UBM

Europe's Emerging Medical Device Regulations and Their Impact on Packaging Decisions

To promote health and safety while supporting medical device innovation, the European Commission, Council, and Parliament are transforming the Medical Device Directives (MDD; Council Directive 90/385/EEC for active implantable medical devices and Council Directive 93/42/EEC for medical devices) into one set of regulations. These European Medical Device Regulations (MDRs) are intended to harmonize the rules for marketing medical devices and their accessories in the European Union.

The Council of the European Union published a tentatively agreed upon "consolidated compromised text" in June 2016; a more polished version was published on the 9th of August 2016 in 23 languages of the European Union. The endeavor was "needed to establish a robust, transparent, predictable and sustainable regulatory framework for medical devices which ensures a high level of safety and health whilst supporting innovation," reads the document. This proposal, also labelled as "stable text," has been finalized and published on 22 February 2017 as position of the European Council at first reading. The council voted and adopted the MDR on the 7th of March and a vote in the Parliament is planned for April.

Under the new regulation, packaging is still considered to be an accessory to a medical device, just as it was under the directives. Compliance with the law's "Essential Requirements" is required; because there are some new Essential Requirements when compared with those in the MDD, there are new expectations for packaging professionals.

New rules, revised standards

Thierry Wagner, regulatory affairs director for Europe, Middle East, and Africa for DuPont Medical & Pharmaceutical Protection, explains that "as soon as they are voted upon by the European Council and Parliament, these regulations will be law in all EU member states. The law will drive true harmonization and create an even playing field."

Thierry Wagner

Henry Sibun

Some of the wording changes beef up existing expectations, explains Henry Sibun of Henry Sibun Associates Ltd., a firm offering consulting, training, and auditing services. "Medical device manufacturers need to have objective evidence of compliance for their packaging (e.g., validation of sealing, validation of transport, shelf life . . . etc.) – nothing new here, but several Notified Bodies have not looked for these (especially for lower risk devices) or not enforced them in the past, so companies who have relied on many years' past experience will need to get their house in order and provide this information."

Standards are expected to help packaging professionals comply. The European Commission mandates that CEN, CENELEC, and ETSI issue technical standards and specifications that facilitate compliance with the Essential Requirements of EU directives and regulations. Once these standards are listed in the Official Journal of the EU as harmonized standards, authorities must then presume that products designed and manufactured according to these standards conform to Essential Requirements as listed in Annex Z. The new regulation will continue to build on the "new approach" concept and considers harmonized standards as "means for manufacturers to demonstrate conformity with the general safety and performance requirements and other legal requirements, such as quality and risk management," Wagner says, quoting the regulation.

However, the law also introduces a new tool, so called "common specifications," which may be introduced where standards may not be considered "sufficient" for meeting all of the Essential Requirements of the new European Medical Device Regulations. Consequently, the European Commission might request that common specifications be solely authored in/by the EU and adopted to make up for anything considered insufficient. Article 9 of the new law states that "where no harmonised standards exist or where relevant harmonised standards are not sufficient, or where there is a need to address public health concerns, the Commission, after having consulted the MDCG [Medical Device Coordination Group], may, by means of implementing acts, adopt common specifications (CS) . . . ."

SHERRY YATES YOUNG/SHUTTERSTOCK.COM

Medical device manufacturers marketing products in Europe currently rely on EN ISO 11607-1, "Packaging for terminally sterilized medical devices: Requirements for materials, sterile barrier systems and packaging systems," to guide packaging development and demonstrate compliance with the MDD. ISO 11607 has been recognized by regulatory authorities around the world (in the United States, for instance, FDA has recognized AAMI/ANSI/ISO 11607 as a consensus standard).

There is some work to be done to accommodate the new European Medical Device Regulations. Annex Z was developed several years ago and added to the EN version of ISO 11607 indicating the relationship with the Essential Requirements of the MDD. A new Annex Z was developed for the 2014 amended version of EN ISO 11607, which is still currently in the process of being reviewed by the EU Commission, and a new Annex Z will need to be developed for meeting the requirements of the new medical device regulation once the final version of the new law is published.

In addition, there are some new Essential Requirements in the MDR, and the current version of EN ISO 11607 is probably not considered "sufficient" for meeting them. Work is underway in ISO Technical Committee 198/Working Group 7, with the hope that the final document will meet all requirements and therefore be able to be harmonized. If the final document does not adequately address all Essential Requirements, then the European Commission could adopt common specifications solely authored in/by the EU to make up for anything considered insufficient when the new MDR is adopted.

Gert Bos, Executive Director & Partner at Qserve Group, says that "at this moment, there is no mandate to harmonize any


Gert Bos

standard under the MDR; it will first have to be published before that may happen. Most likely a mandate to write harmonized standards will be given for horizontal standards, such as those for quality management, risk management, clinical evaluation, sterilization, labeling. Other than that, it will take time to harmonize, as getting new Annex Zs in place will be difficult and time consuming. On the other hand, getting common specifications in place will take considerable time as well."

The legislation, however, "is written at a high level, with generic requirements," Bos continues. "Manufacturers will need specific solutions to their products and production process to meet the interpretation of the requirements to their products. Hence the standard will need to be specific, and linking details to the broader essential requirements is not fully feasible."

ISO Technical Committee 198/Working Group 7 on Medical Packaging (responsible for ISO 11607 as well as the guidance ISO TS 16775) in collaboration with CEN TC 102 Working Group 4 is working to align packaging standards with the MDR. Serendipitously, the group began the revision process for EN ISO 11607 nearly a year ago. In September 2016, the committee reviewed the impact of the EU MDR on packaging to ensure that the upcoming revision of EN ISO 11607 would be considered sufficient and in fact has been actively proposing modifications to the document to achieve this end.


Mike Scholla

"There are requirements in the MDR that aren't in EN ISO 11607," reports Mike Scholla, Convener of ISO TC 198/WG7. (Scholla also serves as Global Director, Regulatory & Standards, and Medical Packaging Fellow for the DuPont Medical and Pharmaceutical Protection business within DuPont Protection Systems.) "If the commission feels that a harmonized standard doesn't adequately address an issue, they will put in place a common specification."

With these new requirements in mind, the committee prepared a draft revision for ballot and comments, a stage known as the CDV, or Committee Draft for Vote. This CDV is expected to cover new expectations involving the generally acknowledged state of the art, usability, validation, and more. Nick Fotis, cochair of the AAMI mirror group responsible for submitting U.S. comments on the revision to ISO TC 198/WG7, says that the revision effort "is trying to prevent the need for common specifications. If the EU were to draft common specifications for packaging, it could require certain materials and specifications, such as those for seal strength and seal width, for instance." Such requirements could ultimately force MDMs to redesign their packaging, he says.


Nick Fotis


AL7/SHUTTERSTOCK.COM

Fotis says the ISO 11607 revision team is also trying to align some common definitions. In the United States, for instance, a medical device plus its package equal the product; in the EU, the product plus its package equal a device. In addition, the definitions of "parameter and variable" are also being clarified. This is important, he says, because it is easy to confuse the two. "Is a temperature set point of 100 a variable setting of the parameter temperature … or is it a parameter setting of the variable temperature?" he asks.

The new MDR also includes new quality management system requirements. In anticipation of this, the latest revision of ISO 13485, "Medical devices -- Quality management systems -- Requirements for regulatory purposes," has been published in 2016, which includes new

requirements and a definition of sterile barrier systems referring to ISO 11607. New requirements for packaging in this standard include preserving products through protecting "the product from alteration, contamination, or damage when exposed to expected conditions and hazards during processing, storage, handling, and distribution by designing and constructing suitable packaging and shipping containers." There are also requirements for preventing contamination of sterile devices with particulate matter during assembly and packaging.

New Requirements

Wagner urges medical device manufacturers to pay close attention to the new law's Essential Requirements in Annex I and the Technical Documentation in Annex II. "These are really what notified bodies will be reviewing," he says. "The requirements to eliminate or to reduce as far as possible the risk of infection have become more explicit by requesting designs that prevent microbial contamination of the device and reduce microbial exposure during use. One area that will get clearly more attention is aseptic presentation. And the package is to be designed so that sterile packaging integrity is clearly evident to the final user."

PIA NIKOLAY/LEITUNG OPERATIONSSAAL/ZSVA/HIRSLANDEN KLINIK BELAIR

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

For packaging, state of the art "simply means that as manufacturer, you will mainly need to justify that your packaging is suitable, and that no new modern type of packaging would improve the safety of the device / reduce its residual risks," Bos says.

Ongoing device protection through packaging is emphasized. Annex I also states that "devices shall be designed, manufactured, and packaged in such a way that their characteristics and performance during their intended use are not adversely affected during transport and storage, for example, through fluctuations of temperature and humidity, taking account of the instructions and information provided by the manufacturer."

Ensuring such protection could present challenges. Beate Klumpp, NAMSA, expects that "to be in compliance with the Essential Requirements, packaging for sterile products must be validated according ISO 11607 and the requirements of material properties must be also fulfilled."

Beate Klumpp

However, while "the sterile barrier properties of the primary packaging material are according to the specification and the sealing process is mostly well validated," says Klumpp, "not so the packaging design, like the size of the sterile barrier packaging." She adds that she often sees sterile barrier systems that are too small or too big for containing the product, which could lead to defects during transport, because of the movement of the product.

"And we see often a lack in the design of the protective packaging, so that the maintenance of the sterile barrier after transport hazards is doubtful. From my experience as former head of a test lab for transport stability, [I believe] the requirements for packaging design should be also focused on the protection against mechanical impacts as vibration and handling," she says.

Bos adds that "the fluctuations of temperature and humidity are just examples of elements that should be part of the

validation, actually already now. One thing that will need further clarification in the future relates to the link to instructions and information provided; as the new MDR will be much more specific in requesting (clinical) validations to match the scope and claims of the product, a more detailed precision also in packaging validation might well be expected."

Focusing on the end-user

There's also a heightened emphasis on ensuring that packaging better serves end-users. The MDD required manufacturers to "ensure that [sterile devices] are sterile when placed on the market and remain sterile, under the transport and storage conditions indicated by the manufacturer, until the protective packaging is damaged or opened." The MDR now states that "unless the packaging which is intended to maintain their sterile condition is damaged," devices shall "remain sterile, under the transport and storage conditions specified by the manufacturer, until that packaging is opened at the point of use. It shall be ensured that the integrity of that packaging is clearly evident to the final user."

This requirement is a "legitimate concern," says Fotis, but seems to "misunderstand that there are holes smaller than the eye can see. It should instead say something such as 'users should visually inspect packaging.' So to address this statement, the proposed revision of ISO 11607 now includes this statement: 'Packaging shall be inspected for holes and tears prior to use."

At the recent AAMI mirror group meeting on the CDV, there was some pushback about telling nurses what to do with packaging. But Fotis points out that ISO 16775, "Packaging for terminally sterilized medical devices -- Guidance on the application of ISO 11607-1 and ISO 11607-2," does provide "information for health care facilities and for the medical devices industry," according to ISO.

DINKO BENCE/SHUTTERSTOCK.COM

The addition of "at the point of use" also underlines the responsibilities of medical device manufacturers to consider the suitability of their packaging for the use environment. In addition, the regulation states that "the design shall . . . allow easy and safe handling."

Bos says that "as it is an additional requirement, it will need to be part of instructions in some cases, and be part of the validation. One can imagine the wording is added, as some practices are to remove the sterile barrier, e.g., for use in procedure packs."

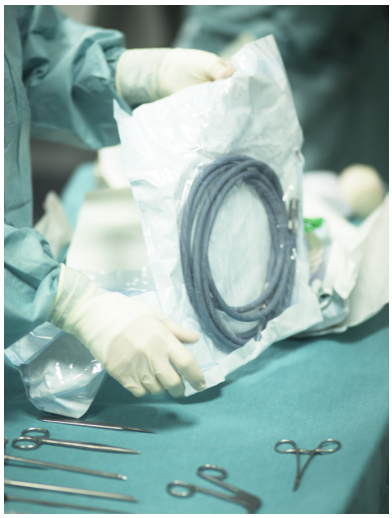
The question is, will point-of-use considerations require different testing cycles and design considerations? While specific regulator expectations remain unknown, there is an emerging need for usability testing during packaging development. "Already at this stage, we see the number of non-conformities issued by notified bodies on this aspect drastically rising," observes Bos. "So it will be crucial to get the usability testing and where appropriate lay user testing reports in place."

Fotis says that MDMs, in alignment with the standard, typically do design packaging so that it can be opened aseptically, but the requirement for user acceptability testing and documentation would be new for many.

"There are also new, explicit directions in the MDR for documentation of the validation efforts for the sterile medical packaging. It is unlikely that this will fundamentally affect practice for any MDMs as companies that are in compliance with FDA's Quality System Regulation are already doing all of this documentation work," says Fotis.

Klumpp believes that if the requirements of EN ISO 11607 are met, no further testing cycles are necessary. "But the design considerations should include the risk for operator errors and how this can be avoided," she says. In addition, "it is to be tested if the sterile product can be easily removed in an aseptic manner. The package must be designed for easy

handling. For example, sealing process validation is mainly focused on a minimum seal strength to ensure the maintenance of sterility, but a specification for maximum seal strength should be also validated to allow aseptic presentation. Failure mode evaluation as described in ASTM F88 must be taken into consideration, also to avoid delamination of the packaging material, which could lead to particles on the medical device."



EDWARDOLIVE/SHUTTERSTOCK.COM

Labeling

The new law includes detailed requirements for labeling. For instance, the use of a symbol and a label indicating that a product is sterile would need to be included. "That is already in place, e.g., "STERILE | R" on a box for sterilisation by radiation," says Bos.

Packaging systems often consist of double packaging, such as an inner and outer pouch or blister, but "it is not always obvious for the end user which package is the sterile barrier," adds Klumpp. "This should be clearly labelled."

Instructions must include information that tells users what to do "in the event of the sterile packaging being damaged or unintentionally opened before use." Klumpp says "the warning to discard the product in case of a defect sterile barrier should be labelled and not just be mentioned in the IFUs."

Unique Device Identification (UDI) carriers will be required "on the label of the device and on all higher levels of packaging," reads Article 27. "Higher levels of packaging shall not be understood to include shipping containers."

"This in principle will be constructed in such a way that one can use the same bar code for US and EU, but that data in the underlying US and EU databases are diverging depending on requirements," says Bos. But he says that there are only high-level ideas at this moment only; more details will follow in implementing legislation.

Would packaging and labeling for already marketed devices need to be redesigned for previously approved products? Bos says that this answer would depend upon the risks involved. "Color coding might be used, pictures on the primary packaging, details in the IFU. There is no common interpretation or guidance yet. The minimum one needs to do is revisit this topic, and either conclude no changes are needed, or do design modifications. In case of no change, [the] best proactive [approach] might include a justification on the current system being sufficiently clear to users into the technical file."

Validation

Annex I states that "devices labelled as sterile shall be processed, manufactured, packaged, and sterilised by appropriate, validated methods," and Annex II details the content of the technical documentation for validation reports with respect to packaging, sterilization, and maintenance of sterility: "The documentation shall contain the results and critical analyses of all verifications and validation tests and/or studies undertaken to demonstrate conformity of the device with the requirements of this Regulation and in particular the applicable general safety and performance requirements."

The expectation for validation isn't new, but that for documentation is. A description of the validation methods used for packaging "is not really new, as manufacturers already have to do the validation at this stage," says Bos. "But now, full details will need to be included in the documentation, including validation methods. Similarly, it might help to get the summary structure of risk management, clinical evaluation, etc. in the dossier as well, rather than only refer to the quality management system that specifies details."

But what if there is incomplete—or missing—documentation from a previous validation? Will marketed products with scant validation documentation be allowed to remain on the market if they have had no post-approval issues? Will any testing need to be redone, including

transportation performance testing, to prepare the documentation now required under the MDR for packages that were developed and validated long ago?

"According to EN ISO 11607 performance testing for stability must already be conducted. I do not see the need for new testing activities to be in compliance as far as EN ISO 11607 is applied," says Klumpp. "If the packaging meets the requirements and is validated according to EN ISO 11607, no further testing is needed. The problem is that most manufacturers did not revalidate packaging that they had validated before the publication of EN ISO 11607. The gap between a former validation and new requirements must be evaluated through a risk assessment. In my opinion, above all, the transport risks can be estimated only by a validation, because we often see unanticipated results after transport simulation."

EDWARDOLIVE/SHUTTERSTOCK.COM

Bos says that "once the physical details of the packaging are changed, one should justify if validation is still valid or needs to be redone. If no changes are needed to physical elements of the packaging, in principle the validation might remain valid. In addition, one is expected to have a policy defining need and frequency for re-validation."

Development of a sampling plan also needs addressing. EN ISO 11607 lacks in a few definitions, such as for a sampling plan, says Klumpp. "It is almost impossible for the manufacturer to establish a sampling plan with inclusion of economic aspects, which is certainly sufficient for all authorities in different countries," she says.

Adds Bos: "In general, it would help if standards are detailing specifics on validation, including statistics on sampling in such validations."

Non-Sterile Devices

The law also states that "packaging systems for non-sterile devices shall maintain the integrity and cleanliness of the product and, where the devices are to be sterilised prior to use, minimise the risk of microbial contamination; the packaging system shall be suitable taking account of the method of sterilisation indicated by the manufacturer." And "if the device is supplied non-sterile with the intention that it is sterilised before use, the appropriate instructions for sterilization."

Klumpp says that "there is a lack of standards for packaging of non-sterile products. Different authorities might have different demands. A harmonized standard for protective packaging of non-sterile products could be helpful for manufacturers to know what they need for being in compliance (e.g., transport stability) with MDR 8.6."

Repackaging and reuse

There are new requirements in the MDR addressing the reprocessing and repackaging of medical devices. "If the device is reusable, information on the appropriate processes for allowing reuse, including cleaning, disinfection, packaging and, where appropriate, the validated method of resterilisation appropriate to the Member State or Member States in which the device is placed on the market. Information shall be provided to identify when the device should no longer be reused, e.g. signs of material degradation or the maximum number of allowable reuses," reads the law.

Bos says that "manufacturers will need to validate the product is in line with their claims. So if they claim single use, they will need to validate it can be used once. And they will need to justify why it cannot be re-used. In most cases this will mainly affect labeling and IFU, not the primary and secondary packaging itself."

Sustainability

Even though sustainability and packaging waste are not addressed in the MDR, medical device manufacturers will have to consider such elements during packaging development given the EU's Packaging and Packaging

Waste Directive. The newly published Circular Economy Roadmap, which seeks waste and landfill reductions and recycling increases, is likely to add further requirements in the future. "Basically a manufacturer of medical devices will have to fulfill all applicable law, including environmental ones. So yes, this needs to be included," Bos says. "However, medical device notified bodies and medical device agencies will not look into the matter other than the occasional glance if you have done anything in the field. And even that is not fully required."

IMAGE SOURCE: SHUTTERSTOCK BY EVGENY ATAMANENKO

Sustainability is also being addressed in EN ISO 11607's revision. "Sustainability has to be addressed in all standards," says Scholla. "So we are proposing that 11607 include Annex D on Environmental Aspects. It suggests applying a life-cycle approach to product development through all stages. We also ask MDMs to consider asking appropriate questions about sustainability and reviewing currently available recycling streams for packaging waste." Scholla suggests reviewing AAMI's standard on sustainability and life-cycle analysis.

Conclusion

Many developments have yet to unfold. "To the extent possible, guidance developed for medical devices at international level, in particular in the context of the Global Harmonization Task Force (GHTF) and its follow-up initiative the International Medical Devices Regulators Forum (IMDRF), should be taken into account to promote the global convergence of regulations which contributes to a high level of safety protection worldwide and to facilitate trade, in particular in the provisions on Unique Device Identification, general safety and performance requirements, technical documentation, classification rules, conformity assessment procedures and clinical investigations," reads the MDR.

As stated earlier, harmonized packaging standards are expected to help. "To recognise the important role of standardisation in the field of medical devices, compliance with harmonised standards as defined in Regulation (EU) No 1025/2012 of the European Parliament and of the Council of 25 October 2012 on European standardization . . . should be a means for manufacturers to demonstrate conformity with the general safety and performance requirements and other legal requirements, such as relating to quality and risk management, laid down in this Regulation," the law reads.

In terms of packaging standards, if publication of both the MDR and the revision of EN ISO 11607 stay on schedule, the revision should be final before the new MDR is enforced. (Entry of force for the regulation is expected in 2020, and publication of the revised EN ISO 11607 is expected by mid 2019.)

However, while Fotis believes it is very unlikely, there is the chance that the revised ISO 11607 draft could be voted down at the final draft standard (FDIS) stage.

Scholla reports that when EN ISO 11607 balloting took place in early 2015, the group voted to reaffirm the current version and revise it. The reaffirmation means that if the latest proposed revision is voted down at the FDIS stage, the previously approved EN ISO 11607 will in remain in place until another revision effort is launched. The industry wouldn't have a harmonized packaging standard, though, leaving open the potential need for EU common specifications.

The good news is that "standards rarely die at the FDIS stage because the technical discussion would already have occurred by the DIS stage, and the standard wouldn't go to the FDIS stage without resolving any technical concerns," Scholla says.

Years ago, a previous revision of EN ISO 11607 was voted down at the FDIS stage. The proposed document had notes referencing EN 868 Part 1 in an attempt toward

harmonization. ISO editors had removed the notes because it wasn't common to include them. The edited FDIS without the notes was then voted down at the urging of the convener. After discussions between the convener and the ISO Central Secretariat, the notes were restored, and the FDIS was approved, Scholla reports. Scholla urges medical device manufacturers to get involved to avoid such situations and to have a voice in standards development. "Anyone can comment up to the DIS stage," he says. To participate, please contact AAMI (www.aami.org; under Standards, select "Join a Technical Committee"). In France, MDMs can contact AFNOR (www.afnor.org); in Germany, DIN (www.din.de); in the UK, BSI (www.bsigroup.com); and so on.

A harmonized EN ISO 11067 would go far to support medical device manufacturers. As the revision process unfolds, companies should continue to educate themselves on the new regulation and begin taking steps toward compliance.

This paper was written by **Daphne Allen**, who serves as executive editor Pharmaceutical & Medical Packaging News, now serving as the pharmaceutical and medical device channel of **PackagingDigest.com**, and **Qmed.com**
She can be reached at **daphne.allen@ubm.com**