AESGP Position Paper on Classification Rule 21

This paper concerns the classification on a case-by-case basis of medical devices composed of substances or of combinations of substances in accordance with the classification rule 21 set in Annex VIII of the Medical Devices Regulation[1] (MDR) taking into account all their characteristics, including in particular their intended purpose and their inherent risks. Its main purpose is to provide actors of the MDR implementation with AESGP's views on the pragmatic, proportionate and science-based interpretation of this classification rule.

Rule 21
Devices that are composed of substances or of combinations of substances that are intended to be introduced into the human body via a body orifice or applied to the skin and that are absorbed by or locally dispersed in the human body are classified as:
- *class III if they, or their products of metabolism, are systemically absorbed by the human body in order to achieve the intended purpose;*
- *class III if they achieve their intended purpose in the stomach or lower gastrointestinal tract and they, or their products of metabolism, are systemically absorbed by the human body;*
- *class IIa if they are applied to the skin or if they are applied in the nasal or oral cavity as far as the pharynx, and achieve their intended purpose on those cavities; and*
- *class IIb in all other cases.*

General explanation to Rule 21

Recalling the recital 59 of the MDR, Rule 21 has been introduced "*in order to obtain a suitable risk-based classification of devices that are composed of substances or of combinations of substances that are absorbed by or locally dispersed in the human body, it is necessary to introduce specific classification rules for such devices. The classification rules should take into account the place where the device performs its action in or on the human body, where it is introduced or applied, and whether a systemic absorption of the substances of which the device is composed, or of the products of metabolism in the human body of those substances occurs*".

This risk-based classification approach is reflected in the general provisions on the classification of medical devices laid down in Art. 51 of the MDR, which states that *devices shall be divided into classes I, IIa, IIb and III, taking into account the intended purpose of the devices and their inherent risks* and the classification rules set in Annex VIII.

While it is acknowledged that the intended use of devices acting in the nasal or oral cavities is generally of a lower risk than those acting in the stomach and lower gastrointestinal tract, some more reflections are needed for what concerns the concept of "systemic absorption", which has been set as a fundamental criterion for risk class assignment only for those devices acting in the stomach or lower gastrointestinal tract.

[1] Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC (Text with EEA relevance), OJ L 117, 5.5.2017, p. 1–175

AESGP
7 avenue de Tervuren
1040 Brussels, Belgium
Tel : + 32 2 735 51 30
Fax : + 32 2 735 52 22
info@aesgp.eu
www.aesgp.eu

Absorption is an important parameter for risk identification. However, it is important to note that Rule 21 distinguishes between two situations: when absorption influences both the efficacy and safety of a product, and when it is only a safety aspect. While, in the case of medical devices falling under the first indent of Rule 21 (systemically absorbed in order to achieve the intended purpose), the determination of the degree of absorption is closely related to both the risk and the performance of the product since its therapeutic activity is linked to the absorption, distribution, metabolism and excretion in the body, in the case of the remaining medical devices falling under rule 21, the level of absorption has no influence on the clinical efficacy of the product, which is expressed by means of a local action.

Accordingly, for medical devices that need to be systemically absorbed in order to achieve their intended purpose, the interpretation of this Rule does not raise real issues. However, for other medical devices, that are composed of substances or combinations of substances, further clarification is needed in order to ensure that the risk-based classification approach laid down in the MDR is implemented in a proportionate manner considering their inherent risks.

In these regards, two elements are of utmost importance and need to be considered:

1. In practice, most of the medical devices composed of substances or of combinations of substances include components that are traditionally used in other areas (e.g. food, cosmetic products, medicinal products, etc.), administered via a similar route (ingestion, topical application, etc.) and generally recognised as safe under certain conditions of use.
2. Systemic absorption is not a trait of ingested products only: it can occur in fact also through other tissues such as, for example, the skin or the buccal or sublingual mucosa.

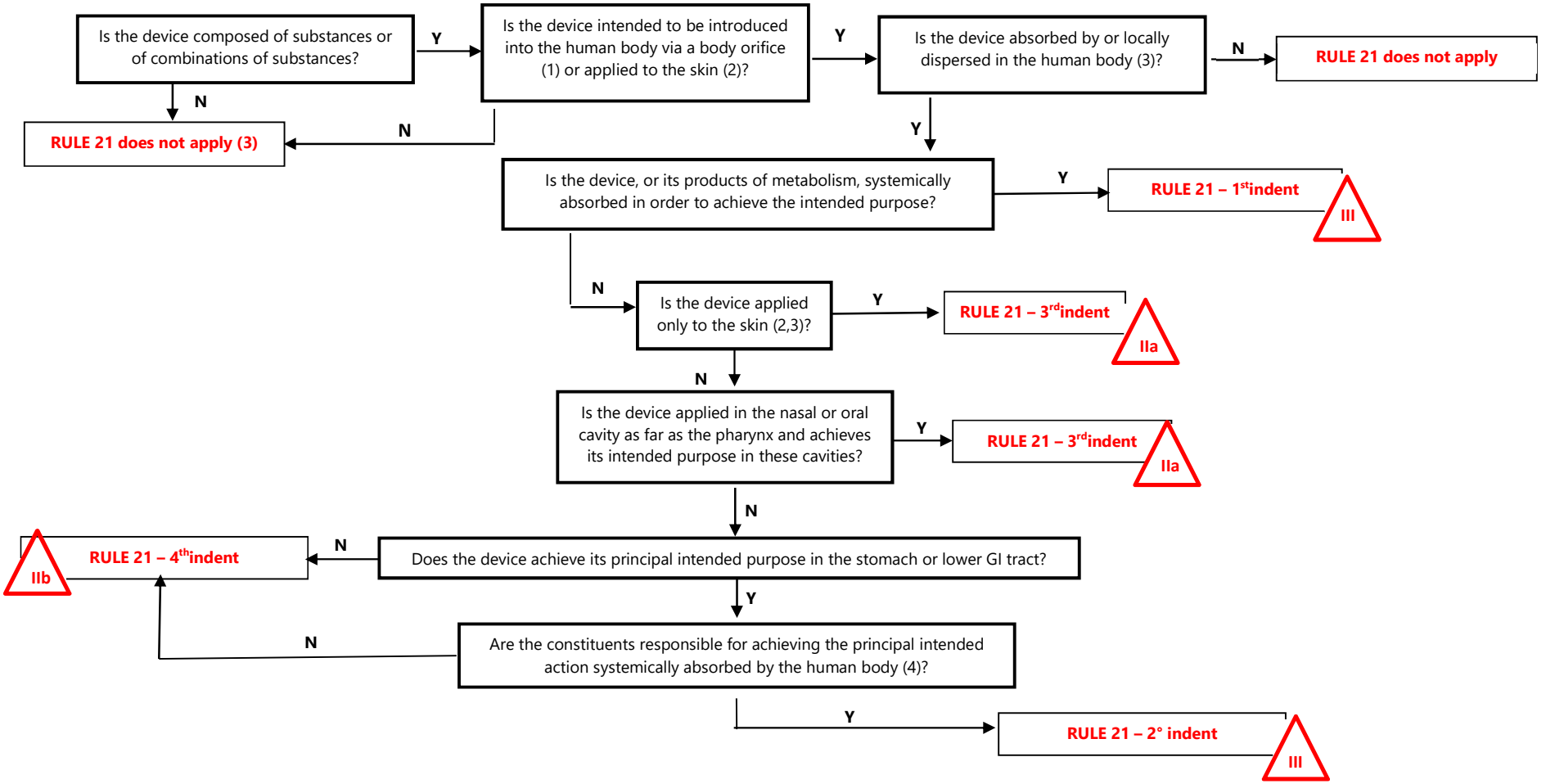
Taking the above into consideration, the meaning of Rule 21 should be placed in its context and interpreted in the light of the provision of the MDR and EU law as a whole, with regards to the objectives thereof and to its state of evolution at the date on which the provision in question is to be applied[2]. Accordingly, the interpretation of Rule 21 should take into account the general principles for the classification of medical devices set in Article 51 MDR (take into account the intended purpose of the devices and their inherent risks) and the general objective of the MDR which is to ensure high standards of quality and safety for medical devices proportionate to the nature of the risk presented by the device.

In accordance with such contextual analysis, if, when taking into account the intended purpose of a device and its inherent risk in light of its characteristics, notably its composition, the risk presented by the device can be scientifically evidenced as negligible, then it would go beyond what is necessary to achieve the objectives of the MDR to classify such device in the highest risk class.

To ensure that Rule 21 is implemented in a proportionate manner, a decision tree to assist with the classification of medical devices composed of substances or of combinations of substances under the MDR is proposed below.

[2]Judgment in *Cilfit and Others*, 283/81, EU:C:1982:335, paragraph 20.

DECISION TREE to assist with the classification on a case-by-case basis of devices composed of substances or of combinations of substances in accordance with Rule 21 (Annex VIII MDR) taking into account all their characteristics, including in particular their intended purpose and their inherent risks.



Explanatory Notes on Rule 21 Decision Tree

1) '*Body orifice' means any natural opening in the body, as well as the external surface of the eyeball, or any permanent artificial opening, such as a stoma* per Annex VIII, Chapter II, Paragraph 2.1.

2) The wording of rule 21 "*intended to be introduced into the human body via a body orifice or applied to the skin*", makes it clear that administration into an orifice or application to the skin are not sufficient, by themselves, to constitute introduction into the human body. These are simply possible routes of introduction into the body. Therefore, devices intended for use in the ear canal up to the ear drum (i.e. on the skin), and not intended to be introduced into the human body, that are not absorbed by or locally dispersed in the human body, fall outside the scope of rule 21.
Nails and hair are not considered to be skin.

3) Absorption or local dispersion in the human body is considered to occur if;
   - The product is ingested ;
   - The device is applied in the nasal cavity or orally and the intended use of the product is below the pharynx.

   There will be other circumstances where absorption might occur but this will be assessed on a case by case basis.

   For products applied to the skin, if the product penetrates only into the layers of the skin composed of non-living cells (e.g. stratum corneum) it is not absorbed 'by' or locally dispersed 'in' the human body but rather 'on' the human body.
   According to the Scientific Committee on Consumer Safety (SCCS) opinion on the "Basic criteria for the in vitro assessment of dermal absorption of cosmetic ingredients" (SCCS/1358/10),
      - *"the epidermis, in particular the stratum corneum, forms the principal in vivo barrier of the skin against penetration and uptake of xenobiotics in the body"* and
      - *"The epidermis renews by continuous outward proliferation, differentiation and desquamation. About one layer of corneocytes is shed off per day. After topical application, xenobiotics detected in vitro in the skin, particularly in the stratum corneum and the pilosebaceous units, might in vivo have been lost from the skin via desquamation or sebum secretion, respectively"*

   'Injured skin or mucous membrane' means an area of skin or a mucous membrane presenting a pathological change or change following disease or a wound per Annex VIII, Chapter II, Paragraph 2.8.

   According to MEDDEV 2. 4/1 Rev. 9 on classification of medical devices (special concepts under Rule 4), a skin might be considered as "injured" either because of pathological (e.g. eczema, psoriasis or diabetic ulcers) or external factors (e.g. burns).

   Thus, substance-based devices applied to injured skin or mucous membrane have a higher potential to be absorbed or locally dispersed in the human body, especially if applied over large surface areas, and so are within scope of rule 21 but this needs to be assessed/justified for each product/and per intended use on a case by case basis.

4) The device classification should be made on a case-by-case basis, taking into consideration to what extent such absorption or local dispersion is materially different to what is already established (in common practice e.g. in food) as being low risk. In particular, the knowledge and the intended purpose of the product composition is crucial in order to identify components of possible safety concern and to evaluate on a case-by-case basis if they present a substantial and real risk due to their absorption.

   For example, devices intended to be ingested that contain low risk constituents responsible for achieving the principal intended action (e.g. honey, mallow polysaccharides, calcium carbonate

or simple sugars, olive oil, fibres with a long history of safe use in other products such as foodstuffs) will not require the same level of supporting evidence. This concept of “generally considered as low-risk” should apply to substances that have been scientifically reviewed by European scientific bodies and committees.

Relevant evidence and justification must be gathered by the manufacturer to support the classification and should be subject to the evaluation of the Notified Body on a case-by-case basis. The justification should take into account the following elements (non-exhaustive list):

- Destination of use of the device (i.e. intrinsic risk of the medical condition to be treated, exposed population, duration of use, etc.);
- The raw materials from which the substances of which the device is composed are manufactured or extracted;
- Quality and manufacturing of all substances entering into the composition of the device;
- Quality and manufacturing of the device itself;
- The risk profile of the substances used (constituents of low-risk (e.g. honey, mallow polysaccharides, calcium carbonate or simple sugars, olive oil, fibres) with a long history of safe and known use in other products such as foodstuffs and that have been scientifically reviewed by European scientific bodies and committees. In that regard, future consideration should be given for exceptions to the classification as laid out in rule 21 to provide proportionate risk-based classification.

In fact, classification in class III according to the MDR for the devices described in the present explanatory note may pose on the entire system a considerable burden that may be detrimental for a pragmatic implementation in those cases where the device is practically devoid of significant intrinsic risks. This applies also in case the notified body makes a proportionate evaluation in terms of the required level of evidence since many of the duties arising from the classification in class III are of an administrative nature, thus obliging both the notified body and the manufacturer to put much effort in the conformity assessment procedure of devices of an intrinsic low risk and creating bottlenecks in the access of patients to therapy.

The table below summarizes the additional requirements that would be applicable to class III only (in full or in part, as explained in the “Notes” column):

Requirement	Manufacturer activities	NB activities	Notes
Summary of Safety and Clinical Performance (Art 32 MDR; MDGC 2019-9)	- Write SSCP - Update SSCP annually, if needed - Translate SSCP	- Assess SSCP - Validate SSCP - Upload SSCP in Eudamed	- The SSCP is only required for class III devices. Very extensive document to be prepared ex-novo by manufacturers on the basis of the technical file and PMS activities (stylistic elements to be adapted to lay users). - Translation in English and in all the languages of the Countries where the device is made available is a very demanding activity, in particular for SMEs. - SSCP is a new requirement also for NBs: fast assessments are needed in order to ensure compliance.
PSUR (Art. 86)	- Write PSUR - Update annually - Submit to NB via Eudamed	- Review and Evaluation of PSUR - Make PSUR available for CAs through EUDAMED	
Clinical Evaluation (Art.61)	- Mandatory clinical investigation for CE marking - Voluntary consultation with expert panel on clinical development strategy	N.A.	- Some exceptions applies to the requirement of mandatory clinical investigation. However, in situations where those exceptions do not apply, a new clinical investigation may be considered unethical (i.e. similar device to one already marketed by another manufacturer). - Need for specific expertise in case the voluntary consultation is asked.
PMCF Report (Art.61)	- Write the PMCF - Update the PMCF at least annually - Submit the PMCF to the NB through EUDAMED	- Review the PMCF - Add the PMCF evaluation to EUDAMED	- The annual frequency for the update of PMCF is required for class IIb and class III devices only - The management of the PMCF through EUDAMED is only required for class III devices

Requirement	Manufacturer activities	NB activities	Notes
Application of UDI Carriers (Art 27; Art 123)	- To update existing labeling for inclusion of UDI carrier from 26 May 2021	N.A.	Class III devices are the first for which the implementation of UDI carrier takes place. Practical implementation of this in the manufacturer production facilities may require investments for adaptation of production lines.
Coordinated assessment procedure for clinical investigations (Art. 78)	NA	NA	Longer evaluation period (+50 days) for assessment of the application for a clinical investigation by Member States. This applies to class III and class IIb devices.
Conformity Assessment (Annexes IX, X, XI)	Overall impact in order to meet higher NB expectations	- Additional elements to be checked during surveillance (i.e. quantities of produced or purchased parts and/or materials correspond to the quantities of finished devices) - Assessment of technical file related to the single device (no sample per group or sample per category allowed)	

Updated March 2020