PHARMACEUTICAL INSPECTION CONVENTION
PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME

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Annex
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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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1. DOCUMENT HISTORY

Adapted by SCC from EMA/CHMP/ CVMP/ SWP/169430/2012	September 2015 – September 2016
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The present PIC/S Guidelines are based on document EMA/CHMP/CVMP/SWP/169430/2012, which has been drafted by the EMA and transposed for PIC/S purpose by the PIC/S Sub-Committee on the Harmonisation of GM(D)P.

These guidelines have been adopted by PIC/S as a guidance document. It is up to each PIC/S Participating Authority to decide whether it should become a legally-binding standard.

2. INTRODUCTION

2.1 When different medicinal products are produced in shared facilities, the potential for cross-contamination is a concern. Medicinal products provide a benefit to the intended patient or target animal; however, as a cross contaminant, they provide no benefit to the patient or target animal and may even pose a risk. Hence, the presence of such contaminants should be managed according to the risk posed which in turn are related to levels that can be considered safe for all populations. To this end, health-based limits through the derivation of a safe threshold value should be employed to identify the risks posed. The derivation of such a threshold value (e.g. 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.

2.2 During the manufacture of medicinal products accidental cross-contamination can result from the uncontrolled release of dust, gases, vapours, aerosols, genetic material or organisms from active substances, other starting materials, and other products being processed concurrently, as well as from residues on equipment, and from operators' clothing. Due to the perceived risk, certain classes of medicinal product 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". Until now no official guidance is available in order to assist manufacturers to

differentiate between individual products within these specified classes. Chapters 3 and 5 of the GMP guideline have been revised to promote a science and risk-based approach and refer to a "toxicological evaluation" for establishing threshold values for risk identification.

2.3 Cleaning is a risk reducing measure and carry-over limits for cleaning validation studies are widely used in the pharmaceutical industry. A variety of approaches are taken in order to establish these limits and often do not take account of the available pharmacological and toxicological data. Hence, a more scientific case by case approach is warranted for risk identification and to support risk reduction measures for all classes of pharmaceutical substances.

2.4 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 threshold levels as referred to in the GMP guideline. These levels can be used as a risk identification tool and can also be used to justify carry over limits used in cleaning validation. While Active Pharmaceutical Ingredients (APIs) are not discussed in Chapters 3 and 5 of the GMP guideline, the general principles outlined in this guideline to derive a threshold value for risk identification could be applied where required.

2.5 Deviation from the main approach highlighted in this guideline to derive safe threshold levels could be accepted if adequately justified.

3. SCOPE

3.1 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 present in food of animal origin as a result of treatment of food producing animals with veterinary medicinal products in which residual active substances are present.

3.2 In doing so, this document aims to recommend an approach for deriving a scientifically based threshold value for individual active substances to be applied for risk identification. The guideline outlines how the data on which the threshold value is derived should be presented in order to achieve a clear and harmonious approach across pharmaceutical industry.

3.3 This guideline should be read in conjunction with:

3.3.1 PIC/S PE 009 Good Manufacturing Practice (GMP) Guidelines, Chapter 3 and 5;

3.3.2 ICH Harmonised Tripartite Guideline, Impurities: Guideline for Residual Solvents Q3C;

3.3.3 VICH GL18(R): Impurities: Residual solvents in new veterinary medicinal products, active substances and excipients;

3.3.4 ICH Harmonised Guideline, Guideline for Elemental Impurities Q3D;

3.3.5 ICH Harmonised Tripartite Guideline, Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk M7; and

3.3.6 Other national regulatory guidance documents, as applicable.

4. DETERMINATION OF HEALTH BASED EXPOSURE LIMITS

4.1 Calculation of a Permitted Daily Exposure (PDE)

4.1.1 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.

4.1.2 Determination of a PDE involves (i) hazard identification by reviewing all relevant data, (ii) identification of "critical effects", (iii) determination of the no-observed-adverse-effect level (NOAEL) 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:

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

4.1.3 In relation to the establishment of health based exposure 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 assuming human exposure. 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.

4.1.4 The derivation of 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].

4.1.5 When the product that may become contaminated with a residual active substance is a veterinary medicinal product for administration to food producing animals, the carryover limit applied must take account of both target animal safety considerations and consumer safety considerations. It should therefore be demonstrated, based on worst case exposure scenarios, that neither the target animal nor the consumer will be exposed to residual active substance levels exceeding the PDE.

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

4.1.7 The use of other approaches to determine health based exposure limits could be considered acceptable if adequately and scientifically justified.

4.1.8 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, in vitro and in vivo genotoxicity studies, reproductive and developmental toxicity studies as well as clinical data (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 will need to be critically assessed with regard to the impact this might have on deriving a reliable health based exposure limit.

[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.

4.1.9 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 findings are not relevant to humans or the target animal. A critical effect would also include any clinical therapeutic and adverse effect.

4.1.10 Establishing NOAEL(s)

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

4.1.11 Application of adjustment factors

4.1.11.1 The PDE is derived by dividing the NOAEL 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 a LOEL is available, a factor of up to 10 could be used depending on the severity of the toxicity.

4.1.11.2 The use of additional modifying factors to address residual uncertainties not covered by the above factors may be accepted provided they are well supported with literature data and an adequate discussion is provided to support their use e.g. lack of

data for reproductive and developmental toxicity (see section 5.4).

4.1.11.3 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. A restriction to use of F2 and potentially F5 may be acceptable when deriving a PDE on the basis of human end points. Deviations from the default values for the adjustment factors presented above can be accepted if adequately and scientifically justified.

4.1.12 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.

4.2 Use of clinical data

4.2.1 The aim of determining a health-based exposure limit 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. Consideration should be given to what extent the active substance in question has been associated with critical adverse effects in the clinical setting.

4.2.2 If the most critical effect identified to determine a health-based exposure limit is based on pharmacological and/or toxicological effects observed in humans rather than animals, the use of the PDE formula may be inappropriate and a substance-specific assessment of the clinical data may be used for this purpose.

4.3 Extrapolation to other routes of administration

4.3.1 While the PDE value derived for an active substance (contaminant) generally is based on` that the route-to-route extrapolation will be performed on a case-by-case basis.

5. SPECIFIC CONSIDERATIONS

5.1 Active substances with a genotoxic potential

5.1.1 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 genotoxicant has been established in various international guidance, including the ICH Harmonised Tripartite Guideline, Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk M7, 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 when exposed over a life time. Given the fact that exposure duration to residual active substances will be much more restricted (for example because, in practice, levels of residual active substance carryover can be expected to diminish on a batch by batch basis), limits based on a maximum, exposure to 1.5 μg/person/day in this case would not exceed a theoretical 1 x 10-6 excess cancer risk. Hence, in the case of residual active substances without a threshold, a limit dose of 1.5 μg/person/day may be applied.

5.1.2 When the product that may become contaminated with a residual active substance is a veterinary medicinal product the same TTC should be used, but expressed on a 'per kg bodyweight' basis (i.e. the TTC is 0.03 μg/kg bw/day). When the contaminated product is for administration to food producing animals, the carryover limit applied must take account of both target animal safety considerations and consumer safety considerations. It should therefore be demonstrated, based on worst case exposure scenarios, that neither the target animal nor the consumer will be exposed to residual active substance levels exceeding the TTC.

5.1.3 For genotoxic active substances where sufficient carcinogenicity data exists, compound-specific risk assessments to derive acceptable intakes should be applied instead of the TTC-based acceptable intake approach.

5.1.4 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.

5.2 Active substances with a highly sensitising potential

5.2.1 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.

5.2.2 As outlined in Chapter 3 paragraph 3.6 of the GMP guideline, dedicated facilities are required for manufacturing active substances and medicinal products with a high sensitising potential for which scientific data does not support an acceptable level of exposure or the risk associated with handling the product at the facility cannot be adequately controlled by organisational or technical measures. Classification of an active substance or medicinal product with a high sensitising potential should consider whether the substance shows a high frequency of sensitising occurrence in humans; or a probability of occurrence of a high sensitisation rate in humans based on animal data or other validated tests. Severity of these reactions should also be considered and should be included in a weight of evidence assessment.

5.3 Therapeutic macromolecules and peptides

5.3.1 Therapeutic macromolecules and peptides are known to degrade and denature when exposed to pH extremes and/or heat, and may become pharmacologically inactive. The cleaning of biopharmaceutical manufacturing equipment is typically performed under conditions which expose equipment surfaces to pH extremes and/or heat, which would lead to the degradation and inactivation of protein-based products. In view of this, the determination of health based exposure limits using PDE limits of the active and intact product may not be required.

5.3.2 Where other potential routes of cross-contamination exist, the risks posed should be considered on a case-by-case basis.

5.4 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 not yet have been generated. 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 NOAEL of a sub-chronic/chronic study may be used in the calculation of a PDE with application of an additional adjustment factor (e.g. 10) if adequately justified. In cases

where appropriate data from reproductive and developmental toxicity studies of related compounds are available a class-specific profile may be used for hazard identification of the not tested contaminant through application of a read across approach.

5.5 Investigational Medicinal Products

For early development (Phase I/II) investigational medicinal products (IMPs) estimation of PDEs may be difficult based on their limited data sets. Where this is apparent, an alternative approach using categorisation into specific default value categories e.g. based on low/high expected pharmacological potency, low/high toxicity, genotoxicity/carcinogenicity, similar to the tiered Threshold of Toxicological Concern approaches proposed by Kroes et al. (2004), Munro et al. (2008), and Dolan et al. (2005)[2], can be considered to derive health-based exposure limits if adequately justified.

Since most default limits are defined for chronic exposure durations, a higher limit may be justified if a drug substance shares equipment with another that is intended for short-term clinical trials (Bercu and Dolan, 2013)3. With the availability of more pharmacological and toxicological data, compound-specific limits should be calculated as described above for the derivation of health-based exposure limits.

6. REPORTING OF THE PDE DETERMINATION STRATEGY

The identification of a "critical effects" in the establishment of a PDE as outlined in section 4 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 PDE determination strategy 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 PDE determination strategy document should be a summary of the assessment process (please see Annex for template example).

[2] Kroes R, Renwick A, Cheeseman M, Kleiner J, Mangelsdorf I, Piersma A, Schilter B, Schatter J, van Schothorst F, Vos JG, Würtzen G. (2004). Structure-based thresholds of toxicological concern (TTC): guidance for application to substances present at low levels in the diet. Fd Chem Toxicol 42, 65-83.

Munro IC, Renwick AG, Danielewska-Nikiel B (2008). The threshold of toxicological concern (TTC) in risk assessment. Toxicol Lett 180, 151-156.

Dolan DG, Naumann BD, Sargent EV, Maier A, Dourson M (2005). Application of the threshold of toxicological concern concept to pharmaceutical manufacturing operations. Regul Toxicol Pharmacol, 43, 1-9.

[3] Bercu JP & Dolan DG, (2013). Application of the threshold of toxicological concern concept when applied to pharmaceutical manufacturing operations intended for short-term clinical trials. Regul Toxicol Pharmacol. 2013 Feb;65(1):162-7.

7. IMPLEMENTATION

7.1 Implementation of this guideline is in accordance with provisions established by applicable national competent authorities.

7.2 This guideline has been developed as a risk identification tool to facilitate the implementation of a science and risk based approach to manufacture of medicinal products using shared manufacturing facilities in accordance with

Chapters 3 and 5 of the GMP Guide. It is recommended that manufacturers apply quality risk management principles in establishing an implementation plan for adoption of principles expressed in this guide.

7.3 Where appropriate, alternative approaches may be deemed acceptable when in accordance with national requirements.

8. DEFINITIONS

F	:	Adjustment Factor
GMP	:	Good Manufacturing Practice
ICH	:	International Conference on Harmonisation
LOAEL	:	Lowest Observed Adverse Effect Level
PDE	:	Permitted Daily Exposure (ADE Allowable Daily Exposure[4])
NOAEL	:	No Observed Adverse Effect Level
TTC	:	Threshold of Toxicological Concern
VICH	:	Veterinary International Conference on Harmonisation

9. REFERENCES:

Kroes R, Renwick A, Cheeseman M, Kleiner J, Mangelsdorf I, Piersma A, Schilter B, Schatter J, van Schothorst F, Vos JG, Würtzen G. (2004). Structure-based thresholds of toxicological concern (TTC): guidance for application to substances present at low levels in the diet. Fd Chem Toxicol 42, 65-83.

Munro IC, Renwick AG, Danielewska-Nikiel B (2008). The threshold of toxicological concern (TTC) in risk assessment. Toxicol Lett 180, 151-156.

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Bercu JP & Dolan DG, (2013). Application of the threshold of toxicological concern concept when applied to pharmaceutical manufacturing operations intended for short-term clinical trials. Regul Toxicol Pharmacol. 2013 Feb;65(1):162-7.

[4] PDE and ADE are effectively synonymous.

10. ANNEX

PDE Determination Strategy
Company Name
Company Address
Expert Name and Signature **Date**
Assessment Review Date
Chemical Name/s

Hazards Identified	**YES**	**NO**	**UNKNOWN**
Genotoxicant			
Reproductive developmental toxicant			
Carcinogen			
Highly sensitizing potential			

Basis for the PDE
Justification for selection of ”lead” critical effect used for final PDE calculation
NOAEL and applied adjustment factors upon which the PDE is based
Reference(s)
Publication(s) used to identify the critical effect and dose
Summary of the Expert CV

11. REVISION HISTORY

Date	**Version Number**	**Reasons for revision**