Limit Values for Cleaning Processes: Implementing Toxicological Risk Assessment – Part 2

5 min. reading time

by Dr. Sabine Paris

In last week's issue you read in the first part of our summary of the seminar entitled "Limit Values for Cleaning Processes: Implementing Toxicological Risk Assessment" details about the former process for establishing limit values, about the new GMP requirements and about the PDE concept.

In part 2 you will learn 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.

How is the PDE value calculated?
In searching for a limit value for lifelong exposure, the following questions in particular must be answered:

- What effect does the substance have?
- At what dosage does the substance take effect?

First of all, a **critical effect** of a substance has to be determined for this. The effect can be desirable (therapeutic) or undesirable (such as allergies, birth defects, genetic damage). The critical effect of a substance is, as it were, its most damaging effect.
Secondly, the **reference dose** for the critical effect must be identified. The so-called dose descriptors determined during the studies are helpful, for example the NO(A)EL (No Observed (Adverse) Effect Level - describes the highest dose at which no adverse effect is observed).

Formula used to calculate the PDE value according to the PDE Guideline

$$PDE = \frac{NOAEL \times Weight\ Adjustment}{F1 \times F2 \times F3 \times F4 \times F5}$$

The unit of the calculated PDEs is mg per person and day. This includes body weight (50kg as standard in the PDE Guideline) and safety factors or corrective factors (F1-F5). The factors must be included, as the data serving as the starting point for the calculation was generally collected for other purposes and does not match the definition of the PDE (for instance studies using animals, dosages that are too high or too low).

The bioavailability must also be considered. Depending on how it is administered (parenterally, inhaled, orally, dermally), this can be very positive or very negative. If the bioavailability for a route of application is low, the exposure here may be higher.

Do the new regulations signify a revolution in cleaning routines?

The three experts agreed: No, the new regulations have not led to a revolution in the cleaning routine. The limit value calculation is the same in principal. The only difference is that the PDE value is now used in the formula for the calculation instead of the traditional criteria. And since in most cases the PDE values are higher than the previously determined limit values (see above), the cleaning procedure will (generally) not have to be changed.

What has to be considered for the PDE report?

The expert report must be written in a manner that non-toxicologists (such as GMP inspectors) can understand. The form and content are outlined in the PDE Guideline. A CV by the expert writing the report must be included. The guideline does not require any special formal qualification (diploma, etc.) for the author of the expert opinions. However, according to Andreas Flückiger, there are only a few experts with adequate experience.
The speakers agreed that for some substances the toxicological assessment can be relatively short and concise, as for calcium carbonate, for example. In such cases, the usual daily intake through food can serve as the basis for the calculation. If this can never be achieved even with the greatest possible residue, then there is no need for a detailed expert opinion.

What does a GMP inspector look for?

"The important thing is that the limit values for the cleaning process be derived from the toxicological limit values understandably and correctly. And the sources used must be given," added Klaus Eichmüller. "If the activity is outsourced, it must be ensured that it is defined, contracted and controlled in agreement with Chapter 7 of the EU GMP Guide. The accountability of the Responsible Person for the contract giver must be unequivocally assigned in the Quality System."
Section 5.20 of the EU GMP Guide requires that the measures taken to prevent cross-contamination be reviewed at periodically following established procedures. "Unfortunately, in practice this is often overlooked," commented Klaus Eichmüller.
For the GMP inspector, the following list includes some of the aspects that are relevant to the cleaning validation during an inspection:

- Use of closed systems
- Ease of cleaning the systems and interfaces
- Interface to qualification
- Limits of processes and equipment

What faults are found during GMP inspections?

From his practical experience as an inspector, Klaus Eichmüller cited a number of widely varied faults that are found during cleaning validation. For example, he mentioned:

- Incomplete equipment/parts to be inspected
- Procedures cannot be validated, as processes are unstable and/or inadequately described
- Intervals between production and commencement of cleaning/duration of the period of validity of the cleaning not adequately defined.

- Analytical procedure not adequately validated
- No logical rationale for accepted limit values
- Procedures not properly defined and/or inadequate training provided (e.g., SOPs too detailed or not in the local language)
- Faults found in calculating surfaces in contact with product
- Incorrect extrapolation of impurities over the entire equipment chain
- Interpretation of the 1/1000-dose criterion as a safety factor
- No consideration of the correct smallest following batch sizes
- Using process times in the validation that differ from those used in the routine
- Worst-case definitions not adequately based on toxicological data
- Inadequate supplier qualification (such as no follow-up on faults found)

Is there an alternative to the PDE report?

"The pharmaceutical technical committee of the BAH (German Medicines Manufacturers' Association) have developed a formula for the calculations to estimate the PDE value from the **workplace limit value (OEL** - occupational exposure limits)," explained Hans-Martin Schwarm. "After all, PDE values are not accessible to the public. Smaller and mid-sized companies often do not have toxicologists on site and have to rely on external information sources and service providers. OEL values are available as an alternative. They are generally based on the same toxicological studies and have already been calculated for many substances. In addition, the values have been widely published. For example, the safety data sheets of the USP (United States Pharmacopeia) are available on the Internet. The OEL represents an "inhalation limit value" and must be converted to an "oral" limit value".

PDE: 7 days/week 24 hours lifelong

OEL: 5 days/week 8 hours lifelong

As the other two speakers also commented, it should be noted that the data sheets do not contain any toxicological grounds for the derivation of the limit values. This by itself does not meet the requirements of the PDE guideline.

For **genotoxic substances**, for which the genotoxic NOEL is often unknown, the PDE Guideline, together with the EMA Genotoxic Impurities Guideline[1], paves the way for use of the **TTC** concept (**T**hreshold of **T**oxicological **C**oncern). As a rule, a threshold value of 1.5 µg per day is considered toxicologically acceptable.

Of course, visually clean cannot be applied as the sole acceptance criterion, but it is very well suited as a detection method. Why?

Hans-Martin Schwarm argued in favour of using the visually-clean detection method: "With this method residues of > 4 µg/cm^2 can be reliably detected. PDE values as acceptance criteria in many cases yield higher maximum permissible residue levels than the traditional criteria, meaning that visually clean is often sufficient. The advantage is that by this means I can conduct a continuous verification of the cleaning concept at the same time.

Summary / Looking Ahead

After an exciting and interactive seminar with a wealth of detailed information and background coverage we can summarise:

- Since 01 March 2015 the EU-GMP regulations require a toxicological risk assessment based on PDE values for the prevention of cross-contamination.

[1] EMEA/CHMP/QWP/251344/2006 – Guideline on the limits of genotoxic impurities

- The new requirement for PDE limit values in cleaning validation does not represent a revolution in everyday cleaning routines.
- The PDE values generally lie well above the limit values of previous calculations. But that is no reason now to do a poorer cleaning job!
- The PDE values stand on a solid scientific foundation, which is not true of the traditional criteria.
- The future will show how the European inspection authorities will proceed during inspections – the catchword is "uniformity".
- Will alternatives to the PDE expert opinions be allowed?

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

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