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Bioassays as part of an integrated control strategy

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Too Much Information…

- *Where is the wisdom we lost in knowledge;*
- *Where is the knowledge we lost in information*
  - *T. S. Eliot – 'The Rock'*
- Too Much Information is a distraction

Reminder: Control Strategy

- Definition from ICH Q10
  - A planned set of controls, derived from current product and process understanding that ensures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control.
- See also ICH Q8

Reminder: Control Strategy

- ICH Q8 section 2.5
  - A control strategy is designed to ensure that a product of required quality will be produced consistently. The elements of the control strategy discussed in Section P.2 of the dossier should describe and justify how in-process controls and the controls of input materials (drug substance and excipients), intermediates (in-process materials), container closure system, and drug products contribute to the final product quality. These controls should be based on product, formulation and process understanding and should include, at a minimum, control of the critical process parameters and material attributes. (..)

Reminder: Control Strategy

- ICH Q8 section 2.5 ctd.
  - A control strategy can include, but is not limited to, the following:
    - Control of input material attributes (e.g., drug substance, excipients, primary packaging materials) based on an understanding of their impact on processability or product quality;
    - Product specification(s);
    - Controls for unit operations that have an impact on downstream processing or product quality (e.g., the impact of drying on degradation, particle size distribution of the granulate on dissolution);
    - In-process or real-time release testing in lieu of end-product testing (e.g. measurement and control of CQAs during processing);
    - A monitoring program (e.g., full product testing at regular intervals) for verifying multivariate prediction models.

Reminder: Control Strategy

- ICH Q8 section 2.5 ctd.
  - A control strategy can include different elements. For example, one element of the control strategy could rely on end-product testing, whereas another could depend on real-time release testing. The rationale for using these alternative approaches should be described in the submission.
  - Adoption of the principles in this guideline can support the justification of alternative approaches to the setting of specification attributes and acceptance criteria as described in Q6A and Q6B.

Reminder: Control Strategy

- ICH Q8 section 3.4
  - The section of the application that includes the justification of the drug product specification (P.5.6) is a good place to summarise the overall drug product control strategy. However, detailed information about input material controls and process controls should still be provided in the appropriate CTD format sections (e.g., drug substance section (S), control of excipients (P.4), description of manufacturing process and process controls (P.3.3), controls of critical steps and intermediates (P.3.4)).

Powerful concept

- The concept of ‘control strategy’ offers a powerful approach:
  - To have a holistic approach towards what and how to control
  - To integrate all the development and validation data
  - To present the data in a way that is meaningful and easily understandable (‘to paint a picture’) in a CTD

- Bioassay does not exist ‘*in vacuo*’

Why bioassay? (1)

- ICH Q6B
  - *'Specifications are chosen to <u>confirm</u> the quality of the drug substance and drug product rather than to establish full characterisation and should focus on those molecular and biological characteristics found to be useful in ensuring the safety and efficacy of the product.'*

Why bioassay? (2)

- ‘Proof of the pudding’
  - General expectation,
    - ICH Q6B; see also e.g. Ph. Eur. <2031> on MAbs.
  - Confirmation of correct product/primary structure/HOS
  - Physico chemical data can tell us only so much….
- Biologicals completely w/o bioassay are rare.
  - Somatropin, Insulin, Epoetin
  - Either relatively simple;
  - Or 3R (no animal testing) driven
- However,….

Complex cases

- Some biologicals have more than one biological activity
- Monoclonal antibodies
- Enzyme Replacement Therapies
  - Enzymatic activity
  - Cellular uptake (not ‘true’ potency; however cf. EPO and FSH bioassays which include –animal- PK).

MoA of MAbs

- Binding
  - Binding
  - Blocking (antagonism)
  - Crosslinking (ligand/receptor dimerization)
- Effector functions
  - CDC (C1q)
  - ADCC (FcgRIIIa, CD16)
  - ADCP (FcgRIIa)
- (FcRn)
  - Impacts PK and therefore total observed clinical effect

Is relative potency variable or fixed? (1)

- ‘Fixed potency’ products
  - Biological activity determined by interaction with fixed Kd
  - Interaction determined by primary structure > folding
  - Fixed conversion factor between mass/mg and Units
  - Bioassay confirmatory
  - Expected bioassay result (close to) 100% of RS
    - Cave: Stability, above assumes close to 100% purity

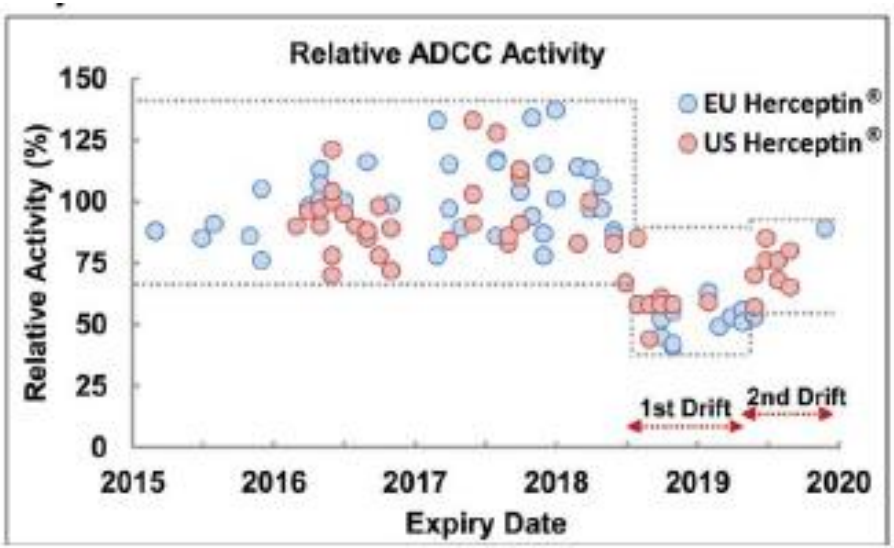
Is relative potency variable or fixed? (2)

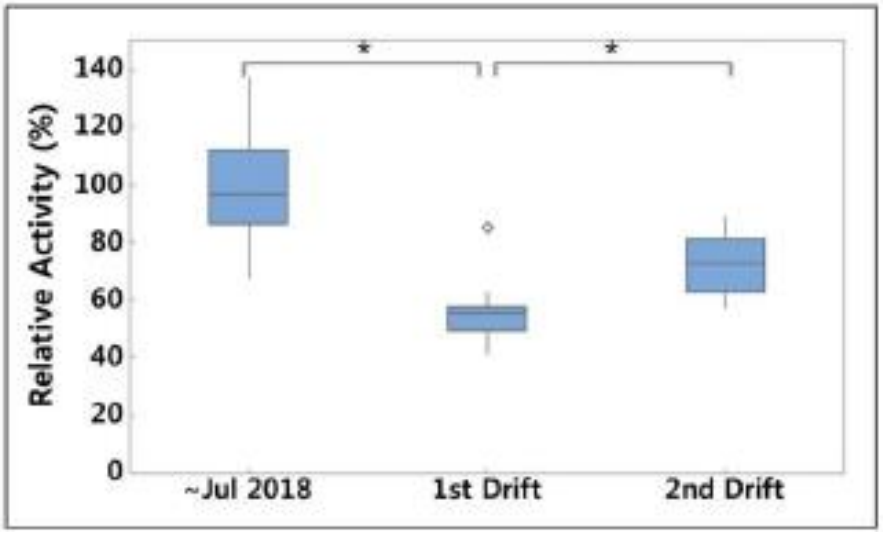
- 'Variable potency' products
  - Interaction not directly determined by primary structure
  - Impact of glycosylation and/or other PTMs
  - No fixed conversion factor between mass/mg and Units
  - Bioassay determines assigned potency
  - 'Any' bioassay result may be expected

In an ideal world…

- ADCC
  - Scientific literature indicates ADCC is important MoA
  - ‘Holistic assay’; includes both binding to target and Fc-function
  - ADCC potency influenced by glycosylation pattern
  - ADCC assay measures important variability to be controlled
  - ADCC would be highly relevant release test!

ADCC shifts can be detected and linked to other CQAs





-Taken from Seokkyun Kim et al. MABS 9(4), 704-14 (2017)

- High assay precision necessary!

Impact on Control Strategy (1)

- Control strategy for MAbs
- If blocking: CBPA (sometimes ELISA) based on binding to target
  - See e.g. Ph. Eur project on TNF-alfa blockers (method 2.7.26)
  - Acceptance criterion of 80-120% achievable(?, mature assay)
- If effector functions involved: CDC
  - Actual relevance disputable
  - Depends on both binding to target and integrity of Fc
- ADCC indirectly controlled
  - ‘afucosylation’

Impact on Control Strategy (2)

- Glycosylation determinants
  - ‘afucosylation’ (absence of fucose) and mannosylation(mount of high mannose)
- Historically, specification for glycosylation derived from manufactured lots/process capability
- Move towards:
  - Characterisation of ADCC as a quantitative function of glycosylation
  - Establish quantitative correlation
  - Correlation drives specification: glycosylation limits such, that ADCC (e.g. approx.) 70-130% achieved.

Other considerations

- Stability testing of product
  - CBPA may perform poorly as stability indicating test
  - Insensitive to small changes
  - Invalid assays after large degradation (no D/R curve fit)
- Recalibration of new (primary/working) standards
  - Esp. for variable potency products
  - Potency of old and new standard may differ, which value to be assigned?
- Stability of standards

Life cycle considerations, ICH Q14

- The holy grail of regulatory flexibility
- Flexibility is only feasible if rooted in a solid scientific basis
- ICH Q14 stresses the importance of systematic/sound analytical development
- Right development >> ‘right’ method description
  - Only critical parameters/elements
  - Meaningful ranges for those parameters
  - Meaningful SST criteria
  - Meaningful Assay/Sample Suitability Criteria

Future?

- Direct control of ADCC through CBPA?
  - RGA assays suggest this option
  - RGA may be less discriminatory (compared to formats with target and effector cells)
  - Change between ADCC formats are not trivial
- At least, improved understanding and standardisation of ADCC highly desirable.
- Generalised link glycosylation <> ADCC

Conclusion

- Biological activity should be controlled
- Not all biological activities need to be release tested
- One potency assay usually suffices
- Whole control strategy (specifications and process parameters) should assure product quality

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