Data, decisions and stakeholders: the biomarker COU problem statement

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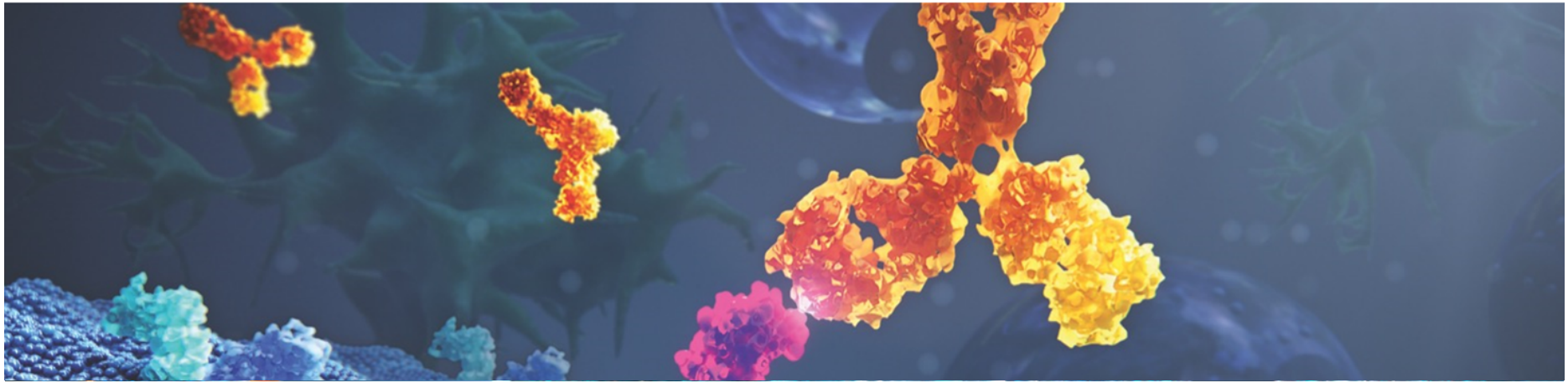
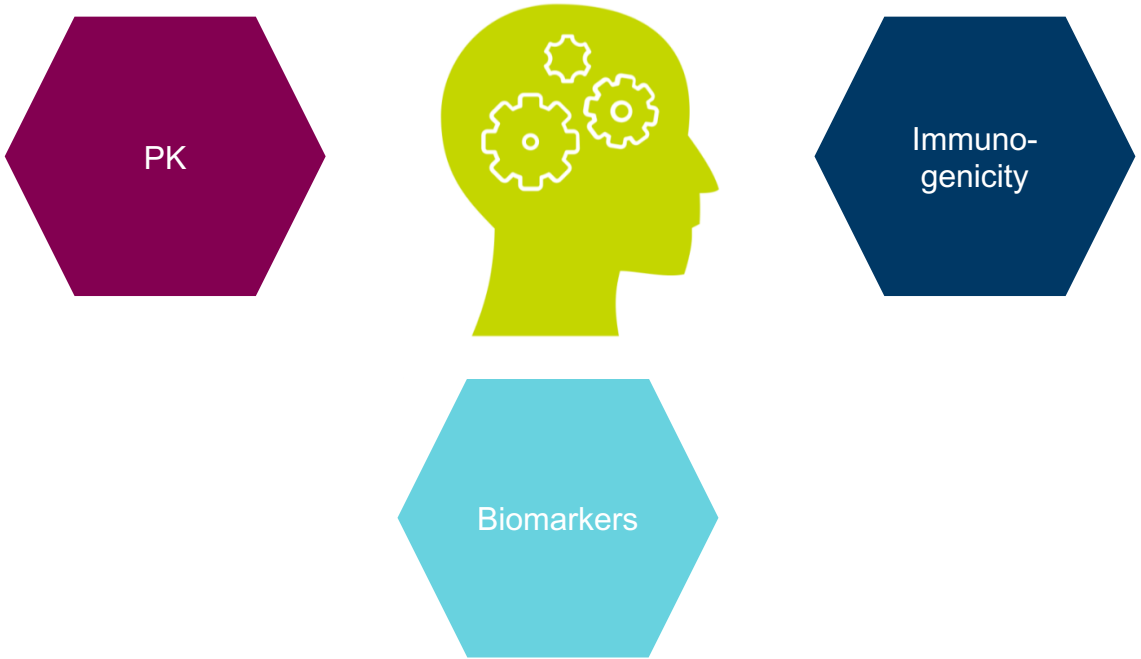
EBF Biomarker Autumn Focus Workshop

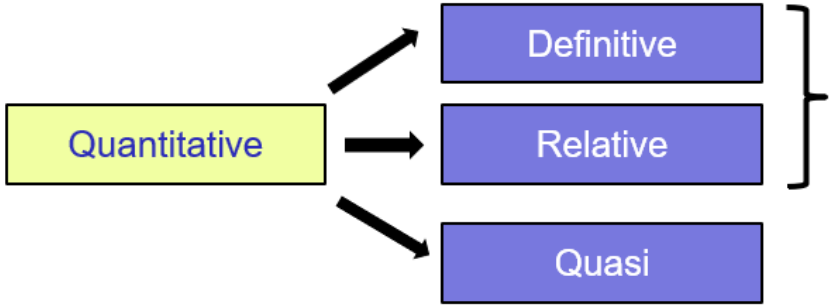
15th September 2020



The mindset shift for biomarkers and context of use (COU)



Biomarker assays come in many shapes and sizes



Biomarker levels determined using a reference standard

Reference material is representative of test samples (parallelism)

Reference material not available or not representative of test samples (non-parallelism)

Biomarker levels expressed in terms of a characteristic of the test sample (e.g. assay signal, titre, % bound)

Qualitative

Biomarker levels expressed in nominal (positive or negative) or ordinal terms (e.g. 1 to 5 scoring scale)

Biomarker assays have multiple challenges

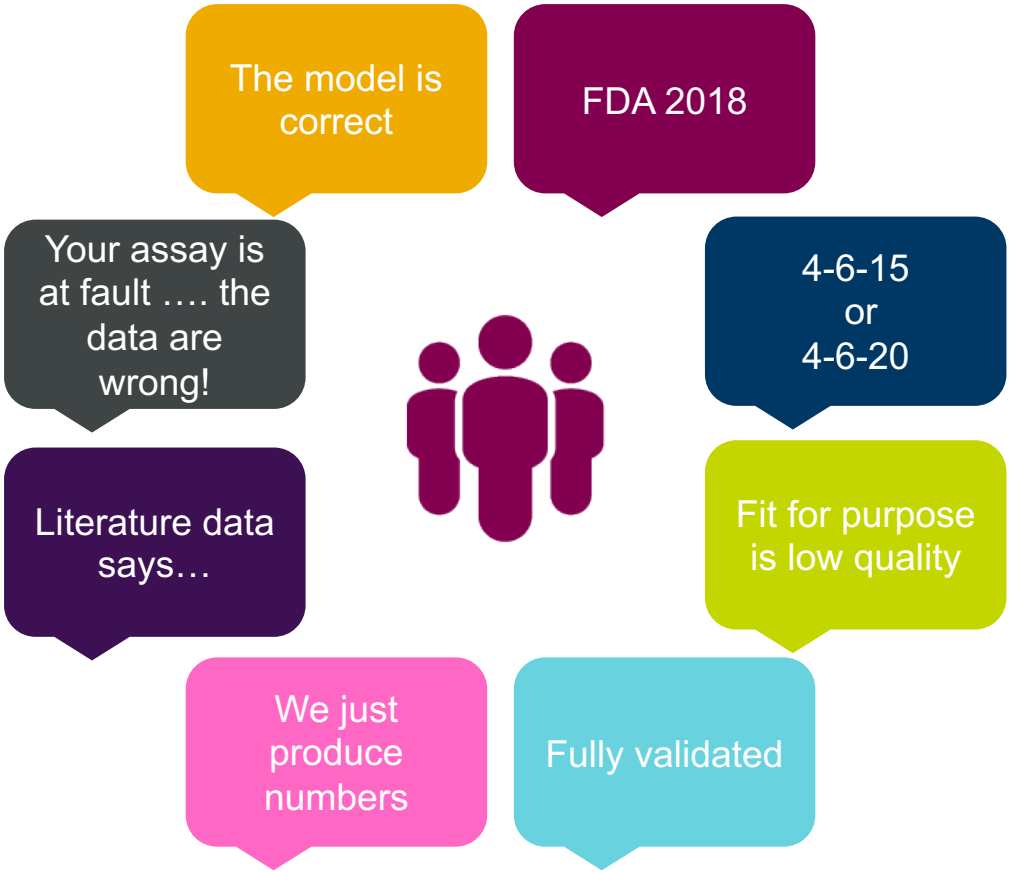
Scientific: understand the biology, PD effects, level of the expected change, free *Vs.* total , who is using the data, the analysis being used

Analytical: platform/technology choice, in-house Vs. commercial kits, true biomarker expertise

Communication: Who?, How?, When?, What?

Regulations: Fear, use of PK validation criteria

Often heard ….


The model is correct
FDA 2018
Your assay is at fault …. the data are wrong!
4-6-15 or 4-6-20
Literature data says…
Fit for purpose is low quality
We just produce numbers
Fully validated

Context of Use (COU) is the "*purpose*" of the assay

- PK assays can be considered to have a single COU, biomarker assays don't share a single COU
- Not to be confused with the clinical protocol terminology of "primary", "secondary" or "exploratory" endpoint
  - Power calculations: statistical analyses and sample size
- COU statement includes more detail and is built in collaboration with stakeholders

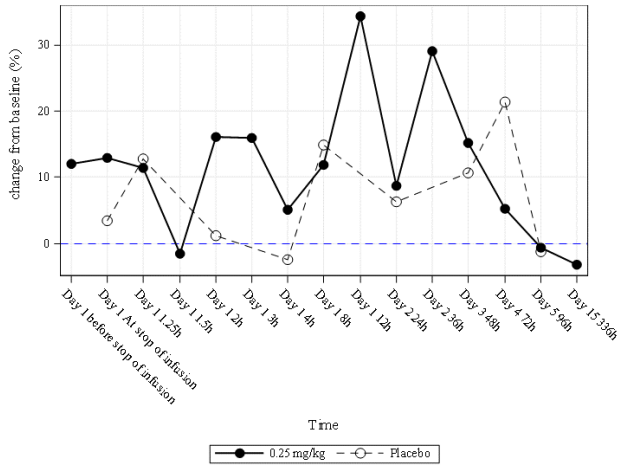
To develop and appropriately validate an immunoassay in matrix A on platform B to evaluate the levels of total (free and bound) analyte C in population X to enable a change of Y% from baseline to allow decision Z

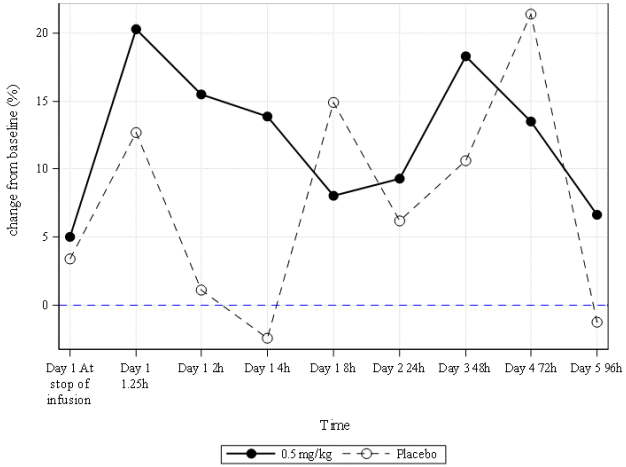
What happens if we don’t get it right?

- Assay is not capable of giving the ‘right’ data
- Incorrect interpretation
- The correct decisions are not being made

- ‘***Wrong***’ numbers are produced
  - Scientific impact
  - Incorrect data interpretation
  - Potential effect for the patient
  - Economical and resource impacts

The intended purpose, i.e. COU is critical





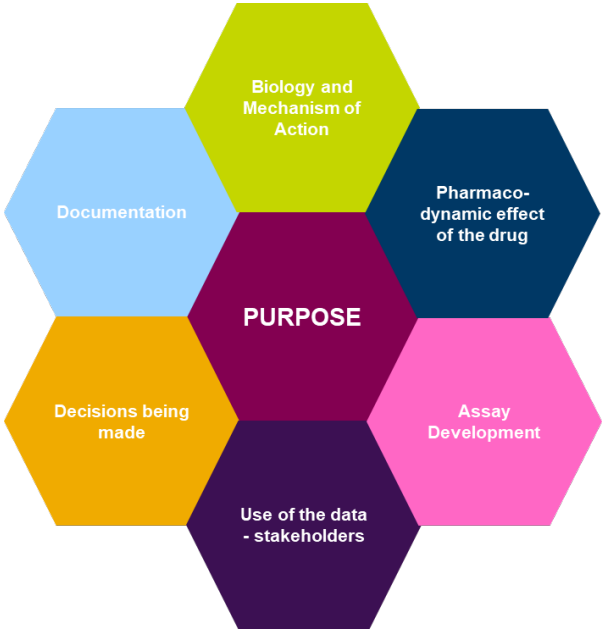
- Assay used successfully in clinics to assess values within a normal range
- Single dose infusion in Phase 1 study
- Assay was validated at the clinic for visits spread weeks-months apart
- The assay had been used to evaluate multiple time points within a day and across days within the clinical trial
- Variability seen in placebo subjects showed that the assay was not fit for the intended use
- Consequence: study reached stopping criteria


P
return
L
K
apply
control

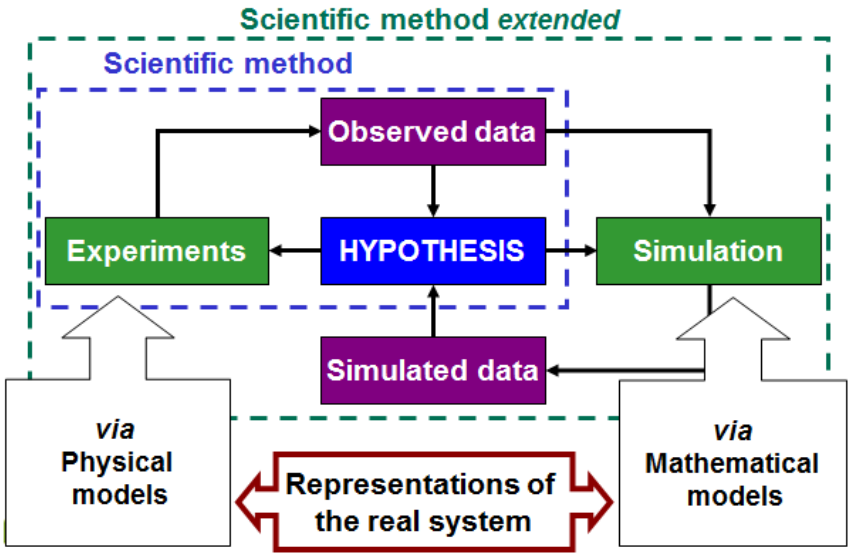
Project team requests an assay

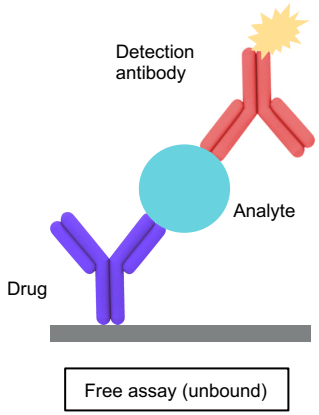
- Project team requests:
  - Demonstrate target engagement biomarker assay
  - Soluble form of analyte used as a surrogate of membrane form
  - “Secondary endpoint in Ph1 clinical trial”
  - “Require a fully validated assay”
  - 4-6-20 criteria

Assays are developed and validated for the COU



Understanding biology, modelling, changes expected



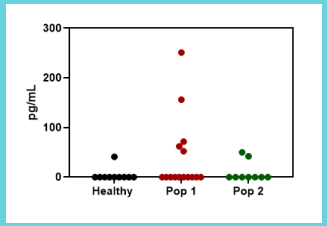


To develop and appropriately validate an immunoassay in human serum on the MSD platform to evaluate the levels of free (unbound) soluble analyte in population X to observe a change of at least 95% suppression for >25 days to demonstrate target engagement in FTIH study

Understanding the assay requirements

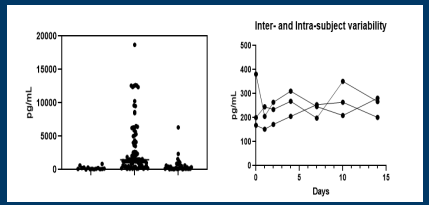
Literature data (if any)

However may not be reflective of the assay



Literature data may not be reflective of commercial samples in the assay

Commercial samples may not reflect the populations evaluated in the clinic



Understanding the population data

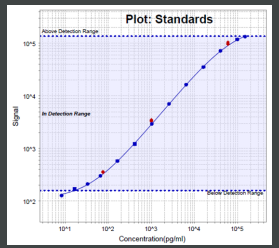
Understanding variability

Inter-subject

Intra-subject

Other confounders

Required precision



Assay range

Parallelism

Drug tolerance

Potential interferents

Sample processing and storage

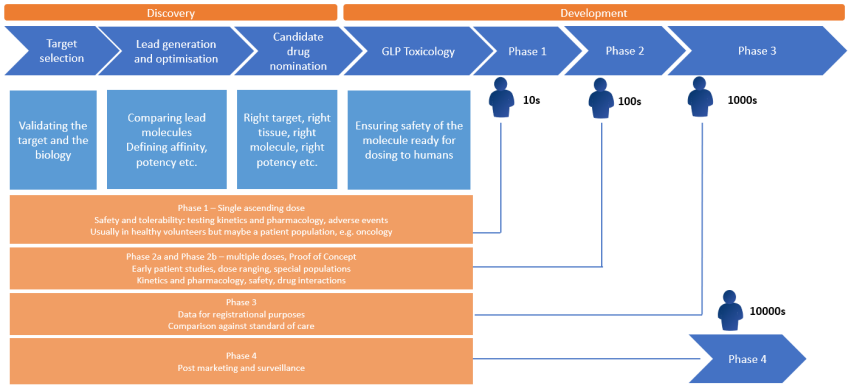
Sample stability

Do you stakeholders also understand these?

Engage the stakeholders and make sure they understand the assay and the data

1. **Identification of all the potential stakeholders**
   - Project teams
   - Users of the data
   - Decision makers
   - QA
2. **Communication**
   - Project
   - Individual(s)
3. **Understanding**
   - The need and importance of biomarker COU
   - The data produced
   - Ability/limitations of the assay
   - Decisions being made with the data
4. **Training**
5. **Agreement**
6. **Documentation**

If the COU changes you need to revisit the assay



- Disease/indication change
- Use for academic collaborations
- Use in another unrelated trial
- Matrix type change
- Diagnostic use
- New/further information

Summary

Apply scientific and biomarker thinking

Be part of the discussions and understand all the components of the COU discussion
Identify and communicate with stakeholders

Ensure stakeholders are educated and trained
Help them understand the limitations of the assay

Gain agreement with stakeholders

Document the discussions and the COU

Develop and appropriately validate the assay for the intended purpose
Understand the use of the data and the decisions that will be made
Be prepared to regularly review


THANK YOU


Questions

Confidentiality Notice