MDR's Article 117: Regulatory Strategy to Comply With the General Safety and Performance Requirements Set Out in Annex I in the Light of a Single Integral Drug Device Combination

Wissenschaftliche Prüfungsarbeit

zur Erlangung des Titels

„Master of Drug Regulatory Affairs“

der Mathematisch-Naturwissenschaftlichen Fakultät

der Rheinischen Friedrich-Wilhelms-Universität Bonn

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Bonn 2019

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List of Abbreviations

ASTM	American Society for Testing and Materials
BSI	British Standards Institution
CA	Competent Authority
CCI	Container Closure Integrity
CCS	Container Closure System
CEN	European Committee for Standardization
CMDh	Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human
CMR	Carcinogenic, Mutagenic or Toxic to Reproduction
CP	Centralised Procedure
CS	Common Specifications
CTR	Clinical Trial Regulation
DDC	Drug Device Combination
EBE	European Biopharmaceutical Enterprises
EC	European Commission
eCTD	Electronic Common Technical Document
ED	Endocrine-Disrupting
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
EO	Ethylene Oxide
ER	Essential Requirement
EU	European Union

FDA	U.S. Food and Drug Administration
GHTF	Global Harmonization Task Force
GMP	Good Manufacturing Practice
GSPR	General Safety and Performance Requirement
HCP	Healthcare Professional
HMA	Heads of Medicines Agencies
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	International Electrotechnical Commission
IFU	Instructions for Use
ISO	International Standard Organization
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MDD	Medical Device Directive
MDR	Medical Device Regulation
NB	Notified Body
NCA	National Competent Authority
OJEU	Official Journal of the European Union
PFS	Pre-filled Syringe
Ph. Eur.	European Pharmacopoeia
PL	Package Leaflet
QRD	Quality Review of Documents

REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RMP-MP	Risk Management Plan for Medicinal Product
SCHEER	Scientific Committee on Health, Environmental and Emerging Risks
SmPC	Summary of Product Characteristics
TBD	To be determined
TSE	Transmissible Spongiform Encephalopathy
USP	United States Pharmacopeia

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Summary

Innovative medicinal products are often presented in the format of single integral Drug Device Combinations (DDCs) such as pre-filled syringes. Accordingly, DDC marketing authorisation applications submitted by pharmaceutical companies are increasing. Special attention should be drawn to the publication of the Medical Device Regulation (MDR) (Regulation (EU) 2017/745) that amends by its Article 117 the Medicinal Product Directive (Directive 2001/83/EC). As a consequence, the marketing authorisation applicant has to submit a notified body opinion on the medical device part of the single integral DDC. A positive opinion is reached by demonstrating compliance with MDR's Annex I listing the General Safety and Performance Requirements (GSPRs). This master thesis brings the relevant changes in legislation to the attention of the interested reader and outlines significant consequences of Article 117 in the context of single integral DDCs. A case study on a pre-filled syringe was performed assessing the applicability of the GSPRs as well as how to demonstrate compliance with the requirements. Within the analysis, new requirements introduced by the MDR were highlighted appropriately. In addition, the GSPRs were mapped to currently existing requirements such as the Essential Requirements of the Medical Device Directive (MDD) (Directive 93/43/EEC) or established medicinal product dossier requirements as applicable. The subsequent discussion outlines which GSPRs are potentially captured by the current marketing authorisation application dossier and would contribute to a redundant review by the competent authority and the notified body. In addition, based on the outcome of the analysis, it can be concluded that there is a significant subset of new requirements introduced by the MDR. Some of them are seen as impactful and should be assessed carefully. In contrast, it can be also determined that many requirements reflect the current state-of-the-art and are aligned with generally recognized technical standards. Furthermore, previous Essential Requirements of the Medical Device Directive are modified including either expanding or updated subclauses. Nevertheless, it was found that another subset of requirements like clinical evaluation or labelling are still unclear in the context of a single integral DDC as of now unless further guidance is published.

1. Introduction

The world of Drug Device Combinations (DDCs) has gained importance over recent years and DDCs have become more and more prevalent as a method of administration for medicinal products. Drug Device Combinations such as pre-filled syringes or pre-filled pens are considered to “have the potential to make treatments safer, more effective, or more convenient or acceptable to patients” [1]. However, they have to fulfil a significant set of additional requirements. In 2017, the European Union (EU) published the new Medical Device Regulation (MDR) (Regulation (EU) 2017/745) [2] to be applied in 2020. At that time, DDCs will have to comply with MDR’s Article 117 [2] amending the Medicinal Product Directive (Directive 2001/83/EC) [3]. It requires the marketing authorisation applicant to submit a notified body opinion on the compliance of so called *single integral* DDCs with the General Safety and Performance Requirements (GSPRs) set out in Annex I [2].

According to European Medicines Agency’s (EMA) review [4], 23% of the initial marketing authorisation applications (MAAs) approved (total number: 593) from January 2010 through June 2018 incorporated device components. Of those MAAs, the majority were DDCs, such as pre-filled syringes, pre-filled pens and inhaler systems. Over this time period, the number of MAAs has increased, resulting in an all-time-high for 2017 (32 MAAs).[4] From an ongoing industry survey performed by the European Federation of Pharmaceutical Industries and Associations (EFPIA)/European Biopharmaceutical Enterprises (EBE)/Vaccines Europe already answered by 13 companies, 66 applications concerning DDCs are planned to be submitted during the period from 2020 to 2022.[1] 25 of these applications will be considered initial MAAs, 15 of which will be processed via EMA’s centralised procedure (CP).[1]

Considering these statistics it becomes clear that the application of the Medical Device Regulation (MDR) (Regulation (EU) 2017/745) [2] replacing the Medical Device Directive (MDD) (Directive 93/42/EEC) [5] and especially MDR’s Article 117 deserve special attention by marketing authorisation applicants for DDCs.

This master thesis brings the relevant changes in legislation to the attention of the interested reader and outlines significant consequences of Article 117 in the context of single integral DDCs. A case study for a pre-filled syringe will analyse the applicability of GSPRs introduced by the MDR and how applicants can demonstrate compliance. Additionally, it will be outlined the extent that GSPRs have already been addressed by current legislation (e.g. MDD). Furthermore, potential redundancies and/or interfaces between medical device and medicinal product requirements as well as gaps in current device and DDC development

will be identified and assessed. Last, open questions still unaddressed by relevant stakeholders will be summed up.

This thesis is based on situation as per 17 May 2019.

2. Background

In order to embed the subject of this master thesis in a broader context relating to regulatory aspects of Drug Device Combinations (DDCs), the following chapter will first introduce general definitions. Based on that, the current EU regulatory pathway for single integral DDCs will be highlighted. To build a connection to the subject of the master thesis, background to the new Medical Device Regulation (MDR) will be given highlighting the Article 117. Attention will then be drawn to current public discussions on the implementation of MDR's Article 117. Annex I of the MDR will be introduced and links will be made to the general handling of i.a. harmonised standards in order to comply with the GSPRs.

2.1. Definitions

2.1.1. Medicinal Product

As outlined in Directive 2001/83/EC [3] a *medicinal product* is:

> *"Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or*
>
> *Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis."* [3 - Article 1(2a,b)]

2.1.2. Medical Device

As outlined in Regulation (EU) 2017/745 [2] a *medical device* is:

> *"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,*
>
> *and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means."* [2 - Article 2 (1)]

2.1.3. Drug Device Combination (DDC)

There is no consistent definition given in the EU for Drug Device Combination Products, as they are either regulated as medicinal product or as medical device. The most meaningful ones describing the combination of both are stated here:

European Medicines Agency (EMA)

Drug Device Combinations (DDCs) are described as following:

> *"The medical device may be supplied as an integral component of the medicinal product (e.g. pre-filled syringe, auto-injector), or separately (co-packaged; e.g. oral syringe, pen-injector), as a non-integral combination with the medicinal product, or independently marketed (in cases where the device meets the requirements for the necessary delivery system stated in the Summary of Product Characteristics (SmPC) for the medicinal product)."* [6]

Single integral DDC is described as following:

> *"If a medical device used to administer a medicinal product is placed on the market in such a way that the device and medicinal product 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, as applicable."* [2 - Article 1(9)]

MEDDEV 2. 1/3 rev 3

So called *drug-delivery devices* are defined as stated below:

> *"A device that is intended to administer a medicinal product in the case where the device and the medicinal product form a single integral product, which is intended exclusively for use in the given combination and which is not reusable."* [7]

2.2. Current regulatory pathways for DDCs in the EU

As outlined in the second subparagraph of Article 1(3) of the Medical Device Directive (MDD) 93/42/EEC [5], "a single integral product which is intended exclusively for use in the given combination and which is not reusable, that single product shall be governed by Directive 2001/83/EC" [5 - Article 1(3)] resulting in a regulation as medicinal product. Medical device characteristics must comply with the *Essential Requirements* (ERs) applicable to performance and safety features set out in Annex I of the MDD.[5] However, cross-reference to the respective section of the MDD is made neither in Directive 2001/83/EC [3] nor in Regulation (EC) No 726/2004 [8].[9] This is recognized as a gap in legislation.[9] It is further in contrast with the guidance [10] listing the expected marketing authorisation application (MAA) dossier content foreseeing relevant sections for the medical device information.

Next, the applicant submits the MAA in the electronic Common Technical Document (eCTD) format including relevant information to the medical device. The current eCTD format governs a section relevant to medical device information within Part 3.2.R of the Module 3 [10] that will be assessed by the medicines competent authority (CA). Compliance to the Essential Requirements as stated previously is expected to be located there unless it is not part of previous sections of Module 3 (section 3.2.P) referring to the container closure system.[11] As presented in a recently published position paper from the European Biopharmaceutical Enterprises (EBE) [11], there are different approaches across the pharmaceutical industry to present the respective data:

Table 1: Location of device related information in Module 3 for a DDC product
source: EBE Reflection Paper [11 - p.9]

Location of information Approach #1	Location of information Approach #2	Location of information Approach #3
3.2 P All Quality information related to device component and combination product safety and performance	3.2 P All Quality information related to combination product safety and performance	3.2 P No information related to device component and combination product safety and performance
3.2 R Compliance with MDD Annex 1 – mentioning applicable studies performed to demonstrate compliance	3.2 R Compliance with MDD Annex 1 – mentioning applicable studies performed to demonstrate compliance	3.2 R Compliance with MDD Annex 1 – mentioning applicable studies performed to demonstrate compliance
May or may not cross refer studies information provided in 3.2.P sections	Technical documentation related to device component in 3.2 P format	Technical documentation related to device component and combination product in 3.2 P format
May cross refer studies handled in the QMS not provided in the dossier		

No notified body (NB) is involved at that time.[6] However, as stated in current publications, some of them perform a voluntary review and assessment of the medical device part that is submitted in the MAA.[9]

2.3. MDR

The Medical Device Regulation (MDR) (EU) 2017/745 [2] repealing the MDD [5] entered into force on 26 May 2017 and shall apply from 26 May 2020.[2] As stated in recital 10 of the MDR, it shall amend the Directive 2001/83/EC [3] to ensure compliance with the *General Safety and Performance Requirements* (GSPRs) (repealing the *Essential Requirements* of the MDD) applicable to the medical device part of the DDC. The second subparagraph of Article 1(9) outlines the regulation of such a “single integral product which is intended

exclusively for use in the given combination and which is not reusable" [2 - Article 1(9)], whereas the device parts having a delivery function only, under Directive 2001/83/EC [3] respectively Regulation (EC) No 726/2004 [8] providing compliance with the GSPRs as set out in Annex I of the MDR. The assessment of that compliance shall be performed by a notified body (NB).[2] The NB within the EU is a third party that is designated by a responsible authority of an European Member State for the conformity assessment of medical devices prior to placement on the market.[12] Companies have free choice of the NB as long as the NB is accredited for the device product types and respective competences.[13 - p.5] However, the MDR places stricter requirements on oversight of NBs [4] and NBs are encouraged to get MDR accreditation prior to 26 May 2020 in order to be operational at that time.

2.3.1. Article 117

Article 117 of the MDR amending the Directive 2011/83/EC [3] is stated as following:

> *"In Annex I to Directive 2001/83/EC, point 12 of Section 3.2. is replaced by the following:*
>
> *'(12) Where, in accordance with the second subparagraph of Article 1(8) or the second subparagraph of Article 1(9) of Regulation (EU) 2017/745 of the European Parliament and of the Council (*), a product is governed by this Directive, the marketing authorisation dossier shall include, where available, the results of the assessment of the conformity of the device part with the relevant general safety and performance requirements set out in Annex I to that Regulation contained in the manufacturer's EU declaration of conformity or the relevant certificate issued by a notified body allowing the manufacturer to affix a CE marking to the medical device. If the dossier does not include the results of the conformity assessment referred to in the first subparagraph and where for the conformity assessment of the device, if used separately, the involvement of a notified body is required in accordance with Regulation (EU) 2017/745, the authority shall require the applicant to provide an opinion on the conformity of the device part with the relevant general safety and performance requirements set out in Annex I to that Regulation issued by a notified body designated in accordance with that Regulation for the type of device in question*." [2 - Article 117]

Accordingly, for a single integral DDC as described in Article 1(9) of the MDR no CE marking of the device part is required.[13 - p.9] The notified body is encouraged to give "an opinion on the conformity of the device part" [2 - Article 117] that should be provided as part of the MAA submission to be assessed by the CA. This is applicable to initial MAA submissions as well as submissions of "substantial design changes to the device component" [14] (including "addition or full replacement of the device" [14]) from 26 May 2020.[14]

2.3.2. Public discussion on Article 117

Since the publication of Article 117, many interpretations [4,9,11,13–16] arose trying to understand the extent of its meaning. However, it becomes clear that even now many questions are not addressed by the responsible parties:

The EBE Working Group of EFPIA published a position paper [13] addressing the industry perspective on Article 117. Several questions paired with previous experiences and future expectations are mentioned: The overall procedure of the NB assessment next to the MAA dossier review by the CA is still unclear. This incorporates different aspects: The timing of both reviews must be clarified to avoid negative impact on approval timelines, as well as delayed market entries of important medicines. Moreover, the scope and boundaries of the NB assessment are not well defined yet in regard to DDCs, as the MAA dossier already covers relevant aspects. In order to avoid unnecessary redundancies, a concept should be developed to provide clear definition. A further pain point outlined in the position paper is the handling of well-known delivery devices that are already established in a similar way on the market. It is recommended that these should follow an abbreviated procedure, leveraging prior knowledge and potentially previous NB opinion.[13]

Meanwhile, NBs are facing challenges as well. Due to the increase in requirements of the MDR, the number of NBs as well as their scope will decrease. This will challenge pharmaceutical manufacturers as the available number of NBs qualified to assess DDCs (dependent on an appropriate designation [17]) is still unknown and may be lower than expected. Also, expectations regarding the presentation of the data showing compliance with the GSPRs are not yet well defined. Further, the assessment report of the NB concluding the requested opinion must be designed in a way that the medicines competent authority can rely on for the final marketing authorisation (MA). Therefore, representatives of the notified body institutions as well as of the EMA should discuss expectations and requirements on that in advance to ensure a consistent procedure.[9]

In September 2016, the EMA published a concept paper [6] addressing the need for a guideline that outlines the Module 3 dossier requirements with regard to DDCs requesting public consultation on that. The draft guideline “Guideline on the quality requirements for medicinal products containing a device component for delivery or use of the medicinal product” [16] is currently pending. It is expected that the guideline give assistance on general considerations (e.g. Good Manufacturing Practice (GMP)/ISO Standards, submission and format of data) as well as considerations on specific dossier contents (Module 1, 2 and 3) and the requested NB opinion for single integral DDCs.[16]

Also, specific topics were discussed with NB representatives [15]: Clarification on aspects to be reviewed by the NB during the MDR conformity assessment, overlapping topics such as shelf life and drug/device interactions. Functionality and usability were also highlighted with the need to reduce review duplication. Additionally, labelling requirements should be clarified.[15] It is the hope of all stakeholders, that this guideline may help towards meeting the expectations triggered by Article 117.

In February 2019, the EMA together with the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) published a long-awaited Question and Answer Document [14] addressing basic aspects of Article 117 [2]. It is outlined that medicinal products with integral medical devices classified either as Class I (i.a. sterile), Class IIa, Class IIb or Class III are obligated to comply with the GSPRs of Annex I [2]. The notified body (NB) opinion should be provided as well. Integral devices classified as Class I devices (i.a. non-sterile) are not subject to a NB opinion.[14]

However, a pre-filled syringe considered as a single integral DDC is classified according to rule 6 of Annex VIII of the MDR [2] and consequently requires a NB opinion.

Rule 6 states:

> *"All surgically invasive devices intended for transient use are classified as class IIa unless they: […] are intended to administer medicinal products by means of a delivery system, if such administration of a medicinal product is done in a manner that is potentially hazardous taking account of the mode of application, in which case they are classified as class IIb."* [2 - Annex VIII]

Where *surgically invasive* is defined as:

> *"An invasive device which penetrates inside the body through the surface of the body, including through mucous membranes of body orifices with the aid or in the context of a surgical operation; and […] a device which produces penetration other than through a body orifice."* [2 - Annex VIII]

Where *transient* is defined as "continuous use for less than 60 minutes". [2 - Annex VIII]

In addition, it is stated in the paper [14] that the NB opinion should, whenever possible, be part of the dossier of the initial marketing authorisation application (MAA). Any other timing should be discussed beforehand with the EMA/national competent authority (NCA).[14]

2.3.3. Annex I – GSPRs

The Annex I of the MDR lists the *General Safety and Performance Requirements* (GSPRs) referenced in Article 1(9) and Article 117. The GSPRs are repealing the *Essential Requirements* (ERs) of the MDD. Fulfilment of Annex I requirements will be essential to show applicable conformity with the MDR as outlined in Article 117.

Annex I is structured in 3 chapters and 23 main requirements in total that are further subdivided into multiple subclauses. Chapter I lists the general requirements to be met by the device. Chapter II details requirements regarding design and manufacture of the device. Finally, chapter III addresses requirements on the information supplied with the device.[2] Compared to the 13 ERs of the MDD, the number of requirements has been significantly increased and the requirements themselves have been expanded and/or have become more precise. However, the scope and topics are consistent besides several exceptions.[18]

A specific example demonstrating this is GSPR 11.1 (11: infection and microbial contamination):

> *"Devices and their manufacturing processes shall be designed in such a way as to eliminate or to reduce as far as possible the risk of infection to patients, users and, where applicable, other persons. The design shall: (a) reduce as far as possible and appropriate the risks from unintended cuts and pricks, such as needle stick injuries, (b) allow easy and safe handling, (c) reduce as far as possible any microbial leakage from the device and/or microbial exposure during use, and (d) prevent microbial contamination of the device or its content such as specimens or fluids."* [2 - Annex I: GSPR 11.1]

The corresponding ER 8.1 of the MDD (8: infection and microbial contamination) states:

> *"The devices and manufacturing processes must be designed in such a way as to eliminate or reduce as far as possible the risk of infection to the patient, user and third parties. The design must allow easy handling and, where necessary, minimize contamination of the device by the patient or vice versa during use."* [5 - Annex I: ER 8.1]

Although both requirements have the same scope, it can be concluded that the GSPR 11.1 is more detailed and precise in its requirements (e.g. specifies sources of contamination to be addressed) whereas ER 8.1 is stated more general. Moreover, the GSPR addresses additional requirements that were not outlined in the corresponding ER such as the risk reduction of unintended cuts and pricks as well as safe handling. In fact, the MDR incorporates safety as a more integral part into the requirements.

2.3.4. Fulfilment of Annex I requirements

Conformance to the GSPRs can be demonstrated by the following indications and references as stated in MDR's *Annex II -Technical Documentation*, section 4 [2 - Annex II: section 4]:

First, the applicability of each requirement must be confirmed or a justification needs to be given why the requirement is not applicable for the device and its intended use. With regard to the method used to conform with the requirement, the manufacturer should consider the application of a *harmonised standard* whereat

> *" 'standard' means a technical specification, adopted by a recognised standardisation body, for repeated or continuous application, with which compliance is not compulsory […]."* [19 - Article 2(1)]

Standards become adopted as *harmonised* "on the basis of a request made by the Commission for the application of Union harmonisation legislation" [19 - Article 2(1c)]. These standards are published in the Official Journal of the European Union (OJEU) [20] once they are harmonised.

Globally recognised technical standards are typically issued by the International Standard Organization (ISO) [21], the International Electrotechnical Commission (IEC) [22] or the ASTM (American Society for Testing and Materials) International [23]. The GSPRs may be met by adhering to the "generally acknowledged state of the art" [2 - Annex I: GSPR 1], in which internationally acknowledged standards of the latest version should be appropriate not yet being harmonised.

Introduced by Article 9 of the MDR, the European Commission is allowed to establish so-called *Common Specifications* (CS) defined as

> *"a set of technical and/or clinical requirements, other than a standard, that provides a means of complying with the legal obligations applicable to a device, process or system."* [2 - Article 1 (71)]

According to Article 9 [2], CS should be issued by the European Commission (EC) for fields where no harmonised standards exist or existing standards are deemed insufficient. They can be expected for clinical evaluations and technical documentation, but also design and manufacturing requirements addressing, for example, physical-chemical characterizations.[24] It should be further noted that conformance with Common Specifications is mandatory for their area applicable to the medical device. Any deviation requires explicit justification. In contrast, standards can be considered voluntary guidance.[25]

However, if none of the previously mentioned standards or specifications exist, the manufacturer should justify any other solution applied. In the field of DDCs, compendial

methods, monographs and pharmaceutical guidelines may be applied as well and should be considered for respective requirements. For further evidence of the conformity to any solution applied as mentioned above, a reference to the respective controlled document should be given that is usually contained in the full technical documentation. If applicable, a summary thereof should be included. No matter the solution adopted to comply with the GSPRs, the Annex II outlines that at least a justification, validation as well as verification of that specific method applied should be documented.[2 - Annex II: section 4]

3. Case Study DDC

As mentioned in chapter 2, at the time the MDR becomes effective, the CA will require a notified body opinion on the conformity with the GSPRs concerning the device component that is an integral part of the DDC. In order to assess these requirements on their applicability to pre-filled syringes, this chapter will include a case study that will be performed on a defined target DDC.

3.1. Structure and objectives of the case study

First, the target Drug Device Combination will be defined in order to identify applicable (harmonised) technical standards, methods and guidance for each GSPR. As no specific exemplary medicinal product will be used, the model will remain generic and only highlight key characteristics. Furthermore, a table will be generated containing reference numbers to each GSPR. The table will provide evaluation for the applicability of each GSPR to the given DDC. If a requirement is not applicable, a short justification thereof will be given. Then, the applicable (harmonised) technical standard or alternative reference will be given which can be used to show conformity. Any additional details necessary to demonstrate compliance will also be mentioned. The last step will include an intelligence mapping, determining if this requirement is already addressed by current European submissions (MAA) due to similar or same requirements that must be currently met (e.g. Essential Requirement (partly) identical to the corresponding GSPR, regulatory guidance for medicinal products etc.).

Several key documents will be used that help interpreting the GSPRs and mapping the right standards to each GSPR in order to fulfil the requested needs. ISO Technical Report 16142:2006 [26] relates the *Essential Principles* developed by the Global Harmonization Task Force (GHTF) to applicable standards. This can be taken as base information, as the GSPRs partly correspond to the Essential Principles. However, there will be additional or missing requirements within the GSPRs. Regarding interpretation of the GSPRs and building the relation to the Essential Requirements of the MDD, the British Standards Institution (BSI) publication [18] gives further information. Moreover, the Technical Report No. 73 [27] lists user requirements regarding pre-filled syringes, details applicable standards/compendial methods or guidance, as well as references to current filing practices in the Common Technical Document specific to the pre-filled syringe.

The published list of harmonised standards from the Official Journal of the European Union [20] references harmonised standards that can be applied to meet the Annex I Requirements of the MDR. However, for the purpose of this case study the latest version of a globally recognized standard will be listed, to demonstrate the state-of-the-art. If a harmonised version exists, the respective technical standard will be marked with an asterisk

(*). Appendix B lists a correlation table (*Table 6*) that links the most current version to the harmonised version and its reference document.

Each standard or guidance document generally references documentation to be generated to contain any necessary tests or assessments. This documentation will be referenced to show compliance with the requirements, as applicable.

For the MAA, *Volume 2b – Notice to Applicants* [10] gives general advice what is currently included in EU medicinal product dossier submissions.

Based on the above analysis, an evaluation will conclude potential redundancies as well as interfaces to the MAA dossier. Any gaps that need to be addressed during product development in order to be compliant with the requirements will be highlighted. Open questions or conclusions resulting from the evaluations will also be summarized.

3.2. Target DDC

The target DDC is a pre-filled syringe (PFS) containing a biological product such as a monoclonal antibody.

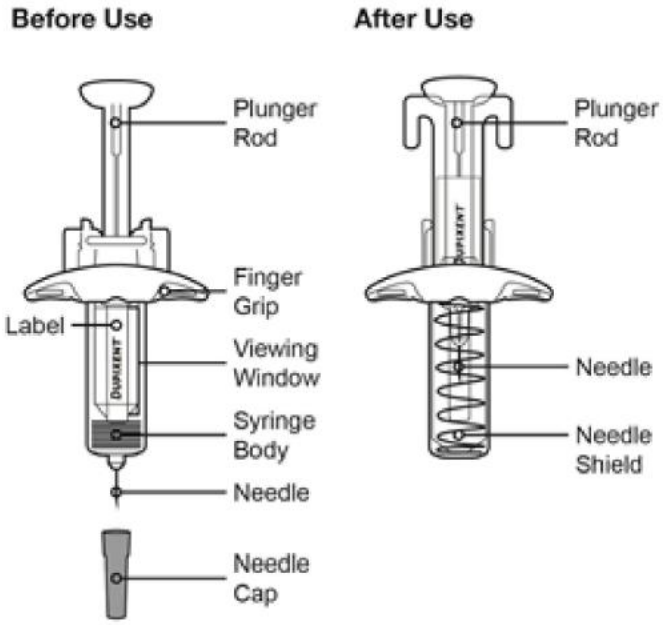
Predefined features:

- Stainless staked needle (lubricated), covered by a needle cap (soft (sterile barrier) and rigid needle shield)
- Siliconized glass barrel
- Plunger: plunger rod & elastomeric stopper (siliconized)
- Finger flange facilitating safe and easy handling
- Delivery volume 1ml
- Safety device for sharps injury protection (needle guard with a spring for activation)
- Intended use: treatment of a chronic disease , subcutaneous injection
- Intended user population: healthcare provider as well as lay caregiver or patient
- Use environment: hospital or homecare

The ready-to-fill bulk syringe (composed of the syringe body (glass barrel), needle, soft and rigid needle shield) and the elastomeric stopper are sterilized via ethylene oxide (EO) and treated appropriately prior to the pharmaceutical aseptic filling step. No further sterilization will take place due to the suitability of the drug product. Assembling of the plunger rod and finger flange as well as the safety device including labelling will take place afterwards.

The below figure shows a schematic drawing:

Figure 1: Target DDC – pre-filled syringe before and after use
source: instructions for use for Dupixent® [28]



3.3. Quality System and General Requirements

Although the Article 117 [2] does not require compliance with the quality system requirements for medical devices [13,29], this should be taken into account in order to be compliant with the GSPRs for a single integral DDC. EN ISO 13485:2016 [30] lists relevant documentation a manufacturer should consider in their quality system.[30 - clause 4] For example the Medical Device File for the device should contain general descriptions of the device, product specifications, procedures for relevant manufacturing activities (e.g. sterilization, packaging) and procedures for environmental monitoring controls. Also production and service provisions [30 - clause 7.5] require defined processes for production and validation thereof, cleanliness of the product and special requirements for sterile devices. Additionally, design and development verification and validation as well as purchasing control processes should be established within the device development.[30] Considering that the manufacturer of a single integral DDC has to also comply with the Pharmaceutical Quality System according to EU Good Manufacturing Practice (GMP) requirements [31] applicable to medicinal products, such as, validations of manufacturing processes and test methods, should be carried out. Not less important are the requirements regarding an established risk management system as required by EN ISO 14971:2012 [32] in order to meet the GSPRs. Considering these facts as a prerequisite, general compliance

to such aspects required by the GSPRs should be fulfilled and will not be routinely listed for completion. The following analysis table focuses on relevant product requirements resulting from the GSPRs and the target DDC.

3.4. Analysis Table

Table 2: Chapter I General Requirements, Chapter II Requirements regarding design and manufacture & Chapter III Requirements regarding the information supplied with the device (GSPRs 1-23.1)

GSPR	Applicable? (Yes or No)	Applicable standard to apply / alternative reference	Demonstration of compliance with respect to target DDC or justification if GSPR is not applicable	Intelligence mapping (reference to current requirements) & comments
Chapter I – General Requirements				
1	Yes	EN ISO 14971:2012 [32] EN ISO 13485:2016 [30] MDR Article 61, Clinical Evaluation [2] Annex XIV Clinical evaluation Part A [2] EN ISO 14155:2011 [33]	Risk Management Plan [32 - clause 3.4] Risk Management Report [32 - clause 8] including risk benefit analysis [2 - Annex II: section 5] Quality Manual [30 - clause 4.2.2] Design development verification & validation plan [30 - clause 7.3] Clinical evaluation report [2 - Annex XIV] Note: Clinical investigations of DDCs are conducted according to Directive 2001/20/EC [34]; Directive 2005/28/EC [35] resp. Regulation EU No. 536/2014 (CTR) [36] & ICH E6 Good Clinical Practice [37] alternatively leveraging literary clinical data showing similar technical, biological and clinical characteristics of the device [2 - Annex XIV]	See ER 1-3 [5], Annex X Clinical Evaluation and ER 6a [5] **EU MAA:** Risk Management Plan for Medicinal Product (RMP-MP) [38,39]
2	Yes	EN ISO 14971:2012 [32]	Risk Management Plan [32 - clause 3.4] Risk Management Report [32 - clause 8]	clarification to ER 2 [5][18] **EU MAA:** RMP-MP [38,39]

GSPR	Applicable? (Yes or No)	Applicable standard to apply / alternative reference	Demonstration of compliance with respect to target DDC or justification if GSPR is not applicable	Intelligence mapping (reference to current requirements) & comments
3 (a-f)	Yes	EN ISO 13485:2016 [30] EN ISO 14971:2012 [32]	Quality Manual [30 - clause 4.2.2](Risk management System) Risk Management Plan [32 - clause 3.4] Risk assessment Summary [32 - clause 4-6] including at least: - hazard identification & analysis (intended use incl. use error and misuse) - risk evaluation - risk control - residual risk evaluation - production and post-production information if applicable Risk Management Report [32 - clause 8]	**New** Aligned with EN ISO 14971:2012 [32], followed by manufacturers [18] **EU MAA**: RMP-MP [38,39]
4 (a-c)	Yes	EN ISO 14971:2012 [32] ISO 11040-8:2016 [40] ISO 23908:2011 [41] IEC 62366-1:2015* [42]	Risk Management Plan [32 - clause 3.4] Risk Management Report [32 - clause 8] Including: - Risk control option analysis - Risk control measures evaluation - Residual risk evaluation including risk benefit analysis [32 - clause 6-7 & Annex J] [42 - clause 4.1.2 & 4.1.3] Summative Evaluation Report [42 - clause 5.9] see also GSPRs 23.1 g, 23.4 g, 23.4 j	See ER 2 [5] **New:** assessment of (overall) residual risk, give users safety information, train users if applicable for all residual risks

GSPR	Applicable? (Yes or No)	Applicable standard to apply / alternative reference	Demonstration of compliance with respect to target DDC or justification if GSPR is not applicable	Intelligence mapping (reference to current requirements) & comments
5	Yes	IEC 62366-1:2015* [42] EN ISO 14971:2012 [32]	Use Specification [42 - clause 5.1] Risk analysis and control report (known and foreseeable hazards, use error) [32 - clause 4.2 & 4.3,42 - clause 5.3] User Interface Specification [42 - clause 5.6] Summative Evaluation Report [42 - clause 5.9]	See ER 1 [5] **EU MAA:** RMP-MP [39]
6	Yes	ICH Q5C [43] ISO 11040-8:2016 [40]	Stability data of representative lot per ICH Q5C [43] Test Report [40 - clause 8] for performance and pharmaceutical requirements as part of stability testing Note: DDC Stability Studies follow ICH guidance [43]	See ER 4 [5] **EU MAA:** eCTD 3.2.P.8 Stability [10,11]
7	Yes	ASTM D4169-16 [44] ISO 11040-8:2016 [40]	Shipping study including Test Report [40 - clause 8] for performance requirements and pharmaceutical requirements	See ER 5 [5] **EU MAA** eCTD 3.2.P.2.4 Container Closure System “for suitability of the container closure system […] used for the storage, transportation (shipping)”[10 - p.17 Module 3] eCTD 3.2.P.3.5 Process Validation for shipping validation [11]

GSPR	Applicable? (Yes or No)	Applicable standard to apply / alternative reference	Demonstration of compliance with respect to target DDC or justification if GSPR is not applicable	Intelligence mapping (reference to current requirements) & comments
8	Yes	EN ISO 14971:2012 [32] MDR Article 61, Clinical Evaluation [2]	Risk Management Report [32 - clause 8] including risk benefit analysis [2 - Annex II: section 5] Clinical Evaluation Report [2 - Annex XIV]	See ER 6 [5] **New:** include known and foreseeable risks & minimization of risks in assessment
9	No	n/a	Refers to devices without medical purpose. PFS has medical purpose.	n/a
Chapter II – Requirements regarding design and manufacture				
10.1 (a-h)	Yes	ISO 11040-8:2016 [40 - clause 7.3] ISO 10993-1:2018* [45] EN ISO 10993-18:2009 [46] EN ISO 10993-17:2009 [47] ISO 10993-11:2017* [48 - Annex F] ISO 10993-10:2010 [49] EN ISO 10993-7:2008 [50] EN ISO 10993-5:2009 [51] ISO 11135:2014* [52 - clause 5.4] ISO 8871-4:2006 [53] USP <87> Biological Reactivity Tests, In Vitro [54] USP <88> Biological Reactivity Tests, In Vivo [54] ISO 8871-1:2003 [55]	Description of the device components including the identity of materials and its specification Biological evaluation report [45 - clause 6 & Annex B] Test reports for product categorization: externally communication device – tissue, limited [45 - Annex A] Impact assessment of manufacturing processes on material properties [45 - Annex B: clause B.4.1.5] (e.g. EO sterilization procedure of device components [52]) Release test reports of representative lots of PFS device components and of finished DDC according to the device specifications [30 - clause 7.3]	See ER 7.1 [5] **New:** GSPR 10.1 c, d, f, g, h **EU MAA:**[10,11] eCTD 3.2.P.2.4 Container Closure System for choice and safety of materials eCTD 3.2.P.5.4 Batch analysis for release test reports of relevant lots of finished DDC eCTD 3.2.P.7 Container Closure System for materials and specification

GSPR	Applicable? (Yes or No)	Applicable standard to apply / alternative reference	Demonstration of compliance with respect to target DDC or justification if GSPR is not applicable	Intelligence mapping (reference to current requirements) & comments
		ISO 8871-2:2003/A1:2005 [56] ISO 11040-5:2012 [57] ISO 11040-4:2015 [58] Ph. Eur. 3.2.1. Glass Container for pharmaceutical use [59] Ph. Eur. 3.1.8. Silicone Oil used as Lubricant [60] Ph. Eur. Monograph Dimeticone [61] EN ISO 13485:2016 [30]		
10.2	Yes	ISO 10993-1:2018* [45] ISO 11135:2014* [52] EN ISO 10993-7:2008 [50]	Biological Evaluation Report [45 - clause 6 & Annex B] Validation/Test Report of sterilization procedure for applicable device components [52 - clause 9] Test Report on residuals of ethylene oxide (EO) and related substances [50]	See ER 7.2 [5]
10.3	Yes	**Finished DDC:** FDA Guidance for Industry Container Closure Systems for Packaging Human drugs and biologics [62] ISO 11040-8:2016 [40] ISO 10993-1:2018* [45] EN ISO 10993-17:2009 [47]	Evaluation of suitability of the pre-filled syringe with regard to the drug product (FDA approach [62]) Data on i.a.: - Protection (sterility, container closure integrity (CCI), moisture, light)	See ER 7.3 [5] **EU MAA:** [10,11] eCTD 3.2.P.2.4 Container Closure System (CCS) for suitability data

GSPR	Applicable? (Yes or No)	Applicable standard to apply / alternative reference	Demonstration of compliance with respect to target DDC or justification if GSPR is not applicable	Intelligence mapping (reference to current requirements) & comments
		USP <1663> Extractables associated with Pharmaceutical Packaging Systems [54] USP <1664> Assessment of drug product leachables associated with Pharmaceutical Packaging/Delivery systems[54] Ph. Eur. 5.1.1. Methods of preparation of sterile products [63] Ph. Eur. 2.6.1. Sterility [64] Ph. Eur. 2.6.8. Pyrogens [65] Ph. Eur. 2.6.14. Bacterial endotoxins [66] Ph. Eur. 2.9.17. Test for Extractable Volume of Parenteral Preparations (Section Pre-filled Syringes) [67] **Device components:** ISO 11040-4:2015 [58] ISO 11040-5:2012 [57] ISO 8871-1:2003 [55] ISO 8871-2:2003+A1:2005 [56]	- Safety (Suitability of materials in accordance with ISO standards & compendial requirements) - Compatibility (data on Extractables/Leachables) - Performance (Test report [40 - clause 8] on performance characteristics)	

GSPR	Applicable? (Yes or No)	Applicable standard to apply / alternative reference	Demonstration of compliance with respect to target DDC or justification if GSPR is not applicable	Intelligence mapping (reference to current requirements) & comments
		ISO 8871-4:2006 [53] Ph. Eur. 3.2.1. Glass Container for Pharmaceutical Use [59] Ph. Eur. 3.1.8. Silicone Oil used as a Lubricant [60] Ph. Eur. 3.1.9. Silicone Elastomer for closures and tubing [68] Ph. Eur. 3.2.9. Rubber Closures for Containers for Aqueous parenteral preparations […][69] Ph. Eur. Monograph Dimeticone [61]		
10.4.1	Yes	Regulation (EC) 1272/2008 Part 3 of Annex VI [70] Regulation (EC) 1907/2006, Article 59 [71] Regulation (EU) No 528/2012, Article 5(3) [72] Commission Delegated Regulation (EU) 2017/2100, Annex Section A [73]	Assessment & statement concerning presence & quantification (weight by weight %) of CMR (carcinogenic, mutagenic or toxic to reproduction) & endocrine-disrupting (ED) substances as listed in regulatory references if applicable for at least needle, adhesive, needle shield, barrel, elastomeric stopper (direct contact with drug product/invasive parts)	See ER 7.5 [5] **New:** scope increased in MDR: CMR, endocrine-disrupting (ED) substances incl. phthalate, substances & particles in concentration above 0,1% w/w

GSPR	Applicable? (Yes or No)	Applicable standard to apply / alternative reference	Demonstration of compliance with respect to target DDC or justification if GSPR is not applicable	Intelligence mapping (reference to current requirements) & comments
10.4.2	Yes	Justification based on scientific data and risk assessment as required in GSPR 10.4.2 [2]	Justification if needed for substances stated for GSPR 10.4.1 as per instructions provided in SCHEER draft guidance [74]	See ER 7.5 [5] **New:** MDR: justification for all substances above 0,1% w/w, consider new guidelines and required content of justification
10.4.3	Yes	Guideline on phthalates [2] (SCHEER Guidance – draft version [74] to be adopted prior to 26 May 2020)	Statement of compliance with the guideline on phthalates if needed	See ER 7.5 [5] **New:** Guideline on phthalates
10.4.4	Yes	Guideline on CMR and endocrine-disrupting substances (TBD)[2]	Statement of compliance with the issued guideline if needed	See ER 7.5 [5] **New:** Guidelines to be considered
10.4.5	Yes	Substances identified and justified acc. GSPR 10.4.2. to be included in labelling	Product labelling specification if needed See GSPRs 23.2 f, 23.4 s	See ER 7.5 [5] **New:** revised labelling requirements
10.5	Yes	EN ISO 10993-7:2008 [50] EN ISO 10993-17:2009 [47] EN ISO 14971:2012 [32] ISO 11040-4:2015 [58 - clause 6.6]	Test Report on residuals of ethylene oxide (EO) and related substances [50] Risk analysis report [47 - Annex D] Risk assessment for potential failure modes of manufacturing process (filling, assembling) and Device System, acceptance criteria of critical product parameter, in process controls for CCI [27]	See ER 7.6 [5] **EU MAA:** [10,11] eCTD 3.2.P.2.5 Microbiological Attributes for container closure integrity eCTD 3.2.P.3.3 Description of Manufacturing Process and Process Controls

GSPR	Applicable? (Yes or No)	Applicable standard to apply / alternative reference	Demonstration of compliance with respect to target DDC or justification if GSPR is not applicable	Intelligence mapping (reference to current requirements) & comments
		ISO 11040-8:2016 [40 - clause 7.4]	Test reports for container closure integrity (CCI) "after the assembly process, shipment and during long-term storage up to end of shelf life" [11 - p.10]	eCTD 3.2.P.3.4 Control of Critical Steps
10.6	Yes	**Bulk syringe (empty):** ISO 11040-4:2015 [58] **Bulk syringe (filled & sealed):** ISO 11040-8:2016 [40 - clause 7.6] Ph. Eur. 2.9.19. Particulate contamination: sub-visible particles [75] Ph. Eur. 2.9.20. Particulate contamination: visible particles [76]	**Bulk syringe (empty):** Test Report particles [58 - clause 6.4] **Bulk syringe (filled & sealed):** Release Test Report/Certificate of Analysis of representative lot Note: container closure system (CCS) relevant for particles as it is in direct contact with the medicinal product	**New** **EU MAA:**[10] eCTD 3.2.P.5 Control of drug product Ph. Eur. Monograph for parenteral preparations requires testing for particles [77] → part of specification for injectable dosage forms
11.1 (a-d)	Yes	EN ISO 14971:2012 [32] ISO 11040-8:2016 [40 - clause 6.10] ISO 23908:2011 [41] Directive 2009/104/EC [78] ISO 11040-4:2015 [58 - clause 6.6] ISO 11040-8:2016 [40 - clause 7.4]	Risk analysis and control report [32] Test report [41 - clause 5] incl. reports for simulated user studies, testing access to the sharp in safe mode [41 - Annex A & B]; Labelling & Instructions for use [41 - clause 6] Test reports for container closure integrity (CCI) "after the assembly process, shipment and during long-term storage up to end of shelf life" [11 - p.10]	See ER 8.1 [5] **New:** a) risk reduction of unintended needle stick injuries, b) includes safe handling **EU MAA: [10]** eCTD 3.2.P.2.5 Microbiological Attributes for container closure integrity

GSPR	Applicable? (Yes or No)	Applicable standard to apply / alternative reference	Demonstration of compliance with respect to target DDC or justification if GSPR is not applicable	Intelligence mapping (reference to current requirements) & comments
			Note: BSI Interpretation [19]: c) relates to sample collecting devices; d) relates to reusable devices or sample collecting devices	
11.2	No	n/a	PFS will not be cleaned, disinfected and/or re-sterilized.	n/a
11.3	No	n/a	Note: container closure system (CCS) of DDC is designated as sterile barrier system. Secondary packaging (assembling of plunger rod, finger flange, safety device) is non-sterile. See GSPR 11.4.	n/a
11.4	Yes	**Device components/bulk syringe:** ISO 11040-4:2015 [58] ISO 11040-7:2015 [79] ISO 11135:2014* [52] ISO 11138-1:2017 [80] ISO 11138-2:2017* [81] ISO 11737-1:2018* [82] EN ISO 11737-2:2009 [83] ISO 11140-1:2014* [84] **Finished DDC:** EN 556-2:2015 [85] EN ISO 13408-1:2015 [86] & further parts of ISO 13408 as applicable	Description of relevant manufacturing/sterilization and packaging/assembly procedures Aseptic process definition [86 - Annex B] Test report device components (bulk syringe & plunger stopper) for sterility [58 - clause 6] Release & stability test report/Certificate of Analysis of representative lot of DDC for sterility Test reports for container closure integrity (CCI) “after the assembly process, shipment and during long-term storage up to end of shelf life”.[40,40 - clause 7.5]	See ER 8.3 [5] **New:** evidence of the package integrity **EU MAA:** [10] eCTD 3.2.P.3.3 Description of Manufacturing Process and Process Controls for aseptic filling and packaging/assembling of DDC

GSPR	Applicable? (Yes or No)	Applicable standard to apply / alternative reference	Demonstration of compliance with respect to target DDC or justification if GSPR is not applicable	Intelligence mapping (reference to current requirements) & comments
		EU GMP Guideline Annex I [87] Ph. Eur. 5.1.1. Methods of preparation of sterile products [63] Ph. Eur. 2.6.1. Sterility [64] Ph. Eur. 2.6.8. Pyrogens [65] Ph. Eur. 2.6.14. Bacterial endotoxins [66] EN ISO 14971:2012 [32] / ICH Q9 [88] ICH Q5C [43] ASTM D4169-16 [44]		
11.5	Yes	**Device components/bulk syringe** EN ISO 13485:2016 [30 - clause 7.5.7] EN ISO 14937:2009 [89] ISO 11135:2014* [52] ISO 11138-1:2017 [80] EN ISO 11138-2:2017* [81] ISO 11737-1:2018* [82] EN ISO 11737-2:2009 [83] ISO 11140-1:2014* [84]	**Device components/bulk syringe** Sterilization process validation including installation qualification, operational qualification, performance qualification [52 - clause 9, Annex D.9] Test Report for sterility [83 - Annex A]	See ER 8.4 [5] **New:** includes processing and packaging **Finished DDC:** **EU MAA:** [10,11] eCTD 3.2.P.3.5 Process Validation for aseptic processing CCS, assembly process of DDC

GSPR	Applicable? (Yes or No)	Applicable standard to apply / alternative reference	Demonstration of compliance with respect to target DDC or justification if GSPR is not applicable	Intelligence mapping (reference to current requirements) & comments
		Filling & sealing of bulk syringe EU GMP Guide Annex I [87] EN 556-2:2015 [85] EN ISO 13408-1:2008 [86] & further parts of 13408 as applicable	Aseptic process validation including Risk assessment for contamination during aseptic processing [86 - clause 5.2] Process simulation report [86 - clause 10.8] Assembly and packaging process validation/critical controls	
11.6	Yes	ISO 14644 all parts [90] ISO 11135:2014* [52] EU GMP Guideline Annex 1 [87]	Manufacturing and environmental control procedures in compliance with ISO 14644 [90] Monitoring and controls of sterilization activities [52 - clause 10] EU GMP Certificate / Manufacturer Authorisation for sterile drug products (1.1.2 aseptically prepared) [91] for DDC activities	See ER 8.5 [5] **New:** includes facilities & packaging **EU MAA:** GMP Certificate/Manufacturer Authorisation of DDC manufacturing site
11.7	No	n/a	DDC is not considered to be sterilized prior to use.	n/a
11.8	No	n/a	DDC is only placed in one configuration on the market (sterile).	n/a
12 (12.1 & 12.2)	No	n/a	See marketing authorisation application (MAA) Directive 2001/83/EC [3].	EU MAA
13.1	No	n/a	Device part does not include materials of human origin.	n/a

GSPR	Applicable? (Yes or No)	Applicable standard to apply / alternative reference	Demonstration of compliance with respect to target DDC or justification if GSPR is not applicable	Intelligence mapping (reference to current requirements) & comments
13.2	Yes	Regulation (EU) No 722/2012 [92] ISO 22442-1:2015* [93] ISO 22442-2:2015* [94]	Risk assessment according to Annex I of Regulation (EU) No 722/2012 [92] Risk control report if applicable (to be assessed if substances of animal origin are present in device components)	See ER 8.2 [5] **New:** scope of GSPR 13: substances of biological origin, reference to regulation **EU MAA:** TSE Statement acc. EMA/410/01 rev.3 [95] for primary packaging material / CCS
13.3	No.	n/a	It is not expected that device components contain biological substances other than those referred in 13.2.	n/a
14.1	No.	n/a	Safety device is already installed so that the DDC is ready to use.	n/a
14.2 (a-g)	Yes, besides d) as there is no interaction with IT/software.	IEC 62366-1:2015* [42] ASTM D4169-16 [44] ISO 11040-4:2015 [58 - clause 6.6] ISO 11040-8:2016 [40] EN ISO 14971:2012 [32] ICH Q5C [43] Ph. Eur. 2.9.17. Test for Extractable Volume of Parenteral Preparations (Section Pre-filled Syringes) [67]	Summative Evaluation Report [42 - clause 5.9] Test reports for container closure integrity (CCI) “after the assembly process, shipment and during long-term storage up to end of shelf life”.[11 - p.10] Risk analysis and control Report for interference with other devices (e.g. alcohol swap, sharps container) [32] Stability data per ICH Guideline [43] Test Report for performance requirements [40 - clause 8]	See ER 9.2 for a, b, f, g [5] See ER 7.3 for c [5] See ER 7.6 for e [5] **New:** GSPR 14.2 c: including liquids, substances; **EU MAA:** [10,11] eCTD 3.2.P.8 Stability eCTD 3.2.P.2.5 Microbiological Attributes for container closure integrity

GSPR	Applicable? (Yes or No)	Applicable standard to apply / alternative reference	Demonstration of compliance with respect to target DDC or justification if GSPR is not applicable	Intelligence mapping (reference to current requirements) & comments
14.3	No	n/a	No risk for explosion or fire given.	n/a
14.4	No	n/a	No adjustment, calibration, maintenance foreseen.	n/a
14.5	No	n/a	Single integral DDC	n/a
14.6	No	n/a	No measurement, monitoring or display scale.	n/a
14.7	Yes	EN ISO 14971:2012 [32] ISO 23908:2011[41 - clause 6]	Risk analysis and control report (safety device) Instructions for safe disposal in IFU see GSPR 23.4 v	**New**
15.1	No	n/a	No measuring function.	n/a
15.2	No	n/a	No measuring function.	n/a
16	No	n/a	No exposure to radiation due to the device.	n/a
17	No	n/a	Device does not incorporate electronic programmable systems and software.	n/a
18	No	n/a	No active device.	n/a
19	No	n/a	No active implantable device.	n/a
20.1	Yes	ISO 11040-8:2016 [40] ISO 23908:2011 [41] EN ISO 14971:2012 [32]	Test Report Performance Requirements [40 - clause 8] Simulation studies [41 -Annex A & B] Risk analysis and control report [32]	See ER 12.7 [5]
20.2	No.	n/a	PFS does not generate vibrations.	n/a

GSPR	Applicable? (Yes or No)	Applicable standard to apply / alternative reference	Demonstration of compliance with respect to target DDC or justification if GSPR is not applicable	Intelligence mapping (reference to current requirements) & comments
20.3	No.	n/a	PFS does not generate noises.	n/a
20.4	No.	n/a	No connection to energy supply.	n/a
20.5	No	n/a	No (re-)fitting applicable. PFS with safety device ready to use.	n/a
20.6	No	n/a	PFS does not attain any dangerous temperatures.	n/a
21.1	Yes	ISO 11040-8:2016 [40,40 - clause 7.5] Ph. Eur. 2.9.17. Test for Extractable Volume of Parenteral Preparations (Section Pre-filled Syringes) [67]	Test Report for extractable volume	See ER 12.8.1 [5] **New:** instead of flow rate → amount to be delivered **EU MAA:** [10] eCTD 3.2.P.5.1 Specifications eCTD 3.2.P.5.4. Batch Analysis
21.2	No	n/a	PFS contains only one dose for injection. There is no risk to overdose.	n/a
21.3	No	n/a	No controls or indicators needed on the PFS.	n/a
22.1	Yes	IEC 62366-1:2015* [42] EN ISO 14971:2012 [32]	Use Specification for lay persons [42 - clause 5.1] Risk analysis and control report (known and foreseeable hazards, use error) [32 - clause 4.2,4.3,42 - clause 5.3] User Interface Specification for lay persons [42 - clause 5.6] Summative Evaluation Report [42 - clause 5.9]	**New**

GSPR	Applicable? (Yes or No)	Applicable standard to apply / alternative reference	Demonstration of compliance with respect to target DDC or justification if GSPR is not applicable	Intelligence mapping (reference to current requirements) & comments
22.2	Yes	IEC 62366-1:2015* [42] ISO 23908:2011 [41]	Use Specification for lay persons [42 - clause 5.1] Risk analysis and control report (known and foreseeable hazards, use error) [32 - clause 4.2 & 4.3,42 - clause 5.3] User Interface Specification for lay persons [42 - clause 5.6] Simulated use study report [41] Summative Evaluation Report [42 - clause 5.9]	**New**
22.3	Yes	IEC 62366-1:2015* [42]	Summative Evaluation Report [42 - clause 5.9] for information for safety as contained in IFU/Labelling [42 - clause 4.1.3]	**New**
Chapter III Requirements regarding the information supplied with the device – General Requirements for Label and IFU				
23.1 a	Yes	IEC 62366-1:2015* [42] ISO 23908:2011 [41 - clause 6.1]	Product Labelling/IFU Specification Information for safety [42 - clause 4.1.3] Summative Evaluation Report[42 - clause 5.9]	**New** **EU MAA:** Readability: Articles 59(3), 61(1), 63(2) of Directive 2001/83/EC [3] User Testing [96]
23.1 b	Yes	QRD Template [97]	Product labelling specification	See ER 13.1 [5] QRD Template [97]
23.1 c	Yes	QRD Template [97]	Product labelling specification	**New** QRD Template [97]
23.1 d	Yes	ISO 23908:2011 [41 - clause 6] EN ISO 14971:2012	Product Information incl. SmPC, Package Leaflet (PL), IFU Packaging design specification	See ER 13.1 [5] QRD Template [97]

GSPR	Applicable? (Yes or No)	Applicable standard to apply / alternative reference	Demonstration of compliance with respect to target DDC or justification if GSPR is not applicable	Intelligence mapping (reference to current requirements) & comments
		[32 - clause 6.2]		
23.1 e	No	n/a	Each finished medicinal product contains one PL/IFU.	n/a
23.1 f	No	n/a	Medicinal product is supplied with paper based product information.	n/a
23.1 g	Yes	EN ISO 14971:2012 [32]	Residual risk analysis and control report [32] Product Information incl. SmPC, Package Leaflet, Instructions for Use	**New**
23.1 h	Yes	EN ISO 15223-1:2016 [98]	Product Information incl. SmPC, Package Leaflet, Instructions for Use	See ER 13.2 [5]

Table 3: GSPRs 23.2 Information on the label & 23.3 Information on the packaging which maintains the sterile condition of a device

GSPR	Applicable? (Yes or No)	Reference to Medicinal Product Label (primary/secondary packaging) Justification if GSPR is not applicable	New Requirement or reference to ER of MDD
23.2 Information on the label			
23.2 a	Yes	Name of medicinal product [97] Note: Trade name of medicinal product is relevant	ER 13.3a [5]
23.2 b	Yes	Pharmaceutical form and contents / method and routes of administration [97]	ER 13.3b [5]
23.2 c	Yes	Name and address of marketing authorisation holder (MAH) [97]	ER 13.3a [5]
23.2 d	Yes	Name and address of marketing authorisation holder (MAH) [97]	ER 13.3a [5]

GSPR	Applicable? (Yes or No)	Reference to Medicinal Product Label (primary/secondary packaging) Justification if GSPR is not applicable	New Requirement or reference to ER of MDD
23.2 e	Yes	Medicinal product label lists medicinal product contained in PFS Note: No further information is addressed (see GSPR 13.2)	**New**
23.2 f	Yes	If substances are present as per GSPR 10.4 to be included on Medicinal Product Label	ER 7.5 [5] **New scope**, needs to be assessed
23.2 g	Yes	Batch number [97] Note: Single integral DDC has only one batch number	ER 13.3d [5]
23.2 h	No.	PFS regulated as medicinal product. No UDI applicable.	n/a
23.2 i	Yes	Expiry date [97]	ER 13.3e [5]
23.2 j	No	Expiry date is labelled.	n/a
23.2 k	Yes	Special storage conditions, methods and route(s) of administration [97]	ER 13.3i [5]
23.2 l	Yes	n/a: no requirement in Directive 2001/83/EC [3]; Note: CCS is sterile barrier system only	ER 13.3c [5] **New**: now requirement and indication of sterilization method
23.2 m	Yes	Other special warnings [97]	ER 13.3k [5]
23.2 n	Yes	method and route(s) of administration [97]	ER 13.3f [5]
23.2 o	No.	PFS will not be reprocessed.	n/a
23.2 p	No.	PFS is not custom-made.	n/a
23.2 q	No.	PFS is not registered as medical device.	n/a
23.2 r	Yes	Statement of active substance(s), list of excipients [97]	**New**

GSPR	Applicable? (Yes or No)	Reference to Medicinal Product Label (primary/secondary packaging) Justification if GSPR is not applicable	New Requirement or reference to ER of MDD
		Note: Device is not composed of but contains medicinal product to be introduced in the human body.	
23.2 s	No.	PFS is not implantable.	n/a
23.3 Information on the packaging which maintains the sterile condition of a device			
23.3	No	There is no packaging maintaining the sterile condition of a device other than the container closure system itself maintaining the sterile condition of the medicinal product and the administration parts of the device. Presentation of single integral DDC follows Directive 2001/83/EC [3]	n/a

Table 4: GSPR 23.4 Information in the instructions for use

GSPR	Applicable? (Yes or No)	Reference to Product Information for Medicinal Product	To be included in IFU	New Requirement or reference to ER of MDD
23.4 a	Yes	SmPC/Package Leaflet (PL) for a, c, k, n	No	ER 13.6a [5] **New:** additional requirements (e, f, l, r)
23.4 b	Yes	SmPC: Pharmaceutical form, clinical particulars [97] Package Leaflet [97]	No	ER 13.4 [5]

GSPR	Applicable? (Yes or No)	Reference to Product Information for Medicinal Product	To be included in IFU	New Requirement or reference to ER of MDD
23.4 c	Yes	Information relevant to medicinal product included in SmPC/Package Leaflet [97]	Information addressing device to be included in IFU Note: device delivery function & needle stick protection	**New**
23.4 d	No	Article 32 [2] only for implantable and class III devices required.	n/a	n/a
23.4 e	Yes	Basic information included in SmPC/PL [97] and references to IFU in SmPC/Package Leaflet	Yes	ER 13.6b [5]
23.4 f	Yes	Reference to IFU	Yes	**New**
23.4 g	Yes	Information should be included in SmPC/Package Leaflet	Address residual risks and information on device and administration in IFU	ER 13.6b [5] **New:** residual risks and contra-indications
23.4 h	Yes	Reference to IFU	Yes	ER 13.6d,p [5]
23.4 i	Yes	Reference to IFU	Yes	ER 13.6i [5]
23.4 j	Yes	SmPC is for healthcare professionals /Package Leaflet indicates training/requirements	Yes	ER 13.3j, 13.6a [5] **New:** training/qualification of user
23.4 k	Yes	Reference to IFU	Yes	ER 13.6d [5]
23.4 l	Yes	Reference to IFU	Yes	**New**
23.4 m	No	PFS is supplied sterile and for single use.	n/a	n/a

GSPR	Applicable? (Yes or No)	Reference to Product Information for Medicinal Product	To be included in IFU	New Requirement or reference to ER of MDD
23.4 n	No	PFS is not reusable.	n/a	n/a
23.4 o	No	PFS is not reusable.	n/a	n/a
23.4 p	Yes	Reference to IFU	Yes	ER 13.6h [5]
23.4 q	Yes	Reference to IFU	Yes	ER 13.6c [5]
23.4 r	No.	No radiation is emitted by PFS.	n/a	n/a
23.4 s	Yes	Information addressing medicinal product included in SmPC/PL	Information addressing device to be included in IFU	ER 13.6k-m [5] **New:** information related to GSPR 10.4
23.4 t	No	Note: medicinal product to be administered, device delivery function only. Information addressed in SmPC/PL.	n/a	n/a
23.4 u	No	PFS is not implantable.	n/a	n/a
23.4 v	Yes	Information of safe disposal included in SmPC/PL [97]	Yes	ER 13.6n [5] **New:** special attention to bio-hazard aspects (e.g. sharps)
23.4 w	Yes	Information provided in PL [97]	Yes	**New**
23.4 x	No	DDC has intended medical purpose, Article 1(2) [2] not applicable.	n/a	n/a
23.4 y	Yes	SmPC/PL underlie version control [97]	Yes	ER 13.6q [5]
23.4 z	Yes	SmPC/PL [97] as safety reporting follows Directive 2001/83/EC [3]	No	**New**

GSPR	Applicable? (Yes or No)	Reference to Product Information for Medicinal Product	To be included in IFU	New Requirement or reference to ER of MDD
23.4 aa	No	PFS is not implantable.	n/a	n/a
23.4 ab	No	PFS does not contain named features.	n/a	n/a

4. Results & Discussion

This chapter first summarizes the high-level conclusions that can be made as an output of this case study analysis. A deeper look will then be taken in order to identify redundancies and between MDR's Annex I and the content of the marketing authorisation application (MAA) dossier (i.a. eCTD Module 3). It will become evident that there are overlapping topics or interfaces that are required to be addressed from a medical device as well as a medicinal product perspective. However, the case study also revealed many new requirements outlined in Annex I that pose a risk for potential gaps in current device development. Therefore, impact needs to be evaluated. As this case study is not able to address all questions that have come up thus far in public discussions, remaining open questions relevant for this target DDC and the GSPRs will be highlighted.

4.1. High level evaluation of analysis

From the case study performed on the pre-filled syringe the following can be concluded from a high-level perspective:

4.1.1. GSPRs

Many GSPRs originate from the ERs of the MDD and are unchanged. For example, GSPR 5 corresponds to the second part of ER 1 outlining requirements around use error and consideration of the technical knowledge possessed by the intended user. Also, GSPR 6 and 7 are equivalent to ER 4 and 5, requiring stability data and shipping studies to ensure that the performance characteristics of the Device/DDC are maintained during the shelf life and its conditions of use.

The arrangement of the GSPRs has partly changed and was regrouped under main topics. For example, the labelling section in Annex I of the MDR distinguishes now clearly between general labelling requirements (GSPR 23.2) and those for a sterile device (GSPR 23.3). The MDD mainly summarized them in ER 13.3.

There are completely new GSPRs as well as expanded GSPRs that are now applicable. Some of the new requirements are the following: GSPR 10.6 requires risk reduction posed by particles resulting of the device. However, the main focus is on nanoparticles which is not a main aspect of this case study. Also, GSPR 11.3 for devices "having a specific microbial state" [2 - Annex I: GSPR 11.3] is a new requirement and probably needs more background in regard to which devices are in scope. GSPR 14.7, ensuring safe disposal of the device is another new requirement that manufacturers also must consider.

Some other GSPRs having their origin in the MDD have now been expanded requiring further detail to demonstrate compliance: GSPR 10.1 introduces new aspects (GSPR 10.1

subparagraphs c, d, f, g, h) to consider with regard to the materials used. Surface and mechanical properties as well as impact of manufacturing processes on materials should be evaluated. Also, GSPR 11 and its subclauses have become more extensive revealing additional requirements. For example, GSPR 11.4 requires additional evidence of package integrity for the intended user. GSPRs 22.1-3 request usability engineering for lay persons, if they are part of the intended user group, which was not addressed to this extent in the MDD.

New requirements introduced with the MDR are a consequence of the current state-of-the-industry. These aspects might be new in the context of the ERs/GSPRs but it is expected that many of them are already addressed by the manufacturers to a specific extent. Globally recognized standards such as EN ISO 14971:2012 [32], IEC 62366-1:2015 [42] and ISO 11040-8:2016 [40], already incorporating certain new aspects found in MDR's Annex I, are considered to be part of a comprehensive device development. This is true in the case of risk management. GSPR 3 is new, although the content is covered by EN ISO 14971:2012 [32].

4.1.2. Target DDC

It can be concluded that a significant subset of the GSPRs is not applicable to a single integral DDC like a pre-filled syringe. Requirements for devices having a diagnostic or measuring function (GSPR 15), emission of radiation (GSPR 16), electronic programmable devices (GSPR 17) active devices (GSPR 18), implantable devices (GSPR 19), devices posing thermal risks (partly GSPR 20) or supplying energy (partly GSPR 21) can be disregarded for this single integral DDC.

The applicability of the product information to be supplied with the device is unclear as the DDC underlies Directive 2001/83/EC [3] and follows the medicinal product labelling requirements in the first instance. The MDR reveals new information that needs to be labelled according to the GSPRs. As of now, there is no further information available if these GSPRs are fully applicable to the medicinal product labelling.

Many GSPRs are fulfilled by showing similar data for compliance. For example, data on container closure integrity is an integral aspect that can demonstrate compliance for several GSPRs (GSPRs 10.5, 11.1 & 14.2).

4.1.3. Mapping with EU MAA

In general, there are some GSPRs (e.g. GSPRs 6, 10.1 & 10.3) that are covered in parallel in the dossier of the European marketing authorisation application (MAA). Drug container interactions in particular comprise the bulk of these requirements. For example, stability

data of the pre-filled syringe or data on suitability of the container closure system with regard to the medicinal product are also relevant contents of Module 3 of the eCTD. Also, aseptic processing of the drug product and its container closure system as well as aspects with regard to sterility and container closure integrity are integral parts of the medicinal product dossier.[10]

Risk management is mainly focused on the drug part in the Risk Management Plan for medicinal products within the submission. However, applicable guidance [38,39] outlines also the consideration of risks related to the administration device in addition to medication errors that may result.

Aspects regarding device components and their processing are not documented in detail in the MAA dossier. Labelling aspects have some common requirements, however it is evident that there are other requirements that need to be addressed.

4.2. Identification of redundancies

This chapter takes a closer look on the GSPRs that are also currently addressed in the MAA due to drug product or DDC aspects. It will be evaluated if the information already provided in the dossier can be leveraged to fulfil the relevant GSPRs.

4.2.1. Risk Management

Important identified and potential risks relating to the administration of the medicinal product by the device must be outlined in the Risk Management Plan for medicinal products (RMP-MP) submitted together with the MAA to the CA.[38] The EMA together with the Heads of Medicines Agencies (HMA) have issued a guideline [38] that highlights valid points to consider in the RMP-MP. Especially mentioned are “risks related to the administration procedure” [38 - p.17] during use of the medical device. Medication errors defined as “an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient” [39 - p.5], are another integral part of the RMP-MP.

The guidance addressing medication errors [39] references ISO standards EN ISO 14971:2012 *Application of Risk Management to Medical Devices* [32], IEC 62366-1:2015 *Medical Devices – Application of Usability Engineering to Medical Devices* [42] and EN ISO 13485:2012 *Medical devices – Quality management systems – Requirements for regulatory purpose*, 7.3.6 (Design and Development Validation) (recently replaced by EN ISO 13485:2016, 7.3.7 (Design and Development Validation) [30]) as applicable for administration devices. Several aspects of the guidance [39] and referenced standards must be considered.

The RMP-MP may include safety considerations with regard to the product design and the potential risks for medication errors if relevant. Representative data related to medication errors and potential corrective and preventive actions are to be included from clinical trials as well as any effects of device failure. If applicable, reports of the marketed product can also contribute to risk management.[39] As stated in the guidance "the manufacturer should assess known and foreseeable hazards associated with the medical device in both normal (intended use) and fault conditions" [39 - p.12]. This statement corresponds with GSPR 3 b and c. Further risk management activities (e.g. risk minimization) are also relevant to medication errors. Considering the application of the relevant standards (EN ISO 14971, IEC 62366, EN ISO 13485) by the manufacturers/MAHs, specific sections of the RMP-MP could cover already important parts of MDR's Annex I (to be considered: GSPRs 1-5 & 8). Vice versa, by applying a comprehensive risk management for the DDC, information relevant for the RMP-MP could be leveraged thereof. However, aspects with regard to PFS devices included in the RMP-MP are expected to be few in comparison to more complex devices.

Training provided to patients and caregivers is also mentioned in this guidance [39] as important tool to avoid medication errors. It is outlined that HCPs are responsible to ensure that patients are appropriately trained on self-administration prior to use. Pharmacists take a key role in verifying that the patient received appropriate treatment and was sufficiently informed of and/or trained on the safe use. This corresponds with GSPR 4 c as well as GSPR 23.4 j & w.

4.2.2. Suitability of the Drug-delivery Device

GSPR 10.3, requiring scientific data demonstrating the suitability of the device for the medicinal product to be administered, is already an integral part of the MAA.[10] In addition, GSPR 10.1, dealing with the choice of materials and biological safety evaluation of the device, can be expected in the MAA as part of the suitability documentation. Within Module 3 of the eCTD, sections 3.2.P.2.4 Container Closure System and 3.2.P.2.6 Compatibility cover aspects to be considered.[10] Especially 3.2.P.2.4 includes the following aspects:

> *"The suitability of the container closure system (described in 3.2.P.7) used for the storage, transportation (shipping) and use of the drug product should be discussed. This discussion should consider, e.g., choice of materials, protection from moisture and light, compatibility of the materials of construction with the dosage form (including sorption to container and leaching) safety of materials of construction, and performance (such as reproducibility of the dose delivery from the device when presented as part of the drug product."* [10 - p.17 Module 3]

Further details of the compatibility of the medicinal product with the delivery device covering aspects like sorption and stability are further addressed in section 3.2.P.2.6 Compatibility of the MAA.[10] eCTD section 3.2.P.7 Container Closure System contains additional information on the pre-filled syringe and its components including relevant specifications.[10 - p.21 Module 3,11] In order to address GSPR 10.1 h, eCTD section 3.2.P.5.4 Batch analyses should minimally contain analysis results of representative DDC lots.[11]

Stability data required per GSPR 6 and GSPR 14.2 g are already included in the Module 3 section 3.2.P.8.[10] According to ICH Guideline Q1A [99] stability studies should be performed minimally in the container closure system to be marketed, including any secondary packaging.[99 - p.7] In addition, ICH Q5C [43] indicates to consider several aspects of the container closure system for stability studies. The sealed bulk syringe would be considered the container closure system in this case study. In order to test the performance requirements of the device, the assembled pre-filled syringe should be the preferred form to generate stability data.[11]

As outlined in GSPR 7, data to support accurate performance characteristics during and after transport as well as storage are captured in the MAA (eCTD 3.2.P.2.4 Container Closure System for suitability of the device and 3.2.P.3.5 Process Validation for shipping validation).[11]

As required by GSPRs 10.5, 11.1 & 14.2, container closure integrity (CCI) of the pre-filled syringe needs to be demonstrated in order to avoid “unintentional ingress of substances” [2 - Annex I: GSPR 10.5] into the device. This is already addressed in eCTD section 3.2.P.2.5 Microbiological Attributes of the MAA: “For sterile products, the integrity of the container closure system to prevent microbial contamination should be addressed.” [10 - p.17 Module 3]. This should include data from development and stability as well as shipping studies.[27 - p.97]

Delivery functionality of the pre-filled syringe should be captured in the performance requirements to be shown for suitability of the drug delivery device (eCTD 3.2.P.2.4) [11 - p.7]. Therefore, the accuracy of the extractable volume as required by GSPR 21.1 is part of this section.[11] Specifications submitted in eCTD section 3.2.P.5.1. should also contain this as a release test item.[27 - p.98]

In conclusion, considering all relevant standards, this documentation should also serve to meet the needs of the notified body.

4.2.3. Process Validation

As required by GSPR 11.5, manufacturing including packaging as well as sterilisation should be performed using validated processes. Documentation regarding aseptic filling of the medicinal product into the bulk syringe and its sealing is required in eCTD section 3.2.P.3.5 Process Validation.[10 - p.18 Module 3] Any further assembling and packaging processes should also follow validated procedures [31] and be part of this dossier section.[11,27,100] However, this covers only the drug device combination part of the manufacturing and does not include validation of the sterilization process for relevant device components.

4.2.4. Labelling

Annex I of the MDR lists multiple requirements to be considered for labelling and information to be supplied (IFU) to the user. A significant part of them are already addressed by the medicinal product information (incl. labelling) to be provided. For example, basic data like name of the product, manufacturer (for medicinal product the MAH is the main reference to be listed), lot number, expiry date as well as information on storage/handling instructions are already considered per medicinal product requirements.[97]

4.3. Identification of potential gaps

This chapter contains a review of the analysis table with regard to new GSPRs not already covered by the ERs of the MDD. Also evaluated, is whether any requirements may have already been addressed to an extent from a medicinal product perspective. Any impact of these new requirements will be assessed.

4.3.1. Risk Management

Chapter 4.2.1 highlighted potential overlaps with the Risk Management Plan for medicinal products. However, as introduced by the MDR, there are new risk management requirements that manufacturers/MAHs should ensure to address throughout the development. Chapter I of MDR's Annex I incorporates relevant GSPRs focusing on risk management: GSPR 2 is new and interpreted as a general clarification on risk reduction. It is highlighted that this should avoid "adversely affecting the benefit-risk ratio" [2 - Annex I: GSPR 2].

> *"The requirement to reduce risks as far as possible remains a discrepancy with the current risk management standard EN ISO 14971:2012, as addressed in Annexes ZA and ZB […]. This requirement continues to be to reduce risks as far as possible without regard for economic consideration."* [18 - p. 2]

GSPR 3 is considered a new requirement regarding risk management. It lists the requirements that should be fulfilled by a risk management process. Although the MDD did not include an equivalent ER, the aspects are aligned with EN ISO 14971:2012 [18,32]. Consequently, this GSPR should not pose a major gap in medical device development in expectation that manufacturers are following this established harmonised standard [32 - Annex ZA]. However, it is now essential to fulfil the GSPRs, giving risk management major importance. Also, as highlighted in chapter 4.2.1, relevant points may also need to be addressed in parallel in the RMP-MP with regard to medication errors.
GSPR 4 originates from ER 2 of the MDD. However, it now includes a residual risk evaluation for each identified hazard as well as an overall residual risk evaluation for acceptability. This is in alignment with EN ISO 14971:2012 Annex ZA Point 4(c) [18,32]. It should also trigger the provision of more information about residual risks and further warnings/contra-indications to the intended user (refer to GSPR 23.1 g, 23.4 g, j).
ER 6 of the MDD was updated and is now represented by GSPR 8 of the MDR. It highlights the risk-benefit evaluation comprehensively, including mention of minimization of “all known and foreseeable risks” [2 - Annex I: GSPR 8]. However, the overall intent has not changed.

In conclusion, the MDR now expands risk management activities to be demonstrated and requires it to be more comprehensive. However, as outlined before, manufacturers who have already proactively applied EN ISO 14971:2012 [32], should not identify a significant gap. Nevertheless, there are still discrepancies between the standard and the GSPRs to be considered.[18]

4.3.2. GSPR 10 - Chemical, physical and biological properties

Within GSPR 10.1 some new requirements were introduced (subparagraphs c, d, f, g, h): compatibility aspects, impact of manufacturing process of device materials, surface characteristics as well as evidence that the specifications are met. This should be already covered by a comprehensive suitability evaluation as well as by the application of standards such as EN ISO 10993-18:2009 [46]. Therefore this is considered as an alignment to current standards as well as further guidance/compendial requirements.

A special focus should be given to the assessment of GSPR 10.4. The scope of relevant substances or particles to be assessed that are potentially released by the device, no longer limited to leaking [5 - Annex I: ER 7.5], is significantly increased by the introduction of GSPR 10.4. ER 7.5 of the MDD was focusing more on leaking of phthalates in the context of carcinogenic, mutagenic or toxic to reproduction (CMR) substances.[2,5] Endocrine-

disrupting substances are now additionally highlighted and also a relevant concentration limit is given (0.1 % weight/weight).[2] A following justification needs to be submitted mentioning the required aspects according to GSPR 10.4.2 in case this concentration of relevant substances will be exceeded. Also, in this case the device needs to be labelled accordingly (refer to GSPRs 23.2 f & 23.4 s). Previously this was required for phthalates only, independent of any concentration as per ER 7.5 [5]. The following legislation should be considered as its applicability in the context of devices is now mandatory: Regulation 1272/2008 Part 3 of Annex VI [61], Regulation (EC) No 1907/2006 (REACH) Article 59 [62] as well as Regulation (EU) No 528/2012 Article 5(3) [63] and resulting compliance with the Commission Delegated Regulation (EU) 2017/2100 Annex Section A [24]. In addition, Commission Implementing Decisions like (EU) 2018/636 [101] and (EU) 2017/1210 [102] identifying further phthalates as of very high concern as per REACH Regulation [71] have to be taken into account as well.[74] New guidance is expected according to GSPRs 10.4.3 & 10.4.4, that should be considered for the justification. The mandate for the guideline on the risk-benefit assessment of phthalates as referred to in GSPR 10.4.3 was approved by the Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) on 28 September 2017, giving it a deadline of 31 March 2019.[103] Subsequently, on 15 March 2019, a preliminary version of this guideline [74] was published for public consultation. According to this publication, in case manufacturers identifying the respective substances in a concentration above 0.1% w/w must provide a comprehensive justification where several aspects need to be considered: the potential use of alternatives “defined as substances, materials, designs and medical treatments that can be used to replace the use of CMR and/or ED substances in medical devices” [74 - p.10] together with their risks identified should be assessed against the use of the phthalate identified. Also, factors like “functionality, performance and the overall benefit risk-ratio of the medical device” [74 - p.9] are in scope of the justification. It is further made clear that this justification is to be generated for each substance, but also for the combination of relevant substances.[74] Although this guideline addresses phthalates, the proposed principles of the benefit-risk assessment can be leveraged for other concerned CMR or ED substances especially as long as there is no further guidance available.[104] As mentioned above, the MDR does no longer limit the wording to *leaking* of substances as the ER 7.5 of the MDD did, but defines it more general as *release*. This could potentially result in further analytical activities beyond an extractable/leachable study for identification of the presence of relevant substances. Overall, GSPR 10.4 is one of the high-impact GSPRs manufacturers have to deal with now in order to ensure compliance with MDR’s Annex I.

GSPR 10.6 focuses on particles released by the device and is first introduced by the MDR. However, as far as a single integral DDC like a pre-filled syringe is concerned, it can be

concluded that particles are already considered accordingly in respective technical standards [40,58] as outlined in the analysis table. By following these standards, compliance is ensured for the empty sub-assembled syringes as well as for the finished pre-filled syringe. Moreover, there are compendial requirements to be met concerning particle free solutions for injection considering both, sub-visible and visible particles (Ph. Eur. 2.9.19. [75], Ph. Eur. 2.9.20. [76]). Test requirements for the finished DDC should also be part of the MAA dossier (eCTD section 3.2.P.5 control of the drug product). According to the BSI publication [18] special consideration is drawn to nanoparticles by this GSPR. Consequently, the impact is regarded as low for a PFS and an alignment to the current state of the art becomes evident.

4.3.3. GSPR 11 - Infection and microbial contamination

GSPR 11.1 introduces increased safety considerations, especially with regard to needle stick injuries. This becomes relevant for the pre-filled syringe. A safety device that avoids needle stick injuries and potential bio-hazards after use, should be fundamental to fulfil this requirement. However, this is already considered in ISO 11040-8:2016 [40 - clause 6.10] with a link to the applicable ISO 23908:2011 [41]. This GSPR also addresses the objective of Directive 2009/104/EC [78] to conform with minimum safety requirements for caregivers administrating the PFS. In conclusion, manufacturers/MAH should ensure that a sharps injury protection is considered for the final PFS or otherwise duly justify why no such protection is needed.

With GSPR 11.4, special consideration is now given to the evidence of package integrity. In general, this is an aspect to be considered and covered in the development of a single integral DDC if applicable. However, in the context of the target DDC used in the case study, this is not applicable to the same extent that it is for sterile devices where primary packaging ensures maintenance of device sterility. The container closure system (bulk syringe) of the PFS is considered to maintain the sterility of the medicinal product as well as of the device components to be introduced in the body. The packaging (e.g. blister) protecting the PFS is not in charge of maintaining the sterility. However, warnings should be included in the product information, that draw the attention of the user to the intactness of the PFS. As verified in a current PFS product information [28] this is already considered by MAHs.

GSPR 11.6 introduces packaging next to manufacturing as well as facilities to be appropriately controlled in the context of sterile processing. However, in the given case study and as outlined above, sterile/aseptic processing of the PFS ends at sealing of the filled bulk syringe. Packaging of the sterilized device components prior to filling as well as aseptic processing should follow the ISO 14644 series [90]. This should already be established. Moreover, as soon as aseptic filling is concerned, EU GMP Annex 1

requirements [87] that ensure additionally the applicability of relevant parts of ISO 14644 [90] should be followed. Manufacturers can rely on their Manufacturer's Authorisation as well as GMP Certificate for the qualification of aseptic manufacturing.[91] Further assembling and packaging of the PFS is considered out of scope as outlined above.

4.3.4. GSPR 13 - Devices incorporating materials of biological origin

GSPR 13 is generally considered a high impact change of the MDR.[18] However, as far as it concerns a PFS, only GSPR 13.2 may be applicable, originating from MDD's ER 8.2. There are only minor changes in the wording. The MDR introduces the applicability of Regulation (EU) No 722/2012 [92] with GSPR 13.2. The content of the Regulation is considered consistent with the requirements of GSPR 13.2.[18] Annex I of this Regulation requires a risk assessment. Moreover, for medicinal products as per EMA/410/01 rev.3 [95] a TSE statement is part of the MAA dossier (eCTD section 3.2.R) [10 - p.26 Module 3]. This also includes primary packaging material as it is in direct contact with the drug product.[95] Therefore, this is considered low-impact to the target DDC.

4.3.5. GSPR 14 - Construction of devices and interaction with their environment

GSPR 14.7 concerning safe disposal is considered a new requirement introduced by the MDR. It is not yet outlined what is required to fully demonstrate compliance with that requirement other than to include an appropriate recommendation for safe disposal in the IFU. It can be assumed, that a comprehensive evaluation and incorporation into risk management is expected. However, with regard to labelling requirements of the MDD, safe disposal was already required to be addressed in the instructions for use by ER 13.6 n. As GSPR 14.7 is now linked to GSPR 23.4 v, it becomes apparent that especially bio-hazardous aspects should be addressed. In the context of a PFS, the sharps injury protection plays another major role in supporting safe disposal of the used PFS. Also, the use of sharps containers as it is current practice [28] is addressed by this GSPR. The MAH should ensure the procedure described in the IFU was adequately assessed and found to be accurate for the intended purpose.

4.3.6. Usability Engineering

The MDR now clearly expands expectations that the medical device manufacturer conducts a comprehensive usability engineering as part of the design validation.

Usability engineering (also known as human factors engineering) is defined as

> *"application of knowledge about human behaviour, abilities, limitations, and other characteristics to the design of medical devices […], systems and tasks to achieve adequate usability"* [42 - clause 3.17],

where *usability* is the

> *"characteristic of the user interface that facilitates use and thereby establishes effectiveness, efficiency and user satisfaction in the intended use environment"* [42 - clause 3.16].

According to the case study and additionally mapped in the MHRA Guidance Appendix 2 [105] the following GSPRs (applicable in the case study) require usability engineering or the results thereof to be included in the risk assessment:

Table 5: Comparison MDD & MDR for usability engineering

MDD ER	MDR GSPR
1	1 & 5
n/a	3 c)
2	4
6	8
9.2	14.2 a)
12.8.1	21.1 (!)
n/a	22 (22.1, 22.2, 22.3)
13.1	23.1

It can be concluded from this overview, that most of the GSPRs requiring usability engineering were already addressed in the MDD. As outlined in the risk management sections (chapters 4.2.1, 4.3.1), GSPR 3 is expected to already be considered by applying EN ISO 14971:2012 [32]. Consideration of usability in the context of GSPR 21.1 is not foreseen within the case study as the PFS delivers only one dose of the medicinal product, posing no further risk such as. overdose. GSPR 22, requiring usability engineering for an intended use by lay persons and respective information to be reflected in the IFU, seems to be new in this extent in the MDR. However, as mentioned in ER 1 of the MDD [5] technical knowledge and experience of different user categories such as lay persons should be considered. Also, by applying IEC 62366-1:2015 [42] the intended user has to be defined in the use specification and the testing has to be aligned with that. However, it can be expected that the NB will focus on compliance with GSPR 22 as use by lay persons is next to general safety aspects one of the key updates in MDR's Annex I.

Moreover, GSPR 23.1 requiring 'readability testing' of the label and instructions for use (IFU) is a new requirement introduced by the MDR. IEC 62366-1:2015 clause 4.1.3. [42] as well as IEC 62366-2:2016 clause 6.5.3 [106] focus on information for safety as part of the user interface. It is stated that the IFU and further accompanying documentation should follow the same usability engineering process. Perception and understanding by the user,

as well as support of the correct use of the DDC, are expected to be characteristics for effective instructions. Characteristics such as size, colour and font of the text as well as symbols should also be considered.[42,106]

In parallel, as outlined in the medicinal product guidance for medication errors [39] usability engineering

> *"can explore whether instructions for use can be adequately understood and followed by users. Where simulated use testing has been performed, the results of this can be provided as supporting evidence in EU marketing authorisation applications. Such data may also be requested during the assessment of the application if assessors have concerns over the risk of medication errors."* [39 - p.10]

Furthermore, the readability testing as required by Articles 59(3), 61(1), 63(2) of Directive 2001/83/EC [3] can bring additional value to GSPR 23.1 a if the single integral DDC is handled as medicinal product. Applicable guidance [96] also requires user testing. Considering the instructions for use supplied together with the package leaflet, the MAH should evaluate to what extent the user testing fulfils GSPR 23.1 a to generate an efficient symbiosis.

The MAH must ensure that these new aspects are covered to an adequate extent in the summative evaluation design within its usability engineering.

Summative evaluation is considered as

> *"user interface evaluation conducted at the end of the user interface development with the intent to obtain objective evidence that the user interface can be used safely."* [42 - clause 3.13]

Also, as outlined in the BSI publication [18] this is considered a low impact provided that in general IEC 62366-1:2015 [42] is applied by the manufacturers/MAH.

4.3.7. Labelling

The following section outlines potential gaps under the assumption that the label requirements are considered fully applicable per expected future guidance along with the medicinal product labelling requirements:

The first new requirement introduced by GSPR 23.1 a is the readability of the information supplied for the intended user. This was already discussed in chapter 4.3.6 and is addressed by respective standards [42,106] and guidance [39]. Also, as requested by GSPR 23.1 h, the use of recognised symbols [98] supporting the information to be labelled is not established within the medicinal product labelling in that extent. However, Article 62 of Directive 2001/83/EC [3] outlines that symbols clarifying given information on the outer packaging and package leaflet may be included. Another aspect currently not completely

followed is GSPR 23.2 e, where it should be additionally labelled that the device contains “tissues or cells of animal origin, or their derivatives, as referred to in Regulation (EU) No 722/2012” [2 - Annex I: GSPR 23.2 e]. Currently this is followed for the active substance of the medicinal product only.[97,107] Moreover, as already referenced within GSPR 10.4.5, GSPRs 23.2 f and 23.4 s outline the need to label relevant substances exceeding the referenced concentration on the product label as well as in the IFU or alternatively in the SmPC/PL. With regard to sterile devices, GSPR 23.2 l requires the device to be labelled as sterile including the sterilization method. As of now, considering labelling requirements of the medicinal product, the DDC is not labelled as sterile nor is the sterilization method indicated. This assumption is supported by an exemplary product information of an authorised single integral DDC.[28,97] However the pharmaceutical form is labelled.[28,97] For example, a solution for injection reveals the fact that this is a sterile solution but this might not be obvious to a lay person. Nevertheless, as outlined below, defined components of the PFS are not considered sterile in this case study. The CCS parts ensure the maintenance of a sterile medicinal product in the first instance. Additionally it is labelled that the product is for single use only [28], which is required by GSPR 23.2 n.

To be highlighted are the explicit requirements for sterile devices. GSPR 23.3 is a new summary of essential label requirements for sterile devices that was not present in the MDD in that extent. However, there is no packaging maintaining the sterile condition of a device other than the container closure system of the PFS that maintains only the sterile condition of the medicinal product and the administration parts of the device. As indicated in the analysis table, this is regarded as not applicable to the target DDC.

Further new requirements to be included in the product information (IFU and/or SmPC/PL) would be the following:

Note: Since there is no explicit guidance for the instructions for use issued by the EMA, it is hard to evaluate whether several requirements are already addressed. For example, although GSPR 23.4 l is considered new in Annex I, an exemplary IFU of a PFS [28] already contains such warnings. In order to evaluate new requirements to consider, only the comparison to the MDD ERs remains as reference no matter if MAHs include these in the current IFUs for single integral DDCs. However, aspects that are already covered by medicinal product guidance will not be highlighted in that extent.

GSPR 23.4 c is new: Clinical benefits of the medicinal product are already covered by the medicinal product information as the primary mode of action originates from the medicinal product. Nevertheless, the device enables delivery of the medicinal product as required by the intended use of an injection. Moreover the needle stick protection (safety feature) of the PFS adds valuable safety considerations for the user as well as the environment. As

assessed within the clinical evaluation required by GSPR 1 and 8, defined clinical benefits should be incorporated in the instructions for use as appropriate.

GSPR 23.4 f requires a verification of suitability of the device for healthcare professionals (HCP). However, because this will be also considered for lay persons in the intended user group, this should be captured. In addition, this also correlates with GSPR 11.4 mentioning evidence of package integrity. As per GSPR 23.4 g residual risks concerning the device should be included in the IFU. This is related to GSPR 4 requiring residual risk to be included within risk management and the provision of respective information to the user. Moreover GSPR 23.4 j requires consideration of respective qualification and training of the user necessary to use the device safely. As outlined in chapter 4.2.1, this should be captured by current medicinal product information as a risk minimization action to prevent medication errors.

GSPR 23.4 l again highlights package integrity and requires instructions in case the sterile barrier system is damaged or unintentionally opened (refer also to GSPR 11.4). GSPR 23.4 v outlines the safe disposal of the device. In fact, that is also covered by the MDD, however special attention is given now to bio-hazards resulting from sharps.

While summarizing the new labelling requirements, it becomes apparent that this is considered a challenge for the MAH to implement the additional information if considered fully applicable in the current medicinal product label information.

4.4. Open questions/potential for clarification with stakeholder

This chapter addresses open questions that remain unanswered by the evaluation of the GSPRs either for their applicability or the information that should be provided to demonstrate compliance.

4.4.1. General Considerations

The MDR highlights the use of harmonised standards first, followed by Common Specifications and any other solutions as a final consideration.[2 - Annex II clause 4] Beyond that, GSPR 1 emphasizes the “generally acknowledged state of the art” [2 - Annex I: 1]. During the case study it becomes apparent that there are a significant amount of technical standards that demonstrate compliance with the GSPRs but that are not harmonised (e.g. ISO 11040-8:2016 [40], ISO 23908:2011 [41]). Also, harmonised standards were recently updated and are available in a more current version in alignment with the state of the art but not yet harmonised (e.g. ISO 10993-1:2018 [45], IEC 62366-1:2015 [42]) (see also Appendix B). Also, the recent harmonisation of current standards

was done under the MDD [5] without consideration for the MDR [2]. In order to get the necessary harmonisations started, the European Commission has to issue respective standardization requests as well as conduct a defined review process considering the GSPRs.[108] More than 100 standards [108,109] are in scope for the MDR. While this overall process is time consuming and requires involvement of several parties like European Committee for Standardization (CEN) as well as different technical committees, it is expected that many standards will not be harmonised under the MDR in time.[108] From the perspective of a global acting company, the harmonisation of standards is no fundamental criterion to apply that explicit version. Global development is focused on the most current globally recognized standard available. Therefore, it is reasonable to say, that in order to meet the state-of-the-art criterion, the manufacturer can justify the use of the most current version over the harmonised version of a respective standard. Furthermore, no Common Specifications have been published that need to be considered in the context of a single integral DDC. Other guidelines announced in the MDR, such as GSPR 10.4, are in progress [74] as of now. The current rolling plan of defined actions to be established until the application of the MDR is published and tracks the expected activities.[110] It is worth saying that the EMA guidance also addressing significant questions with regard to single integral DDCs is highly anticipated.

At first glance, the scope of Article 117 appears broader than intended because fundamental quality system expectations concerning medical devices not addressed by EU GMP should be met in order to be compliant with the GSPRs (e.g. design and development verification and validation).[15] This is also supported by the US regulation of combination products according to the Code of Federal Regulations Title 21 Part 4 Section 4.4. Accordingly, the manufacturer is required to comply with specific quality system regulations of medical devices such as design controls corresponding to design and development verification and validation requirements in case the overarching quality system is based on drug GMP.[111]

Another output from the case study is that the applicability of the GSPRs to a DDC is partially hard to break down to the device part only. As per Article 117 [2], the GSPRs apply on the device components. In fact, the interaction of device and drug product needs to be considered for many requirements. For example, the performance of a pre-filled syringe requires the device filled with the drug product in order to test functionality characteristics. In addition, it becomes apparent that a significant number of GSPRs are fulfilled by applying medicinal product requirements such as ICH guidance for stability [43] or obtaining clinical data from clinical trials conducted under the legislation for investigational medicinal products [34].

4.4.2. Clinical Evaluation

The clinical evaluation required by ER 6a of the MDD has been removed from Annex I of the MDR. Instead, the clinical evaluation is now represented within Article 61 of the MDR. The first subparagraph of Article 61 is stating:

> *"Confirmation of conformity with relevant general safety and performance requirements set out in Annex I under the normal conditions of the intended use of the device, and the evaluation of the undesirable side-effects and of the acceptability of the benefit-risk- ratio referred to in Sections 1 and 8 of Annex I, shall be based on clinical data providing sufficient clinical evidence, including where applicable relevant data as referred to in Annex III. The manufacturer shall specify and justify the level of clinical evidence necessary to demonstrate conformity with the relevant general safety and performance requirements. That level of clinical evidence shall be appropriate in view of the characteristics of the device and its intended purpose. To that end, manufacturers shall plan, conduct and document a clinical evaluation in accordance with this Article and Part A of Annex XIV."* [2 - Article 61(1)]

Considering this subparagraph, the clinical evaluation is still required and increased in its importance as it owns now an article. Also, it is outlined that the fulfilment of GSPR 1 as well as 8 requires a clinical evaluation. Hence, clinical data will be expected in order to support the fulfilment of safety and performance requirements.[112] As outlined in the analysis table, for medicinal products, clinical trials are conducted under the Clinical Trial Directive [34] resp. Clinical Trial Regulation [36] and applying ICH GCP standards [37]. By leveraging data thereof, "addition of key device measures" [112] should be considered. Nevertheless, the extent of clinical data needed should be in relation to novelty and complexity of the device.[112] However, it is still not clear how to interpret the applicability of the clinical evaluation in the context of Article 117.[29]

4.4.3. Usability engineering

Another point to discuss is, if a simplified approach could be accepted for "drug delivery devices with well-established platforms where there are no unusual or novel features introduced" [105 - p.28], such as pre-filled syringes. This would include a risk-based usability assessment instead of conducting usability studies. This assessment would need to take into account the intended users, their environment and a justification why no additional studies are required.[105]

Also, it is outlined in the EBE position paper [13 - p.7] that industry recommends

> *"that prior knowledge of current market products can, and should be utilised, in addition to a single NB opinion being leveraged across different medicinal products, if appropriate, based on similarity of delivery device, to minimise the burden."* [13 - p.10]

However, as the requirements are increasing for usability engineering, the acceptability would require explicit confirmation through guidance issued by the relevant stakeholders.

4.4.4. Labelling

As of now, the single integral DDCs follow the labelling requirements set out by Directive 2001/83/EC [3]. However, it is still unclear to what extent the labelling requirements listed in Annex I of the MDR are applicable. Some requirements are not applicable to a single integral DDC such as an UDI carrier (GSPR 23.2 h) because the product is not regulated as a medical device. It is not evident whether the MAH can skip the device specific label requirements such as indication of sterilization method (GSPR 23.3 c) or manufacturing date for sterile devices (GSPR 23.3 h). However, the industry recommendation clearly prefers that “labelling should conform primarily to the requirements for medicinal products with the relevant labelling requirements specific to device types as it relates to safety or usability” [13 - p.16]. Considering the Annex I of the MDR, experts are generally concerned about disregarding the medical device labelling requirements as they outline important information to the user.[17] Further guidance is strongly recommended if there is broader room for interpretation.

5. Conclusion & Outlook

With the introduction of the Medical Device Regulation (EU) 2017/745 [2], Article 117 amends the Medicinal Product Directive 2001/83/EC [3] requiring a notified body opinion for single integral Drug Device Combinations. Hence, compliance with the General Safety and Performance Requirements outlined in Annex I of the MDR becomes legally binding from 26 May 2020. As the GSPRs are expanded and modified in comparison to the Essential Requirements of the Medical Device Directive 93/42/EEC [5], MAHs are well advised to timely assess the impact on the single integral DDCs that will be submitted for a marketing authorisation at that time.

This thesis incorporates a case study on a defined target DDC. A pre-filled syringe including a safety device was assessed for the applicability of the GSPRs and how MAHs can demonstrate their compliance. Redundancies and interfaces with the current MAA as well as new requirements not yet addressed were highlighted. As shown by many GSPRs, the new aspects introduced are echoed in established (harmonised) technical standards and reflect the current state of the art (e.g. with regard to Risk Management and EN ISO 14971:2012 [32]). A few GSPRs, such as GSPR 10.4, pose higher impact to device development than others. As it becomes evident that safety is a fundamental aspect influencing the GSPRs, a pre-filled syringe should be equipped with a safety feature that prevents the user and the environment from sharps injuries. Safe disposal has also increased in its importance. Furthermore, sterility and potential impact of the device parts have become an integral part of Annex I from design & manufacturing up to labelling requirements. Requirements on usability engineering as well as risk management were aligned to meet the specifications outlined by current standards and to ensure safety and performance requirements of the device to be met. Many interfaces and redundancies to medicinal product requirements, such as stability data or drug-device interactions, exist. Consequently, they are addressed in the MAA but may cause double review by the CA as well as NB. Device labelling requirements are still not well defined and should be clarified by further guidance. Applicability of the clinical evaluation is unclear as Article 117 references consideration of Annex I only. Beyond that, opportunities to reduce effort for well-established devices such as a pre-filled syringe were highlighted (e.g. usability engineering).

At this time, one year remains for the responsible institutions to clarify hot-topics resulting from public discussions of the relevant stakeholders such as the industry. Announced guidance (e.g. to address GSPR 10.4) as well as MDR harmonised standards and Common Specifications, if needed, should be published in a timely manner to allow sufficient preparation by MAHs. EMA's "Guideline on the quality requirements for medicinal products

containing a device component for delivery or use of the medicinal product" [16] is highly anticipated and will move the current discussions forward. Industry expects it to address open questions to allow preparation of suitable submission documentation prior to May 2020.

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Appendix A – Annex I MDR

Appendix A lists MDR's Annex I for reference:

Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC [2]

ANNEX I GENERAL SAFETY AND PERFORMANCE REQUIREMENTS

CHAPTER I GENERAL REQUIREMENTS

1. Devices shall achieve the performance intended by their manufacturer and shall be designed and manufactured in such a way that, during normal conditions of use, they are suitable for their intended purpose. They shall be safe and effective and shall not compromise the clinical condition or the safety of patients, or the safety and health of users or, where applicable, other persons, provided that any risks which may be associated with their use constitute acceptable risks when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety, taking into account the generally acknowledged state of the art.

2. The requirement in this Annex to reduce risks as far as possible means the reduction of risks as far as possible without adversely affecting the benefit-risk ratio.

3. Manufacturers shall establish, implement, document and maintain a risk management system. Risk management shall be understood as a continuous iterative process throughout the entire lifecycle of a device, requiring regular systematic updating. In carrying out risk management manufacturers shall: (a) establish and document a risk management plan for each device; (b) identify and analyse the known and foreseeable hazards associated with each device; (c) estimate and evaluate the risks associated with, and occurring during, the intended use and during reasonably foreseeable misuse; (d) eliminate or control the risks referred to in point (c) in accordance with the requirements of Section 4; (e) evaluate the impact of information from the production phase and, in particular, from the post-market surveillance system, on hazards and the frequency of occurrence thereof, on estimates of their associated risks, as well as on the overall risk, benefit-risk ratio and risk acceptability; and (f) based on the evaluation of the impact of the information referred to in point (e), if necessary amend control measures in line with the requirements of Section 4.

4. Risk control measures adopted by manufacturers for the design and manufacture of the devices shall conform to safety principles, taking account of the generally acknowledged state of the art. To reduce risks, Manufacturers shall manage risks so that the residual risk associated with each hazard as well as the overall residual risk is judged acceptable. In

selecting the most appropriate solutions, manufacturers shall, in the following order of priority: (a) eliminate or reduce risks as far as possible through safe design and manufacture; (b) where appropriate, take adequate protection measures, including alarms if necessary, in relation to risks that cannot be eliminated; and (c) provide information for safety (warnings/precautions/contra-indications) and, where appropriate, training to users. Manufacturers shall inform users of any residual risks.

5. In eliminating or reducing risks related to use error, the manufacturer shall: (a) reduce as far as possible the risks related to the ergonomic features of the device and the environment in which the device is intended to be used (design for patient safety), and (b) give consideration to the technical knowledge, experience, education, training and use environment, where applicable, and the medical and physical conditions of intended users (design for lay, professional, disabled or other users).

6. The characteristics and performance of a device shall not be adversely affected to such a degree that the health or safety of the patient or the user and, where applicable, of other persons are compromised during the lifetime of the device, as indicated by the manufacturer, when the device is subjected to the stresses which can occur during normal conditions of use and has been properly maintained in accordance with the manufacturer's instructions.

7. Devices shall be designed, manufactured and packaged in such a way that their characteristics and performance during their intended use are not adversely affected during transport and storage, for example, through fluctuations of temperature and humidity, taking account of the instructions and information provided by the manufacturer.

8. All known and foreseeable risks, and any undesirable side-effects, shall be minimised and be acceptable when weighed against the evaluated benefits to the patient and/or user arising from the achieved performance of the device during normal conditions of use.

9. For the devices referred to in Annex XVI, the general safety requirements set out in Sections 1 and 8 shall be understood to mean that the device, when used under the conditions and for the purposes intended, does not present a risk at all or presents a risk that is no more than the maximum acceptable risk related to the product's use which is consistent with a high level of protection for the safety and health of persons.

CHAPTER II REQUIREMENTS REGARDING DESIGN AND MANUFACTURE

10. Chemical, physical and biological properties

10.1. Devices shall be designed and manufactured in such a way as to ensure that the characteristics and performance requirements referred to in Chapter I are fulfilled. Particular attention shall be paid to: (a) the choice of materials and substances used, particularly as regards toxicity and, where relevant, flammability; (b) the compatibility between the materials and substances used and biological tissues, cells and body fluids, taking account of the intended purpose of the device and, where relevant, absorption, distribution, metabolism and excretion; (c) the compatibility between the different parts of a device which consists of more than one implantable part; (d) the impact of processes on material properties; (e) where appropriate, the results of biophysical or modelling research the validity of which has been demonstrated beforehand; (f) the mechanical properties of the materials used, reflecting, where appropriate, matters such as strength, ductility, fracture resistance, wear resistance and fatigue resistance; (g) surface properties; and (h) the confirmation that the device meets any defined chemical and/or physical specifications.

10.2. Devices shall be designed, manufactured and packaged in such a way as to minimise the risk posed by contaminants and residues to patients, taking account of the intended purpose of the device, and to the persons involved in the transport, storage and use of the devices. Particular attention shall be paid to tissues exposed to those contaminants and residues and to the duration and frequency of exposure.

10.3. Devices shall be designed and manufactured in such a way that they can be used safely with the materials and substances, including gases, with which they enter into contact during their intended use; if the devices are intended to administer medicinal products they shall be designed and manufactured in such a way as to be compatible with the medicinal products concerned in accordance with the provisions and restrictions governing those medicinal products and that the performance of both the medicinal products and of the devices is maintained in accordance with their respective indications and intended use.

10.4. Substances

10.4.1. Design and manufacture of devices

Devices shall be designed and manufactured in such a way as to reduce as far as possible the risks posed by substances or particles, including wear debris, degradation products and processing residues, that may be released from the device. Devices, or those parts thereof or those materials used therein that: — are invasive and come into direct contact with the human body, — (re)administer medicines, body liquids or other substances, including

gases, to/from the body, or — transport or store such medicines, body fluids or substances, including gases, to be (re)administered to the body, shall only contain the following substances in a concentration that is above 0,1 % weight by weight (w/w) where justified pursuant to Section 10.4.2: (a) substances which are carcinogenic, mutagenic or toxic to reproduction ('CMR'), of category 1A or 1B, in accordance with Part 3 of Annex VI to Regulation (EC) No 1272/2008 of the European Parliament and of the Council[1], or (b) substances having endocrine-disrupting properties for which there is scientific evidence of probable serious effects to human health and which are identified either in accordance with the procedure set out in Article 59 of Regulation (EC) No 1907/2006 of the European Parliament and of the Council[2] or, once a delegated act has been adopted by the Commission pursuant to the first subparagraph of Article 5(3) of Regulation (EU) No 528/2012 of the European Parliament and the Council[3], in accordance with the criteria that are relevant to human health amongst the criteria established therein.

10.4.2. Justification regarding the presence of CMR and/or endocrine-disrupting substances The justification for the presence of such substances shall be based upon: (a) an analysis and estimation of potential patient or user exposure to the substance; (b) an analysis of possible alternative substances, materials or designs, including, where available, information about independent research, peer-reviewed studies, scientific opinions from relevant scientific committees and an analysis of the availability of such alternatives; (c) argumentation as to why possible substance and/ or material substitutes, if available, or design changes, if feasible, are inappropriate in relation to maintaining the functionality, performance and the benefit-risk ratios of the product; including taking into account if the intended use of such devices includes treatment of children or treatment of pregnant or breastfeeding women or treatment of other patient groups considered particularly vulnerable to such substances and/or materials; and (d) where applicable and available, the latest relevant scientific committee guidelines in accordance with Sections 10.4.3. and 10.4.4.

10.4.3. Guidelines on phthalates For the purposes of Section 10.4., the Commission shall, as soon as possible and by 26 May 2018, provide the relevant scientific committee with a mandate to prepare guidelines that shall be ready before 26 May 2020. The mandate for the committee shall encompass at least a benefit-risk assessment of the presence of

[1] Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006 (OJ L 353, 31.12.2008, p. 1).
[2] Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) (OJ L 396, 30.12.2006, p. 1).
[3] Regulation (EU) No 528/2012 of the European Parliament and the Council of 22 May 2012 concerning the making available on the market of and use of biocidal products (OJ L 167, 27.6.2012, p. 1).

phthalates which belong to either of the groups of substances referred to in points (a) and (b) of Section 10.4.1. The benefit-risk assessment shall take into account the intended purpose and context of the use of the device, as well as any available alternative substances and alternative materials, designs or medical treatments. When deemed appropriate on the basis of the latest scientific evidence, but at least every five years, the guidelines shall be updated

10.4.4. Guidelines on other CMR and endocrine-disrupting substances Subsequently, the Commission shall mandate the relevant scientific committee to prepare guidelines as referred to in Section 10.4.3. also for other substances referred to in points (a) and (b) of Section 10.4.1., where appropriate.

10.4.5. Labelling

Where devices, parts thereof or materials used therein as referred to in Section 10.4.1. contain substances referred to in points (a) or (b) of Section 10.4.1. in a concentration above 0,1 % weight by weight (w/w), the presence of those substances shall be labelled on the device itself and/or on the packaging for each unit or, where appropriate, on the sales packaging, with the list of such substances. If the intended use of such devices includes treatment of children or treatment of pregnant or breastfeeding women or treatment of other patient groups considered particularly vulnerable to such substances and/or materials, information on residual risks for those patient groups and, if applicable, on appropriate precautionary measures shall be given in the instructions for use.

10.5. Devices shall be designed and manufactured in such a way as to reduce as far as possible the risks posed by the unintentional ingress of substances into the device taking into account the device and the nature of the environment in which it is intended to be used.

10.6. Devices shall be designed and manufactured in such a way as to reduce as far as possible the risks linked to the size and the properties of particles which are or can be released into the patient's or user's body, unless they come into contact with intact skin only. Special attention shall be given to nanomaterials.

11. Infection and microbial contamination

11.1. Devices and their manufacturing processes shall be designed in such a way as to eliminate or to reduce as far as possible the risk of infection to patients, users and, where applicable, other persons. The design shall: (a) reduce as far as possible and appropriate the risks from unintended cuts and pricks, such as needle stick injuries, (b) allow easy and safe handling, (c) reduce as far as possible any microbial leakage from the device and/or

microbial exposure during use, and (d) prevent microbial contamination of the device or its content such as specimens or fluids.

11.2. Where necessary devices shall be designed to facilitate their safe cleaning, disinfection, and/or re-sterilisation.

11.3. Devices labelled as having a specific microbial state shall be designed, manufactured and packaged to ensure that they remain in that state when placed on the market and remain so under the transport and storage conditions specified by the manufacturer.

11.4. Devices delivered in a sterile state shall be designed, manufactured and packaged in accordance with appropriate procedures, to ensure that they are sterile when placed on the market and that, unless the packaging which is intended to maintain their sterile condition is damaged, they remain sterile, under the transport and storage conditions specified by the manufacturer, until that packaging is opened at the point of use. It shall be ensured that the integrity of that packaging is clearly evident to the final user.

11.5. Devices labelled as sterile shall be processed, manufactured, packaged and, sterilised by means of appropriate, validated methods.

11.6. Devices intended to be sterilised shall be manufactured and packaged in appropriate and controlled conditions and facilities.

11.7. Packaging systems for non-sterile devices shall maintain the integrity and cleanliness of the product and, where the devices are to be sterilised prior to use, minimise the risk of microbial contamination; the packaging system shall be suitable taking account of the method of sterilisation indicated by the manufacturer.

11.8. The labelling of the device shall distinguish between identical or similar devices placed on the market in both a sterile and a non-sterile condition additional to the symbol used to indicate that devices are sterile.

12. Devices incorporating a substance considered to be a medicinal product and devices that are composed of substances or of combinations of substances that are absorbed by or locally dispersed in the human body.

12.1. In the case of devices referred to in the first subparagraph of Article 1(8), the quality, safety and usefulness of the substance which, if used separately, would be considered to be a medicinal product within the meaning of point (2) of Article 1 of Directive 2001/83/EC, shall be verified by analogy with the methods specified in Annex I to Directive 2001/83/EC, as required by the applicable conformity assessment procedure under this Regulation.

12.2. 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 shall comply, where applicable and in a manner limited to the aspects not covered by this Regulation, with the relevant requirements laid down in Annex I to Directive 2001/83/EC for the evaluation of absorption, distribution, metabolism, excretion, local tolerance, toxicity, interaction with other devices, medicinal products or other substances and potential for adverse reactions, as required by the applicable conformity assessment procedure under this Regulation.

13. Devices incorporating materials of biological origin

13.1. For devices manufactured utilising derivatives of tissues or cells of human origin which are non-viable or are rendered non-viable covered by this Regulation in accordance with point (g) of Article 1(6), the following shall apply: (a) donation, procurement and testing of the tissues and cells shall be done in accordance with Directive 2004/23/EC; (b) processing, preservation and any other handling of those tissues and cells or their derivatives shall be carried out so as to provide safety for patients, users and, where applicable, other persons. In particular, safety with regard to viruses and other transmissible agents shall be addressed by appropriate methods of sourcing and by implementation of validated methods of elimination or inactivation in the course of the manufacturing process; (c) the traceability system for those devices shall be complementary and compatible with the traceability and data protection requirements laid down in Directive 2004/23/EC and in Directive 2002/98/EC.

13.2. For devices manufactured utilising tissues or cells of animal origin, or their derivatives, which are non-viable or rendered non-viable the following shall apply: (a) where feasible taking into account the animal species, tissues and cells of animal origin, or their derivatives, shall originate from animals that have been subjected to veterinary controls that are adapted to the intended use of the tissues. Information on the geographical origin of the animals shall be retained by manufacturers; (b) sourcing, processing, preservation, testing and handling of tissues, cells and substances of animal origin, or their derivatives, shall be carried out so as to provide safety for patients, users and, where applicable, other persons. In particular safety with regard to viruses and other transmissible agents shall be addressed by implementation of validated methods of elimination or viral inactivation in the course of the manufacturing process, except when the use of such methods would lead to unacceptable degradation compromising the clinical benefit of the device; (c) in the case of devices manufactured utilising tissues or cells of animal origin, or their derivatives, as referred to in Regulation (EU) No 722/2012 the particular requirements laid down in that Regulation shall apply.

13.3. For devices manufactured utilising non-viable biological substances other than those referred to in Sections 13.1 and 13.2, the processing, preservation, testing and handling of

those substances shall be carried out so as to provide safety for patients, users and, where applicable, other persons, including in the waste disposal chain. In particular, safety with regard to viruses and other transmissible agents shall be addressed by appropriate methods of sourcing and by implementation of validated methods of elimination or inactivation in the course of the manufacturing process.

14. Construction of devices and interaction with their environment

14.1. If the device is intended for use in combination with other devices or equipment the whole combination, including the connection system shall be safe and shall not impair the specified performance of the devices. Any restrictions on use applying to such combinations shall be indicated on the label and/or in the instructions for use. Connections which the user has to handle, such as fluid, gas transfer, electrical or mechanical coupling, shall be designed and constructed in such a way as to minimise all possible risks, such as misconnection.

14.2. Devices shall be designed and manufactured in such a way as to remove or reduce as far as possible: (a) the risk of injury, in connection with their physical features, including the volume/pressure ratio, dimensional and where appropriate ergonomic features; (b) risks connected with 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, temperature, variations in pressure and acceleration or radio signal interferences; (c) the risks associated with the use of the device when it comes into contact with materials, liquids, and substances, including gases, to which it is exposed during normal conditions of use; (d) the risks associated with the possible negative interaction between software and the IT environment within which it operates and interacts; (e) the risks of accidental ingress of substances into the device; (f) the risks of reciprocal interference with other devices normally used in the investigations or for the treatment given; and (g) risks arising where maintenance or calibration are not possible (as with implants), from ageing of materials used or loss of accuracy of any measuring or control mechanism.

14.3. Devices shall be designed and manufactured in such a way as to minimise the risks of fire or explosion during normal use and in single fault condition. Particular attention shall be paid to devices the intended use of which includes exposure to or use in association with flammable or explosive substances or substances which could cause combustion.

14.4. Devices shall be designed and manufactured in such a way that adjustment, calibration, and maintenance can be done safely and effectively.

14.5. Devices that are intended to be operated together with other devices or products shall be designed and manufactured in such a way that the interoperability and compatibility are reliable and safe.

14.6 Any measurement, monitoring or display scale shall be designed and manufactured in line with ergonomic principles, taking account of the intended purpose, users and the environmental conditions in which the devices are intended to be used.

14.7. Devices shall be designed and manufactured in such a way as to facilitate their safe disposal and the safe disposal of related waste substances by the user, patient or other person. To that end, manufacturers shall identify and test procedures and measures as a result of which their devices can be safely disposed after use. Such procedures shall be described in the instructions for use.

15. Devices with a diagnostic or measuring function

15.1. Diagnostic devices and devices with a measuring function, shall be designed and manufactured in such a way as to provide sufficient accuracy, precision and stability for their intended purpose, based on appropriate scientific and technical methods. The limits of accuracy shall be indicated by the manufacturer.

15.2. The measurements made by devices with a measuring function shall be expressed in legal units conforming to the provisions of Council Directive 80/181/EEC[4].

16. Protection against radiation

16.1. General (a) Devices shall be designed, manufactured and packaged in such a way that exposure of patients, users and other persons to radiation is reduced as far as possible, and in a manner that is compatible with the intended purpose, whilst not restricting the application of appropriate specified levels for therapeutic and diagnostic purposes. (b) The operating instructions for devices emitting hazardous or potentially hazardous radiation shall contain detailed information as to the nature of the emitted radiation, the means of protecting the patient and the user, and on ways of avoiding misuse and of reducing the risks inherent to installation as far as possible and appropriate. Information regarding the acceptance and performance testing, the acceptance criteria, and the maintenance procedure shall also be specified.

16.2. Intended radiation (a) Where devices are designed to emit hazardous, or potentially hazardous, levels of ionizing and/or non- ionizing radiation necessary for a specific medical purpose the benefit of which is considered to outweigh the risks inherent to the emission, it

4 Council Directive 80/181/EEC of 20 December 1979 on the approximation of the laws of the Member States relating to units of measurement and on the repeal of Directive 71/354/EEC (OJ L 39, 15.2.1980, p. 40).

shall be possible for the user to control the emissions. Such devices shall be designed and manufactured to ensure reproducibility of relevant variable parameters within an acceptable tolerance. (b) Where devices are intended to emit hazardous, or potentially hazardous, ionizing and/or non-ionizing radiation, they shall be fitted, where possible, with visual displays and/or audible warnings of such emissions.

16.3. Devices shall be designed and manufactured in such a way that exposure of patients, users and other persons to the emission of unintended, stray or scattered radiation is reduced as far as possible. Where possible and appropriate, methods shall be selected which reduce the exposure to radiation of patients, users and other persons who may be affected.

16.4. Ionising radiation (a) Devices intended to emit ionizing radiation shall be designed and manufactured taking into account the requirements of the Directive 2013/59/Euratom laying down basic safety standards for protection against the dangers arising from exposure to ionising radiation. (b) Devices intended to emit ionising radiation shall be designed and manufactured in such a way as to ensure that, where possible, taking into account the intended use, the quantity, geometry and quality of the radiation emitted can be varied and controlled, and, if possible, monitored during treatment. (c) Devices emitting ionising radiation intended for diagnostic radiology shall be designed and manufactured in such a way as to achieve an image and/or output quality that are appropriate to the intended medical purpose whilst minimising radiation exposure of the patient and user. (d) Devices that emit ionising radiation and are intended for therapeutic radiology shall be designed and manufactured in such a way as to enable reliable monitoring and control of the delivered dose, the beam type, energy and, where appropriate, the quality of radiation.

17. Electronic programmable systems — devices that incorporate electronic programmable systems and software that are devices in themselves

17.1. Devices that incorporate electronic programmable systems, including software, or software that are devices in themselves, shall be designed to ensure repeatability, reliability and performance in line with their intended use. In the event of a single fault condition, appropriate means shall be adopted to eliminate or reduce as far as possible consequent risks or impairment of performance.

17.2. For devices that incorporate software or for software that are devices in themselves, the software shall be developed and manufactured in accordance with the state of the art taking into account the principles of development life cycle, risk management, including information security, verification and validation.

17.3. Software referred to in this Section that is intended to be used in combination with mobile computing platforms shall be designed and manufactured taking into account the specific features of the mobile platform (e.g. size and contrast ratio of the screen) and the external factors related to their use (varying environment as regards level of light or noise).

17.4. Manufacturers shall set out minimum requirements concerning hardware, IT networks characteristics and IT security measures, including protection against unauthorised access, necessary to run the software as intended.

18. Active devices and devices connected to them

18.1. For non-implantable active devices, in the event of a single fault condition, appropriate means shall be adopted to eliminate or reduce as far as possible consequent risks.

18.2. Devices where the safety of the patient depends on an internal power supply shall be equipped with a means of determining the state of the power supply and an appropriate warning or indication for when the capacity of the power supply becomes critical. If necessary, such warning or indication shall be given prior to the power supply becoming critical.

18.3. Devices where the safety of the patient depends on an external power supply shall include an alarm system to signal any power failure.

18.4. Devices intended to monitor one or more clinical parameters of a patient shall be equipped with appropriate alarm systems to alert the user of situations which could lead to death or severe deterioration of the patient's state of health.

18.5. Devices shall be designed and manufactured in such a way as to reduce as far as possible the risks of creating electromagnetic interference which could impair the operation of the device in question or other devices or equipment in the intended environment.

18.6.Devices shall be designed and manufactured in such a way as to provide a level of intrinsic immunity to electromagnetic interference such that is adequate to enable them to operate as intended.

18.7. Devices shall be designed and manufactured in such a way as to avoid, as far as possible, the risk of accidental electric shocks to the patient, user or any other person, both during normal use of the device and in the event of a single fault condition in the device, provided the device is installed and maintained as indicated by the manufacturer.

18.8. Devices shall be designed and manufactured in such a way as to protect, as far as possible, against unauthorised access that could hamper the device from functioning as intended.

19. Particular requirements for active implantable devices

19.1. Active implantable devices shall be designed and manufactured in such a way as to remove or minimize as far as possible: (a) risks connected with the use of energy sources with particular reference, where electricity is used, to insulation, leakage currents and overheating of the devices, (b) risks connected with medical treatment, in particular those resulting from the use of defibrillators or high- frequency surgical equipment, and (c) risks which may arise where maintenance and calibration are impossible, including: — excessive increase of leakage currents, — ageing of the materials used, — excess heat generated by the device, — decreased accuracy of any measuring or control mechanism.

19.2. Active implantable devices shall be designed and manufactured in such a way as to ensure — if applicable, the compatibility of the devices with the substances they are intended to administer, and — the reliability of the source of energy.

19.3. Active implantable devices and, if appropriate, their component parts shall be identifiable to allow any necessary measure to be taken following the discovery of a potential risk in connection with the devices or their component parts.

19.4. Active implantable devices shall bear a code by which they and their manufacturer can be unequivocally identified (particularly with regard to the type of device and its year of manufacture); it shall be possible to read this code, if necessary, without the need for a surgical operation.

20. Protection against mechanical and thermal risks

20.1. Devices shall be designed and manufactured in such a way as to protect patients and users against mechanical risks connected with, for example, resistance to movement, instability and moving parts.

20.2. Devices shall be designed and manufactured in such a way as to reduce to the lowest possible level the risks arising from vibration generated by the devices, taking account of technical progress and of the means available for limiting vibrations, particularly at source, unless the vibrations are part of the specified performance.

20.3. Devices shall be designed and manufactured in such a way as to reduce to the lowest possible level the risks arising from the noise emitted, taking account of technical progress and of the means available to reduce noise, particularly at source, unless the noise emitted is part of the specified performance.

20.4. Terminals and connectors to the electricity, gas or hydraulic and pneumatic energy supplies which the user or other person has to handle, shall be designed and constructed in such a way as to minimise all possible risks.

20.5. Errors likely to be made when fitting or refitting certain parts which could be a source of risk shall be made impossible by the design and construction of such parts or, failing this, by information given on the parts themselves and/or their housings. The same information shall be given on moving parts and/or their housings where the direction of movement needs to be known in order to avoid a risk.

20.6. Accessible parts of devices (excluding the parts or areas intended to supply heat or reach given temperatures) and their surroundings shall not attain potentially dangerous temperatures under normal conditions of use.

21. Protection against the risks posed to the patient or user by devices supplying energy or substances

21.1. Devices for supplying the patient with energy or substances shall be designed and constructed in such a way that the amount to be delivered can be set and maintained accurately enough to ensure the safety of the patient and of the user.

21.2. Devices shall be fitted with the means of preventing and/or indicating any inadequacies in the amount of energy delivered or substances delivered which could pose a danger. Devices shall incorporate suitable means to prevent, as far as possible, the accidental release of dangerous levels of energy or substances from an energy and/or substance source.

21.3. The function of the controls and indicators shall be clearly specified on the devices. Where a device bears instructions required for its operation or indicates operating or adjustment parameters by means of a visual system, such information shall be understandable to the user and, as appropriate, the patient.

22. Protection against the risks posed by medical devices intended by the manufacturer for use by lay persons

22.1. Devices for use by lay persons shall be designed and manufactured in such a way that they perform appropriately for their intended purpose taking into account the skills and the means available to lay persons and the influence resulting from variation that can be reasonably anticipated in the lay person's technique and environment. The information and instructions provided by the manufacturer shall be easy for the lay person to understand and apply.

22.2. Devices for use by lay persons shall be designed and manufactured in such a way as to: — ensure that the device can be used safely and accurately by the intended user at all stages of the procedure, if necessary after appropriate training and/or information, — reduce, as far as possible and appropriate, the risk from unintended cuts and pricks such

as needle stick injuries, and — reduce as far as possible the risk of error by the intended user in the handling of the device and, if applicable, in the interpretation of the results.

22.3. Devices for use by lay persons shall, where appropriate, include a procedure by which the lay person: — can verify that, at the time of use, the device will perform as intended by the manufacturer, and — if applicable, is warned if the device has failed to provide a valid result.

CHAPTER III REQUIREMENTS REGARDING THE INFORMATION SUPPLIED WITH THE DEVICE

23. Label and instructions for use

23.1. General requirements regarding the information supplied by the manufacturer 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.

23.2. Information on the label 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.

23.3. Information on the packaging which maintains the sterile condition of a device (‘sterile packaging’) 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.

23.4. Information in the instructions for use

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 B – Correlation of Technical Standards

As outlined in chapter 3.1 of this document, for the purpose of this master thesis, the most current version of technical standards will be cited in order to address the state-of-the-art. Respective standards were marked with an asterisk (*) in the analysis tables. The below table links the most current version of technical standards to the harmonised version as published in the Official Journal of the European Union (OJEU) [20]:

Table 6: Technical standard's version overview

Cited version	Harmonised version	Reference document to harmonised version
IEC 62366-1:2015	EN 62366:2008	IEC 62366:2007
ISO 10993-1:2018	EN ISO 10993-1:2009	ISO 10993-1:2009
ISO 10993-11:2017	EN ISO 10993-11:2009	ISO 10993-11:2006
ISO 11135-1:2014	EN ISO 11135-1:2007	ISO 11135-1:2007
ISO 11138-2:2017	EN ISO 11138-2:2009	ISO 11138-2:2006
ISO 11140-1:2014	EN ISO 11140-1:2009	ISO 11140-1:2005
ISO 11737-1:2018	EN ISO 11737-1:2006 EN ISO 11737-1:2006/AC:2009	ISO 11737-1:2006 incl. Correction 1:2007
ISO 22442-1:2015	EN ISO 22442-1:2007	ISO 22442-1:2007
ISO 22442-2:2015	EN ISO 22442-2:2007	ISO 22442-2:2007

Eidesstattliche Erklärung

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Mannheim, den 17. Mai 2019

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Caroline Schommer