Macedonian pharmaceutical bulletin, 68 (Suppl 1) 161 - 162 (2022)
Online ISSN 1857 - 8969
*DOI:*10.33320/maced.pharm.bull.2022.68.03.076
Short communication

Cleaning validation concept for introduction of product with new active pharmaceutical ingredient in pharmaceutical production

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Introduction

Equipment cleaning is a critical step in the manufacturing process of different pharmaceutical products, especially in shared facilities (EMA, 2014). The cleaning process must prevent cross contamination and reduce residues from previous product to levels that ensure patient safety and regulatory compliance.

Cleaning validation is documented evidence that an approved cleaning procedure will reproducibly remove the residues from the previous product and other residues from equipment surfaces below scientifically established acceptance criteria (ISPE Guide, 2020). Cleaning validation should be properly documented to demonstrate current Good Manufacturing Practice (cGMP) for finished medicinal products.

Introduction of medicinal product with new active pharmaceutical ingredient

Change Control Process

Upon introduction of product containing new active pharmaceutical ingredient (API) in a shared facility in ALKALOID AD Skopje, the activities are documented by an effective change control process within the Quality management system to provide a high degree of knowledge of all necessary activities.

In order to evaluate, approve and implement the new API properly, the proposed change is evaluated by expert team contributing the appropriate expertise and knowledge. The evaluation assesses the level of risk the new API presents regarding cross contamination and whether it can be controlled with appropriate organizational and technical measures. After implementing the change, additional assessment is performed to ensure that there are no adverse effects regarding the products and/or the quality system.

Methodology for risk assessment

Risk identification in the manufacturing process of different medicinal products in shared facilities is a challenging task. Product grouping and worst-case identification is performed to reduce cleaning validation activities in sites with multiple products and processes. The worst-case product is identified by risk assessment considering relevant and scientifically justified criteria. Equipment must be cleaned using validated cleaning procedure based on worst-case product cleaning parameters.

Before introduction of a new API in the production facility, a reevaluation of the risk assessment is performed, in order to characterize the degree of criticality and the specific requirements for API with highly sensitizing or genotoxic potential.

When a new API is introduced, the risk assessment matrix for worst-case determination is updated and:

– If the API is a new worst-case according to the risk assessment matrix, a cleaning revalidation is performed, with the new worst-case product.
– If the new API is not a worst-case according to the risk assessment matrix, the cleaning procedure is confirmed with the applicable methods for cleaning verification.

Assessment criteria

New API evaluation is based on a risk assessment

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matrix in which three main criteria of the active substance and the finished product are evaluated:

- Toxicological profile (PDE value);
- Solubility;
- Difficulty of cleaning;

For each of the three criteria initially the raw data records are collected. Then each raw data is assigned with index number according to defined evaluation scale. In the evaluation scale, a higher index number indicates a worse scenario for each criteria. Multiplication of the obtained index numbers, gives the risk priority number (RPN) for each product and the highest RPN is derived. The highest RPN indicates the "worst-case product" for cleaning validation.

Toxicological profile criteria (Permitted Daily Exposure, PDE)

This toxicological profile criteria is taking into account the requirements of EMA's "Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities" (EMA, 2014). Worst-case identification depending on the Permitted Daily Exposure (PDE) is health based data. The PDE value represents a substance-specific dose that is unlikely to cause an adverse effect if an individual is exposed at or below this dose every day for a lifetime.

The criteria for determination of PDE is described in the toxicological report and includes: physico-chemical characteristics; mechanism of action; dosage and efficacy; pharmacokinetic data; toxicological and critical effects (genotoxic, carcinogenic, reproductive or developmental effects); Upper limit of No Observed Adverse Effect Level (NOAEL) and safety factors for variability among the available data (F1-F5).

PDE reports are prepared by certified toxicology professionals.

PDE values take into consideration all routes of administration of the specific active substance. If several critical effects are identified and they result in calculation of more than one PDE value, the lowest value for PDE is considered for the risk assessment. If the product contains more than one API, the active substance with the lowest PDE value is considered for the risk assessment. When a PDE report for a particular API is updated, reevaluation of the risk assessment for worst-case is performed.

Solubility criteria

Solubility evaluation is based on the rationale that any product less soluble in water, is more difficult to clean. Solubility of the API and the finished product is tested in water, in alkaline and acidic pH environment, according to pH of the detergents in standard cleaning procedures.

Based on a solubility report, each product is assigned with a specific index number, where a higher index number indicates less soluble product. If the product contains more than one API, the active substance that is least soluble in water is considered for the risk assessment.

Cleanability criteria

Cleanability criteria depending on the formulation is based on the rationale that the finished product contains excipients which are responsible for the equipment and the API from the equipment being more difficult to clean. Each product is evaluated individually in context of its own formulation, for having some of the following components:

- Prolonged/Extended release technology;
- Excipients prone to microbiological growth;
- Colored API or other pigments;
- Aromas (flavors);
- Viscosity increasing agents;
- Insoluble parabens as preservatives;
- Granulate for suspension vs. granulate for tablets;
- Solution vs. suspension;
- Tablets vs. film-coated tablets;
- Frequency of production;

Each product is assigned with an index number, where a higher index number indicates a combination of one or more critical cleaning components.

Conclusion

In conclusion, when introducing a product with new API in pharmaceutical production, the worst-case approach for cleaning validation is used. Both active substance and the finished product are assessed. This is performed by risk assessment in which the relevant and scientifically justified criteria are evaluated.

References

EMA, 2014. Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities EMA/CHMP/CV MP/ SWP/169430/2012. European Medicines Agency 2014, 30 Churchill Place, Canary Wharf, London E14 5EU, United Kingdom.https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-setting-health-based-exposure-limits-use-risk-identification-manufacture-different_en.pdf

ISPE® Guide (2020) Cleaning validation lifecycle - Applications, Methods and Controls. The International Society for Pharmaceutical Engineering, 6110 Executive Blvd. Suite 600, North Bethesda, MD 20852, United States. https://ispe.org/publications/guidance-documents/guide-cleaning-validation-lifecycle-applications-methods-controls#