CBG MEB
MEDICINES EVALUATION BOARD

Do we need more guidance for guidelines?
Some meta-guidance

Dr. R.M. van der Plas, Sr assessor MEB, disclaimers apply

15 July 2021

GOOD MEDICINES USED BETTER

Disclaimer

- Personal views only, meant to initiate further discussion. Not to be quoted as the opinion of MEB, EMA, EDQM.

Theory and practice

In theory, theory and practice are the same. In practice, they are not.

Theory is when you know everything, but nothing works. Practice is when everything works, but no one knows why. In our lab, theory and practice are combined: nothing works, and no one knows why.

Structure of ICH Q8 (R2)

- ICH Q8 ‘on pharmaceutical development’
- Part I Pharmaceutical development
  - Introduction
  - Pharmaceutical development
  - Glossary
- Part II Pharmaceutical development – Annex
  - Introduction
  - Elements of pharmaceutical development
  - Submission of pharmaceutical development (..)
  - Glossary
- Annexes

Part I of Q8 - straightforward

- *2.1 Components of the drug product*
  - *2.1.2 Excipients*
  - *The excipients chosen, their concentration, and the characteristics that can influence the drug product performance (e.g., stability, bioavailability) or manufacturability should be discussed relative to the respective function of each excipient. This should include (…)*
- Clear expectations as to 'What should be provided in CTD' !!!
- No tickbox, but directions
- Concise

Part II of Q8 - …

- *2.4 Design Space*
  - The risk assessment and process development experiments described in Section 2.3 can lead to an understanding of the linkage and effect of process parameters and material attributes on product CQAs, and also help identify the variables and their ranges within which consistent quality can be achieved. These process parameters and material attributes can thus be selected for inclusion in the design space.
  - A design space can be described in terms of ranges of material attributes and process parameters, or through more complex mathematical relationships. It is possible to describe a design space as a time dependent function (e.g., temperature and pressure cycle of a lyophilisation cycle), or as a combination of variables such as components of a multivariate model. Scaling factors can also be included if the design space is intended to span multiple operational scales. Analysis of historical data can contribute to the establishment of a design space. Regardless of how a design space is developed, it is expected that operation within the design space will result in a product meeting the defined quality.
  - Examples of different potential approaches to presentation of a design space are presented (..).

Part II of Q8 – Ctd.

- Part II introduced many interesting concepts
- Concepts (and glossary) high level and abstract
  - Top-down development
  - New concepts
  - Little codification of then-current best practice
- Lack of specific guidance
  - 'Reflection Paper' ('*document outlining the view (..) on a particular issue'*)
  - 'White paper' ('*guide that informs readers concisely about a complex issue and presents the issuing body's philosophy on the matter*')

Design Space issues

- Fundamental and practical discussions on ‘what actually constitutes a Design Space (DSp)’
  - Difference between DSp and ‘a bunch of PARs’ (?)
  - Need/use of separate regulatory requirements
- Movement within Design Space
  - Intended (verification requirements?)
  - Unintended (‘deviations’)
- DoE requirements and interpretation
- Models
- Reflection: It seems that ICH Q8 was never intended to be the last word on this

‘Everything is critical’

- Definition of CPP (ICH Q8):
  - *A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality*.
- *Reductio ad absurdum*: everything will become critical if the range becomes sufficiently wide
  - Control of a CPP (to assure CPP within range) mitigates risk but does not change criticality
  - Classification based on PP impact ratios formally problematic; ignores ‘Black Swan Events’
    - events that have low occurrence + high impact

‘Everything is critical’ - example

- ‘Temperature in factory’ is critical: If T > 1000 ^{o}C, then product quality will surely be impacted…

Undervalued concepts

- The ICH Q8/Q10 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
  - Undervalued concept ☹

- However, ICH has yet to provide integrated, unequivocal guidance on the CPP issue.

Reflections 1

- ICH should provide guidance
- This guidance should focus on what to put in CTD
  - ‘What’, not ‘how’
- CTD is a legally binding document
  - Legally Binding (ECs) vs Supportive

Reflections 2

- White papers are useful – but not as ICH guidance
  - Supporting reflections should be minimised, clearly linked to specific guidance, and only offered as such
- Guidance should be firmly rooted in current practice
  - Even if practice needs improvement, it remains starting point
- Be careful with new, highly abstract, concepts
- Realise that guidance docs will be overinterpreted

Final reflection

- Guidance should be <u>useful</u>
  - Definitions and terminology should not only be <u>theoretically</u> correct, but especially be <u>practically</u> applicable

CBG MEB

MEDICINES EVALUATION BOARD

GOOD MEDICINES USED BETTER