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Cleaning Validation of a Multipurpose Plant for Active Pharmaceutical Ingredient Bulk Production

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Abstract: One of the key issues in the manufacture of active pharmaceutical ingredients in multipurpose non-dedicated equipment is to adequately address the potential for cross-contamination. It is therefore important for a production manager to have a scientifically based and organisationally robust cleaning validation concept and program, where resources are neither over- or under-committed. In this paper technical tools, such as implementation of disassembling and cleaning SOPs, the implementation of cleaning and control levels, the definition of acceptance criteria, the execution of swab and rinse sampling methods, the development and validation of analytical methods, the use of worse-case tests, the definition of equipment-train and the preparation of validation protocols will be discussed. A cleaning validation program generates a huge amount of data. At Helsinn this data is processed, analysed and evaluated by means of tri-dimensional matrices. Cleaning validation programs have brought significant technical results that have led to production performance increases. Among them: The adopted model has permitted validation of the cleaning system in an overall manner for the entire production unit and for all products in question. It permits constant monitoring of the system and rapid theoretical verification of the impact of introducing new process/production runs. Allows earlier identification of critical cases where intervention with preventative solutions to avoid cross-contamination by use of more sophisticated cleaning/sampling/analysis methods can be implemented. The standardisation of methods for cleaning and analysis, and the introduction of the concept of cleaning levels, leading to faster product changeovers. The management has further criteria for the evaluation of new processes prior to introduction into the plant.

Keywords: Acceptance criteria · Cleaning levels · Cleaning procedures · Cleaning validation · Multipurpose plants



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1. Introduction

In order to understand better the cleaning validation program selected and carried out by Helsinn Chemicals (HCB), it is useful to briefly review the activities and particular characteristics of the plant. HCB is a multipurpose plant with 13 reactors from 1000 to 6300 l, seven reactors from 50 to 250 l, four vacuum dryers from 2000 to 4000 l and one microniser. HCB began activities in 1984 and since then has produced approx. 60 different Active Pharmaceutical Ingredients (API) or advanced intermediates for the pharmaceutical industry to a total of 200–250 different chemically synthesised molecules in various reaction steps. Annually, approx. ten different multi-step processes are produced while 2–3 new products are introduced yearly.

Characteristics of API Chemical Production

Chemical transformations occur in a reactor, sometimes in drastic conditions and with the aid of potent reagents. When implementing a cleaning validation program, a risk analysis approach should be taken in consideration.

First, there is the necessity to look for many compounds as, for example, the product of the reaction, any intermediates not isolated or formed *in situ*, the starting raw materials and reagents (it is desirable to check for reagents that are used in excess and are toxic), the reaction by-products (inorganic salts, degradation products, impurities), the solvents used for reactions, purification and cleaning, the detergents (soap, acids, bases) or the materials deriving from machine malfunctions or breakdowns. Therefore a deci-

sion should be taken regarding the chemical mixture to be searched for.

Second, chemical production is a multi-step process, where, contrary to finished dosage form productions, a purification step is planned. Therefore the point of maximum alert in the planning and execution of a validation program can be identified in the last chemical step and its purification.

Third, when disassembling in a multi-product/multi-use environment, the new production line is cleaned and reassembled as a puzzle of previously dirty pieces from other products. Therefore the various changeover situations need to be assessed.

2. Start of the Cleaning Program

Given the increased demand for cleaning validation, which from the beginning of the 90s has also involved the API production sector, in late 1994 HCB decided to confront the problem in a systematic and formal way. The most important activities were the study of regulations, the check of the state of the art of the API production sector (conferences, meetings, consultancy), the review of the health authorities' expectations, and the detailed analysis of HCB's internal situation. The examination of the principal deficiencies found in some FDA 483 forms from the literature led to the following observations:

- a) solvents and materials used for the cleaning are not specified;
- b) description and detection limits of the analytical method are missing;
- c) cleaning acceptance criteria are not defined;
- d) no standard cleaning methods are in place;
- e) detergents used are not researched;
- f) no visual inspection is carried out;
- g) technique of swab sampling for difficult-to-clean equipment parts is not used;
- h) sampling methods are not used and sampling plans are not adequate;
- k) recovery factors are not calculated in the analytical method.

Generally speaking 483 forms and/or warning letters were concluded with this statement: *'The FDA expects API manufacturers to verify that cleaning procedures for multi-use equipment will remove residues of previous products and cleaning solvents/detergents to an acceptable level'*. Starting from this minimal list of requirements HCB began the

evaluation of its own internal situation. The cleaning was carried out and documented in check-lists for principal equipment: the methods were not standard and not all described in SOPs. The cleaning limits were not defined on the basis of scientific criteria and not for each equipment component: a general limit of 50 ppm was used. Cleaning was carried out with solvents and/or with aqueous solutions of different pH. In general a quite common industrial practice was used: clean until the cleaning solvent is clear and colourless, and the equipment is clean upon an accurate visual inspection. Fortunately one of the most important results of the program implemented subsequently has shown that even with this limited amount of tools the situation was largely under control.

Objectives of the Working Program

The aim of the implemented program was on the one hand to resolve the situation by the introduction of a working method that was simple and pragmatic, tolerable from a productive point of view, and supported on a scientific and rational bases. On the other hand the program has permitted the collection of data regarding the efficiency of (not yet standard) cleaning methods in use, introducing samplings and standard analytical controls, so as later to plan the necessary corrective actions, and to implement standard cleaning procedures. This data also served as a support for a retrospective validation of the system existing up to 1994. The last objective of the program was to create a data assessment model that ensures attainment and subsequent maintenance of an overall state of validation for the production unit as a whole and for all products/processes and equipment.

3. Implementation of the Working Program

In order to validate a cleaning program, many topics have to be considered. An important action was to describe in a written form and in the most general form for various equipment, how the cleaning and disassembly of equipment were performed. In this way the knowledge developed by the manufacturing personnel during the years could be used. In the cleaning operating instructions the following issues were defined: the maximum time between equipment use and the start of cleaning, the sequence of op-

erating steps including disassembly operations, the volume and temperature of the solvent used, the operating instructions for use of detergents and their quantity, the operating instructions for use of CIP, the time of contact, the duration of agitation, and finally the provision for operator and supervisory sign-off.

After that all equipment was inspected and verified as visually clean, sampling rinse and swab techniques were introduced, and a general applicable sampling solvent was found. The product to be researched should be soluble at least ten times above its limit of detection. HCB demonstrated that almost in all cases it was possible to use isopropanol, which is non-toxic, water soluble, and does not interfere with the analytical method. After that a generally applicable analysis method (including recovery factor) was developed and validated. Although originally there was a great reluctance to accept any analytical method that was not product specific, there has been some moderation in this position. Non-specific methods may actually give a better indication of the cleanliness than product-specific methods. HCB used an UV-method for detecting the researched product at a specific wavelength.

At HCB when a family of products is manufactured in the same equipment and the equipment is cleaned by the same process, a worse-case product has been selected to represent the entire family of products. The worse-case selection was based on a combination of toxicity, pharmacological activity, solubility, and difficulty of cleaning.

Regardless of the cleaning approach, the question inevitably arises as to what is clean enough. The actual numerical limit should be based on one or more of the following: therapeutic dosage, toxicity of the material, solubility of the potential residue, difficulty of cleaning, how the products will be used, the nature and the batch size of other products made in the same equipment. At HCB calculations for maximum acceptable residues are based upon the maximum therapeutic daily dose of the API being cleaned and the worse-case situation for the next API to be made in the same equipment. It is assumed that the next API will be formulated so as to provide the largest prescribed daily dose, that the highest level of residue found at any of the sample points exists throughout the equipment at that level of residue, and that all residue found will transfer uniformly to the first batch of the next product to be made in the equipment. For rinse solvent sam-

pling the maximum acceptable concentration of residue is calculated as follows:

$$b = (A_{\min})(W_B)Fr / V(B_{\max})Fs \quad (1)$$

where b is the maximum allowed concentration of product A in the final wash (g/ml to be transformed in ppm); A_{\min} the minimum prescribed therapeutic dose of product A (g); W_B the weight of lot B to be manufactured in the equipment (g); Fr the recovery factor (-); V the volume of rinse remaining in equipment after draining (ml); B_{\max} the maximum prescribed therapeutic dose of product B (g); and Fs the safety factor (-).

For swab sampling the maximum acceptable concentration of residue is calculated as follows:

$$b = (A_{\min})(W_B)Fr / S(B_{\max})Fs \quad (2)$$

where b is the maximum allowed concentration of product A on equipment surface (g/cm²); A_{\min} the minimum prescribed therapeutic dose of product A (g); W_B the weight of lot B to be manufactured in the equipment (g); Fr the recovery factor (-); S the equipment surface area in common between product A and B (cm²); B_{\max} the maximum prescribed therapeutic dose of product B (g); and Fs the safety factor (-).

Generally a recovery factor of 70% should be assured for an acceptable method. The safety factor represents a measure of a reasonable degree of risk for the given situation and its value depends on the dosage form. HCB applies a safety factor of 5000 for products with known pharmacological characteristics and a safety factor of 10000 if the LD50 is used instead of the daily dose.

One of the requirements for a validation program is to have in place a system for the statistical treatment of the collected data. At HCB this data is evaluated by means of a matrix system of both the calculated acceptance limits and the actual measured values. This system allows a risk analysis to be performed by playing virtual changeovers or to find out the most critical changeover situation of the current plan. An other important aspect of this statistical treatment is the possibility to verify which methods are more reliable than others. HCB could demonstrate that the actual values found are by far below the calculated acceptance limits. Finally the matrix system allows the evaluation of the impact of the introduction of a new process/product in a given manufacturing plan (increasing level of checks, developing more sophisticated

analysis methods, dedicating equipment or part of it).

HCB introduced four levels of cleaning that differ in the thoroughness of the cleaning process, the cleaning conditions, the level of verification of cleaning, and the level of risk associated with a possible contamination. The adopted four levels of cleaning and control are the following:

- a) change from batch to batch in the same manufacturing process; in this case a soft cleaning is performed and no analytical control is applied;
- b) sequential change between intermediates of the same process; in this case a soft cleaning is performed and no analytical control is applied;
- c) change from intermediate to final product (API) of the same process; in this case a medium cleaning is performed and an analytical control according to case is applied;
- d) change from intermediate or API of process A to intermediate or API of process B; in this case an heavy cleaning is performed and an analytical control is applied.

This philosophy allows the cleaning effort to be directed to situations where contamination would have the greatest potential to cause harm, and allows a lesser effort for early steps where there is less risk from cross-contamination.

All of the topics previously discussed (identification of procedures to be validated, analytical methods, sampling methodology, determination of limits) come together in the process of validating the cleaning procedure. Validation of the cleaning process is the accumulation of documentation of testing that demonstrates that the cleaning process consistently reduces the levels of residues remaining on equipment to previously determined acceptable levels.

4. Results of the Validation Program and Conclusions

- The adopted model has permitted the validation of the cleaning system in an overall manner for the entire production unit and for all products in question.
- This program permits the constant monitoring of the system and a rapid theoretical verification of the impact of introducing a new process/production run on production in progress.
- Furthermore the validation program allows earlier identification of critical cases where intervention with pre-

ventative solutions to avoid cross-contamination by use of more sophisticated cleaning/sampling/analysis methods could be implemented.

- The validation program allows the assignment within possible limits of lines dedicated to processes and the adoption of technical solutions that facilitate product changeover (e.g. CIP, dedicating small tools).
- This program improved planning of production campaigns with more rationale use available equipment. The management has further criteria for the evaluation of new process prior to introduction into the plant.

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