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DANISH MEDICINES AGENCY

Setting Specifications for Biotech Products

Session 1: What to Control?

Presentation by an EU Regulator

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WHAT TO CONTROL?

Product

Control of raw and starting materials

Control of cell substrate & cell bank

Control of process parameters

TOTAL QUALITY CONTROL

Validated manufacturing process

Control of DS and DP (characterization, specification, stability)

Good manufacturing Practice

Process

Safe and Efficacious product
Consistent and stable

Kowid Ho, Afssaps

A control system is mandatory

- GMP, Directive 2003/94/EC, Article 11
  - …Manufacturer shall establish and maintain a quality control system…..

What to control

- Directive 2001/83/EC, Annex 1 – ***Dossier requirements for a MAA***
  - Manufacturing process of the active substance(s)
    - Tests and acceptance criteria carried out at every critical step, information on the **quality and control of intermediates** and process validation and/or valuation studies shall be provided as apropriate
  - Control of the **active substance(s)**
    - Detailed information on the specification used for routine control of active substance(s), justification for the choice of these specifications, methods of analysis and their validation shall be provided.
  - Control of the **finished medicinal product**
    - Detailed information on the specification, (release and shelf life) justification for their choice, methods of analysis and their validation shall be provided

What to control? - ICH Q6B

- **Specification** is defined as a list of tests, references to analytical procedures and appropriate acceptance criteria….
- **Specifications** are chosen to **confirm 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***. The methods are picked from a wide range of methods used during characterisation
- **Acceptance criteria** are set based on data obtained from lots used to demonstrate manufacturing consistency, data from stability studies and data from **batches used in clinical trials**

What to control? - ICH Q6B

- Specifications are **one part of a total control strategy** designed to ensure product quality and consistency. Other parts of this strategy include thorough product characterisation during development, upon which many of the specifications are based, adherence to Good Manufacturing Practices, a validated manufacturing process, **raw materials testing**, **in-process testing**, **stability testing**, etc.
  - The quality of the **raw materials** used in the production of the drug substance (or drug product) should meet standards, appropriate for their intended use.
  - The quality of the **excipients** used in the drug product formulation (and in some cases, in the drug substance), as well as the **container/closure systems**, should meet pharmacopoeial standards, where available and appropriate. Otherwise, suitable acceptance criteria should be established for the non-pharmacopoeial excipients.

What to control? - ICH Q6B

- Specifications are **one part of a total control strategy** …….
  - In-process tests are performed at critical decision making steps and at other steps where data serve to confirm consistency of the process during the production of either the drug substance or the drug product. The results of **in-process testing** may be recorded as action limits or reported as acceptance criteria. Performing such testing ***may eliminate the need for testing of the drug substance or drug product***

What to control? - ICH Q6B

- Since specifications are chosen to **confirm the quality** rather than to characterise the product, the **manufacturer should provide the rationale and justification for including and/or excluding testing** for specific *quality attributes.*
- Generally, the following tests and acceptance criteria are considered applicable to all drug substance and drug product:
  - Appearance and description
  - Identity
  - Purity and Impurity
  - Potency
  - Quantity

Quality Attributes (QA)….!

ICH Q8(R2)

- A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.

- Potential Critical QA (CQA)is identified during development and finally defined at time of Marketing Application
  - How to track levels of CQA's retrospectively if not initially recognized and therefore not monitored?
  - How does new knowledge and/or experience change and/or improve the specification during product life-cycle?

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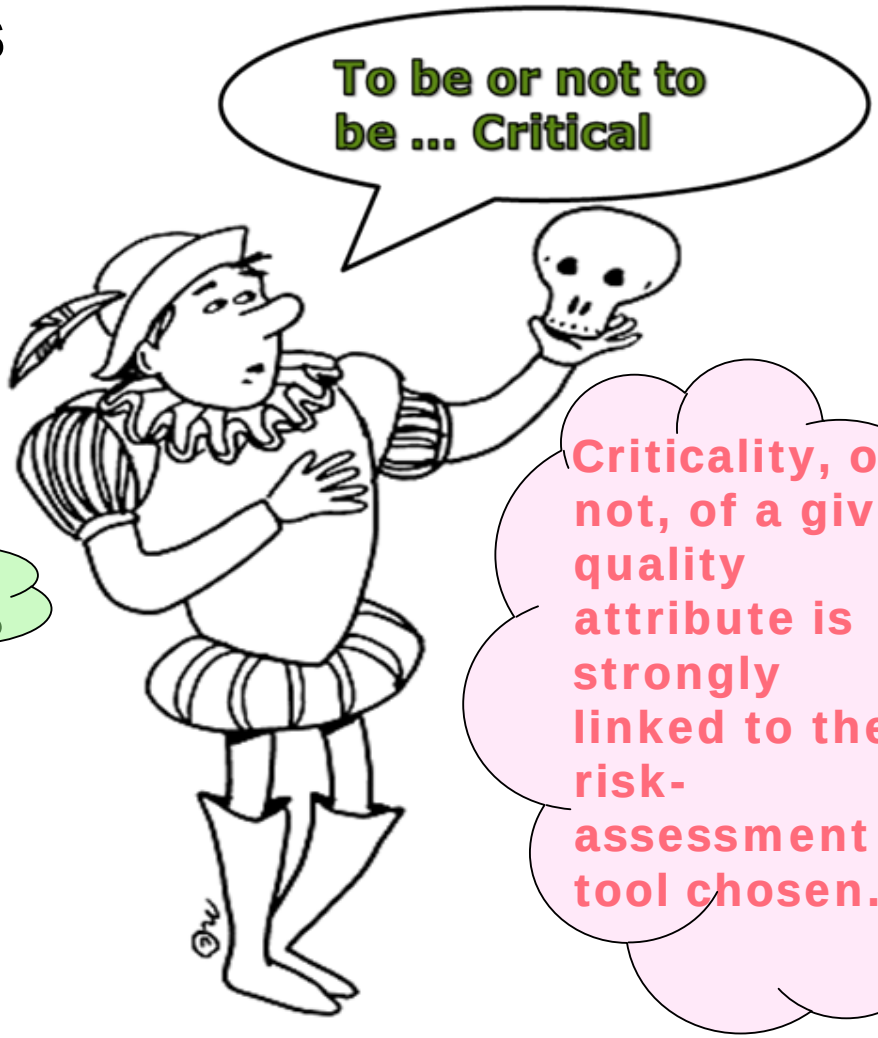
Quality Attributes

Where to draw the line between critical or not ?

Do we need a line ?

What is the most appropriate tools?

Should critical quality attributes “by default” be included in the specification?... Is it always relevant



Criticality, or not, of a given quality attribute is strongly linked to the risk-assessment tool chosen…

Personal view on Risk-Assessment tools:

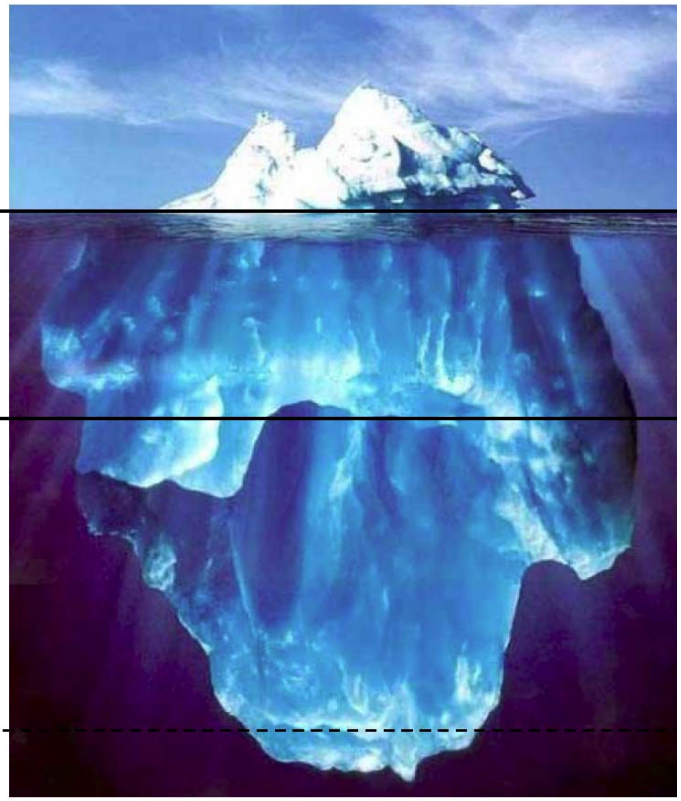
What to control – What to put into the dossier ?

Release Tests (Specifications)

Extended Characterization
(Process & Product)

Process Control
- Procedures
- Materials
- In-process testing
- Monitoring
- Validation

Unknown
Learned over time – update control strategy



Information provided in the dossier for review

Information and knowledge within the Company. Some parts accessible at inspections

from: Koszlowski, S. & Swann, P. (2006) Adv. Drug Delivery Revs.

Is a Minimum Control System needed to safeguard against unpredicted events and to provide consistency measures?

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In-process-, Drug Substance and/or Drug Product control?

- **Protein content**
- **pH**
- **Bioburden**
- **Impurities**
- **Extractable volume**
- **Excipients content**

- **Potency**
- **Glycosylation**
- **Purity – Monomer and Aggregates**
- **Endotoxin**
- **Particulate matter**
- **Sterility**

- **Identity**

Case by Case, - as justified by process development, understanding of process and product relationship, quality risk management and the control strategy applied…….

Thank you for your attention