GMP News
14 May 2007

Justification of Limits for Cleaning Validation in the Manufacture of Active Pharmaceutical Ingredients

Discussion and practical implementation of the requirements of ICH Guideline Q7A

The ECA offers a discussion platform for current GMP compliance topics. The aim of this platform is to collect comments that may help to further develop the discussion papers. Any person or interest group is free to send additional or alternative proposals to the ECA. The Academy does not intend to justify the proposals, but to support a discussion on them.

1. Summary

Unlike in pharmaceutical production, where residues on the surface of equipment may be 100 % carried over to the next product, in API production the carry-over risk is much lower for technical and chemical manufacturing reasons. A group of experts from companies of the VFA discussed the chapter "Cleaning Validation" of ICH Guideline Q7A "Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients", and recommends limits which are 10 times higher than the limits in pharmaceutical production. This is justified with suitable examples in a risk analysis.

2. Regulatory guidelines

In the last 10 years numerous guidelines and articles have been published on the subject of cleaning validation.

In 1993 the FDA first published the "Guide to Inspections: Validation of Cleaning Process". In 1996 the Pharmaceutical Inspection Convention (PIC) published its guide (PH 1/96; current version: Recommendations PI 006-1 dated 3 August 2003), which provided a very detailed account of the fundamental principles of qualification and validation and, in a special chapter, of cleaning validation. Up until then the regulatory guidelines and also the technical literature had been very strongly influenced by experience from pharmaceutical production.

In 1997 therefore a "GMP for Active Pharmaceutical Ingredients" project group consisting of experts from VFA member companies published a commentary on the "Cleaning Validation" section of PIC Draft PH 1/96, taking account of the special nature of API manufacture.

ICH Guideline Q7A "GMP for Active Pharmaceutical Ingredients" was the first globally recognized guide to GMP for API to regulate, *inter alia*, the manufacture of APIs in chemical production. This ICH guideline was adopted by the European Commission as Annex 18 to the EC GMP Guide and, since mid-2001, has formed the basis for API inspections.

It sets out concrete requirements for the validation of cleaning procedures where carryover of materials posses the greatest risk to API quality.

3. Establishment of limits in the pharmaceutical production

With regard to the scale of the work involved and to the prospects of a successful cleaning validation outcome, setting an adequate limit for allowable residues on production equipment has an important role to play.

Calculation is normally done based on known daily doses or on toxicological data along with safety factors. An absolute criterion may be applied as an alternative or adjunct to these.

The 1993 FDA Guideline requires, in the same way as ICH Guideline Q7A for active pharmaceutical ingredients, that the residue limits should be practical, achievable, verifiable and based on the minimum known pharmacological, toxicological or physiological activity of the API.

Defined limits and ways of calculating the limit have deliberately not been prescribed.

In the PIC/S PI 006-01 Guidelines, however, the following statements are made with regard to definition of limits.

Carry-over of product residues should meet defined criteria, for example the **most stringent** of the following three criteria:

a) No more than 0.1% (1/1000th) of the normal therapeutic dose of any product will appear in the maximum daily dose of the following product.

b) No more than 10 ppm of any product will appear in another product.

c) No quantity of residue should be visible on the equipment after cleaning procedures are performed.

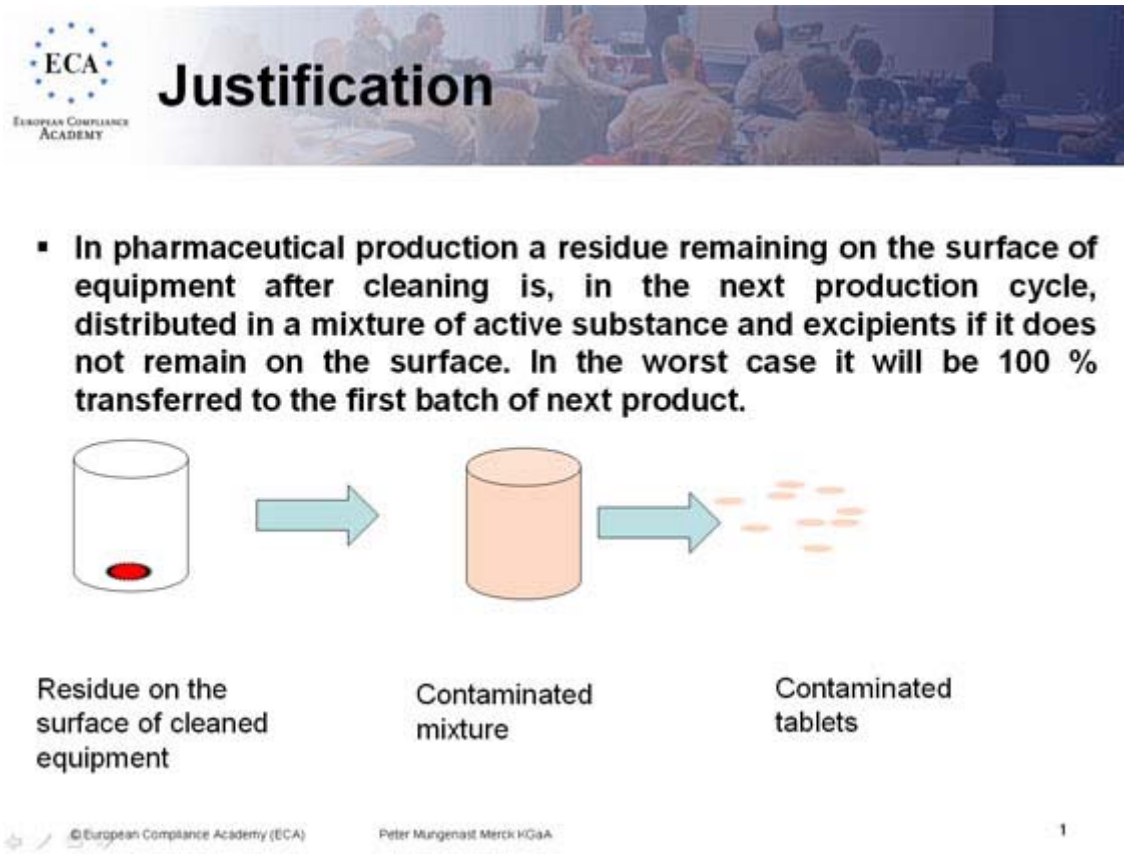
In the last 10 years the dose-based calculation (e.g. 1/1000th dose) has prevailed In the manufacture of pharmaceutical products. Where dose data are not available, an absolute value (e.g. 10 ppm) is prescribed.

For residues where dose data are not available but toxicological data are (e.g. tensides), it is normal to perform the calculation based on the NOEL/ADI (no effect level/acceptable daily intake) value along with a safety factor (SF).

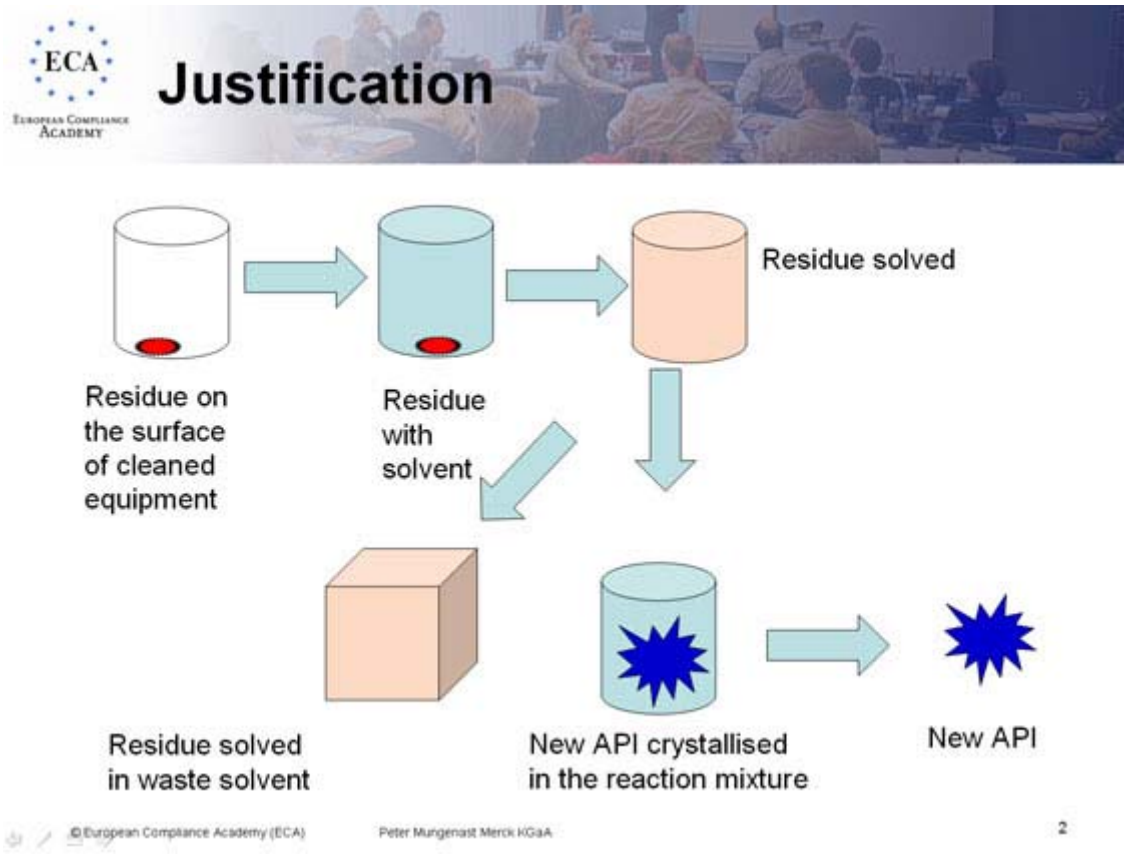
4. Risk analysis for establishment of limits in API manufacture

Assuming that the aforementioned criteria (10 ppm, 1/1000th dose, NOEL/ADI with SF 100) represent the state of the art for pharmaceutical production and are considered sufficiently safety, then the calculation of limits in API manufacture must reflect the different methods used in pharmaceutical production and in the chemical production of active pharmaceutical ingredients to allow comparable risk analyses to be undertaken.

In pharmaceutical production a residue remaining on the surface of equipment after cleaning is, in the next production cycle, distributed in a mixture of active substance and excipients if it does not remain on the surface. In the worst case it will be 100 % transferred to the first batch of next product.



In chemical production a 100 % carry-over of residue from the equipment surface to the next product to be manufactured can be ruled out based on the way the process is run and on technical considerations. The residue remaining on the equipment surface can, during the next production cycle, be carried over into the reaction mixture consisting of solvent and raw materials. In most cases, however, any residue in solution will be eliminated from the process together with the solvent, and insoluble residue by physical separation processes (e.g. filtration), so it will not be present in the end-product.



The final step in a multi-step chemical synthesis is selective purification of the API (e.g. by crystallization), during which contaminants are removed from the process and/or insoluble residues are removed by physical separation).

From the original reaction mixture of educt, agent and solvent there remains only a fraction of the original mass as API at the end of the chemical process.

It is also to be noted that, during subsequent pharmaceutical production, the API is further diluted through the excipients that are added.

Conclusion:

Assuming that there is no intention to impose more stringent yardsticks during API production than in pharmaceutical production but that they should be approximately the same, the logical conclusion is that the limits in chemical production should be set higher than in pharmaceutical production. Based on this rationale, a factor of 10 compared to the established pharmaceutical production limits is both plausible and, in terms of pharmaceutical risk, acceptable.

5. Establishment of limits for chemical API production

Based on the various recommendations for pharmaceutical production and after due consideration of the differences between pharmaceutical production and chemical production, the following scientifically founded calculation methods are proposed for APIs.

Principles:

- In all cases the production equipment, where it can be inspected, has to be visibly clean.
- The acceptable residue must never exceed 1000 ppm, even if this were justifiable based on dosage or toxicological data.

Furthermore, the following procedure is recommended for establishing limit values:

- The limits in chemical production may be 10 times higher than in pharmaceutical production.

5.1 Limit value calculations

The limit value calculations described below also represent a ranking order of application.

5.1.1 Calculation based on dose data - 1/100th dose

Where dose data are available for the previous product and the following product, the limit based on the dose criterion is set at 100th dose in the next product. The minimum daily dose of the previous product and the maximum daily dose of the following product shall be used for the calculation. This type of calculation can be applied when a final API stage follows on directly from the final stage of another API.

5.1.2 Calculation based on toxicological data - Safety factor 10

Where not all the dose data are available for all of the products, but toxicological data for the previous product are, the limit value is calculated according to the usual formula (ADI value, NOEL value).

In the same way as with the dose criterion (reduction from 1/1000th to 100th), the safety factor may also be reduced from 100 to 10.

5.1.3 Absolute criterion - 100 ppm based on the quantity of the following product

When neither dose nor toxicological data are available for the previous product, the limit is set at 100 ppm. In other words, 100 ppm (relative to the batch size of the following product) of a defined previous product may remain as residue on the surface of the equipment.

5.2 Limit value calculations for the "physical processes" special case

Apparatus and equipment that is used for physical end-treatments such as drying, mixing or milling may either be operated together with the previous synthesis equipment or generally be used separately.

During separate physical end-treatments of APIs, there is no decrease of contaminants like in the aforementioned chemical process.

Consequently, we recommend in this case that the calculation methods applied should be those normally used in pharmaceutical production, i.e. 1/1000th dose, NOEL/ADI with SF 100 and 10 ppm criterion.

If, however, these pieces of equipment are directly connected to the chemical synthesis equipment, cleaning validation must have regard to the equipment for the entire synthetic path. In this case it is not practical to view the physical processes separately.

Consequently, for the equipment in toto either the 1/100th dose criterion, safety factor 10 for calculation with toxicological data, or the absolute criterion of 100 ppm are used.

For limitation or comparability of risks it should be noted that, in the (last step) physical processes of API manufacture, the pieces of equipment that are used may contain a maximum of 10 % of the permitted residue for the equipment in toto. Thus, when handling the finished API, virtually the values from pharmaceutical production are adopted.

6. Example of a risk assessment of product residues in pharmaceutical production and in chemical API production:

Example (absolute criterion 10 ppm, simplified)

Pharmaceutical production	**Chemical API production**
10 g of residue from the previous API remain on the equipment = 10 ppm in 1000 kg of next product	**1 g of residue from the previous API remain on the equipment = 10 ppm in 100 kg of next product** (yield of API)
1000 kg = 100 kg API + 900 kg excipients	**1000 kg of next reaction mixture** = 50 kg substance A + 50 kg substance B + 900 kg solvent
gives 10^6 tablets each 1 g	**gives 100 kg API** (from which the 1000 kg tablets can be produced) + 900 kg solvent
At the end of the process the residue may be 100 % contained in the next product, in the tablets.	**At the end of the process the residue may be** **100 % contained in the API** **or 100 % contained in the solvent/filter** **or statistically distributed, i.e.** **10 % in the API and 90 % in the solvent/ filter.** **Or, or ……**
For 1000 kg of tablets as next product a maximum of 10 g of residue from the previous product (API) would be allowed.	**For 1000 kg of tablets at the end of the process chain a maximum of 1 g of residue from the previous product (API) would be allowed in the chemical production equipment.**

Carry-over of residues from chemical production to pharmaceutical production

1 g residue in 100 kg next product (= 10 ppm) in chemical production is distributed as follows.

1 g = 10 ppm in the case of 100 kg of next product **(900 kg solvent and 100 kg API yield)**		
A	**B**	**C**
Improbable distribution	**Statistical distribution**	**Possible distribution**
100 % in the API	10 % in the API 90 % in the solvent	< 10 % in the API > 90 % in the solvent
1 g = 10 ppm in 100 kg API	0.1 g= 1 ppm in 100 kg API	< 0.1 g= <1 ppm in 100 kg API
Subsequent pharmaceutical production 100 kg API + 900 kg excipients		
1 g = 1 ppm in 1000 kg tablets	0.1 g = 0.1 ppm in 1000 kg tablets	< 0.1 g = <0.1 ppm in 1000 kg tablets
1 ppm in 10^6 tablets	**0.1 ppm in 10^6 tablets**	< **0.1 ppm in 10^6 tablets**

If the calculation is performed using a statistical distribution (example B) of residue between API and solvent then, of 10 ppm (1 g) residue on the surface of the production equipment, 0.1 ppm (0.1 g) is found in 10^6 tablets.

In pharmaceutical production equipment, however, 10 ppm = 10 g of another API would be permitted. In this example the requirement of 10 ppm in API production, related to possible contamination in a pharmaceutical product manufactured from it, would be 100 times more stringent than 10 ppm in pharmaceutical production.

This makes it clear that the proposed raising of the limits for API production by factor 10 compared to pharmaceutical production, in consideration of the entire process chain and based on an analysis of risk to patients, is absolutely justified.

This discussion paper will also be presented by one of the authors of the VFA Discussion Papers (Peter Mungenast, Merck) at the following event:

- **Cleaning Validation**, 19 - 20 June 2007, Munich, Germany

Appendix 1

Members of the Cleaning Validation Expert Group

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Aventis	Dr. Friedhelm Adam
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Bibliographic reference:
Pharm. Ind. 66, No. 9, pp. 1142-1145 (2004).

The ECA and the VFA would be happy to receive your comments regarding the discussion papers. Please send your feedback to info@gmp-compliance.org.

You can also discuss this paper during the above mentioned ECA Education Course "Cleaning Validation". If you are further interested in a discussion via Webinar, please let us know (info@gmp-compliance.org).