Limit Values for Cleaning Processes: Implementing Toxicological Risk Assessment – Part 1

by Dr. Sabine Paris

With the revision of Chapters 3 and 5 and Annex 15 of the EU GMP Guide and of the relevant EMA PDE Guideline\(^1\) a paradigm shift took place in establishing limit values for the validation of cleaning processes. Instead of the previously used criteria, such as 10 ppm or 1/1000 of the therapeutic dose of the foregoing product, now the sole admissible criterion is a toxicological risk assessment based on PDE values.

The seminar entitled “Limit Values for Cleaning Processes: Implementing Toxicological Risk Assessment” held by the FORUM · Institut für Management GmbH on 28 June 2016 in Mannheim featured three high-calibre experts from government and industry. The participants were shown in clear and practical ways how a toxicological assessment is made, how limit values for cleaning processes can be established and what a GMP inspector is looking for.

Klaus Eichmüller, Head of Department II 23.3 Pharmaceutics at the Regional Council of Darmstadt, Germany, Dr. Andreas Flückiger, Head of the Division of Health Protection in the Corporate Department of Occupational Health and Safety and Environmental Protection, and Dr. Hans-Martin Schwarm, Senior Advisor for Pharma and Health Care, guided the participants through the informative and interactive programme. This article summarises several major aspects of the day.

What did the process for establishing limit values look like prior to 01 March 2015?

Klaus Eichmüller and Andreas Flückiger presented the history of GMP regulations. Up to 28 February 2015 the former versions of Chapters 3.6 and 5.17 ff. for avoidance of cross-contamination in the manufacture of medicinal products were in effect. Dedicated facilities were required for products with highly sensitising active substances or for biological active substances originating from living micro-organisms. Other medicinal products (“such as certain antibiotics, certain hormones, certain cytotoxics, …”) were likewise supposed to be manufactured in dedicated facilities. Here the term “certain” left much room for interpretation. Only in exceptional cases could production take place in multi-purpose facilities.

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\(^1\) 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

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These exceptions – which, however, became the rule – were intended to be legitimised with risk management in accordance with ICH Q9. “However, industry frequently offered risk analyses based on poorly founded assumptions (such as FMEA without a robust data base). The validation criteria for cleaning processes were conservative but unscientific”, according to Andreas Flückiger.

**Established criteria for the validation of cleaning processes:**

- The 1/1000 of the dose criterion: No more than 0.1% of the therapeutic dose of any product may appear in the maximum daily dose of the following product.
- The 10 ppm criterion: No more than 10 ppm of any product may appear in another product.
- The visually clean criterion: After cleaning, residues may not be visible on surfaces that come into contact with the product. The visibility limit for many substances is approx. 4 µg/cm².
- The LD 50 criterion: No more than a specific fraction of the LD50 (e.g., 1/50,000) may appear in a daily dose of the following product.

*Sources: GMP MANUAL and Dr. Andreas Flückiger*

However, the established criteria say little or nothing about the long-term toxicity of a substance, which would be of interest for the topic of cross-contamination. Also, substance-specific properties are not taken into account at all in the case of the 10-ppm and the visually clean criteria. The therapeutic dose is in fact taken into consideration for the 1/1000-dose criterion; however, it says nothing about other potential effects of the active ingredient. “The LD50 in particular is completely useless, since the value describes the acute toxicity of a single high dose which when considered statistically correlates very poorly with the chronic toxicity that has to be taken into consideration within the context of the cleaning of equipment and facilities,” says Andreas Flückiger.

**What about the GMP regulations for preventing cross-contamination since 01 March 2015?**

Due to the (negative) inspection experiences with previous risk analyses, in the first drafts of Chapter 3 the European GMP supervisory authorities named several product categories which should be mandatory for dedicated facilities (e.g., cytostatic agents, beta lactams). As the document developed further, up to establishment of a scientifically based limit value, the ISPE Risk MaPP document on the risk management of cross-contamination was added, among others. In November of 2014, the EMA published an additional guideline on establishing health-based exposure limit values (PDEs), which describes how the toxicological risk assessment for establishing PDE values has to be conducted.

Section 3.6 of the EU GMP Guide calls for using the basic principles of Quality Risk Management to assess and control. Dedicated (product-specific) facilities for medicinal products are required if

- the risk cannot be adequately controlled by operational and/or technical measures,

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3 See footnote 1.
• scientific data does not support limit values (e.g., high allergenic potential...) or
• the limit values derived from the toxicological evaluation are below the detection limit of the analytical method.

What is the PDE concept?

The PDE concept:
• Toxicological-pharmacological analysis of all data on a substance: Human data, animal data, comparison with other substances, in-vitro data, etc.
• Calculating a dose that causes no adverse effects when taken every day for a lifetime, not even in susceptible groups (children, the elderly, ill persons, pregnant women).
• This dose may not be contained in any daily dose of the product other than the one manufactured immediately afterwards in the facility.
• Any substance that must enter into the equipment and exit it again fundamentally requires a PDE value (with the exception of trace impurities, for instance through degradation or reaction by-products).

Source: Dr. Andreas Flückiger

Why has there been no cross-contamination with consequences even when traditional limit value criteria were used?

“The traditional values are indeed unscientific; however, they are also very conservative, i.e. in most cases they lie well below the PDE value,” explained Andreas Flückiger. “In those cases in which the old values were in fact too high, the effects almost always occurred with a delay (e.g., mutagens or carcinogenic effects). This would only have been found after an intensive search”.

“A comparison of the PDE values with the 1/1000 of the dose of over 300 substances revealed that in 15% the PDE values were below the 1/1000 dose,” he continued. “These 15% would shrink even further if the 10-ppm criterion were also used”.

Next week in part 2 of the article, you will read, how the PDE value is calculated, what you have to consider in preparing a PDE report, if there are alternatives and what a GMP inspector is looking for.

Sources:

Seminar: Reinigungsgrenzwerte: Umsetzung toxikologischer Risikobewertung - Kreuzkontaminationen vermeiden gemäß EU-GMP Leitfaden (Limit Values for Cleaning Processes: Implementing Toxicological Risk Assessment - avoiding cross-contamination in accordance with the EU-GMP Guideline) held by the FORUM · Institut für Management GmbH on 28 June 2016 in Mannheim, Germany

GMP-MANUAL Chapter 8 Cleaning Validation, Maas & Peither AG GMP-Verlag, Schopfheim, Germany, 2016

Alhenn und Anhalt, Reinigungsvalidierung – Positionspapier des BAH, Pharm.Ind. 77, No. 7,1074-1080 (2015)
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