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Review Article

Modern cGMP Requirements for Cleaning Validation and Drugs Toxicological Evaluation

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Abstract

The GMP regulation for cleaning validation in the APIs and pharmaceutical plants has been revised in these last years, introducing Quality Risk Management concepts and a science-based toxicological evaluation.

In particular, the ISPE guideline "Risk-Based Manufacture of Pharmaceutical Products - A Guide to Managing Risks Associated with Cross-Contamination" introduced the concept of ADE (Acceptable Daily Exposure), while the EMA "Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities", introduced the approach based on PDE (Permitted Daily Exposure).

These concepts have now been implemented in the revised EU GMP Annex 15 for cleaning validation.

The article will cover these recent toxicological approaches for drugs toxicity evaluation and cleaning validation activities, taking into account also the necessary considerations based on REACH regulation and Safety and Environment requirements for pharmaceutical facilities.

Keywords: GMP; Cleaning Validation; ADE (Acceptable Daily Exposure); PDE (Permitted Daily Exposure)

Introduction

A scientific and risk-based approach is the modern cGMP requisite for cross contamination risk management in the production facilities. The recommended methodologies are the ones prescribed by ICH Q9 guideline for Quality Risk Management, the revisions of Chapter 3 and 5 of EU GMP and the EMA guideline EMA/CHMP/CVMP/SWP/169430/2012 "Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities" [1].

A possible practical approach is recommended by ISPE Baseline Vol. 7 (Risk-Based Manufacture of Pharmaceutical Products - A Guide to Managing Risks Associated with Cross-Contamination) [2], that reports considerations and methodologies for an adequate balance between product quality and operators safety. This guideline prescribes the adoption of proper risk control strategies, to be designed and evaluated case by case, in order to guarantee product quality and patients safety.

A toxicological risk evaluation should be included in the control strategy, taking into account that general assumption that risk cannot be completely deleted, but it should be mitigated and taken under control.

In particular, the proposed approach is designed for "multi-purpose facilities", where different products can be worked, provided that all the necessary measures for risk evaluation and control are taken, focusing on a correct management of cleaning validation activities.

Certain product residuals could remain on the production equipment surfaces (product direct or indirect contact) after cleaning and, therefore, they could be a significant risk for patients' health. A scientific and risk-based approach for the evaluation of these residuals should be adopted, in order to properly evaluate and control the related risks.

The cleaning procedures should be designed in order to minimize the risks related to product residuals and to reduce these

contaminants up to predetermined acceptable limits, based on the toxicological risk evaluation performed on these compounds.

A proper toxicological evaluation of products residuals, with parameters such as the ADE (Acceptable Daily Exposure) or PDE (Permitted Daily Exposure) values, as suggested by the cGMP guidelines, is the basis for a scientific and risk-based rationale to be provided for risk management.

Definition of acceptable limits

Active ingredients present specific risks related to their biological (pharmacological or toxicological) effects. The parameters related to such risks to be evaluated are:

- The dose-response relationship
- The exposure level
- The absorbed quantity.

The basic principle is that if the exposure to an active ingredient is maintained within acceptable limits which have been evaluated and considered as safe, there will be a low risk of adverse events for individuals exposed to such substance.

In the last years many different approaches and criteria have been recommended in order to establish safety levels for chemicals exposure, taken from pharma as well as from food and chemical industries. Considerations related to active ingredients, impurities, food additives or occupational or environmental parameters have been provided.

The ICH recommended the application of PDE (Permitted Daily Exposure) values for the evaluation of residual solvents in the pharmaceutical products. More recently, the PDE criteria have been introduced in the EMA guideline EMA/CHMP/CVMP/SWP/169430/2012 "Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities" [1], and the revised Annex 15 "Qualification e Validation" of EU GMP [3].

The CHMP (European Medicines Agency Committee on Human Medicinal Products) published a guideline for the determination of limits for genotoxic impurities in the pharmaceutical products.

Finally, the US EPA (Environmental Protection Agency) established reference doses and concentrations for chemical emissions in water and air.

Examples of OEL, Occupational Exposure Limits, include:

- OSHA Permissible Exposure Levels (PELs)
- ACGIH Threshold Limit Values (TLVs)
- AIHA Workplace Environmental Exposure Levels (WEELs)
- UK HSE Workplace Exposure Limits (WELs)
- German AGW e MAK Values
- EC SCOEL Indicative Occupational Exposure Limit Values (IOELs).

The health-related end-points evaluated with these methodologies permit to establish acceptable risk limits.

For effects related to target organs or other non-carcinogenic effects, specific safety factors should be applied, such as "uncertainty factors, assessment factors or chemical-specific adjustment factors". These factors should be applied for No-Observed-Adverse-Effect Levels (NOAEL) of the critical end-points, in order to establish safe exposure levels.

It is important to remember that the patients' critical effects may be different from the ones of the production operators, due to the different way of exposure to the substances.

The toxicological evaluation through PDE (Permitted Daily Exposure) or ADE (Acceptable Daily Exposure) considers the parameters previously described. The more the exposure is below the established limits and the higher is the safety margin.

The methodology suggested by ISPE guideline for ADE (Acceptable Daily Exposure) application is similar to the PDE (Permitted Daily Exposure) approach prescribed by the EMA guideline EMA/CHMP/CVMP/SWP/169430/2012 "Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities" [1].

The evaluation of the critical effects should be applied for the ADE/PDE calculation. Generally, the critical effects should be based on studies performed on the same administration/exposure route used for ADE/PDE calculation. Data extrapolated from different administration/exposure routes could be also taken into account, with proper correction factors.

An exposure below the No-Observed-Adverse-Effect Level (NOAEL) for the critical effect should not lead to other effects which may appear at higher doses.

Determination of No-Observed-Adverse-Effect Level (NOAEL) or Benchmark Dose (BMD)

For many toxicological end-points, there is a clear dose-response relationship for the critical effect. The aim is to define the No-Observed-Adverse-Effect Level (NOAEL) for the critical effect, that can be used for ADE/PDE calculation.

The Lowest-Observed-Adverse-Effect Level (LOAEL) is the dose at which a significant adverse effect is first observed.

Effects observed below the NOAEL/LOAEL values should be not considered as significant. The application of uncertainty and correction factors for ADE/PDE calculation, permit to make the occurrence of further undesirable effects related to the products extremely unlikely.

In some cases, it could be not possible to define the NOAEL for some toxicological data set, therefore it could result necessary to calculate the limits by using the LOAEL. A Benchmark Dose (BMD) approach may be applied in some cases.

The BMD is a value, equivalent to NOAEL, mathematically calculated from the evaluation of the dose-response curve related to the critical effect.

ADE (Acceptable Daily Exposure) or PDE (Permitted Daily Dose) calculation and application of uncertainty factors

Health-based exposure limits, such as the ones based on ADE or PDE parameters, may be established considering the NOAEL for the critical effect (after adjustment for body weight) divided by some uncertainty and correction factors.

The NOAEL value is typically derived from key studies on a limited population of animals or humans.

The ADE or PDE value, which may be used for the determination of acceptable limits (MACO, Maximum Allowable Carry-Over) for cleaning validation studies, considers a whole range of uncertainty and adjustment factors, which take into account the fact that NOAEL values are determined on specific sub-populations and studies and, therefore, constitute an additional safety factor for risk control.

Some uncertainty and adjustment factors to be considered are the following ones:

- UFH = Intra-species Differences (Inter-individual Variability): it takes into account the variability between the considered sub-populations. An uncertainty factor of this type can be used to adjust NOAEL values, derived from animal subjects, for human application. A default value for this uncertainty factor of 10 is typically used in the absence of specific chemical data.
- UFA = Interspecies Differences: this uncertainty factor is used to extrapolate NOAEL (or LOAEL) derived from animal studies, for application to human sub-populations. A commonly used approach is to apply allometric scales, resulting in scaled values from 2 to 12, when extrapolated from various species, due to the difference in the body surface/volume. The US FDA guideline on "Setting doses in initial clinical trials" includes specific species extrapolation factors.
- UFS = Subchronic-to-chronic Extrapolation: when the duration of the study used to identify the critical effect is different from the possible exposure scenario, additional adjustment factors should be used. The evaluation of a large number of toxicological studies suggests the application of a factor 3 as a sufficient risk mitigating factor that a lower NOAEL value can emerge with long-term studies.
- UFL = LOAEL-to-NOAEL Extrapolation: when only LOAEL data are available from a key study for the determination of the critical effect, a dose benchmark must be calculated to extrapolate a dose-response curve or, in the absence of better data, a factor 3 should be applied to extrapolate the NOAEL values from those of LOAEL. This value results from an estimate and evaluation of a large number of toxicological studies and it is considered generally sufficient to mitigate the risk.
- UFD = Database Completeness: an additional uncertainty factor may be required if the global toxicology database is incomplete, for example if no developmental and reproductive toxicity studies have been performed. This factor intends to take into consideration the possibility of finding a lower NOAEL value once these studies have been performed. Available data suggest the application of the value 3 for this factor.
- MF = Modifying Factor: this factor may be required if it is necessary to evaluate elements not taken into consideration by other factors. This factor also allows expert evaluators of the toxicology database to provide a global assessment and assessment. Factors from less than 1 to 10 are applied in these cases.
- PK = Pharmacokinetic Adjustment(s): in some cases, "route-to-route" extrapolations may be appropriate, when it is intended to derive the calculation of the ADE/PDE from a specific route of administration/exposure, for which the available data are different from the ones for the case in exam. Such

extrapolations may be useful to provide adequate protection measures in certain situations. Such adjustments may be necessary when occupational exposure limits are established.

- Additional Factor(s): Additional factors may be necessary, for example, in the case of bioaccumulation due to repeated exposures. For compounds with long elimination half-lives, blood levels increase with continuous exposures until they reach a steady state. The ADE/PDE values established using NOAELs derived from short-term studies may require a downward adjustment of a factor corresponding to the ratio between the blood level relative to a short-term study and the level of the steady state achieved with a study of long duration.

The previously described uncertainty and adjustment factors represent current methodologies commonly applied and supported by scientific rationale. For products that do not present a carcinogenic risk, generally these factors are applied for the parameters previously considered, which are considered sufficiently protective and with a high degree of confidence.

During the development of new products, a whole series of pharmacokinetic and pharmacodynamic data are generated, which can be used to determine factors that appropriately quantify the different inter-individual and interspecies.

For certain categories of compounds (for example, genotoxic compounds), the dose-response curve is considered to be linear at low doses and the assumption is that there is no threshold value below which no adverse effects may be present. This is based on the principle that even a single change in DNA can cause a mutation and a possible tumor. For these cases, a different end-point and safety factor approach must be applied.

An alternative risk-based methodology for the situation described above, involves establishing acceptance criteria for genotoxic compounds, based on one-dose extrapolation that corresponds to a minimum level of risk. The use of linear extrapolation methods is a company choice and must be based on validated methods. EMA (Muller., *et al*. 2006) recommends establishing acceptability levels for genotoxic impurities by assuming 1/100,000 tumor as acceptable, based on a risk/benefit analysis for the patient. Using this intake, a daily dose of 1.5 micrograms/day for a lifetime exposure should be allowed. Higher levels may be acceptable for longer-term exposures. BMD software can be used for tumor model data to extrapolate acceptable risk levels.

The effect of potential sensitization (for compounds other than beta-lactam antibiotics, for which the Regulatory Agencies require dedicated facilities), must be included in the toxicological end-points considered for the determination of ADE/PDE values. For some types of sensitizers, a non-sensitizing dose can be defined and this NOAEL can be used to determine ADE/PDE using a "safety factor" approach.

Determination of "health-based" limits and safety thresholds

Cleaning validation activities require the definition of acceptability limits. Currently, arbitrary limits such as 1/1000 of the minimum therapeutic dose or 10 ppm in a batch are commonly used. Appropriate safety margins should be considered when defining limits, therefore these "old" approaches may be too restrictive or not enough safe and not based on toxicological considerations.

The "cleaning safety margin" is defined as the distance of the obtained cleaning data from the acceptability criterion. The greater the distance, the more secure the data are.

In the following figure (Figure 1), the relation between acceptability limit, cleaning data and LOD (Limit of Detection) of the method is shown. There must be a clear separation between the obtained cleaning data and the limit of acceptability, indicated with the arrow as a "margin of safety".

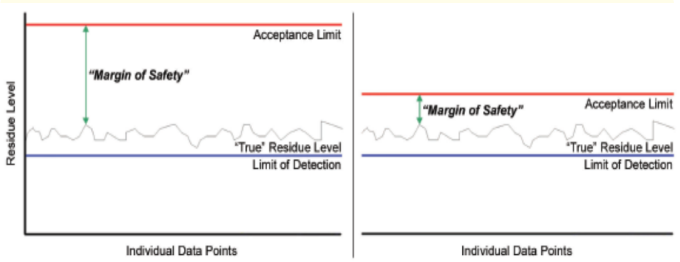

Figure 1

The result of applying additional safety factors to the limits of acceptability can be seen in the figure on the right, where the "margin of safety" is significantly reduced, without any improvement on the other data. In both cases, the patient is exposed to the same level of residues. If the original acceptability criteria were sufficiently secure, the adoption of more restrictive criteria did not lead to greater safety for the patient, but only to an increased risk of failing cleaning validation, with the possible imposition of expensive and unnecessary corrective measures.

In the following figure (Figure 2) it is shown graphically how a better optimization and development of the cleaning process can lead to an increase in the "safety margin", with a lowering of the found residual levels and, in parallel, an improvement of the analytical method with a lower value of LOD.

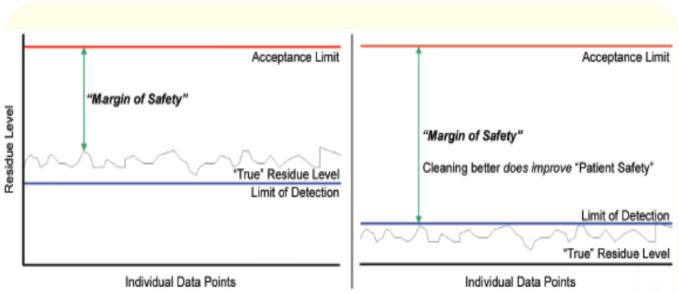

Figure 2

Establishing the acceptability criteria with a health-based approach based on ADE/PDE can offer various improvements. The values of ADE/PDE are derived from toxicological and not simply dose-related assessments. When adequate data are available, all appropriate safety factors are already included in the calculation of ADE/PDE values, which therefore constitutes an appropriate level of safety for cleaning residues. From an operational point of view, the ADE/PDE value make it possible to establish the true "safety margin" when evaluating data in the cleaning validation activities.

The reproducibility of cleaning processes must therefore be evaluated against health-based limits derived from ADE/PDE. Once the cleaning process development studies have been completed, the appropriate "Statistical Process Control" studies must be carried out.

The following figure (Figure 3) shows how the cleaning residual data can be evaluated with the ADE/PDE criterion and as "Process Control Limits" can be derived from such data, using an appropriate Process Capability methodology (e.g. Ppk index).

As previously discussed, the current criteria of 1/1000 minimum clinical dose (Lowest Clinical Dose, LCD) or 10 ppm, for the determination of the limits for cleaning validation, do not always provide adequate protection, especially for compounds such as hormones and antineoplastic agents. In any case, for many compounds these "traditional" approaches still allow to obtain limits with adequate safety margins.

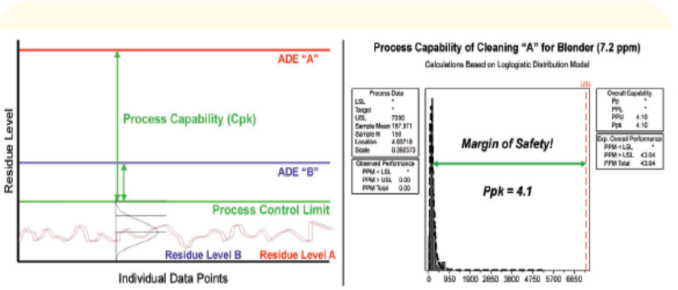

Figure 3

The calculation of Safe Threshold Value (STV) limits and thresholds derived from the values of ADE/PDE, can assist in the quantitative determination of the product cleaning profile and therefore for the necessary considerations for the production possibilities in multi-purpose facility with appropriate measures or with dedicated equipment [4-8].

Conclusions

The GMP regulation for cleaning validation in the APIs and pharmaceutical plants has been revised in these last years, introducing Quality Risk Management concepts and a science-based toxicological evaluation.

In particular, the ISPE guideline “Risk-Based Manufacture of Pharmaceutical Products - A Guide to Managing Risks Associated with Cross-Contamination” introduced the concept of ADE (Acceptable Daily Exposure), while the EMA “Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities”, introduced the approach based on PDE (Permitted Daily Exposure).

These concepts have now been implemented in the revised EU GMP Annex 15 for cleaning validation.

These modern approaches for drugs toxicity evaluation and cleaning validation activities permit to provide adequate scientific and risk-based rationale for cross contamination risk management in the production facilities.

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