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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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Executive summary

When different medicinal products are produced in shared facilities, the potential for cross-contamination becomes an issue for concern. Hence, residues of an active substance which remain after cleaning of production equipment and other product contact surfaces may contaminate other medicinal products produced in the same facility. Active substances provide a medicinal benefit to the intended patient or target animal; however as a cross over contaminant, they provide no benefit to the patient or target animal and may even pose a risk. Hence, the presence of active substance contaminants should be restricted to a level that can be considered safe for all populations. The derivation of a threshold value (permitted daily exposure (PDE) or threshold of toxicological concern (TTC) should be the result of a structured scientific evaluation of all available pharmacological and toxicological data including both non-clinical and clinical data. In cases where scientific data does not support threshold values for safety (e.g., allergenic potential from highly sensitising materials) or where the risk cannot be adequately controlled by operational and/or technical measures, dedicated facilities are required for manufacturing of these high-risk medicinal products.

1. Introduction (background)

Due to the perceived risk, certain classes of active substances have previously been required to be manufactured in dedicated or segregated self-contained facilities including, "certain antibiotics, certain hormones, certain cytotoxic and certain highly active drugs". Pharmaceuticals not considered to be covered under these criteria were addressed by a cleaning validation process involving reduction of the concentration of residual active substance to a level where the maximum carryover from the total equipment train would result in no greater than 1/1000th of the lowest clinical dose of the contaminating substance in the maximum daily dosage of the next product to be manufactured. This criterion was applied concurrently with a maximum permitted contamination of 10 ppm of the previous active substance in the next product manufactured. Whichever of these criteria resulted in the lowest carryover, constituted the limit applied for cleaning validation. However, these limits do not take account of the available pharmacological and toxicological data and may be too restrictive or not restrictive enough. Hence, a more scientific case by case approach is warranted for all classes of pharmaceutical substances.

In order to accommodate a more scientific approach, Chapters 3 and 5 of the GMP guideline have been revised and refer to a "toxicological evaluation" for establishing threshold values for risk identification. The objective of this guideline is to recommend an approach to review and evaluate pharmacological and toxicological data of individual active substances and thus enable determination of safe threshold levels as referred to in the GMP guideline.

In cases where scientific data does not support threshold values (e.g. allergenic potential from highly sensitizing materials) or where the risk cannot be adequately controlled by operational and/ or technical measures, dedicated facilities are required for manufacturing these high risk medicinal products.

2. Scope

This guideline applies to all human and veterinary medicinal products, including investigational medicinal products, and all active substances that are intended for manufacture in premises used for the manufacture of other products or active substances.

The scope of the present guideline is to ensure the safety of human patients and target animals exposed to residual active substances via medicinal products as well as consumers potentially exposed to residual active substances in products derived from treated food producing animals. Moreover, this

document aims to recommend an approach for deriving a scientifically based threshold value for individual active substances to be applied for risk identification. This guideline also outlines how the data on which the threshold value is derived should be presented in the risk assessment report in order to achieve a clear and harmonious approach across pharmaceutical industry.

3. Legal basis

This guideline should be read in conjunction with:
EudraLex - Volume 4 Good manufacturing practice (GMP) Guidelines, Chapter 3 and 5.

Update on the revision of Chapters 3 and 5 of the GMP guide: "Dedicated Facilities" EMA/INS/GMP/809387/2009.

Note for Guidance on Impurities: Residual Solvents (CPMP/ICH/283/95 in conjunction with CPMP/ICH/1507/02, CPMP/ICH/1940/00 corr, CPMP/QWP/450/03, EMEA/CVMP/511/03 and CPMP/QWP/8567/99).

VICH GL18(R): Impurities: Residual solvents in new veterinary medicinal products, active substances and excipients (EMA/CVMP/VICH/502/99-Rev.1).

Guideline on the Limits of Genotoxic Impurities (EMEA/CHMP/QWP/251344/2006 and CPMP/SWP/5199/02).

4. Determination of health based exposure limits

The procedure proposed in this document for determination of health based exposure limits for a residual active substance is based on the method for establishing the so-called Permitted Daily Exposure (PDE) as described in Appendix 3 of ICH Q3C (R4) "Impurities: Guideline for Residual Solvents" and Appendix 3 of VICH GL 18 on "residual solvents in new veterinary medicinal products, active substances and excipients (Revision)". The PDE represents a substance-specific dose that is unlikely to cause an adverse effect if an individual is exposed at or below this dose every day for a lifetime.
Determination of a PDE involves (i) hazard identification by reviewing all relevant data, (ii) identification of "critical effects", (iii) determination of the no-observed-effect level (NOEL) of the findings that are considered to be critical effects, and (iv) use of several adjustment factors to account for various uncertainties. Appendices 3 of the ICH Q3C and VICH GL 18 guidelines present the following equation for the derivation of the PDE:

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

In relation to the establishment of carryover limits that can be accepted in veterinary medicinal products, it would in principle, be possible to use the PDE approach to establish different limits for different target species. However, this would be highly impractical. Consequently, it is considered pragmatic that PDEs should be derived using the assumption that it is the human patient that will be exposed. The level of contamination that can be accepted is then calculated from the human PDE, even when the product that will be contaminated is a veterinary medicinal product. This is considered to represent a pragmatic approach and is in line with the approach taken in VICH GL 18, in which human PDEs are used to calculate residual solvent limits applied for veterinary medicinal products.

The derivation of carryover limits will need to take account of the dose to be administered, which will be influenced by the body weight of the species to be treated. In order to facilitate this the PDE should be calculated on a mg/kg bw basis (i.e. using a weight adjustment figure of 1) rather than on a per person basis.[1]

Alternative approaches to the NOEL such as the Benchmark dose may also be used.

Data requirements for hazard identification

Hazard identification is the qualitative appraisal of the inherent property of a substance to produce adverse effects. For hazard identification, a review of all available animal and human data should be performed for each compound. Data for hazard identification would include non-clinical pharmacodynamic data, repeat-dose toxicity studies, carcinogenicity studies, studies of genotoxicity *in vitro* and *in vivo*, reproductive and developmental toxicity studies as well as clinical data on therapeutic and adverse effects. The availability of data for an active substance will vary depending on the stage of development and indication. If data sets are incomplete, the identified gaps need to be critically assessed with regard to the uncertainty impact this might have on deriving a reliable health based exposure limit.

Identification of critical effects

Critical effects would include the most sensitive indicator of an adverse effect seen in non-clinical toxicity studies unless there is clear evidence (e.g. from mechanistic studies, pharmacodynamic data etc.) that such finding is not relevant to humans or the target animal. A critical effect would also include any clinical therapeutic and adverse effect.

Establishing NOEL(s)

For all critical effects identified, a NOEL should be established. The NOEL is the highest tested dose at which no "critical" effect is observed. If the critical effect is observed in several animal studies, the NOEL occurring at the lowest dose should be used for calculation of the PDE value. If no NOEL is obtained, the lowest-observed-effect level (LOEL) may be used. A NOEL based on clinical pharmacodynamic effects should correspond to the highest dose level tested which is considered therapeutically inefficacious.

Application of adjustment factors

The PDE is derived by dividing the NOEL for the critical effect by various adjustment factors (also referred to as safety-, uncertainty-, assessment- or modifying factors) to account for various uncertainties and to allow extrapolation to a reliable and robust no-effect level in the human or target animal population. F1 to F5 are addressing the following sources of uncertainty:

F1: A factor (values between 2 and 12) to account for extrapolation between species
F2: A factor of 10 to account for variability between individuals
F3: A factor 10 to account for repeat-dose toxicity studies of short duration, i.e., less than 4-weeks
F4: A factor (1-10) that may be applied in cases of severe toxicity, e.g. non-genotoxic carcinogenicity, neurotoxicity or teratogenicity
F5: A variable factor that may be applied if the no-effect level was not established. When only an LOEL is available, a factor of up to 10 could be used depending on the severity of the toxicity.

[1] If the product information for the next medicinal product to be manufactured expresses the daily dose on a per patient basis rather than on a mg/kg bw basis, a standard body weight of 50 kg should be used for human medicinal products. For medicinal products for veterinary use doses are generally expressed on a mg/kg bw basis. In those instances where this is not the case, a standard body weight of 1 kg should be assumed as this would represent the lower end of animal body weights.

Please refer to Appendices 3 of the ICH Q3C (R4) and VICH GL 18 guidelines for further guidance on the choice of adjustment factors F1 and F4. The use and choice of adjustment factors should be justified. F2 and potentially F5 would need to be applied when deriving a PDE on the basis of human end points.

Selection of final PDE

If several critical effects have been identified resulting in calculation of more than one PDE value, a decision with respect to the most appropriate PDE to be used for the cleaning validation process should be made with an appropriate justification. Usually, by default the lowest PDE value will be used.

4.1 Specific considerations

4.1.1 Use of clinical data

The aim of the PDE approach is to ensure human safety, and consequently it is considered that good quality human clinical data is highly relevant. Unintended pharmacodynamic effects in patients caused by contaminating active substances may constitute a hazard thus clinical pharmacological data should be considered when identifying the critical effect. Moreover, it should be considered to what extent the active substance in question has been associated with critical adverse effects in the clinical setting.

4.1.2 Extrapolation to other routes of administration

While the PDE value derived for an active substance (contaminant) generally is based on studies applying the intended clinical route of administration, a different route of administration may be applied for the active substance or medicinal product subsequently produced in the shared facility. Changing the route of administration may change the bioavailability; hence correction factors for route-to-route extrapolation should be applied if there are clear differences (e.g. > 40%) in route-specific bioavailability. As bioavailability may vary between species, the correction factors for route-to-route extrapolation should preferably be based on human data or in the case of veterinary medicinal products, data in the relevant target animal.

In case human or target animal bioavailability data are not available for other routes and it is to be expected that the change in route of administration may result in an increase in systemic exposure for the contaminant (e.g. oral to inhalation), a conservative extrapolation can be performed by assuming 100% bioavailability of the contaminant. For example, in the case of oral-to-inhalation extrapolation, the PDE derived on basis of oral data can be corrected by multiplying with the following correction factor:

Correction factor (oral-to-inhalation): % oral absorption/ 100% respirable absorption.

In case human or target animal bioavailability data are not available for other routes and it can be expected that the systemic exposure to the contaminant will be lower via the route applied for the contaminated active substance/medicinal product, there is no need for applying a correction factor to the PDE calculation. It is expected that the route-to-route extrapolation will be performed on a case-by-case basis.

4.1.3 Active substances with a genotoxic potential

For genotoxic active substances for which there is no discernible threshold, it is considered that any level of exposure carries a risk. However, a pre-defined level of acceptable risk for non-threshold related genotoxicants has been established in the EMA Guideline on the Limits of Genotoxic Impurities in the form of the Threshold of Toxicological Concern (TTC) of 1.5 µg/person/day. The TTC represents the genotoxic impurity exposure level associated with a theoretical cancer risk of 1 additional cancer in 100,000 patients exposed over a life time. In contrast to impurities, residual active substances principally are avoidable and are not associated with a related benefit to the patient, thus a more conservative approach is appropriate when setting threshold values for residual active substances. Hence, in the case of residual active substances without a threshold, a limit dose corresponding to a theoretical 1×10^6 excess lifetime cancer risk should be applied, i.e., 0.15 µg/person/day, or 0.0025 µg/kg bw.

For genotoxic pharmaceutical substances with sufficient evidence of a threshold related mechanism, safe exposure levels without appreciable risk of genotoxicity can be established by using the PDE approach.

4.1.4 Active substances with a sensitising potential

Drug-induced immune-mediated hypersensitivity reactions may develop in sensitive individuals. The observed reactions may range from mild cases of contact sensitisation to potentially lethal anaphylactic reactions.
Concerning topically applied medicinal products, literature data support that a non-sensitizing dose for active substances inducing skin sensitisation exists both with respect to the induction of skin sensitisation and its elicitation. Hence, in case the non-sensitising dose has been established in humans or target or laboratory animals, a PDE value can be derived applying the PDE approach.
For other routes of administration, a safe level of exposure is more difficult to establish. As outlined in point 3.6 of the GMP guideline, dedicated facilities are required for manufacturing active substances and medicinal products for which scientific data does not support a threshold value.

4.1.5 Therapeutic macromolecules and peptides

Generally speaking, therapeutic macromolecules and peptides are characterised by exerting specific primary pharmacodynamic effects to such an extent that the adverse effects observed are restricted to exaggerated pharmacodynamic effects or secondary effects thereof. As a consequence, the critical effect for the derivation of PDE is in many cases solely the pharmacodynamic effect. This would not apply to a therapeutic protein conjugated to a small molecule as pharmacophore (e.g. a cytostatic agent), where the toxicity of the conjugate needs to be considered. A NOEL based on clinical pharmacodynamic effects should correspond to the highest dose level tested which is considered therapeutic inefficacious. For therapeutic macromolecules and peptides, it is not considered acceptable to derive a PDE value based on the LOEL for pharmacodynamic effects. If no clinical pharmacodynamic data are available, the NOEL should be based on non-clinical studies. All available non-clinical *in vitro* and *in vivo* pharmacodynamic data should be considered when establishing a NOEL for pharmacodynamic effects for therapeutic macromolecules and peptides. Animal studies investigating the pharmacodynamic effect should be conducted in a pharmacologically relevant species. Moreover, if basing a PDE value on a pharmacodynamic animal study, potential species differences in target affinity should be compensated for.

4.1.6 Lack of animal data on reproductive and developmental toxicity

In order to ensure protection of all populations, the presence of residual active substance should be reduced to a level that will not pose a risk for effects on reproductive and developmental parameters. However, in the early phases of development, non-clinical data to assess the potential of the new active substance to cause reproductive and developmental toxicity may often be lacking. Gaps in scientific knowledge may also exist for authorised medicinal products, e.g., the potential for a male-specific drug to cause adverse effects on embryo-foetal development. In these cases, the use of a generic threshold value as is applied for genotoxic substances may be considered. Such a threshold value could be conservatively derived from a database of NOAELs obtained in animal studies of fertility and embryo-fetal development conducted for active substances representing a wide selection of pharmacodynamic effects. In order to be acceptable, such a threshold value would need to be available in public literature.
In case the level of residual active substance cannot be reduced to the established threshold value or when insufficient data are available to establish a threshold value, the active substance should be manufactured in a dedicated facility.

4.2 Risk Assessment Report

The risk assessment report should be based on a comprehensive literature search including handbook and monographs as well as searches in electronic scientific databases. The search strategy and the results of the search must be clearly documented. Following an expert review, the company should provide a discussion with respect to the critical endpoints of concern and their rationale for the choice of endpoints and dose that is to be used in the derivation of the PDE. The pivotal animal and human studies used for the derivation of the PDE should be sourced to the original reference and reviewed regarding their quality (study design, description of finding, accuracy of the report etc.). The risk assessment report should provide a clear rationale regarding the adjustment factors that were applied in deriving the PDE. Moreover, in order to provide an overview to the GMP inspectors, the initial page of any prepared risk assessment report should be in the form of a summary of the assessment process (please see Annex for template example).

Definitions

F Adjustment Factor

GMP Good Manufacturing Practice

ICH International Conference on Harmonisation

LOEL Lowest Observed Effect Level

PDE Permitted Daily Exposure

NOAEL No Observed Adverse Effect Level

NOEL No Observed Effect Level

TTC Threshold of Toxicological Concern

VICH Veterinary International Conference on Harmonisation

Annex

Summary of Risk Assessment Report

Company Name

Company Address

Expert Name and Signature **Date**

Assessment Review Date

Chemical Name/s

Hazards Identified

	YES	NO	UNKNOWN
Positive genotoxicant			
Reproductive developmental toxicant			
Potential carcinogen			
Sensitizing potential			

Basis for the PDE

Critical effect observed

Dose upon which the PDE is based.

Reference/s

Publication/s used to identify the critical effect and dose

Derived PDE

Calculation

Summary of the Expert CV