Rationales not Rules – Rethinking Guidance for Industry

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Overview

- Introductory thoughts
- Foundations of non-science
- How this plays out
  - For drug development
  - For bioanalytical sciences
- How do we get back on course?
- Conclusions

Disclaimers/Background

- Views are my own
- Perspective: 25+ years of drug development experience with an insider's view from both CRO and Sponsor organizations
- Goal: doing the best science we can for the benefit of patients and that means…
  - Doing what adds value
  - Shedding that which does not

When do we not do our best science?

Too risky to potentially ‘be wrong’ or disagree with organization’s leadership

Bottom Line: job security = **making our job safer**

Exhaustion – too tired to fight the non-science

Bottom Line: Path of least resistance

= **making our job easier**

Are we doing our best science or choosing to make ourselves feel more comfortable?
How would we explain that to a patient?

Foundations of non-science

"The non-science (nonsense) that pervades our science is a disservice to patients"

Starting with….Reasoning by Analogy

Reasoning by Analogy is a slippery slope

dangerous, lazy and wrong

Reasoning by Analogy…

- Building knowledge and solving problems based on prior assumptions and beliefs, and perceived 'best practices'
- Basically, a comparison:
  - You draw a conclusion on an unknown based on its similarity to a known
  - The analogy makes the assumption that since the unknown is like the known in some ways, it must also be similar in other ways

Not Science

Seductive

Feels like knowledge & experience

Don't stop thinking here!

Reasoning by Analogy…

Or you risk getting it wrong…

Two cars are the same make, model and year; therefore, they must also be the same color.

REMEMBER

There are *always* differences between the unknown and the known – the closeness of fit between your model and your unknown is what counts

And determining the closeness of fit requires…

First Principles Thinking…

- Actively questioning everything you think you know (or assumptions you have) about a given problem and then creating new knowledge and solutions from the ground up
- Requires willingness to rethink – ensures that you rigorously evaluate the differences between the unknown and the known before determining best course

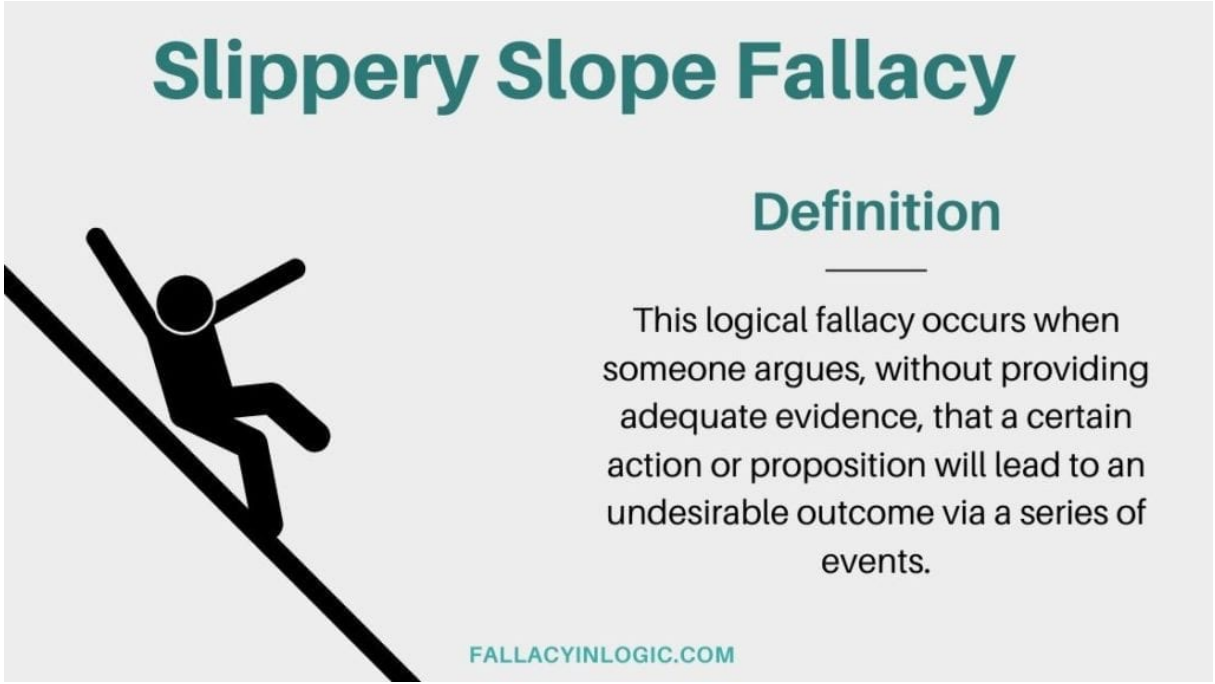
= Doing Science

More non-science:

The folly of fallacies

Folly, noun (merriam-webster.com)

1. A lack of good sense or normal prudence and foresight
2. A foolish act or idea
3. An excessively costly or unprofitably undertaking
4. An often extravagant, picturesque building erected to suit a fanciful taste



The slippery slope fallacy is real…

…but it is not Science

It's for patient safety!

It's in the guidance!

We've always done it this way!

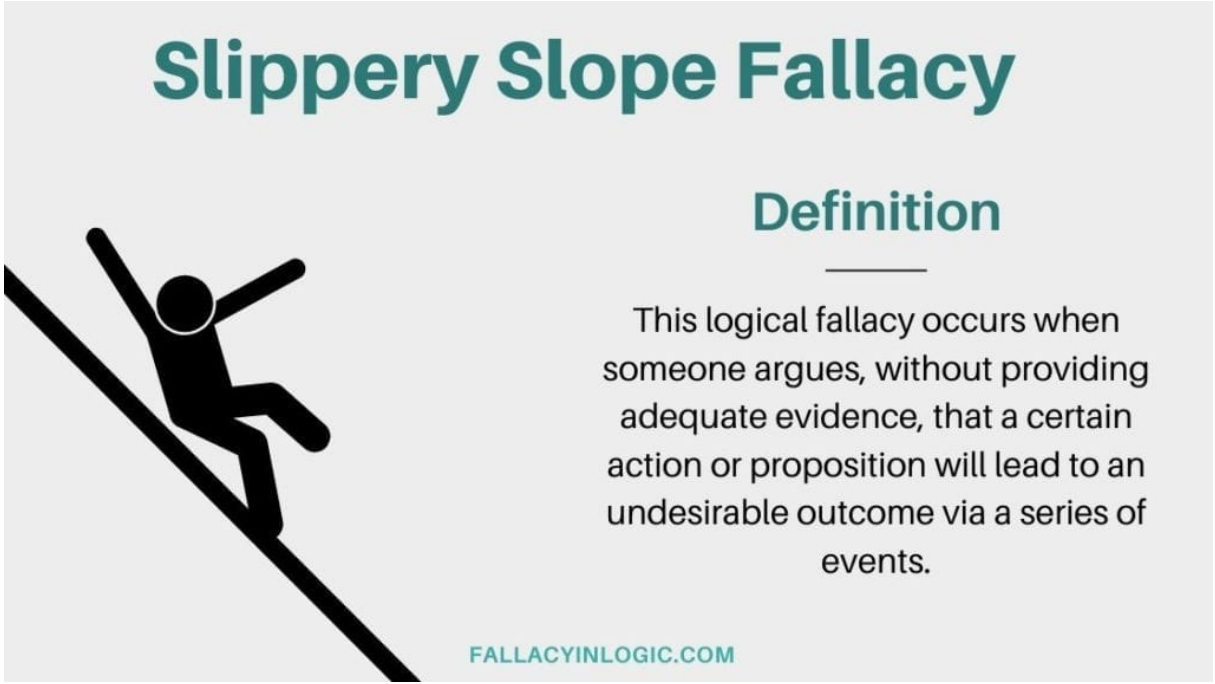
We need to see more data!

It's for patient safety! But I can't explain how it will affect any patient level decisions or outcomes.

It's in the guidance! But I have no scientific rationale to support it.

We've always done it this way! But we never asked why or if it's still relevant.

We need to see more data! But we don't know how much.



This week's slippery slope award winner:

"We need a Nab assay for our Phase 1 trial (for a low-risk molecule) because our regulatory department told us our filing won't be accepted if we don't."

The slippery slope fallacy is real…

…but it is not Science …it's FEAR

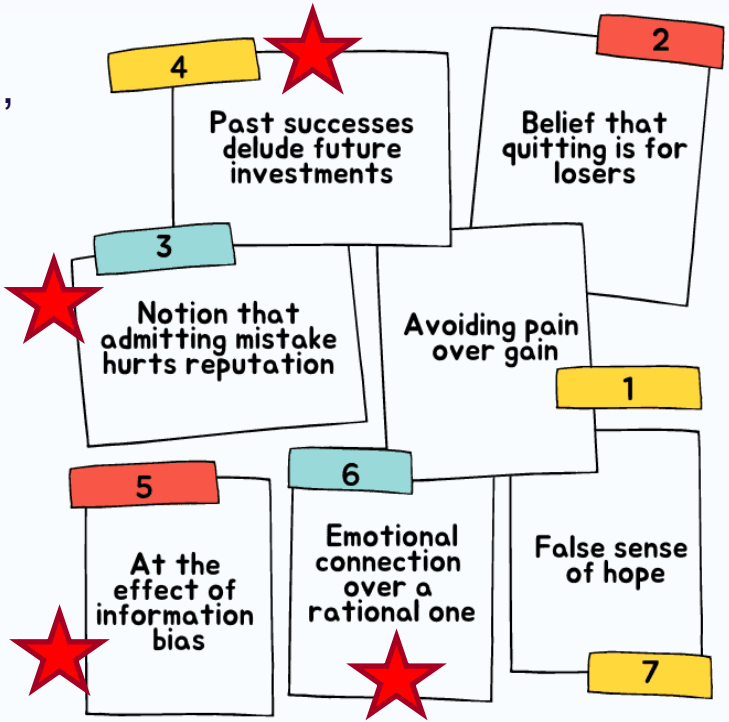
Sunk Cost Fallacy

Sticking with a losing or failed venture because you've already invested a significant amount of time, money, and/or other resources

It's frequently used as a way to justify illogical choices

We've come this far…

Why do we fall for sunk cost bias



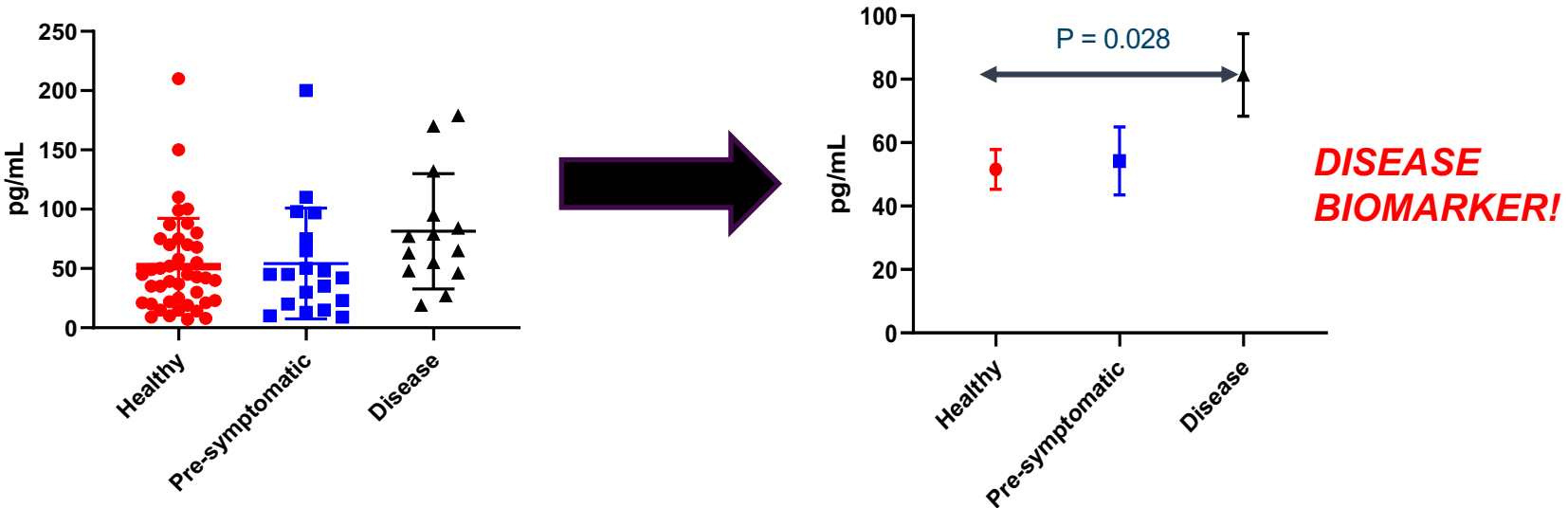
Reference: https://www.techtello.com/sunk-cost-fallacy/

How does all this play out?

…for drug development?

Have you experienced…?

- Program Go/No-go decisions that focus on the experiments that ‘worked’
- Zombie molecules – SO SAFE!
- Plumped up pipelines for sake of appearances (for investors)
- Biomarker discovery by P-value



How often have you heard…?

- But we might miss something!
- Don’t you want to know?
- It's easy enough to do, so why not just do it?
- The Senior Leader/CEO/Board of Directors is worried about….
- Our organization is risk averse…(but apparently not averse to wasting time, money and resources)

Is this Science?

How does all this play out?

…for bioanalytical scientists?

Reasoning by Analogy

cripples our critical thinking!

Case Study 1: Biomarker Assays

Since Crystal City VI in 2015…

Biomarker Assays are not PK Assays!

Alien = Different

Yet, PK-assay-centric approaches have persisted…

Because….reasoning by analogy cripples our critical thinking

And following PK BMV Guidance for Biomarkers is…

Reasoning by Analogy!

LBA PK BMV – Wrong for Biomarkers

- The approaches and acceptance criteria in BMV Guidance are designed for the singular PK assay Context of Use
  - Biomarker assays serve widely varied COUs – one size does NOT fit all
- PK assay validation parameters assume availability of a fully characterized reference standard (the drug product) that is the SAME as the analyte to be measured
  - Most large molecule biomarker assays require measuring an endogenous analyte that is DIFFERENT from the reference standard
- Therefore, assessments that utilizes spike-recovery of purified or recombinant standard calibrator material will NOT address assay performance for the endogenous biomarker

LBA PK Assay Validation Parameters

- Standard Calibrators and Standard Curves
  - Highly characterized ‘reference standard’
  - Known concentrations spiked into m… …uated against nominal concentration
- Accuracy and Precision
  - Accuracy – Recovery of spik… …nce standard against targ… …inal levels
  - Precision – Repeated mea… …nstrate reliability of meas… …ent over time, across analysts, etc.
- Specificity and Selecti…
  - Selectivity = Spike recov… …n individuals
  - Specificity evaluated de… …ent upon expec… …f structurally simi… …olecules in samples
    - Potential interfer… …also characterized … …is detection of … …yte by critical reagents affected?
- Range of Quantificati… …LOQ-ULOQ)*
  - Confirmed by accuracy a… …cision at independently … …l targ… …OQ and ULOQ levels
- Dilutional Linearity and … …llelism
  - Dilutional Linearity – spiked hig… …entration sample with… …strated recovery through dilution
  - Parallelism – requires in-study sa… …n pre-study validation.
- Sample Stability
  - Spiked control samples demonstrate accurate recovery after exposure to storage conditions

Case Study 2: PK Assays

BMV was originally devised for small molecule bioanalysis by LC-MS

Adapting BMV for LBA is a classic example of…

Reasoning by Analogy!

Think about it…there are flaws in our reasoning

- Context of Use for PK data is the same for both small molecule and large molecule therapeutics
- But we use different criteria for LBA and LC-MS – why?
- Because we didn't start from first principles, we 'adapted' for LBA…
- And over-applied and misapplied evaluations to address issues large molecules don't have
  - Testing for interferences without scientific rationale
  - Stability testing of high concentration proteins
  - Not to mention….

The Dilutional Linearity Fallacy

From M10:

- *"Due to the narrow assay range in many LBAs, study samples may require dilution in order to achieve analyte concentrations within the range of the assay. Dilution linearity should be assessed to confirm that measured concentrations are not affected by dilution within the calibration range"*
- **Approach:** Spike sample above ULOQ, make multiple dilutions and demonstrate accurate measurement within assay range
- Let's think it through…
  - How are large molecule drugs formulated?
  - How do we construct the standard curve?
  - How do we prepare QCs?

The Dilutional Linearity Fallacy

- For LBAs, the existence of a standard curve already ‘proves’ dilutional linearity
- First principles thinking would not have led to this assessment, as presented

- This does not devalue the utility of robust dilution schemes and well-trained analysts for testing of study samples by LBA
  - But Dilutional Linearity for LBAs is not an assay parameter
  - It is an evaluation of analyst proficiency at performing dilutions
  - Does this belong in the assay validation or in analyst training records?
  - Both?

The ISR Fallacy…

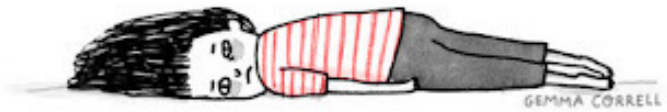
- The poster child for sunk cost fallacy
- And let's reason by analogy and suggest propagating it to biomarkers and immunogenicity assays!

  = Job Security!

Not Science!

Not Value-added!

The EXHAUSTION is real!



Case Study 3: Immunogenicity Assays

Immunogenicity Guidance in Context

- More than 2 decades ago…
  - Biotherapeutics were simpler in structure and complexity (e.g. mAbs and recombinant proteins), yet less human(ized)
  - The relative clinical impact of immunogenicity incidence vs magnitude of immunogenicity response was not known
  - It was not well understood what would truly differentiate high vs low risk – manufacturing processes, drug MOAs, etc.
  - Assays were rudimentary, technology platforms developing
  - Alarming safety events had occurred associated with high-risk molecules (EPO)
- Therefore, an approach to sensitively detect and characterize anti-drug immune responses was desirable
- **Guidance was written to address this high risk COU** – because we didn't know what we didn't know

Scope of Current Guidance

Even with subsequent revisions, limitations on intended scope are evident

- EMA
  - The Applicants need to demonstrate that the ADA assays are applicable for the demonstration of **clinical correlations of ADAs**.
  - The goal of immunogenicity studies is to investigate presence of an immune response to the **therapeutic protein** and its **clinical impact**. Thus, the evaluation of immunogenicity should be based on **integrated analysis** of immunological, pharmacokinetic, pharmacodynamic, as well as clinical efficacy and safety data.
- FDA
  - This guidance provides recommendations to facilitate industry's development and validation of assays for assessment of the immunogenicity of **therapeutic protein products during clinical trials**.
  - For the purposes of this guidance, immunogenicity is defined as the propensity of a **therapeutic protein product** to generate immune responses to itself and to related proteins or to induce immunologically related **adverse clinical events**.

Focus is on **therapeutic proteins** and understanding **clinical impact** in **clinical trials**

But what happened….

- Guidance accepted as gospel and presumed best practice for all contexts
- All therapeutics effectively treated as high risk
  - Everything automatically goes to 3-tiered analysis
  - So-called risk assessments focused only on NAbs (thanks to EPO!)
  - Nab assays for all assets – not a matter of if, but when
- Additional scope creep
  - Preclinical studies, emerging modalities, including some non-biologics!
- Believing (or hiding behind) ‘It’s the only guidance we have, so we must follow it’
- Expectations from regulators focused on set criteria (sensitivity, drug tolerance) regardless of context
  - e.g. PMRs for assay ‘improvements’ even when the study results and interpretation will not change

Reasoning by Analogy

The Nab fallacy for low-risk molecules

It's low risk, so we won't need to do Nab until Phase 3.

Whether any impact on exposure in ADA+ subjects is due to Nab.

Yes, but without a Nab we won't know if it's clearing ADA or Nab.

Yes, but maybe there could be a patient safety risk of lack that we don't know about.

But it's low risk, so I don't need Nab until Phase 3…

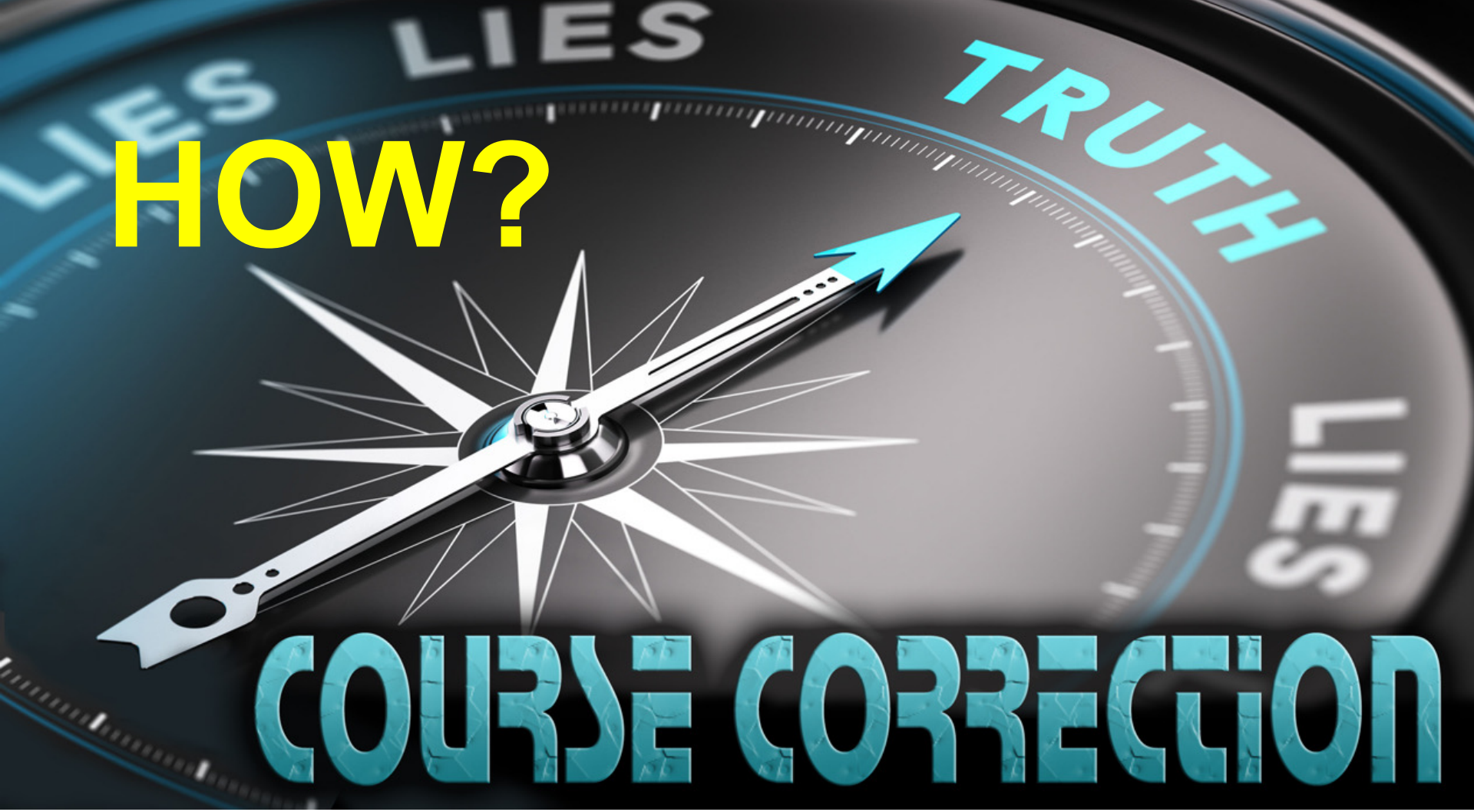
Slippery Slope Fallacy?

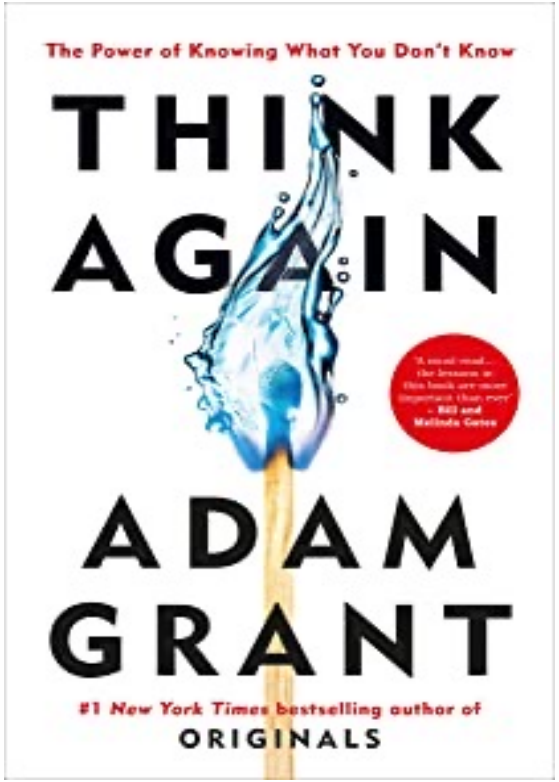
What are you trying to understand in [illegible] that requires a Nab assay?

But won't your PK data tell you if there is an impact on exposure?

Either way, they both have 'neutralizing' impact. They reduce exposure to active drug.

If there were a genuine safety concern related to Nab, wouldn't you have included it in your safety studies?


HOW?
LIES
LIES
TRUTH
LIES
COURSE CORRECTION



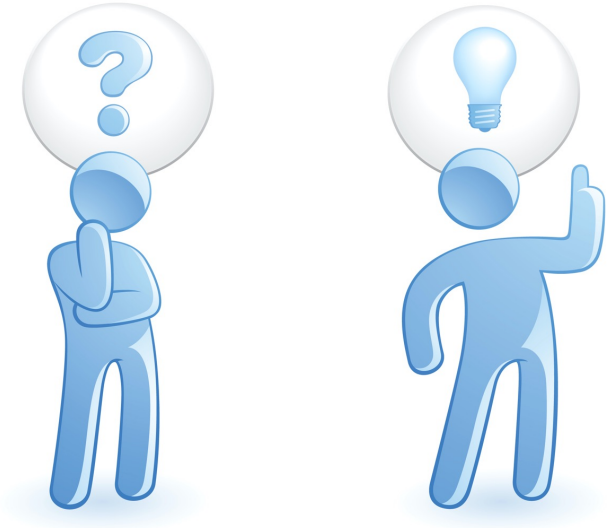
The superhero scientist

If you're a scientist by trade…

- First Principles thinking and regularly Rethinking are fundamental to your profession
- You're paid to be constantly aware of the limits of your understanding
- You're expected to doubt what you know, be curious about what you don't know and update your views based on new data

#BeAScientist

First Principles Thinking



Immunogenicity is a biomarker!

Biomarker Definition

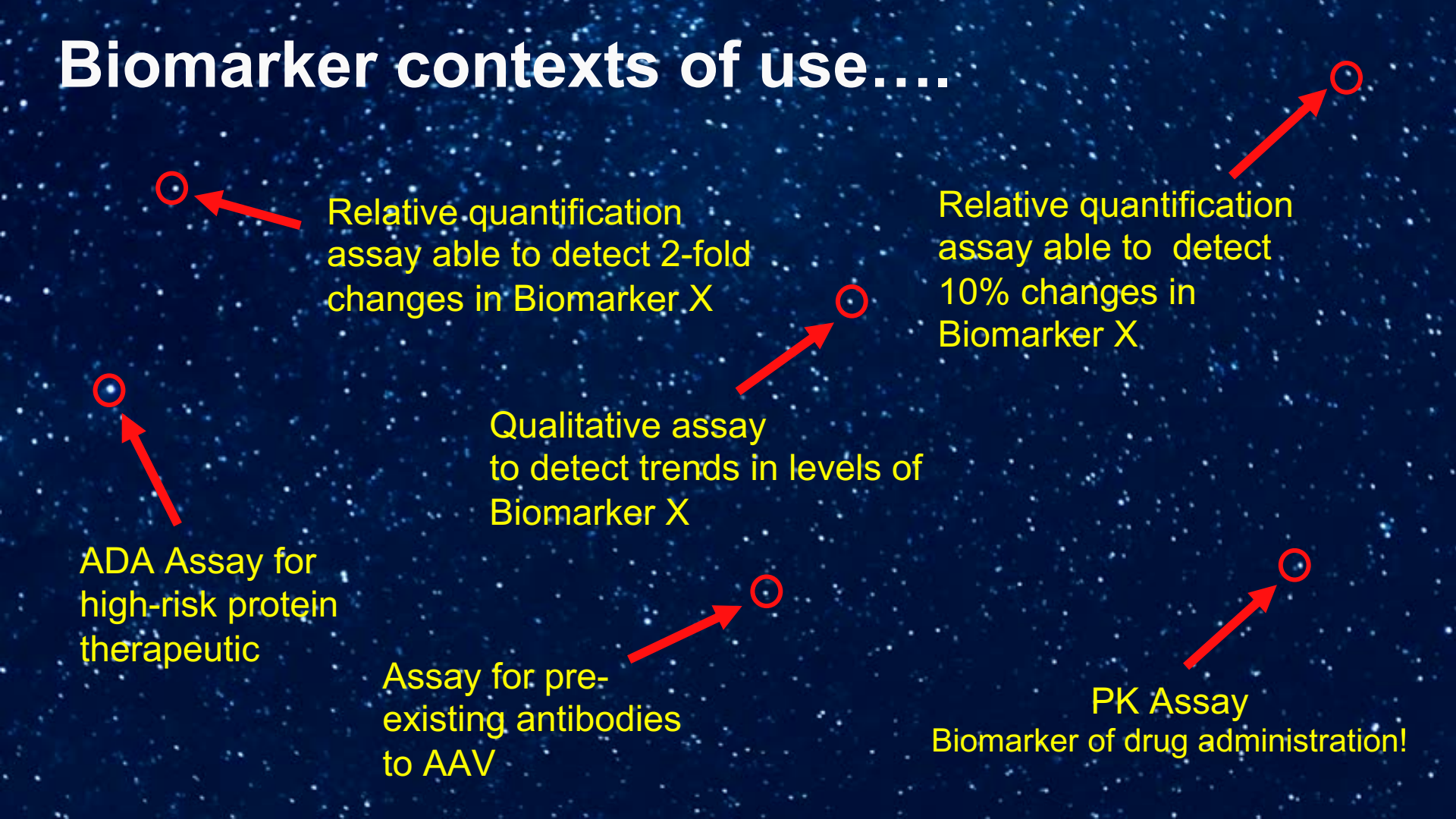
- According to BeST a biomarker is a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or biological responses to an exposure or intervention, including therapeutic interventions

- Immunogenicity is a biological response to a therapeutic intervention = **BIOMARKER**

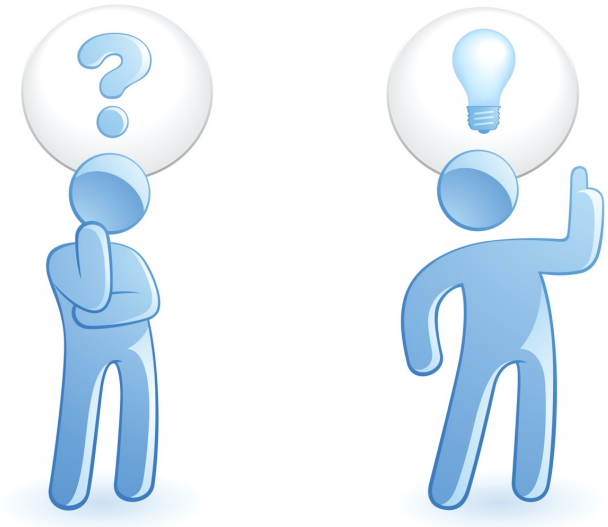
And what do we know about biomarker assays?

We need to understand Context of Use!

Biomarker contexts of use….



Even better First Principles Thinking



It’s all biomarkers!

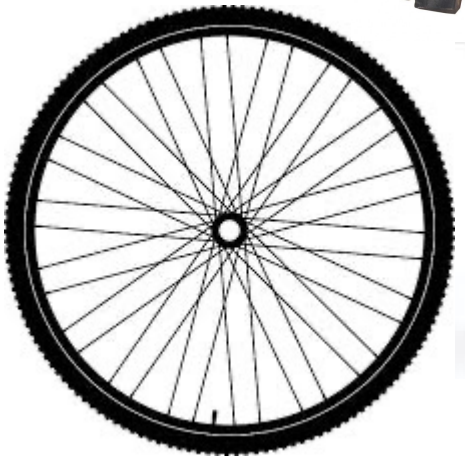
How do we navigate this course?

Lessons from biomarkers

We need considerations, not criteria

- Guidance is just that – guidance; it's a beginning, not the end game
- First Principles thinking required – do good science (no excuses)
- Imagine risk-based thought frameworks that are flexible enough to capture countless COUs
  - Focus on key questions, define COU, design your assays to address COU
  - Accept that there is no single magic bullet for all COUs
  - John Allinson: *"Suck it up and be a scientist"*
- **The rebuttal:** *"But wait! We can't reinvent the wheel every time!"*
  - Start by making sure you need a wheel and not something else altogether
  - And if you do…

Think it through and design the right wheel…



Please…remember the patients

What do patients need?

- Beyond the 3 R's (Replacement, Reduction, Refinement)
- 4th R - ROI for patients
  - Everything we do (industry and regulators alike) should be justifiable to a patient
  - Without value added, doing more ≠ better or safer
  - All of the time, money and resources we expend on non-value-added efforts = wasted time, money and resources
  - The 21st Century Cures Act insists we do better – bring life-saving/life changing therapies to patients efficiently and cost effectively
- 5th R – Rethink Regularly

NO JOKE: IT'S OUR WHOLE JOB

Conclusions

- Reasoning by analogy is dangerous, lazy and wrong
- First Principles Thinking means thinking it *all the way through*…
  - Precisely how will the data impact a drug development decision or a patient level clinical outcome?
- Current guidances were written for specific contexts of use - Avoid misguided application of guidance
- 21st century modalities and their COUs require Scientific Thought Frameworks
- No fear, no fallacies, no excuses – embrace the discomfort

#BeAScientist

IF THERE'S NO SCIENTIFIC RATIONALE, IT'S NOT SCIENCE

спасибо

谢谢

GRACIAS

THANK YOU

ありがとうございました

MERCI

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