Biomarker Assay Validation: the challenge continues

Philip Timmerman, on behalf of the EBF

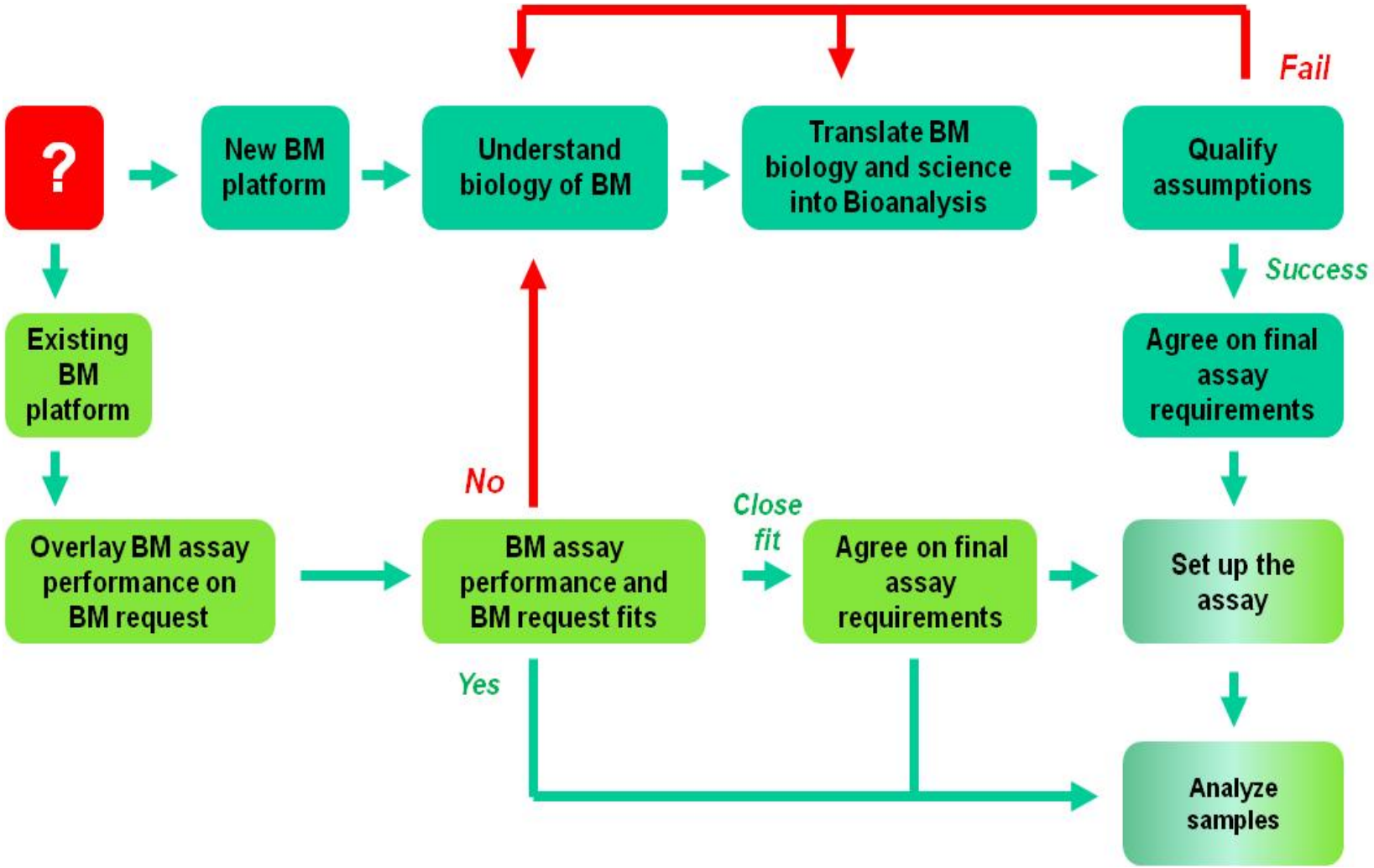
EBF Focus Workshop Biomarkers – Lisbon – 9/10 June 2016

2 Questions

1. Are we ready to bring the EBF Recommendation into practice?

2. What other discussions are needed in industry on BM assay validation.

A recap on the EBF Recommendation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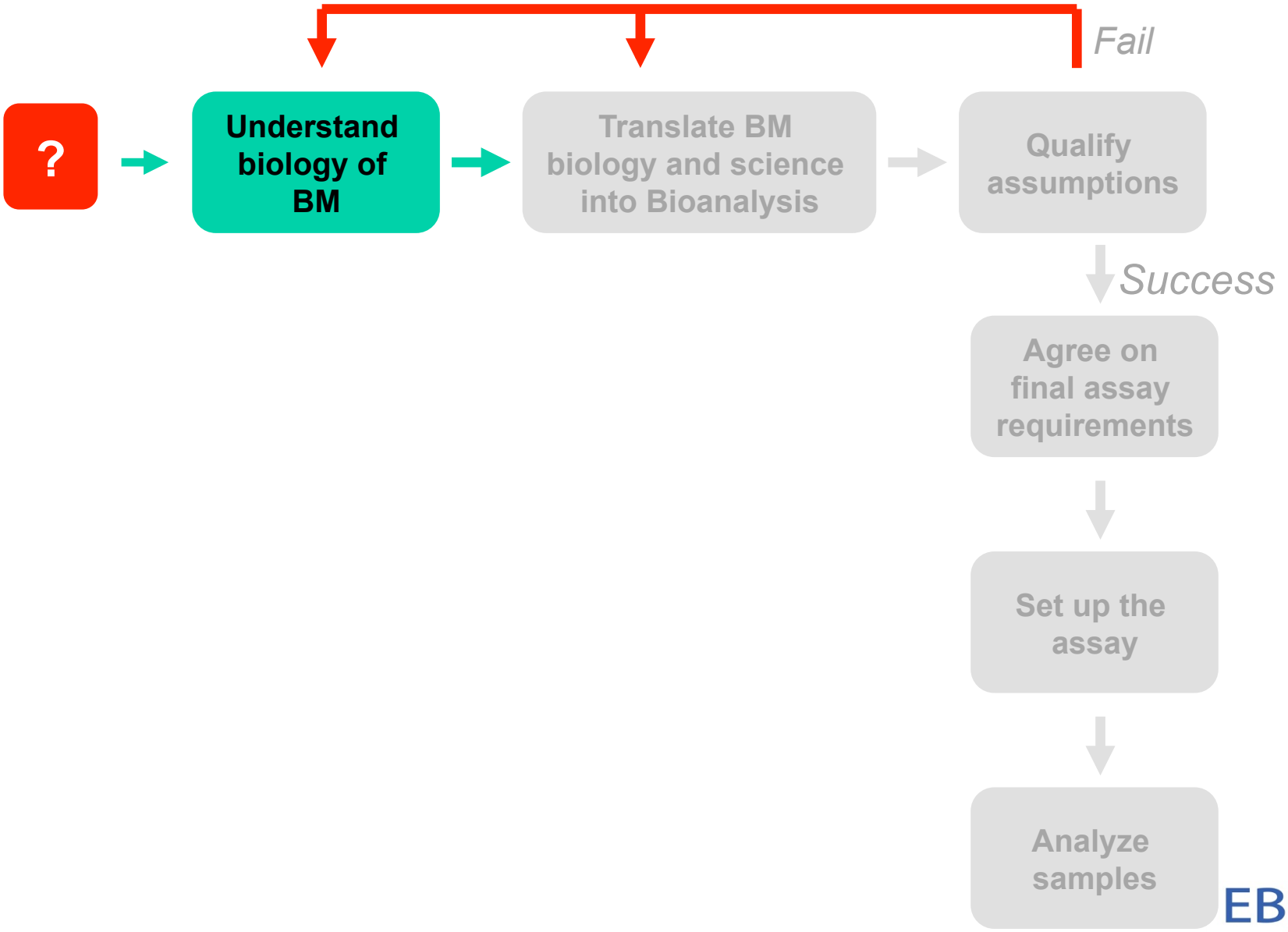
New BM platform
Understand biology of BM
Translate BM biology and science into Bioanalysis
Qualify assumptions
Fail
Success
Existing BM platform
Agree on final assay requirements
Overlay BM assay performance on BM request
No
BM assay performance and BM request fits
Close fit
Agree on final assay requirements
Set up the assay
Yes
Analyze samples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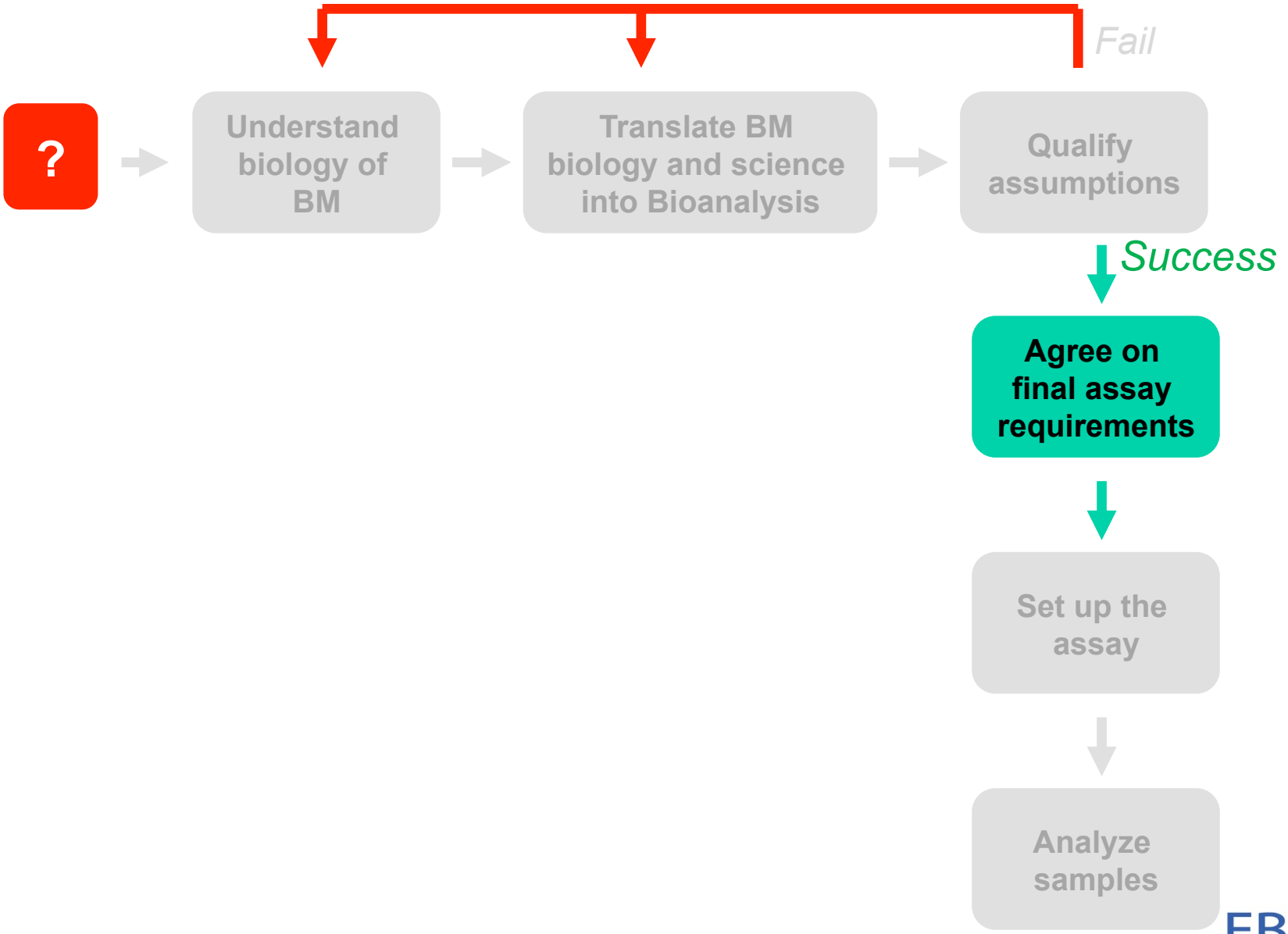
1. Understand the biology and science of BM

- Connect with PK, PD or TK person requesting (='requester') the BM data, and get informed on:
  - PK of BM and PD effect of drug on PK
  - Target species-population and matrix
- Deliverable of step 1 = understand why assay is needed and what is expected outcome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4. Agree on final assay requirements

- Reconnect with requester
  - Provide feedback on bioanalytical pre-work, assumption testing and qualification
  - Only now agree on assay requirements based on
    - Decisions to be taken from the data
    - Potential of assay format
      - Consider change if/when assay is used in later phases of development (species change may require a assay deliverables to be re-assessed)
    - Known Regulatory requirements
      - Consider change if/when assay is used in later phases of development

(lack of) Communication – the Achilles heel of any success stor

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New BM platform

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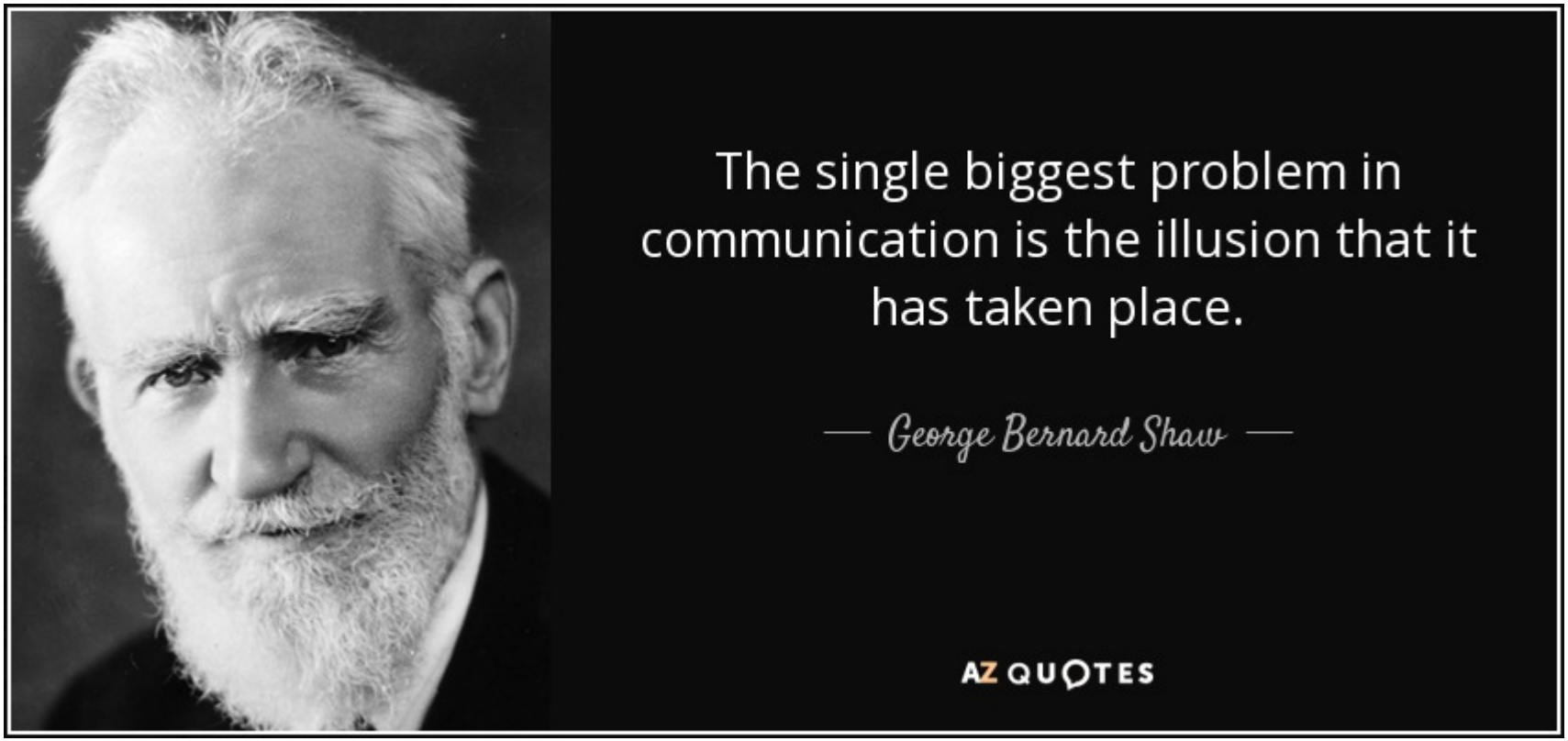
Analyze samples


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

Two way communication

BA

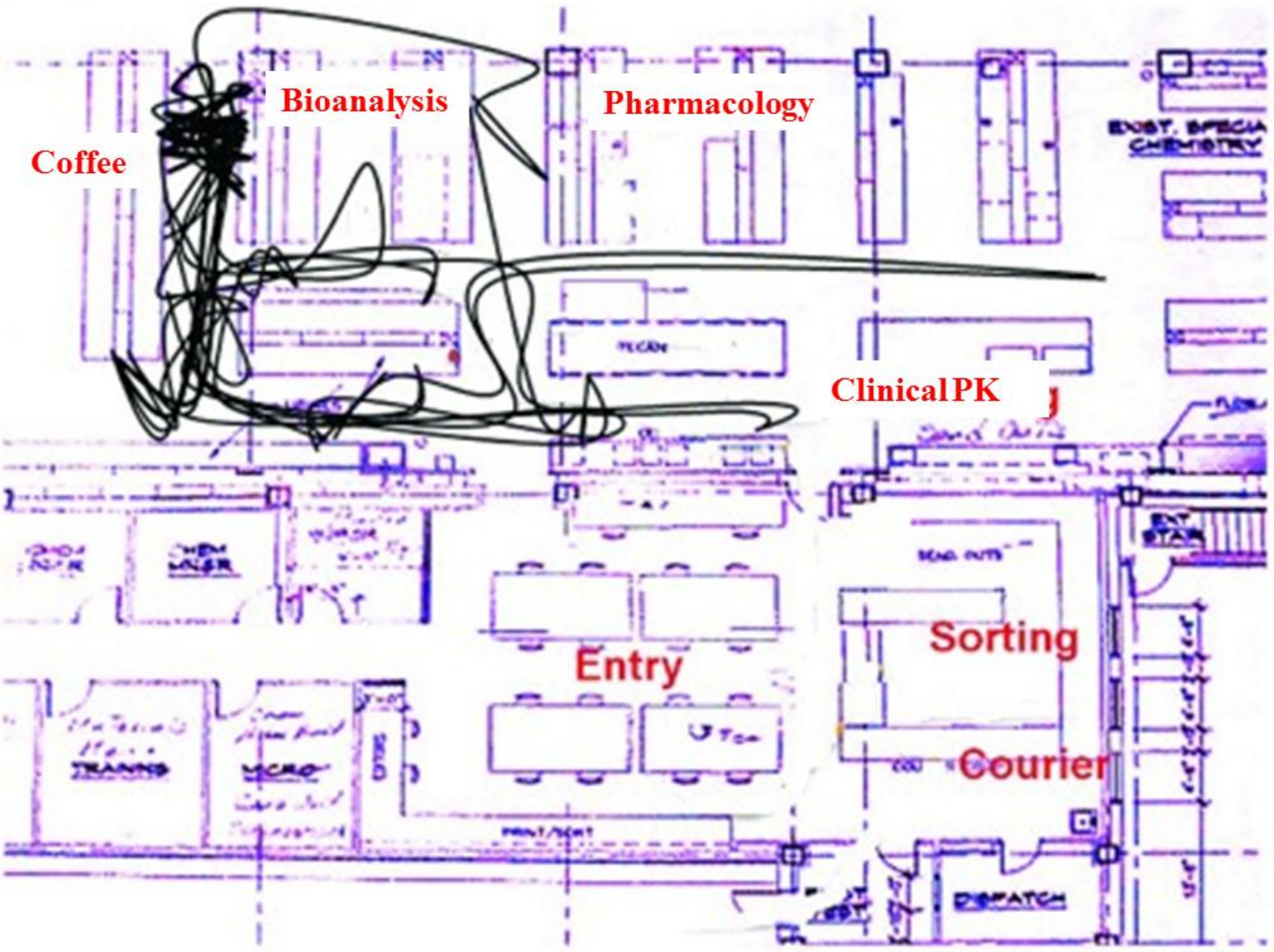
- Performance of the assay
- Requirements of the sample (handling, storage)
- Regulatory landscape from a BA perspective
- Alternative approaches to validation
- Alternative measurements

Stakeholder

- Biology or pharmacology of the BM
- Requirements of the assay
- Decisions taken by the assay data
- Regulatory needs from a PK, PD, TK perspective

Together agree on best way forward

Utopia: all under one roof…



http://www.clpmag.com/2015/03/managing/ Image adapted from Laboratory Alliance of Central New York.

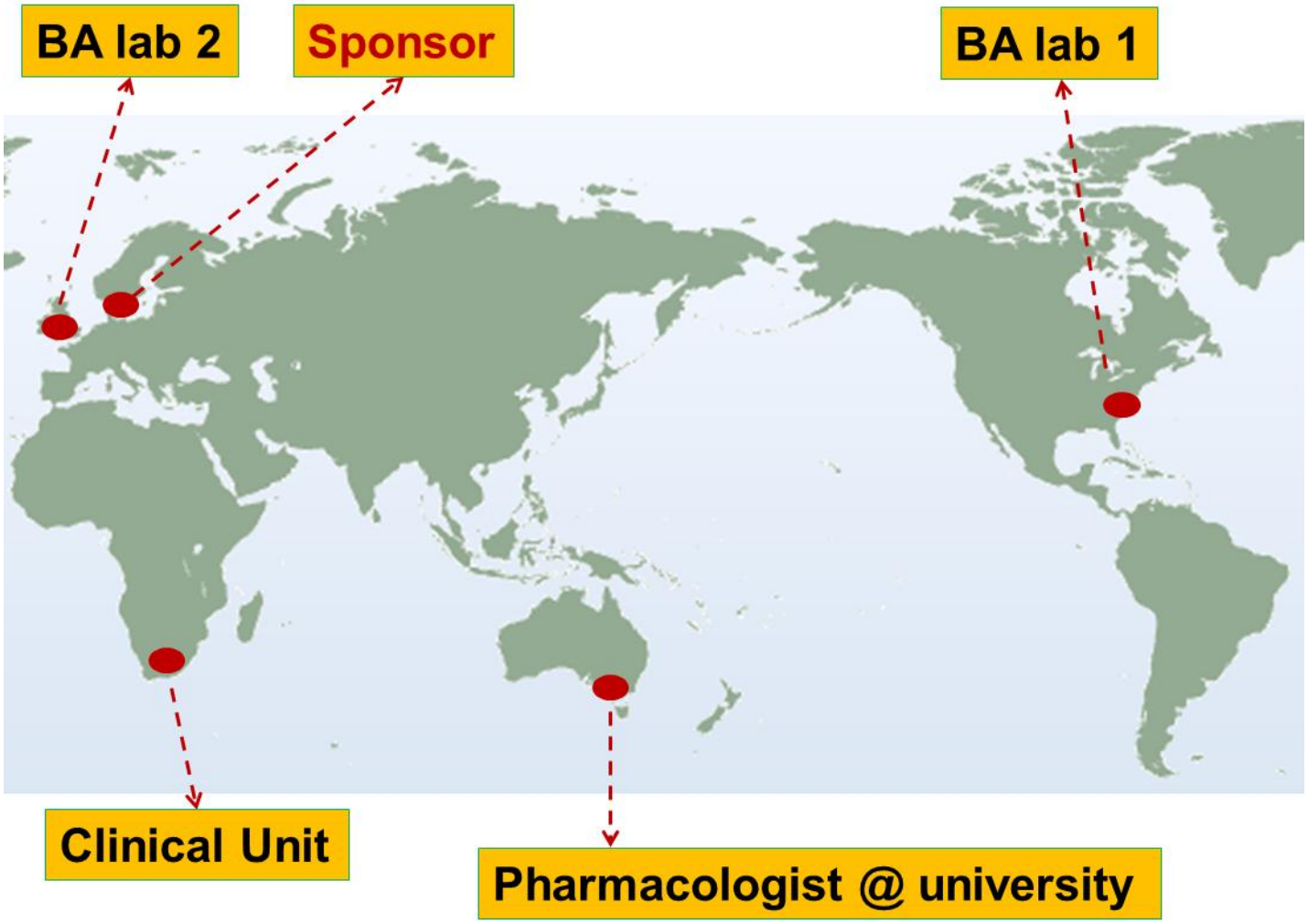
In this situation….

- No geographical / time zone hurdles to optimize the team communication, and involve BA at the right time
- But, the bioanalytical scientist needs to reach out, because inclusion of BA in project teams is not a natural behaviour
- So…

But Utopia was 500 y ago* …

** Original book cover of Utopia (Thomas More, published in 1516, Leuven, Belgium)*

Today, we don't live under 1 roof anymore



Pressure on the CRO-Pharma scientific interface

- Scientific disconnect - BA expert not member of project teams
- BM assay often runs in PK lab → Contamination of scientific discussions and lab processes caused by
  - Comfort zone of SOP
  - Inappropriate Expectations on quality not relevant for BM (GLP).
  - Relative inexperience of 'PK- bioanalyst' in BM world
- Time pressure
- Imbalance "required quality – regulatory needs" negatively affecting cost and timelines

Note: none of above are unique to the Pharma/CRO relationship, but likely an order of magnitude more challenging.

Resulting in…

Project team

+

BA

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BA

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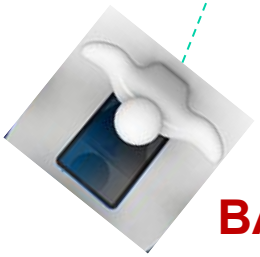
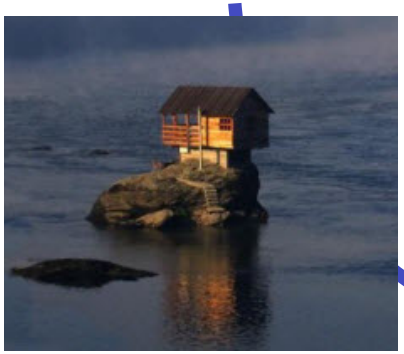
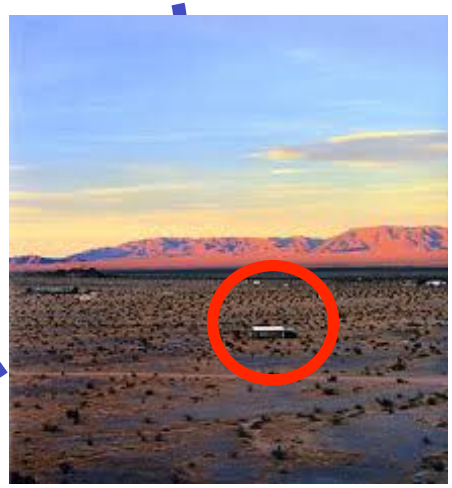
Analyze samples with ‘PK assay’ or worse (e.g. GLP)



BA

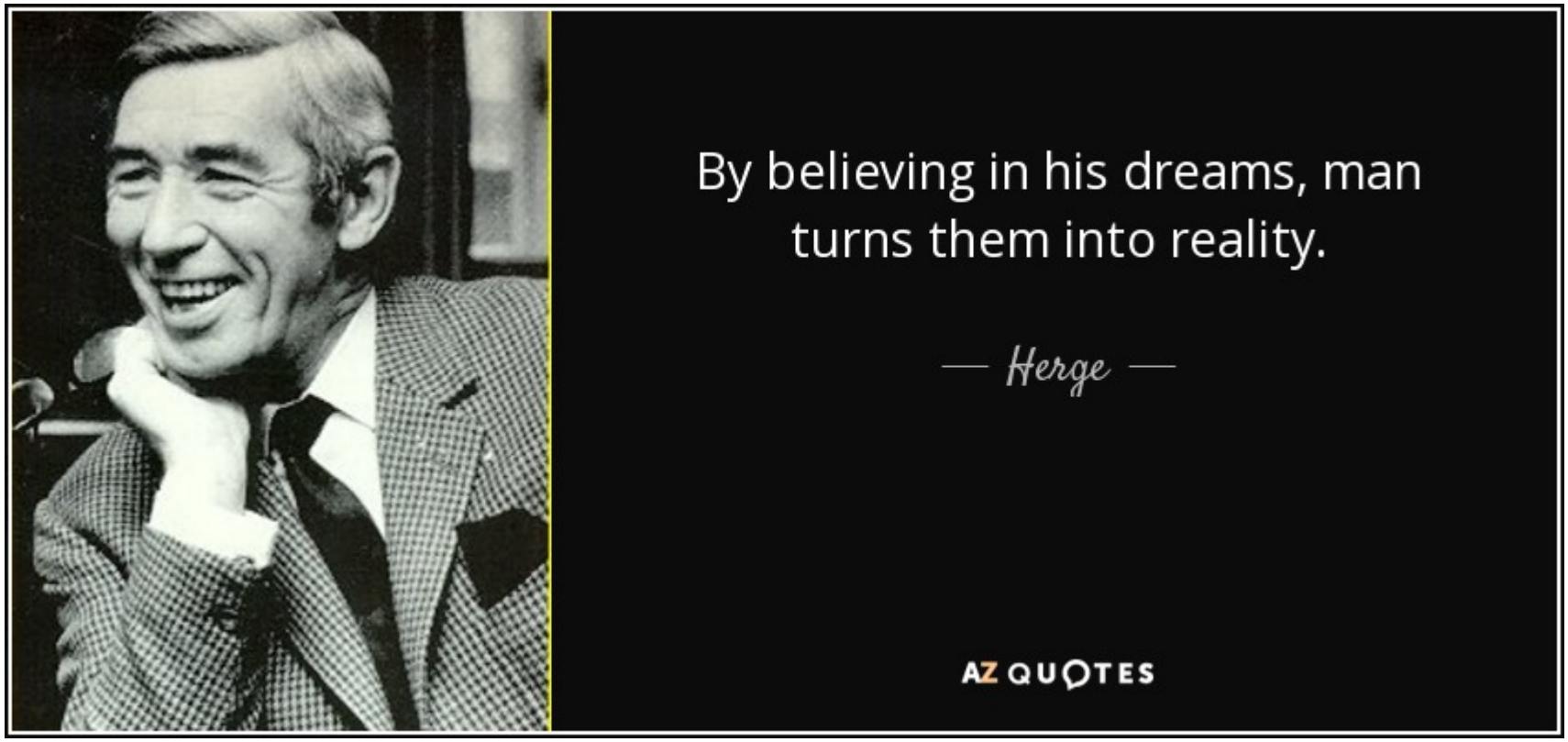
We need to stay connected





The challenges are real

- Impossibility for *(frequent)* face-to-face interactions
- Time zone differences *(Pythagoras introduced time zones by declaring the is world round in 500 BC)*
- In general, CRO scientist not part of sponsor's project teams
- More specifically, BA scientists (CRO or Pharma) not close enough – both scientifically and geographically - to end-users of the BA data
- (scientific) Language and cultural barriers hampering fast and efficient communication
- IP boundaries
- Trust


By believing in his dreams, man turns them into reality.
— Herge —
AZ QUOTES

Prisoners of PK assays?

True explorers of BM ?

What discussions are needed?*

Our stakeholders:

- unaware of (value of) alternative approaches to BM Assay Validation other than PK-assay criteria
- need to become more actively engaged into the bioanalytical discussion.
- create the opportunity to actively listen to each other and mutually appreciate what is the best solution for a given biomarker in a given situation.

* From: ***Biomarker Assay Validation: are we having the right discussions?***, Philip Timmerman, Janssen R&D, Bioanalysis, 2016 (in publication)

EBF

What discussions are needed? *

- Connect all stakeholders in time:
  - In absence of default discussions between all parties involved in BM research (*BA, PK, PD, QA, HA, …*), the expectations on BA data quality will continue to contribute to a trend of over-validation
  - Increase awareness on the different options a bioanalytical lab can offer to achieve adequate scientific and/or regulatory rigor.

* From: ***Biomarker Assay Validation: are we having the right discussions?***, Philip Timmerman, Janssen R&D, Bioanalysis, 2016 (in publication)

What discussions are needed? *

- The regulators:
  - bi-directional interaction with the bioanalytical community needs to continue.
  - Industry need to know for which BMs the regulators expect(ed) to see more solid validation data at filing to stop the '1 size fits all strategy' for BM validation.

* From: ***Biomarker Assay Validation: are we having the right discussions?***, Philip Timmerman, Janssen R&D, Bioanalysis, 2016 (in publication)

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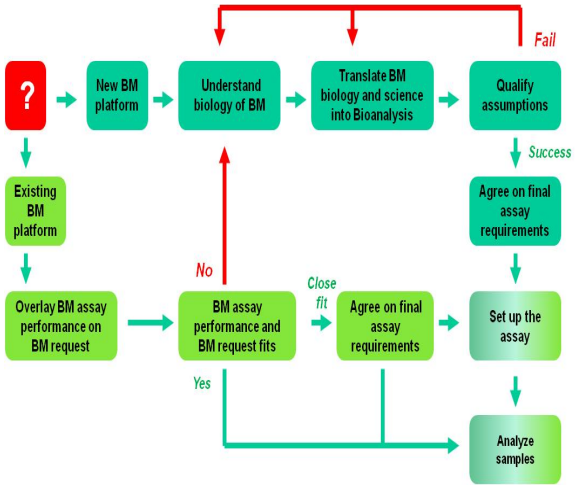
What BMs need…



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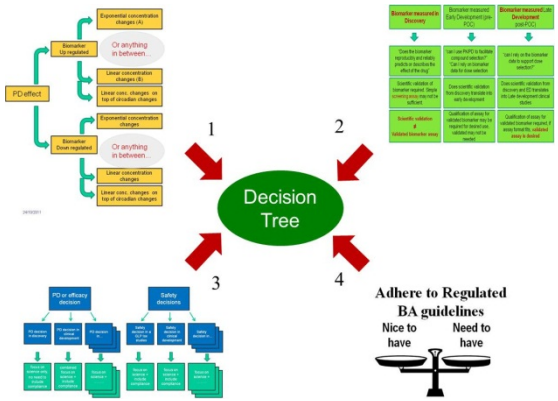

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Analyze following principles of Scientific Validation

EBF BM recommendation 2012

Fit for purpose paper 2009

EBF SV recommendation 2015

Acknowledgment

- EBF BM team
- Co-organizers and presenters at this current workshop
- EBF community
- George Remy (RG, Hergé)
- George Bernard Shaw
- Thomas More
- Achilles
- Pythagoras
- All of you

Time for questions

Back up slides…BMs and SV

- In case I have time and we need it

Understanding the interplay
Fit for Purpose – Tiered Approach

1. Fit for purpose = Lee et. al., 2006
   - Target = biomarkers → and building on the 2003 Biomarker Workshop, a iterative strategy in 4 tiers
     - Preanalytical Considerations and Method Development
     - in-study validation
     - Exploratory method validation
     - Advanced method validation
2. Tiered approach = Viswanathan et al, 2007
   - Target = metabolites → increasing level of validation as compounds progress through development pipeline. Refined to:
     - A science driven fit-for-purpose strategy to apply a predefined appropriate level of bioanalytical quality in preclinical and clinical studies depending on the type of the study, intended use of the concentration data, and/or considering the stage of development. Each tier describes the experiments to be conducted, acceptance criteria to be met and level of documentation required. (EBF, 2014)

Understanding the interplay
Tiered Approach – Scientific Validation

Scientific validation

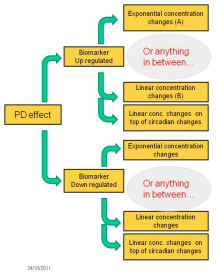
- Subset of tiered approach.
- Defining a practical way forward on how to generate scientifically valid data for area where regulatory standards are not required.
- Current focus of EBF = areas where industry goes in overdrive on trying to comply with regulatory standards:
  1. All Urine analysis
  2. All tissue homogenate analysis
  3. All pre-MAD metabolites analysis (ref to ICH(M3) and EMA-DDI)
  4. A selection of non-pivotal ED clinical studies (i.e. phase), SAD/MAD)
  5. Non pivotal) Early GLP studies
     - principles of scientific validation are compatible with GLP regulations

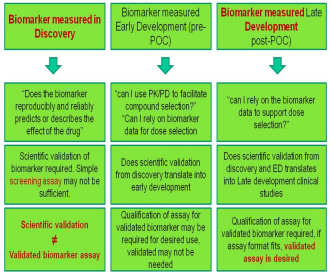
Understanding the interplay
BM assay validation – Scientific Validation

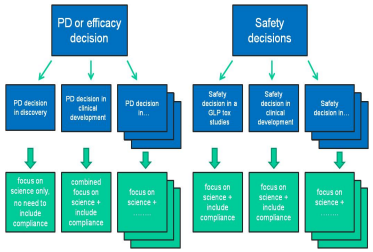
- Biomarker assay validation not explicitly defined in EBF Recommendation paper on Scientific Validation
- Principles could fit philosophy of EBF Recommendation paper on Biomarker Assay Validation

Refinement of the 4th pillars

1 2 3 4

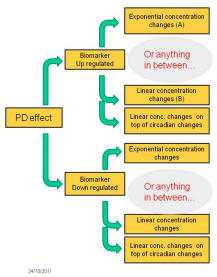


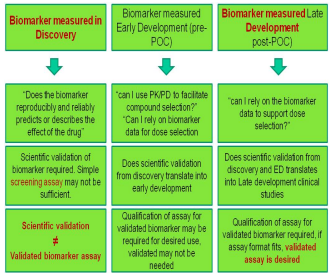


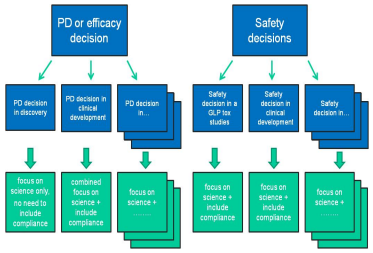


1. Observed or anticipated biomarker level changes
2. Development Phase in which a biomarker is measured
3. Decisions taken from the biomarker data
   - efficacy decisions
   - safety decisions
4. Fit of assay with Regulated Bioanalysis Guidelines

1 2 3 4

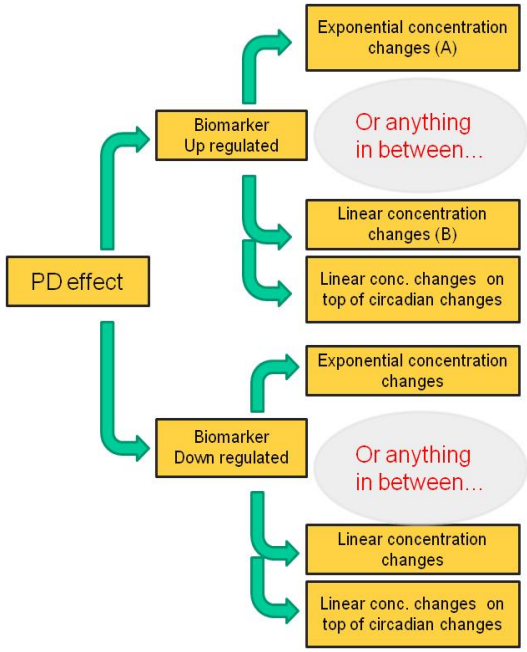






1. Observed or anticipated biomarker level changes
2. Development Phase in which a biomarker is measured
3. Decisions taken from the biomarker data
   - efficacy decisions
   - safety decisions

4. Fit of assay with Scientific validation standards
   - Only than include need for Regulatory standards, since SV standards will likely fit regulatory requirements in many cases



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

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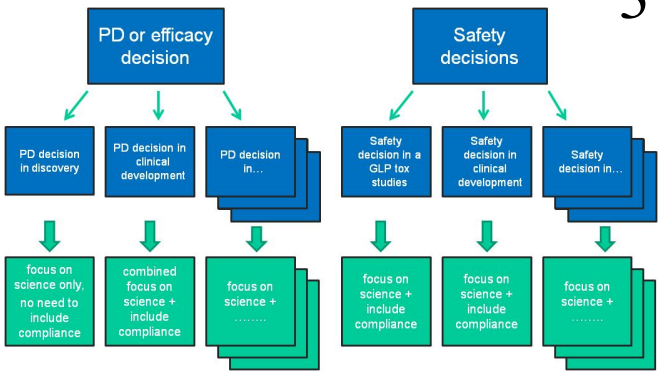
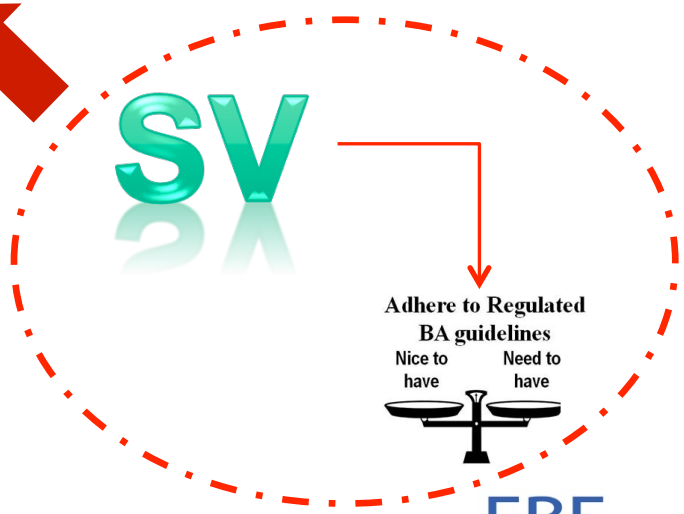
Decision Tree

3

4





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