Run Acceptance Criteria

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on behalf of the EBF

Focus Workshop

(*In collaboration with the AAPS and JBF*)

Industry input into ICH M10: Experimental data as the cornerstone for a science driven bioanalytical guideline

The Altis Grand Hotel Lisbon,
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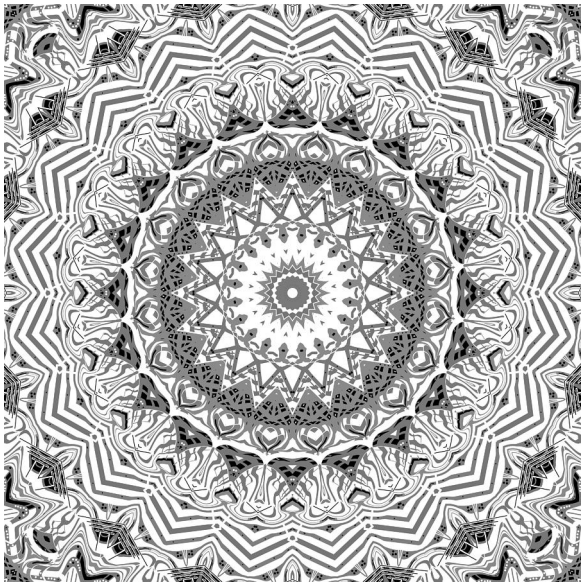
Doing it the same way for 20 years – Does that make it right?

- Long established validation & run acceptance criteria (20+ years)
- Sample analysis acceptance criteria not reflective of the actual assay performance during validation
- Fixed criteria defined by the assay platforms typical in late 1990s
  - 4/6/15 for chromatographic assays
  - 4/6/20 for ligand binding assays
  - The world is no longer black & white

Things have changed since the late `90s...



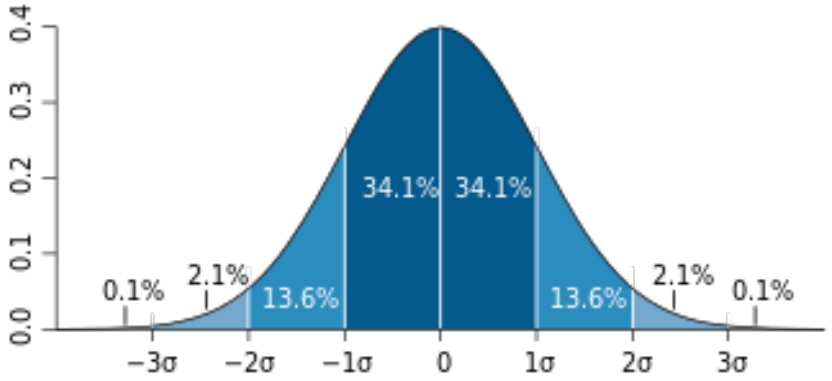
Late 1990s:

- LC-MS/MS (triple quad)
- LBA

2017:

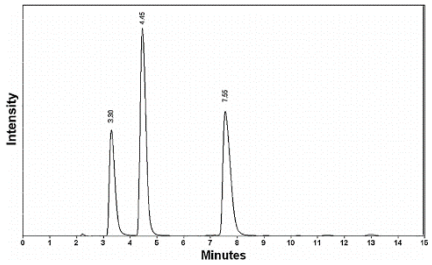
- LC-MS (triple quad & HRMS)
- LBA
- IC-LC-MS
- Enzyme digestion-LC-MS
- Enzyme digestion-IC-LC-MS

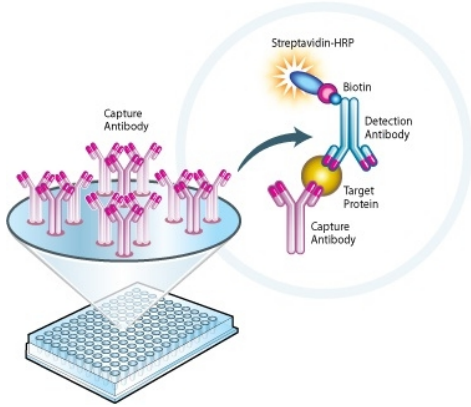
Why 4/6/15 & 4/6/20 ?

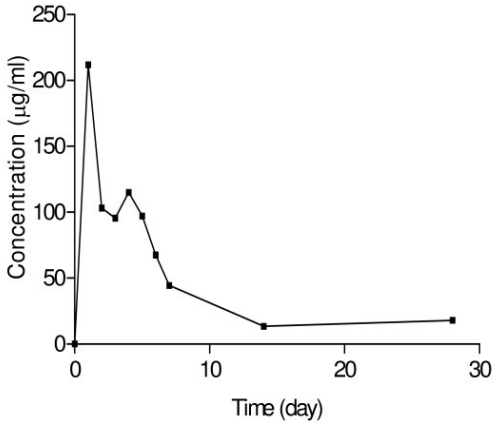


- Early ‘90s:
  - 4/6/20 acceptance criteria applied to Chromatographic & Ligand Binding assays following Crystal City I and subsequent publications (1990, 1992)
- Post Crystal City II (2000):
  - 4/6/15 “announced” for chromatographic assays
  - 4/6/20 continued as “the norm” for LBAs
  - A “blanket” (arbitrary?) criteria for both bias & precision – not reflecting end use of the data
  - Different criteria for Chro/LBA – **Why?**
- 2/3rds of QCs within x% of nominal roughly equates to ± 1x S.D.

Different platform - same conclusion







So Why Different Acceptance Criteria?

The Questions No-one Wants to Ask…

- Why are we applying different acceptance criteria for LBA vs. CHROM assays, when we are making the same PK, PD, TK claims?
- Was/is '4/6/20' not good enough for all data? LBA or CHROM?
- Is there value of even removing the label "CHROM" and "LBA" and refer to "PK assay" with 1 harmonized set of criteria → PK ASSAY
  - Thus removing ambiguity & confusion around so called "hybrid" assays

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 4/6/15 for chromatography and harmonize acceptance criteria for PK assays to the quality level **which is sufficient to make valid decisions.**
- It would remove the need for a non-added value discussion on defining "hybrid assay" criteria
- This is not about introducing "sloppy" chromatographic assays
  - Wider criteria would simply reduce re-work which has no impact on the end data

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Let‘s Challenge the Status Quo...

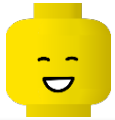
Is there a different way?

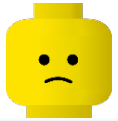
- 4/6/15 (Chrom) & 4/6/20 (LBA) – Status Quo

1. Same criteria regardless of platform – based on an “arbitrary” number
2. Define assay specific acceptance criteria during validation and apply during sample analysis (e.g. ±n x S.D.)… may appeal to the more statistical minded
3. Same criteria regardless of platform – based upon what is relevant for downstream pharmacokinetics

- And there are certainly others (can discuss later)

Is it better just because it‘s different?





Same criteria regardless of platform – based on an “arbitrary” number	Easy to execute “Compatible” with emerging platforms	Not reflective of data end use (PK) Willingness to change
Define assay specific acceptance criteria during validation and apply during sample analysis	Reflective of actual assay performance	Challenging to execute Not reflective of data end use (PK) Willingness to change
Same criteria regardless of platform – based upon what is relevant for downstream pharmacokinetics	Easy to execute Reflective of data end use “Compatible” with emerging platforms	Willingness to change

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What is Pharmacokinetically Relevant?

- In the last decades, did we ever consider what the requirements for a PK assay actually need to be?
  - Statistical power of study *vs.* BA criteria
  - Allowed bias *vs.* inter and intra subject biological variation
  - Biological variation can be bigger than the difference between 15 or 20 %
  - Would AUC change?

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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.

Interesting starting point for experts statisticians:

Consequences of harmonisation

- Common criteria based upon end use of the data (PK) rather than the platform
- Clarity over which criteria apply for so called “hybrid assays”
- Other assay elements (such as stability) also become aligned and not platform dependant
- Likely little to no effect on population PK

Summary

- Chromatographic vs. LBA acceptance criteria invites ambiguity over utilization of alternate ("hybrid") platforms
- Currently different criteria for different platforms whilst the (PK) data is used for the same purpose
- There is now an opportunity to challenge this paradigm
  - or live with the consequences for the next 20+ years

Acknowledgement

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