AEGLE

An Analytics Framework for Integrated and Personalized Healthcare Services in Europe

AEGLE Certification

DOCUMENT IDENTIFIER:	**D7.6**
DUE DATE:	31/08/2018
DELIVERY DATE:	31/08/2018
CLASSIFICATION:	Public
EDITORS:	Anna PALAIOLOGK
DOCUMENT VERSION:	1.0

CONTRACT START DATE:	1st March 2015
CONTRACT DURATION:	42 months

Co-funded by the Horizon 2020 Framework Programme of the European Union under Grant Agreement nº 644906.

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REVISION HISTORY		
Version	**Date**	**Modifications**
0.1	29/07/2018	ToC released
0.5	14/08/2018	Inputs added
1.0	14/11/2017	Review comments addressed

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Executive Summary

In order for the the AEGLE data analytics software be placed into the market, it will have to comply with the **EU legal framework on medical devices**.[1] The Medical Devices Directive and Regulation lay down the rules concerning the placing on the market, making available on the market or putting into service of medical devices for human use and accessories for such devices in the Union.

The AEGLE software is to be considered as a '**medical device**' if the software is used for humans, has a specific medical purpose,[2] and does not achieve its principle intended action by pharmacological, immunological or metabolic means, in or on the human body.

Standalone software shall be deemed as a **medical active device** when **Rule 11** of Annex VIII of the MDR applies.[3] Rule 11 explicitly states that software intended to provide information which is used to take decisions with diagnosis or therapeutic purposes is classified as **class IIb** when such decisions have an impact that may cause a serious deterioration of a person's state of health or a surgical intervention. In cases where the impact of the decision may cause death or an irreversible deterioration of a person's state of health, the software is classified as **class III**.[4] On the other hand, if the software is intended to monitor vital physiological parameters, where the nature of variations of those parameters is such that it could result in immediate danger of the patient, the software is classified as **class IIb**.[5]

In order to place a medical device into the market, the manufacturer needs to comply with the **general safety and performance requirements** (Annex I MDR) and follow a **conformity assessment procedure** (Annexes IX-XI MDR).

If the AEGLE software is considered as a **class III medical device**, the start-up will have the choice between the following options: a) To be subject to a conformity assessment as specified in Annex IX. 'Conformity assessment based on a quality management system and on an assessment of the technical documentation', or b) To apply a conformity assessment based on type-examination as specified in Annex X coupled with a conformity assessment based on product conformity verification as specified in Annex XI.[6]

If the AEGLE software is considered as a **class IIb medical device**, the start-up will have the choice between the following two options: a) To be subject to a conformity assessment based on a quality management system as specified in Chapters I and III of Annex IX, and including an assessment of the technical documentation as specified in Section 4 of Annex IX, or b) To apply a conformity assessment based on type-examination as specified in Annex X coupled with a conformity assessment based on product conformity verification as specified in Annex XI.[7]

When the start-up opts for **option a)**, the start-up will establish, document and implement a **quality management system** as described in Article 10, 9 of the Medical Devices Regulation and maintain its effectiveness throughout the lifecycle of the AEGLE software.[8] The quality management system includes the technical documentation for the device (Annex II) and the **technical documentation** on **post-market surveillance** (Annex III). Overall, the start-up will have to provide a description and specification of the medical device. The start-up will deliver information on

[1] Council Directive 93/42/EEC of 14 June 1993 concerning medical devices, OJ L 169, 1 (hereinafter: MDD); Directive 2007/47/EC of the European Parliament and of the Council of 5 September 2007, OJ L 247, 21; 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) 187/2002 and Regulation (EC) 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC, OJ L 117, 1 (hereinafter referred to as: the Regulation or MDR).

[2] Article 2, 1 MDR: "*Diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease, Diagnosis, prevention, monitoring, treatment, alleviation of, or compensation for an injury or a disability*".

[3] Article 2.4 MDR.

[4] Rule 11 Annex VIII.

[5] Rule 11 Annex VIII.

[6] Article 52, 3 MDR.

[7] Article 52, 4 MDR.

[8] Section 1 Annex IX MDR.

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the design and manufacturing of the device and on the general safety and performance requirements according to the class under which the device is classified. Finally, the start-up will provide a **benefit-risk analysis and risk management plan**, as well as the **product verification and validation**. The confirmation of conformity with the relevant general safety and performance requirements and of the acceptability of the benefit-risk ratio will be based on **clinical data**.[9] After that, the start-up will **lodge an application for assessment** of its quality management system with a notified body.[10] Chapter I of Annex IX describes the **procedures and requirements** for the application for a quality management system assessment, the procedure regarding the audit by the notified body, and the surveillance assessment process of the conformity assessment based on a quality management system. Chapter II of Annex IX describes the rules for the start-up to lodge an **application** with the notified body for assessment of the technical documentation relating to the class IIb or class III device which it plans to place on the market.[11] For class III medical devices specific additional procedures are outlined in Sections 5 to 6 of Annex IX. The latter are not applicable for class IIb devices.

The second option (**option b**) for the start-up is to apply for a conformity assessment based on **type-examination** coupled with a conformity assessment based on **product conformity verification**. As EU type-examination should be considered "*the procedure whereby a notified body ascertains and certifies that a device, including its technical documentation and relevant lifecycle processes and a corresponding representative sample of the device production envisaged, fulfils the relevant provisions of [the Medical Devices] Regulation*"[12]. The conformity assessment based on product conformity verification adds to that with the objective "*to ensure that devices confirm to the type for which an EU type-examination certificate has been issued, and that they meet the provisions of [the Medical Devices] Regulation which apply to them*"[13].

While under the Medical Devices Directive there were no provisions on the traceability of medical the devices, Article 27 of the Regulation introduces a **Unique Device Identification system**.[14] This system will allow the identification and facilitate the traceability of devices.[15]

Once compliance with the applicable requirements has been demonstrated by the applicable conformity assessment procedure, the start-up will draw up an **EU declaration of conformity** and **affix the CE marking of conformity**.[16]

[9] Article 61, 1 MDR, with references to the general safety and performance requirements in Annex I and the benefit-risk ratio in Sections 1 and 8 of Annex I.

[10] Section 2.1 Annex IX MDR.

[11] Section 4 Annex IX MDR.

[12] Section 1 Annex X MDR.

[13] Section 1 Annex XI MDR.

[14] Article 27 MDR and Part C of Annex VI MDR.

[15] Article 27, 1 MDR.

[16] Article 10, 6 MDR.

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1. Introduction

The AEGLE solution is a big data analytics platform featuring two interfaces: an R&D UI serving healthcare research and development purposes and a CDS UI to be used by practitioners in clinical settings. In terms of certification, the R&D UI does not have any special certification requirements other than those envisaged and described for the CDS UI. Therefore, this document, the AEGLE certification roadmap focuses on the rules concerning the CDS UI, which is in a way considered as a medical device. We base our analysis on Directive 93/42/EEC and Regulation 2017/745 (the latter is not applicable yet) which address issues relating to placement of medical devices in the market.

Before placing a medical device on the market, the product needs to undergo a CE marking process[17],[18]. Hence, the AEGLE product(s) / components require an EU declaration of conformity (the CE marking of conformity needs to be affixed on the product). The two options for meeting this requirement are described in this deliverable.

The future start-up of the AEGLE project could collaborate with developers of clinical decision support systems to implement the standalone analytics of the AEGLE project into clinical practice, *i.e.* to extend the function of the AEGLE project outcome to also cover individual patient cases.

Clinical decision support systems are "*computer based tools which combine medical knowledge databases and algorithms with patient specific data. They are intended to provide healthcare professionals and/or users with recommendations for diagnosis, prognosis, monitoring and treatment of individual patients*"[19].

As a consequence, the AEGLE software will target two different goals in the start-up scenario, namely 1) to perform general standalone big data analytics on medical information, and, 2) to provide healthcare professionals with information about individual patients. To this end, the AEGLE software will collect real-time contextual information about individual patients to analyse it by using the insights of AEGLE's big data analytics.

It must be noted that the only AEGLE use case that enables the use of a CDS platform is the Intensive Care Unit (ICU) case. In the CDS scenario, the ICUs require software and hardware modules and interfaces changes in order to be compatible with the AEGLE software. As indicated in a previous section of this report, it is preferred to not include hardware, and to provide the AEGLE software as a platform. If the AEGLE software – in whatever future configuration – is considered as a medical device, it will have to comply with the requirements and procedures provided by the EU legal framework on medical devices before it is placed into the EU market. Currently, the Council Directive 93/42/EEC[20], as amended by Directive 2007/47/EC[21], is applicable to the placing of medical devices into the market. However, as shown in section 3 of this report the overall additional trials' phase of the AEGLE-CDS PLATFORM is estimated to take up approximately four to six years in addition to the project. Hence, it is reasonable to focus this legal analysis on achieving legal compliance with Regulation (EU) 2017/745 on medical

[17] https://europa.eu/youreurope/business/product/ce-mark/index_en.htm

[18] https://ec.europa.eu/growth/sectors/medical-devices/regulatory-framework_en

[19] MEDDEV 2.1/6, 20.

[20] Council Directive 93/42/EEC of 14 June 1993 concerning medical devices, OJ L 169, 1.

[21] Directive 2007/47/EC of the European Parliament and of the Council of 5 September 2007, amending Council Directive 90/385/EEC on the approximation of the laws of the Member States relating to active implantable medical devices, Council Directive 93/42/EEC concerning medical devices and Directive 98/8/EC concerning the placing of biocidal products on the market, OJ L 247, 21 (hereinafter referred to as: the Directive or MDD).

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devices[22], as overall (*i.e.* most provisions of) this new Regulation will be applicable from 26 May 2020.[23] Nonetheless, the current regime (Directive 93/42/EEC) will be taken into account during this short analysis, including the Commission's MEDDEV Guidance documents.[24]

The Medical Devices Directive and Regulation lay down the rules concerning the placing on the market, making available on the market or putting into service of medical devices for human use and accessories for such devices in the Union.[25]

It should be assessed whether the AEGLE software should be considered as a medical device, and if so:

- Under which class the medical device is to be classified in,
- Which general requirements the device should meet before being placed into the market, and
- Which procedures should be followed by the manufacturer.

2. Notified Bodies

All notified bodies can be found in the Nando database[26]. The manufacturer is free to choose any notified body and is not limited to the notified bodies within their member state. The certificates issued by the notified bodies are applicable all over the EU in order to allow the free movements of goods within the EU. The choice of the notified body will depend on the specific expertise of the body - as that the notified body can understand the device and make an accurate assessment, and on the reputation of the body and the services provided. An example of a notified body is Emergo based in The Hague.

3. Medical device

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, prevention, monitoring, treatment, alleviation of, or compensation for an injury or a disability,*
- *Investigation, replacement or modification of the anatomy or of a physiological or pathological process state,*
- *Providing information by means of in vitro examination of specimens derived from the human body, including organ, blood and tissue donations.*

[22] 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) 187/2002 and Regulation (EC) 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC, OJ L 117, 1 (hereinafter referred to as: the Regulation or MDR).

[23] Article 123 MDR.

[24] In particular, MEDDEV 2.1/6, "Guidelines on the qualification and classification of standalone software used in healthcare within the regulatory framework of medical devices", July 2016.

[25] Article 1, 1 MDR.

[26] http://ec.europa.eu/growth/tools-databases/nando/index.cfm?fuseaction=notifiedbody.main

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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 itsmedical the functions by such means"[27].

Following this definition three main criteria can be identified; A medical device is 1) a device that is used for human beings, 2) which has a specific medical purpose, and 3) which may not achieve its principal intended action by pharmacological, immunological or metabolic means.

The second criteria, which requires the device to have one or more of the specific medical purposes, is the most difficult to apply in the context of the AEGLE software. Especially given that the goal of the AEGLE software is limited to provide information about the condition of the patient, while this information is still to be interpreted by the medical staff in order to take a medical decision.

In the SNITEM Philips case of the Court of Justice of the European Union a similar discussion is at stake, namely whether or not the 'IntelliSpace Critical Care and Anaesthesia' (ICCA) software developed by Philips, which provides information to doctors to assist them in their prescribing decisions, is to be considered as a medical device.[28] Whether or not ICCA is to be considered as a medical device depends on whether it serves one of the functions listed in Article 1, 2, a) of Directive 93/42/EEC (as the opinion concerns the scope of the Medical Devices Directive). However, if the software has a general purpose and this general software would only be used in a healthcare environment, the software cannot be considered as a medical device.[29] On the other hand, software has to be considered as a medical device when it does not have solely a general purpose, for example, when it interprets or modifies medical information.[30] In his opinion, Advocate General Campos Sanchez-Bordona states that the ICCA software should be considered as a medical device given that it analyses the information that is aligned with the program for the purpose to provide additional information for medical decisions.[31]

In this view, the function of the AEGLE software to provide information to medical staff in an ICU scenario could similarly fall under the scope of the 'medical device' definition. Hence, the AEGLE software is to be considered as a medical device regardless of the fact that it will be used alone or in combination with the ICU devices.

4. Classification of medical devices

The rules to classify medical devices based on their risk, and determining the general device requirements and procedures for placing the device into the market, is regulated in Annex VIII of the Regulation.

It is important to first determine whether the AEGLE software is to be considered in its own right or not, as "*software, which drives a device or influences the use of a device, shall fall within the same class as the device*"[32], while, "*if the software is independent of any other device, it shall be classified in its own right*"[33].

In the scope of Directive 93/42/EEC, 'standalone software' is described as "*software which is not incorporated in a medical device at the time of its placing on the market or its making available*"[34]. Even though the MEDDEV

[27] Article 2, 1 MDR.
[28] ECJ C-329/16, application 29 July 2016.

[29] Consideration 6 Directive 2007/47.
[30] Opinion Advocate General Campos Sanchez-Bordona, 28 June 2017, C-329/16, §63, referring to MEDDEV 2.1/6, 19.
[31] Opinion Advocate General, C-329/16, §48.
[32] Section 3.1 Annex VIII.
[33] Section 3.1 Annex VIII.

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guidelines are not binding, it is generally accepted that these guidelines can contribute to a systematic interpretation of the provisions of the Directive.[35]

If the AEGLE software would be incorporated into another medical device, *i.e.* the ICU device, and it drives or influences the use thereof, the AEGLE software will fall within the same class as the ICU.

However, the AEGLE software will not be fully incorporated in the ICU, given that the start-up will provide a dashboard and the incorporation of the AEGLE software into the ICU will be limited to measures to facilitate the compatibility of both devices. Moreover, the AEGLE software cannot be considered as a mere 'accessory for a medical device', as it is not intended to be used together with a medical device to specifically enable the medical device to be used in accordance with its intended purpose(s) or to specifically and directly assist the medical functionality of the medical device in terms of its intended purpose.[36] The AEGLE dashboard will have its own independent purposes and is therefore to be classified in its own right.[37] Hence, the AEGLE software is to be considered on its own.

Standalone software shall be deemed to be an active device.[38] The notion 'active device' means "*any device, the operation of which depends on a source of energy other than that generated by the human body for that purpose, or by gravity, and which acts by changing the density of or converting that energy. Devices intended to transmit energy, substances or other elements between an active device and the patient, without any significant change, shall not be deemed to be active devices*"[39].

Rule 11 of Annex VIII explicitly specifies that software intended to provide information which is used to take decisions with diagnosis or therapeutic purposes is classified as class IIb when such decisions have an impact that may cause a serious deterioration of a person's state of health or a surgical intervention.

In cases where the impact of the decision may cause death or an irreversible deterioration of a person's state of health, the software is classified as class III.[40]

On the other hand, if the software is intended to monitor vital physiological parameters, where the nature of variations of those parameters is such that it could result in immediate danger of the patient, the software is classified as class IIb.[41]

For this reason, it is important to clarify the medical purpose of the AEGLE software in the CDS patform context. It could be argued that the "*decision support*"-function of AEGLE is limited to the monitoring of vital physiological parameters. However, given that a CDS system inherently goes beyond monitoring, as the decision support element is crucial in a CDS system, the AEGLE CDS platform will have to be considered as a software intended to provide information which is used to take medical decisions.

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[34] MEDDEV 2.1/6, 7.

[35] Opinion Advocate General, C-329/16, §56.

[36] Article 2, 2 MDR.

[37] Section 3.3 Annex VIII.

[38] Article 2, 4 MDR. Also in the current regime standalone software is considered to be an active medical device (Annex IX, 1.4 Directive 93/42/EEC). Standalone means that the software is not incorporated in a medical device at the time of its placing on the market or its making available (MEDDEV 2.1/6, 7).

[3939] Article 2, 4 MDR.

[40] Rule 11 Annex VIII.

[41] Rule 11 Annex VIII.

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It should be pointed out that under the current classification system, the AEGLE CDS platform would be classified as class IIb. MEDDEV 2.1/6 provides the example of software as a class IIb medical device: "*Software for the presentation of the heart rate or other physiological parameters for intensive care monitoring*"[42].

This means that the qualification of the purposes of the AEGLE software is crucial. It is recommended that the start-up limits the impact of the AEGLE CDS platform to "*a serious deterioration of a person's state of health or a surgical intervention*" as that it can be classified as a class IIb medical device, and to exclude the impact to be "*death or an irreversible deterioration of a person's state of health*", in which case the AEGLE software would be classified as a class III medical device.

5. Placing a medical device on the market

When a device is placed on the market, it needs to be duly supplied and properly installed, maintained and used in accordance with its intended purpose.[43] The 'intended purpose' of a device "*means the use for which a device is intended according to the data supplied by the manufacturer on the label, in the instructions for use or in promotional or sales materials or statements and as specified by the manufacturer in the clinical evaluation*"[44].

Before being able to put a medical device on the market, the product needs to undergo a CE marking process.

Article 10 of the Medical Devices Regulation lists the general obligations for manufacturers. The manufacturer is "*the natural or legal person who manufactures or fully refurbishes a device or has a device designed, manufactured or fully refurbished, and markets that device under its name or trademark*"[45]. When placing a device on the market or putting it into service, the manufacturer shall ensure that the device is designed and manufactured in accordance with the requirements of the MDR.[46]

The requirements for the AEGLE start-up are summarized in Section 5 to Section 12 for class IIb and class III medical devices.

6. General safety and performance requirements

The general safety and performance requirements, which the medical device should meet before it can be placed on the market, are listed in Chapter II. 'Requirements regarding design and manufacture' of Annex I. 'General safety and performance requirements' of the Medical Device Regulation.[47]

Medical devices need to meet the general safety and performance requirements set out in Annex I, which apply to it, taking into account the intended purpose of the device (*infra* risk management system).[48]

[42] MEDDEV 2.1/6, 16.

[43] Article 5, 1 MDR.

[44] Article 2, (12) MDR.

[45] Article 2, (30) MDR.

[46] Article 10, 1 MDR.

[47] The Article 5, 5 MDR exception for devices manufactured and used only within health institutions established in the union cannot apply, as the AEGLE software will not be manufactured within health institutions established in the Union. As opposed to be put into service, the AEGLE software will be placed on the market (cfr. Art. 5, 4 MDR).

[48] Article 5, 2 MDR.

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Chapter II of Annex I distinguishes 13 categories of requirements. The AEGLE start-up will need to consider compliance with the following categories of requirements:

- Section 14 'Construction of devices and interaction with their environment',
- Section 15 'Devices with a diagnostic or measuring function',
- Section 17 'Electronic programmable systems – devices that incorporate electronic programmable systems and software that are devices in themselves',
- Section 18 'Active devices and devices connected to them',

Depending on the technical implementation of the AEGLE start-up, one additional set of requirements might have to be taken into account as well, namely Section 20 'Protection against mechanical and thermal risks'.

Given that the AEGLE software will be used only in intensive care scenarios, the set of requirements in Section 22 for 'protection against the risks posed by medical devices intended by the manufacturer for use by lay persons' can be disregarded. However, if the use-cases of the AEGLE start-up would extend to situations where the software is intended to be used by lay persons, for example, the diabetes use-case of the AEGLE project, this set of requirements should be considered by the start-up as well.

7. Risk management

As previously set out, a medical device that is placed into the market needs to achieve the performance intended by its manufacturer and shall be designed and manufactured in such a way that, during normal conditions of use, it is suitable for its intended purpose. The medical device needs to 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 the use of the device constitutes 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.[49]

This means that the risks of using the device in a normal situation should be balanced with the benefits of the use for the patient concerned. The requirement to reduce risks as far as possible needs to be interpreted as the reduction of risks as far as possible without adversely affecting the benefit-risk ratio.[50]

To this end, a risk management system needs to be established, implemented documented and maintained by the manufacturer of the medical device.[51] Within the Medical Devices Regulation risk management is to be understood as a continuous iterative process throughout the entire lifecycle of the device, requiring regular systematic updating. In carrying out risk management, the start-up shall:

(a) establish and document a risk management plan for the device,

(b) identify and analyse the known and foreseeable hazards associated with that device,

(c) estimate and evaluate the risks associated with, and occurring during, the intended use and during reasonably foreseeable misuse,

[49] Section 1 Annex I MDR.

[50] Section 2 Annex I MDR.

[51] Article 10, 3 MDR and Section 3 Annex I MDR.

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(d) eliminate or control these risks by appropriate risk control measures. These risk control measures shall conform to safety principles, taking into account of the generally acknowledged state of the art. The start-up will need to manage risks so that the residual risk associated with each hazard as well as the overall residual risk is judged acceptable,[52]

(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 associate 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 the risk control measures.[53]

Moreover, the start-up will have to eliminate or reduce the risks related to use error. Therefore, the start-up shall, a.o. give consideration to the technical knowledge, experience, education, training and use environment, as well as to the medical and physical conditions of the intended users of the AEGLE software.[54]

8. Clinical evaluation

The start-up will have to conduct a clinical evaluation in accordance with the requirements set out in Article 61 and Annex XIV of the Medical Devices Regulation, including a post-market clinical follow-up.[55] The confirmation of conformity with the relevant general safety and performance requirements and of the acceptability of the benefit-risk ratio will be based on these clinical data.[56] In other words, the clinical evaluation will be an integral part of the process to demonstrate conformity.[57]

The start-up will specify and justify the level of clinical evidence necessary to demonstrate conformity with the relevant requirements in view of the characteristics of the device and its intended purpose.[58] To that end, the start-up will plan, conduct and document a clinical evaluation of the AEGLE software in accordance with Article 61 and Annex XIV.

If the AEGLE software would be classified as a class III medical device, the start-up may, prior to its clinical evaluation and/or investigation, consult an expert panel, with the aim of reviewing the start-up's intended clinical development strategy and proposals for clinical investigation.[59] In addition, for class III devices, a notified body shall also follow the procedure regarding clinical evaluation consultation as specified in Section 5.1 of Annex IX or as referred to in Section 6 of Annex X, as applicable, when performing a conformity assessment.[60]

The clinical evaluation will follow a defined and methodologically sound procedure set out in Article 61, 3 of the Medical Devices Regulation. First, a critical evaluation of the relevant scientific literature currently available

[52] See Section 4, (a) to (c) Annex I MDR for the criteria to select the most appropriate solutions.

[53] Section 3 Annex I MDR.

[54] Section 5, (b) Annex I MDR. For the full list, see: Article 5 Annex I MDR.

[55] Article 10, 3 MDR.

[56] Article 61, 1 MDR, with references to the general safety and performance requirements in Annex I and the benefit-risk ratio in Sections 1 and 8 of Annex I.

[57] Article 5, 3 MDR.

[58] Article 61, 1 MDR.

[59] Article 61, 2 MDR; Article 106 MDR.

[60] Article 54 MDR.

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relating to the safety, performance, design characteristics and the intended purpose of the device has to be conducted. This evaluation is followed by a critical evaluation of the results of all available clinical investigations. Finally, currently available alternative treatment options for that purpose, if any, are to be considered. In order to plan, continuously conduct and document the clinical evaluation, the start-up needs to comply with the requirements from Part A of Annex XIV. 'Clinical evaluation'.

In the unlikely case that the AEGLE software will be equivalent to an already marketed device that is not manufactured by the AEGLE start-up, the start-up may rely on previous clinical investigations of the equivalent device, and not perform the clinical investigation. For this, it is required that the start-up has a contract in place with the first manufacturer that allows the start-up full access to the technical documentation on an ongoing basis, and that the original clinical evaluation has been performed in compliance with the requirements of the Medical Devices Regulation.[61]

When the demonstration of conformity with general safety and performance requirements based on clinical data is not deemed appropriate by the start-up, it shall give adequate justification for any such exception based on the results of its risk management, the specifics of the interaction between the device and the human body, the clinical performance intended and the claims of the start-up. In this case, the start-up will have to duly substantiate in the technical documentation (referred to in Annex II of the Medical Devices Regulation) why it considers a demonstration of conformity with general safety and performance requirements based on the results of non-clinical testing methods alone, including performance evaluation, bench testing and pre-clinical evaluation, to be adequate.[62]

The clinical evaluation, its results and the clinical evidence derived from it will be documented in a clinical evaluation report, which will be part of the technical documentation referred to in Annex II of the Regulation relating to the device concerned.[63] The clinical evaluation and its documentation will be updated throughout the lifecycle of the device concerned with clinical data obtained from the implementation of the start-up's post-market clinical follow-up plan.[64] For class III medical devices, the post-market clinical follow-up evaluation report will be updated at least annually.[65]

9. Technical documentation for the device

The start-up will draw up and keep up to date technical documentation for the AEGLE software.[66] The technical documentation shall be presented in a clear, organised, readily searchable and unambiguous manner and include the elements set out in Annex II 'Technical documentation' and Annex III. 'Technical documentation on post-market surveillance' of the Medical Devices Regulation.

Overall, the start-up will have to provide a description and specification of the medical device. The start-up will deliver information on the design and manufacturing of the device and on the general safety and performance requirements according to the class under which the device is classified. Finally, the start-up will provide a benefit-risk analysis and risk management plan, as well as the product verification and validation.

[61] Article 61, 5 MDR.

[62] Article 61, 10 MDR.

[63] Article 61, 12 MDR.

[64] Article 61, 11 MDR, Article 84 MDR and Part B Annex XIV.

[65] Article 61, 11 MDR.

[66] Article 10, 4 MDR.

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With regard to the technical documentation on post-market surveillance, the start-up will have to include the post-market surveillance plan in accordance with Article 84 Medical Devices Regulation and the requirements from Annex III.

10. Conformity assessment procedure

Prior to placing the AEGLE software on the market, the start-up shall undertake an assessment of the conformity of the software, in accordance with the applicable conformity assessment procedures set out in Annexes IX to XI.[67]

If the AEGLE software is considered as a class III medical device, the start-up will have the choice between the following options[68]:

a) To be subject to a conformity assessment as specified in Annex IX. 'Conformity assessment based on a quality management system and on an assessment of the technical documentation', or

b) To apply a conformity assessment based on type-examination as specified in Annex X coupled with a conformity assessment based on product conformity verification as specified in Annex XI.

On the other hand, if the AEGLE software is considered as a class IIb medical device, the start-up will have the choice between the following two options:[69]

a) To be subject to a conformity assessment based on a quality management system as specified in Chapters I and III of Annex IX, and including an assessment of the technical documentation as specified in Section 4 of Annex IX,

b) To apply a conformity assessment based on type-examination as specified in Annex X coupled with a conformity assessment based on product conformity verification as specified in Annex XI.

When the start-up opts for option a), the start-up will establish, document and implement a quality management system as described in Article 10, 9 of the Medical Devices Regulation and maintain its effectiveness throughout the lifecycle of the AEGLE software.[70]

The start-up will lodge an application for assessment of its quality management system with a notified body.[71] A 'notified body' is "*a conformity assessment body that is designated in accordance with [the Medical Device] Regulation*"[72]. A 'conformity assessment body' means "*a body that performs third-party conformity assessment activities including calibrating, testing, certification and inspection*"[73]. The start-up may apply to the notified body of its choice, provided that the chosen notified body is designated for conformity assessment activities that relate to the type of the medical device concerned, *i.e.* the AEGLE software.[74] Chapter I of Annex IX describes the procedures and requirements for the application for a quality management system assessment by the start-up, the procedure regarding the audit by the notified body, and the surveillance assessment process of the conformity

[67] Article 52, 1 MDR.

[68] Article 52, 3 MDR.

[69] Article 52, 4 MDR.

[70] Section 1 Annex IX MDR.

[71] Section 2.1 Annex IX MDR.

[72] Article 2, 41 and 42 MDR.

[73] Article 2, 41 MDR.

[74] Article 53, 1 MDR.

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assessment based on a quality management system. Chapter II of Annex IX describes the rules for the start-up to lodge an application with the notified body for assessment of the technical documentation relating to the class IIb or class III device which it plans to place on the market.[75] For class III medical devices specific additional procedures are outlined in Sections 5 to 6 of Annex IX. The latter are not applicable for class IIb devices.

The second option for the start-up is to apply for a conformity assessment based on type-examination coupled with a conformity assessment based on product conformity verification. As EU type-examination should be considered "*the procedure whereby a notified body ascertains and certifies that a device, including its technical documentation and relevant lifecycle processes and a corresponding representative sample of the device production envisaged, fulfils the relevant provisions of [the Medical Devices] Regulation*"[76]. The conformity assessment based on product conformity verification adds to that with the objective "*to ensure that devices confirm to the type for which an EU type-examination certificate has been issued, and that they meet the provisions of [the Medical Devices] Regulation which apply to them*"[77].

Given that the second option is focused on medical devices for larger production, this does not seem to be a viable option for the AEGLE start-up.

11. EU declaration of conformity and CE marking of conformity

Once compliance with the applicable requirements has been demonstrated by the applicable conformity assessment procedure, the start-up will draw up an EU declaration of conformity and affix the CE marking of conformity.[78]

With the EU declaration of conformity the start-up will state and continuously confirm in updates that the requirements specified in the Medical Devices Regulation have been fulfilled in relation to the AEGLE software.[79] The EU declaration of conformity shall contain the information listed in Annex IV of the Medical Devices Regulation.

The AEGLE software will bear the CE marking of conformity.[80] The CE marking, as presented in Annex V of the Regulation, will be affixed visibly, legibly and indelibly to the device or its sterile packaging. For the AEGLE software the CE marking will have to be affixed to the packaging of the software.[81] The start-up will have to consider the rules for affixing as provided by Article 20 of the Medical Devices Regulation and the general principles set out in Article 30 of Regulation (EC) No. 765/2008 setting out the requirements for accreditation and market surveillance relating to the marketing of products.[82] The general principles of CE marking determine, amongst others, by whom the CE marking shall be affixed and for which products CE marking is required.[83]

[75] Section 4 Annex IX MDR.

[76] Section 1 Annex X MDR.

[77] Section 1 Annex XI MDR.

[78] Article 10, 6 MDR.

[79] Article 19, 1 MDR.

[80] Article 20 MDR.

[81] Article 20, 3 MDR.

[82] Article 20, 2 MDR and Regulation (EC) No. 765/2008 of the European Parliament and of the Council of 9 July 2008 setting out the requirements for accreditation and market surveillance relating to the marketing of products and repealing Regulation (EEC) No. 393/93, OJ L 218/20.

[83] Article 30, 1-2 Regulation 765/2008.

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12. Unique Device Identification system

While under the Medical Devices Directive there were no provisions on the traceability of medical the devices, Article 27 of the Regulation introduces a Unique Device Identification (UDI) system.[84] This system will allow the identification and facilitate the traceability of devices.[85]

The UDI is a series of numeric or alphanumeric characters that is created through internationally accepted device identification and coding standards and that allows unambiguous identification of specific medical devices on the market.[86] The UDI contains a Device Identifier (UDI-DI) with static data and a Production Identifier (UDI-PI) with dynamic data.[87] The UDI-DI is specific to a model of device that is used as the 'access key' to information stored in a UDI database.[88] The UDI-PI identifies the unit of device production and consists of a serial number, lot number, software identification and manufacturing or expiry dates or both types of data.[89]

Before being placed on the market, the manufacturer of a medical device will assign a basic UDI-DI to the device and provide it to the UDI database together with the other core data elements to that device referred to in Part B of Annex VI.[90]

Moreover, a UDI carrier shall be placed on the label or on the device itself.[91] The UDI carrier is the means of conveying the UDI in a machine readable (using AIDC[92]) and human readable (using HRI[93]) interpretation.[94]

For software which is commercially available on its own and software which constitutes a device in itself, *i.e.* standalone medical device software, the UDI is assigned at the system level.[95] A new UDI-DI will be required whenever there is a modification that changes the original performance, the safety or the intended use of the software, or the interpretation of the data. Such modifications include new or modified algorithms, database structures, operating platforms, architecture or new user interfaces or new channels for interoperability.[96] Minor software revisions, such as the ones associated with bug fixes, will not require a new UDI-DI, but only a new UDI-PI.

Section 6.5.4 of Part 3 of Annex VI provides the UDI placement criteria for software. Where the software is delivered on a physical medium, such as a CD or a DVD, each packaging level shall bear the HRI and AIDC representation of the complete UDI.[97] Moreover, the HRI portion of the UDI is required in electronic displays of the

[84] Article 27 MDR and Part C of Annex VI MDR.

[85] Article 27, 1 MDR.

[86] Article 2, 15 MDR.

[87] Section 3.3 Part C Annex VI.

[88] Section 1 Part C Annex VI.

[89] Section 1 Part C Annex VI.

[90] Article 29, 1 MDR.

[91] Section 4 Part C Annex VI.

[92] 'AIDC' or 'Automatic identification and data capture' is "a technology used to automatically capture data. AIDC technologies include bar codes, smart cards, biometric and RFID", Section 1 Part C Annex VI.

[93] 'HRI' or 'Human Readable Interpretation' is "a legible interpretation of the data characters encoded in the UDI carrier", Section 1 Part C Annex VI.

[94] Section 1 Part C Annex VI.

[95] Section 6.5.1 Part 3 Annex VI.

[96] Section 6.5.2 Part 3 Annex VI.

[97] Section 6.5.4, a) Part 3 Annex VI.

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software and will be provided on a readily accessible screen for the user in an easily-readable plain-text format, such as an 'about' file, or it will be included on the start-up screen.[98]

All UDIs will come together in a UDI database, namely the European database on medical devices database (Eudamed).[99] The core elements that are provided to the UDI database shall be accessible to the public free of charge.[100]

13. Quality management systems

Next to the CE marking, we would like to point out the relevance of ISO 13485:2016 for AEGLE. ISO 13485:2016 "*specifies requirements for a quality management system where an organization needs to demonstrate its ability to provide medical devices and related services that consistently meet customer and applicable regulatory requirements. Such organizations can be involved in one or more stages of the life-cycle, including design and development, production, storage and distribution, installation, or servicing of a medical device and design and development or provision of associated activities (e.g. technical support). ISO 13485:2016 can also be used by suppliers or external parties that provide product, including quality management system-related services to such organizations. Requirements of ISO 13485:2016 are applicable to organizations regardless of their size and regardless of their type except where explicitly stated. Wherever requirements are specified as applying to medical devices, the requirements apply equally to associated services as supplied by the organization.*"[101].

14. Post-market surveillance

The start-up needs to ensure that procedures will be in place to continuously keep the production of the medical device in conformity with the requirements of the Medical Devices Regulation. It shall establish, document, implement, maintain, keep up to date and continually improve its quality management system that shall ensure compliance with the Regulation in the most effective manner and in a manner proportionate to the risk class and the type of medical device.[102]

The post-market surveillance system as described in Article 83 of the Regulation will be an integral part of the quality management system and must be based on a post-market surveillance plan.[103] The post-market surveillance system must actively and systematically analyse relevant data on the quality, performance and safety of the device throughout its entire lifetime. It should draw necessary conclusions to determine, implement and monitor any preventive and corrective actions.[104] A summary of the results thereof will be reported in a periodic safety update report together with a rationale and description of any preventive and corrective actions taken.[105]

[98] Section 6.5.4, b)-c) Part 3 Annex VI.

[99] Article 33 MDR.

[100] Article 28, 3 MDR.

[101] https://www.iso.org/standard/59752.html

[102] Article 10, 9 MDR.

[103] Article 83, 2 MDR, Article 84 MDR and Section 1.1 Annex III.

[104] Article 83, 2 MDR.

[105] Article 86 MDR.

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15. Data Protection

Concerning certification in terms of data protection, no Data Protection Authorities provided certification since the GDPR became applicable. However, private entities do - some have standards based on the GDPR. However, they are not recognized by Data Protection Authorities, such as ePrivacyseal[106] or EuroPrise[107]. Further, while certification regarding data protection is a way to demonstrate compliance with the GDPR and enhance transparency, it is not mandatory.

Additional information on the topic may be found here:
- ENISA - Recommendations on European Data Protection Certification, 27 November 2017[108];
- EDPB Guidelines 1/2018 on certifications and identifying certification criteria in accordance with Articles 42 and 43 of the regulation 2016/679, 25 May 2018[109].

16. Conclusion

Before the AEGLE software (as developed by the AEGLE project) can be implemented in one or more clinical decision support systems that can be used in individual patient cases, it will have to be determined whether the AEGLE software is going to function as an accessory to existing devices, or on the other hand, that it will act on its own. Given that provisionally it is preferred to have the AEGLE software to function as a platform, the software should be considered to be on its own. Hence, the future start-up that will place the AEGLE software into the market will have to comply with the requirements for medical devices and procedures for placing medical devices into the market as provided by the EU legal framework on medical devices.

[106] https://www.eprivacy.eu/en/privacy-seals/eprivacyseal/
[107] https://www.european-privacy-seal.eu/EPS-en/Home
[108] https://www.enisa.europa.eu/publications/recommendations-on-european-data-protection-certification
[109] https://edpb.europa.eu/our-work-tools/our-documents/guidelines/guidelines-12018-certification-and-identifying-certification_en

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Abbreviations

CDS:	Clinical Decision Support System
D:	Deliverable
DoW:	Description of Work
GDPR	General Data Protection Regulation, Regulation (EU) 2016/679
HW, H/W:	Hardware
R&D:	Research and Development
M:	Month
SW, S/W:	Software
UI:	User Interface

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