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Annex 15 Qualification et Validation
Chapter 10 Cleaning Validation
GMP Practical Guide

G.I.C.
VALIDATION DU NETTOYAGE

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Foreword

With the implementation of the new Annex 15 of the Eudralex European GMP guidelines volume IV in October 2015, the cleaning validation process took on an entirely different dimension in the context of our production activities. Eight paragraphs were added to Chapter 10 which is dedicated to this subject and this represents a major regulatory change!

These modifications have raised many questions on our industrial sites with respect to the practical application of all these paragraphs.
Let us take the PDE value (Permitted Daily Exposure) for example: "How do we find the source data to calculate this value? Should it be based solely on toxicological studies? How is this value calculated? Is there an obligation to call on a Expert CV toxicologist to calculate this PDE?
All attention is focused on this PDE value and its practical application described in the EMA guideline of 2014 "*Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities*".

Nevertheless it is important to mention the following point: beyond the PDE, for which for the following draft document, published by the EMA in January 2017, specified when calculation of this value is obligatory or not *(Questions and answers on implementation of risk based prevention of cross contamination in production* and *Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities)*. It remains the case that all the other points in Chapter 10 are to be applied and incorporated in your cleaning validation strategies.

The 15 paragraphs of Chapter 10 of Annex 15 are complex to interpret. They should serve as a reference for several production areas (sterile and non-sterile medicinal products in the human health sector, biotechnologies, veterinary industry) and can serve as reference for other industrial sectors such as cosmetics and medical devices. In these conditions, it seemed to us opportune to create a working group on the subject, the most comprehensive group possible, composed of producers and suppliers, with a maximum number of industrial sectors represented. In this way the GIC A3P VN came into existence on September 26, 2016.

The objective of this GIC was to provide you with a guide to the interpretation and practical application of the points in Chapter 10 of Annex 15 of the European GMP guidelines. Through this work and our highly informative discussions, we have been able to assess all the difficulties encountered in our organizations regarding the definition and setting up of cleaning validation strategies. This is why we wished to develop a guide for you that is as pragmatic as possible, which does not claim to be the only solution but the most complete working tool possible to help you define a cleaning validation strategy that takes account of the specific features of each of your organizations.

We thank the A3P Association for having believed in us and for having allowed us to carry out this work under excellent conditions.

§10.1 : "Cleaning validation should be performed in order to confirm the effectiveness of any cleaning procedure for all product contact equipment."

Cleaning validation should check the reproducibility and effectiveness of cleaning processes. It therefore ensures the robustness of the cleaning process.

Cleaning validation is dependent:

- on the products (finished product, raw materials, intermediate products of production),
- on the equipment,
- on the processes (manufacturing process and cleaning process),
- on the environment.

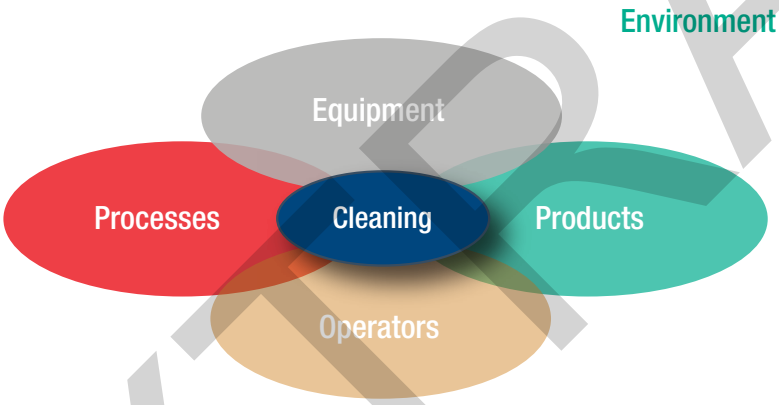

Figure 1: Scope of the cleaning validation

The scope of cleaning validation should include the surfaces of equipment which present a contamination risk for the following product.

Above and beyond the notion of product contact, the following points must be taken into account to define the scope of the validation:

- **The risk of contamination by a product residue (Cross Contamination):** transfer of an ingredient used in the production of product A to product B.
- **Risk of microbiological contamination:** risk of proliferation of microorganisms (for example during DHT) and the presence/generation of endotoxins.
- **The risk of contamination by cleaning and/or disinfection agents:** risque de retrouver des composants utilisés dans le procédé de nettoyage.
- **Risk of contamination by the environment** (during CHT)**:** Risk of contamination by the environment (during CHT):

Elements which present an identified risk of contamination, in direct or indirect contact with the product, should be included in the scope of cleaning process validation.