Regulatory Life cycle management-

ICH Q12

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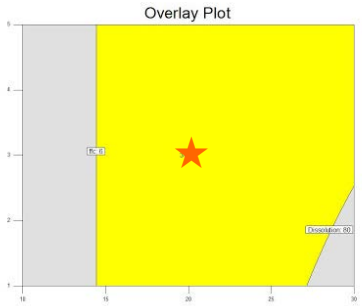
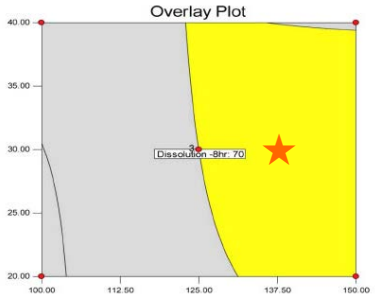
Example : Double sourcing

- 2 membranes are selected
- Design space (pH x conducti) is determined at labscale for both membranes
- Design spaces and target parameters (★) are different for the two membranes

Membrane A
★ pH 7.2 – 250 mM NaCl



Membrane B
★ pH 8.0 – 1M NaCl

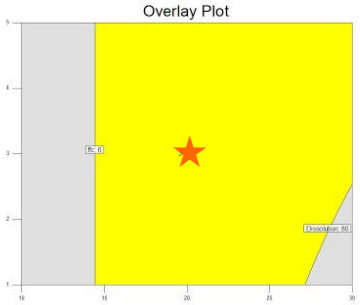


- Membrane A is selected for scale-up, clinical lots and manufacturing – No further development of membrane B
- At some point during lifecycle, membrane A is no longer available → need to shift to membrane B
  - re-check membrane B design space at labscale using starting material from commercial facility
  - produce PPQ batches and demonstrate equivalence of membrane B in terms of DNA clearance and final CQAs
  - shift to membrane B for commercial production → **applicability of ICH Q12 ?**

Example : Double sourcing (cont'd)

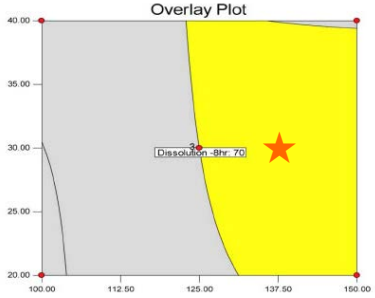
Membrane A

★ pH 7.2 – 250 mM NaCl



Membrane B

★ pH 8.0 – 1M NaCl



- Details of the membrane are described in the file (S 2.2 Description of manufacturing process) but can be concluded of being non-established conditions based on DS experiments.
- Move to membrane B and the supportive info (design space membrane B at labscale and PPQ batches) are documented via PQS
- No regulatory filing.

Other examples of changes to non EC ?

Analytical methods

Minor change to an analytical procedure described in S 4.2 (analytical procedures)

eg replacement of certain equipment but without impacting the overall procedure nor performance characteristics of the method nor acceptance criteria

Example: change of supplier for equipment or reagent

Other examples of changes to non EC ?

Manufacturing

- **Minor change to process equipment documented in module S 2.2 (description of manuf process)**
  - The concerned change is not impacting process performance, clearance of impurities, critical process parameters nor CQAs validated via PPQ (consistency batches) batches; operational ranges documented in S 2.2 could however change due to change of equipment).
  - Examples:
    - Clarification by in depth filtration instead of centrifugation
    - Minor adaptation of buffer composition for purification
    - Clearance of DNA : shift from chromatography on Q sepharose to membrane chromatography (AEX)
    - Replacement of ultracentrifugation to chromatographic step

- **Change in manufacturing parameters not described in module S 2.2 (description of manuf process) but in S 2.5 (process validation)**

ICH Q12- Life cycle change management plan

- **Life cycle management plan = proposal on the reporting category of certain future changes is agreed upon in the initial file or a variation application.**

- E.g. Life cycle plan for frequent manufacturing changes

- Example : proposed as reportable via PQS provided pre-defined protocol with acceptance criteria was agreed upon in initial file
  - extension to life time of purification columns or membrane life times (diafiltration …)
  - changes to working seed, reference standards …