

# Combined Medical Devices: Which Classification for These Borderline Products and Which Consequences for the Manufacturers - About a Use Case in Skin Healing Area

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**Abstract:** Skin healing is a rapidly expanding field, especially with the growing needs of an aging population and the increase in chronic pathologies (diabetes, venous ulcers, bedsores etc...). In order to offer ever more adapted solutions, manufacturers are competing in ingenuity to propose innovative medical devices that meet the expectations of patients, caregivers and the healthcare system. These developments raise many questions, particularly with regard to the classification of devices in the various risk classes and the naming of these wound healing devices. This article will focus on combined medical devices with the difficulties they pose for manufacturers and health authorities in terms of development, financial investment, risk-taking and the difficulty of classifying these so-called borderline products in the medical device universe.

## 1 COMBINED MEDICAL DEVICES DEFINITION AND EXAMPLES

A medical device (MD) is defined as “*any instrument, apparatus, equipment, material, product, except products of human origin, or other article used alone or in combination, [...], the principal intended action of which is not obtained by pharmacological or immunological means or by metabolism, but the function of which may be assisted by such means.*” (Collectif Dalloz: Jean-Paul Markus, 2010). The MD are classified according to their destination and their level of risk for the patient and the user according to 4 risk-categories (Class I: low-risk, IIa: moderate-risk, IIb: elevated-risk and III: highest risk devices (Stralin, 2020):

Combined MD are defined according to Rule 14 of Annex VIII of the European Regulation 2017/745

as “*All devices incorporating as an integral part a substance which, when used separately, may be considered a medicinal product within the meaning of Article 1(10) of the said Directive, and whose action is ancillary to that of the devices, are in Class III.*”

According to the definition of the FDA (U.S. Food and Drug Administration) in 2018, a combined MD is defined as “*diagnostic or therapeutic products that combine drugs, devices, and/or biological products.*” (Morang J., 2019) (FDA, 2018).

Strictly speaking, a combined MD is a device combining 2 elements, one of which is considered to be a MD and the other substance is considered to be a drug or to have a pharmacological or metabolic action (Coronary stent with heparin coating (Biran R, 2016) or Bone substitute (hydroxyapatite) containing an antibiotic (gentamicin) (Freischmidt H., 2020)). The difficulty is then to prove that the main action is brought by the device and not by the ancillary substance. If the level of proof is not sufficient, there

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is a risk that the entire device will be classified as a medicine.

These combined MD, considered as high-risk devices because of the active substance, will be classified in class III.

## 2 MEDICAL DEVICES FOR CUTANEOUS HEALING

The cutaneous healing is currently one of the biggest challenges for healthcare professionals. Indeed, with the aging population, chronic wounds are more and more frequent and lead to considerable expenses in terms of health care costs because they are hard and long to heal (over six weeks) and often recur (Martin P. & N., 2015).

The challenge of manufacturers is then to propose new and efficient MD to improve healing without having a strong pharmacological effect. In these cases, the risk is to be classified as a medicine or alternatively as a combined MD (high-risk class III) which is by definition “*A device incorporating a substance that when used separately can be considered a medicine*” (Européenne, 2017).

High-risk MD necessarily entail more constraints for manufacturers in terms of development, financial investment, and investigation time, which can have a major impact on the company. The aim of manufacturers is to prove the healing efficiency and the safety of the device. In that purpose, each step of MD development must be carefully planned upstream of the development phase. A concrete case of combine device will be used to illustrate the development process and difficulties encountered by industrials and health authorities for the evaluation and classification of such borderline products.

## 3 DRESSINGS AS COMBINED MEDICAL DEVICES

### 3.1 Definition of Dressings for Skin Healing

A dressing is a device covering a wound and providing a physical protection against external attacks (mechanical or bacterial). Dressings also maintain a moist environment in contact with the wound, promoting optimal healing. In 1962, the British researcher George Winters demonstrated the beneficial effects of a moist environment for healing. Since then, this criterion is therefore considered to be

a fundamental characteristic for a twice faster healing (Turner, 1979) and led industrials to focus on the design of modern dressings: occlusive and moisturizer (Chaby G., 2007) (Vaneau M., 2007) (Werdin F., 2009).

Dressings present a high-level of risk and are subjected to great vigilance from the manufacturers as well as the health authorities. These dressings have different compositions and act on different stages of the healing process (reduction of inflammation, improvement of tissue synthesis, intense hydration, absorption of bad odours, elimination of cellular debris etc...).

In general, the main functions of dressings are:

- Promote natural healing by maintaining a moist environment and draining exudates.
- Allow gas exchange.
- Isolate the wound thermally and mechanically from external aggression.
- Provide a bacteriological barrier by preventing infections from the outside.

The development of dressings is vast and varied and requires, as for any MD, a well-determined evaluation framework as allowed by the new European regulation 2017/746 and the standardization of the evaluation of MD.

### 3.2 Classification of Dressings for Cutaneous Healing

The classification of MD, intended for skin healing, is complex and involves following several rules based on dressings characteristics to correctly classify them:

- Their main action.
- The duration of use. The longer the duration of administration, the riskier the MD will be considered. For example, the healing of acute wounds will take less time than chronic wounds, which do not heal in 6 weeks. As a result, chronic wound healing will require treatment for more than 30 days and in accordance with the European regulation 2017/745. “*Duration of use:*
  - “*Temporally*” normally means intended for continuous use for less than sixty minutes.
  - “*Short-term*” normally means intended for continuous use between sixty minutes and thirty days.
  - “*Long-term*” normally means intended for continuous use for more than thirty days.”

- The pharmacological activity of the device: According to Rule 8 of Annex VIII of the new European Regulation 2017/745, “*All invasive surgical-type devices intended for long-term use are classified as Class IIb unless:*
  - *If they have a biological effect or are fully or substantially absorbed, in which case they are Class III [...].*
  - *If they are intended to administer drugs, in which case they are Class III [...].*”

In addition, wound healing devices are applied on open wounds and therefore represent a greater risk of infection or that the carrier substances enter the systemic circulation and induce side effects

Faced with the complexity of classification, each device will be assessed on a case-by-case basis by health authorities and manufacturers are responsible for clearly defining the action of their MD and providing a clear and precise claim. The new European regulation 2017/746, implemented from May 2021, brings more clarity on how to classify MD.

### 3.3 Few Examples of Dressings and Their Classification

Dressings can be classified in different risk classes according to their characteristics. The table 1 illustrate some examples of dressings and their repartition in the different risk-classes.

From this table, it is clear that the majority of combined dressings are classified as Class III. However, it is notable that combined dressings are not automatically classified as Class III device and can be classified in lower class risk like Prevena® or Askina Carbosorb® dressings classified in IIa or the Carbonet® or UrgoStart® dressings classified in IIb.

### 3.4 Reflections on the Classification of Dressings

#### 3.4.1 Silver Dressings

In general, silver dressings are considered as risky MD and therefore classified as class III. Silver molecules provide an antibacterial effect, considered as a secondary function, and they are small molecules which can be toxic if they reach the systemic circulation. However, Prevena® dressing, although claimed as a silver dressing and therefore at risk, is still classified as a class IIa. Health authorities might have considered that a silver dosage of 0.019% was not sufficient to induce a toxic reaction.

Table 1: List of examples of marketed dressings. TLC-NOSF: Technology Lipide-Colloïd-Nano Oligo Saccharide Factor.

Classification	Dressing, composition and intended use
Class I – Not combined	<ul style="list-style-type: none"> <li>▪ Algoplaque® (e-pansement, e-pansement Algoplaque, s.d.): Hydrocolloid dressing composed of ((carboxymethylcellulose (CMC)) and Urgo Hydrogel® (e-pansement, e-pansement Urgo Hydrogel, s.d.): Maintenance of a moist environment.</li> </ul>
Class IIa – Not combined	<ul style="list-style-type: none"> <li>▪ Jelonet Plus® (e-pansement, e-pansement Jelonet Plus, s.d.): Vaseline dressing. Drainage of exudates.</li> </ul>
Class IIa – Combined	<ul style="list-style-type: none"> <li>▪ Prevena® (e-pansement, e-pansement Prevena, s.d.): Hydrocellular dressing with silver (0.019%). Reduction of microbial colonization.</li> <li>▪ Askina Carbosorb® (e-pansement, e-pansement Askina Carbosorb, s.d.): Active carbon dressing. Adsorption of bacteria and odours.</li> </ul>
Class IIb – Not combined	<ul style="list-style-type: none"> <li>▪ UrgoTul® (e-pansement, e-pansement UrgoTul, s.d.) and Ialuset® (Vidal, Vidal Ialuset, s.d.): Hydrocolloid dressing (CMC). Maintenance of a moist environment and management of exudates.</li> <li>▪ Purilon gel® (e-pansement, e-pansement Purilon, s.d.): Hydrogel (sodium CMC). Effective and gentle debridement.</li> </ul>
Class IIb - Combined	<ul style="list-style-type: none"> <li>▪ Carbonet® (Nephew, s.d.): Active carbon dressing. Adsorption of bacteria and odours.</li> <li>▪ UrgoStart® (Vidal, Vidal UrgoStart, s.d.): Hydrocellular dressing composed of a TLC-NOSF matrix. Inhibition of metalloproteinases (MMP).</li> </ul>
Class III – Not combined	<ul style="list-style-type: none"> <li>▪ Duoderm® (Vidal, Vidal Duoderm, s.d.): Hydrocolloid dressing. Maintains a moist environment and aids in autolytic detersion.</li> </ul>
Class III - Combined	<ul style="list-style-type: none"> <li>▪ Urgotul®Ag (Vidal, Vidal UrgoTul Ag, s.d.): Silver dressing. Maintains a moist and antibacterial environment.</li> <li>▪ Promogran® (HAS, 2019): Active dressing with anti-protease effect composed of 55% collagen and 45% regenerated oxidized cellulose. MMP inhibitor.</li> </ul>

#### 3.4.2 Carbon Dressings

Carbon dressings are represented in all risk classes except class III. However, carbon molecule is an ancillary substance, not responsible for the main action of the device (maintaining a moist environment), but which has a supporting function in

wound healing (absorption of malodours). By this definition, and also with regard to the fact that carbon, as a small molecule, can penetrate the systemic system, all carbon-based dressings should be classified as class III MD.

### 3.4.3 Metalloproteinase Regulating Dressings

Another special case is the MMP-regulating dressings. These dressings contain molecules with physiological activity since they are able to induce the inhibition of MMP activity. However, as explained previously, according to rule 8 of Annex VIII of the new European regulation 2017/745, “*All invasive surgical-type devices intended for long term use are class Ib, except: if they have a biological effect or are fully or substantially absorbed, in which case they are class III. [...]*”. This definition clearly states that these MMP-regulator dressings should be classified as class III. However, only the Promogran® dressing is classified in class III. The UrgoStart® is classified as a class Ib MD.

### 3.4.4 Non-combined Dressings Classified in Class Ib or III

On the contrary of combined dressings being classified in class IIa and Ib, it also exists some dressings that might be considered as being at low risk and non-combined, according to their composition and their main action, and which still found classified in higher risk-classes (Ib and III). This is the case for example of the Ialuset dressing®, whose main function is to maintain a moist environment, and which is mainly composed of hyaluronic acid for its strong hygroscopic power, which is classified in class Ib. The explanation for this high-risk classification certainly comes from the hyaluronic acid which, depending on its size (the smaller, the more it will be considered at risk because of the risk of entering the systemic circulation), can be considered as a MD or a drug.

Another example of a careful classification is the UrgoTul® dressing which is composed of a moisturizing matrix (CMC, Vaseline, Paraffin) and apart from the fact that it is used over long periods (more than 30 days), its composition does not represent any particular danger for the patient. Indeed, the Algoplaque® dressing, also composed of CMC is classified as class I MD. Moreover, the association paraffin/vaselin/glycerol is considered as being one of the most moisturizing mixtures and is often used in cosmetic moisturizing cream (Mylan®, Biogaran®, Dextopia®...). The classification of

UrgoTul® as a high-risk class (Ib) is then difficult to understand in view of these elements, especially considering its counterparts, UrgoStart®, which is a combined MD also classified in class Ib.

Another example is the Duoderm® dressing, which is a hydrocolloid dressing composed of a matrix of pectin, gelatin, sodium CMC and a polyurethane foam. The main function is to maintain a moist environment. Despite a description that seems without particular risk, this dressing is classified as class III. It is therefore difficult to explain why this dressing is considered to be riskier than UrgoStart®, for example, or of equivalent risk to all silver dressings.

These are few examples illustrating the lack of uniformity for MD classification before the implementation of the new European regulation.

## 4 CONCRETE EXAMPLE OF AN INDUSTRIAL DRESSING, INTENDED FOR SKIN HEALING, CLASSIFIED AS A COMBINED MD

### 4.1 Medical Device under Study

The MD used as an example to illustrate this research is intended for skin healing of chronic wounds. This MD consists of the association of a moisturizing dressing with a peptide solution. The peptide included in the solution was developed, in partnership with the CNRS, on the basis of the activity of matrikines, molecules derived from natural degradation of elastin. This innovative bifunctional peptide (BFP) has the ability to activate the synthesis of the extracellular matrix (ECM) on one hand and to inhibit, by a competitive mechanism, the molecule responsible for inflammation (MMP) on the other hand (Attia-Vigneau J, 2014) (Figure 1).

The promising performances of the peptide led the industrials, responsible of its development, to consider a medical application. Indeed, considering the effects of the peptide on cellular regeneration, proved by *in vitro* studies (Attia-Vigneau J, 2014), this peptide was integrated to a phosphate buffer solution to be applied on chronic wounds, such as Venous Leg Ulcers (VLU), in association with a secondary dressing to promote healing mechanisms.

Apart from pathological cases, like diabetes or chronic wounds (ulcers), the healing process is 6 weeks. In case of chronic wounds, this healing



process is longer because of an unbalance between the synthesis and the degradation of the ECM (Extracellular Matrix). This state prevents the reconstruction of the matrix and then an impairment of healing. The application of the BFP peptide could bring back the balance and leads to an efficient healing of the wound (Figure 1).

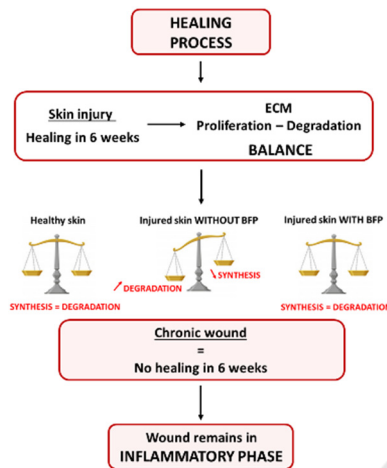


Figure 1: Healing process of wounds and schematic representation of BFP peptide effect.

Most of the marketed MD to treat these kinds of wounds act either on matrix synthesis, by maintaining a moist environment (UrgoTul®, Ialuset®...), or on the inhibition of MMP (UrgoStart® or Promogran®). The new device uses the bifunctional effect of the peptide and propose an innovative device able to act on both phenomenon, synthesis of the matrix and inhibition of MMP. This MD (peptide solution + Secondary dressing) was therefore developed to perform a proof-of-concept trial and to verify the healing efficiency of the device and its safety of use.

#### 4.2 MD Claim: Adequacy with the Business Need

The claim of the MD is of particular importance and consists in highlighting the main action of the secondary dressing (hydration) in wound healing and the supporting action of the BFP peptide which consists in:

- **Hydration** of the microenvironment of the wound, proved by *in vitro* RAMAN spectroscopy and *in vivo* clinical trial on 10 women.
- **Decrease of inflammation** by a competition mechanism of the peptide which acts as a decoy effect for MMP and thus diverts the enzymatic

activity of this protein towards itself, leaving the possibility for the matrix to regenerate properly without having physiological or metabolic effect.

From the industrial point of view, the peptide can be considered as an ancillary molecule, making the proposed device a MD that has been claimed as such by the health authorities.

#### 4.3 Classification of the Developed MD and State of the Art

The French health authorities considered that the claimed device was in fact a medicine. Considering the definition of a medicine by the Public Health Code (Article L. 5111-1) as “Any substance [...] exerting a pharmacological, immunological or metabolic action.”, an argument was developed to respond to the health authorities by comparing the proposed MD to those already on the market such as UrgoStart® or Promogran®, which are protease regulators and can therefore also be considered as having a pharmacological or physiological effect.

Despite this comparison, the French authorities remained on their position because they considered the peptide solution alone as a medicine. They also stated that the dressing is not an impregnated dressing (MD dressing incorporating as an integral part a substance with an accessory pharmacological action) and the peptide release on the wound cannot be evaluated. This lack of safety on peptide release as well as the lack of hindsight of the health authorities regarding this new molecule made it impossible to classify it as a MD.

Another example of MD more comparable to the “Peptide solution + Secondary dressing” is the Caciqliq20®. This Caciqliq20® is a spray, considered as a MD of class III, offering protection of growth factors by decoy effect and whose mode of action can be compared to that of the BFP peptide, which also acts as a decoy for MMP (Barritault, 2020). Additional expertise was therefore requested from another European health authority who stated on this particular case that the Caciqliq20® is accepted as a device but similar products may be considered pharmaceutical. This statement demonstrates the variability of classification that can be obtained from one country to another.

The opinion of other European health authorities is quite unanimous and in agreement with that of the French health authorities. Only the Czech health authorities (SUKL) considered the device presented as a combined device of class III. As a risk device this MD is subject to great vigilance in terms of

traceability and monitoring and consequently, a GMP synthesis of the peptide has been required by the health authorities in order to carry out a clinical trial. DM. This GMP synthesis not originally planned by the industrial and that will have heavy consequences for the future of the project.

## 5 IMPACT OF A CLASSIFICATION AS A COMBINED MD OF CLASS III

A device classified in class IIb or III is considered as high-risk class by health authorities and a GMP synthesis would be required in any case. The debate is not about the classification of the MD but about a wrong evaluation of the project in its entirety and a poor knowledge of the field. How this wrong estimation impacts the project and its budget according to the development stage of the MD?

### 5.1 MD Conception

The MD conception stage is an essential step determining the whole project technically and financially. A correct calibration is essential to avoid budget expense and project delay. The longer is a project and the more expensive it will be. The correct definition of the MD is possible with a deeper knowledge of the field of MD. Indeed, a MD classified in class IIb or in class III as a combined MD present risk and although the safety and innocuity proof are high. Health authorities will not take any chances to propose a product on which they do not have hindsight and without strong, recorded and tracked guarantees on the safety. Moreover, with the sanitary scandals of the past few years, health authorities are extra careful regarding new devices.

### 5.2 Clinical Phases

A poorly estimated project at the outset will have the greatest impact during the clinical phases. The acceptance of the clinical trial is submitted to the approbation of health authorities that will request the GMP synthesis. As the budget allocated for the trial is not sufficient to cover this additional expense, the project will inevitably fall behind schedule.

For clinical trial, the quantity of necessary peptide (or molecule) is rather small, and the costs are extremely high due to the tracking system to implement, and the documentation requested for a GMP synthesis (Figure 2).

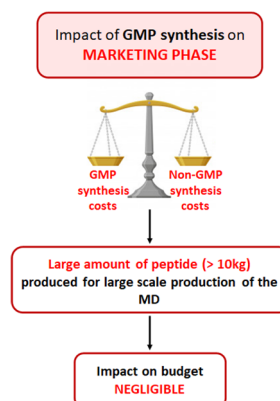


Figure 2: Impact of unplanned GMP synthesis on clinical phase of a project.

- Produce a small amount of peptide, just enough for the trial, pending verification that the clinical trial is providing the expected results.
- Produce a larger amount of peptide in anticipation of the continuation of the project and the commercialisation of the MD after the clinical trial.

The 2 options of production will have an equivalent price and difference will not be significant. A larger production of peptide during the clinical phase can save valuable time for the commercialization phase where important quantity of peptide will be requested. It is then important to correctly estimate the financial costs and benefits of a larger molecule production upstream.

It is necessary to be well trained and advised by experts of the field to avoid taking decision urgently and make bad choices for the project.

### 5.3 Marketing and Post Marketing

An unplanned GMP synthesis at the marketing phase can have a financial impact mainly according to the decision taken at the previous steps. During the marketing phase, there is 2 possibilities:

- The peptide quantity produced at the previous step was just sufficient to complete the trial. In that case an additional budget and time increase is to plan for the production of GMP synthesis.
- The peptide quantity produced at the previous step was increased in anticipation for the marketing. In that case, the manufacturing of the device can be launch immediately.

However, a reflexion is to be considered for the future of the project and according to the marketing

plan of the industrial. Indeed, either the industrial is the exclusive manufacturer and seller of the MD, in which case it will be necessary to provide a budget for the GMP synthesis throughout the marketing and life cycle of the MD. Or the industrial commercializes its devices in the form of licensing by granting licenses for the exploitation of its product. In this case, the manufacturer does not have to budget the GMP synthesis for the marketing part.

However, it is important to highlight that the greater the quantity of GMP synthesis, the lower the price per kilo will be. Therefore, for 10 kg of GMP peptide produced, the price per kilo is equivalent to that of a non-GMP synthesis (Figure 3).

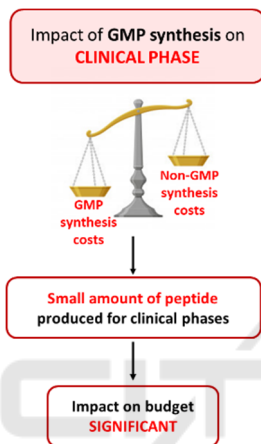


Figure 3: Impact of unplanned GMP synthesis on marketing phase of a project.

Therefore, the impact of a GMP synthesis not foreseen by the industrial during the design of the project will have no financial impact for the later phases of the project, if the GMP synthesis is very important (equivalent to about 10 kilo).

## 6 CONCLUSION

The classification of MD and in particular combined devices is a very complicated process, hardly harmonized before the implementation of the new European regulation 2017/746. Some examples of dressings classifications that do not comply with the new European regulation can be cited as UrgoStart® (a combined MD classified as class IIb) or Prevena® dressing (a combined MD containing silver classified as class IIa) or a product like Caciqliq20® that can be considered as a medicine and yet is positioned as class III MD under the old directive. In this logic, the mechanism of action of the UrgoStart® dressing, whose main function is the inhibition of proteases by

the NOSF molecule, could be considered as a pharmacological activity (Européenne, 2017) and then classified as a combined MD of class III. To understand this classification, an expert opinion has been requested from European health authorities who stated that, in their opinion and according to the regulation in force, the substance NOSF meets the status of a medicine. According to the regulation, combined MD are defined following the rule 14 of Annex VIII of the European Regulation 2017/746 as “All devices incorporating as an integral part a substance which, when used separately, may be considered as a medicinal product within the meaning of Article 1(10) of the said Directive, and the action of which is ancillary to that of the devices, fall within Class III.” On this basis, the UrgoStart® MD could therefore be considered as a combined MD.

The status of combined MD is not clear, and it was noted through this article that:

- Combined MD dressings are not clearly defined as such on the contrary of combined MD as stent or injector pens.
- Combined MD dressings are widely represented within the different risk classes, and they are not systematically classified in class III as they should be as high-risk MD.

As part of the evaluation of a MD, it is currently essential to carry out one, or even several, clinical trials to demonstrate efficiency and safety of the device. In this case, the balance benefit-risk is very important and cannot be unbalanced in one direction or the other under penalty of considering the device as a drug. Indeed, in the case of a combined MD, the main objective is to prove the ancillary action of the associated molecule compared to the main MD. Although the manufacturer transmits all the safety information and considers the benefit-risk to be well balanced, the health authorities will tend to perceive an unbalanced in the direction of risk.

Those combined MD are considered as “borderline products”, they are indeed, at the frontier between the MD and the medicine, it is then a question of claim and most of all to prove the effect of the ancillary substance, associated with the main MD. Moreover, an associated and innovative substance will always be considered at risk by health authorities who will not take any risk and will systematically classify it as a high-risk MD. It is also clear that regardless of the classification of the device, in class III as a combined MD or in class IIb, such as UrgoStart®, a GMP synthesis will be requested for the associated molecule in order to have a better traceability.

The debate is therefore not about being classified as a class IIb MD or as class III combined MD, but really about avoiding being classified as a medicine. The aim is then to provide as much proof of safety as possible and to make a good claim that will avoid being classified as a medicine by health authorities.

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