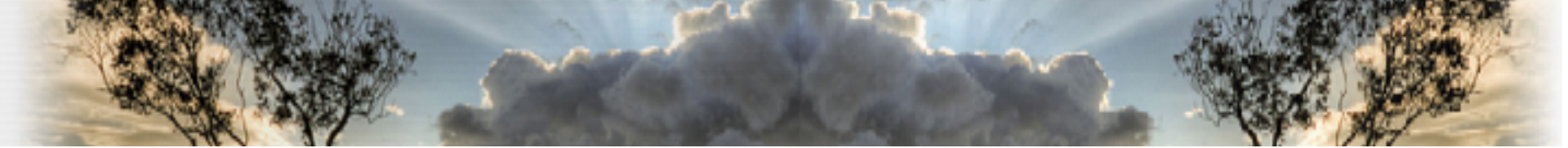


Future challenges for BioA

Philip Timmerman, EBF

11th EBF Open Symposium
Raise the Anchor – Set sail for Science
21-23 November 2018

Five bioanalytical trends/challenges for the 21st Century

1. Biomarkers
2. Outsourcing
3. Regulations
4. Accept exceptions
5. Technology

Five bioanalytical trends/challenges for the 21st Century

1. Biomarkers
2. Outsourcing
3. Regulations
4. Accept the exception
5. Technology

Challenge Nr. 1

Biomarker assays are slowly but gradually becoming PK assays in the minds of many…

…because this is what is nearest to comfort zone

I will be short…

12 years into the Lee paper*…Where are we today?

FDA-2018 “expects something” for pivotal files = FAIR

BA community tries to adhere and copies BMV PK criteria = FAIR

** Fit-for-purpose method development and validation for successful biomarker measurement. Lee JW, Devanarayan V, Barrett YC et.al. Pharm Res. 2006;23:312–328*

I will be short…

BA community is not a BM community

Have we connected enough with the BM end users?

Have we connected globally as a BA community?

Are we actively preventing a scope creep of BM BMV to all BM?

Again, FDA expects something for pivotal trials…but, and we should reach out to all stakeholders to inform us on which trials are pivotal…

Rest assure, they know!!

And if they don't, it's worth the discussion

A suggestion

1. The 2012 EBF recommendation paper* continues to be a good starting point to discuss BA BMV with the project team – complementary to Lee et. al.
   – Prevents silo discussions: BA experts and PD experts unite
2. Probably, only a few studies and BMs are pivotal from a filling perspective
   – Get informed - Prevent going overboard.
3. Bring global experts and initiatives together.
   – Prevent regional isolation: BA experts and BA experts unite

Later in this session (1) and conference (2)

1. EBF past and future plans on bioanalysis of BM
2. Workshop on exploratory biomarkers – incl. case studies

**European Bioanalysis Forum recommendation on method establishment and bioanalysis of biomarkers in support of drug development Timmerman P, Herling C, Stoellner D et al. Bioanalysis, Aug 2012, Vol. 4, No. 15, Pages 1883-1894.*

Five bioanalytical trends/challenges for the 21st Century

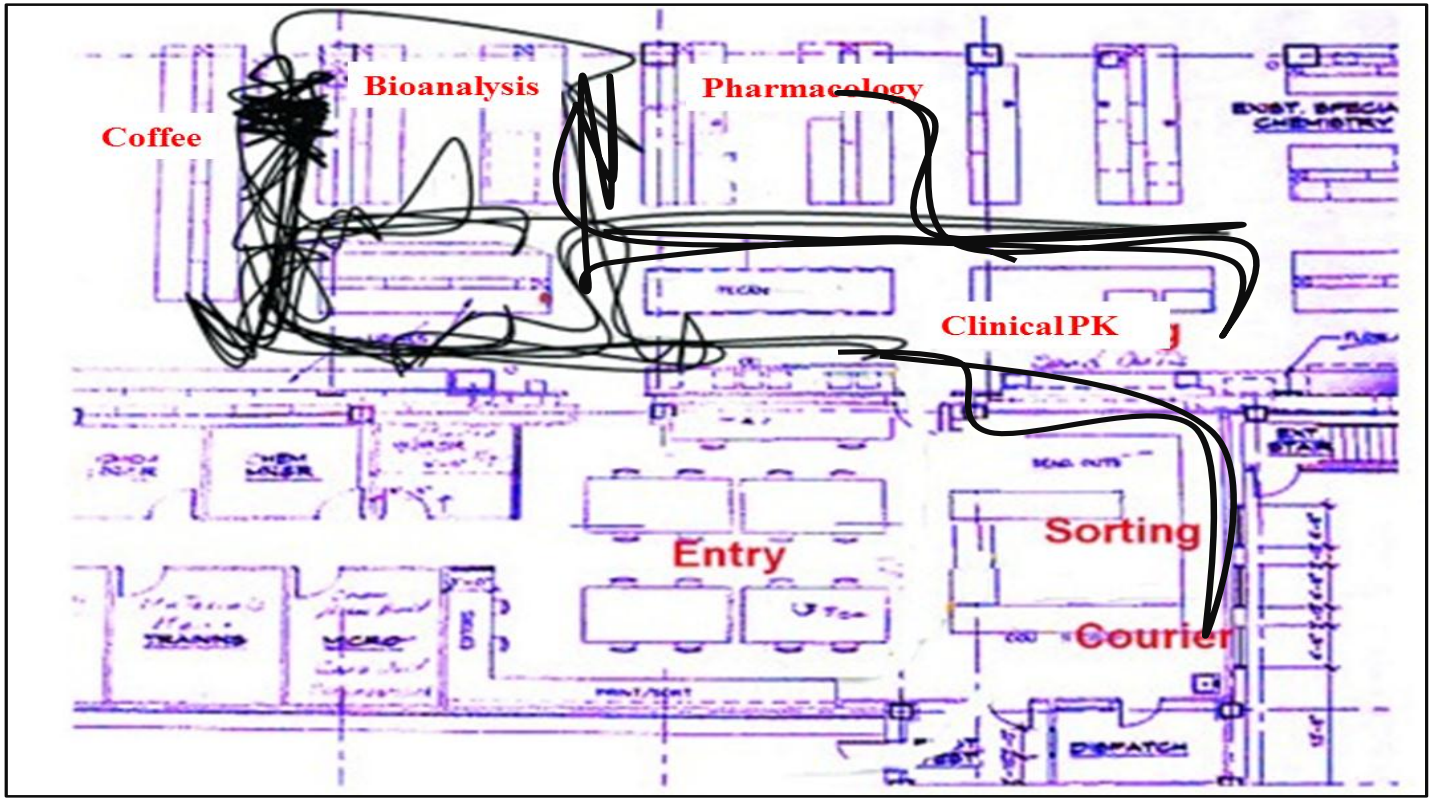
1. Biomarkers
2. Outsourcing
3. Regulations
4. Accept the exception
5. Technology

Challenge Nr. 2

The current outsourcing model doesn’t invite for open discussions required to build a 21st century scientific community…

…because the model is, in essence, built on revenue and IP barriers, not leaving enough room innovation or « teaming up for science »

Utopia: all under one roof…

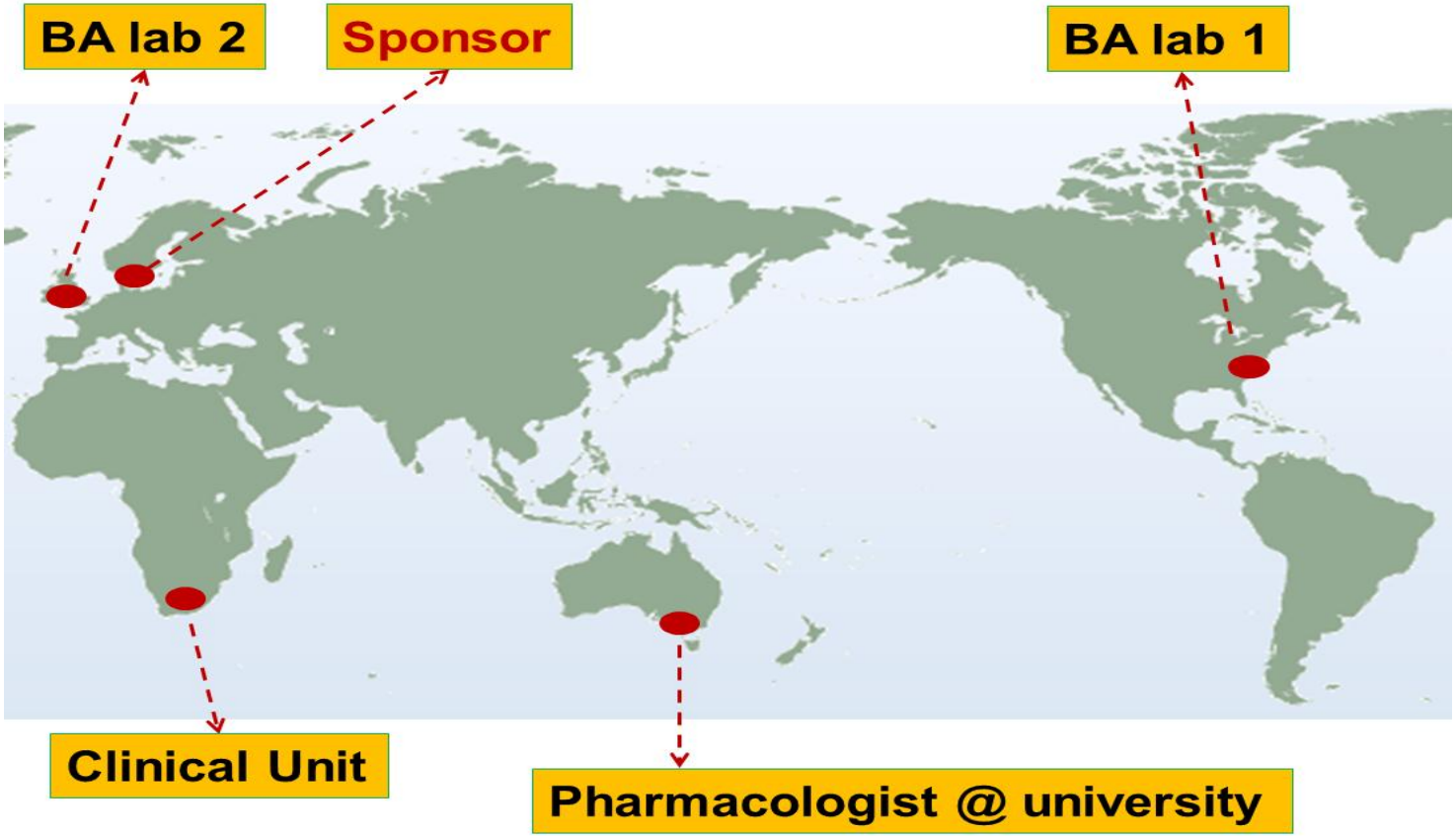


http://www.clpmag.com/2015/03/managing/ Image adapted from Laboratory Alliance of Central New York.

In this situation….

- No geographical / time zone hurdles to optimize the team communication, and involve BA at the right time
- Communication happened naturally at the coffee machine, without interference from procurement, QA or other people that didn't drink coffee at our coffee machine

Today, we don't live under 1 roof anymore



Pressure on the CRO-Pharma scientific interface

- Scientific disconnect - BA expert not member of project teams
- BM assay often runs in PK lab → Contamination of scientific discussions and lab processes caused by
  - Comfort zone of SOP
  - Inappropriate Expectations on quality not relevant for BM (GLP).
  - Relative inexperience of 'PK- bioanalyst' in BM world
- Time pressure
- Imbalance "required quality – regulatory needs" negatively affecting cost and timelines

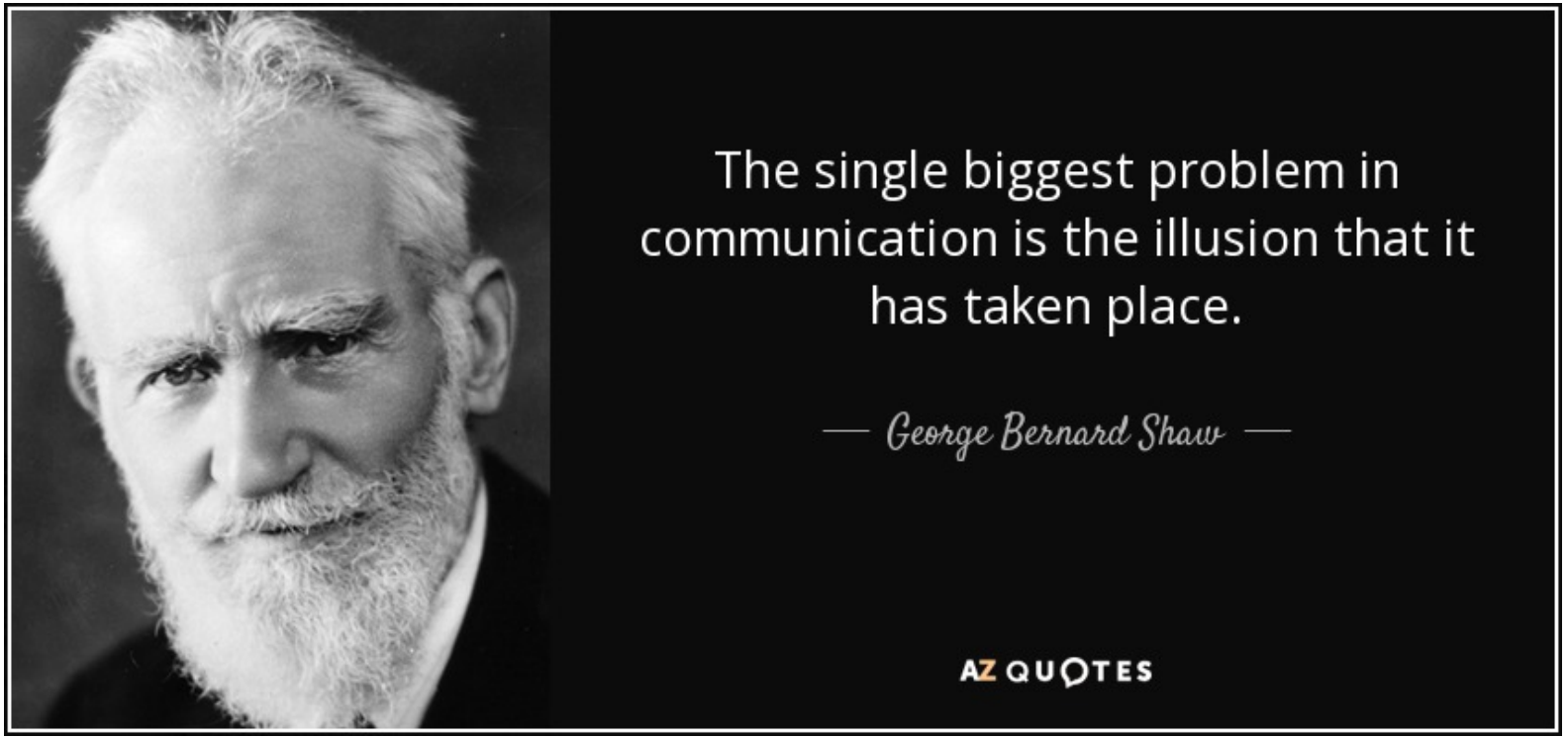
Note: none of above are unique to the Pharma/CRO relationship, but likely an order of magnitude more challenging.

The challenges are real

- Impossibility for *(frequent)* face-to-face interactions
- Time zone differences
  - *Introduced by a bloke named Pythagoras around in 500 BC*
  - *Confirmed by Magelhaes at the turn of the 15th century BC*
  - *First photographed by Apollo 9*

- Unless exception, CRO scientist not part of sponsor's project teams
  - *Can be a problem for internal to Pharma teams too*
  - *BA scientists (CRO or Pharma) not close enough – both scientifically and geographically - to end-users of the BA data*
- (scientific) Language and cultural barriers hampering fast and efficient communication
- IP boundaries
- Trust

(lack of) Communication



risk…

Project team

+

…

BA BA

+

Analyze samples with ‘PK assay’ or worse (e.g. GLP)

BA

hope…

Project team

Five bioanalytical trends/challenges for the 21st Century

1. Biomarkers
2. Outsourcing
3. Regulations
4. Accept the exception
5. Technology

Challenge Nr. 3

Scope creep continuous to impact open discussions required to built a 21st century scientific community working leaner and more focussed…

…because of a lack of incentive or reward

- BA is only peanuts in a total drug development cost
  - Why save 0,001%, who cares?
- Don’t be too visible as a BA scientist. A BA scientist in a team meeting always means ”bad news”.
- Ticking boxes /following SOPs is what is nearest to lab staff’s comfort zone
- “Fear for 483”
  - Industry seems to be afraid for HA citing that never happened, and as such raise the bar themselves
  - Regulatory creep = ISRc (Industry Self-inflected Regulatory creep)

Areas of required application with today's regulations

Plasma
Serum
Blood
Urine
Tissues
Other body fluids
In vitro solutions

originating from

In vitro systems
Rat, Mice, Dog, Rabbit
[NPH]
Human volunteers
Patients

Discovery

- Toleration
- Formulation
- Range Finding
- Salt Form Selection
- Plasma Protein Binding
- Transporter studies
- Inhibition-Induction
- ADME

Preclinical

- PK/PD, Efficacy
- Short term (4wk) and Long Term (3m +) GLP
- Carcinogenicity, genetic and reproductive toxicology
- Mechanistic
- Bioavailability (IV/ORAL)
- ADME

Clinical

- SAD, MAD (?)
- Metabolite assessment (MIST)
- Metab. Quant post ICH M3
- Food Effect, DDI, POC
- PD
- ADME
- F_{rel}, BE
- Population PK

Areas at risk of over-application today

Plasma
Serum
Blood
Urine
Tissues
Other body fluids
In vitro solutions

originating from

In vitro systems
Rat, Mice, Dog, Rabbit
[NPH]
Human volunteers
Patients

Discovery

- Toleration
- Formulation
- Range Finding
- Salt Form Selection
- Plasma Protein Binding
- Transporter studies
- Inhibition-Induction
- ADME

Preclinical

- PK/PD, Efficacy
- Short term (4wk) and Long Term (3m +) GLP
- Carcinogenicity, genetic and reproductive toxicology
- Mechanistic
- Bioavailability (IV/ORAL)
- ADME

Clinical

- SAD, MAD
- Metabolite assessment (MIST)
- Metab. Quant post ICH M3
- Food Effect, DDI, POC
- PD (Pivotal as per FDA)
- ADME
- F_{rel}, BE
- Population PK

Is there also a growing desire in academia to claim GLP or compliance with FDA Guidance?

- Fully regulated Bioanalytical studies (BE, GLP, GcP) are rare in academia, yet, we see guidelines being copied or referred to into academic research
- Academic/industry partnerships and industry-pollination have resulted in a blurring “process boundary” between industry and academy BA labs

- The questions/principles to ask/follow are the same:
  - What are the data used for?
  - Who are your business partners and what is there GxP focus?

Origin of samples and goal in academia?

Plasma
Serum
Blood
Urine
Tissues
Other body fluids
In vitro solutions

originating from

In vitro systems
Rat, Mice, Dog, Rabbit
[NPH]
Human volunteers
Patients

- PK
- PD
- ADME

- TDM
- Illicit drugs, Doping testing
- (Contracted) Clinical/preclinical research

So, also for academic research, the questions of "*what are the data used for?"* is a valid one

Is/are your lab/studies impacted by Guidelines?

- If "Yes":
  - Which Guidelines?
  - Who regulates you?
    - From a 'Guidance/Guideline', Accredation or inspection perspective.
- If "No": are you sure? Maybe next question to ask:
  - Who are your business partners = end users of your data?
  - Which Guidelines regulate your business partners?
  - So "No" may be a "Yes"
- If really "No":
  - Back to the real question: what are the data used for and what scientific rigor is needed to allow decision taking using the data?
    - Did you copy BMV guidelines for no good reason?
    - In doing so, have you set the bar too high?
    - Is there an valid and robust alternative?

Five bioanalytical trends/challenges for the 21st Century

1. Biomarkers
2. Outsourcing
3. Regulations
4. Accept the exception
5. Technology

Challenge Nr. 4

We fail to contextualise the exceptions, and they risk ending up as general requirements in guidelines

Recognise this?

We go to meetings, proudly present an interesting scientific case, (btw....this is what our meetings should be all about)

….but we forget to mention [illegible] off special case….

Project specific required special [illegible] ad to stability issues, somebody messed up, we w[illegible] to brag about it…

The case study is taken out of context, the specific context is forgotten (or not shared because project IP) and…

… the case is generalised and becomes a new requirement for all studies, molecules...

The exception is the exception, and guidelines should not regulate exceptions

Let's Copycat

Disclaimer for industry?

The case study discussed in this presentation is specific to the project and should not be generalised to all projects.

Disclaimer used by HA

The views expressed in this presentation are my own and do not represent the view of the <<HA agency I work for >>

Five bioanalytical trends/challenges for the 21st Century

1. Biomarkers
2. Outsourcing
3. Regulations
4. Accept the exception
5. Technology

Challenge Nr. 5

Fitting new technology in a regulatory straight jacket too soon stifles early and broad adoption of new technologies

A few examples

- DBS
- AMS
- Flow Cytometry
- qPCR

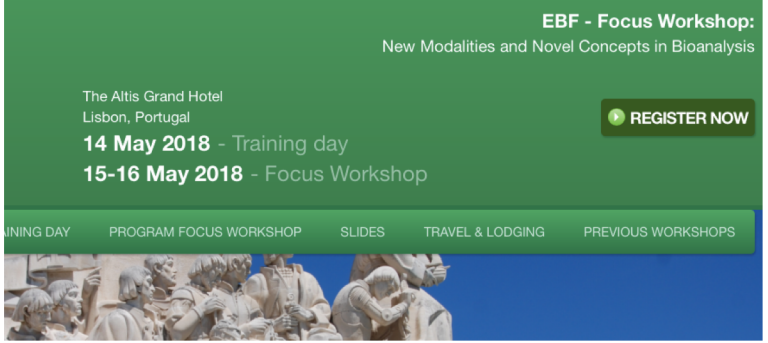
New modalities, beyond “Small or large”

LBA

LC-MS

…..Gene and cell therapy, novel formulations… requiring a whole host on (unexplored) technologies like HRMS, PCR, FC,…

Spring Focus Workshop:
Session 4: Closing panel discussion
How do we integrate New Modalities and Novel Concepts in Bioanalysis in regulations?



Closing: regulatory aspects of New Modalities and Novel Concepts

- From which stage is a “new” or novel” really “new and novel” from a BA perspective, i.e. are we at risk of creating ambiguity in regulations when there is no need for it?
- Can and should industry take the lead in shaping regulatory requirements for novel concepts? And if so, how should we build the discussion in a positive way?
- New Modalities and Novel Concepts: what should be regulated and what should be left to the responsibility of the scientist? And why?
- Specific to New Modalities and Novel Concepts already on the horizon: What requirements for method validation and acceptance criteria should be applied? Lots of guidance are available for ELISA and LC-MS based approaches but guidance is much more limited for qPCR and bDNA type assays….

EBF

And the big question….which acceptance criteria to apply for all these new technologies

4-6-15?
4-6-20?

And why, or why not? And what else

The discussion started at an EBF meeting in Lisbon on hybrid assays.

We seem to copy LBA or LCMS criteria without good understanding why. Because we are doing so since the nineties…

Interesting starting point for experts statisticians:

Pharmaceutical Research, Vol. 11, No. 4, 1994

An Assessment of the 4-6-20 Rule for Acceptance of Analytical Runs in Bioavailability, Bioequivalence, and Pharmacokinetic Studies

Robert O. Kringle[1]

Received May 28, 1993; accepted September 30, 1993

A recent conference report described a decision rule, hereafter referred to as the 4-6-20 rule, for acceptance/rejection of analytical runs in bioavailability, bioequivalence, and pharmacokinetic studies. This procedure requires that quality control specimens at three concentrations (low, medium, and high) be assayed in duplicate in each run. For run acceptance, at least four of the six assay values must be within ±20% of their respective nominal concentrations, and at least one of the two values at each concentration must be within these limits. An inherent flaw in this decision rule is that the risk of rejecting runs, when the assay performance has in fact not deteriorated, varies for each assay and is neither known nor controlled. In this paper simulation methods are used to evaluate the operating characteristics of the 4-6-20 rule in comparison to those of classical statistical quality control procedures.

KEY WORDS: quality control; Shewhart control; multivariate control; operating characteristics; power.

What are we NOT suggesting?

- This is **NOT** a suggestion to bring LBA to 4/6/15
- But…a suggestion for the industry and regulators to reconsider what harmonized acceptance criteria defines the quality level **which is sufficient to make valid decisions.**

Towards decision-based acceptance criteria for Bioanalytical Method Validation: a proposal for discussion from the EBF

Philip Timmerman[1], Michaela Golob[2], Joanne Goodman[3], Magnus Knutsson[4], Robert Nelson[5], Marianne Scheel Fjording[6] and Steve White[7]

Pulished online, August 2018, Bioanalysis 10(16)

Five bioanalytical trends/challenges for the 21st Century

Biomarkers	BM assays are becoming PK assays
Outsourcing	Current outsourcing model may need revisiting to support innovation and closer collaboration
Regulations	Scope creep may continue to increase the bar (ISRc)
Accept exceptions	Exceptions are exceptions, and should not become guideline
Technology	Fitting new tech in a regulatory straight jacket too soon stifles adoption