Labeling of Drug-Device Combination (DDC) Products in Europe under the new Medical Device Regulation (EU) 2017/745

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„You can never be overdressed or overeducated."

Oscar Wilde

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List of Abbreviations

CE	Conformité Européene
CHMP	Committee for Medicinal products for Human Use
CHRN	Swiss Single Registration Number
CP	centralized procedure
DDC	drug-device combination
EMA	European Medicines Agency
e.g.	Latin: *exempli gratia*, English: for example
eIFU	electronic instructions for use
ePI	electronic product information
EU	European Union
EUDAMED	European database on medical devices
EU PI	European Union product information
FDA	Food and Drug Administration
GSPR	general safety and performance requirements
iDDC	integral drug-device combination
i.e.	Latin: *id est*, English: that is
IFU	instructions for use
ISO	International Organization for Standardization
MA	marketing authorization
MAA	marketing authorization application
MAH	marketing authorization holder
MDCG	Medical Device Coordination Group
MDD	medical device directive
MDR	medical device regulation
MHRA	Medicines and Healthcare products Regulatory Agency
NANDO	New Approach Notified and Designated Organisations

NB	notified body
NBOG	Notified Body Operations Group
NBOp	notified body opinion
PL	package leaflet
PRRC	person responsible for regulatory compliance
QMS	quality management system
QRD	quality review of document
SmPC	Summary of Product Characteristics
SOP	standard operating procedures
UDI	unique device identification
UDI-DI	UDI device identifier
UDI-PI	UDI production identifier
UK	United Kingdom
UKCA	U.K. Conformity Assessed
US	United States (of America)

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Glossary

Co-Packaged Drug-Device Combination Products

In chapter "*1. Introduction*" of the European "*Guideline on quality documentation for medicinal products when used with a medical device*", co-packaged drug-device combination (DDC) products are defined as "*a medicinal product and medical device packed together into a single pack (e.g. carton), which is placed on the market by the Marketing Authorisation Holder (MAH)*".[1]

Drug-Device Combination

The term 'drug-device combination' is neither defined in the European requirements for medicinal products, Directive 2001/83/EC and Regulation (EC) No 726/2004, nor in the medical device regulation (MDR), Regulation (EU) 2017/745. But the term is used by the European Medicines Agency (EMA), *e.g.* in the guidance document "*Questions & Answers for applicants, marketing authorisation holders of medicinal products and notified bodies with respect to the implementation of the Medical Devices and In Vitro Diagnostic Medical Devices Regulations ((EU) 2017/745 and (EU) 2017/746)*". In the introduction (sentence 10) of Regulation (EU) 2017/745, some information on what is considered a combination product is provided stating, "*Products which combine a medicinal product or substance and a medical device are regulated either under this Regulation or under Directive 2001/83/EC […]"*[2].

In this thesis, DDC is used for any combination of a medicinal product or substance and a medical device, *i.e.* integral, co-packaged or referenced DDC. Referenced DDCs are out of scope of this thesis and will not be further discussed.

Immediate packaging

Immediate packaging describes a container or other form of packaging which is in direct contact with the medicinal product; also called primary packaging.[3]

Intended Purpose

According to Article 2 (12) MDR, the intended purpose describes the primary use for which the device is designed and manufactured, and which is included in form of labeling claims

on the label, the instructions for use or in promotional or sales materials or other claims made by the manufacturer.[2]

Instructions for Use

Instructions for use (IFU) contain information for the user (healthcare professionals and/or patients or caregivers) on the intended use of a medical device and the precautions which need to be followed for a safe use of the medical device (Article 2 (14) MDR).[2]

Integral Drug-Device Combination Products

According to Regulation (EU) 2017/745, integral DDC products are defined as a combination of a medicinal product and medical device which "*form a single integral product intended exclusively for the use in the given combination and which is not reusable*" (Article 1 (9) MDR).[2]

Label

FDA defines 'label' as information which can be found on the immediate packaging of a medicinal product or on the medical device itself.[4] According to Article 2 (13) MDR, 'label' describes all "*written, printed or graphic information appearing either on the device itself, or on the packaging of each unit or on the packaging of multiple devices*".[2,4]

Labeling

The term labeling is used in this thesis to describe all printed material related to a medicinal product or medical device and which contains information the intended user needs to know to identify and to use the medicinal product or medical device safely and effectively; *e.g.* the label on the medical device itself or on the primary packaging of a medicinal product, information on the outer packaging, product information, instructions for use or package insert. Comparing all the different terms describing labeling documents they can be ordered from a high level description becoming more specific: labeling > labelling > label.

Labelling

According to the definition on the EMA website, labelling constitutes the information which can be found on the immediate or outer packaging of a medicine. In this document labelling is also used to describe the information on the immediate and outer packaging of a medical device.[3,5]

Medical Device

The term 'medical device' is described in Article 2 of the Regulation (EU) 2017/745, regulation for medical devices. According to the regulation "*'medical device' means any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes:*

- *diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease,*
- *diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability,*
- *investigation, replacement or modification of the anatomy or of a physiological or pathological process or state,*
- *providing information by means of in vitro examination of specimens derived from the human body, including organ, blood and tissue donations, […]*"

In addition to the above, the principal intended purpose of the medical device is neither achieved by pharmacological, immunological nor metabolic means, in or on the human body but it may be assisted in its function by agents which perform in such a manner.[2]

Medical Device Coordination Group

The Medical Device Coordination Group (MDCG) is an expert committee consisting of experts in medical devices from each Member State. The MDCG shall ensure a harmonized implementation of the MDR. It provides advice to the European Commission and assists in fulfilling the tasks of the MDR.[2]

Medicinal Product

According to Article 1 of Directive 2001/83/EC, a medicinal product is described as "*Any substance or combination of substances presented for treating or preventing disease in human beings. Any substance or combination of substances which may be administered to human beings with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings is likewise considered a medicinal product*".[3]

Mock-up

Mock-ups map the flat, colored artwork design for a medical device's or medicine's inner and outer packaging to visualize the final labeling documents.[6]

Outer packaging

The outer packaging contains the medicinal product in the immediate packaging and the package leaflet.[3] In case of a medical device, the outer packaging consists of the medical device and the instructions for use.

Package Leaflet

The package leaflet contains all information for the patient or caregiver for the safe and effective use of the medicinal product.[3]

Product Information

The product information contains all approved medicinal and scientific information to inform the healthcare professional and patient or caregiver of the safe and effective use of a medicinal product. In Europe, it contains the Summary of Product Characteristics, the package leaflet, and labelling.[7]

Specimen

A sample of the actual printed outer and inner packaging materials and package leaflet for a medicine.[8]

Summary of Product Characteristics

The Summary of Product Characteristics (SmPC) is the European document for medicinal products approved by EMA via the centralized procedure which contains all information for healthcare professionals on the safe and effective use of a medicinal product.[9]

Introduction

On 26 May 2021, the medical device regulation (MDR) 2017/745 came into force. This new regulation replaced the old medical device directives (MDD) 93/42/EEC on medical devices and 90/385/EEC on active implantable medical devices.[10] The purpose of evolving the new MDR was to "*establish a robust, transparent, predictable and sustainable regulatory framework for medical devices which ensures a high level of safety and health whilst supporting innovation*".[2] One reason for updating the outdated MDDs were increased incidents of breast implant adverse events around 2009. Based on this breast implant scandal and further implant scandals, it was decided to improve the medical device framework by implementing the MDR with strengthened safety and control requirements.[11]

Compared to the MDDs, which needed to be translated into national law, the MDR is directly binding and therefore harmonizes the regulatory requirements of medical devices within the European Union (EU). Consequently, this leads to a free movement of medical devices within the EU which requires an intensified monitoring system to control the safety of registered medical devices. In addition, the new MDR intends to enable a high standard of quality and safety for medical devices to protect the health of users and patients in the EU with increased transparency and traceability.[2]

One component to enable the development and registration of a medical device, which can be used safely and effectively by the intended user, is the labeling of medical devices which comprises of the label, the outer packaging, and the instructions for use (IFU).

The focus of this thesis mainly lies on the labeling obligations for drug-device combination (DDC) products. In the introduction (10) of the MDR it is stated that "*Products which combine a medicinal product or substance and a medical device are regulated either under this Regulation* [MDR 2017/745] *or under Directive 2001/83/EC of the European Parliament and of the Council*". This means that based on the primary intended purpose DDC products are either regulated by the MDR or by the medicinal products regulation. Although in the introduction of the MDR only Directive 2001/83/EC is mentioned, in MDR Article 1 (8) it is further specified that this description includes medicinal products regulated either by Directive 2001/83/EC or Regulation (EC) 726/2004. DDCs cannot be regulated by both regulations (medical device and medicinal product regulations) or a mixture of both regulations.

Therefore, labeling obligations for medical devices in general will also be discussed in this thesis since they apply to DDC products regulated by the MDR.

In Article 1 (6b) of the MDR, it is clearly stated that the MDR "*does not apply to medicinal products as defined in point 2 of Article 1 of Directive 2001/83/EC*". Furthermore, it is stated in the MDR that "*For medicinal products that integrate a medical device part, compliance with the general safety and performance requirements laid down in this Regulation for the device part should be adequately assessed in the context of the marketing authorisation for such medicinal products.*" That means that in general for an integral DDC product, for which the primary intended purpose is based on the medicinal part, this DDC is regulated by the medicinal product legal framework, but for the device part the general safety and performance requirements (GSPR) described in the MDR are applicable, and need to be assessed prior granting a marketing authorization for the DDC product.

With the implementation of the new MDR, new labeling requirements were introduced, *e.g.* affixing a unique device identification (UDI) carrier to medical devices or implementing a new format for the IFUs. The introduction of the MDR led to several challenges regarding the labeling of devices since only limited guidance for the practical implementation was available.

In this thesis, the impact of the MDR on DDC products will be assessed and discussed, focusing on the labeling of devices and taking registration processes into account for which mock-ups of the final label need to be created. In addition, the labeling impact of the MDR on co-packaged and integral DDC products which are regulated by the medicinal product legal framework will be investigated. Labeling differences and similarities will be highlighted by performing case studies and establishing a labeling profile for a co-packaged and integral (intended purpose is based on the medicinal product) DDC product. In addition, the current available labeling guidance documents for medical devices will be assessed and limitations presented in detail. Furthermore, a draft template based on the quality review of document (QRD) template published by EMA will be developed to cover the labeling requirements for integral DDC products regulated as a medical device by the MDR.

Labeling obligations for *in vitro* diagnostic devices regulated by Regulation (EU) 2017/746, implantable devices, and referenced DDC products are out of scope and will not be further assessed or discussed in this thesis. In addition, this thesis will only focus on medicinal

products which are approved via the centralized procedure by EMA. National or decentralized authorization, and mutual recognition procedures are out of scop and will not be further considered.

Material and Methods

For the creation of this thesis, the MDR was assessed, and applicable labeling requirements presented and discussed in detail. For considering labeling requirements for medicinal products, relevant sections of Directive 2001/83/EC and Regulation (EC) 726/2004 were assessed as well.

In addition, available guidance documents published by the Medical Device Coordination Group (MDCG), Team-NB (notified body), and EMA as well as publicly accessible articles via the internet were considered for this thesis. International Organization for Standardization (ISO) standards were also considered but the access to these standards was limited since a license needs to be purchased. Nevertheless, a summary of the standards and table of content was publicly accessible and considered.

For the creation of labeling documents for co-packaged and integral DDC products, the SmPC guideline and QRD templates published by EMA were considered in particular (see Appendices XI to XIII) to present a sample how to support manufacturers with more detailed guidance in case the MDR is the umbrella to authorize the medical device.

Results and Discussion

1. Overview on labeling requirements for DDC products

1.1. Labeling obligations for medical devices according to the new MDR

1.1.1. General labeling requirements

Before assessing labeling requirements for a drug-device combination (DDC) product, it needs to be defined if the concerned product applies to the definition of a medical device as laid down in Article 2 (1) of the MDR. The MDR does not apply to medicinal products (MDR Article 1 (6b)). DDCs are products which combine a medical device and a medicinal product. Since they can only be regulated by one regulation, either the MDR or the medicinal product legal framework consisting of Directive 2001/83/EC or Regulation (EC) 726/2004, the principal mode of action of the product determines the leading regulation (MDR Article 1 (6b)).

If a product is regulated by the MDR, the risk class of the medical device needs to be determined according to the classification rules in Annex VIII of the MDR. In general, medical devices can be assigned to class I, class IIa, class IIb, or class III with increased risks for higher classes (MDR Article 51 (1)). Based on the risk class, different labeling obligations apply. In general, it can be stated that with increased risks of a device stricter labeling obligations need to be considered. For example, for implantable devices and class II devices, the manufacturer needs to create a summary of safety and clinical performance which needs to be made publicly available. A reference also needs to be made on the label or IFUs where this information is located and how it can be accessed (MDR Article 32).

According to the MDR, it is the obligation of the manufacturer to ensure that the labeling, including labels and IFUs, follows the current MDR (Article 10). Therefore, a new role was introduced: the person responsible for regulatory compliance (PRRC). The PRRC shall ensure that the technical documentation which includes the labeling information is in compliance with the MDR (Article 15). In addition and according to MDR Articles 11, 13, and 14, the authorized representative, importers, and distributors, if applicable, need to ensure that the labeling of the device complies with the regulation.

In Article 7 of the MDR, it is stated that it is prohibited to claim information or use symbols on the labelling or in the IFU which might be misleading for the user, especially with regards to the intended purpose, safety, and performance of the medical device. Further indications providing information for what is requested to be included in the labeling documents of medical devices can be found in the Annexes of the MDR: Annex I '*General Safety and Performance Requirements*', Annex II '*Technical Documentation*', Annex V '*CE mark*', and Annex VI Part C 3.1 '*UDI label on the device*'.[2]

For some medical devices it is also possible to only provide an electronic IFU (eIFU). This applies at the moment only to implantable devices, fixed installed devices, and devices with a build in visual display when they are used by professional users only. It also applies to medical device software used either by professionals or lay persons.[12]

According to MDR Article 1 (8) and (9), Annex I, which defines the GSPRs, is also applicable to DDC products which are regulated by Directive 2001/83/EC or Regulation (EC) 726/2004 if the safety and performance of the medical device part is concerned. Annex I Chapter III 23.1 "*General requirements regarding the information supplied by the manufacturer*" of the GSPR checklist provides an overview of topics relevant for labeling of a DDC product (see Appendix I). In general, all information which is needed for the identification of the medical device and its safe use needs to appear on the device itself, on the packaging, or in the IFU.[2]

1.1.2. Information on the label

According to Article 10 (11) of the MDR, the information provided on the label shall be durable, easily legible, and written in a way that it is understandable for the intended user who can be a professional (*e.g.* healthcare professional) or lay person (*e.g.* patient or caregiver).[2] Further guidance how this can be achieved or transposed into the labels or verified by the manufacturer is not provided in the MDR.

A detailed list of information which should be provided on the label can be found in MDR Annex I Chapter III 23.2 "*Information on the label*" (see Appendix II).[2] Reviewing that extensive list raises questions how this amount of details shall be provided on a label which is directly attached on a medical device; especially if the space on the label is limited, *e.g.* a label of an autoinjector with inspection window. A potential workaround is the use of

symbols which need to comply with harmonized standards or common specifications as stated in Annex I Chapter III 23.1 (see also 1.1.7).[2]

1.1.3. Sterile packaging

In case a medical device, *e.g.* a pre-filled syringe, needs to be provided in a sterile condition, an additional sterile packaging is required prior placing the pre-filled syringe in the outer carton together with the IFU. MDR Annex I Chapter III 23.3 "*Information on the packaging which maintains the sterile condition of a device ('sterile packaging')*" provides details which information needs to be placed on the sterile packaging. Among other things, the information on the sterile packaging consists of a declaration that the device is sterile including an expiry date, a short description of the device, and a reference to the attached IFU (see Appendix III).[2]

1.1.4. Outer Packaging

MDR Annex I Chapter III provides detailed lists for information which needs to be addressed on the device label, sterile packaging, or IFU, but there is no separate list for information which need to be placed on the outer carton of a medical device. From MDR Annex II "*Technical Documentation*" (2) "*Information to be supplied by the manufacturer*" it can be assumed that MDR Annex I Chapter III 23.2 "*Information on the label*" also applies for the information which needs to be placed on the outer packaging. In this MDR chapter it is stated that the manufacturer needs to provide "*a complete set of: — the label or labels on the device and on its packaging, […]*". In MDR Article 2 (13), the label is clearly defined as any information printed on the device itself or the packaging.[2] Since the MDR makes no distinction whether a label on the device or a label on the outer packaging is meant, it might be not clear for the manufacturer on which of these two labels the required information listed in Annex I Chapter III 23.2 needs to be displayed. It is not clear, if the information can be split on both labels or if both labels need to carry all required information to comply with the MDR. This leaves the interpretation of the MDR open and might raise questions by the assessing body during the registration process of medical devices.

1.1.5. Information in instructions for use

In MDR Article 10 (11), it is requested that the instructions for use (IFU) shall be easily legible and understandable for the intended user, *i.e.* professional or lay person. Similar to the requested information on the label (see 1.1.2), no further guidance can be found in the MDR what is meant by easily legible and understandable. Thinking especially of the diversity of the European population, skills of the different age groups, differences in the educational background, and possible mental or physical disabilities of lay persons, it might be challenging to create a harmonized standard for the above-mentioned requirements. Manufacturers can consider a US guidance published by the Food and Drug Administration (FDA) in 2016 for "*Applying Human Factors and Usability Engineering to Medical Devices*"[13] to gain further insights what aspects might need to be considered to comply with the MDR requirements. For medicinal products, a "*Guideline on the Readability of the Labelling and Package Leaflet of Medicinal Products for Human Use*" is available. Since this is a European guideline published by the European Commission, manufacturers can also consult this guideline to gain more insight what is expected for preparing readable and legible medical device labels (see also section 1.3.5).

In general, the IFU should inform the intended user how to safely use the medical device. In Article 61 of the MDR, it is stated that the information in the IFU should be based on clinical data and needs to comply with the relevant GSPRs as laid down in MDR Annex I Chapter III 23.4 "*Information in the instructions for use*" (see Appendix IV). Based on this detailed list, the IFU should comprise information on describing the medical device and its performance, the expected risks, contraindications, any preparation prior using the device, and necessary training of the user. The training is not only limited to lay persons but can also be applicable for professional users, *e.g.* if an *intraocular* administration needs to be performed which requires special training based on the identified risks. Further information in the IFU should be included in case a medical device is sterile or re-usable, including especially risks which can occur if the device is re-used, information for combination products, in case devices emit radiation, any warnings and precautions the user needs to be made aware of, for implants and absorbable devices, and information for the disposal of the device.[2]

As stated in section 1.1.1, for some medical devices only an eIFU needs to be made available and a printed version is not needed.

1.1.6. Unique Device Identification

One requirement of the new MDR is an enhanced traceability of medical devices to improve the safe use of the devices. Therefore, a unique device identification (UDI) system was established. This system is used to track and control the movement of medical devices until it has reached the intended user and it should also be used for reporting any incidents during the post-marketing phase. Assigning a specific UDI to each medical device allows the competent authority an enhanced monitoring of the safety of medical devices.

In Article 27 and in Part C of Annex VI of the MDR, requirements for setting up UDIs and a UDI database are described. A UDI is a series of numeric or alphanumeric characters and consists of two elements, a UDI device identifier (UDI-DI) and a UDI production identifier (UDI-PI). According to the definition in the MDR, the UDI-DI is a "*unique numeric or alphanumeric code specific to a model of device and that is also used as the 'access key' to information stored in a UDI database*". Whereas the UDI-PI is a "*numeric or alphanumeric code that identifies the unit of device production*" (see also Table 1).[2]

Table 1: Information covered by the UDI device identifier (UDI-DI) and a UDI production identifier (UDI-PI)

UDI-DI	**UDI-PI***
• version or model of a device	• lot/batch number
• labeler of the device	• serial number
• package quantity (unit of sale, multi-pack, etc.)	• software identification
	• expiry date or manufacturing date

*Not all information needs to be captured by the UDI-PI. But if the information is placed on the label, it should appear in the UDI-PI. The UDI-PI characteristics, *e.g.* lot or serial number, are based on the manufacturer's individual internal guidance documents.[14]

The UDI is assigned to the medical device by the manufacturer. But for the creation of a UDI, an independent agency is contacted to create the UDI. Currently accepted issuing entities are GS1, HIBCC, ICCBBA, and IFA.[15]

Before a medical device is placed on the market, a UDI needs to be assigned to the device itself or its packaging. The description in Article 27 of the MDR is not clear and might lead to confusion by the manufacturer when assigning the UDI. In Article 27 (1b) it is stated that the UDI shall be placed on the device or on its packaging, whereas in Article 27 (4) it says a UDI shall be placed on the label of the device and all higher levels of packaging. In Annex VI Part C 3.1, it is clearly stated that a "*UDI shall be assigned to the device itself or its packaging*" so that this can be considered as the current practice.

Besides the possibility to track a device, the UDI shall be used to report serious incidents and field safety corrective actions to improve the safety and protect the user's health and well-being (Article 87 MDR). Therefore, a UDI database was established in accordance with Article 28 MDR to facilitate the tracking and reporting of medical devices. In addition, the European database on medical devices, EUDAMED, is a tool for the competent authorities to exchange information during the registration process and post-marketing phase of a medical device. The basic UDI-DI and UDI-DI need to be registered in EUDAMED. In contrast to the UDI-DI, which is placed on the labels, the basic UDI-DI is the primary identifier used to enter device-related information in EUDAMED. The basis UDI-DI is also referenced in the relevant documents, *e.g.* certificates or the EU declaration of conformity. The purpose of the basic UDI-DI is to combine information related to devices with the same intended purpose, risk class, design, and manufacturing characteristics. It is not part of the labeling documents but used for collecting information and identifying similar devices in the database.[2,14]

Since EUDAMED is not yet fully developed it becomes only mandatory to use when all functions are available in 2026. The MDR provides a transition phase from 1 to 5 years for placing a UDI on the medical devices to guarantee a smooth introduction of the UDI system. This allows manufacturers to assign UDIs to all of their already registered medical devices with the next upcoming conformity assessment.[2,16]

1.1.7. Symbols

In Annex I of the MDR, an extensive list of information which needs to be placed on the label of a medical device is provided (see Appendix II). Based on the design of the medical device, the manufacturers may face space constraints when trying to cover all the

requested information on the label. The MDR allows the replacement of written information by using internationally recognized symbols (MDR Annex I Chapter III 23.1.h). These symbols need to comply with harmonized standards or common specifications. It is also possible to use symbols which are not yet covered by harmonized standards. These symbols need to be described in the technical documentation and the IFU until they are incorporated in any standard.[2]

The MDR does not refer to symbols which might be used on the labels or IFUs and are addressing lay persons only. These symbols should always be described in the IFU for clarity, in my opinion, since it is unknown which education the lay persons have and to avoid misunderstanding. Symbols should be easily and unambiguously understood by all users to guarantee the safe use of the medical device. They are an efficient tool to convey information without using much space and long texts. Hence, they are also a cost-effective alternative for manufacturers to provide information.

ISO documents are internationally accepted standards and are widely used to transpose regulatory obligations in practice. ISO 15223-1:2021 "*Medical devices — Symbols to be used with information to be supplied by the manufacturer — Part 1: General requirements*" was updated to integrate symbols on the newly requested information in the MDR. The guidance contains various symbols which can be used to replace written language on the medical device labels (see Appendix V).[17,18]

1.1.8. National language requirements

For the registration process, the proposed labeling documents shall be provided in a language that is understood by all concerned Member States which means that the documents are usually provided in English language (Article 41 MDR). But for placing the medical devices on the market, the manufacturer needs to deliver all required information accompanying the medical device in an official Union language or multiple languages based on the single Member State requirements (Article 10 MDR).[2]

Currently, the EU has 24 official national languages. A list of the official languages per EU country can be found in Appendix VI. Unfortunately, there is no guidance yet available from the MDCG which languages are acceptable for each EU country. Manufacturers need to consult each country legislation to collect the information needed in which language the

labeling material needs to be provided for each EU country. For medicinal products, EMA has published a guidance with details for each labeling document.[19]

1.1.9. Post-market surveillance system

According to MDR Article 83, the manufacturer shall establish a post-market surveillance system "*to actively and systematically gather, record and analyse relevant data on the quality, performance and safety of a device throughout its entire lifetime*". Based on the assessment of the data and events reported and collected in EUDAMED, the manufacturer may also need to update the IFU and labelling of a medical device (Article 83 (3b)).[2]

It is therefore necessary that professional and lay users of medical devices report any incident, so that manufacturers are able to update the technical documentation of the device to cover all relevant and important safety information to prevent the user of any harm by the medical device. A new version of the technical documentation may also affect the labeling of devices. Therefore, a close collaboration between the responsible functions within a company is required to retain the current status of the labeling information.

1.2. Summary - What is new for labeling with the MDR coming into force?

On 26 May 2021, the new MDR became effective. From this date on, new devices were required to apply for a certificate meeting the MDR requirements prior placing them on the market. For medical devices which were already certified before that date, the transition period will end on 26 May 2024 which means that they need to undergo an assessment according to the MDR requirements to renew the certification. Due to the high workload for the limited number of notified bodies and to ensure a continuous supply of safe medical devices the European Commission has recently published an extension of the transition period. This means that CE certificates issued for medical devices with a higher risk class will remain valid until December 2027 and certificates for medical devices with a medium or lower risk remain valid until December 2028.[20,21]

The MDR is more detailed than the superseded medical device directives (MDD) and consists of 123 Articles and 17 Annexes compared to the old MDD with 23 Articles and 12 Annexes. In the following sub-sections key changes of the new MDR and their effect on the labeling of medical devices are described (see also Figure 1).

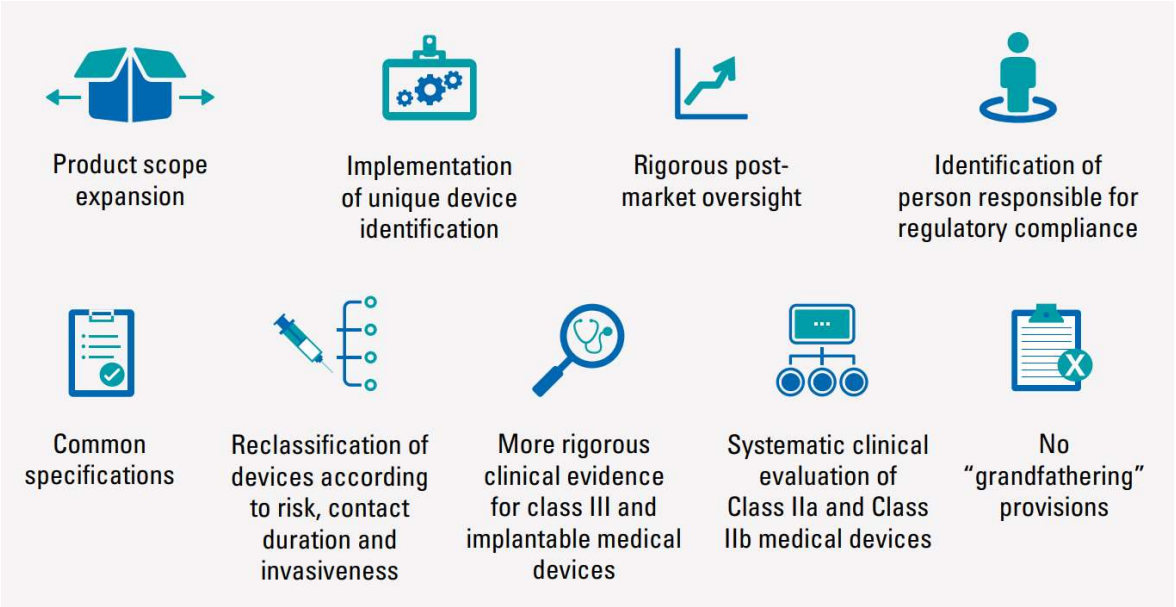


Figure 1: Overview of key changes of the Medical Device Regulation (EU) 2017/745[*]

1.2.1. Medical device classification

The classification rules for invasive and active devices, incl. software as a medical device, were strengthened with the implementation of the new MDR. A lot of medical devices which were previously classified as class I will now be allocated to higher risk classes according to MDR Annex VIII.[2,22]

The re-classification of medical devices has also an impact on the related labeling, since with an increased risk class also the labeling requirements are strengthened. According to MDR Annex I Chapter III 23.1.d, no IFU is required for class I and class IIa medical devices if they can be used safely without any further instructions. With the re-classification in higher risk classes, it is now possible that manufacturer also need to provide IFUs.

1.2.2. Quality management system

According to MDR Article 10 (9), manufacturers need to establish a quality management system (QMS) to ensure compliance with the MDR. With the MDR, a procedure for clinical evaluation and establishment of a post-market surveillance system as well as a post-market clinical follow-up for every device was introduced. The QMS is part of the conformity assessment procedure conducted by a notified body to ensure compliance with the MDR.[2,22]

[*] Graphic taken from https://www.tuvsud.com/en/-/media/global/pdf-files/infographics/tuv-sud-mdr-infographic.pdf (2022)[20]

Any new data collected by the above systems will need to be assessed for safety findings which might lead to an update of the technical documentation and therefore also an update of the labeling documents of the affected medical devices.

1.2.3. Notified bodies

Requirements for the designation of notified bodies which perform the conformity assessment were increased and specified. Notified bodies are now under the control of the national competent authorities and the European Commission.[22]

The role of the notified bodies, including any labeling activities, is described in section 2.

1.2.4. Independent expert panels

For class IIa, class IIb, and class III medical devices a notified body needs to be assigned to perform the conformity assessment. In addition, an independent expert panel can be consulted for class IIb active devices which are intended to administer or remove a medicinal product. In any case, this independent expert panel needs to be involved in the conformity assessment for implantable class III devices (Article 54 MDR). Based on the clinical data and clinical evaluation report, the notified body prepares a clinical evaluation assessment report which is shared with the expert panel to provide a scientific opinion considering the benefit-risk of the medical device.[2,22]

Any identified risk needs to be reflected in the labeling documents to inform the user of the risks and to protect the user from any harm.

1.2.5. Clinical evaluation

The requirements for the clinical data were strengthened with the implementation of the MDR to enhance the safety of medical devices. According to MDR Article 61, a clinical evaluation needs to be performed to ensure that the medical device can be used safely and effectively for the intended purpose and complies with the GSPRs. The clinical evaluation includes clinical trial data as well as scientific information based on literature research. In exceptional cases, clinical trials are not needed to demonstrate equivalence with an already existing medical device. In such circumstances, the manufacturer needs access to the complete set of clinical data from the competitor including the technical documentation. The

clinical data is also needed to support the labeling claims and intended purpose as well as any safety information included in the labeling documents.[2,22]

1.2.6. Traceability

Another tool to improve the safety of medical devices is the introduction of a tracking tool for traceability reasons. MDR Article 27, describes the UDI system which allows the tracking of each medical device until it is handed over to the end-user. The UDI applied to each device is needed for reporting of any incidents which might occur while using the medical device (see also section 1.1.6). A UDI needs to be assigned to all new and all already registered and marketed medical devices. According to the MDR, the UDI needs to be placed on the label of the device itself. Based on the relevance of the reported incidences, the labeling documentation needs to be updated.[2,22]

1.2.7. Transparency

Another requirement for enhancing the safety of medical devices was the improvement of the transparency of the available data and making it accessible for the public by implementing a European database, EUDAMED, for information exchange. The platform is still under development and is planned to be used by competent authorities, Member States, and manufacturers, whereas lay persons only have read access to specific elements. The platform is intended to collect all available information on a medical device in one place and will facilitate the exchange of that information between the concerned parties once it is fully established (see also section 1.1.6).[2,22]

1.2.8. Labeling documentation

With the implementation of the MDR, the requirements for the creation of an IFU were strengthened. More details are now required regarding the expected clinical benefits and clinical performance. A note should be included in the IFU to encourage users, including lay persons, to report any serious adverse events to the manufacturer and competent authorities to enhance the safety of the device. In case special training is required prior using the device, an appropriate note should be also included in the IFU.

In general, the complete structure of the IFU was revised to improve the safety and to include information based on the summary of safety and clinical performance (MDR Annex I

Chapter III). For transparency reasons, the content of the IFU shall also be made available on the website of the manufacturer and be accessible for professional and lay users.

In addition to the IFU, new symbols were introduced to cover the new requirements which need to be placed on the label of the device itself and outer packaging of a device. For some medical devices an implant card is introduced for improved safety and traceability with including a serial number.

According to MDR Articles 13 and 14, additional labeling requirements are available for importers and distributors. The addresses need to be printed on the device or packaging for transparency reasons.[2]

1.3. Labeling obligations for medicinal products approved by EMA

Medicinal products are defined as substances or a combination of substances which are *"intended to treat, prevent or diagnose a disease, or to restore, correct or modify physiological functions by exerting a pharmacological, immunological or metabolic action*".[3,23] At first glance, the definition resembles the definition of a medical device (see Glossary). The difference is that the function of medical devices is based on physical means, whereas the function of medicinal products is based on physiological means.

Labeling obligations for medicinal products within the EU are described in Title V of Directive 2001/83/EC. In general, the labeling documents of a medicinal product approved via the centralized procedure consist of the outer packaging, immediate packaging, summary of product characteristics (SmPC), and package leaflet (PL). The labeling requirements for medicinal products approved via the national, decentralized, or via mutual recognition procedure are out of scope of this thesis and will not be further discussed.[3]

For the evaluation of medicinal products, which need to or are planned to be assessed via the centralized procedure, a European Medicines Agency (EMA) was established. The labeling documents of a medicinal product are part of the evaluation process when applying for a new marketing authorization, an extension of the marketing authorization, or need to be submitted to EMA in case a change to the labeling documents is proposed for evaluation and approval. Therefore, detailed guidance, including templates, standard headings as well as standard terms, how to create appropriate labeling documents for human medicines is available on the EMA website or the website of the European Commission for marketing

authorization holders (MAH) and assessors. Homoeopathic or herbal medicines for human use as well as medicinal products for veterinary use are out of scope of this thesis.[24,25]

The European Union product information (EU PI) for medicinal products consists of Annex I (SmPC), Annex II (information on CHMP opinion and specific obligations), and Annex III (A - Labelling and B - Package Leaflet). Further details are described in the following sections. Once the EU PI is approved for a medicinal product, it is published on the website of the EMA in all EU languages as well as Icelandic and Norwegian and is publicly accessible. A list of medicines approved in the EU by the mutual recognition or decentralized procedure is available at the website of the Heads of Medicines Agencies, called MRI Product Index. Medicines approved in the UK can be found on the electronic medicines compendium website which includes a detailed search option to filter for specific topics either by the SmPC or patient leaflet.[24,26,27]

1.3.1. Labeling requirements for the outer packaging

Article 54 of Directive 2001/83/EC provides the legal foundation of information to be implemented on the outer packaging of a medicinal product. Detailed guidance is provided in the QRD template published by EMA. The QRD templates contain standard headings in a certain order with instructional text for the information to be entered. In general, the information applied on the outer packaging should follow the information stated in the SmPC.[28]

The outer packaging shall contain amongst others, details for identifying the medicinal product like the name, the active substance, the pharmaceutical form, and the strength. Further information to be included comprise the method or route of administration, specific warnings, and administrative information, including expiry date, storage conditions, advice for disposal, name and address of the MAH, the marketing authorization (MA) number, and the batch number. In case there is no outer packaging, all information needs to be applied to the immediate packaging. For the detailed list of information requested to be added to the outer packaging, see Appendix VII.[3]

According to Article 57 of Directive 2001/83/EC, some Member States may request to add specific national information on the outer packaging. This is handled via a so called ‘blue box’ or blue box concept (applicable for centrally authorized and nationally recognized

products). A single boxed area is provided on the outer packaging where national specific requirements can be entered.[29]

1.3.2. Labeling requirements for the immediate packaging

Article 55 of Directive 2001/83/EC provides the legal foundation of information to be implemented on the immediate packaging of a medicinal product with supporting detailed guidance from the QRD templates. In general, all information required for the labeling of the outer packaging as laid down in Article 54 shall apply to the labeling of the immediate packaging. Exemptions exist for blister packs which are placed in an outer packaging or small immediate packaging with space constraints. For these exemptions only limited information needs to be applied to the label of the immediate packaging, *e.g.* name of the medicinal product, name of the MAH, expiry date, and batch number. For the detailed list of information requested to be added to the immediate packaging, see Appendix VII.[3]

1.3.3. Labeling requirements for the SmPC and the PL

For medicinal products, two documents need to be created to inform on the safe and effective use of a medicinal product; a summary of product characteristics (SmPC) intended for healthcare professionals and a package leaflet (PL) intended for patients and caregivers, which is written in lay language. In Article 59 of Directive 2001/83/EC, the legal basis for the creation of a package leaflet is described. Further details what should be included in the SmPC are not mentioned by Directive 2001/83/EC. In Article 59, it is only stated that "*the package leaflet shall be drawn up in accordance with the summary of the product characteristics*" which means that the SmPC should be the basis for all information included in the PL.[3,25]

In addition to the QRD templates, which provide guidance on the required structure of the SmPC and PL and which include standard terms, a detailed guidance, including training videos and slide decks for drawing up an SmPC, is available on the EMA website prepared by the SmPC Advisory Group and the European Commission.[25,30]

According to Article 59 of Directive 2001/83/EC, information for identifying the medicinal product like the name, active substance and excipients, the pharmaceutical form, the pharmacotherapeutic group, and the names of the MAH and manufacturer shall be added to

the PL. Further information to be included in the PL comprise the therapeutic indication, relevant information needed to know prior use (*e.g.* contraindications, precautions for use, interactions, or special warnings and precautions) considering the intended patient population, instructions for the proper use (*e.g.* dosing scheme and duration of treatment), a list of known undesirable effects, a note to report any undesirable effects, storage conditions, and revision date of the PL. For the detailed list of information requested to be added to the PL, see Appendix VII.[3]

1.3.4. Medical devices regulated as medicinal products

The MDR provides only labeling guidance for medical devices and DDC products which are regulated by the MDR 2017/745. In Article 1 (8) and (9) of the MDR, special cases of medical devices are described which include as an integral part a medicinal product. In case the principal action is based on the medicinal component of the DDC product, the complete DDC is regulated either by Directive 2001/83/EC or Regulation (EC) 726/2004. Furthermore, in Article 1 (9) of the MDR it is stated without referring to the principal mode of action that if a "*device intended to administer a medicinal product and the medicinal product are placed on the market in such a way that they form a single integral product which is intended exclusively for use in the given combination and which is not reusable, that single integral product shall be governed by Directive 2001/83/EC or Regulation (EC) No 726/2004*".[2]

In addition, it is stated that the GSPRs according to Annex I of the MDR need to be considered and apply to the device part of the DDC; meaning that a notified body needs to be involved in the approval process. Therefore, an amendment to Directive 2001/83/EC is included in Article 117 of the MDR. In case the DDC products are regulated as a medicinal product, the results of the conformity assessment or the notified body opinion, whatever is applicable, need to be included in the MA dossier considering the GSPRs of the device part.[2] Further guidance for applicants, MAH, and notified bodies how this amendment should be understood and implemented can be found in a Question & Answer paper published by EMA.[31]

Further details on the responsibilities of notified bodies and the corresponding conformity assessment or notified body opinion procedure are described in section 2.

1.3.5. Labeling of medicinal products compared to labeling of medical devices

General Labeling requirements

The labeling documents for medicinal products and medical devices comprise in general an immediate and outer packaging as well as a document intended to inform the user of the safe and effective use of the product concerned. For medicinal products, there are two different documents available; one intended for healthcare professionals with extended scientific information (SmPC) and one for patients or caregivers written in lay language and provided together with the medicinal product in one carton (PL). For medical devices, only one IFU is created which need to be directed to the end-user, *i.e.* professional and/or lay user.

According to Article 58 of Directive 2001/83/EC, the PL is mandatory to be provided with the medicinal product unless all information can be already found on the immediate or outer packaging which might be challenging considering the amount of requested information to be added. For medical devices, an IFU is also mandatory to accompany a device in a printed version with some exemptions where only an eIFU needs to be provided (see section 1.1.1).

For both, medicinal products and medical devices, a detailed list of information to be included in the labeling documents is provided by the regulatory documents Directive 2001/83/EC and Regulation (EC) 2017/745, respectively. For medicinal products, additionally guidance documents and templates are available on the EMA website to support MAHs with creating high quality documents in a standardized format.[2,3,32]

Labeling Guidance

As mentioned above, detailed guidance documents including templates are available for the preparation of labeling documents for medicinal products which can be found on the websites of EMA or the European Commission. The publishing of such guidance documents is also requested by the respective legislation. According to Article 65 of Directive 2001/83/EC, specific guidelines shall be drawn up by the Commission for the formulation of certain special warnings and precautions for specific topics, self-medication, legibility of the labelling and PL, and excipients including standardized warning statements.[3]

For medical devices, the MDR often refers to "*international recognized guidance documents*" which include ISO standards. These are often not publicly available, and licenses

must be purchased to gain full access to the documents. In Europe, only a limited number of publicly available guidance documents is available at that point of time, although it is mentioned for some topics in the MDR that the Commission and the MDCG shall develop guidance documents, *e.g.* for notified bodies according to Article 48 MDR or for the clinical evaluation as stated in Article 106. Whereas in the US, FDA provides more detailed guidance for medical devices with an easily accessible search option on the FDA website. Filtering for medical devices and labeling guidelines turns 61 hits for various US guidance documents (for the detailed list see Appendix X).[33]

An extract of available guidance documents for medical devices and medicinal products in the EU can be found in Appendix VIII and Appendix IX.

Readability and comprehensibility of the labeling documents

In Article 56 of Directive 2001/83/EC, it is stated that information on the immediate and outer packaging "*shall be easily legible, clearly comprehensible and indelible*" and in Article 63 it is stated that the PL "*must be written in clear and understandable terms for the users and be clearly legible […]*". Similar requirements are available for medical devices. In Article 10 (11) of the MDR it is stated, that "*particulars on the label shall be indelible, easily legible and clearly comprehensible to the intended user or patient*". For medicinal products, a "*Guideline on the Readability of the Labelling and Package Leaflet of Medicinal Products for Human Use*" is available published by the European Commission to support MAHs in the creation of labeling documents with a high quality fulfilling the requirements from Directive 2001/83/EC. The guideline does not only focus on stylistic matters but in addition provides information how to perform the user testing and involving patients and caregivers in the creation process to optimize the final labeling documents. For medical devices, no such guidance is currently available on the website of the MDCG. ISO 20417:2021 (*Medical devices — Information to be supplied by the manufacturer*) provides some guidance for the legibility of labels and test methods and can be used to establish internal standards within a company.[2,3,34,35]

The labeling documents for medicinal products are part of the assessment procedure and need to be submitted to EMA for evaluation prior approval. EMA does not only focus on the content of the labeling documents but requests in addition the submission of mock-ups and specimens to evaluate the final design of the labeling documents and to confirm

the readability of information (Article 61 of Directive 2001/83/EC). In the MDR, the provision of a mock-up is only mentioned once in Article 16 in case a distributor or importer has re-labeled a medical device. Nevertheless, the labeling documents are part of the technical documentation which is assessed by notified bodies. Further details regarding the review for labeling specifics are not provided in the MDR.[2,3]

Symbols and Pictograms

For medical devices, manufacturers are encouraged by the MDR to use symbols which follow harmonized standards to replace information on the labeling documents, *i.e.* the immediate packaging, the outer packaging, and the IFU (Annex I Chapter III 23.1.h). According to Article 62 of Directive 2001/83/EC, symbols or pictograms can be used on the outer packaging or in the PL to "*clarify certain information*". Considering the "*Guideline on the Readability of the Labelling and Package Leaflet of Medicinal Products for Human Use*" symbols and pictograms should only be used to "*aid navigation, clarify or highlight certain aspects of the text and should not replace the actual text*". Reading the guidance published by the European Commission creates the impression that symbols should only be used in exceptional cases and might not be accepted by the competent authority in case there is any doubt of the clear understanding of the symbols used.[2,3,35]

National specific requirements

In Article 63 of Directive 2001/83/EC, it is stated that the labeling information on the PL and outer packaging shall appear in an official language of the Member States. Similar information is requested for medical devices. In Article 10 (11) of the MDR, it is stated that the information on the immediate and outer packaging as well as in the IFU shall be provided in "*an official Union language determined by the Member State in which the device is made available to the user or patient*". In Annex II of the MDR it even says, "*in the languages accepted in the Member States where the device is envisaged to be sold*". This means that a manufacturer needs to perform an assessment for each EU country in which language the labeling information for medical devices need to be provided. An overview of acceptable languages for medical devices is provided in Appendix VI. For medicinal products, EMA has published a "*List of official languages per country*" informing the MAH in which language(s) the information for the different labeling documents needs to be provided.[2,3,19]

For medicinal products, a linguistic review process is part of the approval procedure to ensure a high quality and consistency related to the content of the translated labeling documents. EMA has published guidance documents to harmonize this process. For medical devices, no such process is mentioned in the MDR.[2,36]

In addition, a blue box concept is available for medicinal products to print specific national required information on the outer packaging (Article 57 Directive 2001/83/EC). This concept is not described for medical devices in the MDR.[2,29]

1.4. Conclusion on Medical Device Labeling

1.4.1. General aspects

Analyzing the labeling requirements as laid down in the MDR raises several questions thinking of the practical implementation and user friendliness for manufacturers who need to create the labeling documents and register the medical device.

Currently, there is no guidance published by the MDCG how to ensure that the format, content, and legibility of the labeling documents are fulfilling the requirement to be easily understood by the users of medical devices. Compared to medicinal products, this seems quite challenging since for medical devices only one IFU needs to be created which is intended to inform the actual intended user. The user can be a professional or lay user or it can be used by both, professional and lay users. Especially when an IFU is intended to be used by lay users, the use of scientific terminology should be avoided, and lay language should be used to guarantee that the information is understood. Considering the wide variety of the cultural diversity in the European Union, it is challenging to create an IFU which is understandable by each user of a medical device. A detailed guidance published by the MDCG would be supportive for the creation of high-quality labeling documents to ensure consistency of the documents throughout the EU. Furthermore, this might probably also lead to an improved assessment of these labeling documents due to consistent information.

In addition, it would be helpful for manufactures if standardized templates with clear instructions, fixed headers, and standard terms exist. This will not only ease the creation of medical device labeling documents but will also help users to easily find information and

navigate through the IFU if a harmonized standard is available. Hopefully, the MDCG is working on further guidance documents to fill this gap in future.

Whereas symbols are only rarely used in labeling documents for medicinal products, manufacturers are encouraged to replace information by internationally recognized symbols whenever possible for medical devices. Although it is stated that the symbols need to be internationally recognized, it is hard to believe that each lay user is familiar with specialized symbols for medical devices. Although there is no requirement mentioned in the MDR to explain the symbols, considering the diverse educational background of lay users in the EU, symbols should be explained in the IFU to avoid misunderstanding. A summarizing guidance from the MDCG would also improve the quality of the labeling documents by defining a list of symbols which can be used to harmonize labeling of medical devices within the EU.

There is also no clear guidance, summarizing the language requirements for providing the labeling information. A list as published by EMA for medicinal products would facilitate the creation of the translations of the IFUs. From the MDR it is not clear if the quality of the translated labeling documents is checked. A linguistic review process as available for medicinal products approved via the centralized procedure by EMA would further improve the quality of the medical device labeling documents which may result in a safer and more effective medical device.

With the implementation of the MDR, a UDI needs to be assigned to all new and all already registered medical devices. The UDI shall ensure the traceability of the devices and improve the safety by reporting serious incidents. Therefore, UDIs should be entered in the European database EUDAMED which should be also used for the reporting. At the moment, not all functions of EUDAMED are available and a transition phase to enter UDIs is granted. From 2026 on, EUDAMED should be fully functionable and will become mandatory to be used. This means that currently not all safety information can be collected and tracked in one database which complicates the safety assessment of medical devices by the competent authority. A quick implementation of the safety data collection is desirable to allow a broad assessment of incidences which may occur in for example devices manufactured at one specific location or in devices based on a similar design development.

Improved transparency is another goal of the MDR. Therefore, manufacturers need to make certain clinical reports available for lay users. These can be accessed via EUDAMED.

It is not clear if also the labeling documents are available at that platform. Manufacturers shall at least provide the IFUs to the users at their own websites so that users can look for them. For medicinal products, EMA is more progressive and publishes the complete EU PI on its website which is publicly available. Besides the SmPC, PL, and labelling specifics also details on conditions on the approval process are publicly available. This approach of one location collecting all labeling information in the EU would also be desirable for medical devices. It may facilitate the access of medical device related information and may also facilitate the research of information placed in medical device documentation when provided in one place with appropriate filter options.

Labeling is an important part of medical device development and registration since it is the documentation which accompanies the medical devices and supports an effective and safe use. Therefore, I see a high need for creation of further harmonized guidance documents to support the preparation of such material.

1.4.2. Labels

According to the MDR, label is the information which is placed on the device itself and /or on the outer packaging. Since there is no further guidance available where the information listed in Annex I of the MDR needs to be placed, conflicts might arise with the assessing notified body in case a different understanding exists how the information should be conveyed.

Furthermore, it is stated in the MDR that the required information shall be placed on the medical device itself and only if this is not "*practicable or appropriate*" it shall be placed on the outer packaging. Since there is no further guidance, the decision criteria for these requests are not clearly defined which might lead to potential conflicts with the decision body during the assessment and registration process of the medical device in case the understanding is different. In the end, manufacturers need to agree to the requests by the assessment body if they want to register the medical device. Since there are different notified bodies available in the EU, a different understanding of the regulation is possible. A clear guidance by the MDCG specifying the label requirements would improve the harmonization of medical device labeling within the EU.

According to Annex I of the MDR, many details need to be placed on the label of medical devices. As mentioned above, symbols can be used in case of space constraints. For medicinal products, further labeling guidance is available for blisters or small immediate packaging units, *e.g.* vials. Only limited information needs to be applied to these labels respecting the limited available space for labeling information. Such detailed guidance would also be helpful to ease the understanding for the labeling of medical devices, which only allow the attachment of a small label. This may avoid potential conflicts with the assessing notified body since a clear specification is available and may harmonize the medical device labels within the EU.

In case, there are national requirements for specific information to be placed on the label, a blue box concept as existing for medicinal products, would also be beneficial for medical devices to cover country specific requirements.

1.4.3. Instructions for Use

In the MDR, it is stated that the Instructions for Use (IFU) shall be provided together with medical devices. A list of details which should be covered by the IFU is provided in Annex I Chapter III of the MDR. Whereas for medicinal products, EMA has published QRD templates which dictate the format of the labeling documents, including the order of standardized headers and standard terms to be used, no clear guidance for the setup of an IFU is published by the MDCG. Using standardized templates would harmonize the content and format of the IFUs. Furthermore, it may simplify the location of specific information within the IFUs, especially for lay users.

For medicinal products, EMA has started an electronic product information (ePI) initiative which already published EU ePI Common Standards to be considered when implementing an EU ePI.[24] The current medicinal product regulation still requires the provision of printed package leaflets, but this might be changed in future with evolving technical requirements. For medical devices, currently only in exceptional cases eIFUs are acceptable and otherwise the IFU needs to be provided in a printed format together with the medical device. For consistency, it would be desirable to establish an eIFU initiative to discuss the implementation of eIFU standards by following the same innovative approach EMA is leading.

2. Notified Bodies

In Article 2 (42) of the MDR, notified body is defined as "*a conformity assessment body designated in accordance with this Regulation*".[2] The European Commission further states that a notified body is "*a conformity assessment body officially designated by the national authority to carry out the procedures for conformity assessment within the meaning of applicable Union harmonisation legislation*".[37]

2.1. Responsibilities of notified bodies

As stated above notified bodies are third parties which perform the conformity assessment for a medical device. According to Article 38 of the MDR, notified bodies need to apply for the role as a conformity assessment body to a competent authority. Guidance what needs to be considered for applying as a notified body can be found in the Notified Body Operations Group's (NBOG) Best Practice Guide.[38] With the application, the notified bodies need to demonstrate that they comply with Annex VII of the MDR and need to indicate for which type of conformity assessment as well as for which type of medical device they would like to be designated. Once the notified bodies have completed the application process led by a competent authority, the Member State informs the European Commission of the newly designated notified body (MDR Article 42). A list of the designated notified bodies including their responsibilities is published according to MDR Article 43 in the NANDO (New Approach Notified and Designated Organisations) information system by the European Commission. The competent authorities, in the country where the notified body is located, are responsible for the monitoring of the notified bodies to ensure continuous compliance with the current MDR (MDR Article 35).[2,39]

With the implementation of the MDR, a new designation process of the notified bodies was established. Meaning that in a certain time a sufficient number of notified bodies had to be designated in accordance with the new regulation to ensure a continuous certification process of medical devices and to avoid any shortage of registered medical devices on the European market. According to MDR Article 120, there was a transitional phase established for certificates issued under the old MDD. If there is no significant change of the design or intended purpose of the medical device, the certificate remains valid until its declared expiry date. The last certificates will expire end of 2027 or 2028 depending on the risk class

of the medical device. With the expiration of a high number of certificates from registered medical devices, the burden on notified bodies increased to master the re-certification of the relevant medical devices. In August 2022, the MDCG has published a position paper "*Notified body capacity and availability of medical devices and IVDs*" to discuss this issue and to take countermeasures.[2,21,40]

According to MDR Article 52, a medical device must pass a conformity assessment before it can be placed on the market considering one of the conformity assessment procedures according to MDR Annexes IX to XI. For most of the medical devices, a notified body, which can be chosen by the manufacturer, provided that the notified body is designated for the requested process and type of medical device, needs to be involved in the performance of the conformity assessment (MDR Article 53). The process of the conformity assessment is described in section 2.2. In MDR Annex VII, the requirements which need to be met by the notified bodies are described in detail.[2]

2.2. Conformity assessment vs. notified body opinion

2.2.1. Conformity assessment according to MDR Article 52

According to the MDR, a conformity assessment procedure involving a notified body must be performed for medical devices which are categorized in the following risk classes: class I_m[†], class I_s[†], class I_r[†], class IIa, class IIb, or class III. An exemption is made for medical devices assigned to risk class I. For these devices the conformity assessment procedure is the sole responsibility of the manufacturer due to the low level of vulnerability associated with these devices and a notified body should not be involved.

With performing the conformity assessment, the manufacturer demonstrates that the medical device fulfils the requirements of the MDR and can be placed on the market (MDR Articles 2 (49) and 5). The type of conformity assessment to be performed is depending on the assigned risk class (MDR Article 52). An overview of the different types of conformity assessments is described in Figure 2.

[†] class I_m: measurable, class I_s: sterile, class I_r: re-usable

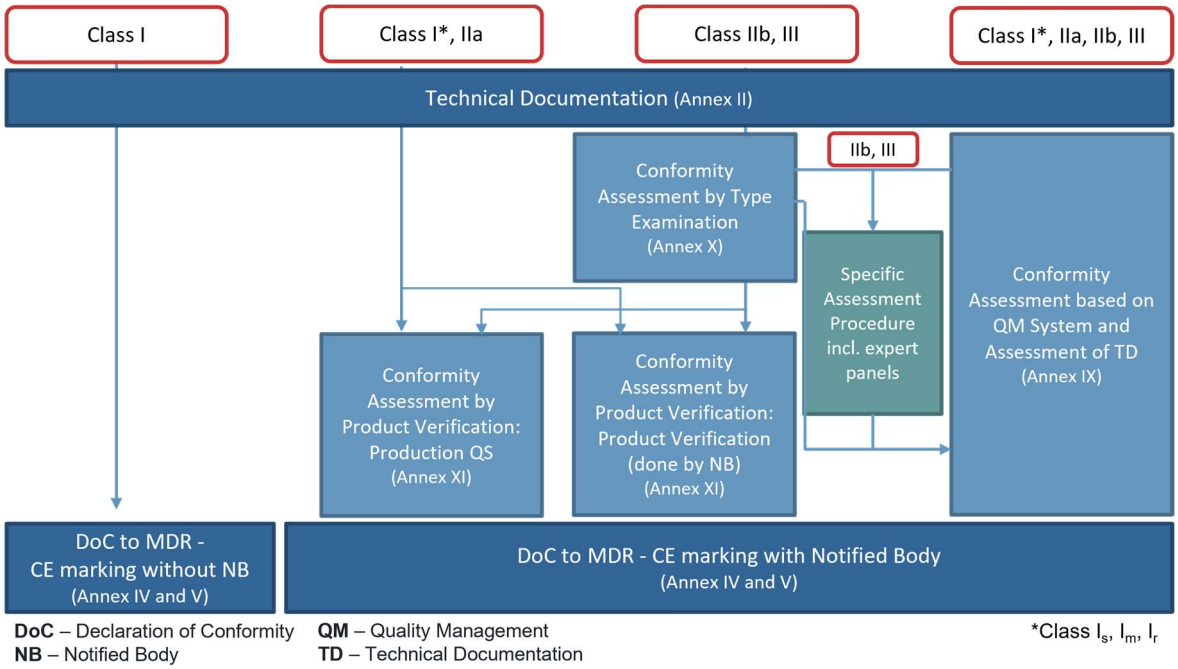


Figure 2: Overview conformity assessment procedures according to the MDR (taken and adapted from https://www.johner-institute.com/articles/regulatory-affairs/and-more/conformity-assessment/)[‡]

Independent of the respective details for each conformity assessment, manufacturers need to draw up the technical documentation according to Annex I of the MDR for each medical device as a basis of the conformity assessment. For class IIb active devices intended to administer and/or remove a medicinal product and class III implantable devices, the notified body needs to include a clinical evaluation consultation procedure for the completion of the conformity assessment (MDR Article 54).

If the medical device successfully passes the conformity assessment, a certificate of conformity is issued and the medical device needs to be CE marked (see section 2.3). As mentioned above, for class I medical devices the manufacturer does not need to involve a notified body and can add a CE mark after creation of the technical documentation. Certificates of conformity remain valid for a maximum of 5 years and then a re-certification or renewal of the certification needs to be initiated to ensure a continuous high quality of marketed medical devices (MDR Article 56).[2]

[‡] MDR Annex IX Conformity Assessment based on a Quality Management System and on Assessment of Technical Documentation, MDR Annex X Conformity Assessment based on Type-examination, MDR Annex XI Conformity Assessment based on Product Conformity Verification

2.2.2. Notified Body Opinion (NBOp)

In the MDR Article 117, which is an amendment to Directive 2001/83/EC, it is stated that in the marketing authorization dossier of a medicinal product, when it is combined with a medical device, an EU declaration of conformity issued by a notified body or a notified body opinion (NBOp) to ensure the compliance with the relevant GSPRs needs to be included.

The conformity assessment procedure which applies to products regulated as medical devices is described in section 2.2.1. In case the intended purpose of an integral DDC product is based on the medicinal product part, the complete product is handled by the medicinal product legal framework and approved by EMA and the European Commission. But a NBOp is necessary to be included in the marketing authorization dossier to ensure compliance with the relevant GSPRs according to MDR Annex I as stated above.[2,41]

TÜV Süd is currently one of the designated notified bodies in Germany according to the new MDR which is performing an evaluation of the GSPRs and issuing a NBOp. According to the information on the website of TÜV Süd, test reports, risk management reports, clinical evaluation, biological evaluations, and the assessment of the manufacturer on the applicability of the GSPRs to the affected device are part of the notified body assessment. All these documents are assessed to ensure that the medical device is suitable for the claimed intended purpose, the relevant patient population, and the clinical setting or use environment. TÜV Süd has created a standardized application form which is accessible at the website to apply for a NBOp.[42–44]

In addition, Team-NB has published a proposal for a NBOp template to harmonize the reporting of the outcome of the assessment. The template is structured in different sections including the following topics to be assessed by the notified body, if applicable: design and manufacturing of the integral device, validation of design and performance, benefit-risk analysis and risk management, biocompatibility, stability and shelf life, labelling and leaflet (considering the outcome of the risk assessment and IFU related to the device part), microbiology, tissues/cells of human or animal origin, connection to other devices, and measuring function. This list of topics to be reviewed for the integral device part resembles the content of the SmPC for medicinal products (see Appendices VII and XI). The assessment of the integral device part by the notified body builds therefore an important milestone for granting a marketing authorization for an integral DDC. EMA will perform a benefit-risk

assessment of the medicinal product part of the DDC before a final recommendation for an approval can be made.[45]

2.3. CE marking

In general, medical devices should undergo a conformity assessment and bear the CE mark according to Article 20 and Annex V of the MDR (see Figure 3). According to MDR Article 2 (43), the CE mark is a sign easily recognizable for the user of the device to be informed that the device complies with the requirements of the new MDR. The prerequisites for attaching the CE mark to medical devices are described in section 2.2.1.[2]

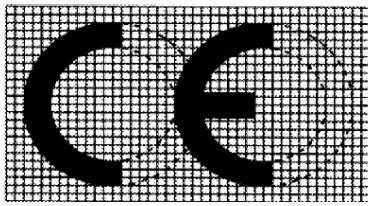


Figure 3: CE mark according to MDR Annex V[2§]

According to Article 20 of the MDR, the medical device shall be labelled with a CE mark in a way that the CE mark is "*visibly, legibly and indelibly to the device*". In case it is not possible to affix the CE mark directly to the device due to its design, the CE mark shall be assigned to the outer packaging of the device. In addition, the CE mark needs to appear in the IFU. In case, a conformity assessment was performed by a notified body, the identification number of the notified body should be mentioned together with the CE mark for transparency reasons. Affixing the CE mark is one requirement for placing a medical device on the market in the EU.[2]

According to EMA's "*Guideline on quality documentation for medicinal products when used with a medical device*", a CE mark must not be affixed to an integral DDC product which is due to its intended purpose regulated as a medicinal product. The labeling documents are then prepared in accordance with Directive 2001/83/EC, the SmPC guideline, and the QRD templates published on the EMA website. This means that the product information of integral DDCs should not include any administrative information on the device part, including details of the medical device manufacturer, CE mark, notified body number, device

§ Figure of CE mark taken from Annex V of Regulation (EU) 2017/745

symbols, or UDI. But relevant information which is needed for the safe and effective use of the medical device part can be included in the relevant sections of the SmPC and package leaflet.

Similar rules apply to a co-packaged medical device. The medicinal product of a co-packed DDC is regulated either by Directive 2001/83/EC or Regulation (EC) 726/2004 which means that no administrative information related to the medical device part should appear in the product information of the medicinal product, including the outer packaging, immediate packaging of the medicinal product, the SmPC, and package leaflet. Since the medical device and medicinal product are co-packaged and share the outer packaging no CE mark or other device-related administrative information shall appear on the outer packaging. But a CE mark needs to be affixed to the medical device to fulfil the requirements of the MDR. The co-packaged medical device is regulated by the MDR, needs to undergo a conformity assessment, and therefore also needs to comply with the labeling requirements of the MDR. All relevant information needed for the safe and effective use of the co-packaged medical device can be mentioned in the relevant sections of the SmPC and package leaflet and a separate IFU as requested for medical devices is not needed.[1]

2.4. Centralized Procedure – approval process for medicinal products

According to EMA's glossary, the centralized procedure (CP) is a "*procedure for the authorisation of medicines, where there is a single application, a single evaluation and a single authorisation throughout the European Union*".[46] This means that a pharmaceutical company only needs to submit one single marketing authorization application (MAA) to EMA for making the medicine available in all EU countries after approval, instead of submitting separate MAAs to each of the national competent authorities. A further advantage is that EMA will handle the complete assessment which leads to an approval of the medicine in all EU countries as well as in the European Economic Area (EEA) countries Iceland, Liechtenstein, and Norway at the same time. The Committee for Medicinal products for Human Use (CHMP) performs the scientific assessment for human medicines and provides a positive opinion in case the benefit-risk of the medicine is considered to be positive. The official authorizing body is the European Commission which will issue the legally binding decision, called the Commission Decision, based on the scientific assessment performed by EMA.[47]

The CP is highly regulated, and a timetable is published at the EMA website informing about submission slots and the expected dates for the milestones during the assessment procedure. In general, the CP procedure takes up to 210 so-called 'active' days which describe the days, the CHMP needs to perform the assessment. In between, questions are raised and addressed to the applicant. Responding to these questions leads to clock-stops about 1 to 3 months which extend the approval process of the medicine. At Day 210 the CHMP issues a positive opinion, followed by the Commission Decision after additional 67 days. Taking also the time needed for the clock-stops into account, the duration of the approval of a medicinal product in general takes more than a year. For transparency, the Commission Decision and a redacted assessment report are published and publicly available.[47,48]

According to MDR Article 4 (4), EMA needs to be consulted during the conformity assessment of a medical device, if the medical device is regulated by the MDR and incorporates a medicinal product.[2]

3. Labeling of DDC products

EMA published two guidance documents "*QWP-BWP Guideline on medicinal products used with a medical device*" and "*Questions & Answers for applicants, marketing authorisation holders of medicinal products and notified bodies with respect to the implementation of the Medical Devices and In Vitro Diagnostic Medical Devices Regulations ((EU) 2017/745 and (EU) 2017/746)*" which provide information on the regulation of drug-device combination products (DDC), touching also the labeling of these products. In these guidance documents it is stated that if the primary intended purpose of the DDC is led by the medicine, the complete DDC is regulated as a medicine and the labeling requirements according to Directive 2001/83/EC or Regulation (EC) 726/2004 for medicinal products apply. This means that an EU PI will be created for submission including all relevant labeling information for the DDC. This EU PI should not include any administrative information on the medical device, *e.g.* CE mark or address of the device manufacturer.[1,31]

For medicinal products, the QRD templates and SmPC guideline need to be considered for creation of the labeling documents, *i.e.* EU PI. In the annotated QRD template, devices are only mentioned in the PL section 1. There it is stated that "*if the medicine is an advanced therapy medicine which contains medical devices or active implantable medical devices, a*

description of those devices and their specific origin should be provided […]". In the SmPC guideline, devices are only mentioned in section 6 "*Pharmaceutical particulars*". Information on devices supplied together with a medicinal product can be included in SmPC section 6.3 "*Shelf life*", providing further information on the in-use shelf life of the device, or in SmPC section 6.5 "*Nature and contents of container*". Any device included in the package should be mentioned, *e.g.* "*needles, swabs, measuring spoons, syringes, or inhaler devices*" and the "*graduation on measuring devices should be explained*". Neither the SmPC guideline nor the annotated QRD template provide further guidance how the labeling of integral or co-packaged DDC should look like in detail.[28,30]

Therefore, two case studies were created to evaluate how an EU PI for an integral DDC regulated as a medicinal product, *e.g.* pre-filled pen, and co-packaged DDC, *e.g.* dry powder inhaler, could look like (see sections 3.1 and 3.2).

3.1. Case study – Integral DDC (example pre-filled pen)

According to the "*Guideline on quality documentation for medicinal products when used with a medical device*" integral DDC products are regulated by Directive 2001/83/EC or Regulation (EC) 726/2004 when the intended purpose is based on the medicinal component meaning that the labeling requirements for medicinal products apply. In Article 1 (9) of the MDR it is stated, that integral DDCs can only be regulated by one regulation since they are considered a single entity and cannot be used separately.[1,2]

The above-mentioned guideline clearly specifies that the labeling requirements should follow the medicinal product regulation. Therefore, the QRD templates provided on the EMA webpage need to be considered for creation of the EU PI. Administrative information on the device part itself should not be included in the EU PI of integral DDC products. This means that neither the device manufacturer nor the CE mark, notified body number, device symbols, UDI, or references to device market surveillance reporting will be mentioned in the EU PI. But it is requested to include information on the device part which is needed for the safe use of the integral DDC.[1]

Appendix XI displays how an EU PI for an integral DDC, *i.e.* pre-filled pen, can be set up. In case of an integral DDC product, the medical device can be considered as the immediate

packaging of the medicine. This is for example reflected in Annex III A of the EU PI which includes the required text of the labels and outer carton.

In general, the medical device is mentioned in SmPC sections 1 "*Name of the medicinal product*" and 3 "*Pharmaceutical form*". SmPC sections 4 "*Clinical particulars*" and 5 "*Pharmacological properties*" mainly focus on details regarding the medicine, *e.g.* the safety and efficacy outcomes and description of the mechanism of action. In SmPC section 4.2 "*Method of administration*", a brief description is included on how the integral DDC should be administered to guide the treating physician. For a standalone medical device this information would be part of the technical documentation. For integral DDC, this information is included in the dossier submitted to the notified body to receive the notified body opinion.

SmPC section 6 is mostly affected by information related to the medical device part and is based on the design development of the device component. SmPC section 6 includes information related to incompatibilities, shelf life, storage conditions, description of the container, and any information relevant for handling and disposal which also affects the medical device part of the DDC since it is considered to be marketed as a single unit.

According to the "*Guideline on quality documentation for medicinal products when used with a medical device*" details of the device part should not be included in the EU PI. This means SmPC section 7 "*Marketing authorisation holder*" only contains information related to the integral DDC regulated as a medicinal product, *i.e.* only the addresses of the manufacturer and MAH of the DDC are mentioned but no information of the manufacturer of the medical device part is included.

The EU PI Annex III A "*Labelling*" follows the QRD template and contains label information for immediate packaging, *i.e.* the pre-filled pen label, and the outer carton of the integral DDC. As mentioned above no device related administrative information, *e.g.* UDI, CE mark or device symbols, is allowed to be placed on the labels.

In general, the PL of an integral DDC informs the user or patient about the safe use of the medicine, including the medical device since it is considered a single entity. Information included in the SmPC should be aligned with information in the PL. Therefore, medical device specific information can be found in the PL section 3 "*How to use X*" which refers to the route of administration, specific required trainings prior use, and a reference to the handling instruction which can be found at the end of the PL.

Further information related to the medical device component can be found in PL section 5, describing the storage conditions, and section 6 which includes information on the contents of the pack and other editorial information like address of the manufacturer, list of local representatives of MAH, and the last revision date.

A section referring to handling instructions of a medical device combined with a medicinal product is not mentioned in the annotated QRD template. But there are examples of approved medicinal products in the EU which follow the same approach and include such a section at the end of the PL.[49–52] Since there is no specific guidance, this section is named and organized differently for different products. Overall, this section includes general safety information related to the use of the integral DDC and a step-by-step description (often with pictures) how to use the device.

3.2. Case study – Co-packaged DDC (example dry powder inhaler)

Similar to integral DDC products with an intended purpose based on the medicinal product part, also the EU PI of co-packaged DDC products follows the labeling regulation of medicinal products in general and needs to comply with the SmPC guideline and QRD templates. In contrast to integral DDC products, the MDR applies for co-packaged DDC products in addition but only to the device part. The medicinal product part is regulated by Directive 2001/83/EC or Regulation (EC) 726/2004. According to the MDR the medical device part needs to be CE marked and a UDI is assigned to it. But according to the QRD template this information should not be mentioned in the EU PI of the co-packaged DDC. An example how the medical device label, in this case the dry powder inhaler, could look like, see Appendix XIII which includes a template for medical device labels.[1]

Appendix XII describes how an EU PI for a co-packaged DDC, *i.e.* dry powder inhaler combined with a medicinal product, could look like. As described above, according to the QRD template the EU PI only contains labeling information for the medicinal product part which includes the immediate and outer packaging of the medicinal product component. The medical device label of the co-packaged device is not part of the EU PI according to the "*Guideline on quality documentation for medicinal products when used with a medical device*". Similar to the labeling requirements of integral DDC products, the inclusion of administrative information on medical devices in the EU PI is not accepted by EMA. This means

for example that the outer carton of the co-packaged DDC product should not bear any information like the device manufacturer or authorized representative, CE mark, notified body number, device symbols, or UDI.[1,28]

As already described in section 3.1 for integral DDCs, relevant information for the safe use of the co-packaged device in combination with the medicinal product should be included in the appropriate sections of the SmPC and PL. Since co-packaged DDCs consist of a medicinal product and a co-packaged medical device, information in the SmPC mainly refers to the medicinal product part. Some information on the medical device part can be found in SmPC sections 6.5 "*Nature and contents of container*" (mentioning that a device is co-packaged with the medicinal product) and 6.6 "*Special precautions for disposal and other handling*" (referring to handling instructions for the DDC or special cleaning requirements which need to be considered for the medical device). According to the "*Guideline on quality documentation for medicinal products when used with a medical device*" the shelf life mentioned should refer to the shortest shelf life of all components included in the pack. This means that if the shelf life according to the device development and documented in the technical documentation of the medical device component is shorter than the one for the medicinal product part, this information needs to be stated in the SmPC, outer carton, and PL since they are marketed together in one pack.

In addition, information related to the medical device is available indirectly in SmPC section 4.2 "*Posology and method of administration*" since the delivery of the accurate dose and the uniformity of the administered doses with the device should be demonstrated supporting the final recommended dose of the DDC.

For the EU PI example described in Appendix XII, detailed handling information of the device were not included in the SmPC but only a reference to the PL was added. Since there is no detailed guidance available, both scenarios for creation of an EU PI are possible from my understanding; (a) the SmPC includes a detailed handling information section, or (b) the SmPC only refers to the PL for detailed information how to safely handle the DDC.

According to the "*Guideline on quality documentation for medicinal products when used with a medical device*", the "*MAH of the medicinal product is responsible for the co-packaged medicinal product and its traceability […]*". This means that only the MAH of the

medicinal product is mentioned in SmPC section 7 "*Marketing authorisation holder*" and no further information related to the medical device is included.

The EU PI Annex III A "*Labelling*" follows the QRD template and contains labeling information for the immediate packaging (*i.e.* blisters for the hard capsules) and the outer carton for the medicinal product (*i.e.* hard capsules in blisters) as well as for the co-packaged device component (*i.e.* dry powder inhaler). As mentioned above no device related administrative information, *e.g.* UDI, CE mark, or device symbols, is allowed to be attached to the label of the outer carton and no further label information for the device component is included in the EU PI.

Nevertheless, the co-packaged device is labeled according to the MDR and needs to comply with the labeling requirements for device labels as stated in the MDR. Therefore, a layout and mock-up for the label of the medical device needs to be prepared by the MAH. Since this label is not part of the EMA assessment for registration of the co-packaged DDC, it is not allowed to include any information in the EU PI. For completeness and consistency with other products, it is advisable for MAHs to also create a template for medical devices and archive the label drafts together with the EU PI draft internally. The medical device label is part of the technical documentation and will be assessed by a notified body during a conformity assessment procedure. An example how this template could look like can be found in Appendix XIII and is described in section 3.3.

In the PL, information on the medical device part can be found in section 3 "*How to use X*". In this section general information on the safe use of the medicinal product is described for the patient and information is included that this medicinal product needs to be used together with the co-packaged device. In addition, a reference to the handling instructions, which are included at the end of the PL, is made to provide detailed information on the safe use and handling of the DDC. Further information related to the medical device component can be found in PL sections 5. "*How to store X*" and 6 "*Contents of the pack and other information*" mentioning the content of the pack.

As for integral DDCs, a section referring to handling instructions of a medical device combined with a medicinal product is not mentioned in the annotated QRD template. But there are examples of approved medicinal products in the EU which follow the same approach and include such a section at the end of the PL. As mentioned in section 3.1, there is no

specific guidance for including a handling instruction and therefore this section is named and organized differently for different products. Overall, this section includes general safety information related to the use of the co-packaged DDC and a step-by-step description (often with pictures) how to use the medicinal product in combination with the applicable device.[53–56]

3.3. Draft QRD template for medical devices

For medical devices (regulated by the MDR as a medical device), no detailed labeling guidance and templates as for medicinal products provided by EMA exist. Current labeling guidance is provided in the MDR and its Annexes. Further information can be obtained from international standards, *e.g.* ISO standards (see section 1.1). But most of them are not publicly available and can probably not be considered as complete regarding the MDR requirements. Considering the different stakeholders affected by the development and registration process of a medical device, it would be beneficial to develop further guidance documents to harmonize the creation and content as well as layout of medical device labeling documents.

Harmonization of labeling documents for medical devices and standardized templates can support the intended user in better understanding the labeling documents and might support them even in finding relevant information easier and faster. For manufacturers, templates would support the creation of harmonized labeling documents with high quality. This may also ensure that MDR requirements are followed and implemented in the proposed medical device labeling documents when submitted for registration. Annotated templates, as available for medicinal products (*e.g.* annotated QRD templates), can include additional labeling guidance to avoid misunderstanding of the MDR requirements in providing further detailed information. In addition, a harmonized approach might be also beneficial for notified bodies and can ease the conformity assessment procedure in case standardized labeling requirements are used and relevant information is displayed in a similar manner for different products by different manufacturers.

Based on the labeling requirements listed in the MDR and the current QRD template published by EMA for medicinal products, a QRD template for medical devices was drafted as

part of this thesis and which could be used for the creation of medical device labels and the instructions for use (see Appendix XIII).

The draft QRD template for medical devices starts with instructions how to set up the labelling for the outer packaging and sterile packaging of a medical device followed by guidance on the medical device label itself. According to the MDR the manufacturer is encouraged to replace text by internationally recognized symbols whenever possible to reduce the amount of written information on the medical device labels. According to the MDR a lot of information needs to be placed on the labels which can be overwhelming, confusing, or being overseen by the intended user when trying to read all relevant information.

In addition to the requirements for medicinal product labeling, a section for the UDI carrier, a reference that this is a medical device, a special section informing about the sterile condition of the medical device, and an indication if the medical device is for single use or custom made was added to the template.

For sterile medical devices several symbols exist to further inform the user of the sterilization method and providing details on the exact sterile condition. In the QRD template for medicinal products, no such specific information about the sterile condition is provided. In the annotated EMA QRD template, there is only information for sterile medicines related to the expiry date included and a reference to further guidance provided by the CHMP made which need to be considered "*Note for Guidance on Maximum Shelf Life for Sterile Products for Human Use after First Opening or Following Reconstitution*"[28].

For medicinal products, information in Braille needs to be added on the labels. This is not requested by the MDR but might be beneficial if some users face visual impairment or have other disabilities. These users might benefit by adding information in Braille to recognize the medical device which supports their independence in daily life.

According to the MDR the instructions for use (IFU) needs to be created for the intended user (see section 1.1.5). The MDR does not differentiate if the intended user is a healthcare professional or lay user. In contrast to medicinal products, only one labeling document needs to be created to inform the user of the safe use of the medical device, the IFU. For medicinal products two different documents, an SmPC intended to be used by healthcare professionals and a PL for patients, need to be drafted.

The IFU contains all relevant information to inform the user on the medical device itself and how it should be used correctly. The drafted template organizes and structures the MDR labeling requirements for IFUs and supports the manufacturer in creation of IFUs with high quality and in compliance with the MDR requirements.

The proposed template for the IFU starts with an overview section, informing the user which information is included in the IFU and where it can be found. Afterwards a description of the medical device is added with an explanation of the intended use (section "*1. What <X> is and what it is used for*". Depending on the intended user, professional or lay user, the complete IFU should be written in scientific or lay language to ensure that the intended user understands the information needed for a safe and effective use of the medical device. The next section "*2. What you need to know before you use <X>*" informs the user of important information prior starting using the medical device. This information can include special training needed, special handling requirements to be considered, *e.g.* based on the sterile condition of the medical device, or any risks or contraindications informing about situations or conditions when the medical device should not be used. It can furthermore include a subsection specifying information which need to be considered when the medical device should be used by children or together with other medical devices or medicines. In case there is any information available for pregnant or breast-feeding women or any information they need to be aware of as well as specific information related to the use of the medical device and driving or handling of machines, this guidance or warning can also be placed in this section of the IFU.

IFU section "*3. How to use <X>*" provides detailed information how the medical device should be used. It informs the user of specifics to be considered prior starting the use, when to use the medical device and can include a detailed step-by-step description with pictures informing on how to use the medical device. Furthermore, information of cleaning the medical device, if used more often than requested, forgetting, or stopping the use of the device is also included in this section.

Section "*4. Possible side effects or serious incidents*" is focusing on side effects or serious incidences related to the use of the medical device. With the addition of such a section the safety of the medical device can be improved significantly. In line with the MDR requirements, a statement is added to the draft IFU template that any recognized side effects or

incidences, independently if they are already mentioned in the IFU, should be reported to increase the safety data of medical devices. With directly adding the respective contact into the IFUs, the chances that the user really reports such cases is increased as well.

In line with the QRD template for medicinal products, section "*5. How to store <X>*" provides relevant information needed to know for the storage of the device. Information about the sterile state can also be included in this section and any information on disposing the medical device can be found here. In the MDR Annex I Chapter II 14.7 it is mentioned that the manufacturer shall also take the responsibility to protect the environment and therefore need to inform the user how to correctly dispose of the medical device in case it is no longer needed or used.

In section "*6. Contents of the pack and other information*" the user is informed about the content of the pack, any specific additional substances included in the medical device, the contact details of the manufacturer as well as direct details for the local representative who can be contacted in case of any questions. The IFU ends with information when the content was approved and last updated and can include, *e.g.* hyperlinks to websites of the manufacturer, where additional information can be found, comprising for example videos on how to use the medical device.

Considering the long list of information to be added to the labeling of medical devices, I think it might be highly beneficial to standardize the labeling documents for medical devices in a similar way as it was done for medicinal products. It needs to be awaited if the MDCG, for example, will publish similar guidance or templates in future.

4. Challenges for Labeling

4.1. Implementing the new MDR

With the MDR becoming effective, manufacturers of devices needed to be prepared to have implemented the new regulation into their running processes to ensure compliance with the MDR. Based on the number of registered medical devices, this might have resulted into an increased additional workload for manufacturers of medical devices. The existing internal standard operating procedures (SOPs), including all labeling processes, needed to be adapted to the regulations mentioned in the MDR. For the labeling processes most of them are listed in Annex I of the MDR.

Besides the internal processes, a gap analysis needed to be performed for all already registered medical devices to get an overview which requirements are applicable and for example which additional data (*e.g.* pre-clinical or clinical data) is needed to comply with the MDR in future. This was not only applicable for already registered medical devices but also for medical devices which were under development and for which additional or different data needed to be collected due to the implementation of the MDR.

In the MDR, it is requested that common specifications need to be set up when no harmonized standards exist. All of this newly set up common specifications had to be reviewed and internally assessed if an update to the registered medical devices was necessary. From a labeling perspective, for example, the ISO standards listing new medical device symbols had to be checked and any changes needed to be implemented in time. In addition, an internal process for the assignment and administrations of UDIs to identify and track a medical device and a process for the registration of the UDIs in EUDAMED had to be set up. In general, a registration and relevant trainings in EUDAMED were required to be performed by manufacturers. This is also considered relevant in future since this platform shall be used for reporting of serious incidences and side effects once it is fully functional. Currently the use is still optional since not all functions are available, but the use will become mandatory, and an internal reporting process needs to be set up by manufacturers to comply with the requirements (see section 1.4.1).

Besides the new requirements for the labels of medical devices which led to an update of most of them, the IFUs had to be adapted as well to comply with the new requirements and manufacturers now need to ensure that a current version of the IFU is made available on their website in addition. According to the MDR, the content of the IFU needs to be consistent with information provided in the risk analysis, clinical reports, and summary of safety and clinical performance.

In addition, any change of the IFU content needed to be assessed if it triggered the involvement of a notified body or if the current certificates of conformity remained applicable. For integral DDC products, marketing authorization holders needed to apply for a notified body opinion before submitting a marketing authorization application to EMA. The submission to the notified body needs to be planned in advance to avoid time conflicts. Based on the additional process step needed and limited number of applicable notified bodies available

during the transition phase, probably ending end of 2027 or 2028, respectively (see sections 1.2 and 4.2), there is a risk that the approval process of integral DDC products might be extended. But this does not only apply to manufacturers which need to organize a re-assessment of their medical devices. In addition, manufacturers and MAHs which recently started the development and registration of medical devices can also face issues during the device registration phase, in case the capacity of the notified bodies is fully engaged and they face time constraints in assessing newly developed devices.

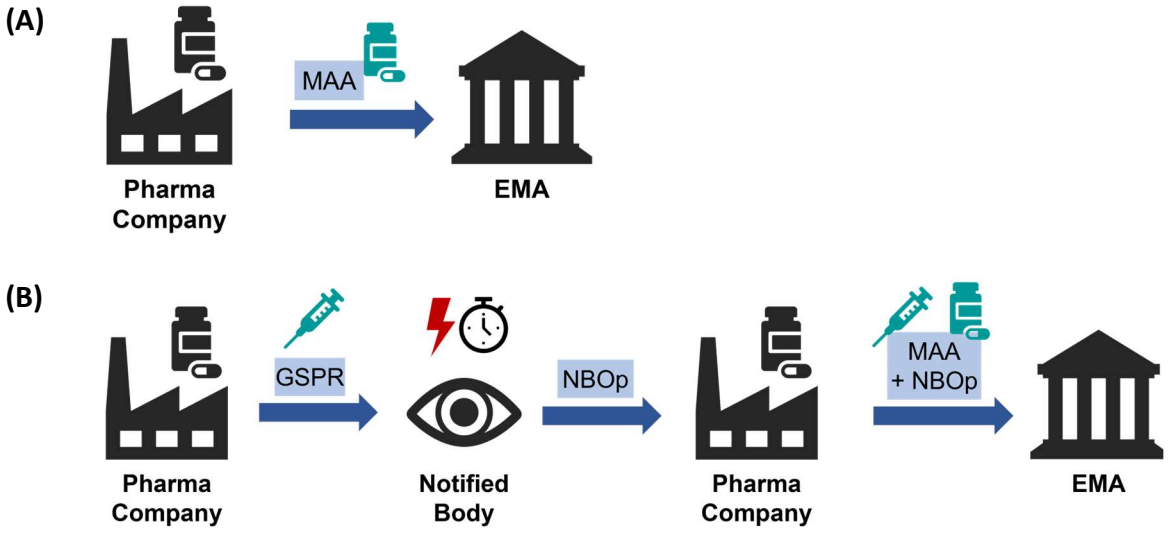
4.2. Approval process of DDC products

For co-packaged and integral DDCs regulated as medicinal products different approval processes apply in the EU.

For co-packaged DDCs, the marketing authorization holder prepares the marketing authorization application (MAA) dossier as described in Directive 2001/83/EC or Regulation (EC) 726/2004 with a proposal for an EU PI (in case of a centralized approval pathway performed by EMA) which does not contain any administrative information related to the medical device part (see section 3.2). But the manufacturer of the medical device part needs to apply for a conformity assessment procedure performed by a notified body to ensure compliance with the MDR, *e.g.* technical documentation, and to receive the permission to attach a CE mark to the medical device (see sections 2.2.1 and 2.3). In case the marketing authorization holder is also the manufacturer of the medical device part, this process needs to be planned in a timely manner to avoid extension of the approval process of the co-packaged DDC.

For medicinal products approved by EMA according to the centralized procedure, one MAA dossier needs to be prepared and these products will undergo a pre-defined and structured approval process led by EMA (see section 2.4 and Figure 4). In contrast to co-packaged DDCs, integral DDCs need to undergo a two-step approval process involving two independent organizations, a designated notified body and the EMA (see section 2.2.2 and Figure 4). According to the "*Questions & Answers for applicants, marketing authorisation holders of medicinal products and notified bodies with respect to the implementation of the Medical Devices and In Vitro Diagnostic Medical Devices Regulations ((EU) 2017/745 and (EU) 2017/746)*", applicants are advised to submit the notified body opinion directly with the MAA to avoid the extension of the approval process due to potential additional or longer

clock stops. Any delay in the approval process will increase the costs and reduce the market exclusivity period. The additional step in the approval process can be considered critical based on the before mentioned reasons and since additional resources are needed to prepare the required documentation to obtain a notified body opinion.[31]



MAA: marketing authorization application; GSPR: general safety and performance requirements; NBOp: notified body opinion

Figure 4: Overview of the approval process for (A) centralized approved medicinal products and (B) integral DDC products

Regarding the labeling and approval process of integral DDCs, there are still some open questions which are not answered sufficiently by the available guidance documents. In 2019, a reflection paper was published by pharmaceutical industry organizations for co-packaged DDCs, titled "*Reflection paper on regulatory uncertainties for co-packaged and cross-labelled drug-device combinations under the new Medical Devices Regulation Affiliations*" to raise some uncertainties regarding the MDR applicability for co-packaged DDCs and to provide the current understanding from MAH perspective. But some of the considerations raised by this group, *e.g.* the uncertainty of placing the UDI on the outer packaging, is meanwhile clarified by additional guidance documents provided by EMA.[31,57]

According to the new approval process, the notified body focuses on the conformity of the medical device part with the GSPRs listed in the MDR, whereas EMA assesses the medicinal product part only. The aim of the notified body opinion is to prove that manufacturers demonstrate compliance of the GSPRs of the medical device part with the MDR. The GSPRs are not applicable to the device part only but can also affect the compatibility of the device

part with other products or substances. This applies especially for integral DDCs when the medical device has direct contact with the medicinal substance.

What happens if a contradictory comment from EMA on the labeling is received during the assessment procedure or what happens if EMA raises a new risk identified during the assessment and approval procedure? How will the feedback from EMA affect the notified body opinion and the approval timelines? Currently, there is no direct interaction or exchange foreseen between the notified body and EMA.[58,59]

In case substantial changes to the GSPRs are observed, a new notified body opinion (NBOp) needs to be requested. According to a position paper from the TEAM-NB, labeling changes can also require an updated NBOp. The position paper was developed to provide MAHs further guidance by explaining what is meant by a "*substantial change*" and includes several examples and decision trees to reduce the uncertainty. A substantial change affects the performance and safety characteristics of a device. Substantial changes include for example device related claims, a change of the intended use, or a different user/patient population. But does an updated NBOp also trigger a variation of the MAA and needs to be approved by EMA? If a change to the labeling documents, *i.e.* the EU PI, is requested, probably yes. Any variation to the MAA requires further resources, time, and produces additional costs which need to be taken into account by the MAH or applicant, respectively.[59,60]

The PL and therefore also handling instructions are part of the documentation which is submitted to the designated notified body to obtain a NBOp. Taking the timing into account when such documentation is prepared, clinical trials for integral DDCs might still be running so that only a draft PL can be shared with the notified body and the final PL will be assessed by EMA only. Since the notified body only focuses on the medical device parts and the development of these should be concluded by then, any information regarding the medicinal product added to the EU PI afterwards should not affect the decision of the notified body.

In case the MAH is not the manufacturer of the integral medical device part, it needs to be ensured that the supplier of the medical device shares the technical documentation needed for preparation of the submission documents with the MAH. There might be also the option that the supplier shares the respective documents directly with the notified body in case there are valid obligations which limit or restrict the access of the MAH to these documents.[59]

4.3. Leading labeling guidance for DDC products

As discussed in section 3, EMA has published two guidance documents which provide further labeling guidance for marketing authorization holders who develop DDC products. These two documents do not focus on labeling guidance but provide an overall summary of regulatory advice to be followed when marketing a DDC. In general, it is quite simple: in case the DDC is regulated as a medicinal product, it should follow the labeling guidance of medicinal products.[1,31]

The main labeling guidance documents to be followed are the SmPC guideline and QRD template published by EMA and being publicly available at its webpage. But these documents do not fully cover medical device labeling guidance for DDCs and an update to provide further guidance might be beneficial to improve the EU PI quality of DDC products.[24,25,61]

For medical devices, no specific additional labeling guidance is available which could be considered comparable to the detailed information provided by EMA. Therefore, a harmonized approach of medical device labeling documents is hardly feasible with the general instructions provided by the MDR only at the moment. It would be highly beneficial to publish further labeling guidance for medical devices to improve the quality and harmonization of such labeling documents. A harmonized labeling document supports the notified bodies in their safety assessment and can reduce review timelines since the expectations are met with the first submission of the documents. In addition, harmonized labeling documents may also support the user (lay and professional user) in understanding the labeling information. In case the same information, especially important safety information, is always displayed at the same place and in the same manner, it might be not overlooked by the reader and is easier to locate. A proposal how such labeling templates can be set up is discussed in section 3.3 and Appendix XIII.

4.4. BREXIT and Switzerland

4.4.1. Medical device regulation in UK

On 31 January 2020, the United Kingdom (UK) left the European Union (EU). With leaving the EU, UK became a third country. This means that the MDR does not apply anymore to medicinal products registered and marketed in the UK and specific requirements according

to third country responsibilities, described in the MDR, apply for medical devices manufactured in the UK and which shall be placed on the European market.[62,63]

This means in addition that the CE mark and conformity assessment performed by notified bodies located in the EU will no longer be accepted in the UK. The UK Medicines and Healthcare products Regulatory Agency (MHRA) took over the regulation of medical devices and need to implement them into UK law which means that also a U.K. Conformity Assessed (UKCA) mark is required. A fully implementation of medical devices in the UK law is planned for July 2024. Starting from 01 January 2021, medical device manufacturers need to register the devices at the MHRA. Nevertheless, the CE marking of EU notified bodies will still be accepted until 30 June 2023 to allow for a smooth transition phase. Based on recent publications it seems that this deadline was extended until 31 December 2024, considering that MHRA faced a lot of challenges. These challenges included especially time constraints considering the implementation of a medical device regulation as well as updating the regulation for medicinal products according to the national law after the BREXIT. Another challenge for medical device manufacturers is, that the UKCA mark will not be accepted in the EU since all notified bodies located in the UK have been removed from the NANDO website. Manufacturers need to apply for an EU conformity assessment leading to a CE marking of their medical devices in addition if they want to enter the EU market with their medical devices. For Northern Ireland, a particularity applies since medical devices will require both, a CE and a UKCA mark to be registered and marketed.[62,64–66]

For medical devices being sold in the EU, this means that the CE mark and EU notified body number need to be placed on the device label according to the MDR. Any other regulatory information should not be placed on the label, meaning that the UKCA mark should not appear. Furthermore, manufacturers located in the UK need a European authorized representative located in the EU for placing UK medical devices on the EU market. According to the MDR this local representative for third countries needs to be mentioned on the medical device label.[2,65]

For manufacturers located in the EU who want to place medical devices on the UK market, this means additional workload in parallel to the ongoing implementation activities of the MDR. They now also need to make sure to comply with the UK regulation and requirements, including potential different labeling requirements for their medical devices.

4.4.2. Medical device regulation in Switzerland

In Switzerland, European medical device manufacturers currently face a similar situation as in the UK. In the past, a mutual recognition agreement was valid to allow a smooth import and export of medical devices between the EU and Switzerland. With the entry into force of the new MDR this mutual recognition agreement expired, and no new agreement is signed yet. Therefore, Switzerland is also considered a third-party country similar as the UK and specific import and export requirements need to be considered for medical devices; meaning an authorized representative located in Switzerland is needed to place European medical devices on the market and the other way round.[67,68]

This has also an impact on the labeling of medical devices placed on the Swiss market. Since Switzerland has currently no access to EUDAMED and the functionality is not fully available, a UDI cannot be assigned to medical devices manufactured in Switzerland and no reporting of serious incidences using EUDAMED is possible at the moment. Therefore, manufacturers, distributors and importers need to register with Swissmedic for a Swiss Single Registration Number (CHRN) which needs to be included in the labeling documentation. If the missing recognition agreement also affects other part of the labeling, *e.g.* the IFU, is not clear at the moment. The current information published on the Swissmedic website states that the product information requirements for Swiss medical devices, including medical device labels and the instructions for use, need to follow the EU-MDR requirements.[68,69]

Conclusion and Outlook

In this thesis, the labeling requirements for co-packaged and integral DDC products according to Regulation (EU) 2017/745 were assessed. As initially claimed, detailed labeling guidance for medical devices is not publicly available to support manufacturers in creation of harmonized labeling documents for medical devices. The MDR, especially the Annexes, provides a detailed list of content which needs to be introduced but lacks detailed guidance to guarantee a harmonized approach of labeling documents. In the MDR, it is stated that harmonized standards should be considered. In case of ISO standards, these are not publicly available, and licenses need to be purchased to gain access to the content.

For DDC products, regulated as a medicinal product, the labeling requirements of medicinal products according to Directive 2001/83/EC or Regulation (EC) 726/2004 apply. EMA has published detailed additional guidance to guide marketing authorization holders in the preparation of labeling documents for medicinal products. This guarantees a harmonized approach for the creation of the EU PIs and overall high quality of labeling documents in general. But the SmPC guideline and available QRD template hardly mention labeling details for medical devices or DDC products regulated as medicinal products.

For the future, it would be desirable for manufacturers of medical devices as well as marketing authorization holders of DDC products if further detailed guidance and labeling templates, similar to the QRD template for medicinal products, would be publicly available. Benefits would include a harmonized approach of labeling documents for medical devices which could simplify the conformity assessment procedure by notified bodies, could support the manufacturers in creation of labeling documents of high quality with correct content and format at the first try, and could improve the safe and effective use by the intended user since information would be easier to locate and understood when always presented in a similar way. The MDCG started to publish additional guidance documents for medical devices to support manufacturers in understanding and implementing the MDR requirements. But currently there is no labeling guidance available based on the published list from the European Commission[70].

Challenges for the creation of such guidance documents can be the diversity of medical devices and the variety of different notified bodies within the EU from which manufacturers can choose and which will perform the conformity assessment for a medical device.

Based on the NANDO list[39], which informs about available notified bodies, these are distributed within several EU countries and consist of private organizations not depending on or belonging to any national government or authority. For medicinal products, approved via the centralized procedure, EMA performs the assessment of all documentation and grants a positive opinion in case the benefit-risk assessment of the medicinal product is considered positive. Afterwards, the European Commission approves the medicinal product. Based on this centralized authorization process and available guidance documents, the assessment and approval process follows a clear order and can be considered a harmonized and fair process. Due to the strict regulated procedure, MAHs know exactly which documents to prepare and when to expect major milestones, feedback, and approval of the medicinal product.

For medical devices, such a harmonized approach is difficult to reach due to different assessing notified bodies. A progress is reached with the release of first position papers created by the TEAM-NB which are published on its website, and which might lead to a more harmonized approach.[71] Furthermore, it is stated in the MDR that harmonized standards should be considered which should lead to harmonized labeling documents and a harmonized assessment in general.

For integral DDC products regulated as a medicinal product, a notified body opinion needs to be submitted with the MAA application to EMA. First, a notified body needs to assess the conformity with the GSPRs of the device part before a submission of the marketing authorization application dossier is performed to EMA for the assessment of the medicinal product. Based on the current approval procedure, an exchange or interaction with the notified body and EMA is not foreseen (see section 4.2). Since the process is still new and experience needs to be gained, it is unpredictable in which extent EMA might also raise comments on the integral device part. If any major changes are requested by EMA, *e.g.* a change of the intended user group which is part of the labeling information, a new notified body opinion might be needed. Therefore, major comments from EMA can delay the anticipated approval time of the integral DDC which leads to the detriment of the MAH by producing additional costs and maybe even giving competitors the chance to enter the market first. In the end, EMA, more specifically the European Commission, is the approving body and will need to consider the notified body opinion. But it needs to be awaited how

EMA's comments on the proposed labeling documents will affect the notified body opinion and the overall approval process of the integral DDC.

Summary

With the entry into force of the new Regulation (EU) 2017/745 (MDR) applicable for medical devices on 26 May 2021, the labeling requirements for drug-device combination (DDC) products, among other things, were affected. In this thesis, labeling requirements for DDC products, including co-packaged and integral DDCs regulated either as a medical device or medicinal product, according to the new MDR were assessed and challenges for medical device manufacturers and marketing authorization holders were highlighted and discussed.

The main labeling requirements applicable for medical devices are listed in Annex I "*General safety and performance requirements*" of the MDR. Compared to medicinal products, for which detailed additional guidance documents published by the European Medicines Agency (EMA) are available, hardly any additional labeling guidance is available for medical devices at the moment. The medical device coordination group (MDCG) started to publish additional guidance for several other topics related to the implementation of the new MDR, but no labeling paper is published yet. In the MDR, manufacturers are advised to consider internationally harmonized standards, *e.g.* ISO standards, which are often not publicly available and request the purchase of a license to be reviewed and considered. For some medical devices only an electronic instructions for use (eIFU) is required. EMA has initiated a project for implementing electronic product information (ePI) for medicinal products but up to now no such initiative includes and considers the electronic labeling of medical devices, *e.g.* eIFUs or ePIs. This is an additional task which should be added to the worklist of the MDCG and EMA. An initiative, starting an exchange between the two working groups for medicinal products and medical devices may also lead to an improvement of the overall quality of labeling documents considering the harmonized approach of the creation and assessment of the labeling for medical devices or DDCs.

In addition to the missing labeling guidance for DDC products, the different applicable approval and registration processes were accessed. For DDCs regulated as a medical device, a conformity assessment performed by a notified body is needed for placing the DDC on the European market. For DDCs regulated as a medicinal product, a two-step approach is applicable including a notified body opinion (NBOp) assessing the safety of the medical device part followed by a benefit-risk assessment for the medicinal product, *i.e.* the integral DDC, performed by EMA. Up to now, no direct interaction between the designated notified

body and EMA is foreseen. Therefore, it is unclear how any comments or changes requested by EMA related to the medical device component can affect the approval process of the integral DDC or the notified body opinion.

For the future, the release of further labeling guidance for medical devices and DDCs would be desirable. First of all, this would improve the quality of the labeling documents for medical devices due to a harmonized approach. Harmonized labeling documents might ease the review process performed by notified bodies and EMA for registering and approving a DDC. At the moment, manufacturers can choose from a list of various notified bodies for performing the assessment and medical devices are very diverse so that a consistent assessment would be desirable for a smooth and fair approval of DDCs. In addition, a harmonized approach will most likely improve the safety and effectiveness of DDCs. Information will be easier to find and understand for the intended user if labeling documents are set up in a similar manner. Even though the MDR requires that the labeling should be readable and understandable, no guidance is available what this exactly means, how it is ensured by the manufacturers or assessed by the notified bodies or how it can be tested by the manufacturer prior applying for a conformity assessment. EMA started to provide some guidance for DDCs regulated as medicinal products. Nevertheless, no such guidance is accessible from the MDCG for medical devices or DDCs at the moment. Therefore, it is to be hoped that the MDCG will also consider the labeling as an important part of the medical device assessment and considers publishing further guidance documents in future. These documents could include labeling templates with additional explanations how to interpret and implement the MDR requirements comparable to the QRD templates published by EMA for medicinal products. In addition, it is desirable that EMA may consider an update of their available labeling documents to provide further guidance for DDC products increasing the focus on the medical device part.

Furthermore, it needs to be awaited if additional guidance regarding the approval of DDCs including a NBOp and EMA assessment is published, *e.g.* by EMA, in future. Due to the strict split of the technical assessment for the medical device part performed by the notified body and the benefit-risk assessment performed by EMA for the medicinal product part, no exchange and communication between these two assessment parties is foreseen. If this is planned to be the future process, further guidance specifying the requirements for a re-

assessment by the notified body is needed in case EMA requests major changes of the labeling documents. Any change of the labeling documents can have a potential impact on the design development and therefore also the performed risk-assessment of a medical device and may potentially lead to a re-assessment. Respecting the transition period, only few DDCs might have been assessed by EMA up to now and marketing authorization holders as well as notified bodies and EMA need to gain further experience in the assessment of DDCs before a conclusion of the impact of the new MDR requirements on the overall approval process can be made. Nevertheless, a highly structured and transparent approval process as currently performed and published by EMA would be highly beneficial to be implemented for medical devices as well. Considering especially the number of different notified bodies and the potential imbalance of performed assessments due to no harmonized approach. For manufacturers, it would be also a benefit to better understand the requirements and timelines so that they can improve the planning and registration process of their medical devices.

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Appendix

Appendix I: MDR Annex I Chapter III 23.1. "General requirements regarding the information supplied by the manufacturer"[2]

Each device shall be accompanied by the information needed to identify the device and its manufacturer, and by any safety and performance information relevant to the user, or any other person, as appropriate. Such information may appear on the device itself, on the packaging or in the instructions for use, and shall, if the manufacturer has a website, be made available and kept up to date on the website, taking into account the following:

a) The medium, format, content, legibility, and location of the label and instructions for use shall be appropriate to the particular device, its intended purpose and the technical knowledge, experience, education or training of the intended user(s). In particular, instructions for use shall be written in terms readily understood by the intended user and, where appropriate, supplemented with drawings and diagrams.

b) The information required on the label shall be provided on the device itself. If this is not practicable or appropriate, some or all of the information may appear on the packaging for each unit, and/or on the packaging of multiple devices.

c) Labels shall be provided in a human-readable format and may be supplemented by machine-readable information, such as radio-frequency identification ('RFID') or bar codes.

d) Instructions for use shall be provided together with devices. By way of exception, instructions for use shall not be required for class I and class IIa devices if such devices can be used safely without any such instructions and unless otherwise provided for elsewhere in this Section.

e) Where multiple devices are supplied to a single user and/or location, a single copy of the instructions for use may be provided if so agreed by the purchaser who in any case may request further copies to be provided free of charge.

f) Instructions for use may be provided to the user in non-paper format (e.g. electronic) to the extent, and only under the conditions, set out in Regulation (EU) No 207/2012 or in any subsequent implementing rules adopted pursuant to this Regulation.

g) Residual risks which are required to be communicated to the user and/or other person shall be included as limitations, contra-indications, precautions or warnings in the information supplied by the manufacturer.

h) Where appropriate, the information supplied by the manufacturer shall take the form of internationally recognised symbols. Any symbol or identification colour used shall conform to the harmonised standards or CS. In areas for which no harmonised standards or CS exist, the symbols and colours shall be described in the documentation supplied with the device.

Appendix II: MDR Annex I Chapter III 23.2. "Information on the label"[2]

The label shall bear all of the following particulars:

a) the name or trade name of the device;

b) the details strictly necessary for a user to identify the device, the contents of the packaging and, where it is not obvious for the user, the intended purpose of the device;

c) the name, registered trade name or registered trade mark of the manufacturer and the address of its registered place of business;

d) if the manufacturer has its registered place of business outside the Union, the name of the authorised representative and address of the registered place of business of the authorised representative;

e) where applicable, an indication that the device contains or incorporates: — a medicinal substance, including a human blood or plasma derivative, or — tissues or cells, or their derivatives, of human origin, or — tissues or cells of animal origin, or their derivatives, as referred to in Regulation (EU) No 722/2012;

f) where applicable, information labelled in accordance with Section 10.4.5.;

g) the lot number or the serial number of the device preceded by the words LOT NUMBER or SERIAL NUMBER or an equivalent symbol, as appropriate;

h) the UDI carrier referred to in Article 27(4) and Part C of Annex VII;

i) an unambiguous indication of t the time limit for using or implanting the device safely, expressed at least in terms of year and month, where this is relevant;

j) where there is no indication of the date until when it may be used safely, the date of manufacture. This date of manufacture may be included as part of the lot number or serial number, provided the date is clearly identifiable;

k) an indication of any special storage and/or handling condition that applies;

l) if the device is supplied sterile, an indication of its sterile state and the sterilisation method;

m) warnings or precautions to be taken that need to be brought to the immediate attention of the user of the device, and to any other person. This information may be kept to a minimum in which case more detailed information shall appear in the instructions for use, taking into account the intended users;

n) if the device is intended for single use, an indication of that fact. A manufacturer's indication of single use shall be consistent across the Union;

o) if the device is a single-use device that has been reprocessed, an indication of that fact, the number of reprocessing cycles already performed, and any limitation as regards the number of reprocessing cycles;

p) if the device is custom-made, the words 'custom-made device';

q) an indication that the device is a medical device. If the device is intended for clinical investigation only, the words 'exclusively for clinical investigation';

r) in the case of 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, the overall qualitative composition

of the device and quantitative information on the main constituent or constituents responsible for achieving the principal intended action;

s) for active implantable devices, the serial number, and for other implantable devices, the serial number or the lot number.

Appendix III: MDR Annex I Chapter III 23.3 "Information on the packaging which maintains the sterile condition of a device ('sterile packaging')"[2]

The following particulars shall appear on the sterile packaging:

(a) an indication permitting the sterile packaging to be recognised as such,

(b) a declaration that the device is in a sterile condition,

(c) the method of sterilisation,

(d) the name and address of the manufacturer,

(e) a description of the device,

(f) if the device is intended for clinical investigations, the words 'exclusively for clinical investigations',

(g) if the device is custom-made, the words 'custom-made device',

(h) the month and year of manufacture,

(i) an unambiguous indication of the time limit for using or implanting the device safely expressed at least in terms of year and month, and

(j) an instruction to check the instructions for use for what to do if the sterile packaging is damaged or unintentionally opened before use.

Appendix IV: MDR Annex I Chapter III 23.4. "Information in the instructions for use"[2]

The instructions for use shall contain all of the following particulars:

(a) the particulars referred to in points (a), (c), (e), (f), (k), (l), (n) and (r) of Section 23.2;

(b) the device's intended purpose with a clear specification of indications, contra-indications, the patient target group or groups, and of the intended users, as appropriate;

(c) where applicable, a specification of the clinical benefits to be expected.

(d) where applicable, links to the summary of safety and clinical performance referred to in Article 32;

(e) the performance characteristics of the device;

(f) where applicable, information allowing the healthcare professional to verify if the device is suitable and select the corresponding software and accessories;

(g) any residual risks, contra-indications and any undesirable side-effects, including information to be conveyed to the patient in this regard;

(h) specifications the user requires to use the device appropriately, e.g. if the device has a measuring function, the degree of accuracy claimed for it;

(i) details of any preparatory treatment or handling of the device before it is ready for use or during its use, such as sterilisation, final assembly, calibration, etc., including the levels of disinfection required to ensure patient safety and all available methods for achieving those levels of disinfection;

(j) any requirements for special facilities, or special training, or particular qualifications of the device user and/or other persons;

(k) the information needed to verify whether the device is properly installed and is ready to perform safely and as intended by the manufacturer, together with, where relevant:

- details of the nature, and frequency, of preventive and regular maintenance, and of any preparatory cleaning or disinfection,
- identification of any consumable components and how to replace them,
- information on any necessary calibration to ensure that the device operates properly and safely during its intended lifetime, and
- methods for eliminating the risks encountered by persons involved in installing, calibrating or servicing devices;

(l) if the device is supplied sterile, instructions in the event of the sterile packaging being damaged or unintentionally opened before use;

(m) if the device is supplied non-sterile with the intention that it is sterilised before use, the appropriate instructions for sterilisation;

(n) if the device is reusable, information on the appropriate processes for allowing reuse, including cleaning, disinfection, packaging and, where appropriate, the validated method of re-sterilisation appropriate to the Member State or Member States in which the device has been placed on the market. Information shall be provided to identify when the device should no longer be reused, e.g. signs of material degradation or the maximum number of allowable reuses;

(o) an indication, if appropriate, that a device can be reused only if it is reconditioned under the responsibility of the manufacturer to comply with the general safety and performance requirements;

(p) if the device bears an indication that it is for single use, information on known characteristics and technical factors known to the manufacturer that could pose a risk if the device were to be re-used. This information shall be based on a specific section of the manufacturer's risk management documentation, where such characteristics and technical factors shall be addressed in detail. If in accordance with point (d) of Section 23.1. no instructions for use are required, this information shall be made available to the user upon request;

(q) for devices intended for use together with other devices and/or general purpose equipment:

- information to identify such devices or equipment, in order to obtain a safe combination, and/or
- information on any known restrictions to combinations of devices and equipment;

(r) if the device emits radiation for medical purposes:

- detailed information as to the nature, type and where appropriate, the intensity and distribution of the emitted radiation,
- the means of protecting the patient, user, or other person from unintended radiation during use of the device;

(s) information that allows the user and/or patient to be informed of any warnings, precautions, contra- indications, measures to be taken and limitations of use regarding the device. That information shall, where relevant, allow the user to brief the patient about any warnings, precautions, contra-indications, measures to be taken and limitations of use regarding the device. The information shall cover, where appropriate:

- warnings, precautions and/or measures to be taken in the event of malfunction of the device or changes in its performance that may affect safety,
- warnings, precautions and/or measures to be taken as regards the exposure to reasonably foreseeable external influences or environmental conditions, such as magnetic fields, external electrical and electromagnetic effects, electrostatic discharge, radiation associated with diagnostic or therapeutic procedures, pressure, humidity, or temperature,
- warnings, precautions and/or measures to be taken as regards the risks of interference posed by the reasonably foreseeable presence of the device during specific diagnostic investigations, evaluations, or therapeutic treatment or other procedures such as electromagnetic interference emitted by the device affecting other equipment,
- if the device is intended to administer medicinal products, tissues or cells of human or animal origin, or their derivatives, or biological substances, any limitations or incompatibility in the choice of substances to be delivered,
- warnings, precautions and/or limitations related to the medicinal substance or biological material that is incorporated into the device as an integral part of the device; and
- precautions related to materials incorporated into the device that contain or consist of CMR substances or endocrine-disrupting substances, or that could result in sensitisation or an allergic reaction by the patient or user;

(t) in the case of devices that are composed of substances or of combinations of substances that are intended to be introduced into the human body and that are absorbed by or locally dispersed in the human body, warnings and precautions, where appropriate, related to the general profile of interaction of the device and its products of metabolism with other devices, medicinal products and other substances as well as contra- indications, undesirable side-effects and risks relating to overdose;

(u) in the case of implantable devices, the overall qualitative and quantitative information on the materials and substances to which patients can be exposed;

(v) warnings or precautions to be taken in order to facilitate the safe disposal of the device, its accessories and the consumables used with it, if any. This information shall cover, where appropriate:

- infection or microbial hazards such as explants, needles or surgical equipment contaminated with potentially infectious substances of human origin, and
- physical hazards such as from sharps. If in accordance with the point (d) of Section 23.1 no instructions for use are required, this information shall be made available to the user upon request;

(w) for devices intended for use by lay persons, the circumstances in which the user should consult a healthcare professional;

(x) for the devices covered by this Regulation pursuant to Article 1(2), information regarding the absence of a clinical benefit and the risks related to use of the device;

(y) date of issue of the instructions for use or, if they have been revised, date of issue and identifier of the latest revision of the instructions for use;

(z) a notice to the user and/or patient that any serious incident that has occurred in relation to the device should be reported to the manufacturer and the competent authority of the Member State in which the user and/or patient is established;

(aa) information to be supplied to the patient with an implanted device in accordance with Article 18;

(ab) for devices that incorporate electronic programmable systems, including software, or software that are devices in themselves, minimum requirements concerning hardware, IT networks characteristics and IT security measures, including protection against unauthorised access, necessary to run the software as intended.

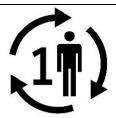
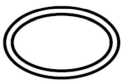
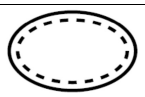
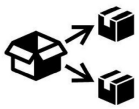
Appendix V: Symbols to be used on medical device labels according to ISO 15223-1:2021

Based on the required information as laid down in MDR Annex I Chapter III 23.2 and 23.3 and according to ISO 15223-1:2021, the following symbols are available to replace written information on the device label (see Table (Appendix) 1).

Table (Appendix) 1: Symbols according to ISO 15223-1:2021[18,72]

ISO Reference number (MDR reference)	Title	Symbol**
5.1.1 (23.2.c)	Manufacturer	
5.4.6 (23.2.e)	Contains human blood or plasma derivatives	
5.4.7 (23.2.e)	Contains a medicinal substance	
5.4.9 (23.2.e)	Contains biological material of human origin	
5.4.8 (23.2.e)	Contains biological material of animal origin	
5.4.10 (23.2.f)	Contains hazardous substances	
5.1.5 (23.2.g)	Batch code	
5.1.7 (23.2.g)	Serial number	
5.7.10 (23.2.h)	Unique Device Identification	

** ISO 15223-1:2021 contains further symbols which can be used to inform the user of storage conditions of the device according to MDR requirements in Annex I Chapter III 23.2.k. ISO reference numbers: 5.3.1, 5.3.2, 5.3.3, 5.3.4, 5.3.5, 5.3.6, 5.3.7, 5.3.8, and 5.3.9.[18]

ISO Reference number (MDR reference)	**Title**	**Symbol**[**]
5.2.1 (23.2.l)[††]	Sterile	
5.4.12 (23.2.n)	Single Patient - multiple use	
5.7.7 (23.2.q)	Medical Device	
5.4.11 (23.2.r)	Contains nano materials	
5.2.11 (23.3.a)	Single sterile barrier system	
5.2.12 (23.3.a)	Double sterile barrier system	
5.2.13 (23.3.a)	Single sterile barrier system with protective packaging inside	
5.2.14 (23.3.a)	Single sterile barrier system with protective packaging outside	
5.7.8 (MDR Article 16)	Translation	
5.7.9 (MDR Article 16)	Repackaging	
5.1.8 (MDR Article 13)	Importer	
5.1.9 (MDR Article 14)	Distributor	

[††] Several symbols combining the indication that the medical device is sterile with the used sterilization method are available in ISO 15223-1:2021 to comply with the MDR requirement in Annex I Chapter III 23.2.l.

Appendix VI: Member States and languages requested for medical device labeling

The content of Table (Appendix) 2 is taken form an article published by Mastermind Translations in October 2021.[73]

Table (Appendix) 2: Languages of the EU member states to be considered for labeling of medical devices

Member State	Language for lay persons (*for professional users*)
Austria	German (*or English*)
Belgium	French, Dutch, and German (*or English*)
Bulgaria	Bulgarian
Croatia	Croation (*or English*)
Cyprus	Greek (*or English*)
Czech Republic	Czech
Denmark	Danish (*exemptions possible*)
Estonia	Estonian (*exemptions possible*)
Finland	Finnish and Swedish (*or English*)
France	French
Germany	German (*or English*)
Greece	Greek (*or English*)
Hungary	Hungarian
Ireland	English or Irish and English
Italy	Italian
Latvia	Latvian
Lithuania	Lithuanian
Luxembourg	French, German or Luxembourgish
Malta	English, Maltese
Netherlands	Dutch (*or English*)
Poland	Polish or Polish and English
Portugal	Portuguese
Romania	Romanian (*or English*)
Slovakia	Slovak
Slovenia	Slovene (*exemptions possible*)
Spain	Spanish
Sweden	Swedish (*exemptions possible*)

Appendix VII: Labeling requirements for medicinal products according to Directive 2001/83/EC[3]

OUTER PACKAGING (ARTICLE 54)[‡‡]

(a) the name of the medicinal product followed by the common name where the product contains only one active substance and if its name is an invented name; where a medicinal product is available in several pharmaceutical forms and/or several strengths, the pharmaceutical form and/or the strength (baby, child or adult as appropriate) must be included in the name of the medicinal product;

(b) a statement of the active substances expressed qualitatively and quantitatively per dosage unit or according to the form of administration for a given volume or weight, using their common names;

(c) the pharmaceutical form and the contents by weight, by volume or by number of doses of the product;

(d) a list of those excipients known to have a recognized action or effect and included in the guidelines published pursuant to Article 65. However, if the product is injectable, or a topical or eye preparation, all excipients must be stated;

(e) the method and, if necessary, the route of administration;

(f) a special warning that the medicinal product must be stored out of reach of children;

(g) a special warning, if this is necessary for the medicinal product;

(h) the expiry date in clear terms (month/year);

(i) special storage precautions, if any;

(j) special precautions for disposal of unused medicinal products or waste materials from medicinal products, if appropriate;

(k) the name and address of the holder of the authorization for placing the medicinal product on the market;

(l) the number of the authorization for placing the medicinal product on the market;

(m) the manufacturer's batch number;

(n) in the case of self-medication, instructions on the use of the medicinal products.

IMMEDIATE PACKAGING (ARTICLE 55)

1. The particulars laid down in Articles 54 and 62 [*symbols and pictograms*] shall appear on immediate packagings other than those referred to in paragraphs 2 and 3.

2. The following particulars at least shall appear on immediate packagings which take the form of blister packs and are placed in an outer packaging that complies with the requirements laid down in Articles 54 and 62.

- the name of the medicinal product as laid down in Article 54(a),
- the name of the holder of the authorization for placing the product on the market,

[‡‡] In case there is no outer packaging, the information needs to be applied to the immediate packaging of the medicinal product.

- the expiry date,
- the batch number.

3. The following particulars at least shall appear on small immediate packaging units on which the particulars laid down in Articles 54 and 62 cannot be displayed:

- the name of the medicinal product and, if necessary, the strength and the route of administration,
- the method of administration,
- the expiry date,
- the batch number,
- the contents by weight, by volume or by unit.

PACKAGE LEAFLET (ARTICLE 59)

1. The package leaflet shall be drawn up in accordance with the summary of the product characteristics; it shall include, in the following order:

(a) for the identification of the medicinal product:

- the name of the medicinal product, followed by the common name if the product contains only one active substance and if its name is an invented name; where a medicinal product is available in several pharmaceutical forms and/or several strengths, the pharmaceutical form and/or the strength (for example, baby, child, adult) must be included in the name of the medicinal product,
- a full statement of the active substances and excipients expressed qualitatively and a statement of the active substances expressed quantitatively, using their common names, in the case of each presentation of the medicinal product,
- the pharmaceutical form and the contents by weight, by volume or by number of doses of the product, in the case of each presentation of the product,
- the pharmaco-therapeutic group, or type of activity in terms easily comprehensible for the patient,
- the name and address of the holder of the authorization for placing the medicinal product on the market and of the manufacturer;

(b) the therapeutic indications;

(c) list of information which is necessary before taking the medicinal product:

- contra-indications,
- appropriate precautions for use,
- forms of interaction with other medicinal products and other forms of interaction (e.g. alcohol, tobacco, foodstuffs) which may affect the action of the medicinal product,
- special warnings;

this list must:

- take into account the particular condition of certain categories of users (e.g. children, pregnant or breastfeeding women, the elderly, persons with specific pathological conditions),

- mention, if appropriate, potential effects on the ability to drive vehicles or to operate machinery,
- detail those excipients, knowledge of which is important for the safe and effective use of the medicinal product and included in the guidelines published pursuant to Article 65;

(d) the necessary and usual instructions for proper use, in particular:

- the dosage,
- the method and, if necessary, route of administration,
- the frequency of administration, specifying if necessary, the appropriate time at which the medicinal product may or must be administered,

and, as appropriate, depending on the nature of the product:

- the duration of treatment, where it should be limited,
- the action to be taken in the case of an overdose (*e.g.* symptoms, emergency procedures),
- the course of action to take when one or more doses have not been taken,
- indication, if necessary, of the risk of withdrawal effects;

(e) a description of the undesirable effects which can occur under normal use of the medicinal product and, if necessary, the action to be taken in such a case; the patient should be expressly invited to communicate any undesirable effect which is not mentioned in the leaflet to his doctor or to his pharmacist;

(f) a reference to the expiry date indicated on the label, with:

- a warning against using the product after this date,
- where appropriate, special storage precautions,
- if necessary, a warning against certain visible signs of deterioration;

(g) the date on which the package leaflet was last revised.

2. Notwithstanding paragraph 1(b), the authority competent may decide that certain therapeutic indications shall not be mentioned in the package leaflet, where the dissemination of such information might have serious disadvantages for the patient.

*Appendix VIII: Guidance documents for medical devices[§§,***]*

Summary list of titles and references of harmonised standards published by the European Commission - https://single-market-economy.ec.europa.eu/single-market/european-standards/harmonised-standards/medical-devices_de

MEDDEV Guidance documents available at the European Commission website - https://health.ec.europa.eu/system/files/2022-01/md_guidance_meddevs_0.pdf

Medical Devices - Sector – Publications at the European Commission website - https://health.ec.europa.eu/medical-devices-sector/publications_en?f%5B0%5D=oe_publication_type%3Ahttp%3A//publications.europa.eu/resource/authority/resource-type/PUB_GEN

Guidance - MDCG endorsed documents and other guidance available at the European Commission website - https://health.ec.europa.eu/medical-devices-sector/new-regulations/guidance-mdcg-endorsed-documents-and-other-guidance_en

Medical Devices guidance in case the involvement of EMA is necessary - https://www.ema.europa.eu/en/human-regulatory/overview/medical-devices

ISO 13485 Medical devices

ISO 20417:2021 Medical devices — Information to be supplied by the manufacturer

ISO 15223-1 Medical devices - Symbols to be used with information to be supplied by the manufacturer — Part 1: General requirements

ISO 15223-2 Medical devices — Symbols to be used with medical device labels, labelling, and information to be supplied — Part 2: Symbol development, selection and validation

ISO 639-1:2002 Language codes Part 1: Provides a 2-letter code that has been designed to represent most of the major languages of the world.

ISO 3166-1 Part 1: Country code: Codes for the representation of names of countries and their subdivisions

ISO/IEC 15415:2011 Information technology — Automatic identification and data capture techniques — Bar code symbol print quality test specification — Two-dimensional symbols

ISO/IEC 16022:2006 Information technology — Automatic identification and data capture techniques — Data Matrix bar code symbology specification

[§§] **Fehler! Verweisquelle konnte nicht gefunden werden.** provides only an excerpt of available guidance documents. The list is not considered complete.

[***] ISO standards are not publicly available and need to be purchased for full access. An overview of the content is accessible for each ISO at https://www.iso.org/standards.html.

Appendix IX: Guidance documents for medicinal products approved by EMA[†††]

Product information: Reference documents and guidelines available at the EMA website – https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/product-information/product-information-reference-documents-guidelines

Compilation of QRD decisions on stylistic matters in product information - https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/compilation-quality-review-documents-qrd-stylistic-matters-product-information_en.pdf

List of official languages per country - https://www.ema.europa.eu/en/documents/other/list-official-languages-country_en.pdf

QRD form for submission and assessment of user testing bridging proposals - https://www.ema.europa.eu/documents/template-form/quality-review-documents-qrd-form-submission-assessment-user-testing-bridging-proposals_en.doc

QRD recommendations on the expression of strength in the name of centrally authorised human medicinal products - https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/quality-review-documents-recommendations-expression-strength-name-centrally-authorised-human_en.pdf

Tables of non-standard abbreviations to be used within the SmPC - https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/tables-non-standard-abbreviations-be-used-summary-product-characteristics_en.pdf

Tables of non-standard abbreviations Summary of Product Characteristics - https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/addressing-paediatric-incapacitated-patient-package-leaflet_en-0.pdf

Excipients labelling - https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/product-information/reference-guidelines/excipients-labelling

Product-information templates – Human - https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/product-information/product-information-templates-human

Guideline on the Readability of the Labelling and Package Leaflet of Medicinal Products for Human Use published by the European Commission - https://health.ec.europa.eu/system/files/2016-11/2009_01_12_readability_guideline_final_en_0.pdf

How to prepare and review a summary of product characteristics - https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/product-information/how-prepare-review-summary-product-characteristics

A Guideline on Summary of Product Characteristics (SmPC) published by the European Commission - https://health.ec.europa.eu/system/files/2016-11/smpc_guideline_rev2_en_0.pdf

Guideline on the Packaging Information of Medicinal Products for Human Use Authorised by the Union published by the European Commission - https://health.ec.europa.eu/system/files/2021-04/2018_packaging_guidelines_en_0.pdf

[†††] **Fehler! Verweisquelle konnte nicht gefunden werden.** provides only an excerpt of available guidance documents. The list is not considered complete.

Appendix X: FDA Guidance Documents (filtered for medical devices and labeling)[33]

Summary	Issue Date	Status	Docket Number
Enforcement Policy for Telethermographic Systems During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency: Guidance for Industry and Food and Drug Administration Staff	04/16/2020	Final	FDA-2020-D-1138
Infectious Disease Next Generation Sequencing Based Diagnostic Devices: Microbial Identification and Detection of Antimicrobial Resistance and Virulence Markers: Draft Guidance for Industry and Food and Drug Administration Staff	05/13/2016	Draft	FDA-2016-D-0971
Testing and Labeling Medical Devices for Safety in the Magnetic Resonance (MR) Environment: Guidance for Industry and Food and Drug Administration Staff	05/20/2021	Final	FDA-2019-D-2837
Enforcement Policy for Imaging Systems During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency: Guidance for Industry and Food and Drug Administration Staff	04/23/2020	Final	FDA-2020-D-1138
Enforcement Policy for Face Masks, Barrier Face Coverings, Face Shields, Surgical Masks, and Respirators During the Coronavirus Disease (COVID-19) Public Health Emergency (Revised): Guidance for Industry and Food and Drug Administration Staff	09/15/2021	Final	FDA-2020-D-1138
Enforcement Policy for Non-Invasive Fetal and Maternal Monitoring Devices Used to Support Patient Monitoring During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency: Guidance for Industry and Food and Drug Administration Staff	04/23/2020	Final	FDA-2020-D-1138
Enforcement Policy for Sterilizers, Disinfectant Devices, and Air Purifiers During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency: Guidance for Industry and Food and Drug Administration Staff	03/29/2020	Final	FDA-2020-D-1138
Labeling for Electronic Anti-Theft Systems: Guidance for Industry	08/15/2000	Final	FDA-2020-D-0957
Device Labeling Guidance #G91-1 (Blue Book Memo)	03/08/1991	Final	FDA-2020-D-0957
Breast Implants - Certain Labeling Recommendations to Improve Patient Communication: Guidance for Industry and Food and Drug Administration Staff	09/29/2020	Final	FDA-2019-D-4467
Saline, Silicone Gel, and Alternative Breast Implants: Guidance for Industry and FDA Staff	09/29/2020	Final	FDA-2004-D-0124
Developing and Labeling In vitro Companion Diagnostic Devices for a Specific Group of Oncology Therapeutic Products: Guidance for Industry	04/13/2020	Final	FDA-2018-D-3380
Clinical Considerations for Investigational Device Exemptions (IDEs) for Neurological Devices Targeting Disease Progression and Clinical Outcomes: Guidance for Industry and Food and Drug Administration Staff	11/07/2016	Final	FDA-2016-D-0539
Procedures for Meetings of the Medical Devices Advisory Committee: Guidance for Industry and Food and Drug Administration Staff	09/01/2017	Final	FDA-2015-D-0838
FDA and Industry Procedures for Section 513(g) Requests for Information under the Federal Food, Drug, and Cosmetic Act: Guidance for Industry and Food and Drug Administration Staff	12/16/2019	Final	FDA–2010–D–0153
Medical Devices and Clinical Trial Design for the Treatment or Improvement in the Appearance of Fungally-Infected Nails: Guidance for Industry and Food and Drug Administration Staff	03/07/2016	Final	FDA-2014-D-1849
Evaluation and Reporting of Age-, Race-, and Ethnicity-Specific Data in Medical Device Clinical Studies: Guidance for Industry and Food and Drug Administration Staff	09/12/2017	Final	FDA-2016-D-0734
Assessment of Radiofrequency-Induced Heating in the Magnetic Resonance (MR) Environment for Multi-Configuration Passive Medical Devices: Guidance for Industry and Food and Drug Administration Staff	03/22/2016	Final	FDA-2015-D-2104
Product Labeling for Certain Ultrasonic Surgical Aspirator Devices: Guidance for Industry and Food and Drug Administration Staff	10/30/2017	Final	FDA-2016-D-3275

Display Devices for Diagnostic Radiology: Guidance for Industry and Food and Drug Administration Staff	09/28/2022	Final	FDA-2016-D-0270
Enforcement Policy for Non-Invasive Remote Monitoring Devices Used to Support Patient Monitoring During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency (Revised): Guidance for Industry and Food and Drug Administration Staff	10/28/2020	Final	FDA-2020-D-1138
Content and Format for Abbreviated 510(k)s for Early Growth Response 1 (EGR1) Gene Fluorescence In-Situ Hybridization (FISH) Test System for Specimen Characterization Devices: Guidance for Industry and Food and Drug Administration Staff	06/17/2015	Final	FDA-2014-D-1242
Technical Performance Assessment of Digital Pathology Whole Slide Imaging Devices : Guidance for Industry and Food and Drug Administration Staff	04/20/2016	Final	FDA-2015-D-0230
Clinical Performance Assessment: Considerations for Computer-Assisted Detection Devices Applied to Radiology Images and Radiology Device Data in Premarket Notification (510(k)) Submissions: Guidance for Industry and FDA Staff	09/28/2022	Final	FDA-2009-D-0503
Premarket Notification (510(k)) Submissions for Electrosurgical Devices for General Surgery: Guidance for Industry and Food and Drug Administration Staff	03/09/2020	Final	FDA-2014-D-0217
Premarket Notification (510(k)) Submissions for Bipolar Electrosurgical Vessel Sealers for General Surgery: Guidance for Industry and Food and Drug Administration Staff	08/15/2016	Final	FDA-2014-D-0218
Peripheral Vascular Atherectomy Devices - Premarket Notification [510(k)] Submissions: Guidance for Industry and Food and Drug Administration Staff	05/20/2021	Final	FDA-2018-D-2494
Peripheral Percutaneous Transluminal Angioplasty (PTA) and Specialty Catheters - Premarket Notification (510(k)) Submissions: Draft Guidance for Industry and Food and Drug Administration Staff	01/13/2020	Draft	FDA-2019-D-5422
Deciding When to Submit a 510(k) for a Software Change to an Existing Device: Guidance for Industry and Food and Drug Administration Staff	10/25/2017	Final	FDA-2016-D-2021
Deciding When to Submit a 510(k) for a Change to an Existing Device: Guidance for Industry and Food and Drug Administration Staff	10/25/2017	Final	FDA-2011-D-0453
Compliance with Section 301 of the Medical Device User Fee and Modernization Act of 2002, as amended – Prominent and Conspicuous Mark of Manufacturers on Single-Use Devices: Guidance for Industry and FDA Staff	05/01/2006	Final	FDA-2005-D-0156
List of Highest Priority Devices for Human Factors Review: Draft Guidance for Industry and Food and Drug Administration Staff	02/03/2016	Draft	FDA-2015-D-4599
Postmarket Management of Cybersecurity in Medical Devices: Guidance for Industry and Food and Drug Administration Staff	12/28/2016	Final	FDA-2015-D-5105
Applying Human Factors and Usability Engineering to Medical Devices: Guidance for Industry and Food and Drug Administration Staff	02/03/2016	Final	FDA-2011-D-0469
Product Labeling for Laparoscopic Power Morcellators: Guidance for Industry and Food and Drug Administration Staff	12/30/2020	Final	FDA-2014-D-1804
Addition of URLs to Electronic Product Labeling: Guidance for Industry and FDA Staff	09/30/2010	Final	FDA-2020-D-0957
Enforcement Policy for Digital Health Devices For Treating Psychiatric Disorders During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency: Guidance for Industry and Food and Drug Administration Staff	04/14/2020	Final	FDA-2020-D-1138
Labeling for Permanent Hysteroscopically-Placed Tubal Implants Intended for Sterilization: Guidance for Industry and Food and Drug Administration Staff	10/31/2016	Final	FDA-2016-D-0435
Laser-Assisted In Situ Keratomileusis (LASIK) Lasers - Patient Labeling Recommendations: Draft Guidance for Industry and Food and Drug Administration Staff	07/28/2022	Draft	FDA-2022-D-1253
Remanufacturing of Medical Devices: Draft Guidance for Industry and Food and Drug Administration Staff	06/24/2021	Draft	FDA-2018-N-3741

Updating Labeling for Susceptibility Test Information in Systemic Antibacterial Drug Products and Antimicrobial Susceptibility Testing Devices (Final)	06/26/2009	Final	FDA-2008-D-0339
Guidance on Medical Device Patient Labeling: Final Guidance for Industry and FDA Staff	04/19/2001	Final	FDA-2000-D-0067
Guidance Document for the Preparation of IDEs for Spinal Systems - Guidance for Industry and/or FDA Staff	01/13/2000	Final	FDA-2020-D-0957
CPG Sec. 396.400 Policy on Warned on Sunlamp Products	03/01/1995	Final	FDA-2020-D-0957
CPG Sec. 300.300 Ineffective Devices - 502(f)(I) Labeling Requirements	03/01/1995	Final	FDA-2020-D-0957
CPG Sec. 300.400 Contamination of Devices Labeled as Sterile	03/01/1995	Final	FDA-2020-D-0957
CPG Sec. 345.200 Diaphragms - Rx Devices	09/24/1987	Final	FDA-2020-D-0957
Clarification of Radiation Control Regulations For Manufacturers of Diagnostic X-Ray Equipment: Draft Guidance for Industry and Food and Drug Administration Staff	12/17/2018	Draft	FDA-2018-D-4115
Surgical Staplers and Staples for Internal Use - Labeling Recommendations: Guidance for Industry and Food and Drug Administration Staff	10/08/2021	Final	FDA-2019-D-1262
Oral Drug Products Administered Via Enteral Feeding Tube: In Vitro Testing and Labeling Recommendations: Draft Guidance for Industry	06/02/2021	Draft	FDA-2021-D-0391
Unique Device Identification: Policy Regarding Compliance Dates for Class I and Unclassified Devices, Direct Marking, and Global Unique Device Identification Database Requirements for Certain Devices: Guidance for Industry and Food and Drug Administration Staff	07/25/2022	Final	FDA-2017-D-6841
Unique Device Identification System: Form and Content of the Unique Device Identifier (UDI): Guidance for Industry and Food and Drug Administration Staff	07/07/2021	Final	FDA-2016-D-1853
Enforcement Policy Regarding Use of National Health Related Item Code and National Drug Code Numbers on Device Labels and Packages: Guidance for Industry and Food and Drug Administration Staff	05/21/2021	Final	FDA-2016-D-0199
Unique Device Identification: Convenience Kits : Guidance for Industry and Food and Drug Administration Staff	04/26/2019	Final	FDA-2015-D-4048
Unique Device Identification: Direct Marking of Devices : Guidance for Industry and Food and Drug Administration Staff	11/17/2017	Final	FDA-2015-D-2245
Unique Device Identifier System: Frequently Asked Questions, Vol. 1 : Guidance for Industry and Food and Drug Administration Staff	08/20/2014	Final	FDA-2020-D-0957
Logical Observation Identifiers Names and Codes for In Vitro Diagnostic Tests : Guidance for Industry and Food and Drug Administration Staff	06/15/2018	Final	FDA-2017-D-6982
Unique Device Identification System: Small Entity Compliance Guide: Guidance for Industry and Food and Drug Administration Staff	08/13/2014	Final	FDA-2011-D-0790
Global Unique Device Identification Database (GUDID): Guidance for Industry and Food and Drug Administration Staff	06/27/2014	Final	FDA-2013-D-0636
Investigational IVDs Used in Clinical Investigations of Therapeutic Products: Draft Guidance for Industry, Food and Drug Administration Staff, Sponsors, and Institutional Review Boards	12/18/2017	Draft	FDA-2017-N-6356
Intravascular Catheters, Wires, and Delivery Systems with Lubricious Coatings - Labeling Considerations: Guidance for Industry and Food and Drug Administration Staff	10/10/2019	Final	FDA-2018-D-1788

Appendix XI: Case study – EU PI for an integral DDC[‡‡‡§§§]

Creation of an EU PI for an integral DDC (iDDC) regulated as a medicinal product based on its intended purpose

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

[‡‡‡] EU PI is based on QRD template version 10.3, 09/2022

[§§§] The example was created considering the current QRD template, SmPC guideline, Regulation (EU) 2017/745, Directive 2001/83/EC, and the approved Skyrizi EU PI (https://www.ema.europa.eu/en/documents/product-information/skyrizi-epar-product-information_en.pdf; site accessed 09 Jan 2023). This is a fictitious example. Any resemblance to an approved medicinal product or a medicinal product in development is purely coincidental.

1. NAME OF THE MEDICINAL PRODUCT

Atopen 100 mg solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Atopen 100 mg solution for injection in pre-filled pen

Each pre-filled pen contains 100 mg atopizumab in 1 mL solution.

Atopizumab is a humanised immunoglobulin G1 (IgG1) monoclonal antibody selective to the interleukin (IL)-X protein produced in Chinese Hamster Ovary cells using recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection)

Atopen 100 mg solution for injection in pre-filled pen

The solution is blue and clear to slightly opalescent.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Atopen is indicated for the treatment of moderate to severe atopic dermatitis in adult and adolescent patients from 12 years of age.

4.2 Posology and method of administration

Posology

The recommended dose is 100 mg atopizumab administered as a subcutaneous injection every 4 weeks.

Missed dose

If a dose is missed, the dose should be administered as soon as possible. Thereafter, dosing should be resumed at the regular scheduled time.

Special populations

Paediatric population

The safety and efficacy of atopizumab in children below the age of 12 years have not yet been established. No data are available.

Elderly

No dose adjustment is required (see section 5.2). There is limited information available in subjects aged ≥ 70 years.

Renal and / or hepatic impairment

These conditions are generally not expected to have any significant impact on the pharmacokinetics of monoclonal antibodies and no dose adjustment is considered necessary (see section 5.2)

Method of administration

Atopen is administered by subcutaneous injection.

The injection should be administered in the thigh or abdomen. Patients should not inject into areas where the skin is tender, bruised, erythematous, or indurated.

The patient or their caregivers may self-inject Atopen after training in subcutaneous injection technique. Patients and caregivers should be instructed to read the 'Handling instructions' provided in the package leaflet before administration.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

<List of further special warnings and precautions related to the use of the medicinal substance.>

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Pregnancy

<Information related to the use of the medicinal substance in pregnant women.>

Breast-feeding

<Information related to the use of the medicinal substance in breast-feeding women.>

Fertility

<Information related to the fertility when using the medicinal substance.>

4.7 Effects on ability to drive and use machines

Atopen has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

<Description of the most frequently reported and any serious adverse reactions related to the use of the medicinal substance.>

Tabulated list of adverse reactions

Adverse reactions for atopizumab from clinical studies (Table 1) are listed by MedDRA system organ class and are based on the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000); and not known (cannot be estimated from the available data).

<Listing adverse reactions from clinical studies related to the use of the medicinal substance.>

Table 1: List of adverse reactions

System Organ Class	Adverse reactions	Frequency

Description of selected adverse reactions

<Information on specific adverse reactions which may be useful to prevent, assess or manage the occurrence of an adverse reaction in clinical practice related to the use of the medicinal substance.>

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In the event of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment be instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, interleukin inhibitors, ATC code: not yet assigned

Mechanism of action

<Information related to the mechanism of action of the medicinal substance.>

Pharmacodynamic effects

<Information related to pharmacodynamic effects of the medicinal substance.>

Clinical efficacy and safety

<Information related on the efficacy and safety outocmes of the iDDC in the pivotal trial.>

Paediatric population

<Information related on the efficacy and safety outocmes of the iDDC in clinical trials with children.>

The European Medicines Agency has deferred the obligation to submit the results of studies with atopizumab in one or more subsets of the paediatric population in the treatment of atopic dermatitis (see section 4.2. for information on paediatric use).

5.2 Pharmacokinetic properties

<Information related to the pharmacokintetics of the medicinal substance.>

Absorption

Distribution

Biotransformation

Elimination

Linearity/non-linearity

Pharmacokinetic/pharmacodynamic relationship(s)

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium acetate trihydrate
Acetic acid
Polysorbate 20
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

<Shelf life for iDDC>

2 years

6.4 Special precautions for storage

<Storage conditions for the iDDC>

Store in a refrigerator (2 – 8 °C). Do not freeze.
Keep the pre-filled pen in the outer carton in order to protect from light.

Atopen pre-filled pen may be stored out of the refrigerator (up to a maximum of 25 °C) for up to 24 hours in the original carton to protect from light.

6.5 Nature and contents of container

<Relevant information for the iDDC>

Pre-filled glas syringe assembled in a pre-filled pen with an automatic needle sleeve.

6.6 Special precautions for disposal and other handling

<Relevant information for the safe use of the iDDC>

Before injecting, patients should remove the carton from the refrigerator and allow to reach room temperature out of direct sunlight (for 30 to 90 minutes) without removing the pre-filled pen from the carton.

The solution should be blue and clear to slightly opalescent.

Prior to use, a visual inspection of the pre-filled pen is recommended. The solution may contain a few translucent to white product-related particles. Atopen should not be used if the solution is cloudy or discoloured, or contains large particles. Do not shake the pre-filled pen.

Comprehensive handling instructions are provided in the package leaflet.

Each pre-filled pen is for single use only.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

PHARMACompany GmbH
Industrial Street 123
45678 Manufacturing Village
Germany

8. MARKETING AUTHORISATION NUMBER(S)

<Marketing authorisation number assigned by EMA for the iDDC.>

EU/1/12/345/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 January 2023

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

PHARMACompany GmbH
Industrial Street 123
45678 Manufacturing Village
Germany

Name and address of the manufacturer responsible for batch release

PHARMACompany GmbH
Industrial Street 123
45678 Manufacturing Village
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING[****]

[****] Shaded text can be used by applicants to highlight text which will not be printed in the actual SmPC, PL or label. Its use should be limited. https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/quality-review-documents-qrd-convention-be-followed-european-medicines-agency-qrd-templates_en.pdf (site accessed 09 Jan 2023)

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Atopen 100 mg solution for injection in pre-filled pen
atopizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One pre-filled pen contains 100 mg atopizumab in 1 mL.

3. LIST OF EXCIPIENTS

Excipients: sodium acetate trihydrate, acetic acid, polysorbate 20, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

solution for injection
1 pre-filled pen

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use
For single use only.

For more information and support on Atopen go to www.atopen.eu or scan this code.
QR code to be included

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

<Optional section to include any specific important information for use needed to know prior opening the outer carton and reading the package leaflet which includes the handling instructions.>

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

Keep the pre-filled pen in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

PHARMACompany GmbH
Industrial Street 123
45678 Manufacturing Village
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/345/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Atopen 100 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA††††

PC
SN
NN

†††† PC: product code, SN: serial number, NN: national reimbursement number or other national number identifying the medicinal product. Part of the variable data and will be printed on each outer carton.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED PEN LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Atopen 100 mg injection
atopizumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Atopen 100 mg solution for injection in pre-filled pen
atopizumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you or your child.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you or your child only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours or your childs.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Atopen is and what it is used for
2. What you need to know before you use Atopen
3. How to use Atopen
4. Possible side effects
5. How to store Atopen
6. Contents of the pack and other information

1. What Atopen is and what it is used for

<Information how the medicinal substance works and can improve the quality of life of the patient. The package leaflet is written in lay language to be understood by the patient and caregivers.>

Atopen contains the active substance atopizumab. Atopen is used to treat the inflammatory disease atopic dermatitis.

How Atopen works
This medicine works by stopping a protein called IL-X, which causes inflammation.

Atopen is used to treat adults and adolescents with moderate to severe atopic dermatitis. Atopen reduces inflammation and can therefore help to reduce symptoms of atopic dermatitis such as itching, redness, swollen, and cracked skin[‡‡‡‡].

2. What you need to know before you use Atopen

Do not use Atopen
- if you are allergic to atopizumab or any of the other ingredients of this medicine (listed in section 6). If you think you may be allergic, ask your doctor for advice.
- *<Further information in consisteny with section 4.3 Contraindications of the SmPC in lay language.>*

Warnings and precautions
Talk to your doctor, pharmacist or nurse before and during the use of Atopen:
- *<Further information in consisteny with section 4.4 Special warnings and precautions of the SmPC in lay language.>*

[‡‡‡‡] Symptoms of atopic dermatitis: https://en.wikipedia.org/wiki/Atopic_dermatitis (site accessed 09 Jan 2023)

Allergic reactions
Seek medical help immediately if you notice any signs of an allergic reaction while you are taking Atopen such as:
- Difficulty breathing or swallowing
- Swelling of the face, lips, tongue or throat
- Severe itching of the skin, with a red rash or rasied bumps.

Children and adolescents
Atopen is not recommended for children under 12 years of age. This is because Atopen has not been studied in this age group.

Other medicines and Atopen
Tell your doctor, pharmacist or nurse:
- if you are using, have recently used or might use any other medicines.
- *<Further information in consisteny with section 4.5 Interactions of the SmPC in lay language.>*

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

<Further information in consisteny with section 4.6 Fertility, pregnancy and lactation of the SmPC in lay language.>

Driving and using machines
Atopen is not likely to affect your driving and use of machines.

3. How to use Atopen

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

This medicine is given as an injection under your skin (called a 'subcutaneous injection').

How much Atopen to use

Each dose is 100 mg given as a single injection. After the first dose, you will have the next doses every 4 weeks.

You and your doctor, pharmacist or nurse will decide if you should inject this medicine yourself or your child. Do not inject yourself or your child with this medicine unless you have been trained by your doctor, pharmacist or nurse. A caregiver may also give your injection after they have been trained.

Read the 'instructions on how to use Atopen' at the end of this leaflet before injecting Atopen yourself.

If you use more Atopen than you should
If you have used more Atopen than you should or the dose has been given sooner than prescribed, talk to your doctor.

If you forget to use Atopen
If you forget to use Atopen, inject a dose as soon as you remember, talk to your doctor if you are not sure what to do.

If you stop using Atopen
Do not stop using Atopen without talking to your doctor first. If you stop treatment, your symptoms may come back.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
<Further information in consisteny with section 4.8 Undesirable effects of the SmPC in lay language.>

Your doctor will decide if you can keep using Atopen.

Other side effects
Tell your doctor, pharmacist or nurse if you get any of the following side effects.
<Further information in consisteny with section 4.8 Undesirable effects of the SmPC in lay language.>

Very common: may affect more than 1 in 10 people
- …

Common: may affect up to 1 in 10 people
- …

Uncommon: may affect up to 1 in 100 people
- …

Rare: may affect up to 1 in 1,000 people
- …

Very rare: may affect up to 1 in 10,000 people
- …

Not known: frequency cannot be estimated from the available data
- …

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Atopen

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the pre-filled pen label and outer carton after 'EXP'. The expiry date refers to the last day of that month.
- Store in a refrigerator (2 – 8 °C). Do not freeze.
- Keep the pre-filled pen in the original carton in order to protect from light.
- If needed, you may also store the pre-filled pen out of the refrigerator (up to a maximum of 25 °C) for up to 24 hours in the original carton to protect from light.
- Do not use this medicine if the liquid is cloudy or contains flakes or large particles.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Atopen contains
- The active substance is atopizumab. Each pre-filled pen contains 100 mg of atopizumab in 1 mL solution.
- The other ingredients are sodium acetate trihydrate, acetic acid, polysorbate 20, and water for injections.

What Atopen looks like and contents of the pack
Atopen is a blue and clear to slightly opalescent liquid in a pre-filled pen. The liquid may contain tiny white or clear particles.

Each pack contains 1 pre-filled pen.

Marketing Authorisation Holder and Manufacturer
PHARMACompany GmbH
Industrial Street 123
45678 Manufacturing Village
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
{Nom/Naam/Name}
Tél/Tel: +{N° de téléphone/Telefoonnummer/ Telefonnummer}

България
{Име}
Тел.: +{Телефонен номер}

Česká republika
{Název}
Tel: +{telefonní číslo}

Lietuva
{pavadinimas}
Tel: + {telefono numeris}

Luxembourg/Luxemburg
{Nom}
Tél/Tel: +{N° de téléphone/Telefonnummer}

Magyarország
{Név}
Tel.: +{Telefonszám}

Danmark
{Navn}
Tlf: +{Telefonnummer}

Deutschland
{Name}
Tel: +{Telefonnummer}

Eesti
{Nimi}
Tel: +{Telefoninumber}

Ελλάδα
{Όνομα}
Τηλ: +{Αριθμός τηλεφώνου}

España
{Nombre}
Tel: +{Teléfono}

France
{Nom}
Tél: +{Numéro de téléphone}

Hrvatska
{Ime}
Tel: +{Telefonski broj}

Ireland
{Name}
Tel: +{Telephone number}

Ísland
{Nafn}
Sími: +{Símanúmer}

Italia
{Nome}
Tel: +{Numero di telefono}

Κύπρος
{Όνομα}
Τηλ: +{Αριθμός τηλεφώνου}

Latvija
{Nosaukums}
Tel: +{telefona numurs}

Malta
{Isem}
Tel: +{Numru tat-telefon}

Nederland
{Naam}
Tel: +{Telefoonnummer}

Norge
{Navn}
Tlf: +{Telefonnummer}

Österreich
{Name}
Tel: +{Telefonnummer}

Polska
{Nazwa/ Nazwisko}
Tel.: +{Numer telefonu}

Portugal
{Nome}
Tel: +{Número de telefone}

România
{Nume}
Tel: +{Număr de telefon}

Slovenija
{Ime}
Tel: +{telefonska številka}

Slovenská republika
{Názov}
Tel: +{Telefónne číslo}

Suomi/Finland
{Nimi/Namn}
Puh/Tel: +{Puhelinnumero/Telefonnummer}

Sverige
{Namn}
Tel: +{Telefonnummer}

United Kingdom (Northern Ireland)
{Name}
Tel: +{Telephone number}

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Detailed and updated information on this product us available by scanning the QR code included below or on the outer carton with a smartphone. The same information is also available at the following URL: www.atopen.eu.

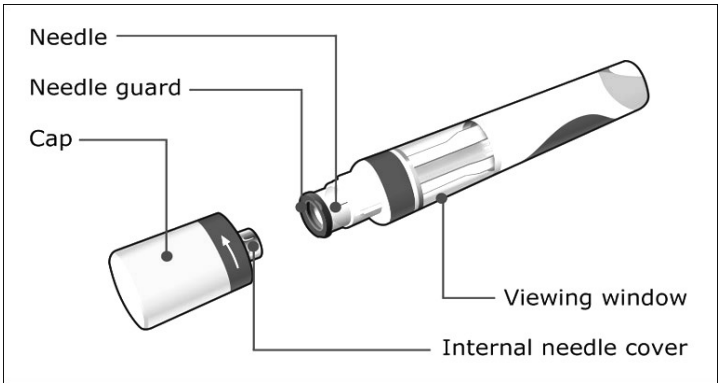
QR code to be included

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

Instructions on how to use Atopen[§§§§]
<Information and instructions for the user how to safely and effectively use the iDDC. Information is based on the development of the medical device and in consistency with information included in the SmPC.>

Please read all of section 'handling instructions' before using Atopen.

Atopen pre-filled pen
<Schematic drawing of the iDDC, i.e. pre-filled pen, describing the single parts of the device.>[*****]



Important information to know before you inject Atopen
- You should receive training on how ot inject Atopen before giving yourself or your child an injection. Talk to your doctor, pharmacist or nurse if you need help.
- Mark the dates on your calendar so you know when to inject Atopen.
- Keep Atopen in the original carton to protect the medicine from light until it is time to use it.
- Take the carton out of the refrigerator and leave it at room temperature, out of direct sunlight, for **30 to 90 minutes** before injecting.
- **Do not** inject of the liquid in the inspection window is cloudy or contains flakes or large particles. The liquid should look clear blue and may contain tiny white or clear particles.
- **Do not** shake the pre-filled pen.
- *<Further important information for the user how to safely and effectively use the pre-filled pen.>*

Return this medicine to the pharmacy
- if the expiry date (EXP) has passed.
- if the liquid has ever been frozen (even if thawed).
- if the pre-filled pen has been dropped or damaged.

[§§§§] This section is not included in the current QRD template 10.3. In the current QRD template additional information intended for healthcare professionals only is considered.
[*****] Taken from https://www.erelzi.eu/home/sensoreadypen/ (site accessed 09 Jan 2023)

- if the carton perforations are broken.

Follow the steps below each time you use Atopen

Step 1 <*Placeholder schematic illustration*>	**Preparing the pre-filled syringe** Take the carton out of the refrigerator and leave it at room temperature for **30 to 90 minutes** before injecting. • **Do not** remove the pre-filled pen from the carton allowing Atopen to reach room temperature. • **Do not** warm Atopen in any other way. For example, **do not** warm it in a microwave or in hot water. • **Do not** use the pre-filled pen if liquid has been frozen, even if it has been thawed.
Step 2 <*Placeholder schematic illustration*>	**Gathering the supplies** Place the following items on a clean, flat surface: • 1 pre-filled pen (not included in the carton) • 1 alcohol pad (not included in the carton) • 1 cotton ball or gauze pad (not included in the carton) • Special disposal container (not included in the carton) Wash and dry your hands.
Step 3 <*Placeholder schematic illustration*>	**Choosing an injection site** Choose from these areas to inject • thigh • your belly (abdomen) at least 5 cm from your belly button (navel)
Step 4 <*Placeholder schematic illustration*>	**Cleaning the injection site** Before the injection, wipe where you will inject in a circular motion with an alcohol pad. • **Do not** touch or blow on the injection site after it is cleaned. Allow the skin to dry before injecting. • **Do not** inject through clothes. • **Do not** inject into skin that is sore, bruised or red. • **Do not** inject into areas that are affected by atopic dermatitis.
Step 5 <*Placeholder schematic illustration*>	**Inspecting the pre-filled pen** Check the liquid through the inspection window. • It is normal to see bubbles in the liquid. • The liquid should look clear blue and may contain white or clear particles. • **Do not** use if the liquid is cloudy or contains flakes or large particles.
Step 6 <*Placeholder schematic illustration*>	**Removing the cap** Hold the pre-filled pen as shown. • Pull the cap straight off. • Throw the cap away.
Before injecting, review steps 7 ot 10 to learn the correct way to inject. <u>*Important:*</u> **Do not** move the pre-filled pen while injecting or when removing the needle from your skin.	
Step 7 <*Placeholder schematic illustration*>	**Pinch the skin** Hold the pre-filled pen so that the side with the needle points toward the injection site. Gently pinch the skin at your injection site to make a raised area and hold it firmly. Place the pre-filled pen straight (90° angle) against the raised injection site.

Step 8 <*Placeholder schematic illustration*>	**Injecting Atopen** Hold the pre-filled pen so that you can see the viewing window. Push and keep pressing the pre-filled pen down against the raised injection site. Press the activator button and hold the pre-filled pen for 15 seconds. A loud 'click' means the start of the injection.
Step 9 <*Placeholder schematic illustration*>	**Completion of the injection** Keep pressing the pre-filled pen down against the injection site. The injection is complete when the pre-filled pen has made a second 'click'. This takes **up to 15 seconds**.
Step 10 <*Placeholder schematic illustration*>	**Removing the pre-filled pen** When the injection is complete, slowly pull the empty pen out from the skin. The inserted needle cover will cover the needle tip and make another 'click'. After completing the injection, place a cotton ball or gauze pad on the skin at the injection site. • **Do not** rub the injection site. • Slight bleeding at the injection site is normal.
Step 11 <*Placeholder schematic illustration*>	**Disposal of the pen** Throw away the used pen in a special disposal container straight after use. • **Do not** throw away the used pen in the household waste. • Your doctor, pharmacist or nurse will tell you how to return the full special disposal container.

Appendix XII: Case study – EU PI for a co-packaged DDC[††††‡‡‡‡‡]

Creation of an EU PI for a co-packaged DDC regulated as a medicinal product

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

[†††††] EU PI is based on QRD template version 10.3, 09/2022

[‡‡‡‡‡] The example was created considering the current QRD template, SmPC guideline, Regulation (EU) 2017/745, Directive 2001/83/EC, and the approved Enerzair Breezhaler EU PI (https://www.ema.europa.eu/en/documents/product-information/enerzair-breezhaler-epar-product-information_en.pdf; site accessed 09 Jan 2023). This is a fictitious example. Any resemblance to an approved medicinal product or a medicinal product in development is purely coincidental.

1. NAME OF THE MEDICINAL PRODUCT

BreathAIR Inhaler 100 micrograms inhalation powder, hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 120 mcg bronchisone furoate.

Each delivered dose (the dose that leaves the mouthpiece of the inhaler) contains 100 mcg bronchisone furoate.

Excipient(s) with known effect

Each capsule contains 20 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Inhalation powder, hard capsule (inhalation powder)

Capsules with blue cap and uncoloured transparent body containing a white powder. The product logo and the product code ‘BAI100’ are printed in black on the body.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BreathAIR Inhaler is indicated for the treatment of moderate to severe asthma in adult patients.

4.2 Posology and method of administration

Posology

The recommended dose is 1 capsule to be inhaled once daily.

The maximum recommended dose is 100 mcg bronchisone furoate once daily.

Treatment should be administered at the same time of the day each day. It can be administered irrespective of the time of the day.

Missed dose

If a dose is missed, it should be taken as soon as possible. Patients should be instructed not to take more than one dose in a day.

Special populations

Paediatric population

The safety and efficacy of bronchisone furoate in paediatric patients below 18 years of age have not yet been established. No data are available.

Elderly

No dose adjustment is required in elderly patients (see section 5.2).

Renal and / or hepatic impairment

No dose adjustment is required in patients with mild to moderate renal and/or hepatic impairment. No data is available in patients with severe renal and/or hepatic impairment. Therefore, the use in these patients is not recommended (see section 5.2).

Method of administration

For inhalation use only. The capsules must not be swallowed.

The capsules must be administered only using the inhaler provided (see section 6.6) with each new prescription.

Patients should be instructed on how to administer the medicinal product correctly. Patients who do not experience improvement in breathing should be asked if they are swallowing the medicinal product rather than inhaling it.

The capsules must only be removed from the blister immediately before use.

After inhalation, patients should rinse their mouth with water without swallowing (see sections 4.4 and 6.6).

For handling instructions of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Deterioration of disease

This medicinal product should not be used to treat acute asthma symptoms for which a short-acting bronchodilator is required.

Patients should not stop treatment without physician supervision since symptoms may recur after discontinuation.

It is recommended that treatment with this medicinal product should not be stopped abruptly. If patients find the treatment ineffective, they should continue treatment but must seek medical attention. Increasing use of reliever bronchodilators indicates a worsening of the underlying condition and warrants a reassessment of the therapy. Sudden and progressive deterioration in the symptoms of asthma is potentially life-threatening and the patient should undergo urgent medical assessment.

<List of further special warnings and precautions related to the use of the medicinal substance.>

Excipients

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

<Information related to the use of the medicinal substance in combination with other substances based on interaction studies performed.>

4.6 Fertility, pregnancy and lactation

Pregnancy

<Information related to the use of the medicinal substance in pregnant women.>

Breast-feeding

<Information related to the use of the medicinal substance in breast-feeding women.>

Fertility

<Information related to the fertility when using the medicinal substance.>

4.7 Effects on ability to drive and use machines

Atopen has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

<Describing the most frequently reported and any serious adverse reactions related to the use of the medicinal substance.>

Tabulated list of adverse reactions

Adverse reactions for bronchisone furoate from clinical studies (Table 1) are listed by MedDRA system organ class and are based on the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000); and not known (cannot be estimated from the available data).

<Listing adverse reactions from clinical studies related to the use of the medicinal substance.>

Table 1: List of adverse reactions

System Organ Class	Adverse reactions	Frequency

Description of selected adverse reactions

<Information on specific adverse reactions which may be useful to prevent, assess or manage the occurrence of an adverse reaction in clinical practice related to the use of the medicinal substance.>

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In the event of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment be instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for obstructive airways diseases, ATC code: not yet assigned

Mechanism of action

<Information related to the mechanism of action of the medicinal substance.>

Pharmacodynamic effects

<Information related to pharmacodynamic effects of the medicinal substance.>

Clinical efficacy and safety

<Information related on the efficacy and safety outocmes of the medicinal substance in the pivotal trial.>

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with bronchisone furoate in one or more subsets of the paediatric population in the treatment of asthma (see section 4.2. for information on paediatric use).

5.2 Pharmacokinetic properties

<Information related to the pharmacokintetics of the medicinal substance.>

Absorption

Distribution

Biotransformation

Elimination

Linearity/non-linearity

Pharmacokinetic/pharmacodynamic relationship(s)

5.3 Preclinical safety data

<Information related to the non-clinical data of the medicinal substance, including safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.>

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents

Lactose monohydrate
Magnesium stearate

Capsule shell

Hypromellose
Titanium dioxide
Printing ink

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 30 °C.

Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

<Description of the material the inhaler is made of.>

Perforated aluminium unit-dose blister. Each blister contains 10 hard capsules.

Single pack containing 10 x 1, 30 x 1 or 90 x 1 hard capsules, together with 1 inhaler.

6.6 Special precautions for disposal and other handling

<Relevant information for the safe use of the DDC>

The inhaler provided with each new prescription should be used. The inhaler in each pack should be disposed of after all capsules in that pack have been used.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

For details on the handling instructions please refer to the package leaflet.

7. MARKETING AUTHORISATION HOLDER

PHARMACompany GmbH
Industrial Street 123
45678 Manufacturing Village
Germany

8. MARKETING AUTHORISATION NUMBER(S)

<Marketing authorisation number assigned by EMA for the DDC.>

EU/1/12/678/001
EU/1/12/678/002
EU/1/12/678/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 January 2023

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

PHARMACompany GmbH
Industrial Street 123
45678 Manufacturing Village
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING§§§§§

§§§§§ Shaded text can be used by applicants to highlight text which will not be printed in the actual SmPC, PL or label. Its use should be limited. https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/quality-review-documents-qrd-convention-be-followed-european-medicines-agency-qrd-templates_en.pdf (site accessed 09 Jan 2023)

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

BreathAIR Inhaler 100 micrograms inhalation powder, hard capsules
bronchisone furoate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each delivered dose contains 100 micrograms bronchisone furoate.

3. LIST OF EXCIPIENTS

Excipients: lactose, magnesium stearate. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Inhalation powder, hard capsule

10 x 1 capsules + 1 inhaler
30 x 1 capsules + 1 inhaler
90 x 1 capsules + 1 inhaler

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For use only with the inhaler provided in the pack.
Do not swallow the capsules.
Inhalation use.

For more information and support on BreathAIR Inhaler go to www.breathair-inhaler.eu or scan this code.
QR code to be included

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

<Optinal section to include any specific important information for use prior opening the outer carton and reading the package leaflet which includes the handling instructions.>

8. EXPIRY DATE

EXP
The inhaler in each pack should be disposed of after all capsules in that pack have been used.

9. SPECIAL STORAGE CONDITIONS

Do not store above 30 °C.
Store in the original package in order to protect from light and moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

PHARMACompany GmbH
Industrial Street 123
45678 Manufacturing Village
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/678/001	10 x 1 capsules + 1 inhaler
EU/1/12/678/002	30 x 1 capsules + 1 inhaler
EU/1/12/678/003	90 x 1 capsules + 1 inhaler

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

BreathAIR Inhaler

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA******

PC
SN
NN

******PC: product code, SN: serial number, NN: national reimbursement number or other national number identifying the medicinal product. Part of the variable data and will be printed on each outer carton.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER LID OF OUTER CARTON OF UNIT PACK

1. OTHER

<Short description how to prepare the inhaler for the inhalation and how to perform the inhalation.>

1 Insert
2 Pierce and release
3 Inhale deeply
4 Check capsule is empty

Read the package leaflet before use.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

BreathAIR Inhaler 100 micrograms inhalation powder, hard capsules
bronchisone furoate

2. NAME OF THE MARKETING AUTHORISATION HOLDER

PHARMACompany GmbH

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Inhalation use only

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

BreathAIR Inhaler 100 micrograms inhalation powder, hard capsules
bronchisone furoate

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What BreathAIR Inhaler is and what it is used for
2. What you need to know before you use BreathAIR Inhaler
3. How to use BreathAIR Inhaler
4. Possible side effects
5. How to store BreathAIR Inhaler
6. Contents of the pack and other information

1. What BreathAIR Inhaler is and what it is used for

<Information how the medicinal substance works and can improve the quality of life of the patient.The package leaflet is written in lay language to be understood by the patient.>

BreathAIR Inhaler contains the active substance bronchisone furoate. BreathAIR Inhaler is used to treat asthma.

Asthma is a serious, long-term lung disease where the muscles around the smaller airways become tight (bronchoconstriction) and inflamed. Symptoms come and go and include shortness of breath, wheezing, chest tightness and cough.

How BreathAIR Inhaler works
This medicine belongs to a group of medicines called corticosteroids (or steroids).

Corticosteroids reduce the swelling and irritation (inflammation) in the small airways in the lungs and so gradually ease breathing problems. Corticosteroids also help to prevent attacks of asthma.

2. What you need to know before you use BreathAIR Inhaler

Do not use BreathAIR Inhaler
- if you are allergic to bronchisone furoate or any of the other ingredients of this medicine (listed in section 6). If you think you may be allergic, ask your doctor for advice.
- *<Further information in consisteny with section 4.3 Contraindications of the SmPC in lay language.>*

Warnings and precautions
Talk to your doctor, pharmacist or nurse before and during the use of BreathAIR Inhaler:
- *<Further information in consisteny with section 4.4 Special warnings and precautions of the SmPC in lay language.>*

Children and adolescents
Do not give this medicine to children or adolescents (below the age of 18 years) because it has not been studied in this age group.

Other medicines and BreathAIR Inhaler
Tell your doctor, pharmacist or nurse:
- if you are using, have recently used or might use any other medicines.
- *<Further information in consisteny with section 4.5 Interactions of the SmPC in lay language.>*

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. Your doctor will discuss with you whether you can use BreathAIR Inhaler.

<Further information in consisteny with section 4.6 Fertility, pregnancy and lactation of the SmPC in lay language.>

Driving and using machines
It is unlikely that this medicine will affect your ability to drive and use machines.

BreathAIR Inhaler contains lactose
This medicine contains about 20 mg of lactose per capsule. If you have been told by your doctor that you have an intolerance to some sugars, speak with your doctor before taking this medicine.

3. How to use BreathAIR Inhaler

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

How much BreathAIR Inhaler to inhale
The usual dose is to inhale the content of one capsule each day. You only need to use the medicine once a day. Do not use more than your doctor tells you to use.

You should use BreathAIR Inhaler every day, even when your asthma is not troubling you.

When to inhale BreathAIR Inhaler
Inhale BreathAIR Inhaler at the same time each day. This will help control your symptoms throughout the day and night. It will also help you to remember to use it.

How to inhale BreathAIR Inhaler
- BreathAIR Inhaler is for inhalation use.
- In this pack, you will find an inhaler and capsules that contain the medicine. The inhaler enables you to inhale the medicine in the capsule. Only use the capsules with the inhaler provided in this pack. The capsules should remain in the blister until you need to use them.
- Peel the backing away from the blister to open it, do not push the capsule through the foil.
- When you start a new pack, use the new inhaler supplied in this new pack.
- Dispose of the inhaler in each pack after all capsules in that pack have been used.
- Do not swallow the capsules.
- **Please read the instructions on how to use the BreathAIR Inhaler at the end of this leaflet before you start using BreathAIR Inhaler.**

If your symptoms do not improve
If your asthma is not getting better or if it gets worse after you have started using BreathAIR Inhaler, talk to your doctor.

If you use more BreathAIR Inhaler than you should
If you accidently inhale too much of this medicine, contact your doctor or hospital for advice immediately. You may need medical attention.

If you forget to use BreathAIR Inhaler
If you forget to inhale a dose at the usual time, inhale one as soon as possible on that day. Then inhale the next dose at the usual time on the next day. Do not inhale two doses on the same day.

If you stop using BreathAIR Inhaler
Do not stop using BreathAIR Inhaler unless your doctor tells you to. Your asthma symptoms may come back if you stop using it.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Stop using BreathAIR Inhaler and get medical help immediately if you have any of the following:

<Further information in consisteny with section 4.8 Undesirable effects of the SmPC in lay language.>

Other side effects
Tell your doctor, pharmacist or nurse if you get any of the following side effects.
<Further information in consisteny with section 4.8 Undesirable effects of the SmPC in lay language.>

Very common: may affect more than 1 in 10 people
- …

Common: may affect up to 1 in 10 people
- …

Uncommon: may affect up to 1 in 100 people
- …

Rare: may affect up to 1 in 1,000 people
- …

Very rare: may affect up to 1 in 10,000 people
- …

Not known: frequency cannot be estimated from the available data
- …

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store BreathAIR Inhaler

– Keep this medicine out of the sight and reach of children.
– Do not use this medicine after the expiry date which is stated on the carton and blister after 'EXP'. The expiry date refers to the last day of that month.
– Do not store above 30 °C.
– Store the capsules in the original blister, in order to protect from light and moisture, and do not remove until immediately before use.
– Do not throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What BreathAIR Inhaler contains
- The active substance is bronchisone furoate. Each hard capsule contains 120 micrograms bronchisone furoate. Each delivered dose (the dose that leaves the mouthpiece of the inhaler) contains 100 micrograms bronchisone furoate.
- The other ingredients are lactose monohydrate and magnesium stearate (see "BreathAIR Inhaler contains lactose" in section 2).

What BreathAIR Inhaler looks like and contents of the pack
In this pack, you will find an inhaler together with capsules in blisters. The capsules have a blue cap and a transparent body and contain a white powder. They have a black product logo and product code 'BAI100' printed on the body.

The following pack sizes are available:
Single pack containing 10 x 1, 30 x 1 or 90 x 1 hard capsules, together with 1 inhaler.

Marketing Authorisation Holder and Manufacturer
PHARMACompany GmbH
Industrial Street 123
45678 Manufacturing Village
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
{Nom/Naam/Name}
Tél/Tel: +{N° de téléphone/Telefoonnummer/ Telefonnummer}

Lietuva
{pavadinimas}
Tel: + {telefono numeris}

България
{Име}
Тел.: +{Телефонен номер}

Česká republika
{Název}
Tel: +{telefonní číslo}

Danmark
{Navn}
Tlf: +{Telefonnummer}

Deutschland
{Name}
Tel: +{Telefonnummer}

Eesti
{Nimi}
Tel: +{Telefoninumber}

Ελλάδα
{Όνομα}
Τηλ: +{Αριθμός τηλεφώνου}

España
{Nombre}
Tel: +{Teléfono}

France
{Nom}
Tél: +{Numéro de téléphone}

Hrvatska
{Ime}
Tel: +{Telefonski broj}

Ireland
{Name}
Tel: +{Telephone number}

Ísland
{Nafn}
Sími: +{Símanúmer}

Italia
{Nome}
Tel: +{Numero di telefono}

Κύπρος
{Όνομα}
Τηλ: +{Αριθμός τηλεφώνου}

Latvija
{Nosaukums}
Tel: +{telefona numurs}

Luxembourg/Luxemburg
{Nom}
Tél/Tel: +{N° de téléphone/Telefonnummer}

Magyarország
{Név}
Tel.: +{Telefonszám}

Malta
{Isem}
Tel: +{Numru tat-telefon}

Nederland
{Naam}
Tel: +{Telefoonnummer}

Norge
{Navn}
Tlf: +{Telefonnummer}

Österreich
{Name}
Tel: +{Telefonnummer}

Polska
{Nazwa/ Nazwisko}
Tel.: +{Numer telefonu}

Portugal
{Nome}
Tel: +{Número de telefone}

România
{Nume}
Tel: +{Număr de telefon}

Slovenija
{Ime}
Tel: +{telefonska številka}

Slovenská republika
{Názov}
Tel: +{Telefónne číslo}

Suomi/Finland
{Nimi/Namn}
Puh/Tel: +{Puhelinnumero/Telefonnummer}

Sverige
{Namn}
Tel: +{Telefonnummer}

United Kingdom (Northern Ireland)
{Name}
Tel: +{Telephone number}

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Detailed and updated information on this product us available by scanning the QR code included below or on the outer carton with a smartphone. The same information is also available at the following URL: www.breathair-inhaler.eu.

QR code to be included

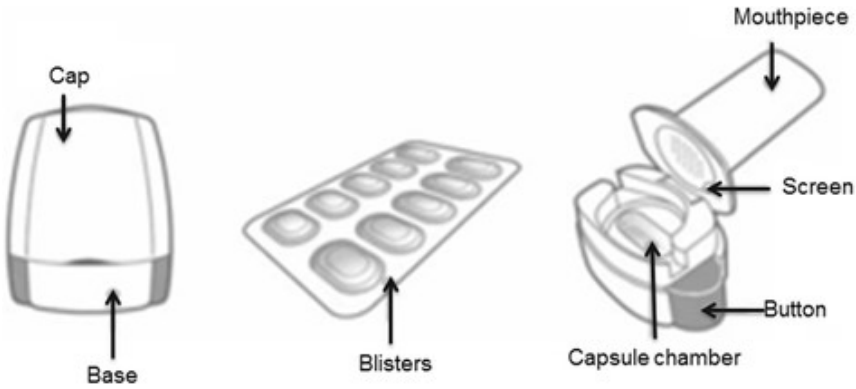
This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

Instructions on how to use the BreathAIR Inhaler[††††††]
<Information and instructions for the user how to safely and effectively use the DDC. Information is based on the development of the medical device and in consistency with information included in the SmPC.>

Please read all of section 'handling instructions' before using BreathAIR Inhaler.

BreathAIR Inhaler
Your BreathAIR Inhaler pack contains:
- One BreathAIR Inhaler
- One or more blister cards, each containing 10 BreathAIR Inhaler capsules to be used in the inhaler

<Schematic drawing of the DDC, i.e. dry powder inhaler, describing the single parts of the device.>[‡‡‡‡‡‡]



[††††††] This section is not included in the current QRD template 10.3. In the current QRD template additional information intended for healthcare professionals only is considered.
[‡‡‡‡‡‡] Taken from https://link.springer.com/article/10.1186/s40248-017-0092-5/figures/3 (site accessed 11 Jan 2023)

Important information to know before you inject BreathAIR Inhaler

- BreathAIR Inhaler capsules must always be stored in the blister card and only removed immediately before use.
- **Do not** push the capsule through the foil to remove it from the blister.
- **Do not** swallow the capsule.
- **Do not** use the BreathAIR Inhaler capsules with any other inhaler.
- **Do not** use BreathAIR Inhaler to take any other capsule medicine.
- Never place the capsule into your mouth or the mouthpiece of the inhaler.
- **Do not** blow into the mouthpiece.
- **Do not** handle capsules with wet hands.
- Never wash your inhaler with water.
- *<Further important information for the user how to safely and effectively use the inhaler.>*

Return this medicine to the pharmacy

- if the expiry date (EXP) has passed.

Follow the steps below each time you use BreathAIR Inhaler

Step 1 *<Placeholder schematic illustration>*	**Insert the capsule**
Step 1a *<Placeholder schematic illustration>*	**Pull off the cap**
Step 1b *<Placeholder schematic illustration>*	**Open the inhaler**
Step 1c *<Placeholder schematic illustration>*	**Remove capsule** • Separate one of the blisters from the blister card. • Peel open the blister and remove the capsule. • **Do not** push the capsule through the foil. • **Do not** swallow the capsule.
Step 1d *<Placeholder schematic illustration>*	**Insert the capsule** • **Never** place a capsule directly into the mouthpiece.
Step 1e *<Placeholder schematic illustration>*	**Close the inhaler**
Step 2 *<Placeholder schematic illustration>*	**Pierce and release**
Step 2a *<Placeholder schematic illustration>*	**Pierce capsule once** • Hold the inhaler upright. • Pierce the capsule by firmly pressing both side buttons at the same time. • You should hear a noise as the capsule is pierced. • Only pierce the capsule once.
Step 2b *<Placeholder schematic illustration>*	**Release side buttons**
Step 3 *<Placeholder schematic illustration>*	**Inhale deeply**
Step 3a *<Placeholder schematic illustration>*	**Breath out fully** **Do not** blow into the inhaler.
Step 3b *<Placeholder schematic illustration>*	**Inhale medicine deeply** • Hold the inhaler as shown in the picture. • Place the mouthpiece in your mouth and close your lips firmly around it. • **Do not** press the side buttons. • Breathe in quickly and as deeply as you can. • During inhalation you will hear a whirring noise. • You may taste the medicine as you inhale.

Step 3c <*Placeholder schematic illustration*>	**Hold breath** • Hold your breath for up to 5 seconds.
Step 3d <*Placeholder schematic illustration*>	**Rinse mouth** Rinse your mouth with water after each dose and spit it out.
Step 4 <*Placeholder schematic illustration*>	**Check capsule is empty**
Step 4a <*Placeholder schematic illustration*>	**Check capsule is empty** • Open the inhaler to see if any powder is left in the capsule. • If there is powder left in the capsule: o Close the inhaler. o Repeat steps 3a to 3d.
Step 4b <*Placeholder schematic illustration*>	**Remove empty capsule** • Put the empty capsule in your household waste. • Close the inhaler and replace the cap.
Step 5	**Cleaning the inhaler** • Wipe the mouthpiece inside and outside with a clean, dry, lint-free cloth to remove any powder residue. • Keep the inhaler dry. • Never wash your inhaler with water.

Disposing of the inhaler after use
Each inhaler should be disposed of after all capsules have been used. Ask your pharmacist how to dispose of medicines and inhalers that are no longer required.

Appendix XIII: Proposal for a labelling template for medical devices based on the QRD template for medicinal products and the current MDR requirements.[§§§§§§]

ANNEX III

LABELLING AND INSTRUCTIONS FOR USE

[§§§§§§] The draft templates were created considering the current QRD template (version 10.3, 09/2022), SmPC guideline, and Regulation (EU) 2017/745.

A. LABELLING[*******]

[Information needs to be aligned with requirements from the current MDR, technical documentation and information in the IFU created for the medical device during development]

[*******] Shaded text can be used to highlight text which will not be printed on the actual labels or instructions for use (IFU). Its use should be limited. https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/quality-review-documents-qrd-convention-be-followed-european-medicines-agency-qrd-templates_en.pdf (site accessed 09 Jan 2023)

PARTICULARS TO APPEAR ON THE MEDICAL DEVICE LABEL[†††††††],[‡‡‡‡‡‡‡]

{NATURE/TYPE}
[In case of multipack presentations, the outer and inner labelling should be presented as separate labelling components. In cases where a product is also supplied as an individual presentation in addition to a multipack, this should be presented separately and not be combined with either the outer or inner carton label of the multipack presentation.]

1. NAME OF THE MEDICAL DEVICE

{Name or trade name}

2. INTENDED PURPOSE OF THE DEVICE

3. CONTENTS OF THE PACKAGING

[Contents by number of units of administration of the medical device (i.e. pack size, including a reference to any ancillary items included in the pack such as needles, swabs, etc.). The information should be as simple and descriptive as possible using terms used in the IFU. Grey shading can be used to avoid repetitive mentioning of already stated information in another section, e.g. name of the medical device, on the printed material.
In case of a combined labelling text covering different pack sizes, each pack size should be listed on a separate line in grey-shading,
e.g. 30 cotton balls
90 cotton balls
120 cotton balls]

[In case of multipacks presentation, please follow the below example:
On the outer carton or label: "Multipack: 180 (2 packs of 90) cotton balls."
On the inner carton: "90 cotton balls. Component of a multipack, can't be sold separately."]

4. NAME AND ADDRESS OF THE MANUFACTURER

[Including town, postal code (if available) and country name of the manufacturer in the language of the text (telephone, fax numbers or e-mail addresses may be included). If the manufacturer has its registered place of business outside the Union, the name of the authorised representative and address of the registered place of business of the authorised representative should be mentioned.]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

[†††††††] According to MDR Annex I Chapter III 23.2. Information on the label.
[‡‡‡‡‡‡‡] The medical device label includes the outer packaging or immediate packaging of a medical device.

5. SPECIAL WARNING(S)

[An indication that the device contains or incorporates a medicinal substance (including a human blood or plasma derivative), tissues or cells (or their derivatives) of human origin, or tissues or cells of animal origin (or their derivatives) as referred to in Regulation (EU) No 722/2012.]

[Information labelled in accordance with section 10.4.5. of Annex I of the MDR; substances which are carcinogenic, mutagenic or toxic to reproduction ('CMR'), of category 1A or 1B or substances having endocrine-disrupting properties for which there is scientific evidence of probable serious effects to human health and which are included in concentrations above 0,1 % weight by weight (w/w).]

6. OTHER SPECIAL WARNING(S)

[Warnings or precautions to be taken that need to be brought to the immediate attention of the user of the device, and to any other person. This information may be kept to a minimum in which case more detailed information shall appear in the IFU, taking into account the intended users.

A reference to the IFU should be made, e.g. "Read the instructions for use before use".]

7. BATCH OR SERIAL NUMBER

LOT NUMBER
or SERIAL NUMBER
or an equivalent symbol

[For active implantable devices, the serial number, and for other implantable devices, the serial number or the lot number need to be mentioned.]

8. UDI CARRIER

UDI CARRIER
or an equivalent symbol

9. EXPIRY DATE

[An unambiguous indication of the time limit for using or implanting the device safely, expressed at least in terms of year and month.
Where there is no indication of the date until when it may be used safely, the date of manufacture. This date of manufacture may be included as part of the lot number or serial number, provided the date is clearly identifiable.]

EXP

10. SPECIAL STORAGE AND/OR HANDLING CONDITIONS

11. STERILE MEDICAL DEVICES

[If the device is supplied sterile, an indication of its sterile state and the sterilisation method.]

STERILE

12. SINGLE USE

[If the device is intended for single use, an indication of that fact. If the device is a single-use device that has been reprocessed, an indication of that fact, the number of reprocessing cycles already performed, and any limitation as regards the number of reprocessing cycles.]

13. CUSTOM MADE

<Custom-made device>

14. MEDICAL DEVICE

[An indication that the device is a medical device. If the device is intended for clinical investigation only, the words 'exclusively for clinical investigation' need to be added.]

MD

<Exclusively for clinical investigation>

15. SUBSTANCES TO BE INTRODUCED INTO THE BODY OR APPLIED TO THE SKIN

[In the case of 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, the overall qualitative composition of the device and quantitative information on the main constituent or constituents responsible for achieving the principal intended action need to be mentioned.]

MINIMUM PARTICULARS TO APPEAR ON STERILE PACKAGING§§§§§§§

{NATURE/TYPE}

1. DECLARATION OF STERILITY

[An indication permitting the sterile packaging to be recognised as such and a declaration that the device is in a sterile condition.]

STERILE

2. METHOD OF STERILISATION

3. NAME AND ADDRESS OF THE MANUFACTURER

[Including town, postal code (if available) and country name of the manufacturer in the language of the text (telephone, fax numbers or e-mail addresses may be included). If the manufacturer has its registered place of business outside the Union, the name of the authorised representative and address of the registered place of business of the authorised representative should be mentioned.]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

4. DESCRIPTION OF THE DEVICE

5. MONTH AND YEAR OF MANUFACTURE

6. EXPIRY DATE

[An unambiguous indication of the time limit for using or implanting the device safely expressed at least in terms of year and month.]

EXP

§§§§§§§ According to MDR Annex I Chapter III 23.3 Information on the packaging which maintains the sterile condition of a device (‘sterile packaging’)

7. INSTRUCTIONS FOR USE

[An instruction to check the IFU for what to do if the sterile packaging is damaged or unintentionally opened before use.]

<Do not use if package is damaged and consult instructions for use.>[********]

8. OTHER INFORMATION

[If the device is intended for clinical investigations, the words 'exclusively for clinical investigations'. If the device is custom-made, the words 'custom-made device'.]

<Exclusively for clinical investigations>
<Custom-made device>

[********] https://www.bsigroup.com/globalassets/meddev/localfiles/it-it/webinars/bsi-md-symbols-and-information-to-be-provided-by-the-manufacturer-webinar.pdf (site accessed 16 Jan 2023)

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS[††††††††]

{NATURE/TYPE}

1. NAME OF THE MEDICAL DEVICE

{Name or trade name}

2. EXPIRY DATE

[An unambiguous indication of the time limit for using or implanting the device safely, expressed at least in terms of year and month.
Where there is no indication of the date until when it may be used safely, the date of manufacture. This date of manufacture may be included as part of the lot number or serial number, provided the date is clearly identifiable.]

EXP

3. BATCH OR SERIAL NUMBER

LOT or SN

[For active implantable devices, the serial number, and for other implantable devices, the serial number or the lot number need to be mentioned.]

4. UDI CARRIER

UDI

5. STERILE MEDICAL DEVICES

[If the device is supplied sterile, an indication of its sterile state.]

STERILE

[††††††††] According to MDR Annex I 23.1.b "*The information required on the label shall be provided on the device itself. If this is not practicable or appropriate, some or all of the information may appear on the packaging for each unit, and/or on the packaging of multiple devices.*" In case of space constraints this is a proposal for information which should be applied to the device directly.

6. MEDICAL DEVICE

[An indication that the device is a medical device.]

MD

7. SPECIAL WARNING(S)

[An indication that the device contains or incorporates a medicinal substance (including a human blood or plasma derivative), tissues or cells (or their derivatives) of human origin, or tissues or cells of animal origin (or their derivatives) as referred to in Regulation (EU) No 722/2012.]

[Information labelled in accordance with section 10.4.5. of the MDR; substances which are carcinogenic, mutagenic or toxic to reproduction ('CMR'), of category 1A or 1B or substances having endocrine-disrupting properties for which there is scientific evidence of probable serious effects to human health and which are included in concentrations above 0,1 % weight by weight (w/w)]

B. INSTRUCTIONS FOR USE

Instructions for use: Information for the user

{Name or trade name of the medical device}

Read all of this instructions for use carefully before you start using this medical device because it contains important information for you.

- Keep this instructions for use. You may need to read it again.
- If you have any further questions, ask your healthcare professional.
- This medical device has been <prescribed for> <given to> you only. Do not pass it on to others. It may harm them.
- If you get any side effects or experience serious incidents using the medical device, talk to your healthcare professional. This includes any possible side effects or serious incidents not listed in this leaflet. See section 4.

What is in this instructions for use

1. What <X> is and what it is used for
2. What you need to know before you use <X>
3. How to use <X>
4. Possible side effects or serious incidents
5. How to store <X>
6. Contents of the pack and other information

1. What <X> is and what it is used for

[A description of the device's intended purpose, the performance characteristics of the device, information allowing the healthcare professional to verify if the device is suitable, indications, the patient target group or groups, and of the intended users, and where applicable, a specification of the clinical benefits to be expected.]

[For devices with no intended medical purpose, information regarding the absence of a clinical benefit.]

[Addition of a schematic drawing of the medical device describing the single parts of the device.]

2. What you need to know before you use <X>

[Information if the device is intended for single use, an indication of that fact. A manufacturer's indication of single use shall be consistent across the Union.]

[Any requirements for special facilities, or special training, or particular qualifications of the device user and/or other person.]

[If the device is supplied sterile, instructions in the event of the sterile packaging being damaged or unintentionally opened before use.]

[An indication, if appropriate, that a device can be reused only if it is reconditioned under the responsibility of the manufacturer to comply with the general safety and performance requirements.]

[Description of any residual risks, contraindications, measures to be taken and limitations of use regarding the device, including information to be conveyed to the patient in this regard.]

[For devices intended for use by lay persons, the circumstances in which the user should consult a healthcare professional need to be listed.]

[For devices with no intended medical purpose, information regarding the risks related to use of the device.]

Do not use <X>
[If the device is reusable, information shall be provided to identify when the device should no longer be reused, e.g. signs of material degradation or the maximum number of allowable reuses.]

[In the case of devices that are composed of substances or of combinations of substances that are intended to be introduced into the human body and that are absorbed by or locally dispersed in the human body contraindications related to these substances need to be listed.]

Talk to your healthcare professional
- <if you are allergic to {active substance(s)} or any of the other ingredients of this medical device (listed in section 6).> *[include reference to residues, if applicable.]* <If you think you may be allergic, ask your healthcare professional for advice.>

Warnings and precautions
[Warnings, precautions and/or measures to be taken in the event of malfunction of the device or changes in its performance that may affect the safety,
- *warnings, precautions and/or measures to be taken as regards the exposure to reasonably foreseeable external influences or environmental conditions, such as magnetic fields, external electrical and electromagnetic effects, electrostatic discharge, radiation associated with diagnostic or therapeutic procedures, pressure, humidity, or temperature,*
- *warnings, precautions and/or measures to be taken as regards the risks of interference posed by the reasonably foreseeable presence of the device during specific diagnostic investigations, evaluations, or therapeutic treatment or other procedures such as electromagnetic interference emitted by the device affecting other equipment,*
- *warnings, precautions and/or limitations related to the medicinal substance or biological material that is incorporated into the device as an integral part of the device; and*
- *precautions related to materials incorporated into the device that contain or consist of CMR substances or endocrine-disrupting substances, or that could result in sensitisation or an allergic reaction by the patient or user.*
- *If the device bears an indication that it is for single use, information on known characteristics and technical factors known to the manufacturer that could pose a risk if the device were to be re-used. This information shall be based on a specific section of the manufacturer's risk management documentation, where such characteristics and technical factors shall be addressed in detail.]*

Talk to your healthcare professional <if> <before using X>. *[addition of warnings and precautions in a bulleted list]*

Children and adolescents
[When the medical device is also used by children, the warnings and precautions which are specific to this population should be included under this sub-heading. Where relevant, parents/carers should also be alerted in this section of potential children/teenager specific warnings included under "driving and using machines".]

[If the medical device should not be used by some or all subsets of the paediatric population, this information should be reflected in this sub-section, e.g. "Do not give this medical to children

between the ages of x and y <years> <months> because <of the risk of […]> <it does not work> <the potential benefits are not greater than the risks>, <it is unlikely to be safe> ".]‡‡‡‡‡‡‡‡

Other medical devices or substances and X

[For devices intended for use together with other devices and/or general purpose equipment:

- *information to identify such devices or equipment, in order to obtain a safe combination, and/or*
- *information on any known restrictions to combinations of devices and equipment.]*

[If the device is intended to administer medicinal products, tissues or cells of human or animal origin, or their derivatives, or biological substances, any limitations or incompatibility in the choice of substances to be delivered.]

[In the case of devices that are composed of substances or of combinations of substances that are intended to be introduced into the human body and that are absorbed by or locally dispersed in the human body, warnings and precautions, where appropriate, related to the general profile of interaction of the device and its products of metabolism with other devices, medicinal products and other substances.]

<Tell your <doctor> <or> <pharmacist> if you are <taking> <using>, have recently <taken> <used> or might <take> <use> any other medicines or medical devices.>

Radiation

[If the device emits radiation for medical purposes the following needs to be added:

- *detailed information as to the nature, type and where appropriate, the intensity and distribution of the emitted radiation,*
- *the means of protecting the patient, user, or other person from unintended radiation during use of the device.]*

Pregnancy, breast-feeding and fertility

[Description of any information (including warnings and precautions) relevant for pregnant or breast-feeding women when using the device. In case the use of the device is contraindicated in this sub-population this should also be mentioned here.]‡‡‡‡‡‡‡‡

<If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your healthcare professional for advice before using this medical device.>

Driving and using machines

[Users should be made aware of any influence the use of the medical device might have on driving or using machines.
Manufacturers should bear in mind that medical devices used by children may need specific advice. For example, regarding road safety, children who may not be old enough to drive may nevertheless cycle. The advice should include an explanation as to why the user is advised not to drive or undertake these tasks, and whether or not they should discuss this with their healthcare professional if they wish to do so.]‡‡‡‡‡‡‡‡

3. How to use <X>

<Always use this medical device exactly as your healthcare professional has told you. Check with your healthcare professional if you are not sure.>

‡‡‡‡‡‡‡‡ This recommendation is not based on guidance from the current MDR but based on the QRD template published by EMA for medicinal products and my own assumptions after reviewing both guidance documents.

Before using <X>
[Description of details of any preparatory treatment or handling of the device before it is ready for use or during its use, such as sterilisation, final assembly, calibration, etc., including the levels of disinfection required to ensure patient safety and all available methods for achieving those levels of disinfection:
– *If the device is supplied non-sterile with the intention that it is sterilised before use, the appropriate instructions for sterilisation.]*

[Information needed to verify whether the device is properly installed and is ready to perform safely and as intended by the manufacturer, together with, where relevant:
– *details of the nature, and frequency, of preventive and regular maintenance, and of any preparatory cleaning or disinfection,*
– *identification of any consumable components and how to replace them,*
– *information on any necessary calibration to ensure that the device operates properly and safely during its intended lifetime, and*
– *methods for eliminating the risks encountered by persons involved in in-stalling, calibrating or servicing devices.]*

<Use in children <and adolescents>>
[When the medical device is used by different age groups with specific instructions for use for each age group this information should be clearly identified.]

When to use <X>
[Information allowing the healthcare professional (and user) to verify if the device is suitable and select the corresponding software and accessories.]

How to use <X>
[Specifications the user requires to use the device appropriately, e.g. if the device has a measuring function, the degree of accuracy claimed for it.]

Follow the steps below each time you use <X>

Step <X>	**<Header for Step X>**
[Inserting schematic illustrations supporting the required steps in using the device]	*[Detailed description of actions required to correctly perform the step in using the device. Important safety information can be included.]*
[…]	[…]

<Cleaning of X>
[If the device is reusable, information on the appropriate processes for allowing re-use, including cleaning, disinfection, packaging and, where appropriate, the validated method of re-sterilisation appropriate to the Member State or Member States in which the device has been placed on the market.]

<If you use X more often than you should>
[In the case of devices that are composed of substances or of combinations of substances that are intended to be introduced into the human body and that are absorbed by or locally dispersed in the human body, risks relating to overdose of these substances need to be listed.]

<If you forget to use X>
[Users should be informed what they should do after irregular use of a medical device, e.g.: if in-formation is available.]

<If you stop using X>
[A statement on the potential consequences of stopping the use of the medical device before finishing the intended course of use and the need for a prior discussion with a healthcare professional should be included as appropriate.]

<If you have any further questions on the use of this medical device, ask your <doctor> <,> <or> <pharmacist> <or nurse>.>

4. Possible side effects or serious incidents

[Description of any undesirable side effects, including information to be conveyed to the user in this regard.]

[In the case of devices that are composed of substances or of combinations of substances that are intended to be introduced into the human body and that are absorbed by or locally dispersed in the human body, undesirable side effects related to these substances need to be listed.]

<This medical device contains medicine X. Like all medicines, this medicine can cause side effects, although not everybody gets them.>

Serious side effects or incidents
Stop using X and get medical help immediately if you have any of the following:
[The most serious side effects need to be listed prominently first with clear instructions to the user on what action to take (e.g. to stop using the medical device and/or seek urgent medical advice.]

Other side effects or incidents
Tell your healthcare professional if you get any of the following side effects.

<**Very common:** may affect more than 1 in 10 people>
<Common: may affect up to 1 in 10 people>
<Uncommon: may affect up to 1 in 100 people>
<Rare: may affect up to 1 in 1,000 people>
<Very rare: may affect up to 1 in 10,000 people>
<Not known: frequency cannot be estimated from the available data>

Reporting of serious incidents
[A notice to the user and/or patient that any serious incident that has occurred in relation to the device should be reported to the manufacturer and the competent authority of the Member State in which the user and/or patient is established.]

If you get any side effects or experience serious incidents, talk to your healthcare professional. This includes any possible side effects or serious incidents not listed in this leaflet. You can also report these observations directly via the national reporting system of the <competent authority of the Member State> and to the manufacturer of the medical device. By reporting serious incidents you can help provide more information on the safety of this medicine.

5. How to store <X>

[An indication of any special storage and/or handling condition that applies.]

Keep this medicine out of the sight and reach of children.

[Expiry date]
[Where a specific abbreviation for expiry date is used on the labels, it should be mentioned here.]

<Do not use this medical device after the expiry date which is stated on the <carton label> <device label> <...> <after {abbreviation used for expiry date}>.> <The expiry date refers to the last day of that month.>

[Storage conditions]
[Where applicable, shelf life after reconstitution, dilution or after first opening the container.]

[Where appropriate, warnings against certain visible signs of deterioration.]
<Do not use this medical device if you notice {description of the visible signs of deterioration}.>

Disposal of the medical device
[Warnings or precautions to be taken in order to facilitate the safe disposal of the device, its accessories and the consumables used with it, if any. This information shall cover, where appropriate:
– *infection or microbial hazards such as explants, needles or surgical equipment contaminated with potentially infectious substances of human origin, and*
– *physical hazards such as from sharps.]*

<Do not throw away any medical devices via wastewater <or household waste>. Ask your healthcare provider how to dispose of devices that are no longer <required> <used>. These measures will help protect the environment.>

<Sterile state>
[Information if the device is supplied sterile, an indication of its sterile state and the sterilisation method.]

6. Contents of the pack and other information

[In the case of 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, the overall qualitative composition of the device and quantitative information on the main constituent or constituents responsible for achieving the principal intended action of MDR Annex I section 23.2.

- *An indication that the device contains or incorporates:*
  - *a medicinal substance, including a human blood or plasma derivative, or*
  - *tissues or cells, or their derivatives, of human origin, or*
  - *tissues or cells of animal origin, or their derivatives, as referred to in Regulation (EU) No 722/2012.*
- *Information labelled in accordance with section 10.4.5. of Annex I of the MDR; substances which are carcinogenic, mutagenic or toxic to reproduction ('CMR'), of category 1A or 1B or substances having endocrine-disrupting properties for which there is scientific evidence of probable serious effects to human health and which are included in concentrations above 0,1 % weight by weight (w/w).]*

[In the case of implantable devices, the overall qualitative and quantitative information on the materials and substances to which users can be exposed.]

What <X> contains
The medical device includes <substances> <a combination of substances> that are introduced into the human body or applied to the skin. The active substance(s) is (are)…

Contents of the pack
[All pack sizes for this medical device should be detailed here, including a reference to any ancillary items included in the pack such as needles, swabs, etc. For multipacks, clearly indicate the

pack content, e.g. "X is available in packs containing Y, Z or W {name of the medical device} and in multipacks comprising N cartons, each containing M {name of the medical device}".
If appropriate indicate that not all pack sizes may be marketed.]

<In this pack, you will find […]>.

<The following pack sizes are available:>

Manufacturer
[The name, registered trade name or registered trademark of the manufacturer and the address of its registered place of business.]
{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

For any information about this medical device, please contact the local representative of the manufacturer:

België/Belgique/Belgien
{Nom/Naam/Name}
<{Adresse/Adres/Anschrift }
B-0000 {Localité/Stad/Stadt}>
Tél/Tel: +{N° de téléphone/Telefoonnummer/ Telefonnummer}
<{e-mail}>

България
{Име}
<{Адрес}
{Град} {Пощенски код}>
Тел.: +{Телефонен номер}
<{e-mail}>

Česká republika
{Název}
<{Adresa}
CZ {město}>
Tel: +{telefonní číslo}
<{e-mail}>

Danmark
{Navn}
<{Adresse}
DK-0000 {by}>
Tlf: +{Telefonnummer}
<{e-mail}>

Lietuva
{pavadinimas}
<{adresas}
LT {pašto indeksas} {miestas}>
Tel: + {telefono numeris}
<{e-mail}>

Luxembourg/Luxemburg
{Nom}
<{Adresse}
L-0000 {Localité/Stadt}>
Tél/Tel: +{N° de téléphone/Telefonnummer}
<{e-mail}>

Magyarország
{Név}
<{Cím}
H-0000 {Város}>
Tel.: +{Telefonszám}
<{e-mail}>

Malta
{Isem}
<{Indirizz}
MT-0000 {Belt/Raħal}>
Tel: +{Numru tat-telefon}
<{e-mail}>

Deutschland
{Name}
<{Anschrift}
D-00000 {Stadt}>
Tel: +{Telefonnummer}
<{e-mail}>

Eesti
{Nimi}
<{Aadress}
EE - {Postiindeks} {Linn}>
Tel: +{Telefoninumber}
<{e-mail}>

Ελλάδα
{Όνομα}
<{Διεύθυνση}
GR-000 00 {πόλη}>
Τηλ: +{Αριθμός τηλεφώνου}
<{e-mail}>

España
{Nombre}
<{Dirección}
E-00000 {Ciudad}>
Tel: +{Teléfono}
<{e-mail}>

France
{Nom}
<{Adresse}
F-00000 {Localité}>
Tél: +{Numéro de téléphone}
<{e-mail}>

Hrvatska
{Ime}
<{Adresa}
{Poštanski broj} {grad}>
Tel: +{Telefonski broj}
<{e-mail}>

Ireland
{Name}
<{Address}
IRL - {Town} {Code for Dublin}>
Tel: +{Telephone number}
<{e-mail}>

Ísland
{Nafn}
<{Heimilisfang}
IS-000 {Borg/Bær}>
Sími: +{Símanúmer}
<{Netfang }>

Nederland
{Naam}
<{Adres}
NL-0000 XX {stad}>
Tel: +{Telefoonnummer}
<{e-mail}>

Norge
{Navn}
<{Adresse}
N-0000 {poststed}>
Tlf: +{Telefonnummer}
<{e-mail}>

Österreich
{Name}
<{Anschrift}
A-0000 {Stadt}>
Tel: +{Telefonnummer}
<{e-mail}>

Polska
{Nazwa/ Nazwisko}
<{Adres:
PL-00 000{Miasto}>
Tel.: +{Numer telefonu}
<{e-mail}>

Portugal
{Nome}
<{Morada}
P-0000–000 {Cidade}>
Tel: +{Número de telefone}
<{e-mail}>

România
{Nume}
<{Adresă}
{Oraş} {Cod poştal} – RO>
Tel: +{Număr de telefon}
<{e-mail}>

Slovenija
{Ime}
<{Naslov}
SI-0000 {Mesto}>
Tel: +{telefonska številka}
<{e-mail}>

Slovenská republika
{Názov}
<{Adresa}
SK-000 00 {Mesto}>
Tel: +{Telefónne číslo}
<{e-mail}>

Italia
{Nome}
<{Indirizzo}
I-00000 {Località}>
Tel: +{Numero di telefono}
<{e-mail}>

Κύπρος
{Όνομα}
<{Διεύθυνση}
CY-000 00 {πόλη}>
Τηλ: +{Αριθμός τηλεφώνου}
<{e-mail}>

Latvija
{Nosaukums}
<{Adrese}
{Pilsēta}, LV{pasta indekss }>
Tel: +{telefona numurs}
<{e-mail}>

Suomi/Finland
{Nimi/Namn}
<{Osoite/Adress}
FIN-00000 {Postitoimipaikka/Stad}>
Puh/Tel: +{Puhelinnumero/Telefonnummer}
<{e-mail}>

Sverige
{Namn}
<{Adress}
S-000 00 {Stad}>
Tel: +{Telefonnummer}
<{e-mail}>

United Kingdom (Northern Ireland)
{Name}
<{Address}
{Town} {Postal code} – UK>
Tel: +{Telephone number}
<{e-mail}>>

<Date of issue of the instructions for use>
<These instructions for use were last revised in>
[Date of issue of the instructions for use or, if they have been revised, date of issue and identifier of the latest revision of the instructions for use.]

Other sources of information
[Where applicable, a link to the summary of safety and clinical performance referred to in Article 32 shall be added.]
The summary of safety and clinical performance is available on the EUDAMED web site: https://ec.europa.eu/tools/eudamed/#/screen/home.

<Detailed information on this medical device is available on the web site of the manufacturer: {enter URL}.>

<QR code>

Eidesstattliche Erklärung

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Wiesbaden,

_____

Unterschrift (Dr. Denise N. Fabian)