Feedback and Reflections from the AAPS PharmSci Workshop on COU:
Be Specific – Biomarker Assay Validation in Context

18 November 2020

Lauren Stevenson, on behalf of the Workshop speakers

Overview

- Workshop agenda
- Pre-workshop survey results – Challenges with implementation of COU-driven biomarker assay validation
- Foundational concepts & summary
- Current Challenges

Workshop Agenda – Day 1

- **Session 1 – Foundations of Context of Use**
  - *Setting the stage for COU* – Lauren Stevenson, ILX
  - *How do we get from a biomarker assay request to an analytical method which is validated to meet COU?* – John Allinson, ILX
  - *Start with the answer and work backwards! [The devious guide to biomarker assay development and validation]* – Steve Piccoli (SPARC)
- **Session 2 – 2020 Scientific Perspectives**
  - *EBF Perspective: Updates of the EBF recommendations for biomarker assay validation: overcoming the hurdles of bringing CO"U into practice* – Philip Timmerman, Jo Goodman, Kyra Cowan (on behalf of EBF)
  - *Perspective from the Biomarker Qualification Program: How COU influences analytical validation* – Abbas Bandukwala (FDA)
  - *Statistical Perspective: Establishing fit-for-purpose requirements on precision of a biomarker assay* – Viswanath Devanarayan (GSK)

Workshop Agenda – Day 2

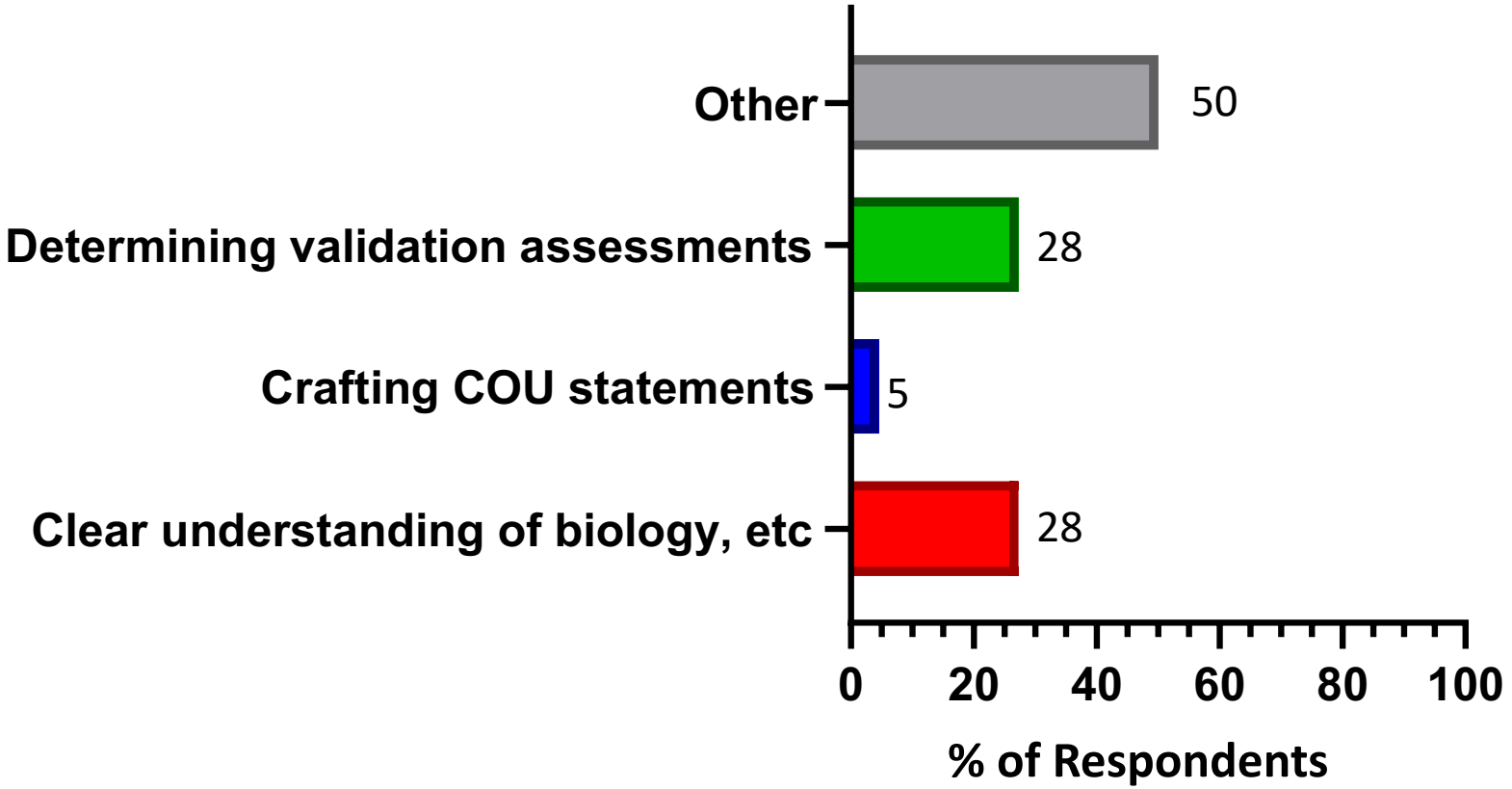
- **Session 3 – Case studies**
  - *Do you have a validated assay for biomarker X? Making haste, slowly, in bioanalysis of biomarkers* – Rob Nelson (Covance)
  - *Staging biomarker development* – Devangi Mehta (ILX)
  - *Strategies to monitor and anti-AAV NAb assay supporting clinical trials* – Liching Cao (Sangamo)
- **Session 4 – Bringing COU into practice**
  - *Evolving team mindset to meet COU* – Linda Terry (GSK)
  - *Common challenges in the real world (survey results)* – Lauren Stevenson (ILX)
  - Extended panel discussion

Pre-Workshop Survey Questions

1. What are your greatest scientific challenges with implementing COU?
2. What are your greatest process/organizational challenges with implementing COU?
3. What tools or resources would be most helpful to support implementing a COU-based approach for biomarker assay validation?
4. Please briefly describe and other specific challenges/issues associated with implementation of COU-driven biomarker assay validation

Note: Small data set! (N=22) Qualitative biomarker!

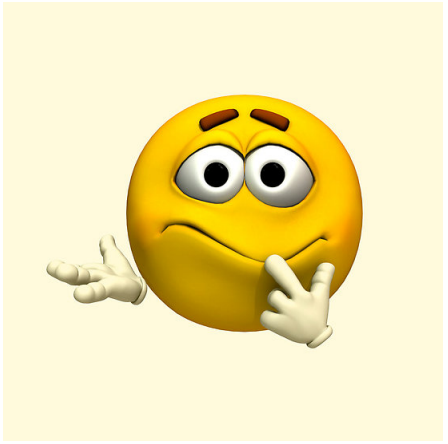
What are your greatest scientific challenges with implementing COU?



What are your greatest scientific challenges with implementing COU?

Other

- Obtaining parallelism when needed – 11%
- No Biomarker Guidance – 89%

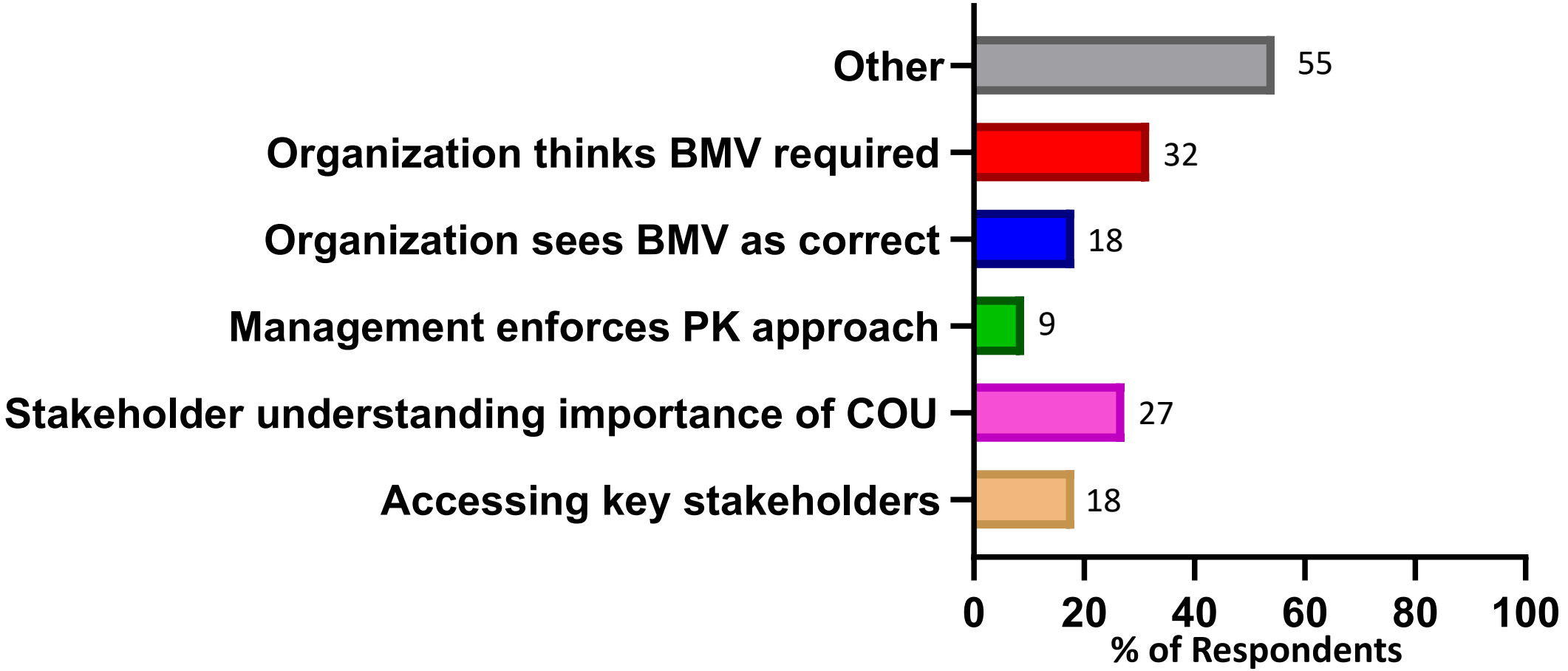


1350 BCE

BIOMARKER SCIENCE GUIDANCE

1. BE A SCIENTIST
2. EMBRACE FIT-FOR-PURPOSE
3. DEMAND CONTEXT OF USE
4. DEMONSTRATE FIT-FOR-COU = DO GOOD SCIENCE

What are your greatest process/organizational challenges with implementing COU?



What are your greatest process/organizational challenges with implementing COU?

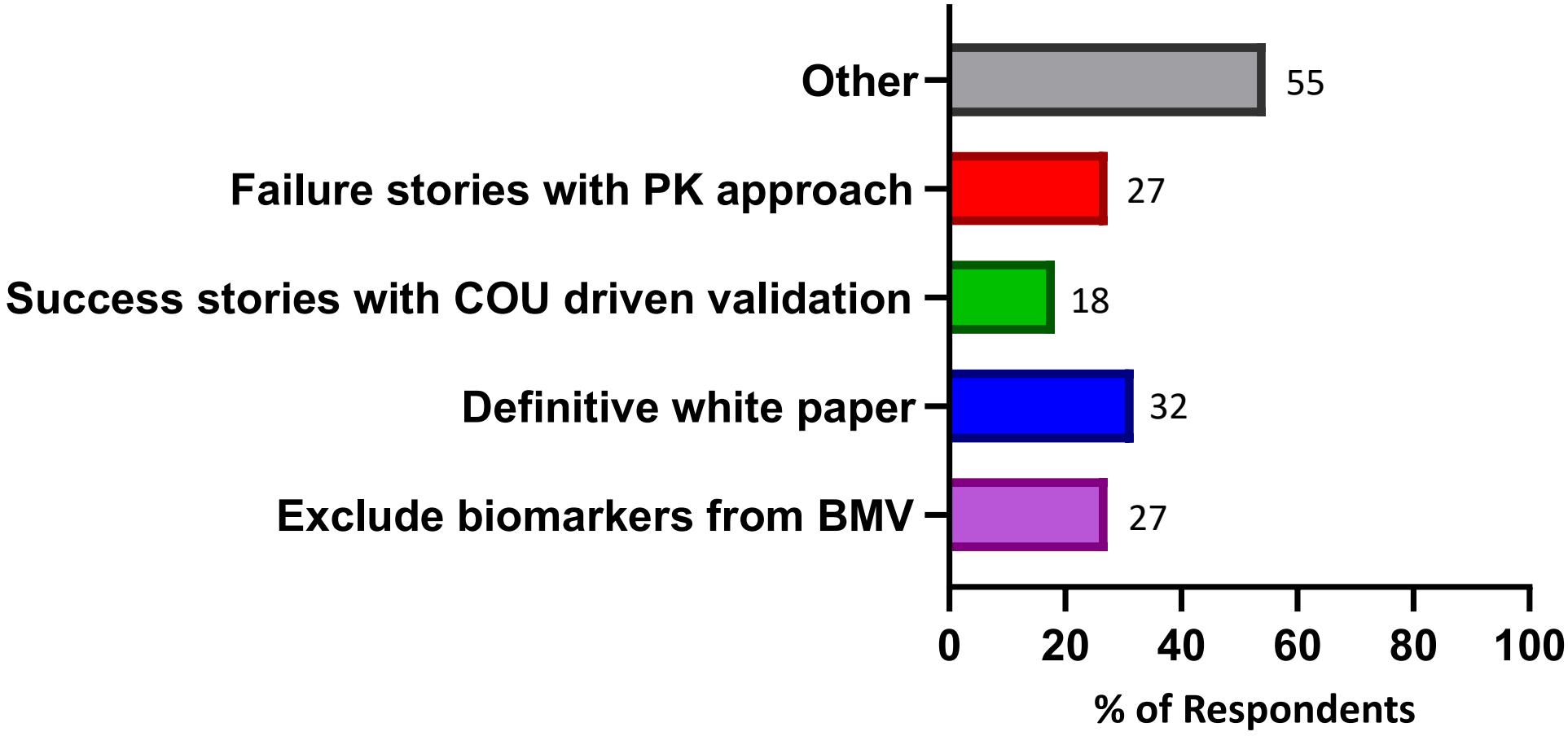
Other

- Misunderstanding/misalignment with key stakeholders about following BMV and/or appropriate approach for validation (36%)
- No Biomarker Guidance (55%)

Given that biomarkers have been utilized for millennia…and implemented clinically for many decades…

Why is it that scientific organizations in 2020 cannot seem to function without Guidance?

What tools or resources would be most helpful to support implementing a COU-based approach for biomarker assay validations?



What tools or resources would be most helpful to support implementing a COU-based approach for biomarker assay validations?

Other

- Biomarker Guidance (100%)
    - Of these, 23% suggested that C-Path or WRIB recommendations be adopted as Guidance

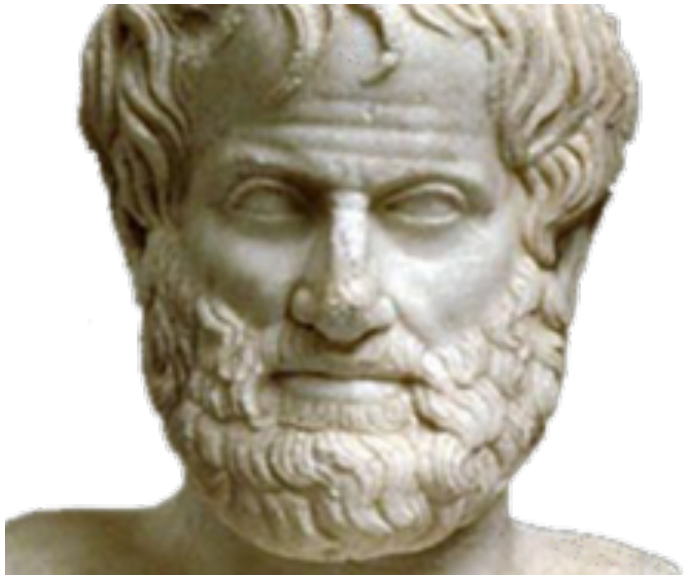
Please briefly describe any other specific challenges/issues associated with implementation of COU-driven biomarker assay validation (N = 12)

- Lack of Biomarker Guidance (75%)
- No regulatory support for industry white papers
- Clear delineation of when full PK-like validation is needed and examples of where it's acceptable to leave out certain elements
- Absence of clarity surrounding the future use of the biomarker assay; for example, could a fit-for-purpose, qualified biomarker assay still be used if the biomarker becomes a primary or secondary endpoint?

Foundational Concepts

Biomarkers Require First Principles Thinking

Over 2000 years ago… Aristotle



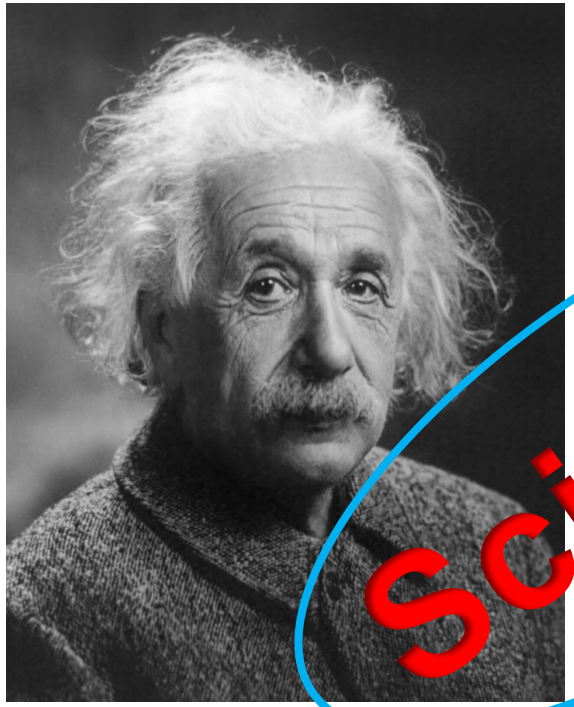
Also known as “think like a scientist”

First Principles Thinking vs Reasoning by Analogy

- 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
  - #BeAScientist
- Reasoning by Analogy
  - Building knowledge and solving problems based on prior assumptions and beliefs, and perceived ‘best practices’
  - Analogical reasoning proceeds from the observation that things which are similar in some respects are probably similar in other respects too

First Principles

"If I had an hour to solve a problem, I'd spend 55 minutes thinking about the problem and 5 minutes thinking about solutions" – Albert Einstein



Science

Reasoning by Analogy

"The person who says he knows what he thinks but cannot express it usually does not know what he thinks" – Mortimer Adler

- That's how we've always done it
- It's in the (BMV) guidance
- Because regulators might ask about it

Not Science

The Risks of Reasoning by Analogy

- Reasoning by Analogy tends to lead to bad decisions
  - Misapplication/overapplication
  - Hasn't been fully thought through
  - Example: Applying PK Assay BMV Guidance for biomarker assays
- Consider Context of Use
  - PK (drug concentration) assays serve one context of use
  - Drug concentration in a biological sample is a biomarker of dose administration
  - PK assays can be viewed as biomarker assays with a specific context of use
- Some other biomarker assays…
  - ADA assays, NAb assays, inhibitor assays, vaccine titers…
  - Biomarker assays serve numerous, widely variable COUs
  - BMV Guidance is not applicable!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Validation

- A process to establish that the performance of a test, tool or instrument is acceptable for its intended purpose (BEST)
- **Validated = Fit for Purpose!**

Context of Use

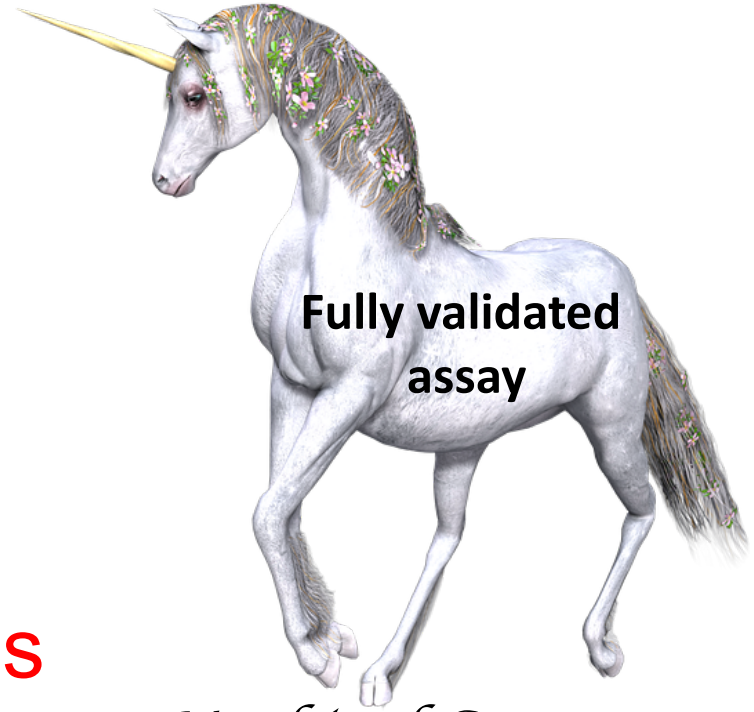
- The Context of Use (COU) is “A statement that fully and clearly describes the way the medical product development tool is to be used and the medical product development related purpose of the use” (BEST)
- Or, more succinctly…**Context of Use = The ‘Purpose’ in Fit-For-Purpose**

Validation Requires COU

- If Validated = Fit-for-Purpose, and
- COU = the Purpose in FFP
- Restated: **Validation = Fit-for-COU**

- No context, no validated assay

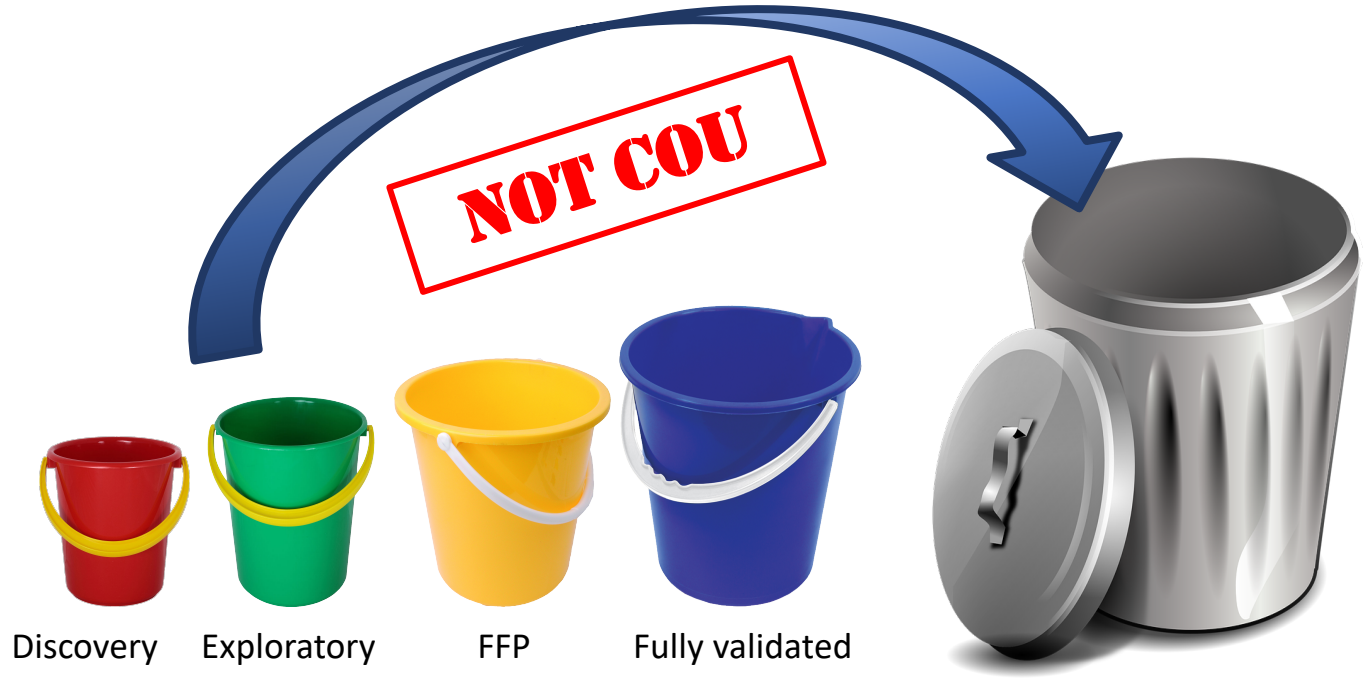
- Without COU, there is no such thing as a fully validated biomarker assay



Mythical Creature

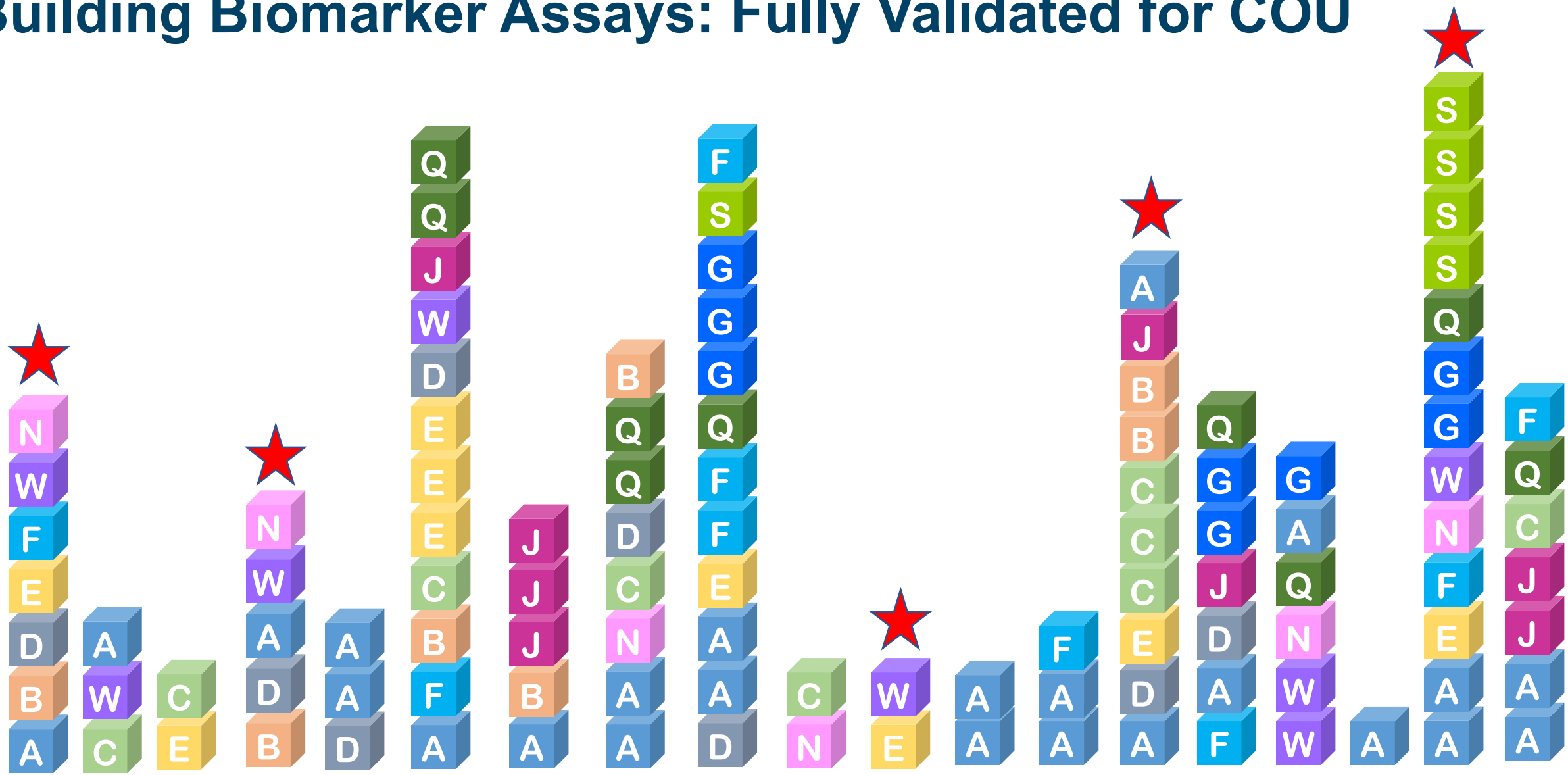
COU is Specific

- ‘Buckets’ of biomarkers are not specific enough
- ‘Tiers’ of validation cannot address needs of specific COUs



- ‘Exploratory’ and ‘endpoint’ are not specific enough
  - Need to understand how the data will specifically be used
  - The same biomarker for the same ‘bucket’ may have very different assay performance requirements depending upon the specific COU

Building Biomarker Assays: Fully Validated for COU



In Summary

- First Principles Thinking is required – it's how biomarkers have been done for millennia
- Reasoning by Analogy has led us astray
  - Using BMV Guidance for biomarkers is a recent misapplication and is not appropriate for biomarker measurement
- COUs are specific and diverse
- Therefore single, prescriptive Guidance is neither feasible, nor scientifically appropriate
- And yet….

A Theme from the Survey

We need some guidance here…

The Challenges

Overcoming reasoning by analogy

- By industry professionals: Bioanalytical scientists, Clinical teams, Clin Pharm & other internal stakeholders & leadership
- By Regulators/Reviewers
- Stopping misapplication of BMV guidance because it feels familiar

- That's how we've always done it
- It's in the (BMV) guidance
- Because regulators might ask about it

"Far better to be uncomfortably uncertain than comfortably wrong"

- Ozan Varol 'Think Like a Rocket Scientist'

The Challenges

Risk Aversion Perspective – What Risk?

- Perceived Risks
  - Risk of receiving a question from Regulators – this is desirable as it enables scientific discourse
  - Risk (fear) of being wrong – unwillingness to take scientific accountability
  - Risk of repercussions from within one's own organization – from leaders and key stakeholders
- The Real Risks
  - Getting it wrong for patients
  - Propagating expensive superstitions and sacrificing science
  - Lost opportunity to do meaningful work

The Challenges

Biomarker Guidance

- How can Guidance address all COUs?
  - We must avoid misguided Guidance
  - Biomarker assays require a framework of considerations, not prescriptive approaches and preset criteria
- Recognizing that, an appropriately flexible guidance will require:
    - #BeA Scientist = Application of First Principles
    - Building comfort with discomfort

The Challenges – Some Questions

- Do we only have a science problem, or do we also (or even mostly) have a people problem?
  - Is it more about mindsets than science?
- How do we address this?
- For our own community…
  - Overt exclusion of biomarker assays from BMV guidance
  - White paper/definitive publications that clearly delineate appropriate approaches for biomarker assay validation and/or why PK centric approaches are incorrect for biomarkers
  - Examples of success stories with clear COU statements and associated validation approaches
  - Examples where misapplication of PK assay validation principles ‘got it wrong’
  - **Help demonstrate that the biggest risk is getting it wrong for patients**

The Challenges – Some Questions

- How to we address this beyond our own community to reach ALL the stakeholders?
- Recognize that the balance of power is disproportionate
  - Regulators have greater influence, because…
  - Stakeholders who are removed from the scientific expertise defer to Guidance and these stakeholders have organizational power over the scientists
  - Partnership with regulators is critical to successfully shift the mindsets of the powerful but uninformed
- Other Questions
  - Are we the right/only experts to address this?
  - Who else can help? People experts? Policy experts?
  - It will likely take a village…

The 5th Pillar (Communication) is the foundation on which future progress must be built

Critical thought partners: John Allinson (ILX) Devangi Mehta (ILX) Linda Terry (GSK)

If there's no scientific rationale, it's not science

No Context, No Validated Assay