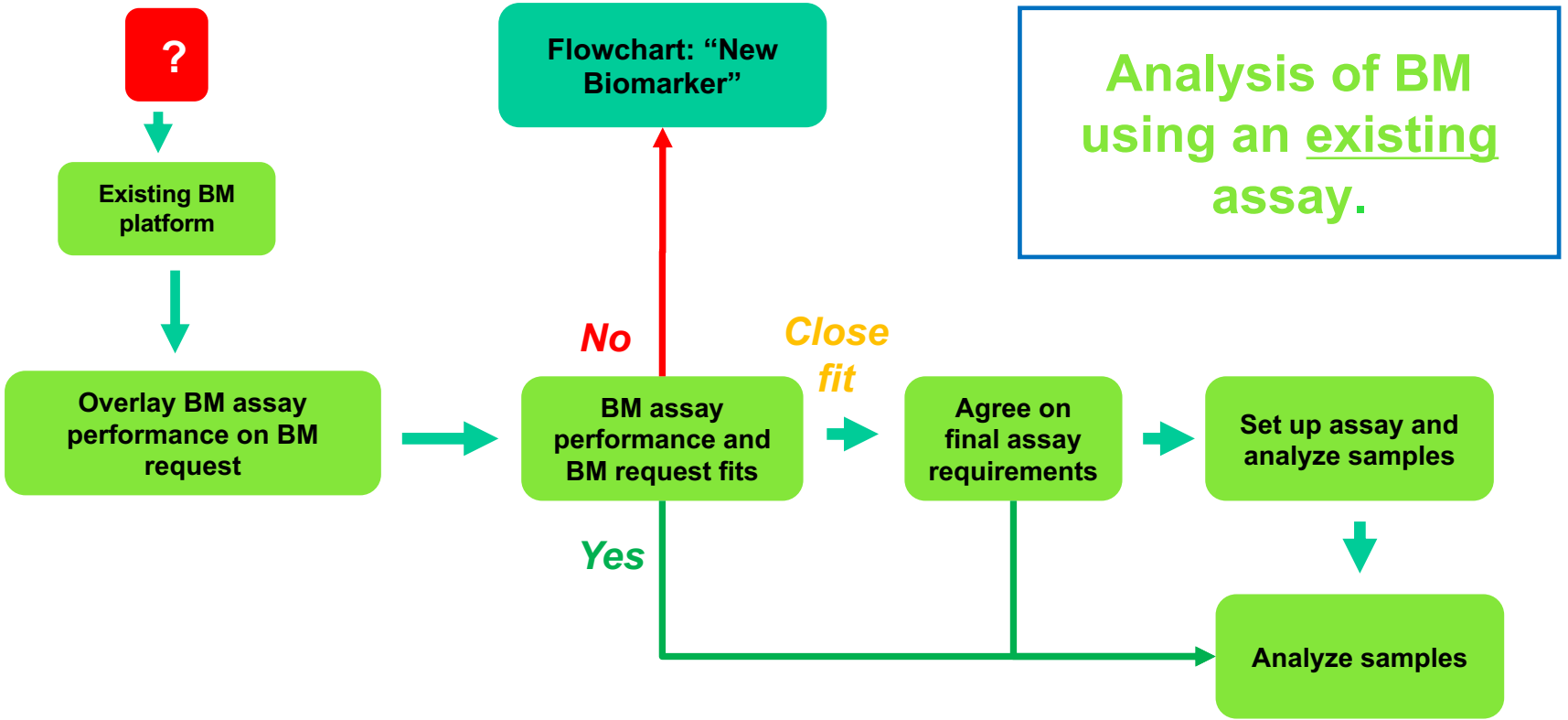
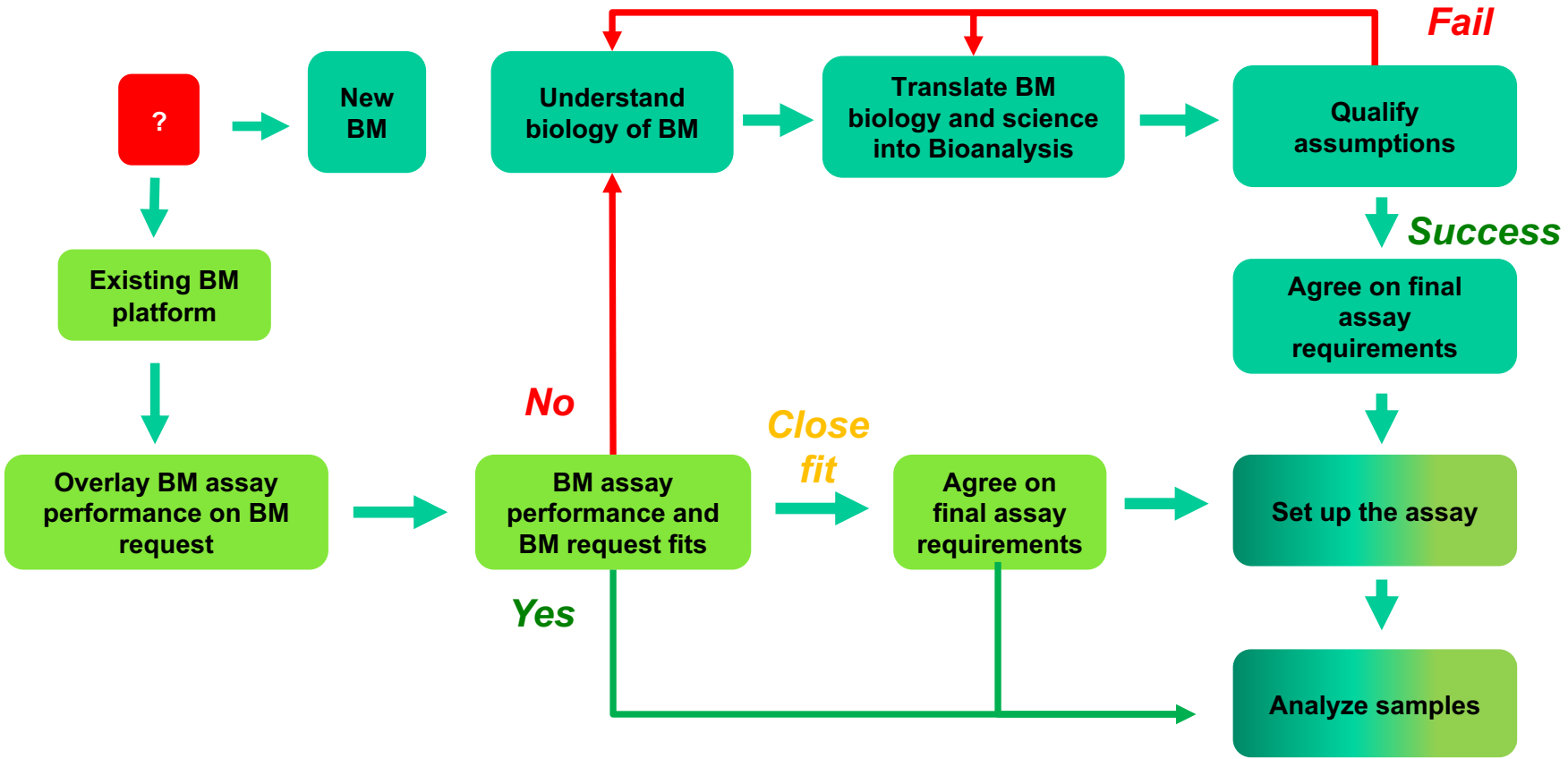
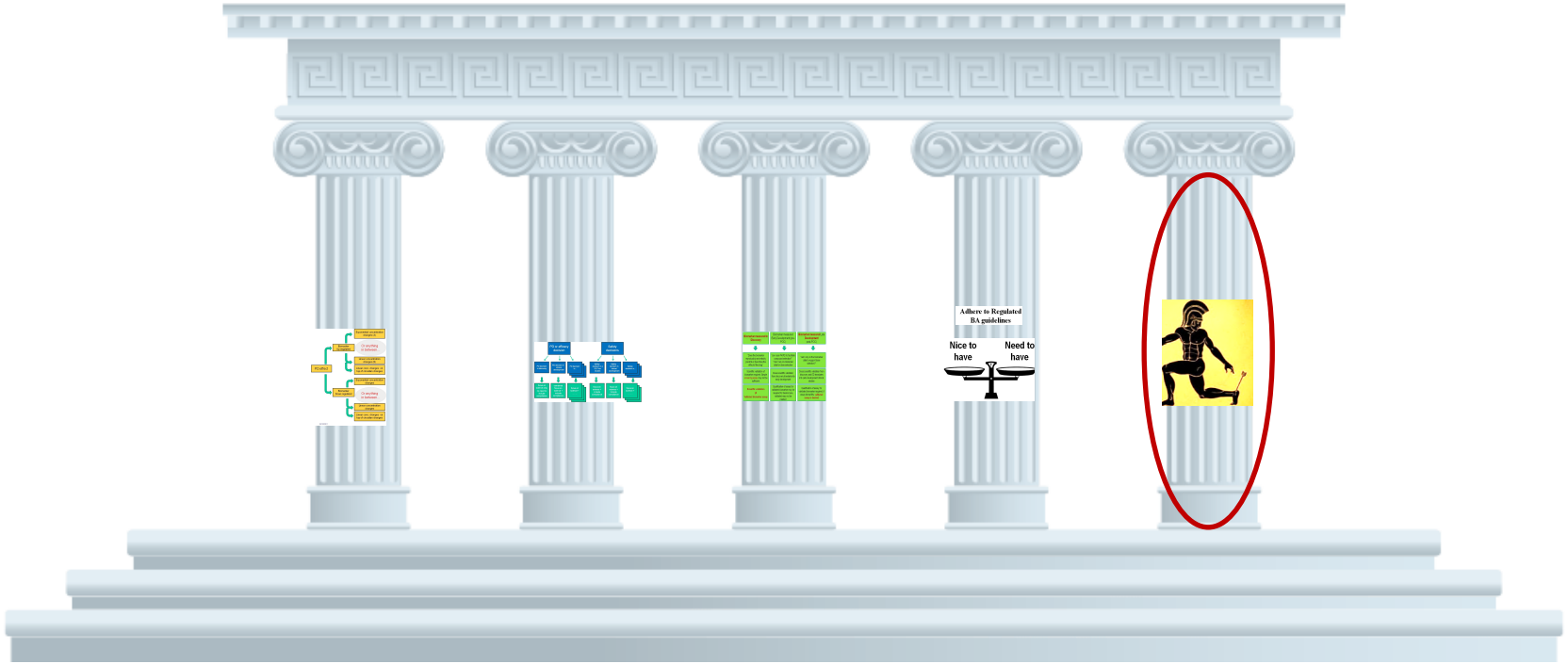


Combined flowchart



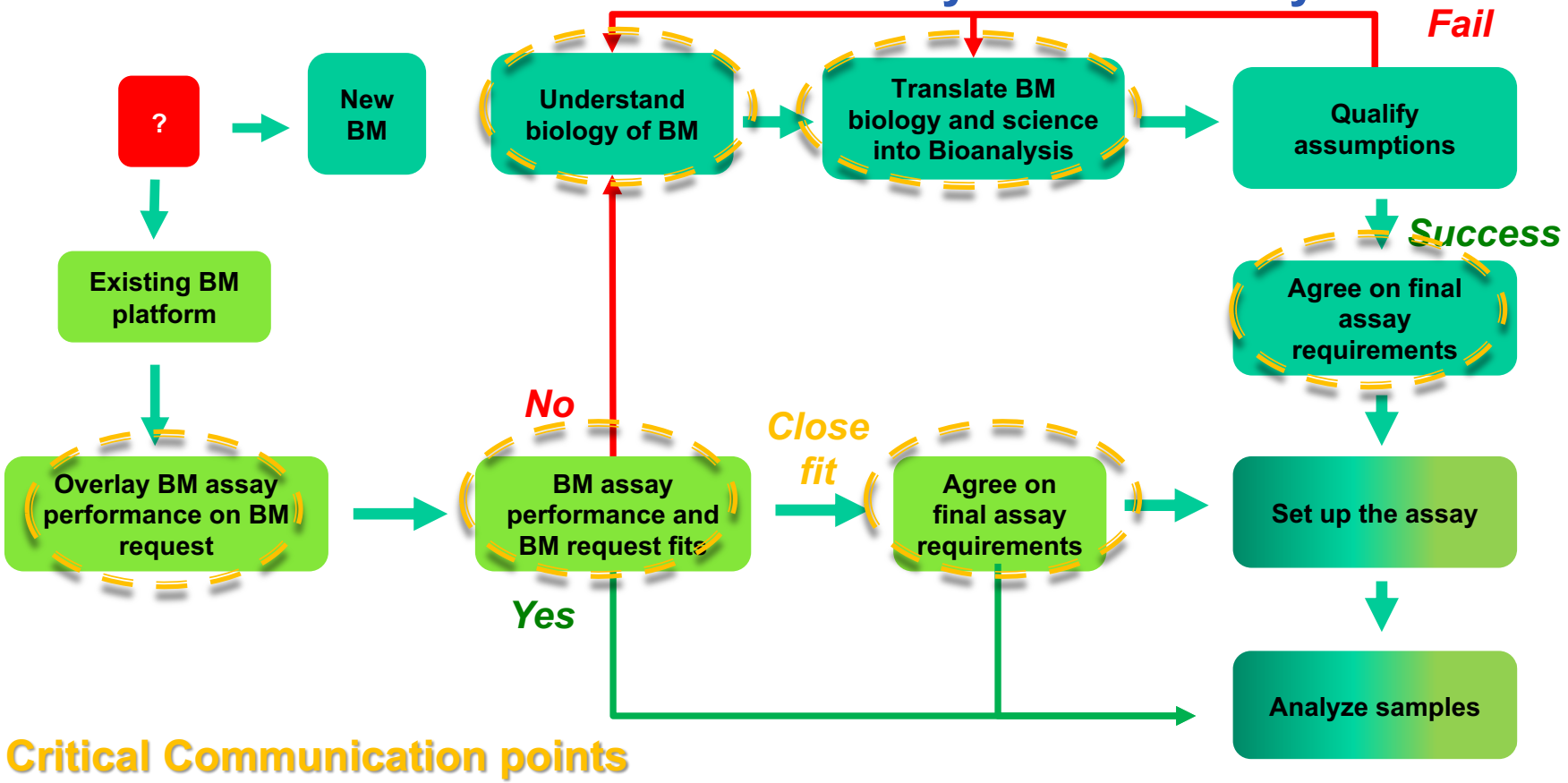

Adhere to Regulated BA guidelines
Nice to have
Need to have

The 5th pillar - COMMUNICATION

Communicate, communicate, communicate:

- To understand the biology, pharmacological effect... of the BM
- To understand what the data will be used for
  - Scientific decisions taken
  - Safety decisions taken
  - Other?
- To share what is possible from a BA perspective (can be more or less)
- To share what is not realistic from a BA perspective
- To ensure optimal cost/benefit

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



Critical Communication points

Additional reflections

With more BMs amenable to LC-MS or LBA assays improving, industry may think "*we can easily reach 4-6-15 (20) quality*", stimulating regulated PK-BA standards for BM analysis, but:

- A significant number of biomarkers are novel and analysis involves the use of cutting edge or developing science
  - High resolution MS, novel hyphenated techniques, novel LBA/cell based assay formats, assays combining LBA and MS technology,…
- More importantly, a significant number of biomarkers **don't need** this level of precision at all…(often less, but could be higher too)

- "***Yes, can do !***" shouldn't mean "***Yes, let's do !***" if there is no scientific driver.
  - "Yes, let's do !" may increase cost with no added value for the patient.
  - "Yes, let's do !" may jeopardize science to progress.

And today….

- We see industry gravitating towards using PK criteria for BM assays, and health authorities stimulating towards it
  - Once ICH M10 goes live for PK assays…will FDA-2018 become a BM guidance?
- Industry should be mindful not to go in ‘regulatory overdrive’ when working in the BM assay validation space and consider the positive outcome of CC-VI and scientific freedom/responsibility given in both (FDA) BM categories

In this Focus Workshop….

Let’s nail it down

Acknowledgment

- EBF community
  - Recommendation paper team 2012
  - Several teams working on the subject from 2012-2019
    - Naming 10 would mean forgetting 10 others
- OC of this workshops