Biomarker classification: a philosophical introduction.

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on behalf of the EBF biomarker team (TT-14)

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Background

A few no-brainers to start the conference

- Biomarker (BM) analysis happens in all stages of drug development
- BM classification can be done by looking at the analytical or regulatory challenge
- BM assays should be built on science:
  - considering biology and biochemistry of the biomarker
  - considering the analytical chemistry aspect of the assay
- Different levels of ‘compliance’ may be required to provide a documented answer to the question.

Background

- Appreciating different BM classification allows the right balance between science and compliance in designing the bioanalytical strategy.

- Next slides give an overview providing the bioanalytical scientist a teaser on factors influencing the level of validation/qualification needed or achievable in BM quantification

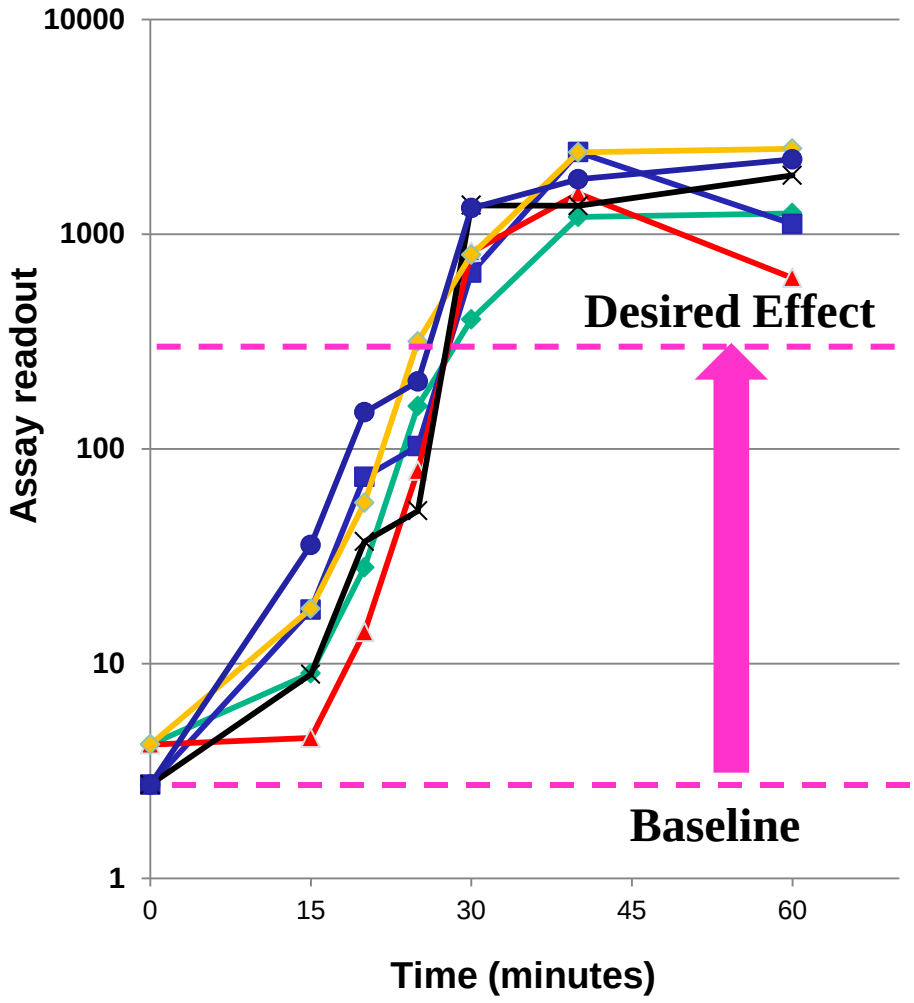
- Note: if BM is a drug on it's own…regulations are clear

Let’s start with some examples

challenging a simple ‘4-6-15’ approach…

Biomarker 1:

desired effect = 2 log units up regulation (- - - - - -)



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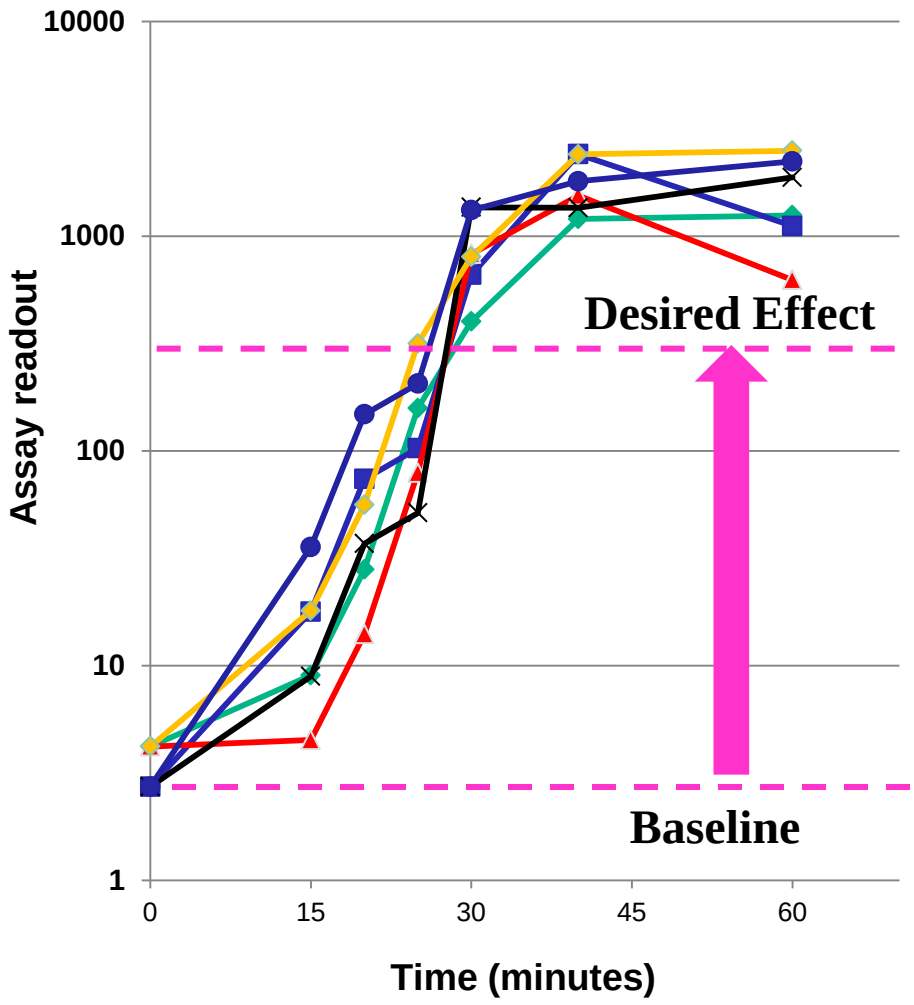


Replicate (n=6) analysis

QC data:

- Assay barely meets "4/6/**100**"

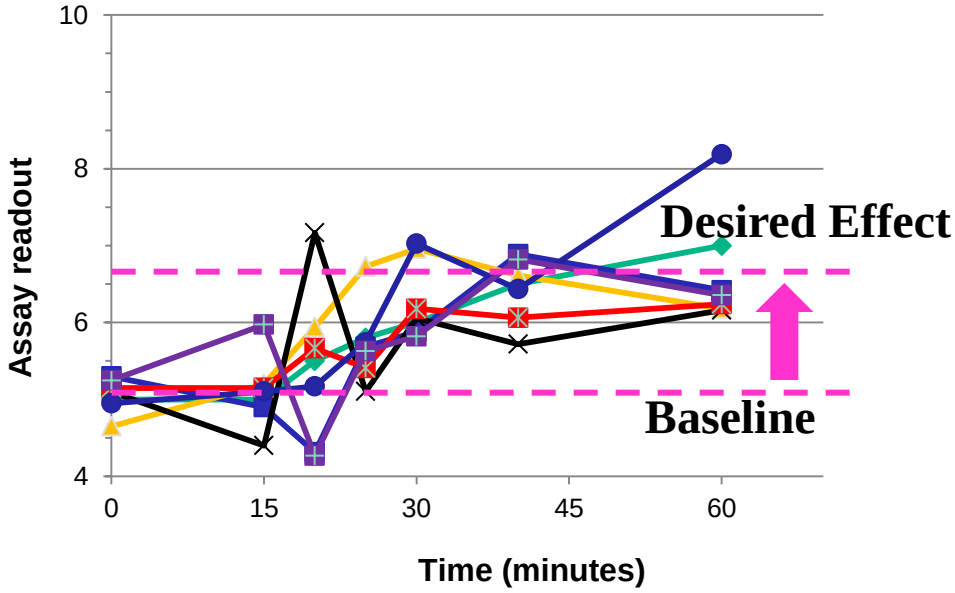
Evaluation:

- Average of 6 assays allows a scientific decision
- Each individual run allows a scientific decision

'4-6-15' would be far too good

Biomarker:

desired effect = 30% increase on baseline



Time after dosing (min.)	Observed effect	STDEV	Increase from baseline
0	5,07		Baseline
15	5,12	0,51	0,05
20	5,42	1,10	0,35
25	5,72	0,55	0,65
30	6,32	0,54	1,25
40	6,42	0,46	1,35
60	6,59	0,79	1,52

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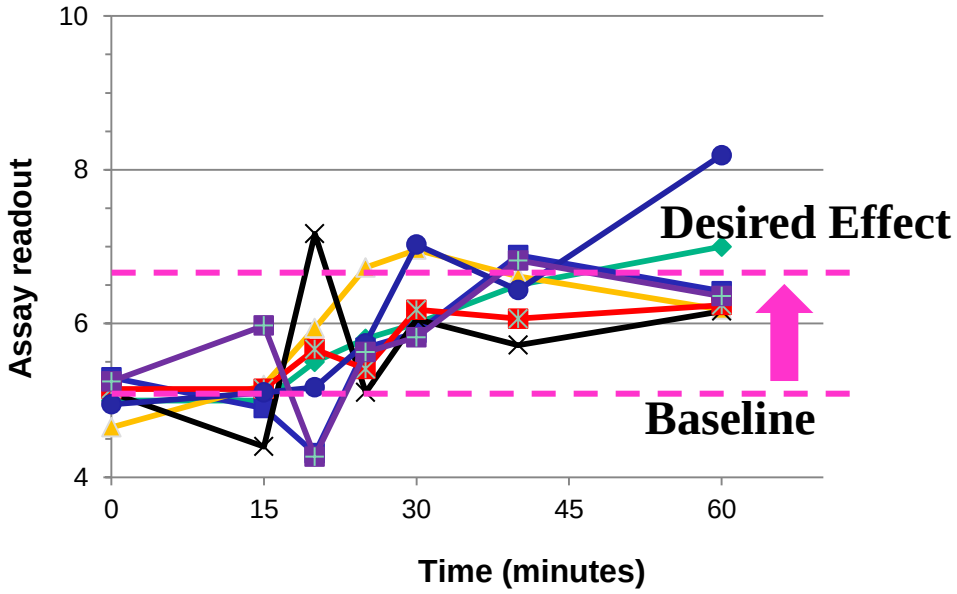

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Replicate (n=6) analysis

QC data:

- Assay meets “4/6/15”
- Assay even meets “4/6/10”

Evaluation:

- Average of 6 assays allows scientific decision, but only by throwing in statistics
- No individual run allows any scientific decision

4-6-15 not good enough

So, what should drive the BA strategy for BM?

1. Observed concentration changes (PD effect)?
2. Development Phase in which BM is measured?
3. Decisions taken from the BM data?
4. Possible fit of the assay specifics with conventional Regulated Bioanalysis (FDA, EMA)?
5. ……..?

1. Observed concentration changes (PD effect)

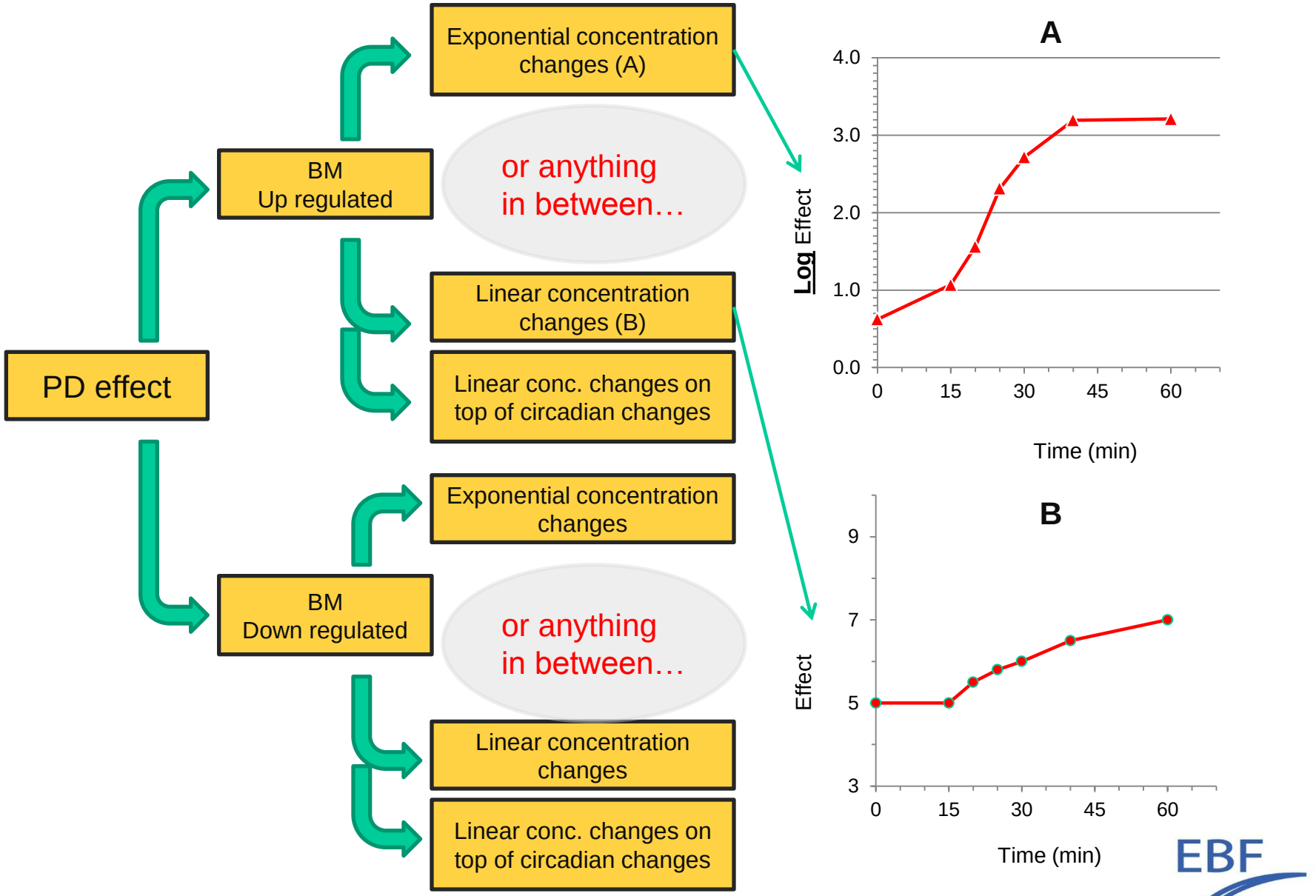
Observed/anticipated changes in BM concentrations are a major driver to design assay performance.

Following situations can occur, impacting method development and (full) validation requirements:

- Biomarker may be up or down regulated.
- Up or down regulation may lead to small/linear (e.g. < 50%) or huge/exponential (e.g. >100 fold) concentration changes.
- BM concentration changes can be superimposed on circadian fluctuations.
- Often, BM changes follow PK profile and are subject to a combination of above bullets

Truly a complex situation

1. Observed concentration changes (PD effect)



2. Development Phase

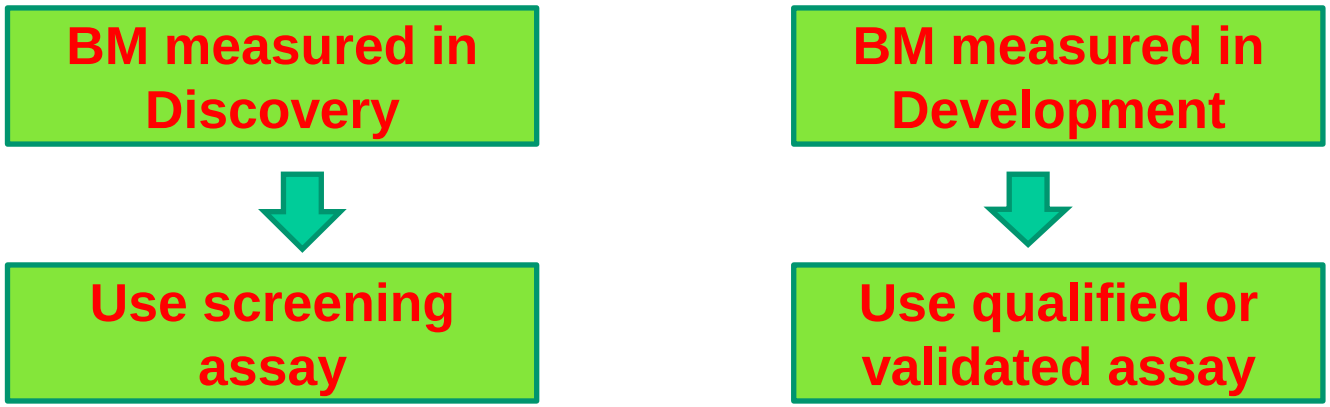
Predominantly affecting the need to include compliance

- Discovery phase
  - Allows focus on science only
- Development phase
  - May call for combined focus on science + compliance

Doesn't sound like a good driver. Compliance questions only triggered by the development phase may have limited added value or hamper good science in trying to fit the biomarker assay into a regulated process.

However, it can give some guidance if used appropriately.

Oversimplification looks like this:



2. Development Phase

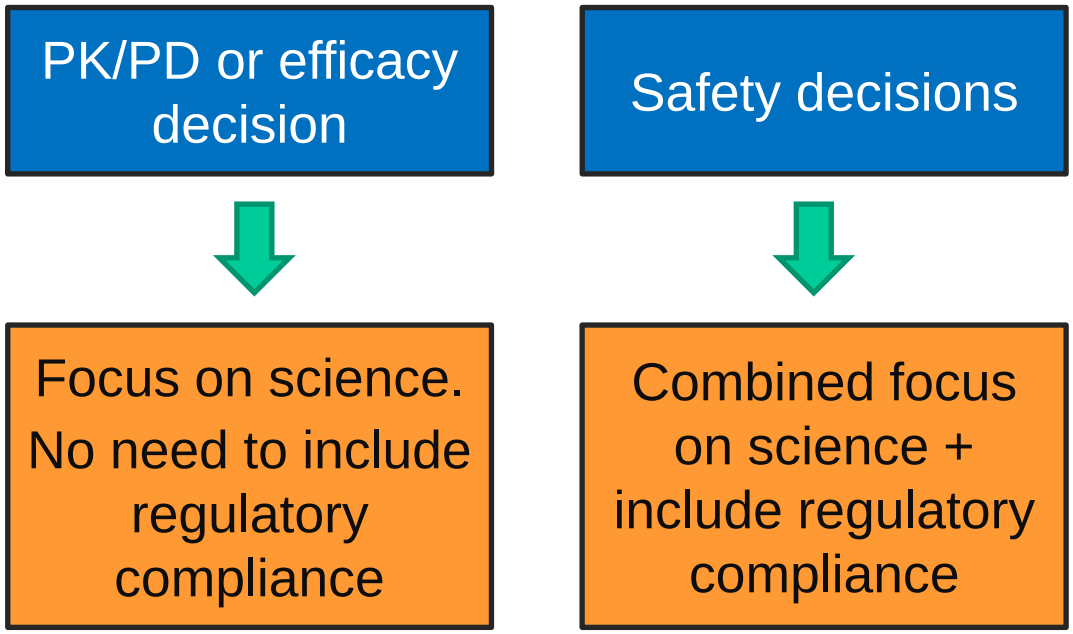
Of course, the real world is more complex:

BMmeasured in Discovery	BM measured Early Development (pre-POC)	**BM measured** Late **Development** (post-POC)
“Does the BM 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 BM data to support dose selection?”
Scientific validation of BM 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 BM assay	Qualification of assay for validated BM may be required for desired use, validated may not be needed	Qualification of assay for validated BM required, if assay format fits, **validated assay is desired**

3. Decisions taken from the data?

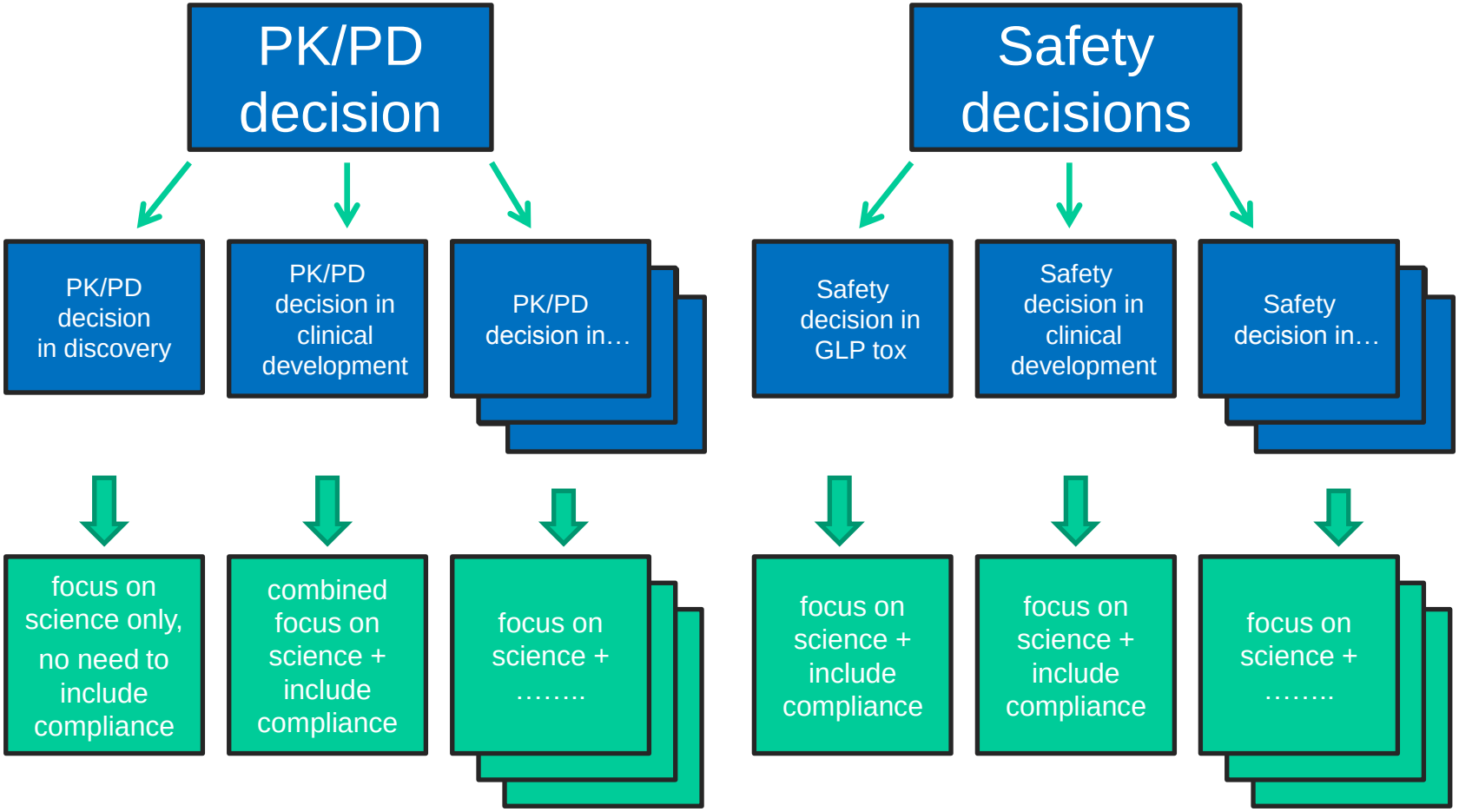
Decisions taken from the data can significantly affect level of inclusion of compliance / regulated bioanalysis guidelines

Oversimplification looks like this:



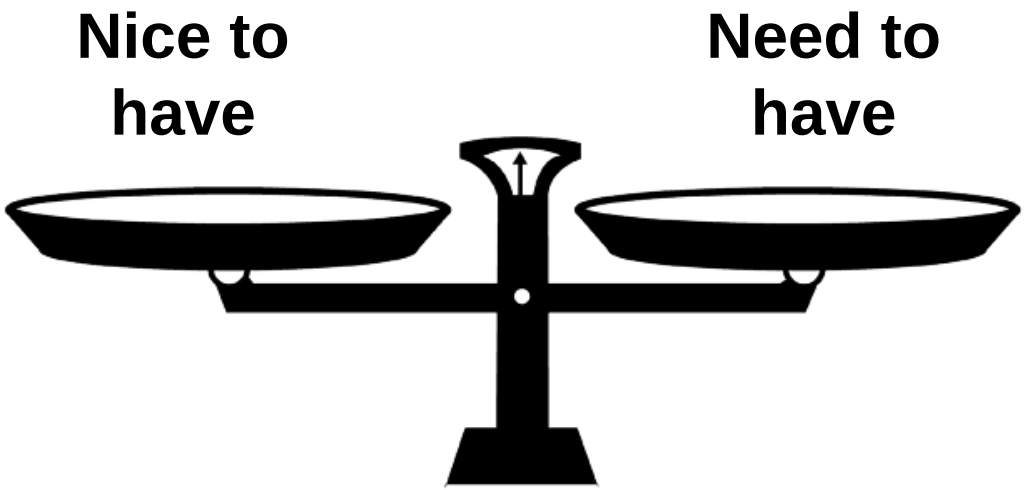
3. Decisions taken from the data?

Of course, again the real world is more complex:



4. Possible fit of assay specifics with guidelines for Regulated Bioanalysis (FDA, EMA)

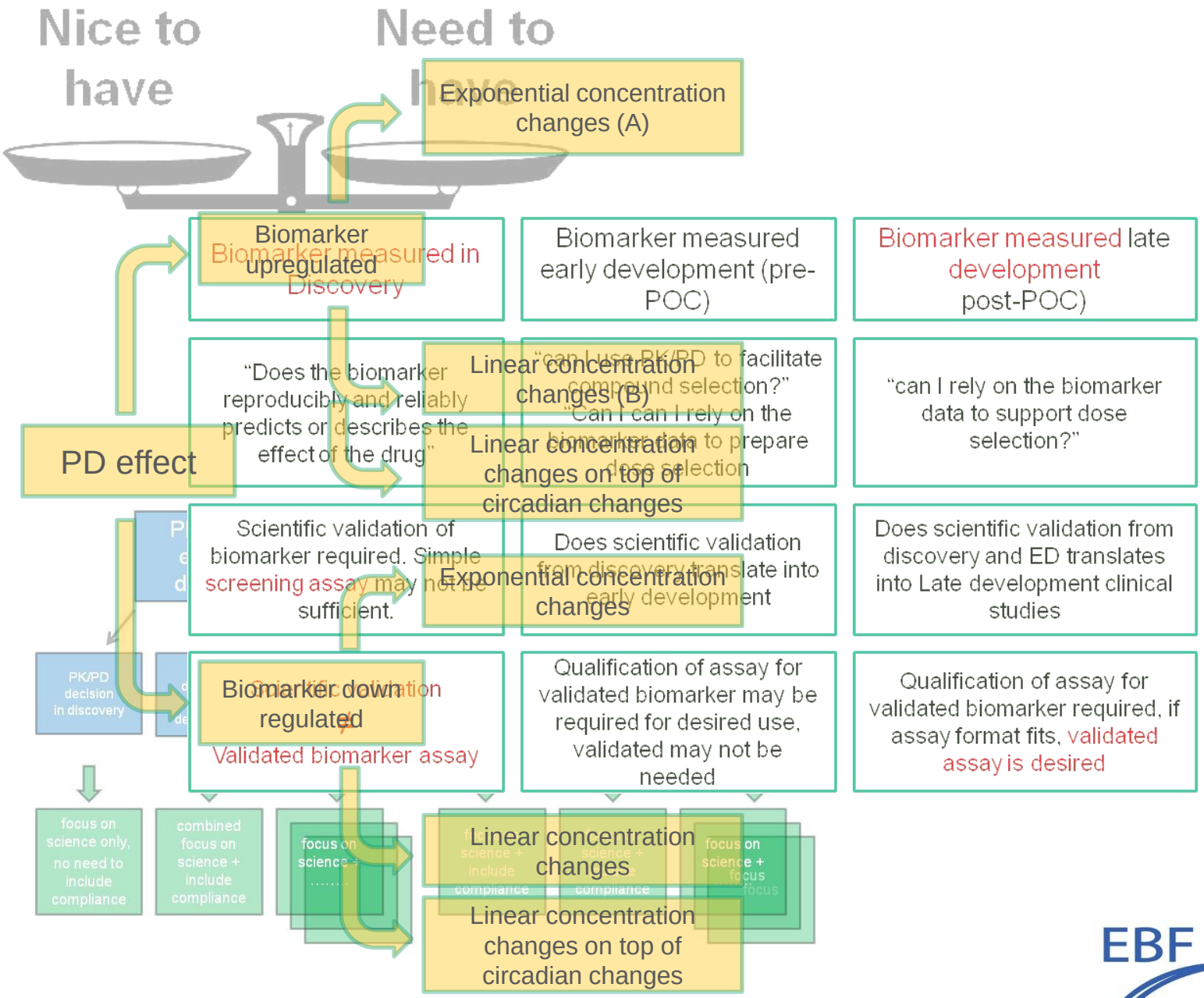
Some assay specifics and/or formats may fit perfectly with the current guidelines on Regulated Bioanalysis (cfr. FDA and EMA).

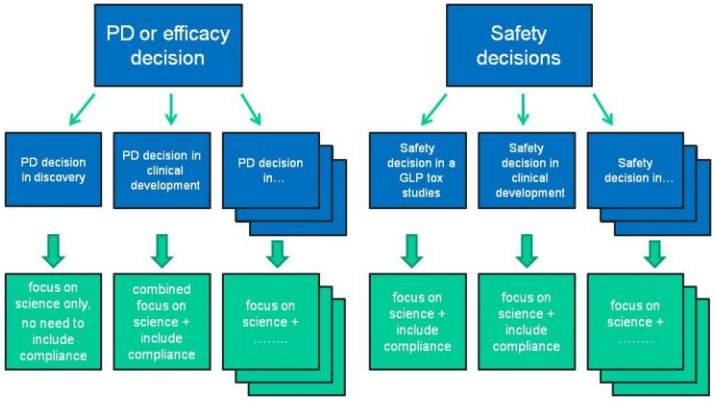


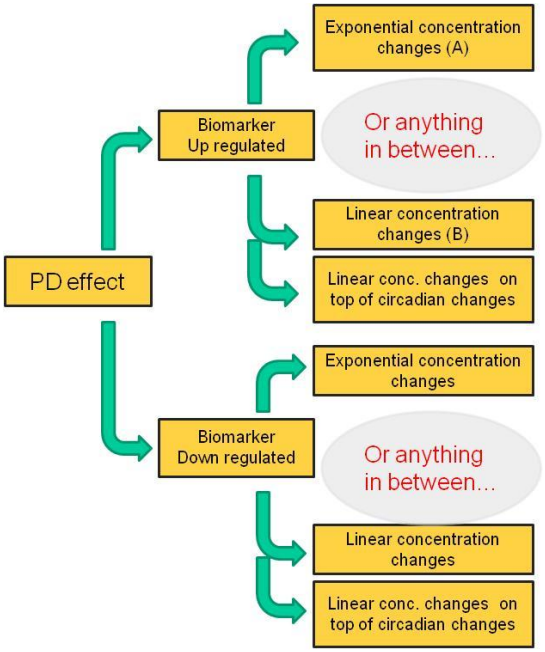
Are scientific needs of the assay at risk because we try to squeeze the assay into a format which fits Regulated Bioanalysis?

All 4 classification systems :

- are super imposable
- impact bioanalytical strategy in a different way
- exemplify the potential need to ‘individualize’ the bioanalytical strategies of a BM


Nice to have
Need to have
Exponential concentration changes (A)
Biomarker upregulated
Biomarker measured in Discovery
Biomarker measured early development (pre-POC)
Biomarker measured late development post-POC)
PD effect
"Does the biomarker reproducibly and reliably predicts or describes the effect of the drug"
Linear concentration changes (B)
"can I use PK/PD to facilitate compound selection?"
"Can I can I rely on the biomarker data to prepare dose selection
"can I rely on the biomarker data to support dose selection?"
Linear concentration changes on top of circadian changes
Scientific validation of biomarker required. Simple screening assay may not be sufficient.
Exponential concentration changes
Does scientific validation from discovery translate into early development
Does scientific validation from discovery and ED translates into Late development clinical studies
PK/PD decision in discovery
Biomarker down regulated
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
focus on science only, no need to include compliance
combined focus on science + include compliance
Linear concentration changes
Linear concentration changes on top of circadian changes





Decision Tree

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?"
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Adhere to Regulated BA guidelines

Nice to have **Need to have**

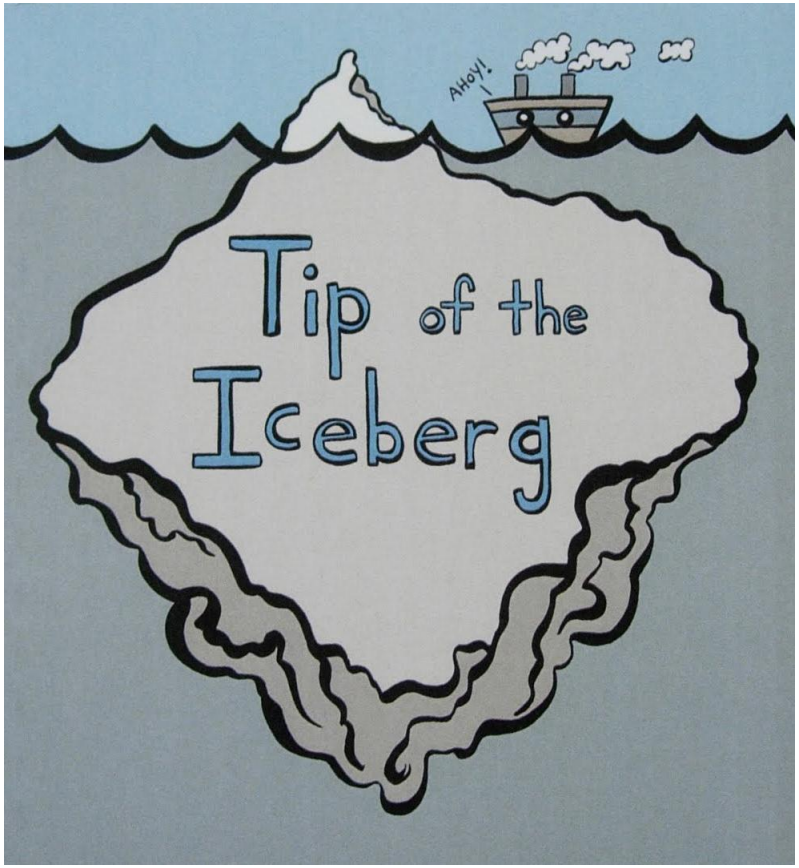
Additional reflections

With more BM analysis amenable to LC-MS, industry is boasting "*we can easily reach 4-6-15 quality*", stimulating regulators to expect/require "regulated bioanalysis" standards for (LC-MS) 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,
  - assays combining LBA and MS technology,…
- "***Yes, can do !***" shouldn't mean "***Yes, let's do !***" if there is no scientific or regulatory driver.
  - "Yes, let's do !" mentality may increase cost with no added value for the patient.
  - "Yes, let's do !" mentality may jeopardize science to progress.

But…

- Maybe it is too soon for a decision tree, and more discussion is needed
- More/other scientific drivers may need to be considered
- EBF is only starting the discussions and certainly wants to take time to discuss in depth



I now give the word to Christian to provide a first insight in the preliminary discussions in the EBF TT