NEWSLETTER DECEMBER 2018

New Business Unit: Medical devices

Chemsafe started operating in the field of Medical Devices two years ago, following some "spot" request from occasional customers. The incoming new Regulation (EU) 2017/745 (MDR), replacing the Council Directive 93/42/EEC on Medical Devices, and the sister Reg. (EU) 2017/746 (IVDR) for in vitro Diagnostic Medical Devices gave us a "*good reason*" to decide to invest in such new field of activities. We got a Biomedical Engineer and together with one of our biotechnologist (medical expertise) we created a small group belonging to our Pharma BU. In July 2018, due to increase of expertise and, at the same time, increase in inquiries from customers, after the acquisition of the quality system, we formally create the forth Chemsafe Business Unit: the Medical Device one as an independent BU.
Nowadays the Medical Devices Unit staff is composed by three people: a Biotechnologist with medical expertise acting as the Head of the BU, a Biomedical Engineer and a Quality expert.
We believe that Chemsafe MD BU, together with cooperation with the other BUs with and integrated approach, can support companies for many needs. In particular, due to our huge experience in data search and evaluation, we are very confident to be able to help companies with the clinical and safety evaluation of their products. Within our company, well experience toxicologists are available to guide the selection of the safety test as for the last guideline. Capacity to coordinate, by study monitoring, external safety and clinical studies as well as to prepare the complete technical dossier conclude our expertise in such area.

The services offered by the Medical Devices BU are the following.

- Feasibility studies and data gaps analysis on borderline products (medical devices/pharmaceuticals, cosmetics, biocides and food supplements)
- Strategic/regulatory consultancy on Directive 93/42 EEC and Regulation (EU) 2017/745
- Expert Report on toxicological/biological evaluation for the definition of pre-clinical studies
- Support for the elaboration of biological evaluation in compliance with UNI EN ISO 10993-1
- Monitoring of biocompatibility tests, clinical and pre-clinical studies, efficacy tests and usability
- Preparation of the clinical evaluation report in accordance with MEDDEV 2.7/1
- Support for the drafting of the risk management plan in compliance with UNI EN ISO 14971
- Review/preparation of technical documentation (Technical File)
- Implementation of the Quality Management System in compliance with UNI EN ISO 13485
- Registration of Medical Devices in National Databases
- Identification and management of contacts with Competent Authorities (EU and non-EU)
- Role of Person Responsible for regulatory compliance as requested by Regulation (EU) 2017/745
- Training courses on Medical Device

FDA and ISO 13485

FDA plans to use ISO 13485 for medical devices regulation

The International Standard for quality management systems for the medical devices sector, ISO 13485, is designed to be integrated in an effective and transparent way with other management systems. The last edition of standard, published in 2016, has received strong support from the FDA, in line with its drive for global convergence of medical device regulatory processes.
FDA intends to harmonize and modernize its current Quality System regulation for medical devices. The revisions will replace the existing requirements with the specifications of an international consensus standard for medical device manufacture as the ISO 13485:2016. The revisions are intended to reduce compliance and recordkeeping charges on device manufacturers by harmonizing national and international requirements. The reviews will also modernize the regulation.

Finalization of the Guidance on Breakthrough Medical Device Pathway

https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM581664.pdf

Contains Nonbinding Recommendations

Breakthrough Devices Program
Guidance for Industry and
Food and Drug Administration Staff

Document issued on December 18, 2018.

The draft of this document was issued on October 25, 2017.

This document supersedes "Expedited Access for Premarket Approval and De Novo Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Diseases or Conditions," issued on April 13, 2015.

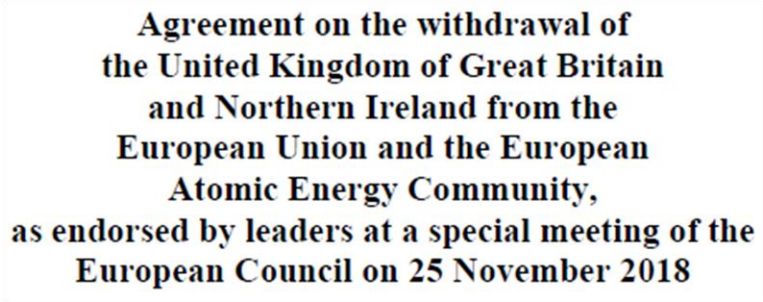
US FDA has published final guidance on its Breakthrough Medical Device market pathway for novel devices and combination products.
The new program incorporates elements of prior FDA programs including the Expedited Access Pathway (EAP) and Priority Review program.
Devices that use novel and cutting-edge technologies to address life-threatening or permanently debilitating diseases may qualify for the new program.
The US Food and Drug Administration has finalized details of a new registration route for breakthrough medical devices first announced in 2017.
This Final guidance covers cutting-edge medical devices as well as combination products with devices as primary components developed to more effectively target life-threatening or debilitating diseases and health conditions. These devices would otherwise undergo Premarket Approval (PMA), 510(k) premarket notification or De Novo classification request review in order to be sold in the US.
FDA's final guidance involves two main phases: a Designation Request phase wherein device manufacturers and sponsors request Breakthrough Device designation, and a second phase that includes processes to expedite device development and prioritize premarket reviews.

Digital therapeutic- the first prescription digital therapeutic approved by the FDA

reSET, a substance use disorder treatment, was the first software-only therapeutic cleared by the FDA. Now it is commercially available for clinicians to prescribe to their patients, according to a release from Pear Therapeutics and Sandoz, a division of Novartis with which Pear partnered back in April.
reSET is a 12-week digital cognitive behavioral therapy program accessed through an app and designed to accompany outpatient care delivered by a physician.
It is the only treatment authorized by the FDA for patients aged 18 years and older, experiencing addiction to and dependency on stimulants, cannabis and cocaine (as well as alcohol).
Depending on its success, the novel treatment could serve as a model for any subsequent prescription digital therapies looking to go to market within the next few years.

Pear's dealings with Novartis is not limited to reSET alone. In March, the companies signed an agreement to collaborate on the development of two other similar products, one for multiple sclerosis and another for schizophrenia. These products sit alongside the rest of the digital therapeutic maker's pipeline, which includes reSET-O for opioid use disorder, and are supported in part by the $50 million the company collected from investors at the beginning of 2018.

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/759019/25_November_Agreement_on_the_withdrawal_of_the_United_Kingdom_of_Great_Britain_and_Northern_Ireland_from_the_European_Union_and_the_European_Atomic_Energy_Community.pdf


Agreement on the withdrawal of
the United Kingdom of Great Britain
and Northern Ireland from the
European Union and the European
Atomic Energy Community,
as endorsed by leaders at a special meeting of the
European Council on 25 November 2018

The Agreement of the United Kingdom and Northern Ireland from the European Union has been published.
About Medical Devices, the agreement holds some interesting aspects.

New Notified Body in NANDO database

In late summer 2018, BSI The Netherlands (BSI-NL) announced that they had successfully completed the Joint Assessment for designation to the MDD, AIMDD and IVDD. Now, BSI-NL is listed on NANDO and is able to issue certificates according to the Directives, although the first Notified Bodies (NBs) will soon be designated to the European Medical Devices Regulation (EU) 2017/745 (MDR). Moreover, BSI-NL has indicated to be in the process of getting designated to the new Regulations as well.

Although the MDR applies from May 26, 2020, the designation of a new NB in the EU-27 outside the UK is still good news. Brexit may affect the validity of certificates issued by UK-based NBs. In the event of a Cliff-edge or Hard Brexit, by March 29, 2019 UK-issued certificates may become void. This could also happen during the transition period until December 31, 2020, for which the UK Parliament still has to vote. Unless a lasting agreement is reached concerning a

so-called “Soft Brexit”, UK-issued certificates will become void sooner or later anyway, and it is widely predicted this will be rather soon.

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

As of November 30, 2018 the NB applications sent to SANTE/F were 28 for MDR and 7 for IVDR with an overall scope coverage, namely the entirety of MDR and IVD codes.
The preliminary assessment reports received by SANTE/F were 20 for MDR and 5 for IVDR.
18 on-the-spot assessments have been carried out from April 2018 to November 2018 (14 for MDR and 4 for IVDR) and 7 on-the-spot assessments have been scheduled for the period December 2018-January 2019 (6 for MDR and 1 for IVDR).
Regarding the post-assessment activities, 7 CAPA (Corrective And Preventive Action) plans were received by SANTE/F and reviewed by JAT (Joint Assessment Team). 4 JAT reviews have been already issued (3 for MDR and 1 for IVDR) and 3 JAT reviews have been under preparation.

ISO 14971 Risk Management Updates in ISO/DIS 14971:2018

https://s3-eu-west-1.amazonaws.com/static.wm3.se/sites/16/media/227639_prEN_ISO_14971.pdf?1535906215

The process to revise and update the ISO 14971 standard began in Tampa, Fla., in 2016. The TC210 working group assigned to update the standard (JWG1) was tasked with improving guidance for implementation of ISO 14971, but the committee was also tasked with making these improvements without changing the risk management process. In addition, the committee was asked to move the informative annexes at the end of ISO 14971 from the standard to the guidance document ISO/TR 24971.
Now, following two years intensive work on the two documents, in July 2018 the committee released a draft for comment and voting.
What is important to the industry is the direction this update process is taking: per ISO’s instructions, the aim is not to revise the risk management process, but rather to improve the information on implementation of the risk management process. Therefore, companies with processes that currently conform to the standard should not have to make large revisions to their processes to comply with the new document, as it is presently being envisioned.
The main changes compared to the previous edition are reported below.
The ISO/DIS 14971 standard has only three annexes:

A. Rationale for the requirements
B. Risk management process for medical devices
C. Fundamental risk concepts (formerly Annex E).

The other 7 annexes were moved to the draft of ISO/TR 24971. The reason stated for moving these Annexes to the guidance document was to make future revisions to the guidance easier to implement, because it is a guidance rather than a standard.
A normative references clause has been included even though no normative references are cited. This means that most clause numbers have been changed compared to the previous edition.
Three new definitions are introduced in the draft standard: benefit, reasonably foreseeable misuse and state of the art. More attention is given to the benefits that are expected from the use of the medical device. The term benefit-risk analysis is aligned with terminology of the MDR and IVDR.

It is highlighted that the process described in ISO 14971 can be used for managing all types of risks associated with medical devices, including those related to data and systems security.
The requirements for the evaluation of overall residual risk have been refined. The method for the evaluation of the overall residual risk as well as the criteria for its acceptability need to be defined in the risk management plan. The evaluation method can include gathering and reviewing data and literature for the medical device and similar devices on the market.
The criteria for the acceptability of the overall residual risk can be different from the criteria for acceptability of individual risks.
The requirements to disclose residual risks are merged into one requirement. If the overall residual risk is judged acceptable, the manufacturer has to decide which residual risks to disclose and what information to include in the accompanying documentation.
Before release of the medical device for commercial distribution, the execution of the risk management plan has to be reviewed. The results of the review are recorded in a risk management report. The manufacturer needs to determine when reviews and updates of the risk management report are to be undertaken.
The clause on production and post-production information has been clarified and restructured. More detail is given on the information to be collected and the actions to take when the collected information is determined to be relevant to safety.
The DIS text include drafts of the European Annex Zs, showing the relationship between the clauses of the standard and the requirements of the European Directives for medical devices, as well as the MDR and IVDR.

ISO/CD 10993-23: Biological evaluation of medical devices -- Part 23: Determination of skin irritation of medical device extracts using Reconstructed human Epidermis (RhE)

Under development

An alternative in vitro approach (Toxicology in Vitro 50 (2018) 439–449) was published by ISO group based on the direct exposure of eluates on reconstituted skin model (72h in hydrophilic and lipophilic solvents as requested by ISO 10993-10).
Both the EpiDerm™and SkinEthic™RHE tissues were reported able to correctly identify virtually all of the irritant polymer samples either in the saline, sesame oil or solvent extracts. The results indicate that RhE tissue models (in vitro test system described in OECD Test Guideline 439 for classification of skin irritation by neat chemicals) can detect the presence of strong skin irritants at low levels in dilute medical device polymer extracts. Therefore, these models may be suitable replacements for the rabbit skin irritation test to support the biological evaluation of medical devices.
This *in vitro* approach allows to conclude either for the cytotoxicity of ingredients and for the skin irritation potential.
This standard will provide a usefull help to Biological evaluation of medical devices.

https://reader.elsevier.com/reader/sd/pii/S0887233318300018?token=4B91DFD1BDCE3E70BE2DEE49A903630EAA27043D285C7EB61897AC3B9EF94EE64E4CAB918D5235671DC42EBB242CF66F

Round robin study to evaluate the reconstructed human epidermis (RhE) model as an in vitro skin irritation test for detection of irritant activity in medical device extracts

Wim H. De Jong[a,*], Sebastian Hoffmann[b], Michelle Lee[c], Helena Kandárová[d], Christian Pellevoisin[e], Yuji Haishima[f], Beau Rollins[g], Austin Zdawczyk[h], Jamin Willoughby[i], Michael Bachelor[j], Timothy Schatz[k], Shelby Skoog[l], Sherry Parker[m], Anita Sawyer[n], Paolo Pescio[o], Kristina Fant[p], Kwang-Mahn Kim[q], Jae Sung Kwon[q], Helge Gehrke[r], Hana Hofman-Hüther[r], Marisa Meloni[s], Conrad Julius[t], Damien Briotet[u], Silvia Letasiova[d], Reiko Kato[f], Atsuko Miyajima[f], Liset J.J. De La Fonteyne[a], Christelle Videau[e], Carine Tornier[e], Audrey P. Turley[c], Nicholas Christiano[v], Thor S. Rollins[c], Kelly P. Coleman[w]

The MEDICAL DEVICE team wishes everyone Merry Christmas and have a good start in 2019!!!