ANNEX

to the Decision No. of the Board

of the Eurasian Economic Commission

dated

# GUIDELINES
## on setting health exposure limits for use in risk identification in the manufacture of different medicinal products at single facility

## I. General Provisions

1. These Guidelines have been developed to create scientifically based approaches and methodological framework for analyzing and assessing the risks that are possible in the manufacture of different, including highly active, medicinal products at the same production facilities, taking into account the permissible human health exposure limits.

2. When different medicinal products are manufactured in shared production facilities, the potential cross-contamination hazard gives rise to concern. At the same time, the multi-purpose use of production facilities based on scientific knowledge is a reasonable, expedient and important development mechanism that will have a significant impact in the near future on the development of the pharmaceutical industry not only for the Member States of the Eurasian Economic Union, but also for the global pharmaceutical industry.

3. Medicinal products provide a benefit to the intended patient or relevant animal species, however, as a cross contaminant, they pose a risk to the patient or relevant animal species. Hence, the presence of such contaminants should be controlled according to the risk posed. Risk is determined by the level that can be considered safe for all populations. To

this end, health limits derived from a safe threshold value should be used to identify the risks posed. The determination 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.

4. Scientific approach tools for identifying risks in the manufacture of medicinal products using the shared production facilities provided in these Guidelines have been developed in accordance with Chapters 3 and 5 of the Rules of Good Manufacturing Practice of the Eurasian Economic Union approved by the Decision No. 77 of the Eurasian Economic Commission's Council dated November 3, 2016 (hereinafter referred to as the GMP Rules) and are based on the use of pharmacological and toxicological data – evaluation criteria: permitted daily exposure (PDE), threshold of toxicological concern (TTC), allowable daily exposure (ADE), occupational exposure level (OEL) to analyze risks and control the effects of cross-contamination products on humans.

5. Deviation from the main approach provided in these Guidelines to determine such safe threshold levels is acceptable if adequately justified.

6. During the medicinal products manufacture accidental cross-contamination can result from the uncontrolled release of dust, gases, vapors, aerosols, genetic material or organisms from active pharmaceutical ingredients, other source materials, and other products being processed concurrently, as well as from residual impurities on equipment and from operators' clothing. Due to the perceived risk, certain classes of medicinal products have been required to be manufactured in dedicated or allocated isolated facilities including, «certain antibiotics, certain hormones, certain cytotoxics and certain highly active pharmaceuticals».

7. Cleaning as a measure for reducing contamination risk and carry-over limits (norms) for cleaning validation studies are widely used in the pharmaceutical industry. A variety of approaches are used to establish these limits, which often do not take into account the available pharmacological and toxicological data. Therefore, a more scientific case by case approach is required for risk identification and to support risk reduction measures for all classes of pharmaceutical substances.

8. The objective of these Guidelines is to provide a recommended approach to review and evaluate pharmacological and toxicological data of individual active pharmaceutical ingredients and thus enable the determination of threshold levels (content) referred to in the GMP Rules. These levels can be used as a risk identification tool and to justify carry-over limits of contaminant residues to subsequent products used in cleaning validation. Despite active pharmaceutical ingredients are not considered in Chapters 3 and 5 of the GMP Rules, the general principles outlined in these Guidelines may be used in relevant cases to obtain a threshold value for risk identification.

9. Deviation from the main approach provided in these Guidelines to determine such safe threshold levels is acceptable if adequately justified.

## II. Scope

10. The scope of these Guidelines is to ensure the safety of human patients and target animals exposed to residual active substances (contaminants) 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 containing residual active substances. For that matter, this document contains a recommended approach for obtaining a scientifically based

threshold value for individual active substances to be applied for risk identification. In order to achieve a clear and harmonious approach across the pharmaceutical industry, the guidelines set out how the data underlying the threshold value determination should be presented.

## III. Definitions

11. For the purpose of these Guidelines, concepts shall be used with their following meanings:

«Active substance» – means an active pharmaceutical ingredient that makes part of the pharmaceutical.

«No Observed Adverse Effect Level (NOAEL)» – means the highest concentration or amount of a substance that showed in the experiment no undesirable effect on the morphology, functional capacity, growth, development or length of life of the target organism, which is distinguishable from normal (control) organisms of the same species and line in given exposure conditions (mg of active pharmaceutical ingredient per 1 kg of bodyweight).

«Permitted Daily Exposure (PDE)» – means the maximum allowable dose of a particular substance that will cause no negative effects when exposed to this dose daily for the entire life of a person.

«Lowest Observed Adverse Effect Level (LOAEL)» – means the smallest dose of a substance that exhibited in the experiment an undesirable effect on the morphology, functional capacity, growth, development or length of life of the target organism, which is distinguishable from normal (control) organisms of the same species and line in given exposure conditions;

«Threshold of Toxicological Concern (TTC)» – means a genotoxic impurity exposure level, which leads to a theoretical cancer risk equal to 1 additional case of cancer in 100,000 patients during lifelong exposure.

## IV. Determination of Health Based Exposure Limits

### 1. Calculation of Permitted Daily Exposure (PDE)

12. The procedure described in these Guidelines for determination of health exposure limits for a residual active substance is based on the method for establishing the Permitted Daily Exposure (PDE). 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:

a) hazard identification by analyzing all relevant data;

b) identification of «critical effects»;

c) determination of the no observed adverse effect level (NOAEL) in relation to the events that are considered to be critical effects;

d) use of several adjustment factors to account for various uncertainties.

PDE is calculated by the formula:

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

where:

NOAEL – no observed adverse effect level;

F1 – an adjustment factor for extrapolation between animal species;

F2 – a factor accounting for inter-individual variability;

F3 – a factor taking into account repeat-dose toxicity studies of short duration, i.e. less than 4 weeks;

F4 – a factor used in cases of severe toxicity, for example, non-genotoxic carcinogenicity, neurotoxicity or teratogenicity;

F5 – a variable factor applied where the no observed adverse effect level has not been established.

13. In order to establish health exposure limits that have been developed for 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.

14. Therefore, a practical approach is to determine PDE based on data on the impact on human health. The level of contamination that can be accepted is then calculated from the human PDE, even when the contaminated product is a veterinary medicinal product. This is considered a pragmatic approach and is in line with the approach, in which human PDEs are used to calculate residual solvent limits applied for veterinary medicinal products.

15. The determination of limits will need to take account of the dose to be administered, which will depend on the bodyweight of the animal species used. In order to facilitate this, the PDE should be calculated on «mg/kg bodyweight» basis (i.e. using a weight adjustment factor of 1) rather than on a «per animal as a whole» basis. Where the information on the subsequent medicinal product to be manufactured is expressed as a daily dose for the patient rather than in mg/kg bodyweight, a standard bodyweight of 50 kg should be used for human medicinal products. For medicinal products for veterinary use, doses are generally expressed on mg/kg bodyweight basis. Where this is impossible, it should be based on the standard mass of 1 kg, since it will reflect a lower limit of animal bodyweight.

16. 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 used should take account of both relevant animal safety and consumer safety. In this regard, it should be demonstrated, using the worst-case exposure scenarios, that neither the relevant animal species nor the consumer will be exposed to residual active substance levels exceeding the PDE.

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

18. The use of other approaches to determine health exposure limits is acceptable if justification is based on scientific data.

## Requirements to Data for Hazard Identification

19. Hazard identification is the qualitative assessment of the individual properties of a substance to cause adverse effects. For hazard identification, an analysis of all available animal and human data should be performed for each substance. Data for hazard identification 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 set is incomplete, the identified gaps will need to be critically assessed from the perspective of the impact this might have on determining a reliable health exposure limit.

## Identification of Critical Effects

20. Critical effects would include the most sensitive indicator of an adverse effect found in non-clinical toxicity studies with no clear evidence (e.g. from *in vitro* studies, pharmacodynamic data etc.) that such information is not significant for humans or target animals. Critical effect also include any clinical pharmacological and adverse effect.

## Establishing NOAEL Value

21. For all critical effects identified, a no observed adverse effect level (NOAEL) should be established.

22. If the critical effect is observed in several animal studies, the NOAEL recorded at the lowest dose should be used for calculation of the PDE value.

23. If NOAEL is unknown, the lowest observed adverse effect level (LOAEL) may be used.

24. NOAEL based on clinical pharmacodynamic effects should correspond to the highest dose tested which is considered therapeutically inefficacious.

## Use of Adjustment Factors

25. The PDE is determined 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 provide extrapolation to a reliable and proven no-effect level in the human or relevant animal.

26. F1 – F5 adjustment factors are addressing the following sources of uncertainty:

F1 – a factor (which values are between 2 and 12) to account for extrapolation between species.

F2 – a factor of 10 to account for inter-individual variability.

F3 – a factor of 10 taking into account repeat-dose toxicity studies of short duration, i.e. less than 4 weeks;

F4 – a factor (1-10) used in cases of severe toxicity, for example, non-genotoxic carcinogenicity, neurotoxicity or teratogenicity.

F5 – a variable factor applied where the no observed adverse effect level has not been established. When only a LOAEL is available, a factor of up to 10 may be used depending on the severity of the toxicity.

27. The use of additional modifying factors to address residual uncertainties not covered by the above factors is acceptable if they are well supported with literature data and an adequate analysis is provided to support their use e.g. in case of lack of data for reproductive and developmental toxicity (see subsection 4 of Section V of these Guidelines).

28. The use and choice of adjustment factors should be justified. It is allowed to follow the guidelines on the choice of F1 and F4 adjustment factors provided in the published scientific guides, and a bibliographic reference to such guidelines should be given.

29. A restriction to use of F2 and potentially F5 factors is acceptable when calculating PDE on the basis of human endpoints. Deviations from the default values for the adjustment factors presented above are acceptable if scientifically justified.

### Selection of Final PDE Value

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

## 2. Use of Clinical Data

31. The aim of determining a health exposure limit is to ensure human safety, and therefore good quality clinical data is highly relevant. Undesirable pharmacodynamic effects in patients caused by contamination of active substances may constitute a hazard so clinical pharmacological data should

be considered when identifying the critical effect. It should be considered to what extent the active substance in question has been associated with the development of a critical adverse effect in a clinical setting.

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

Extrapolation to Other Routes of Administration

33. Despite the PDE value calculated for an active substance (contaminant) is generally based on studies with the intended clinical route of administration, a different route of administration may be intended for the active substance or medicinal product subsequently manufactured at the same production facility. Changing the route of administration may change the bioavailability; hence adjustment factors for route-to-route extrapolation should be applied if there are clear differences (e.g. differences > 40%) in route-specific bioavailability. As bioavailability may vary between species, the adjustment 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 animal species.

34. In case human or relevant animal bioavailability data are not available for other routes and it is expected that the change in route of administration may result in an increase in systemic exposure for the contaminant (e.g. from oral to inhalation), a conservative extrapolation may be performed based on 100% bioavailability of the contaminant. For example, in the case of extrapolation from oral to inhalation route of

administration, the PDE obtained on basis of oral data may be corrected by multiplying with the following adjustment factor:

Adjustment factor for recalculation of data obtained for the oral to inhalation route of administration (for which respirable absorption is 100%):

$$\text{Adjustment factor} = \frac{\text{oral absorption, \%}}{\text{100 \%}}$$

Where human or relevant animal species bioavailability data are not available for other routes and it is 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 to apply a adjustment factor to the PDE calculation. The route-to-route extrapolation should be performed on a case-by-case basis.

## V. Special Cases

### 1. Active Substances with a Genotoxic Potential

35. It is considered that any level of exposure to genotoxic active substances for which there is no discernible threshold carries a risk. However, a pre-defined level of acceptable risk for non-threshold genotoxicants has been established in the form of the threshold of toxicological concern (TTC) of 1.5 μg/person/day. The TTC is the genotoxic impurity exposure level leading to a theoretical cancer risk equal to 1 additional case of cancer in 100,000 patients during lifelong exposure. Taking into account that exposure duration to residual active substances will be much more restricted (for example because, in practice, levels of residual active substance carryover will decrease on a batch by batch basis), limits based on a maximum exposure of 1.5 μg/person/day in this case would not exceed a theoretical $1x10^{-6}$ cancer risk. Therefore, in the case of residual active substances without a threshold, it is allowed to use a limit dose of 1.5 μg/person/day.

36. If the product potentially 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 bodyweight/day). When the contaminated product is intended for administration to food producing animals, the carryover limit applied must take account of both animal safety considerations and consumer safety considerations. It should therefore be demonstrated, based on worst-case exposure scenarios, that neither the relevant animal species nor the consumer will be exposed to residual active substance levels exceeding the TTC.

37. For genotoxic active substances where sufficient carcinogenicity data exists, compound-specific risk assessments should be applied instead of the TTC.

38. For genotoxic active substances with sufficient evidence of a threshold mechanism, safe exposure levels may be established by using the PDE approach without significant risk of genotoxicity.

## 2. Active Substances with a Highly Sensitizing Potential

39. Drug-induced immune-mediated hypersensitivity reactions may develop in sensitive individuals. The observed reactions may range from mild cases to potentially lethal anaphylactic reactions.

40. As indicated in paragraph 3.6 of Chapter 3 of the GMP Rules, dedicated facilities are required for manufacturing active pharmaceutical ingredients and medicinal products with a high sensitizing potential for which scientific data does not support an acceptable level of exposure or the risk associated with the handling the product at the facility. This is applicable when the specified risk cannot be adequately controlled by organizational or technical measures. Classification of an active substance or medicinal product with a high sensitizing potential should consider whether the

substance shows a high frequency of sensitizing occurrence in humans; or a probability of occurrence of a high sensitization rate in humans is based on animal data or other validated tests. Severity of these reactions should also be considered when included in a weight of evidence assessment.

### 3. Therapeutic Macromolecules and Peptides

41. Therapeutic macromolecules and peptides are subject to degradation and denaturation when exposed to pH extremes and/or heat, and may become pharmacologically inactive. The cleaning of biopharmaceutical manufacturing equipment is typically performed under conditions when equipment surfaces are exposed 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 for the non-inactivated active substance may not be required.

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

### 4. Lack of Data on Reproductive and Developmental Toxicity

43. 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 have been generated yet. Gaps in scientific knowledge may also exist for authorized medicinal products, e.g., the potential for a male-specific medicinal products to cause adverse effects on embryo-fetal development. In this case, the NOAEL of a long-term/medium-term study may be used in the PDE calculation with application of an additional adjustment factor (e.g. 10)

if adequately justified. If 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 non-tested contaminant through application of a read-across method.

## 5. Investigational Medicinal Products

44. For early development (Phase I/II) investigational medicinal products estimation of PDE may be difficult due to limited data. In such cases, an alternative approach using categorization into specific default value categories e.g. based on low (high) expected pharmacological potency, low (high) toxicity, genotoxicity (carcinogenicity), similar to the tiered approaches based on the threshold of toxicological concern may be used to determine health exposure limits if adequately justified.

45. Since most default limits are defined by repeated exposure durations, sometimes a higher limit may be justified if a medicinal product, when manufactured, shares equipment with another one that is intended for short-term clinical trials.

46. With more pharmacological and toxicological data becoming available, compound-specific limits should be calculated as described above for the determination of health exposure limits.

## 6. Providing Data on PDE Determination Strategy

47. The identification of «critical effects» in the establishment of PDE described in Section 4 of these Guidelines should be based on a comprehensive literature search including handbooks and monographs as well as search in electronic scientific databases.

The search strategy and its results must be clearly documented. Following the specialist’s review, the company should provide a discussion

of critical endpoints of concern and its rationale for the choice of endpoints and dose that is to be used in the PDE calculation.

48. The pivotal animal and human studies used for the PDE calculation should be sourced to the original reference and reviewed regarding their quality (study design, description of results, accuracy of reports, etc.). The PDE calculation strategy should provide a clear basis regarding the choice of adjustment factors that were used for the determination of the PDE. Moreover, in order to provide an overview to the pharmacist inspectors, the cover page of any prepared PDE calculation strategy document should be a summary of the assessment process according to the Annex to these Guidelines.

ANNEX

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**PDE Determination**

**STRATEGY**

Company Name

Company Address

Specialist Name and Signature Date

Assessment Date

Chemical Name(s)

Hazards Identified

| | YES | NO | UNKNOWN |
|---|---|---|---|
| Genotoxicant | □ | □ | □ |
| Reproductive/Developmental Toxicant | □ | □ | □ |
| Carcinogen | □ | □ | □ |
| Highly Sensitizing Potential | □ | □ | □ |

**Justification for PDE calculation**

Justification for selection of a «leading» critical effect used for final PDE NOAEL calculation and applied adjustment factors upon which the PDE is calculated.

**Reference**

Publication(s) used to determine the critical effect and dose

**Summary of the specialist's CV**