A practical approach to chemical cleaning validation planing of active pharmaceutical ingredients: establishing a safe cleaning limit – present and future

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Abstract

Current trends in determinining a practical and safe establishment of a science-based maximum allowable carryover (MAC) value (or by other words the acceptance limit of the chemical cleaning) of an active pharmaceutical ingredient (API) has been moving since the new recommendation entitled „Risk-based manufacture of pharmaceutical products" (the so-called Risk-MAPP) was issued. The essence of these two approaches – the „old" and the „new" – are desribed and compared in this paper for the possible cross-contamination of any subsequent product occurring on a multipurpose, non-dedicated production line, in general. The latter concept satisfies two main requirements: 1) decisions have to be based on sound scientific knowledge and 2) during assessment tools of quality risk management (QRM) have to be used. This paper can also be used as tutorial.
Key words: chemical cleaning validation, MAC, cleaning limit, GMP

Introduction

As known for industrial practitioners, Quality Assurance of pharmaceutical companies is estblished within the frame of GMP, i.e the Good Manufacturing Practice rules. These rules are continously developing and thus compliance always expected with the current GMP, i.e. manufacturers must employ technologies and systems which are up-to-date to comply with the actual regulations [1].

The main goal of GMP is to ensure the production of safe, pure and effective drugs or veterinary medicines those represent a minimal risk for the consumers. Therefore validation of process are required. In this aspect validation means the documented act of demonstrating that a procedure, process, and activity will consistently lead to the expected results. Actually, the validation system includes the qualification of systems and equipments. The most known area of pharmaceutical validations is the analytical method validation (see e.g. Refs. [2-5]). However it also comprises process validation [6-9], computer system validation [10] as well as cleaning validation [1,9,11-15].

Chemical cleaning validation is a critial activity among the pro-active steps of producers in the production of active pharmaceutical ingredients (APIs) and its function is to ensure a minimal risk of cross-contamination by retention on the contact surface of equipments (see e.g. [1,9,11-15]). In case of Active

Pharmaceutical Ingredient (API) production on multipurpose production lines, the cleaning is performed according to optimized, API-specific cleaning procedures. If these procedures are different from each other, it is not possible to determine a single most-difficult-to clean product, i.e. the cleaning procedures has to be validated one by one from the point of view of chemical cleaning validation [1]. When a chemical cleaning validation program (and in case of final production stage, microbiological cleaning validation as well) is implemented, a risk-analysis approach is expected by the authorities.

In this paper an approach for the establishment of a scientific-based maximum allowed carryover (MAC) limit is presented, which was developed and inspected in accordance with the requirements of the European, American and Japanese authorities. Furthermore, the Risk-Mapp approach is also presented and compared to the previous „traditional" one.

1. Meeting health authorities' requirements

The presented approach was developed and used based on inspection experiences with the requirement of fulfilling expectations of the European, American and Japanese authorities, and thus it is considered as a sound cleaning validation strategy that is the foundation of an organisationally roboust cleaning validation concept. This concept was already established at the end of the '90s (see e.g. [16]) and it is still in line with the requirements of health authoirities.

1.1. Activities before chemical cleaning validation starts

As a part of the succesful technological development activities, an effective, optimized API-specific cleaning procedure has to be elaborated. This procedure depends on the physico-chemical properties of the API to be cleaned, e.g. solubility in different solvents, the temperature dependence of the solubility and adsorption characteristics of the API on the surface of equipments [17].

In paralel, the effectiveness of the cleaning procedure has to be tested by a suiatable, selective analytical method. Thus an analytical method has to be developed and validated in compliance with the current method validation directives for the detection of residues of the produced API. It is a GMP requirement that the method validation of the analytical test has to be finished in advance of the chemical cleaning validation [1, 9, 11-14, 18-19]. For the detection of the most difficult to clean component suitable surface sensitive measurement methods, e.g. IRRAS can be used (see e.g. [20]).

Sampling of the equipments can be carried out by testing the contamination of washing liquid/rinse[a] and/or by swabbing. The combination of washing and swabing samples allows the selective representation of the pipe surfaces by the liquid sample while swabbing ensures the quantitative determination of the API-residue in equipments. It is also important that how the sampling area for swabbing is defined. It is a good practice to swab those critical areas which are difficult to clean (sharp edges, corners) such as on axis of the mixer, any shaft, baffle-plates or reactor dome. It is also a good practice to add photographs of the sampled area to the cleaning validation plan in order to define unambiguously each of the sampling

areas. The sampling plan has to be organized with regard to each equipment of a given production line that was in contact with the API to be cleaned. Every pipe section has to be represented by a liquid sample (washing liquied or rinse sample) or swabbed, and at least three different critical places of each equipment have to be swabbed. All of the obtained analytical results have to be rigorously documented.

Suppose, a TLC method is validated for the quantitative determination of the PrA determination. Then it is known from the analytical method validation report that the swabbed area is 0.04 m^2, the lowest visible quantity of PrA on the TLC plate is 0.05 μg, the sample volume is 30 μL and the volume of the stock solution is 50 mL. Moreover, it is extremely imporant for the quantification to determine the recovery factor, that is 80% both on glass-lined and on stainless steel surface in this case. Thus, the detected PrA quantity is 26μg per 0.01 m^2. All the aforementioned characteristic partameters of the analytical method have to be verified during the analytical method validation, and the precise desription of the method itself has to be presented. For the aspects of analytical method development for swab samples an excelent reference was published by Yang et al. [21].

Summing up the preliminary activities: When the chemical cleaning validation starts[b], a selective analytical method for the analyte of interest (i.e. the API to be cleaned!) has to be validated, the cleaning method has to be developed and the corresponding cleaning sheet and test sheet/instruction have to be approved by the proper authorized persons. The latter documentation demands ensure the registered success of relevant standpoints including the control by quality assurance. The approved cleaning instructions/sheet have to include: the solvents and materials used for the cleaning; detergents are used or not, and if yes, which detergent is used; the standard or the actual cleaning method; the fact that the worker visually inspected the equipment; the place and way of sampling. The corresponding approved test instructions have to include the detailed description of the analytical test both for swab and liquid samples; detection limit of the analytical method; recovery factor.

1.2. Establishment of the maximum allowed carryover (MAC) value

The final requirement during the cleaning validation activity is that the quantity of residuals detected by the selective analytical method has to be lower than the MAC value established based on the technical parameters of the actual production line (equipment train, see Table 1.) and the physico-chemical properties of the produced API, in case of every sample taken.

It is important to define well the equipment train on which the production is carried out. The equipment train has to include every reactor and other equipment that is in contact with the API. It is recommended to give a description of every equipment, the identification number and the contact area (e.g. see Table 1).

The detected quantity of the API under validation can be calculated from the detection limit of the analytical method, the experimentally established recovery value, swabbed area and other parameters defined in the test sheet. In case of e.g a thin layer chromatography test, the swabbed area, the volume of the stock solution and the pipetted sample volume must be known. All these data are the outcomes of

the method validation of the actual analytical test that is performed in advance. The analytical method has to be developed that way that – after taking into account the recovery, dillution, etc. – the detected amount of API residue (in micro gramms/ surface unit) is under the calculated MAC. Thus, if all the swab samples are under the dectection limit then the quantity of the contamination is under the MAC for sure.

Table 1. The production line where the API is produced

Type and name of equipment	**Id. number of eq.**	**Contact surface area [0.01 m^2]**
1600 L glass-lined reactor	41	1050
1000 L glass-lined autoclave	42[#]	950
6300 L glass-lined reactor	43	2080
Filter type XX	45	640
Centrifuge type CF	47	620
Tray vacuum drier	48	1500
Stainless steel mill	49	225
Homogenizator	50	100
pipes	–	185
	Total contact surface area	6400

[#]The No. 42 reactor is only used for adding the solvent, thus, it is not in contact with the API and not included in the total contact surface area.

Before starting the calculation of MAC it is important to keep in mind that the visual criterion always has to be fulfilled. It means that the personal cannot see any residue on the wall of the vessel/equipment. Usually, the value of the visible quantity is higher than the MAC obtained from the quantitative criteria (see e.g. Ref. [22]). Therefore it has to be determined quantitatively if the other criteria result in high value.

Since each of the cleaning procedures is specific to the actual API to be cleaned, it is not possible to find a single last-to-leave component, unlike in case of equipment trains of final products (e.g. tablets). Thus a specific strategy should be established based on the characteristics of the whole list of possible produced APIs (e.g. toxicity, maximum applied daily dose). The neccessary data are summarized in the so-called validation matrix (see Table 2, in which the solubility of the products in water can be added if desired).

The quantitative criteria are the toxicity criterion, the dose criterion and the 10ppm criterion (or the 100ppm criterion for intermediates, except for steroids, which have to fulfill always the 10 ppm criterion because of their high biological activity) (see e.g. [15, 23]). That means the analytical test has to ensure that the residue of the API remaining after the cleaning procedure is not more than the Maximum Allowable Carryover (MAC) predetermined based on the criteria.

Table 2. Important caracteristics of the subsequent products synthesized on the production line under study

APIs	Smallest Batch Size [kg]	Comercial form	Daily therapeutic dose of the API min.-max. [mg]	LD_{50} (oral, rat) [mg/kg]	$\left\lceil \frac{SBS}{MDD} \right\rceil$
PrA	62	tablet	1.5	90	41 333333
PrB	35	tablet	5-20	2000	1 750000
PrC	22.5	tablet	5-10	1900	2 250000
PrD	120	tablet	2-10	550	12 000 000
PrE	76	Injection, capsule	50-100	1300	760 000
PrF	41	tablet, sirup	2-5	610	8 200 000
PrG	95	cream	100	1700	950 000

1.2.1. MAC based on the toxicity (LD_{50}) of APIs

The formulae for the calculation of MAC_{tox} is eq.(1):

$$MAC_{tox} = \frac{NOEL_{AAW}}{SF} \cdot \left\lceil \frac{SBS}{MDD} \right\rceil_{\min} \tag{1}$$

where

$NOEL_{AAW}$: is the so-called No Observable Effect Level, i.e. the mass of the pure API that does not cause any biological effect in an average adult.

SF is a safety factor. It has to be defined in the corresponding standard operation procedure (SOP) of the company, i.e. in the policy of the producer. Its a good practice to define it 5000, if any of the APIs in the given calculation is commercialized as injection or infusion, and 1000, if both of the APIs are used in tablets, capsules or cream.

SBS: is Smallest Batch Size of the „worst-case" subsequent product.

MDD: is the Maximum Daily Dose of the same subsequent product.

The first quotient, $\frac{NOEL_{AAW}}{SF}$ always corresponds to the active being the subject of cleaning, and the second one, $\left\lceil \frac{SBS}{MDD} \right\rceil$ corresponds to the so-called "worst-case" among the possible subsequent products. The worst-case subsequent product can be determined as can be seen in Table 2. That means the $\left\lceil \frac{SBS}{MDD} \right\rceil$ value is calculated

for every possible subsequent product, and the smallest value, the $\left[\frac{SBS}{MDD}\right]_{\min}$ is considered as worst-case. The MAC_{tox} calculation is finally carried out with this value. As can be seen from Table 2, in the present example PrE is considered as "worst case". If the average weight of an adult (AAW) is taken as 70 kg and the EF empirical factor is 5 x 10^{-4} in case of LD_{50} value[c] that was established for orally administered rats. The No Observed Effect Level (NOEL) is calculated based on eq.(2):

$$NOEL_{AAW} = LD_{50} \cdot EF \cdot AAW \tag{2}$$

Thus the NOEL of PrA is 3.15 mg/(70kg.day), which has to be substituted in eq(1). Presently, PrE is the "worst case" (see Table 1), therefore the $MAC_{tox} = 478.8$ mg.

1.2.2. MAC based on the dose of the APIs

The corresponding formulae for the calculation of MAC based on the maximum daily dose is eq.(3) (see e.g. Refs. [15, 23])

$$MAC_D = \frac{STD}{SF} \cdot \left[\frac{SBS}{MDD}\right]_{\min} \tag{3}$$

STD: is the Smallest Therapeutic Dose used at once. As can be seen from Table 2. it is 1.5 mg for PrA.

SF: is the same Safety Factor as seen above in case of eq.(1). The „worst case" subsequent product is still PrE thus, by substituting the actual values, the MAC_D is 228 mg.

1.2.3. MAC based on the 10 ppm criterion

Fort he definition of 10 ppm criterion (see for instance in Refs. [15, 23]):
The formulae to be used can be seen below (eq(4)):

$$MAC_{10ppm} = SBS \cdot 10 \cdot 10^{-6} \tag{4}$$

As can be seen in Table 2., the lowest value among the possible smallest batch sizes corresponds to PrC, i.e. 22.5 kg (PrC), thus MAC_{10ppm} is 225.0 mg.

1.2.4. Determination of the Surface Specific Cleaning Limit

Among the three different MAC values the lowest has to be chosen for the calculation of specific cleaning limit (SCL) as worst case, i.e. the 225.0 mg. Since the total surface area of the equipment line (A_{tot}) is 64 m^2, the $SCL = MAC_{\min} / A_{tot}$ =35.1 µg/ 0.01 m^2 for the presented equipment train.

Finally, it can be concluded that on the production line of PrA the calculated specific cleaning limit (35.1 µg/0.01 m^2) is greater than the detectable quantity (26.0 µg/0.01 m^2) thus the analytical procedure is suitable for the verification of the given cleaning procedure subjected to chemical cleaning validation.

Recently there are some suggestions to establish MAC value based on different calculation algoritms that, for instance, includes the sum of swabbed (sampled) surface area (see e.g. Ref. [24]). This algoritm [24] is relatively liberal since it does not require that each sample result should be under the detection limit. However, the authors do not find suitable the application of this approach because, it is believed, it effaces the possible technical/technological and/or analytical errors and it leads an increased risk of cross-contamination. However, all suggestions are open for discussion for the professional community.

2. The Risk- MAPP concept – the future

As it was mentioned earlier, the Risk-MAPP concept was outlined in the baseline „Risk-based manufacture of pharmaceutical products" [25] by the International Society for Pharmaceutical Engineering. This guideline is in line with the point of view of FDA and it is to sutisfied two main requirements: 1) decisions have to be based on sound scientific knowledge and 2) tools of quality risk management (QRM) have to be used for the prioritization of the possible failure modes.

In comparison with the traditional cleaning validation concept, the viewpoint of Risk-Mapp differs in the following aspects:

1) It considers only residual API as cross-contamination. Thus, it does not handle the retention of intermediate preoducts or starting material of another product, residual solvent or cleaning agent, mechanical contamination caused by structural material (e.g. small metal particles after functional error) or microbiological contamination.
2) However, it considers more possible sources for cross-contamination. They are mix-up, retention, mechanical transfer and air-born cross-contamination. The most hazardous group of failure modes is mix-ups, which are clearly the results of wrong practice, human error, e.g. mixing of different materials due to wrong labeling, wrong storage practice, unacurate documentation or movement in the warehouse, inadequate movements of materilas and/or personel in the production area. Mechanical transfer means the indirect cross-contamination through tools, safety glasses, gloves, etc. Air-born cross-contamination may occure int he vicinity o fan equipment where open operation takes place. For instance, if the filling of a centrifuge, or packiging in bags is an open operation, dust of the given API may be carried to another equipment by air. Retention is the only group of failure modes, which is treated in cleaning validation and it means when residual API is dissolved in the following API.
3) During the process of toxicological data-based calculations, the usage of any safety fator is completely avoided.
4) Toxicological calculations are based on the so-called Acceptable Daily Exposure (ADE) value. This value is based on the toxicological properties and pharmacology of the specific API. According to the Risk-MaPP document, the ADE of an API is defined as the estimated dose that is unlikely to cause an adverse effect if an individual is exposed to the API by any route, at or below this dose every day for a lifetime. It is obvious that ADE value has no any

connection with the LD_{50} of the same API, since the latter one considers only the lethal effect of the chemical. Classification of APIs based on their ADE value:

a) compounds those are likely to be carcinogenic. (ADE = 1 µg/day)

b) compounds those are likely to be potent or highly toxic. (ADE = 10 µg/day)

c) compounds those are not likely to be potent, highly toxic, or genotoxic. (ADE = 100 µg/day)

5) The characteristics of the production process (risk factors) and the frequency of the production. Thus theworst case is that when a toxic API is often produced with unadvatageous production characteristics.

A toxicologist can establish the ADE based on experimental data as follows (eq.(5):

$$ADE(mg/day) = \frac{NOAEL \cdot BW}{UF_c \cdot MF \cdot PK} \tag{5}$$

where

NOAEL is No-Observed-Adverse-Effect-Level (mg/kg/day) (that is not NOEL!!!),

BW is body weight (kg),

UF_c is a composite uncertainty factor,

MF is a modifying factor and

PK means pharmakokinetic adjatment(s). According to this approach, cleaning limit is given by the Safety Threshhold Value (STV), instead of the MAC value (see eq.(6))

$$STV = ADE \cdot \frac{SBS}{MDD} \tag{6}$$

Since no safety factor is used in the Risk-MAPP approach, most of the time STV is somewhat higher than the MAC of the same API. However, in case of chemicals showing strong biological activity (eg. charcinogenic, mutagenic agents or steroid hormonal APIs, i.e. any high potency APIs) it can be the other way around.

Conclusion

In case of the use of a multipurpose / non-dedicated production line, the cleaning validation program delineated in part 1. is suitable to successfully handle the various changeovers between APIs from the point of view of potential cross-contamination. The final goal of this activity is to ensure that the applied cleaning procedure removes the previous products and cleaning agents/detergents to an acceptable level applicable for the whole multi-purpose equipment-train. The Risk-MAPP concept (Part 2,) is a milestone in handling the hazard of cross-contamination. It is a basically different approach in handling the risk of cross-contamination.

Notes

[a]*The rinse sample is obtained by known volume of the solvent, thus accurate/quantitative cleaning limit can be calculated from the result of this test, whereas the washing liquid does not provide accurate quantitative information. In the latter case, the only expectation is not to detect any API residue in the washing liquid.*

[b]*Moreover in case of final products, the API production finishes in a clean room area, thus microbiological cleaning has to be validated simultaneously in these instances.*

[c]$LD_{50\ is}$*= lethal dose 50%, ie. the dose of which half of the rat population dies.*

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