NEWSLETTER MARCH 2019

Health Canada updated the List of Recognized Standards for Medical Devices

https://www.canada.ca/en/health-canada/services/drugs-health-products/medical-devices/standards/list-recognized-standards-medical-devices-guidance.html

Health Canada has updated its *List of Recognized Standards for Medical Devices* used to demonstrate safety, effectiveness and labeling requirements of the Canadian Medical Devices Regulations. Updates to the list will affect manufacturers applying to Health Canada for Medical Device Licenses (MDL).
The changes to the Therapeutic Products Directorate's List of Recognized Standards for medical devices have specifically been altered as follows:

- 14 new standards added to the List
- 13 new editions of currently recognized standards replace previous editions
- 8 standard removed from the List

Additions, removals and updates to Health Canada's list include standards from ISO, ASTM, IEC 60601 and CLSI.

Contingency legislation covering regulation of medicines and medical devices in a no deal scenario

http://www.legislation.gov.uk/ukdsi/2019/9780111179260/pdfs/ukdsi_9780111179260_en.pdf

Draft Regulations laid before Parliament under paragraph 1(1) of Schedule 7 to the European Union (Withdrawal) Act 2018, for approval by resolution of each House of Parliament.

DRAFT STATUTORY INSTRUMENTS

2019 No.

EXITING THE EUROPEAN UNION

CONSUMER PROTECTION

The Medical Devices (Amendment etc.) (EU Exit) Regulations 2019

In a no deal scenario, contingency legislation is needed in order for the Medicines and Healthcare products Regulatory Agency (MHRA) to be able to take on regulatory processes for human medicines and devices that are currently undertaken by the European Medicines Agency and other bodies.
The three separate pieces of legislation will allow for the continued sale of, and access to, medicines, medical devices and clinical trials:

- Human Medicines Regulations 2012, as amended by the Human Medicines (Amendment etc) (EU Exit) Regulations 2019
- The Medical Devices (amendment) (EU exit) Regulations 2019
- The Medicines for Human Use (Clinical Trials) (amendment) (EU exit) Regulations 2019.

These Regulations set out a comprehensive regime for the authorisation of medicinal products for human use; for the manufacture, import, distribution, sale and supply of those products; for their labelling and advertising; and for pharmacovigilance.
They also provide for enforcement powers for the authorisation and supervision of medicinal products for human use.
The Agency is the designated competent authority that administers and enforces the law on medical devices in the UK. It has a range of investigatory and enforcement powers to ensure their safety and quality. These regulations ensure that the required powers are provided for.
The Clinical Trial Regulations require all interventional clinical trials of medicines to be authorised by the MHRA, as the national competent authority in the UK; to have a favourable ethics opinion; and to be conducted according to Good Clinical Practice. They also include requirements for the assessment and supply of investigational medicinal products and for safety reporting.

First Notified Body for MDR in NANDO database

The Medicines and Healthcare products Regulatory Agency (MHRA) announced that BSI Assurance UK has successfully completed the Joint Assessment for designation to the European Medical Devices Regulation (EU) 2017/745 (MDR). Following the application, requested in November 2017, BSI has been designated as a "full-scope" organization. Now, BSI Assurance UK is listed on NANDO database and is able to issue certificates according to the MDR.

State-of-play of joint assessments of Notified Bodies in the MDR and IVDR sectors

As of February 19, 2019 the **NB applications** sent to SANTE/F were **33 for MDR** and **9 for IVDR** with an overall scope coverage, namely the entirety of MDR and IVD codes. The average time from conformity assessment body's (CAB's) application to its dispatch to SANTE/F by the national designating authority (DA) is 60 days.
The preliminary assessment reports (**PARs**) received by SANTE/F were **24 for MDR** and **6 for IVDR**. The average time from CAB's application to PAR's dispatch to SANTE/F by the national DA is 138 days.
Regarding the post-assessment activities, 7 CAPA (Corrective And Preventive Action) plans were received by SANTE/F and reviewed by JAT (Joint Assessment Team). 7 **JAT reviews** have been already issued (**6 for MDR** and **1 for IVDR**). The average time from the appointment of the joint assessment team (JAT) to on-site assessment is 111 days.

Interpretation of Article 54(2)b of Regulation (EU) 2017/745

A proposed interpretation of Article 54(2)b of MDR has been published by the Medical Device Coordination Group (MDCG). Article 54(2) of the MDR lays down three criteria that exempt devices from the pre-market clinical evaluation consultation procedure with the involvement of expert panels. In particular, point (b) of the Article states that:

"The procedure referred to in paragraph 1 shall not be required for the devices referred to therein:

(b) where the device has been designed by modifying a device already marketed by the same manufacturer for the same intended purpose, provided that the manufacturer has demonstrated to the satisfaction of the notified body that the modifications do not adversely affect the benefit-risk ratio of the device;"

Interpretation of point (b) is unclear, notably in relation to the application of the word “marketed”. In fact, there is no indication of whether a “device already marketed” refers to devices already marketed under the Directives or the Regulations.
The following considerations seem to indicate that the expression “device already marketed” cannot be intended to refer to a device already marketed uniquely under the new Regulation:

- If the co-legislators had decided to restrict the application of point “b” to devices marketed uniquely under the MDR, they would have explicitly stated so;
- Article 54, together with other Articles (such as Article 61(6) and Article 120(3)), was written at the end of the negotiation process with a view to smoothen the implementation of the new Regulation. Therefore, the interpretation of the exemption should be understood in line with the spirit and intention of the co-legislators.

It has to be noted that, in respect to devices that have been marketed already under the relevant Directives, the word “modification” shall be meant as limited only to those modifications needed in order to comply with the new legal requirements introduced by the MDR.

Manual on borderline and classification in the community regulatory framework for medical devices

https://ec.europa.eu/docsroom/documents/33782

The new version of the Manual on borderline and classification for medical devices, Version 1.21, has been published in February. Two new borderline cases has been added: solution for adhesive bandage removal and pill organizer boxes.
The first is a solution intended by the manufacturer for removal of adhesive tapes and elastic adhesive bandages. According to the manufacturer, it also removes any adhesive residue which may be left on the skin. It is intended to be applied to the bandage to soak it and acts by dissolving the adhesive, allowing easy removal from the skin.
In general, these solutions do not fulfil the definition of medical devices, since there is no medical purpose for the solutions themself intended by the manufacturer. They also cannot be considered as accessories to adhesive tapes and elastic adhesive bandages, if those are medical devices, because it is neither intended to enable them to be used in accordance with their intended use (the bandages can be used without the adhesive remover), nor do them directly assist the medical functionality of those bandages in terms of their intended purpose.
Examples of adhesive remover solutions that could be considered as medical devices or accessories to medical devices could be solutions intended to be used with ostomy bags in order to prevent injuries to the stoma if the bags are not removed correctly. In this case, the solutions are specifically intended for a medical purpose or to enable the correct use of a specific medical device.
In conclusion, a solution for removal of adhesive tapes and adhesive bandages with no specific medical intended purpose and which cannot be considered as an accessory to a medical device should not be qualified as such.
Pill organiser boxes are intended for storing the pills in dedicated compartments for a given period for administration at the right time. There are different kinds of boxes: boxes for one day, boxes for one week, 7-day boxes consisting of seven daily compartments and others. The purpose of these boxes is to facilitate and control medication.
Although taking the correct dose of medication at the right time is an important part of medical treatment, tools facilitating this do not fulfil the definition of a medical device, because they are not intended to diagnose, prevent, monitor, treat or alleviate disease themselves. The box is only a convenient tool to help the patient remember whether or not they have taken their medication. These pill organiser boxes should not be qualified as medical device.

First guidance on new rules for certain medical devices

https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/questions-answers-implementation-medical-devices-vitro-diagnostic-medical-devices-regulations-eu/745-eu-2017/746_en.pdf

27 February 2019
EMA/37991/2019
Human Medicines Evaluation Division

Questions & Answers on Implementation of the Medical Devices and In Vitro Diagnostic Medical Devices Regulations ((EU) 2017/745 and (EU) 2017/746)

EMA has recently published the first of a series of guidance documents to help applicants prepare for obligations stemming from the new EU regulations on medical devices.
The new regulations introduce new roles and responsibilities for EMA and national competent authorities (NCAs) in relation to certain types of medical devices and *in-vitro* diagnostics. The Agency is working closely with the EU regulatory network and with stakeholders from the pharmaceutical and medical device industries, including notified bodies, to ensure a smooth transition to the new regulatory framework.
This first questions and answers (Q&A) document, developed jointly by EMA and the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), in close collaboration with the European Commission, focuses on the implementation of Article 117 of the medical devices regulation (MDR), which stipulates that marketing authorisation applications for medicines with an integral medical device must include the results of the device's assessment of conformity by a notified body. Approximately one in four centrally authorised medicines includes a medical device component, and the majority of these involve an integral device. This includes for example pre-filled syringes and pens, patches for transdermal drug delivery and pre-filled inhalers.
EMA will publish further updates to the Q&A document addressing other requirements for various categories of devices, including those made of substances that are systemically absorbed, products which are not clearly defined as medicinal products (borderline products), and *in vitro* diagnostic tests used to determine patients' eligibility for a specific medical treatment.

Italian medical device nomenclature to be adapted for Eudamed database

Authorities overseeing implementation of Eudamed have decided to adapt medical device codes used by the Italian Ministry of Health for use as nomenclature for the database.
The Medical Device Coordination Group's (MDCG) decision stems from requirements in the MDR and In-Vitro Diagnostic Medical Devices Regulation (IVDR) that free nomenclature for devices be made available in Eudamed. Global Medical Device Nomenclature (GMDN), currently used worldwide as a nomenclature tool, requires membership fees for access.
To meet MDR and IVDR requirements, MDCG will map Italian CND (Classificazione Nazionale dei Dispositivi medici) codes to GMDN codes for ease of use by manufacturers and other entities utilizing Eudamed. The Italian coding system has been in use since 2007 to support that country's device database; the CND system is up-to-date and used on a daily basis.

European Union published a market study on the telemedicine

https://ec.europa.eu/health/sites/health/files/ehealth/docs/2018_provision_marketstudy_telemedicine_en.pdf

Market study on telemedecine

The aim of the study is examining the European telemedicine market and understanding the factors that determine its development. The document describes the application types and the telemedicine solutions. It examines the market dynamics and the potential obstacles that limit telemedicine diffusion, and it evaluates the cost-efficacy ratio of large-scale dissemination of telemedicine in current and future market conditions, to provide policymakers with advice and considerations for a wider dissemination of telemedicine.

The study was carried out by applying qualitative and quantitative analysis methods to the data obtained with surveys and interviews with telemedicine stakeholders, obtained from scientific journals and research reports, as well as contained in statistics.

The study underlines how many of the telemedicine solutions available on the market are used at national or regional level, while few are used in more than one member State or have an international diffusion outside the EU due to the significant differences between national laws and social and health systems.

Another interesting aspect is that many of the laws and guidelines in this sector are established by international organisms and are technical documents. However, member States can establish their national laws, in particular to provide accurate requirements for the telemedicine solutions related to a particular medical specialties.

Based on this study, the market potential of telemedicine is interesting, with an annual growth of about 14% in the next years. However, the development of telemedicine in Europe is being held back by various factors in all countries: the absence of consensus and interesting from the stakeholders, unfavorable regulatory frameworks, insufficient funding, inadequate IT infrastructures.

Telemedicine is generally perceived and judged to be cost-effective, as demonstrated by evidence documented in academic literature. The systematic review of the cost-effectiveness of telemedicine conducted for the study confirms that telemedicine is economically advantageous in 73.3% of the cases analysed in literature. Factors or cost parameters that have a strong impact on the cost-effectiveness ratio include: distance between the patient and the nearest healthcare professional, time needed for consultation, cost of a medical examination, mortality rate.

Literature suggests that telemonitoring solutions are among the most effective solutions in relation to a wide range of diseases, with particular attention to chronic medical conditions. However, the results obtained are related to small pilot projects and not to the use of these solutions on large-scale. Consequently, the general conclusions on the cost-effectiveness of telemedicine based on literature studies should be formulated with caution.

Regarding the cost-effectiveness ratio, the study does not go into the merits of how the savings that telemedicine can guarantee are evaluated. This is a crucial aspect that is often partially tackled with questionable criteria and which, in any case, often requires a profound reorganization of services and care models to be able to materialize and become real and tangible.

ISO/TS 21726:2019: Biological evaluation of medical devices -- Application of the threshold of toxicological concern (TTC) for assessing biocompatibility of medical device constituents

ISO/TS 21726:2019 has been published in February. The document describes the basis for, selection of, and general applicability of a threshold of toxicological concern (TTC) value for a constituent present in/on a medical device or released from a medical device. The TTC values in this document can be used for:

- comparing to a maximum concentration of an identified or unidentified constituent in an extract (ISO 10993-18);
- supporting toxicological equivalence;
- comparing to a maximum exposure dose estimate of an identified constituent (ISO 10993-17).

ISO 10993-18 specifies how to convert TTC (µg/d) into a concentration (µg/ml).
TTC is not applicable to constituents with adequate toxicity data for deriving a tolerable intake (TI) value.
The TTC values established in this document are protective for carcinogens, systemic toxicants, and reproductive toxicants. This document does not include TTC values for other biological endpoints assessed as part of the biological evaluation of a medical device, per ISO 10993-1 (i.e. cytotoxicity, irritation, sensitization, hemocompatibility, material mediated pyrogenicity, local effects that occur in tissues at the site of contact between a medical device and the body).
The TTC values in this document do not apply to potential exposure via gas pathways of medical devices. For application of TTC for constituents present/released from these devices, see the ISO 18562 series.
The TTC values presented in this document are not applicable for the safety assessment of cohort of concern.
The ISO is composed of 6 pages only, but are anyway a signal that things are moving for defining state of the art in medical device toxicological assessment. It is also stated clearly that some biocompatibility testing cannot be excluded using this approach.

ISO 11607-1:2019: Packaging for terminally sterilized medical devices – Part 1: Requirements for materials, sterile barrier systems and packaging systems

ISO 11607-1:2019 has been published in February. The document specifies requirements and test methods for materials, preformed sterile barrier systems, sterile barrier systems and packaging systems that are intended to maintain sterility of terminally sterilized medical devices until the point of use.
It is applicable to industry, to health care facilities, and to wherever medical devices are placed in sterile barrier systems and sterilized.
It does not cover all requirements for sterile barrier systems and packaging systems for medical devices that are manufactured aseptically. Additional requirements can be necessary for drug/device combinations.
It does not describe a quality assurance system for control of all stages of manufacture.
It does not apply to packaging materials and/or systems used to contain a contaminated medical device during transportation of the item to the site of reprocessing or disposal.
The first edition of this standard was ISO 11607-1:2006, and the 2019 version, as the second edition, differs from the previous version in numerous ways.

- Definitions were aligned with *ISO 11139:2018 – Sterilization Of Health Care Products – Vocabulary Of Terms Used In Sterilization And Related Equipment And Process Standards*
- New information for the evaluation of usability for aseptic presentation was added.
- New information for inspecting sterile barrier system integrity prior to use was added.
- A new subclause for revalidation in accordance with ISO 11607-2 was added.

- Annex B, “Standardized test methods, guides and procedures that can be used to demonstrate conformity with the requirements of this document” was updated, and various national, international, and European test methods were added or deleted.
- New Annex D, “Environmental aspects”.
- New Annex E, “Draft guidance on ways to differentiate a sterile barrier system from protective packaging”

ISO 11607-2:2019: Packaging for terminally sterilized medical devices – Part 2: Validation requirements for forming, sealing and assembly processes

ISO 11607-2:2019 has been published in February. The document specifies requirements for the development and validation of processes for packaging medical devices that are terminally sterilized. These processes include forming, sealing and assembly of preformed sterile barrier systems, sterile barrier systems and packaging systems.
It is applicable to industry, to health care facilities, and to wherever medical devices are packaged and sterilized.
It does not cover all requirements for packaging medical devices that are manufactured aseptically. Additional requirements can be necessary for drug/device combinations.
Like the first part of ISO 11607, ISO 11607-2:2019 revises the first, 2006 edition of its corresponding standard. However, unlike the first part, ISO 11607-2:2019 underwent changes associated primarily with terminology.

- Terms and definitions for “process variable”, “process parameter”, and “monitoring of processes” were added.
- The terminology of critical process parameters was discontinued, and the concept of a process specification was introduced to include all elements for manufacturing a product that consistently meets specifications.
- Various definitions in this standard were aligned with ISO 11139:2018.

New “home” for biomedical companies: Confindustria medical devices was born!

A new Federation is born in Confindustria: **Confindustria Medical Devices**. The aim is to bring together the entire world of medical device companies and give voice to a growing market, composed also by the new categories of products that are entering in the last few years in medicine and people's lives.
It deals with 1.5 million of medical devices ranging from surgical equipment to large diagnostic equipment, from laboratory tests to genetic tests to predict some diseases, from software for monitoring vital signs thanks to telemedicine to medical apps, from prosthetics dental to health aids. Biosensors, robotics or artificial intelligence applied to health are medical devices too, in addition to 3D printers that one day will allow to print human tissues or entire organs and maybe use them for transplants. A revolution that the companies of the sector present in Italy are contributing to realize, welcoming the challenges of health 4.0.
Overall, the medical device sector in Italy generates a market worth 16.5 billion euros between exports and the internal market, with 3957 companies emploing 76400 people. For the first time, the entire device industry will be represented by a single trade association that brings together all the companies that produce medical devices, as they will be classified and regulated by the new European Regulations starting from 2020.
The president of the new Association will be elected next March 28th, at the inauguration event of the Milan office.

CHEMSAFE attendance 2019

Baltimore (USA), March 10-14
USA SOT (Society of Toxicology), Exhibition booth + two poster presentations, 4 people

London (USA), March 20-21
BCPA PESTEX, 1 people attending

Nurnberg (GE), May 21-23
MEDTECHLive, Exhibition booth

Basel (CH), May 7-9
VITAFOODS 2019, Exhibition booth + oral presentation

Rimini (ITALY) June 5-7
AFI 59° SIMPOSYUM, Exhibition booth + MD workshop organization

Bruxelles, June 12-13
CHEMICAL WATCH EXPO: GLOBAL CHEMICAL REGULATION, Exhibition booth + oral presentation

Helsinki (FI), September 8-11
EUROTOX 2019, Exhibition booth + two poster presentations