

Biomarkers Require Reason, not Rules

#BeAScientist

EBF Open Symposium

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Overview

- Problem statement(s)
- Why do we find ourselves here?
- What's really going on – big picture perspective
- Solving the problem





**Houston, we've had a
problem...**



A Theme: Biomarker Assays are not PK Assays

- Nor are they the sons/daughters of PK assays
- Or the distant cousins
- Or the even same species

- Biomarker assays are not PK assays

- And they don't one to grow up to be PK Assays either



Nonstop for 6+ years...

Biomarker Assays are not PK Assays!

Alien = Different





**Houston, we have a
problem...**



What's the problem here?

- Lack of broad understanding of essential concepts
 - Fit-for-Purpose
 - Validation
 - Context of Use
- Not listening to understand (within and beyond our own community)
- Reasoning by analogy
 - e.g. Treating Biomarker assays like PK assays
 - Biomarker assays are not PK Assays 
- Thinking the messaging is done



Essential Concepts



Essential Concepts – FFP & Validation

- Validation = a process to establish that the performance of a test, tool or instrument is acceptable for its intended purpose (BEST)
- Method/Assay Validation
 - Method validation is the process used to confirm that the analytical procedure employed for a specific test is suitable for its intended use (Ludwig Huber, *Validation and Qualification in Analytical Laboratories*)
 - Assay validation provides an assurance of reliability during normal use and is sometimes referred to as "the process of providing documented evidence that the method does what it is intended to do" (www.fws.gov)
- **Validated = Demonstrated Fit-for-Purpose!**



Essential Concepts - Context of Use

- BEST resource 2016:
 - 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”
- Or, more succinctly...
 - Context of Use = The ‘Purpose’ in Fit-For-Purpose



Essential Concepts - Validation Requires COU

- Validated = Demonstrated Fit-for-Purpose
- COU = the Purpose in Fit-for-Purpose
- Validation = Demonstration of Fit-for-COU

Without COU, the assay cannot be validated!
(it can, however, be analytically characterized)



FFP and COU...



Context of Use is Specific...



“Ice” is not specific enough to be a COU



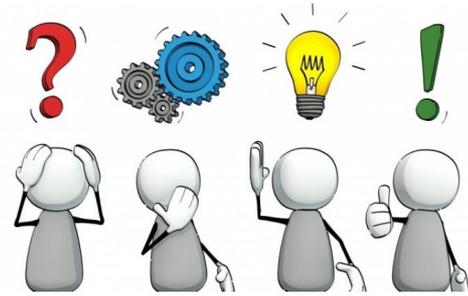
2019-2021....COU a Hot Topic

- C-Path: *Points to Consider Document: Scientific and Regulatory Considerations for the Analytical Validation of Assays Used in the Qualification of Biomarkers in Biological Matrices* brings **Context of Use** into focus (2019)
- [EBF Focus Workshop](#) – Biomarker Assay Validation – Bringing **Context of Use** into Practice (2019)
- [AAPS PharmSci 360 Biomarker Workshop](#) - Best Practices for the Development and **Fit-for-Purpose** Validation of Biomarker Methods (2019)
- [AAPS PharmSci 360 Rapid Fire](#) – Biomarker Assay Validation – Putting Guidance in **Context** (2019)
- [AAPS OSDs on Context of Use](#) x2 (2019)
- 15th Annual Biomarkers Congress – Workshop on Biomarker Qualification: Technical Validation and Regulatory Aspects – Understanding **Context of Use** and Practicalities of Applying Technical Validation Requirements (2020)
- [EBF Focus Workshop](#) – Biomarkers in Pharma R&D: A roadmap from **Context of Use** to using the data (2020)
- [AAPS Workshop](#) - Be Specific – Biomarker Assay Validation in **Context** (2020)
- [EBF Focus Workshop](#) – Biomarkers/**COU** – Case Studies Dissected (2021)
- [AAPS OSD](#) - Putting Biomarker Assay Validation in **Context (of Use)** – Real World Challenges and Solutions (2021)



2015 – 2021

Despite the nonstop discussions...



**Why aren't we listening to
understand?**



The Siren Call of Reasoning by Analogy...



But not so comfortable now...



It feels familiar and comfortable....and that can be seductive



Reasoning by Analogy vs First Principles Thinking

- 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 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
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The Risks of Reasoning by Analogy

- Reasoning by Analogy tends to lead to bad decisions
 - Misapplication/overapplication
- Hasn't been fully thought through



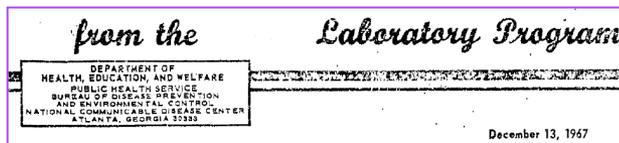


**So why do we find
ourselves here?**

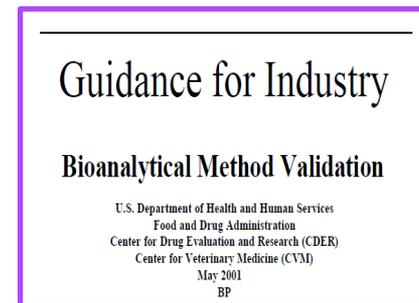


Biomarker History in Perspective

- Its not a new Science - Earliest recording – **4000BC**
- ‘Validation’ of several quantitative methods date back to **1904**
- International Validation recommendations for biomarker assays – **1960s**



- Guidance for Bioanalytical (not biomarker) Assays – **2001**



Because at the same time (2001-2015)...

- Explosion in utilization of biomarkers in drug development
- And...
- Repurposing/Expansion of Bioanalytical scientist responsibilities to include development and validation of biomarker assays



Invasion of the Bioanalytical Mindset

A Tragic Tale of Reasoning by Analogy



2015-2021 Despite nonstop repetition...

Biomarker Assays are not PK Assays!

**Invasion of the
Bioanalytical
Mindset**

Persists



2018 FDA BMV Guidance: The approach used for drug assays should be the starting point for validation of biomarker assays (**Reasoning by Analogy!**) although the FDA realizes that some characteristics may not apply or that different considerations may need to be addressed (**Use First Principles thinking!**)



What's really going on here?



Too risky to potentially 'be wrong'

Bottom Line – job security = **keeping job safe**

Exhaustion – too tiring to fight the non-science

Bottom Line – Path of least resistance

= **making job easier**



Stakeholder Problems....

How often have you heard....

- But we could 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....
- What if a regulator asks...
- Our organization is risk averse...

Is this Science?





**Houston, are we ready
to solve the problem?**

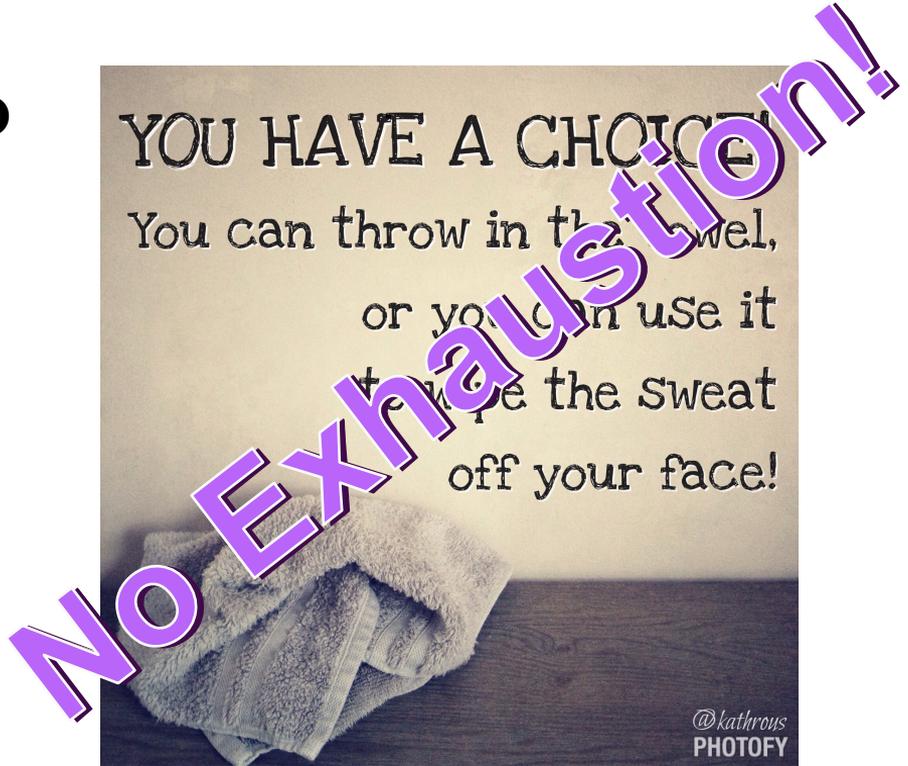


Are we willing to do what it takes?

**Cite Guidance or do
Science?**



YOU HAVE A CHOICE!
You can throw in the towel,
or you can use it
to wipe the sweat
off your face!



How?

- Start with science – First Principles
 - Let go of bad habits (Reasoning by Analogy)
 - Get curious and ask questions - *what exactly do you mean by fully validated?*
 - Stop worrying about ***being right*** and focus on ***getting it right***
- Engage a broader audience
 - We can't just keep talking amongst ourselves
 - We need to reach broader audiences in broader forums, but also
 - Leverage every daily scientific micro-interaction to...
- Repeat the message as many times as it takes



You can lead a horse to water...



You can lead a horse to water...



No fear, No exhaustion, No excuses

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Patients are waiting



Thank you and remember...

Biomarker Assays are not PK Assays!



Backup



How many times do you have to repeat your message before people remember it?

1885, *Successful Advertising* by British businessman Thomas Smith

The **first** time people look at any given ad, they don't even see it.

The **second** time, they don't notice it.

The **third** time, they are aware that it is there.

The **fourth** time, they have a fleeting sense that they've seen it somewhere before.

The **fifth** time, they actually read the ad.

The **sixth** time, they thumb their nose at it.

The **seventh** time, they start to get a little irritated with it.

The **eighth** time, they start to think, "Here's that confounded ad again."

The **ninth** time, they start to wonder if they're missing out on something.

The **tenth** time, they ask their friends and neighbors if they've tried it.

The **eleventh** time, they wonder how the company is paying for all these ads.

The **twelfth** time, they start to think that it must be a good product.

The **thirteenth** time, they start to feel the product has value....

....The **twentieth** time, they buy the product

Don't notice
Not hearing

Annoyed
Actively not listening

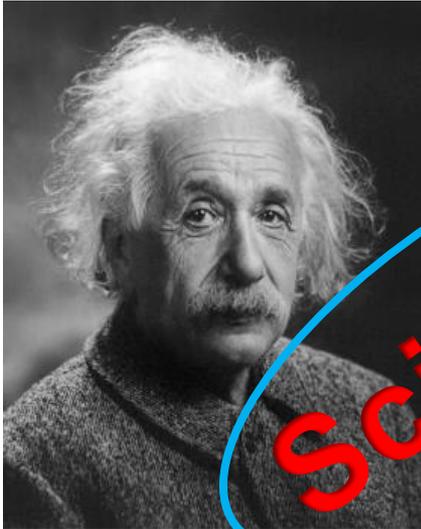
Get curious

Willing to act



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