T.C. SAĞLIK BAKANLIĞI
TÜRKİYE İLAÇ VE
TIBBİ CİHAZ KURUMU

BEŞERİ TIBBİ ÜRÜN TESİSLERİ RİSK DEĞERLENDİRME BAŞVURU KILAVUZU

İLAÇ DENETİM DAİRESİ BAŞKANLIĞI

These guidelines do not constitute an interpretation of the current legislation and has been prepared solely to guide applications.

2021

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1. PURPOSE

This guidelines document has been prepared to guide the procedures and principles regarding the content and process of the applications to be made to the Agency for the manufacture of veterinary medicinal products in appropriate form and class and supplementary foods in appropriate form in the same area in the facilities for which the manufacturing site permit has been issued by Türkiye Medicines and Medical Devices Agency for manufacture of medicinal products for human use or the manufacture of applied biocidal products, human tissue and cell products, medical devices, and cosmetic products by using separate areas, separate equipment and separate ventilation systems.

2. INTRODUCTION

In the event that different product groups are planned to be produced in human medicinal product manufacturing facilities, appropriate measures should be taken to prevent a possible cross-contamination. There is a risk that medicinal products for human use intended to benefit a particular patient group may not be able to show the intended effect or even harm the user due to cross-contamination. Therefore, such contaminants should be kept at levels that may be considered safe. To that end, health-based limit values should be used, starting from a safe threshold value, to identify emerging risks. Such a threshold value should have been derived from a scientific evaluation of all available pharmacological and toxicological data, including clinical and non-clinical data (e.g. the Permitted Daily Exposure (PDE) or the Threshold of Toxicological Concern (TTC) value).

Contamination of the starting material and the product with another substance or product should be avoided. The risk of accidental cross-contamination arises from uncontrollable dust, gases, vapors, sprays, substances in the process, organisms in products, residues on equipment, and workers' clothing. The significance of such risk varies with the type of contagious agent and the product contaminated. Among the most dangerous contagious agents come the highly sensitizing substances, the biological preparations containing living organisms, certain hormones, cytotoxic substances and highly active substances. Injection drugs, medicine administered at high doses and/or for long periods of time occur to be the products with the highest risk of contamination.

In chapters 3 and 5 of Section I of the Good Manufacturing Practices (GMP) Guidelines for Medicinal Products for Human Use, it is recommended to use toxicological evaluation in line with a scientific and risk-based approach in order to determine the threshold values in risk definition.

Cleaning is a risk reduction measure, and carry-over limits are widely used in the pharmaceutical industry in cleaning validation studies. Various approaches are applied to achieve these limit values, yet still, available pharmacological and toxicological data must be taken into account. Therefore, a case-based scientific approach is required to support risk identification and risk reduction measures for all classes of pharmaceuticals.

The purpose of this guidelines document is to suggest an approach to evaluate and examine the pharmacological and toxicological data of each active substance, making it possible to determine the threshold values also specified in the GMP guidelines. These values may be used as a risk identification tool as well as to verify the carry-over limits used in cleaning validation. Although active substances are not covered in chapters 3 and 5 of Section 1 of the GMP Guidelines, all principles outlined in this guideline may be used when necessary to obtain a threshold for risk identification.

Deviations from the main approach highlighted in this guideline to achieve a safe threshold are acceptable in case they are appropriately justified and adequate precautions are taken.

3. BASIS

This guidelines document has been prepared based on the Pharmaceutical and Medical Preparations Law with date 14.05.1928 and no. 1262, and the Regulation Regarding the Manufacturing Sites of Medicinal Products for Human Use, published in the Official Gazette with date 21.10.2017 and no. 30217, and the current GMP Guidelines.

4. SCOPE

This guideline document only covers applications to be made under Paragraph 3 of Article 7 of the Regulation Regarding the Manufacturing Sites of Medicinal Products for Human Use. However, in order to be able to apply within the scope of the relevant legislation and this guidelines document, the facility for which the application will be made must have a manufacturing site permit within the scope of the Regarding the Manufacturing Sites of Medicinal Products for Human Use. Except for veterinary medicinal product manufacturing facilities, the applications of facilities that do not already have a human medicinal product manufacturing site permit issued by the Agency shall not be evaluated. In applications made for a human medicinal product manufacturing facility within the scope of this guideline, the product groups are limited to the following:

- Veterinary medical products
- Supplement foods
- Biocidal products administered to humans
- Human tissue and cell products
- Medical devices
- Cosmetic products

The basis of the applications to be made to the Agency is to prevent a possible risk of cross-contamination with medicinal products for human use if the aforementioned product groups are manufactured in the manufacturing facilities of medicinal products for human use authorized by our Agency. For this reason, the content of the aforementioned product groups should be included in the application content, not the medicinal products for human use. Issues regarding the risk of cross-contamination that may occur in the manufacture of medicinal products for human use shall be evaluated on-site in the GMP (GMP) inspections to be carried out by our Institution.

4.1 General Considerations and Exceptions

In facilities that only carry out secondary packaging and storage activities, secondary packaging areas and equipment used for human medicinal products can be used jointly for veterinary medicinal products, food supplements and medical devices, provided that the following conditions are met;

- Making production on a campaign basis for different product groups, not working with different product groups at the same time in any case, and recording such issues in writing
- Preparing detailed procedures and recording the operations and checks conducted in order to purify the lines (assuring that there is no previous product and no piece of equipment, container, tool, document, box etc. related to the product) and to eliminate the risk of contamination
- In case of unexpected situations such as breaking, scattering, spillage etc., and in cases where the primary packaging loses its integrity for various reasons,

Establishing a procedure for what to do in such cases, and preparing cleaning instructions at the appropriate level for the contamination risk presented by the product since the product may come into contact with the environment and equipment

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However, as per the Regulation, biocidal products, human tissue and cell products or cosmetic products applied to human beings may only be produced in dedicated areas in facilities authorized by the Agency, therefore it is not appropriate to use the sections and equipment where the secondary packaging processes of human medicinal products are performed for the aforementioned product groups. For this reason, the dedicated area requirement defined in the Regulation must be met in the product groups listed.

On the other hand, sections where medicinal products for human use are stored may also be used for veterinary medicinal products, food supplements, medical devices, biocidal products administered to humans, human tissue and cell products, and cosmetic products, provided that they are made on shelves/areas that are appropriately defined and separated (with chains, lattices, walls, panels etc.) for storage operations, while, nonetheless, necessary procedures must be in place in order to avoid the risk of contamination and contamination.

Therefore, within the scope of this guideline, it is not necessary to apply separately to the Agency for the secondary packaging and storage operations of the product groups in question, and thus, the necessary precautions should be taken and written procedures should be established by the facility authorities for the secondary packaging and storage processes. The aforementioned measures, written procedures and records will be evaluated on-site during the inspections to be carried out by the inspectors at the facility.

5. ABBREVIATIONS AND DEFINITIONS

Dedicated Area : The building part that has separate personnel and material entrances and exits from other sections and rooms, which are completely isolated from other areas, departments and rooms in the same manufacturing building by means of an impermeable wall and similar building materials, have an independent ventilation system, and special personnel carrying out the processes in the area, where necessary.

Document type : The titles of the application, service or document type defined under the unit that will evaluate each application in respect to the scope of the application to be made to the Agency,

EAS : Electronic Application System,

Endpoint

- : The term "endpoint" for the substance or mixture is used in the following senses: An endpoint is an information requirement or data point regarding specific information such as physico-chemical properties, environmental fate and behavior of the substance, ecotoxicological information, toxicological information, according to a specific chemical regulation program (e.g. action against target organisms or residues in food and nutrients). In a broader sense, additional information on the endpoint such as the safe handling guide, literature review information and the container section to add to the evaluation report is also included.

  The toxic endpoint is the result of the study performed to determine how hazardous a substance is. Data collected from such studies are used to report the relative (comparative) toxicity of the compound to various regulatory agencies and environmental compliance groups. The toxic endpoint may include death, behavior, reproductive status, or physiological and biochemical changes.

  Researchers conduct *in vitro* studies outside the living organism, and *in vivo* studies are performed inside the living organism. Endpoints for *in vitro* studies include changes in reproductive status or hormone levels.The advantage of *in vivo* studies is that researchers can study the effects of the compound on the whole organism. On the other hand, *in vitro* studies are advantageous as they only work with living cells in culture and are generally considered more ethical because they are not studied on live animals. *In vivo* endpoints may include enzyme production or gene expression.

  Toxicity endpoints are used to determine toxicity thresholds, that is, the level of no adverse effects observed.

ERT	: European Register of Toxicologists
F	: Factor
Price tariff	: The price list, updated at the beginning of each year and published on the website of our Agency, covering the documents issued by the Agency and the service fees,
Genotoxic carcinogen	: A term used when describing a cancer-causing chemical due to directly altering the genetic material of target cells.
GMP	Good Manufacturing Practices
ICH	: International Conference on Harmonisation
GMP	: Good Manufacturing Practices
GMP Guidelines	: A guidelines document to good manufacturing practices for facilities manufacturing medicinal products for human use
Agency	: Türkiye Medicines and Medical Devices Agency,
LOAEL	: Lowest Observed Adverse Effect Level
NOAEL	: No Observed Adverse Effect Level
Neurotoxicity	: Toxic effect caused by natural or man-made toxicants, causing damage or dysfunction in the brain or peripheral nervous system
PDE	: Permitted Daily Exposure
Read-across	: Technique of estimating the endpoint of the target substance using data from other source substances with the same endpoint
Risk assessment	: Comparison of estimated risk with risk criteria, given by using a quantitative or qualitative degree, in order to determine the significance of the risk.
Risk identification	: Systematic use of information to identify potential sources of harm (hazard) that reference the problem definition or risk question.
Teratogenicity	: Toxic effect caused by exposure to various (toxic) factors during pregnancy, causing malformation or damage to the embryo/fetus.
TTC	: Threshold of Toxicological Concern
PTS	: Pharmaceutical Tracking System
VICH	: International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products
Harm	: Negative impact on health due to problem in product quality or usability.

6. DETERMINATION OF DAILY EXPOSURE LIMITS BASED ON HEALTH

6.1 Calculation of Permitted Daily Exposure (PDE)

In this guidelines document, the recommended procedure for determining health-based exposure limits for active substance residue is based on the determination of "Permitted Daily Exposure (PDE) as defined under the annexes of ICH Q3C (R6) Annex-3 "Impurities: Guidelines for Residual Solvents" and VICH GL 18 Annex-3 "Residue Solvents, Active Substances and Excipients in New Veterinary Medicinal Products".

PDE refers to a substance-specific dose that is unlikely to cause an adverse effect if an individual is exposed to doses at or below this dose daily throughout their lifetime.

The determination of the PDE includes the following elements:

i. Identification of the hazard by evaluating all relevant data
ii. Identification of critical effects
iii. Determination of the non-observed adverse effect level (NOAEL) from the findings thought to have critical effects
iv. Use of a number of correction factors to explain various uncertainties

Equation for the derivation of PDE in Annex 3 of the ICH Q3C and VICH GL 18 guidelines;

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

Regarding the determination of health-based exposure limits for veterinary medicinal products, although it is possible to use the PDE approach to establish different limits for different target species, it is not very useful. Ultimately, it is recognized that PDEs should be derived assuming human exposure. Even if the contaminated product is a veterinary medicinal product, the acceptable contamination level is calculated based on human PDE and the use of human PDEs to calculate residual solvent limits applied for veterinary medicinal products conforms to the approach discussed in VICH GL 18.

When deriving the limits, it should be considered that the dose to be applied will be affected by the body weight of the species to be treated. To facilitate this, the PDE should be calculated on a mg/kg body weight basis (i.e. using 1 as the weight adjustment figure), [1]not on patient basis.

If the product contaminated with the residual active substance is a veterinary medicinal product to be used in animals manufactured for food purposes, both the target animal's and the consumer's safety should be taken into account in the applied carry-over limit. Therefore, based on worst-case exposure

[1] For human medicinal products, the standard 50 kg body weight should be used if the product information for the next medicinal product to be manufactured refers to the daily dose on a patient basis and not on a mg/kg body weight basis. For medicinal products for veterinary use, doses are usually expressed on a mg/kg body weight basis. Where this is not the case, it should be assumed that 1 kg standard body weight will represent the lower end of the animal body weight.

scenarios, it should be demonstrated that neither the target animal nor the consumer will be exposed to residual active substance limits exceeding PDE.

Alternative approaches to NOAEL, such as benchmark dose, can also be used.

It is acceptable to use other approaches in setting health-based exposure limits provided that they are adequate and scientifically justified.

Data for hazard identification

Hazard identification indicates the qualitative assessment of the characteristics of a substance to cause adverse effects. For identification of the hazard, all available animal and human data for each compound should be reviewed. Data to be used in hazard identification will include non-clinical pharmacodynamic data, repeated 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 and indication pertaining to its development. In the event datasets are incomplete, any identified gaps (gaps) will need to be critically evaluated for their effect in establishing a reliable health-based exposure limit.

Determination of critical effects

Critical effects will include the most sensitive indication of an adverse effect seen in non-clinical toxicity studies unless there is clear evidence (e.g. from mechanical 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 effects.

Determination of NOAEL value

A NOAEL should be determined for all identified critical effects. NOAEL is the highest tested dose at which no “critical” effect was observed. If a critical effect is observed in some animal studies, the NOAEL occurring at the lowest dose should be used to calculate the PDE value. Where the NOAEL cannot be obtained, the lowest observed adverse effect level (LOAEL) may be used. A NOAEL based on clinical pharmacodynamic effects should correspond to the highest dose considered therapeutically ineffective.

Application of adjustment factors

PDE is obtained by dividing the NOAEL by various adjustment factors (also called safety, uncertainty, evaluation, or modification factors) to account for various uncertainties for critical effect and to allow extrapolation to the level at which no reliable and robust effect is observed in the human or target animal population. Definitions of uncertainty factors F1 to F5 are as listed below.

F1: A factor that takes into account extrapolation between species (values 2 to 12)

F2: A factor with a value of 10 that takes into account inter-individual variability.

F3: A factor with a value of 10 that takes into account short-term (i.e. less than 4 weeks) repeat dose toxicity studies.

F4: A factor with a value of 1-10 that can be applied in cases of severe toxicity (e.g. non-genotoxic carcinogenicity, neurotoxicity or teratogenicity).

F5: A variable factor that can be applied if the non-effect level has not been determined. A factor usable when only LOAEL is present, as up to 10 depending on the severity of the toxicity.

The use of additional adjustment factors to remove residual uncertainties not covered by the above factors is acceptable provided that they are well supported by literature data and sufficient discussion is provided to support their use (e.g. lack of data for reproductive and developmental toxicity (see Section 7.4).

See Annex 3 of the ICH Q3C (R6) and VICH GL 18 guidelines for more information on the selection of F1 and F4 adjustment factors. The use and selection of adjustment factors must be justified.

When deriving a PDE based on human endpoints, it is acceptable to restrict the use of F2 and potentially F5.

Deviations from the default values for the adjustment factors presented above are acceptable if appropriate and scientifically justified.

Selection of Final PDE

If several critical effects have been identified in the calculation of more than one PDE value, the most appropriate PDE value to be used for the cleaning validation process should be determined with appropriate justification. Generally, the lowest PDE value will be used.

6.2 Use of Clinical Data

The purpose of setting the health-based exposure limit is to ensure human safety, and as a result, good quality human clinical data is considered highly relevant. Undesirable pharmacodynamic effects in patients from contaminating active substances may pose a hazard, and therefore clinical pharmacological data should be considered when determining the critical effect. The extent to which the active substance in question is associated with adverse critical effects in the clinical setting should be considered.
In the event the most critical identified effect in determining the health-based exposure limit is based on the pharmacological and/or toxicological effects observed in humans rather than animals, the use of the PDE formula may not be appropriate and a substance-specific assessment of clinical data may be used for this purpose.

6.3 Extrapolation to Other Administration Routes

While the derivation of the PDE value for an active substance (contaminant) is generally based on studies using the intended clinical route of administration, there may be a different route of clinical administration for the active substance or medicinal product to be produced later in the facility.
Changing the route of administration may alter bioavailability; therefore, correction factors should be used to extrapolate from one route of administration to another route of administration if there are significant differences (e.g. >40%) in bioavailability specific to the route of administration. As

bioavailability may vary between species, correction factors used for extrapolation from one route of administration to another should preferably be based on human data or, in veterinary medicinal products, data on the relevant target animal.

In the absence of human or target animal bioavailability data for other routes of administration, a change in route of administration (e.g., inhalation rather than oral administration) may result in an increase in systemic exposure of the pollutant. A conservative extrapolation may be made for the contaminant assuming the bioavailability of the contaminant is 100%. For instance, in the case of extrapolation (conversion) from the oral to the inhalation route, the PDE obtained based on the oral data can be corrected by multiplying the following correction factor:

$$\text{Correction factor (oral to inhalation):} \quad \frac{\text{\% Oral Absorption}}{\text{100\% Breathable (Respirable) Absorption}}$$

Where human or target animal bioavailability data are not available for other routes and the systemic exposure to the pollutant will be lower than the route of administration of the contaminated active substance/medicinal product, there is no need to apply a correction factor to the PDE calculation. Extrapolation from route-to-administration route is expected to be performed on a case-by-case basis.

7. SPECIAL CONSIDERATIONS

7.1 Active Substances with Genotoxic Potential

For genotoxic active substances that do not have an identifiable threshold (non-threshold), any exposure level is considered to be risky.

However, a predefined acceptable level of risk for non-threshold genotoxic substances is set at the Threshold of Toxicological Concern (TTC) as 1.5 µg/person/day in the EMA Guidelines for Genotoxic Impurity Limits.

TTC represents the exposure level of genotoxic impurities associated with an additional theoretical cancer risk of 1 in 100,000 individuals when exposed to a chemical throughout their lifetime. Considering that the exposure time to residual active substances will be much more limited (for example, in practice, it may be expected that the residual drug transport limits will decrease from one batch to another), if the maximum exposure limit is taken as 1.5 µg / person / day, theoretically high cancer risk will not exceed 1×10^{-6}. Therefore, in the case of residual active substances without threshold (PDE value not determined), a limit dose of 1.5 µg / person / daily may be applied.

If the product contaminated with residual active substance is a veterinary medicinal product, the same TTC value should be applied but expressed per kg body weight (i.e. TTC 0.03 µg / kg body weight / day). When the contaminated product is administered to animals produced for food purposes, both target animal and consumer safety should be considered in the applicable carry-over limit. Therefore, based on worst-case exposure scenarios, it should be demonstrated that neither the target animal nor the consumer will be exposed to residual active substance levels exceeding TTC.

Regarding genotoxic active substances for which there is sufficient carcinogenicity data, substance-specific risk assessments should be applied, rather than an acceptable intake approach based on the TTC, when determining acceptable intakes.

For genotoxic pharmaceuticals with sufficient evidence of a threshold-related mechanism, safe exposure levels without significant risk of genotoxicity may be determined using the PDE approach.

7.2 Active Substances with High Sensitization Potential

Immune-mediated hypersensitivity reactions caused by the medicinal products may develop in sensitive individuals. Observed reactions range from mild cases of contact sensitization to potentially fatal anaphylactic reactions.

As stated in under item 3.6 in Chapter 3 of Section 1 of the GMP guidelines, dedicated facilities are required for the production of active substances and medicinal products with high potential for sensitivity where scientific data do not support an acceptable level of exposure or the risk associated with product handling at the facility cannot be adequately controlled by organizational or technical measures.

Classification of the potentially sensitive active substance or medicinal product should be based on whether it causes high sensitization in humans based on animal data or other validated tests. The severity of such reactions should also be taken into account and there should be an evidence-based assessment.

7.3 Therapeutic Macromolecules and Peptides

Therapeutic macromolecules and peptides are known to degrade and become denatured when exposed to extreme pH levels (too high or too low) and/or heat, rendering these molecules pharmacologically inactive.

Cleaning of biopharmaceutical manufacturing equipment is typically performed under conditions that expose equipment surfaces to extreme pH and/or heat, resulting in degradation and inactivation of protein-based products. Therefore, it may not be necessary to set health-based exposure limits using the PDE limits of the active and intact product.

In the event other potential cross-contamination routes exist, the resulting risks should be considered on a case-by-case basis.

7.4 Lack of Animal Data on Reproductive and Developmental Toxicity

To ensure the protection of all populations, the presence of residual active substance should be reduced to a level that does not pose a risk to reproductive and developmental parameters. However,

in the early stages of product development, non-clinical data may not yet be available to assess the potential of the new active substance to cause reproductive and developmental toxicity.

Gaps in scientific knowledge may also exist for licensed medicinal products, such as the potential for a male-specific drug to cause adverse effects on embryo-foetal development.

In these cases, the NOAEL from a sub-chronic/chronic study may be used to calculate PDE by applying an additional adjustment factor (e.g. 10) when appropriately justified. Where appropriate data from reproductive and developmental toxicity studies of relevant compounds are available, a class-specific profile may be used to identify the hazard of the untested contaminant by applying the read-cross approach.

7.5 Clinical Trial Reports

Estimation of PDE for investigational products (IP) in the early stages of clinical trials (phase 1/2) may be difficult due to limited datasets on IP. Where this is evident, an alternative approach using classification in a particular default value category may be considered to set health-based exposure limits when properly justified (e.g. similar to the TTC approach proposed by Kroes et al. (2004), Munro et al. (2008) and Dolan et al. (2005) based on low / high expected pharmacological effect, low / high toxicity, genotoxicity / carcinogenicity). Since most of the assumed limits are defined for chronic exposure times, a higher limit may be reasonable if a medicinal substance shares equipment with another medicinal substance belonging to a short-term clinical trial (Bercu and Dolan, 2013). Compound-specific limits should be calculated as described above to derive health-based exposure limits from the availability of more pharmacological and toxicological data.

8. REPORTING THE PDE DETERMINATION STRATEGY

As noted in Section 6, when calculating the PDE value, “critical effects” should be identified based on an extensive literature review that includes searches in guidelines and monographs and electronic scientific databases. Search strategy and search results should be clearly documented.

Following an expert review, the applicant should make an assessment of the critical endpoints of concern and the rationale for choosing the doses and endpoints to be used in the derivation of the PDE.

Pivotal animal and human studies used to derive PDE should be based on original references and reviewed for quality (study design, explanation of finding, accuracy of report, etc.). The PDE determination strategy should provide a clear justification for the adjustment factors applied in obtaining the PDE. Furthermore, in order to grant inspectors an overview, the first page of each PDE identification strategy document should have a summary of the evaluation process. (e.g. PDE Report Example annexed to Guidelines)

9. APPLICATION METHOD, CONTENT and PROCESS

9.1 Application over Article 7 of the Regulation Regarding the Manufacturing Sites of Medicinal Products for Human Use

The manufacture of the products within the scope of the application may not commence before the application made to the Agency is evaluated and approved by the relevant Board.

Separate applications must be made **for products to be manufactured by the manufacturer using the same section and/or equipment as for human medicinal products**, and **for products to be manufacture in a dedicated area**.

In the event that a different product is desired to be manufactured in the facility within the scope of Article 7 of the Regulation in addition to the products approved by the Agency to be manufactured in the same area and/or equipment, or changes are made in the documents (equipment, area, cleaning validation, unit formula, etc.) submitted regarding the existing approved products, an application must be made to the Agency and approval must be obtained from the Board before the changes are put into effect.

In case of a change in the dedicated area approved by the Agency for the manufacture of the products subject to the application, a re-application must be made to the Agency.

If manufacturing new products in the same product class in the same dedicated area as the product classes allowed to be manufactured in a dedicated area, **it is not necessary to obtain approval from the Agency again**. However, if a new dedicated area is created, a re-application must be made within the scope of this Guidelines document and relevant approval must be obtained.

If the deficiencies reported by the Board are not eliminated within one year following the notification to the applicant, a re-application fee is accrued.

The approval to be given by the Agency is limited to the evaluation of the measures defined within the framework of the information and documents submitted for the assessment of the products in question in terms of the risk of cross-contamination on the medicinal products for human use. Thus, GMP Certificate / Permit Document shall not be issued for products of which manufacture is approved by BİRDEK, and certificates and documents issued by our Agency shall not be valid for product groups other than medicinal products for human use.

On the other hand, such permission to be given does not replace the permissions and other obligations arising from the legislation to which the products other than human medicinal products are subject. In this regard, it is the applicant's responsibility to apply to the relevant units of our Agency and other public institutions and organizations, to obtain the necessary permits and to fulfill other obligations in the legislation.

9.1.1 Application for Products to be Manufactured Using the Same Section and/or Equipment

- The application must be made through the Electronic Application System (EAS) in the document type *"Application and Evaluation within the Scope of Article 7 of the Regulation Regarding the Manufacturing Sites of Medicinal Products for Human Use"* defined under the Domestic Facility Inspections Application and Follow-Up Unit affiliated to the Department of Medicine Inspection.

- In the application cover letter, it should be clearly stated in which facility the products applied for will be manufactured.
- For the products to be manufactured **in the same section and/or with the same equipment**, the following documents should be submitted electronically in the annex of the application.
    - Document indicating the product class of the product for which approval is requested
        - Veterinary medicinal product authorization for veterinary medicinal products
        - Approval certificate for supplementary foods obtained from the Agency
        - Product tracking system (PTS) registration for medical devices
    - PDE report prepared by a specialist ERT registered toxicologist in accordance with the draft report presented as annex to this guideline
    - Risk assessment report drawn up from health-based exposure limits for cross-contamination and technical and organizational measures approved by the facility quality assurance manager and responsible manager pharmacist
    - Evidence of technical and organizational measures in the case of products to be manufactured in the same area and/or using the same equipment as a result of the risk assessment
    - Cleaning validation protocol (and report if available) for cases where same equipment is used and reports of analytical methods implemented within the scope of cleaning validation
    - Unit formulas and flow chart of the products planned to be manufactured
    - Annex-1 table containing the active substance information of the products planned to be manufactured
    - A separate table (with equipment numbers) on which equipment the products will be manufactured

9.1.2 Application for Products to be Produced in a Dedicated Area

- The application must be made through the Electronic Application System (EAS) in the document type *"Application and Evaluation within the Scope of Article 7 of the Regulation Regarding the Manufacturing Sites of Medicinal Products for Human Use"* defined under the Domestic Facility Inspections Application and Follow-Up Unit affiliated to the Department of Medicine Inspection.
- For the applications to be made regarding the products to be manufactured in a **dedicated area**, the following documents should be submitted electronically.
    - Product list prepared according to the classes of the products for which approval is requested
    - Document indicating the product class of the product(s) for which approval is requested
        - Veterinary medicinal product authorization for veterinary medicinal products
        - Certificate of approval for supplements

- Cosmetic declaration for cosmetic products, PTS registration (Record of the Agency's registration of the relevant product notification as a cosmetic product by our Agency)
- PTS registration for medical devices
- Authorization certificate / permit document for human tissue and cell products
- Registration/approval etc document for biocidal products applied to humans

- Sketches proving that the dedicated area requirement is met
- HVAC drawings
- Validation documents
- Personnel-material flowcharts
- Statement of the facility's responsible manager pharmacist stating that the products for which approval is requested will be manufactured in dedicated areas defined in accordance with the Regulation Regarding the Manufacturing Sites of Medicinal Products for Human Use.
- Technical drawings such as facility plans etc. showing that the dedicated area of the facility is independent and does not constitute a risk.

9.1.3 Evaluation of the Application

- After the application reaches the Agency, the documents pertaining to the application shall be evaluated by the Agency and any deficiencies in application dossier, if any, shall be notified in writing.
- In case of any deficiency notified, a re-application must be made and the application dossier must be submitted again in full. In order to facilitate the follow-up of the process, the deficiency notification letter written by the Agency should be kept in the system.
- The absent documents sent for eliminating deficiency shall be re-evaluated by the Agency and the above process shall be repeated until all deficiencies are eliminated.
- In order to facilitate the examination of the application dossier by the Board and to speed up the process, the content of the application to be submitted to the Board must contain all the documents in full, and the documents should not be sent separately in more than one application.
- The application that reaches the unit in full shgall be evaluated under the agenda of the Board.
- Decisions taken in conclusion of the Board meeting shall be notified to the applicant in writing.
- In case additional documents are requested from the company in the decision of the Board, the additional documents requested shall be submitted to the Agency in the document type "BIRDEK Missing Document". While submitting the missing documents, the missing documents notification letter sent by the Agency shall be kept as a reference in the system.
- Following the submission of additional documents by the company, the documents sent shall be evaluated at the Board meeting.
- The decision of the Board as a result of the evaluation of the application shall then be notified to the applicant in writing.

10.ANNEXES

- BİRDEK Application Form
- Sample Risk Assessment Report draft

11.REFERENCES

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12.REVISION HISTORY

First issue

13.EFFECTIVE DATE

This guideline goes into effect on the day of approval.