

Challenges in dealing with different regulations by different Health Authorities

(A challenge only becomes an obstacle when you bow to it - Ray A. Davis)

Pictured above: The structure of HIV

Vera Hillewaert - Barcelona, 15 Nov 2017

Different Regulations - background

It all started with GLP regulations in 1972 (Denmark, New-Zealand)

In US: GLP regulations by FDA in 1978

Because of irregularities that were found, there was a shift from trusting data to asking for proof that data was correct and to auditing labs

First for non-clinical studies

Later: regulations also for clinical studies



Different Regulations - background

We now have a wide variety of regulations, talking about the same, but sometimes asking for slightly or completely different things



Different Regulations - harmonization

We need harmonization:

- As it is now, we need to comply with different regulations
- We sometimes need to repeat testing in a slightly different way

ICH (International Council for Harmonisation) is working on that

- Via face-to-face meetings, e-mail consultations and teleconferences, a concept paper and business plan were drafted and are now endorsed (Oct 2016)
- Draft guideline is planned by June 2018
- Adoption of the ICH harmonized guideline is planned by June 2019



Interpretation of regulations – medium QC

EMA requirement: “Within-run accuracy should be determined by analysing in a single run a minimum of 5 samples per level at a minimum of 4 concentration levels which are covering the calibration curve range: the LLOQ, within three times the LLOQ (low QC), around 30 - 50% of the calibration curve range (medium QC), and at least at 75% of the upper calibration curve range (high QC).”

Compared to FDA: “one near the center of the standard curve (middle QC)”, or “one in the midrange”

Interpretation of regulations – medium QC

In the EBF Whitepaper: The European Bioanalysis Forum community's evaluation, interpretation and implementation of the European Medicines Agency guideline on Bioanalytical Method Validation, the following is stated:

Four QC samples: LLOQ, low, medium and high during validation is common practice, but for the medium level QC, in contrast to what the guideline indicates "...around 50% of the calibration curve range (medium QC)... ", there was a common understanding among the members that the 50% should be interpreted on a geometric scale rather than arithmetic

Interpretation of regulations – medium QC

However, unfortunately, alas, regrettably



EMA inspectors don't agree with that understanding

Interpretation of regulations – medium QC

In a recent filing, we received the following comment:

For the bioanalysis of the analytes, a medium QC around 30-50% of the calibration curve range was lacking, as was also the case during validation. The middle parts of the calibration curves from about 10% to 80% of the calibration curve range are not covered now by QC samples and analytical runs can therefore not be assessed on the precision and accuracy in this part of the calibration curves

The complete calibration curves should fulfil the criteria regarding precision and accuracy based upon the calibration samples and the QC samples

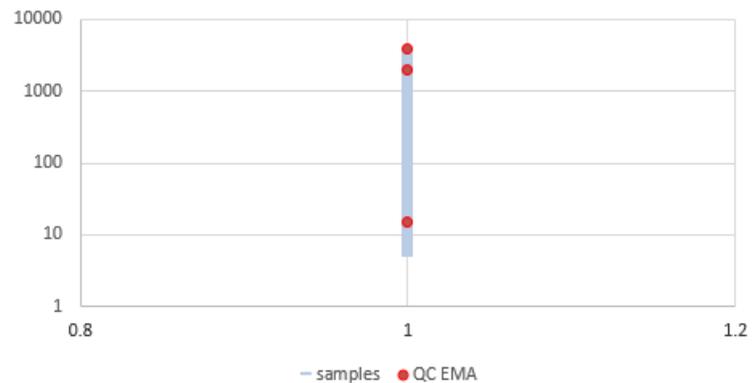
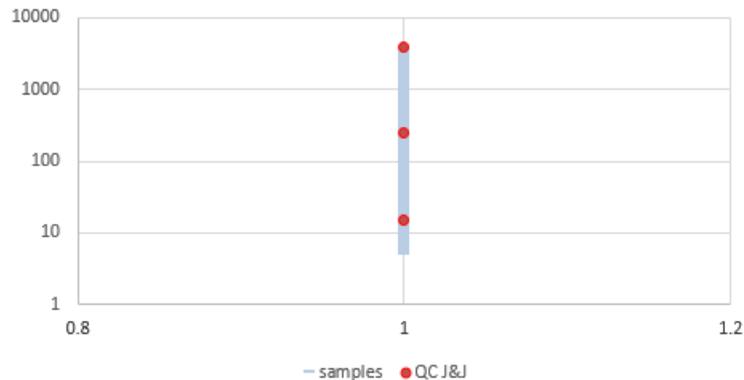
Interpretation of regulations – medium QC

Our response was (in line with the common understanding):

For the assays used in these studies, the medium QCs were selected close to the geometric mean of the calibration curve. We are aware this is not at 50% of the ULOQ as stated in the EMA guidance. However, section 5.3 of the same guidance also states that “At least 2 QC sample levels should fall within the range of concentrations measured in study samples. ” If the medium QCs would have been selected at 40% of the ULOQ the latter criterion would not have been met.

Interpretation of regulations – medium QC

We had provided plots showing medium QC at geometric middle and arithmetic middle



EMA replied that if you look on an arithmetic scale, the main part of the curve is lacking a QC

Interpretation of regulations – medium QC

On the common understanding, EMA replied: During the development of the BA guideline on Bioanalytical Method Validation (2011) they have already made this comment and the response from the EMA was:

A low QC at three times the LLOQ, a median QC concentration around 50% of the calibration curve range and a high QC concentration at at least 75% of the calibration curve range is recommended. The applicant is free to choose additional concentrations

C_{\max} is solely based on one concentration measurement, is one of the primary PK parameters, is found in the middle of the curve, accuracy is important, so the middle QC needs to be at 30-50% of ULOQ

Interpretation of regulations – medium QC

EMA recommendation: reject all runs, reanalyze all samples with additional QC, both for validation and clinical study

In this case, the study samples were outside of the long term stability window, so they couldn't be reanalyzed

We revalidated the method with a mid QC at 30-50% of the ULOQ.
File was accepted

Interpretation of regulations – medium QC

In a second recent filing, we received the following comment:

During validation of all analytical methods as well as during analysis of subject samples, a medium QC (around 30-50% of the calibration range concentration) was lacking. Thus, the middle parts of the calibration curves are not covered. The Applicant should explain the lack of the medium QC and discuss the potential impact on the accuracy of C_{\max} values

Analytical method: wide range (1 – 2000 ng/ml) to cover various dose levels and formulations. In recent studies: low dose is used, resulting in C_{\max} around 250 ng/ml

Approach driven by team: Validation with 2 additional QCs: one at 250 ng/ml (C_{\max}) and one at 600 ng/ml (30% of ULOQ)

Interpretation of regulations – Stability - Health Canada

Health Canada issued a notice: Clarification of bioanalytical method validation procedures (Oct 08, 2015), saying that during stability testing it is not sufficient to take multiple aliquots out of one bulk stability sample, as this doesn't provide multiple replicates of the storage conditions

For all method validations where only one bulk tube was used, stability testing needs to be repeated

Beginning of 2016, we received remarks on this in some of our recent filings. We replied to this by listing all stability samples used during the validation, showing for instance for long term stability testing, a lot of different tubes are used

Interpretation of regulations – Stability - Health Canada

Health Canada noticed that there were a lot more filings than expected impacted by their notice of Oct 2015

They made an amendment (March 09, 2016), in which is stated that for submissions filed before Oct 2015, this requirement will not be taken into account



For further filings, we repeated stability testing with different aliquots as requested

Interpretation of regulations – Comedication

In a lot of filings, we get asked about selectivity testing towards comedication
This issue is raised by different health authorities

Our reply to this is the following, in line with the EBF recommendation paper:

Based on the molecular weight of the concomitant medication, no MS/MS interference is anticipated with analyte X and its internal standard. Moreover, the quantification uses a STIL (Stable Isotope Labeled internal standard), further safeguarding any matrix effect issues in case of undue co elution. Interferences were not observed in the chromatograms.

We also add a table with all MWs involved

Interpretation of regulations – Anvisa (Brazil)

Anvisa guidance was mostly built around BE studies on generic and similar drugs

- First version in 2003 RE 899
- Current version in 2012 RDC 27

Anvisa requires that labs that analyze samples from BE studies (generics and similars) are Anvisa certified

Where other guidances are really a 'guidance', Anvisa is a law and must be applied as such

Some uncertainty on what applies to studies on new drugs

Interpretation of regulations – Anvisa (Brazil)

Anvisa has some regulations that are not found in other guidelines

- Selectivity: 4 normal plasma samples, 1 lipemic, 1 hemolyzed
- Matrix effect: 4 normal plasma samples, 2 lipemic, 2 hemolyzed
- At least 3 injections of blank sample, 1 just before the ULOQ and 2 right after the ULOQ

Filing in Brazil - issues

In a planned filing in Brazil

- BE study conducted and analyzed in 2011
- Method validation applicable in our 2011 study does not contain everything requested by current Anvisa regulations

Concerns caused by other filing: in the area of formulations there were issues around

- certificates for compounds and excipients
- analysis methods
- the language in which these documents are to be provided

Result of this: local operating company people in Brazil are questioning the bioanalysis for the upcoming filing

Filing in Brazil - issues

- Medium QC: Clarify the criteria adopted to establish the concentration of medium quality control sample (within a factor 2.5 of the median calibration standard). The Resolução-RDC 27, de 17 de maio de 2012 establishes the concentration of medium quality control sample is close to the average between low and high quantification limits
- Lack of hemolyzed and lipemic sample in selectivity testing
- Lack of hemolyzed and lipemic samples in matrix effect testing
- Lack of hemolyzed and lipemic samples in testing of interference by concomitant drugs (requested in Nota Técnica #04/2014 of ANVISA, this is a note on RDC 27 dealing with comediation)

Filing in Brazil - issues

- In reply to the questions from our local operating company people, we summarized what we have and what is missing
- Way forward ???

Conclusions

A challenge only becomes an obstacle when you bow to it
(Ray A. Davis) can lead to: A challenge can become a pain if
you are forced to bow to it (me)

But let's remember: If you find a path with no obstacles,
it probably doesn't lead anywhere (Frank A. Clark)



Globally harmonized guidelines are the only efficient
way forward

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