Medicines & Healthcare products
Regulatory Agency

Process Validation GMP Guideline for Biopharmaceuticals

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Overview

- **Approach to development**
- **Critical Quality Attributes**
- **Control Strategy**
- **Quality Risk Management**
- **Quality by Design**
- **Design space**
- **Multivariant analysis**
- **Process Performance Qualification and process monitoring**
- **Continuous process verification**
- **Guidelines and requirement references**

Outline approach to Development

Q8 and Q11

- **Define Quality Target Product Profile (QTPP)**
- **Define Critical Quality Attributes (CQAs)**
- **Define Manufacturing Process**
- **Define Control Strategy**

QTPP

Defines product characteristics and sets development goals and eventually final product characteristics

Important areas from GMP perspective include:

- **Quality characteristics: sterility, purity etc. (including specific safety-related impurities where necessary)**
- **Pharmacokinetic characteristics: dissolution etc.**
- **Shelf life**
- **Stability**
- **Dosage form**
- **Route of administration**
- **Primary/secondary packaging**

CQAs

- **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. (ICHQ8 & Q11)**

Desired product quality?

- **Safe and efficacious (positive benefit/risk ratio)**
- **Addresses the Quality Target Product Profile (DP)**
- **Encompasses prior knowledge**

CQAs

- **A CQA ≠ a range; an attribute is critical or it is not**
- **Cannot assume that properties/characteristics used in the DS/DP specifications for clinical trials are the CQAs at MAA**
- **Dismissing properties/characteristics that are difficult or resource-intensive to measure**
- **When a CQA is controlled it does not stop being critical; risk ≠ criticality**

Define a control strategy (to ensure process performance and Drug Substance/Product quality)

- **The traditional approach** – it was made like this for pivotal clinical trials, we may not know what different quality variants do or why they vary, but it can be made in the same way with the same variants in the same proportions.
- **The enhanced approach** (Quality by Design)
- Addresses the sources of variability - a control strategy spans all the key factors that affect product quality and its consistent production e.g. input materials, specs, controls, IPC or RTRT through measurement and control of CQAs during manufacture plus a monitoring programme based on developments studies and/or manufacturing knowledge.
- Effects on CQAs of sources of variability are examined, ranked and controlled

Design Space

- 'The multidimensional combination and interaction of input variables (e.g. material attributes) and process parameters that have been demonstrated to provide assurance of quality.'
- Design Space may allow changes without Post Approval Variations

Quality Risk Management

QRM (Q9) – cycles of identification and assessment of risk followed by control of risk.

Q8 – *'Quality risk management can be used to prioritize the list of potential CQAs for subsequent evaluation.'* ≠ Rank identified CQAs

Q8 – *'Relevant CQAs can be identified by an iterative process of quality risk management and experimentation that assesses the extent to which their variation can have an impact on the quality of the drug product.'*
≠ If it doesn't affect measurable potency it isn't critical.

- **Use information from development studies regarding clinical significance of quality attributes and the ability to control them during processing to 'decide' whether risks are adequately controlled or further control is necessary**

Quality Risk Management

- **Quantifying the knowns based on data evidence**
- **Quantifying the unknowns (severity, likelihood) and agreeing that residual risk is acceptable**

Observation►theory ► test ► analyse ► data does/does not support theory.

Easier to go straight to the conclusion that something isn't critical or it doesn't need controlling

……but not recommended!

Traditional and QbD

Successful submissions are clear on:

- **how deviations from critical and non-critical controls will be handled**
- **how the acceptable limits have been derived**

And additionally for QbD

- **correlations between process parameters and CQAs; if a process parameter affects a CQA it's a CPP**
- **which process step(s) a design space is claimed for**
- **univariate experiments►Proven Acceptable Ranges; multivariate experiments► Design Space; theoretical models; Design of Experiments**

Design Space Issues

Multiple univariate experiments ≠ multivariate experiments

Upstream

- **small scale real-time measurements relatively easy; limitations on production bioreactors sensors and sampling make it difficult to demonstrate extrapolation to production scale**
- **very large number of variables to examine in multivariate experiments**

Downstream

- **extent of experiments to demonstrate viral clearance capacity of chromatography steps is acceptable throughout the design space and design space is applicable throughout column life**
- **capacity to demonstrate that a series of steps with design spaces generate a consistent product**

Examples of multivariant inputs-Upstream

- **Master cell/seed bank storage preparation**
- **Working cell/seed bank preparation (number of passages etc)**
- **Incubation temperatures, pressures, DO, pH**
- **Growth media**
- **Growth rate**
- **Volume**
- **Harvesting (filtration, centrifugation etc)**

Examples of multivariant inputs-Downstream

- **Storage conditions of intermediates**
- **Chromatographic conditions, packing type, supplier, loading, buffers, pH, flow rates, bed heights, maximum number of cycles, storage of column, sanitisation of column, method of detection, temperature.**
- **Bioburden loads of filters, filter types, suppliers**
- **Viral removal steps, pH, filtration etc**

Process Performance Qualification

Provides proof that the process is well controlled and establishes a baseline for future process evaluation. It is dynamic.

The established process will require monitoring.

Process Monitoring and Evaluation

Short term

- In process controls (starting materials through to bulk final product)
- Release criteria (finished product specification)

Long term

- Continuing process verification

Continuous process verification

- **Can be used where a QBD approach has been used to develop product and the established control strategy provides assurance of product quality.**
- **The verification process must be defined and should be a scientifically based control strategy for all required attributes including: starting materials, CTAs and critical process parameters.**
- **There should be regular evaluation of the control strategy to ensure continued fit for purpose.**
- **All other requirements for process validation should be followed (Annex 15 5.1 – 5.14)**
- **Ongoing process verification during product life cycle is also required.**

Ongoing process verification

- **State of control must be demonstrated through out life cycle of the product.**
- **Process trends evaluated.**
- **The frequency of ongoing process verification should be periodically reviewed.**
- **Conducted under an approved protocol**
- **Statistical analysis of outcomes to demonstrate variability and capability of a given process.**

Hybrid approach to PV

- **A hybrid of traditional approach to validation and CPV can be used where there is a substantial amount of knowledge and understanding of the product and process gained from historical batch data and manufacturing experience.**

- **It is possible to use this approach for validation activities after or during ongoing process verification even if the product was initially validated using traditional process validation.**

Application to ATMPs

- **Could be used in instances where process is exactly the same but product is different.**

For example homogenic treatment for individual patients where the processing of material is the same (stem cells, antibodies etc)

- **Must be a detailed risk assessment in place and a robust control strategy that has been proven to ensure that the products are of appropriate quality, safe and efficacious.**

Note that as yet no full QBD biotechnology product has been inspected by MHRA.

Summary

- **Possible to apply subsequent CPV after tradition validation process**
- **Possible to use QBD but will initially be very expensive due to multivariant analysis at outset**
- **Control strategies must be robust**
- **Risk assessments are key at outset.**

ICH Guidance and GMP References

Q8 Pharmaceutical Development (CTD 3.2.P.2)

Q9 Quality Risk Management (3.2.P.2 & 3.2.S.2.6)

Q10 Pharmaceutical Quality Systems (? 3.2.P.2 & 3.2.S.2.6)

Q11 Development & Manufacture of Drug Substances (3.2.S.2)

Q12(draft) Lifecycle Management

Eudralex Volume 4 Annex 15

- Q8, 9 & 10 were intended to be implemented together
- Q8 & 11 include that traditional development approaches are still acceptable, but enhanced approaches, i.e. QbD based on sound scientific principles could provide more scope for manufacturing efficiency and flexibility

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