Change control

– change of Material source
– specifications
– other considerations

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Change control objective

To administer a change in Material(s) and/or manufacturing process but maintaining the integrity, performance, safety and efficacy of the existing product.

Changes and control

Covered by Regulatory/Product application and Inspectorate/GMP.

Interaction with both Sections required.

Reasons

Material/components manufacturer supply shortages or shortcomings.

Cost ie cheaper

Other.

Financial consequences

Cost of Materials.

Cost of introducing, validating and approving changes.

Timing

Urgent to maintain supply of essential medicines supply.

At comparative convenience.

Stakeholders/coordination

Purchasing/logistics/Inventory, financial, QA, Production, Regulatory.

Must be in constant communication and document decisions.

cGMP PE009 requirements

TGA interpretation September 2020 - https://www.tga.gov.au/resource/pe009-pics-guide-gmp-medicinal-products

Change control applies to all GMP-related activities (p17)

It is an existing expectation that change control does not just apply to validation activities, but to all GMP-related activities undertaken by a manufacturer.

cGMP PE00914 requirements

Pharmaceutical Quality System

1.4 (xii) Arrangements are in place for the prospective evaluation of planned changes and their approval prior to implementation taking into account regulatory notification and approval where required;

(xiii) After implementation of any change, an evaluation is undertaken to confirm the quality objectives were achieved and that there was no unintended deleterious impact on product quality;

cGMP PE00914 requirements

Validation

5.25 Significant amendments to the manufacturing process, including any change in equipment or Materials, which may affect product quality and/or the reproducibility of the process, should be validated.

cGMP PE00914 requirements

5.29 The supply chain and traceability records for each active substance (including active substance starting Materials) should be available and be retained by the manufacturer of the medicinal product.

Material/components supply changes

Within existing specifications.

Requiring adjusted specifications.

Distinguish manufacturing source and supplier - may or may not be the same.

Material Specifications

Required for safety, efficacy and performance.

Basic foundation to assess changes.

Material Specifications

Do existing specifications cover important parameters in assessing change?

Formal specifications, particularly Pharmacopeial, may not cover critical parameters for your product. This applies particularly for physical attributes.

Material Specifications

Term “Specifications” is defined in ICH Q6 as:

A specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described.

Material Specifications

Specifications are a critical parameter of "**Control Strategy**" systems and outcomes.

also of

"**Critical Quality Attributes**" in ensuring safety, efficacy and consistency of product performance across batches and throughout their shelf lives.

Material Specifications

"Specifications" are used for routine batch test requirements, although ***the other characteristics are still expected to be consistent and compliant***.

As well as specifications, CQA cover ***non-routine*** characteristics and properties, which are critical parameters of "Control Strategy" eg NMR & MS identification, crystallography etc.

Material Specifications

Term “Critical Quality Attributes” for API is defined in ICH Q11 as:

“A CQA is 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.”

Specifications

Recommended reading Q11

https://www.ema.europa.eu/en/documents/scientific-guideline/draft-ich-guideline-q11-development-manufacture-drug-substances-chemical-entities-biotechnological/biological-entities_en.pdf

API/Excipient
Physical Properties

Appearance (Colour, particle description etc)

Solubility (Detailed)

Hygroscopicity

Crystal properties (Polymorphic forms, different crystalline forms, solvation or hydration products and amorphous forms)

Particle size, type & distribution

Bulk and tap density

API/Excipient
Physical Properties

These have a direct effect on Formulated Product at one or more of manufacturing steps, active rate of release from Product and (later) stability parameters.

Such parameters affect process validations.

eg in manufacture:

- Preparation steps of solutions
- Wet and dry granulations

API/Excipient Physical Properties

and in subsequent product performance:

- ***change in dissolution profiles of tablets and capsules***
- emulsion characteristics & performance
- suspension characteristics & performance
- change of solubilising characteristics in lyophilised injections for reconstitution

Specifications
Packaging

Packaging must ***ensure sealing integrity throughout shelf life*** ie be impermeable and perform and protect the Product under storage in low and high humidity, especially under bathroom and refrigerated conditions.

Specifications of packaging Materials and packaging design must enable fulfilment of these objectives.

Test Methods

Are these capable of achieving meaningful comparative data which differentiates any existing differences before and after?

Evaluation processes - new Materials ‘

Manufacture x number of batches of y batch size(s).

Evaluate for specification conformance/deviations and product performance.

Commence stability trials.

External factors

Changes by service providers - eg test laboratories.

Changes required by contractors.

Changes required by Inspectors or auditors.

External factors

Reliability of new source - especially if re-located to a new country - short & long-term consequences,

Change of management/ownership of source.

External factors

Source needs to advise of any changes to manufacturing processes of product ingredients and components for end-users' assessment.

This requires a close working relationship.

Final points

Purified natural products can be more variable than synthesised, especially from different sources.

Consider long term consequences in identifying a source.

Final points

Existing specifications do not necessarily cover parameters that determine equivalence.

Change of supply – combination of in-house, Regulatory, QA and Production and Authority Regulatory and Inspectorate.

Final points

Personal view - once a product is developed and registered, change of source of Materials is a last resort and requires careful consideration.