CROM SOURCE
advise | agree | deliver

White Paper

Changes to EU Medical Device Legislation

What you need to know

MEDICAL DEVICE

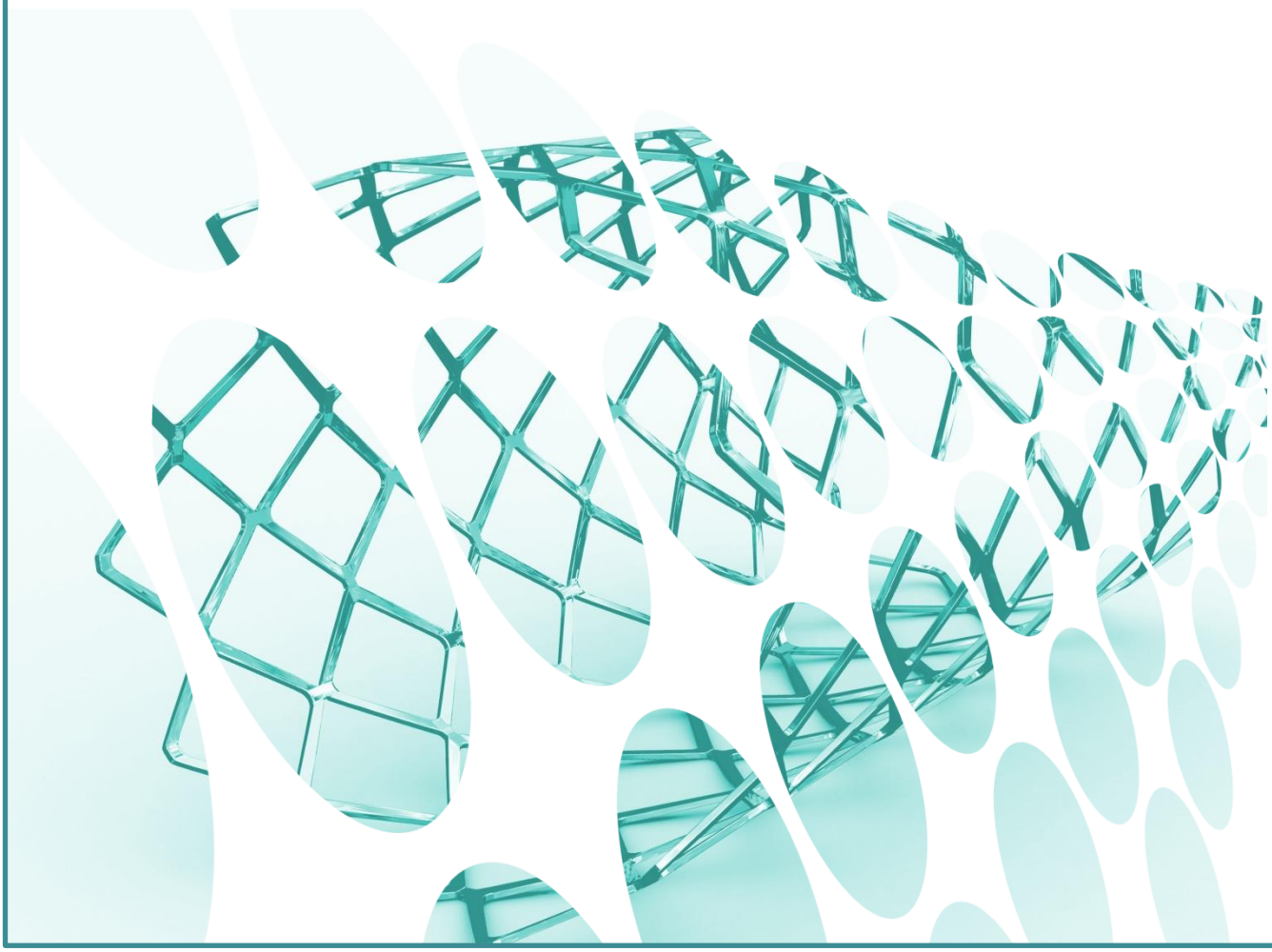


Table of Contents

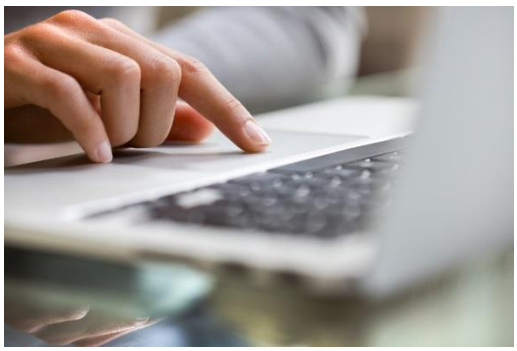
1. The final text of the Medical Device Regulation has been made available

The current EU regulatory framework for medical devices consists of the Medical Devices Directive 93/42/EEC and Active Implantable Medical Devices Directive 90/385/EEC. The revision, proposed by the European Commission in 2012, will combine the two directives and will be introduced as a regulation instead of a directive. A "regulation" is a binding legislative act that must be applied in its entirety across the EU.

On 15 June 2016, the Council of the European Union's Permanent Representatives Committee endorsed the agreement reached with the European Parliament on 25 May 2016 on the proposed Medical Device Regulation (MDR). In its consolidated version the Council has thoroughly revised the Commission's proposals in terms of structure and with respect to the requirements. Before implementation across the European Union, the consolidated negotiated text will undergo legal review and translation into all EU member languages, followed by formal publication. After that publication, expected in late 2016 or early 2017, there will be a three-year transition period.

CROMSOURCE obtained a copy of the consolidated MDR text from the Transparency and Access to Documents Unit of the General Secretariat of the Council of the European Union. The 352-page long document, dated 27 June 2016, is broken down into 10 chapters and 16 annexes. Here we highlight some of the key changes to the legislation.

2. Scope of the Regulation will be extended to non-medical devices



Regulation will be extended to groups of products without an intended medical purpose (Ch. I, Art. 1). These products, which are listed in Annex XV, are similar to medical devices in terms of their characteristics and risks. Examples are contact lenses, facial dermal fillers, equipment for liposuction, lasers for skin resurfacing or hair removal, and equipment for electromagnetic brain stimulation. Also new to the MDR are common specifications (Ch. I, Art. 7). These can replace harmonized standards for risk management of Annex XV products and, where necessary, clinical evaluation regarding safety. Common specifications can be adopted where no harmonized standards exist or are not sufficient or where there is a need to address public health concerns.

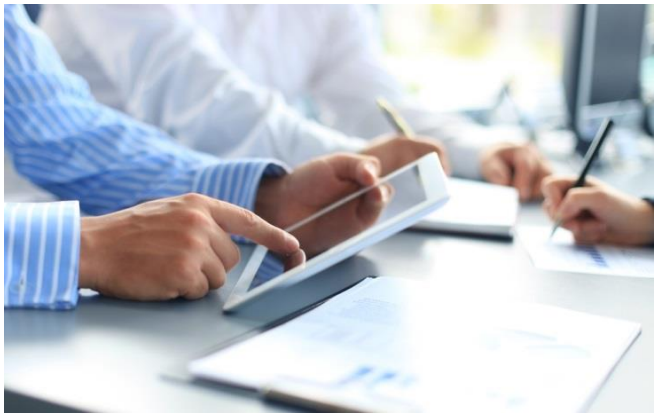
3. Post market surveillance will require periodic updates

General obligations of the manufacturer, authorized representatives, importers, distributors are described extensively in Chapter II. The manufacturer, for example, is obliged to monitor products placed on the market. The postmarket surveillance plan must be constantly updated, and this also includes a plan for the post-market clinical follow-up. Chapter VII establishes explicit provisions on manufacturers' responsibilities for post-market surveillance of devices placed on the market. For devices other than custom made-devices, the post-market surveillance plan shall be part of the technical documentation (Art. 60b). Article 60c introduces the requirement for Periodic safety update reports for manufacturers of devices in class IIa, IIb and III. These will summarise the results and conclusions of the analyses of the gathered post-market surveillance data.

4. Increased traceability of devices, tighter control over distribution

The Regulation seeks to ensure that it will be possible to identify economic operators to whom devices are supplied or from whom devices are purchased (Ch. III, Art. 23). Devices will have a unique identification number to provide for traceability throughout the supply chain to the end-user or patient, allowing fast and effective measures in case of safety problems (Ch. III, Art. 24). The Unique Device Identification (UDI) system is described in Annex V, Part C. Production of a UDI will comprise the following: a device identifier (DI) specific to a manufacturer and a device, and a production identifier (PI) that identifies the produced device's unit and if applicable the packaged devices. UDI codes must be included on all medical device labels. UDI product identification system is to be integrated into Eudamed, a European database (Ch. III, Art. 24).

5. Eudamed database will increase the transparency of devices



The Eudamed database will provide patients, healthcare professionals and the public with comprehensive information on devices placed on the EU market. Major parts of Eudamed are to be made accessible to the public whilst observing data protection needs (Ch. III, Art. 27). In the case of devices classified as class III and implantable devices, other than custom-made or investigational devices, the manufacturer shall write a summary of safety and clinical performance in a way that is clear to the intended user and, if relevant, to the patient. The draft of this summary shall be part of the documentation to be submitted to the notified body involved in the conformity assessment and shall be validated by that body. After validation the notified body shall upload this summary report to Eudamed (Ch. III, Art. 26).

6. Introduction of a scrutiny mechanism for conformity assessments

The requirements concerning notified bodies (Chapter IV) and the procedures for classification and conformity assessment have been extensively expanded. Article 44 (Chapter V), introduces a mechanism for scrutiny of conformity assessments of certain class III and class IIb devices. A notified body shall notify the competent authorities of certificates it has granted to devices, the conformity assessment of which has been performed. Such notification shall include the summary of safety and clinical performance information, the assessment report by the notified body, the instructions for use, and, where applicable, the scientific opinion of the expert panels. A competent authority and, where applicable, the Commission may, based on reasonable concerns apply further appropriate procedures.

The assessment procedure in specific cases of implantable devices classified as class III, and for Class IIb active devices intended to administer and/or remove a medicinal product is discussed in Annex VIII (Ch. II, sect. 6 "Specific procedures"). According to this procedure the notified body prepares a clinical evaluation assessment report based on its review of clinical evidence supplied by the manufacturer and transmits this report together with the relevant documentation of the manufacturer to the Commission. The latter submits the documents to an expert panel, who may, but is not obliged to give a scientific opinion within a specified period. Where an opinion is obtained, the notified body should take it into account when continuing with the conformity assessment procedure.

7. Classification rules will change for certain devices

Devices shall be divided into classes I, IIa, IIb and III, taking into account the purpose intended by the manufacturer and inherent risks (Ch. V, Art. 41). Classification criteria are set out in Annex VII. The classification rules will change for certain devices. The following are new class III designations:

Rule 3: added "All non-invasive devices consisting of a substance or a mixture of substances intended to be used in vitro in direct contact with human cells, tissues or organs taken off from the human body or with human embryos before their implantation or administration into the body are in class III".

Rule 8: "Active implantable devices or their accessories" added as class III devices

Rule 8: "surgical meshes" added as class III devices

Rule 9: added "All active devices that are intended for controlling, monitoring or directly influencing the performance of active implantable devices are in class III".

Rule 10: subrule 10a added "Software intended to provide information which is used to take decisions with diagnosis or therapeutic purposes, is in class IIa, except if such decisions have

an impact that may directly or indirectly cause: the death or an irreversible deterioration of the state of health, in which case it is in class III".

New Special Rule 19: All devices incorporating or consisting of nanomaterial are in class III if they present a high or medium potential for internal exposure.

New Special Rule 21: Devices that are composed of substances or combinations of substances that are intended to be introduced into the human body via a body orifice, or applied on skin and that are absorbed by or locally dispersed in the human body are: in class III if they, or their products of metabolism, are systemically absorbed by the human body in order to achieve the intended purpose; in class III if they achieve their intended purpose in the stomach or lower gastrointestinal tract and they, or their products of metabolism, are systemically absorbed by the human body.

New Special Rule 23: Active therapeutic devices with an integrated or incorporated diagnostic function, which significantly determinates the patient management by the device are in class III, such as closed loop systems or automated external defibrillators.

8. Stricter rules will apply to clinical data requirements

Significant changes and stricter rules will also apply to the clinical evaluation and clinical investigations of devices (Ch. VI, Arts. 49 to 60). Manufacturers may rely on equivalent products only under very strict conditions. According to Section 4a of Part A of Annex XIII, a clinical evaluation can only be based on clinical data of a similar device for which equivalence to the device in question can be demonstrated. Manufacturers must be able to clearly demonstrate that they have sufficient levels of access to the data on devices to which they are claiming equivalence in order to justify that claimed equivalence. Article 49, 2(a) states that in the case of implantable devices and class III devices, clinical investigations shall be performed, except if the device has been designed by modifications of an equivalent device already marketed by the same manufacturer. According to Art. 49, 2(aa) a manufacturer of a device demonstrated to be equivalent to an already marketed device not manufactured by him, may also rely on paragraph 2(a) provided that the following additional conditions are fulfilled: the two manufacturers have a contract in place that explicitly allows the manufacturer of the second device full access to the technical documentation on an ongoing basis; the original clinical evaluation has been performed in compliance with the requirements of this Regulation; and the manufacturer of the second device provides clear evidence thereof to the notified body.

The endpoints of the clinical investigation shall address the intended purpose, clinical benefits, performance and safety of the device (Annex XIV, 2.4a). Clinical investigations shall be subject to scientific and ethical review (Ch. VI, Art. 50). According to article 51, the sponsor of a clinical investigation will be required to submit by means of the electronic system described in Art. 53 (which will create a single identification numbers for clinical

investigations) an application to the Member State(s) in which the investigation is to be conducted accompanied by all the documentation listed in Chapter II of Annex XIV.

9. Safety and performance requirements replace Essential Requirements

The general safety and performance requirements according to Annex I must be fulfilled in future and these will take the place of the current "Essential Requirements". Manufacturers will therefore need to perform gap analysis of consequences of changed requirements for recertification of their existing devices. Annex I describes: General Requirements; Requirements regarding design; and Manufacturing Requirements regarding the information supplied with the device.

10. Specific instructions issued on device technical documentation

Annex II describes new technical file requirements. The technical documentation is to be organized in a readily searchable format and include in particular the following elements: Device description and specification; Information (labeling) supplied by the manufacturer; Design and manufacturing information; General Safety and Performance Requirements; Risk/benefit analysis and risk management; Product verification and validation (including pre-clinical and clinical data, and, if appropriate, additional information in specific cases). There are also specific instructions relating to technical documentation requirements on post-market surveillance (Annex Ia).

11. About CROMSOURCE Regulatory Services

The CROMSOURCE Regulatory Services Unit works with Clients to develop integrated clinical and regulatory strategy proposals for EU and US clients regarding both new molecular entities, biologics and generics as well as rapidly evolving areas such as medical devices, combination products, advanced therapy medicinal products and biosimilars. Regulatory writing services are provided for a variety of global regulatory applications and submissions. The unit follows developments in the global regulatory frameworks and publishes a quarterly regulatory newsletter.

12. About the Author

Beata Wilkinson PhD, MTOPRA is Head of the Regulatory Services Unit. Beata has extensive experience of regulatory intelligence and regulatory/medical writing together with the management of client-focused projects. Her main area of expertise is in regulation of medical devices. Prior to joining CROMSOURCE, Beata was at the Clinical & Regulatory Affairs Department at ConvaTec, an international medical device company, where she oversaw the preparation of the Company's clinical evaluation reports. Her earlier experience as a biomedical business and regulatory intelligence specialist involved work with leading pharmaceutical and medical device companies during which she authored over 50 biomedical business reports for sale by global publishers of healthcare information.

13. About CROMSOURCE

CROMSOURCE is a high quality ISO-certified international provider of outsourced services to the pharmaceutical, biotechnology and medical device industries, specialized in clinical development and staffing solutions.

Operating through offices across all regions of Europe and North America CROMSOURCE delivers a comprehensive breadth of services. We seamlessly move biopharmaceutical products from first-in-human studies conducted in our exceptional early phase unit, through all subsequent phases of pre- and post-approval research internationally. Our Medical Device experts oversee projects through regulatory strategy and submission, to pilot and pivotal clinical investigations in Europe and North America. Our Staffing Solutions Team ensures that high quality professionals are available to support your work whenever you need more resources.

Passionate about your projects. High quality, on time, on budget. Guaranteed.

It's a simple concept, really. Quality data. On time. On Budget. Guaranteed.

At CROMSOURCE we believe experts should keep their word. After 18 years of success we provide the industry's only End-to-End Guarantee™. Starting at the RFP stage with our uniquely detailed Feasibility Plus™ process we guarantee:

1. **Your study will start on time**
2. **We will enroll 100% of the contracted patients**
3. **We will finish on time with a set date for database lock**
4. **The price you contracted is the price you pay. There will be no CRO-initiated changes-in-scope.**

We know that budgets must be competitive, and you can rest assured that our End-to-End Guarantee™ does not come with a premium price. As an ISO-certified organization, you can also rest easy about quality.

Don't you owe it to your project to learn more? Contact us to request more information.

END-TO-END GUARANTEE™
TIME, COST & QUALITY GUARANTEED

ONE TRIAL ONE PRICE™
GUARANTEED FIXED PRICE BUDGET

FEASIBILITY PLUS™
GUARANTEED ENROLMENT & TIMELINES

CROM SOURCE
advise | agree | deliver

North American Headquarters:
309 Waverley Oaks Road, Suite 101
Waltham, MA 02452 - USA
Phone +1 617 871 1128

European Headquarters:
Via Giorgio De Sandre, 3
37135 Verona - Italy
Phone +39 045 8222811

e-mail us at:
cromsource@cromsource.com