

## Safety through risk management throughout the whole product life cycle

The European Directive 93/42/EEC specifies the regulations for placing medical devices on the market.

This Directive has been implemented into national law in the German Medical Devices Act (MPG), the provisions of which are in turn set out in detail in statutory regulations such as the Medical Devices Ordinance and the Medical Devices Safety Plan Ordinance.

This regulatory framework is supplemented by guidelines and harmonised standards, especially by the standards for the quality management system for medical devices in accordance with DIN EN ISO 13485 and for the risk management system in accordance with DIN EN ISO 14971 as well as by the vigilance guidelines MEDDEV 2.12.

The requirements governing the marketing of a medical device referred to here represent only a fraction of the activities necessary developing these products. In particular, they intended to illustrate the risk-based approach.

## Pre-launch: development phase/ risk analysis/ risk management records

The risk-to-benefit assessment, i.e the assessment of the relation of risk versus benefit, is an essential part of the development and marketing of these products. The aim is to identify, assess and minimise risks at as early a stage as possible.

The first step is to determine the intended purpose of the medical device and to identify the applicable risk class. The risk classes (Class I, II or III) are determined in accordance with Annex IX of the European Directive.

Since preliminary tests and investigations of the active ingredients and the probable duration the product remains in the body are already required, these findings are the basis for the risk analysis. This means the requirements of DIN EN ISO 14971 regarding the risk management system must already be integrated into the product development concept. As part of the risk management process, the risk analysis is to be continuously verified and, if necessary, expanded during subsequent stages of development.

Every update of the risk analysis is to be recorded in the risk management documentation, which must be maintained and archived throughout the whole product life cycle.

Biocompatibility tests as well as a clinical evaluation are to be carried out in the course of the development process in order to assess the risk for each medical device.

If a Class III medical device is being developed, clinical trials are mandatory in some cases.

Following the amendment to Directive 93/42/EEC in March 2010 the proof of fitness for intended use and safety of a medical device has been codified in the “Essential requirements” and therefore must be observed in designing medical devices.

## Launch: Conformity assessment procedure/declaration of conformity

Technical documentation has to be prepared as proof of compliance with the “Essential requirements” of Directive 93/42/EEC, Annex I.

This contains all required data, such as the justifications for the classification, the list of the harmonised standards used, the current risk assessment, the biocompatibility

and clinical evaluation as well as the most current instructions for use based on that evaluation. In addition, the technical documentation contains the guideline certificate of the manufacturer. The technical documentation is thus a statement of the documented safety and function of the medical device.

The issuing the declaration of conformity by the manufacturer marks the conclusion of the conformity assessment procedure for the medical device that has been developed and the manufacturer may attach the CE label to the product.

## Post-launch: annual surveillance audit/post-marketing surveillance system/post-market clinical follow-up

Additional safety-relevant requirements have to be satisfied in order to ensure that a medical device can continue to be marketed after its market launch. For example, a functional, documented monitoring and reporting system is required in which market monitoring data are recorded and assessed over the entire product life cycle.

In cases where risks or incidents become known, the manufacturer or their safety representative has to implement measures. Incidents must be reported to the national authority. Corresponding requirements are set out in the vigilance guideline MEDDEV 2.12/1 and in the German Medical Devices Safety Plan Ordinance. Strict rules governing the notification timelines have to be observed in the event of an incident.

The findings generated by marketing surveillance must be documented in the post-marketing surveillance system and regularly assessed (usually at least once a year) as part of the risk management activities. The results of this assessment have to be implemented in the technical documentation, i.e. the clinical evaluation and/or the instructions for use may need to be revised in addition to the risk analysis. Further biocompatibility tests and studies may be required in this context. In accordance with MEDDEV 2.12/2, the person responsible for marketing the product is obliged to verify whether post-market clinical follow-up is necessary.

In order to maintain the certification issued under the guidelines and/or DIN EN ISO 13485 a check should be made at least once a year by the Notified Body during the surveillance audit that a documented, “active” vigilance system exists.

## Summary: a functional safety system resulting from to a risk-based approach

The risk-to-benefit assessment is already carried out during the development of the medical device, at various milestones before and after the initial marketing of the device. All the findings obtained during development as well as from market monitoring over the entire product life cycle after successful certification are included in this risk assessment and in the resultant measures taken to minimise risks.

As a result, medical devices have a high degree of safety resulting from a sophisticated system in which adequate measures to protect the user are required. The system is also regularly checked by the Notified Body to ensure that it is functioning correctly and that the entity responsible for placing the device on the market is complying with the requirements.

STERILE A

# Position paper Substance-based Medical Devices

BPI





### What are medical devices?

As with the term “medicinal product”, the term “medical devices” is not self-explanatory even among experts.

In general, the classic term “medical devices” is generally understood to mean primarily ancillary products such as plasters (bandages), catheters or devices such as pacemakers and X-ray machines.

**As per § 3 Sect. 1 of the German Medical Devices Act (MPG), medical devices are defined as follows:**

*“... all ... substances and preparations made from substances or other articles ..., intended by the manufacturer to be used for human beings, by virtue of their functions, for the purpose of diagnosis, prevention, monitoring, treatment or alleviation of diseases [...] and which do not achieve their principal intended action in or on the human body by pharmacological, immunological or metabolic means, ...”.*

**Medicinal products, on the other hand, are defined in the German Medicines Act (AMG § 2, Sect.1, No.1 as follows:**

*“Medicinal products are substances or preparations made from substances, ... which are intended for use in or on the human or animal body and are intended as agents with properties for curing or alleviating or preventing human or animal diseases or disease symptoms ...”.*

Therefore, medical devices and medicinal products are the only products on the European market whose intended purpose includes the diagnosis and treatment of diseases.

The definition of a medical device is very similar to that of a medicinal product, except that medical devices are intended for use solely in or on human beings.

An essential criterion for differentiating between the two product groups lies in their different modes of action. While the medicinal product achieves its effect by pharmacologic, immunologic or metabolic means, a medical device does this in other ways.

Medical devices are therefore clearly distinguished from medicinal products by their properties and mode of action.

### What are “substance-based medical devices”?

Substance-based medical devices (or medical devices with drug-like characteristics) are not generally associated with the term “medical device” because their pharmaceutical form or formulation is similar to that of a medicinal product.

Nevertheless, they meet the legal definition of a medical device because their principal mode of action is neither pharmacologic, immunologic nor metabolic in nature.

Examples of substance-based medical devices include solid, semisolid and liquid preparations such as lozenges, ultrasound gel and artificial tears or saliva. All of these have no pharmacological effect on human beings or their cells but nevertheless serve to make diagnoses and treat diseases.

### How can medical devices be distinguished from medicinal products?

As previously described, the criterion of “diagnosis and treatment of diseases” alone is insufficient to distinguish between the two product groups. Instead, the difference lies in their mode of action.

Unlike medicinal products, the mode of action of medical devices is not primarily pharmacologic, immunologic or metabolic in nature. As the term “pharmacological mode of action” in particular is not clearly defined, problems in differentiating between the two product groups frequently arise. Therefore, an exact analysis of the mode of action and the intended use as defined by the manufacturer is necessary for classifying many of these medical devices.

The intended use of a product is defined by the manufacturer. The effect of the medical device must be objectively supported by its scientific rationale.

**The classification problems described above are illustrated by the following examples:**

Dexpanthenol or D-panthenol is widely recognized by lay persons as a constituent of skin care cosmetics. Another characteristic of dexpanthenol is its water-binding capacity. As a result, dexpanthenol is also found in medical devices for moistening the nose, skin or surface of the eye. In addition, dexpanthenol is used as a pharmacologically active ingredient in a concentration of 5% or higher in medicinal products for the treatment of wounds.

This example illustrates the difficulties in classifying a product: not only the material components but also the intended use must be taken into account.

Another example that shows the difficulty in differentiating between the two product groups is sodium chloride, which is used both in medicinal products (in solutions for infusion) and in medical devices (in irrigation solutions).

Generally speaking, simethicone or polyethylene glycol are surface-active substances which cause gas bubbles to collapse in the gastrointestinal tract, thereby eliminating flatulence. The general scientific and technical consensus is that these substances are chemically inert which means that a pharmacologic and metabolic mode of action can be ruled out. The normalisation of physiological processes as a result of the physical mode of action of medical devices cannot be used as a justification for classifying the product as a medicinal product, despite some decisions to the contrary by regulatory authorities.

These examples clearly demonstrate problems one is faced with in differentiating between medicinal products and medical devices. As a result, discussions surrounding the classification of these products often result in legal disputes.

### What requirements have to be satisfied before medical devices can be placed on the market?

Legislators have adopted a new approach relating to the placing of medical devices on the market. This imposes an obligation on the manufacturer to commission an independent body (known as a Notified Body) to verify compliance with the relevant regulations governing medical devices in accordance with a risk-based graded classification system.

Medical devices must meet the same standards of functionality, safety and quality as medicinal products, particularly as regards the implementation of a risk management system in all divisions/departments of the responsible manufacturer.



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