Speed Up Your Compliance Process — With Help from DuPont™ Tyvek®

October 5, 2017
DuPont Presenters

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Topics of Today’s Discussion

• Regulatory Update
  - Global Regulatory Changes
  - Impact of the New EU MDR/IVDR on Sterile Packaging
  - Revision Process ISO 11607
• Tools to Help You with Packaging Design and Regulatory Submissions
• All New Technical Reference Guide
• We’re Here to Help
Regulatory Update
Disclaimer

This information corresponds to our current knowledge on the subject and may be subject to revision as new knowledge becomes available.

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Global Regulatory Changes

- **European Union**
  Adopted its MDR/IVDR in April 2017 to replace the MDD/IVDD

- **Association of Southeast Asian Nations (ASEAN)**
  Medical Device Directive 2015

- **India**
  “Medical Device Rules, 2017” notified in January 2017

- **Eurasian Economic Union (EAEU)**
  2016 Legal framework for medical products

- **International Medical Device Regulators Forum (IMDRF)**
  Guidance and harmonization

- **ISO TC210** published **ISO 13485:2016**, a significant revision of **QMS** requirements
Revision of EN ISO 13485:2016

Introduction of state-of-the-art QMS approaches

- Scope now includes the life cycle of the device:
  - Design, resource management and product realization
  - **Storage and distribution**, including disposal
  - Technical support
  - Complaint handling
  - Post-market surveillance
- Risk-based thinking
- Enhanced supplier controls
- Explicitly includes **sterile barrier systems (SBS)**
- Increased focus on work environment for **sterile items**
- **New**: Identify and implement changes to ensure and maintain device safety and performance
EU Medical Device Regulations

AIMDD
EU Directive 90/385/EEC
Active Implantable Devices
Ends May 26, 2020

MDD
EU Directive 93/42/EEC
Medical Devices
Ends May 26, 2020

MDD—Regulation
(EU) 2017/745
Medical Devices
Adopted April 2017
Legal start date May 26, 2017
Fully applies May 26, 2020

3-yr Transition Period

IVDD
EU Directive 98/79/EC
In-vitro Diagnostic Medical Devices
Ends June 26, 2022

IVDR—Regulation
(EU) 2017/746
In-vitro Diagnostic Devices
Legal start date May 26, 2017
Fully applies June 26, 2022

5-yr Transition Period

...... MDD Certificates can be valid up to 4 more years after date of application
...... IVDD Certificates can be valid up to 2 more years after date of application
MDR and IVDR—What’s New?

• Moving from “CE marking” to **life-cycle** approach
• Integration of MEDDEV guidance on:
  - Clinical evaluations (clinical data)
  - Vigilance and post-market clinical follow-up
  - Requirements for economic operators (authorized representatives)
• Rigorous **Notified Body** qualification, designation and auditing requirements
• Mechanism for **scrutiny of conformity** assessments of certain Class III/IIb devices
• Preparing for Unique Device Identification (UDI) and **EUDAMED** database
• Will continue to build on “**harmonized standards**”
• Introduction of **Delegated Acts** and **Common Specifications** (CS) by the Commission
• Formal introduction of the Medical Device Coordination Group (**MDCG**)
• Extended, **updated annexes**
MDR Annexes—Changes for Sterile Packaging Shown in Red

I. General safety and performance requirements
II. Technical documentation
III. Technical documentation on post-market surveillance
IV. EU declaration of conformity
V. CE marking of conformity
VI. Information to be submitted upon the registration of devices and economic operators…core data elements to be provided to the UDI database…
VII. Requirements to be met by Notified Bodies
VIII. Classification rules
IX. Conformity assessment based on a quality management system and assessment of the technical documentation
X. Conformity assessment based on type examination
XI. Conformity assessment based on product conformity verification
XII. Certificates issued by a Notified Body
XIII. Procedure for custom-made devices
XIV. Clinical evaluation and post-market clinical follow-up
XV. Clinical investigations
XVI. List of groups of products without an intended medical purpose referred to in Article 1(2)
XVII. Correlation Table
MDR Annexes

• Annex I
  MDD Essential Requirements (ERs) become General safety and performance requirements (SPRs) under the MDR

• Annex II
  Technical documentation must include “validation reports, with respect to packaging, sterilization and maintenance of sterility”

• Annex VII
  Requirements to be met by Notified Bodies: Quality management system auditing: … draw up and keep up to date, for Class IIa and Class IIb devices, a sampling plan for the assessment of technical documentation

• Annex VII
  Requirements to be met by Notified Bodies: Specific qualification criteria shall be defined at least for … packaging,…and the different types of sterilization processes
The MDR General Safety and Performance Requirements

What changes for sterile packaging?
Key MDD Essential Requirements for Sterile Medical Packaging—EN ISO 11607

In summary:

8.1 ...eliminate, or reduce as far as possible, the risk of infection to the patient

Design must allow for easy handling and, where necessary, minimize contamination of the device by the patient or vice versa during use

8.3 ...remain sterile, under the specified storage and transport conditions until the protective packaging is damaged or opened

8.4 ...manufactured and sterilized by an appropriate **validated method**

Note: In addition to the Essential Requirements (ERs) listed above, there are other ERs that must be met, such as general ERs 1-6, labeling, etc.
Key MDR Safety and Performance Requirements for Sterile Medical Packaging—EN ISO 11607

In summary:

11.1 ...eliminate, or reduce as far as possible, the **risk of infection** to the patient

Design shall allow for easy **and safe** handling and...

**NEW**

**minimize microbial contamination**

11.4 ...**remain sterile**, under the specified storage and transport conditions:

**NEW**

Until that packaging is **damaged or opened at the point of use**

“That packaging” = “packaging that is intended to maintain its sterile condition”

**NEW**

It shall be ensured that the integrity of that packaging is clearly evident to the final user

11.5 ...processed, manufactured, **packaged and sterilized by an appropriate validated method**

*Note: In addition to the Essential Requirements (ERs) listed above, there are other ERs that must be met, such as general ERs 1-6, labeling, etc.*
The New MDR vs. the MDD—In Relation to Sterile Packaging

Annex I  General safety and performance requirements

Chapter III  Requirements regarding the information supplied with the device

23  Label and instructions for use

23.3  Information on the “sterile packaging” (packaging that maintains the sterile condition of a device)

The following particulars shall appear on the sterile packaging:

**NEW**

(a) an indication permitting the sterile packaging to be recognized as such

(b) a declaration that the device is in a sterile condition

**NEW**

(j) an instruction to check the “Instructions for Use” for what to do if the sterile packaging is damaged or unintentionally opened before use

Note: Particulars (c) through (i) are not pertinent to this discussion.
Aseptic Presentation—Example of a Double Entry Sterile Barrier System

Where is the Sterile Barrier System (SBS)?
One or two validated SBS?

Outer Barrier

Inner Barrier
New Labeling Must Be Developed for the MDR

One of the new key requirements: …an indication permitting the sterile packaging to be recognized as such

• Essential for double or triple entry packaging systems to optimize aseptic presentation

Symbol proposal by the Sterile Barrier Association indicates a validated SBS as a closed line and protective packaging as dotted lines, even if it looks like an SBS
Symbol Proposal by the Sterile Barrier Association

• This proposed symbol:
  - Provides healthcare professionals with essential information about how to aseptically present the device
    
    and
  - Would allow compliance with the MDR—discussion ongoing
Summary of Impact of New EU MDR/IVDR on Sterile Packaging

• **Validation of packaging**, clear requirement, same level as sterilization—**all must be included in technical documentation**

• Adding concepts of:
  - “sterile up to the point of use”
  - “prevention of microbial contamination”
  - “easy and safe handling”
  - “integrity being evident”

• New labeling requirements (for example: “SBS to be recognized as such”)

• **Notified Body** involvement growing

• Delegated acts, common specifications, **MDCG**
  → **more changes expected**
EN ISO/DIS 11607:2017 Revision (Draft)—Key Focus Areas

- Alignment of definitions with other standards and ISO/DIS 11139
- Editorial changes for clarity and better flow of the document
- **Evaluation to assess aseptic presentation (usability evaluation)**
- Visual inspection of SBS before aseptic presentation
- Design changes and revalidation
- Process validation section
- New environmental Annex D following ISO and CEN guidance
- Considerations of recent changes to regulatory requirements (i.e., MDR)
  - EN ISO version: Annex ZABC (MDD, AIMDD & IVDD)
  - ISO + EN ISO version: Annex E with informal guidance on elements to be included in a future Annex “Z-MDR”

Next meeting: February 2018—review DIS comments, finalize DIS (target is FDIS)
EN ISO/DIS 11607:2017 Revision (Draft)—Key Focus Areas

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DIS published for ballot on 18 Sept 2017 – 11 Dec 2017

Next meeting: February 2018—review DIS comments, finalize DIS (target is FDIS)
Conclusion

• Many regulatory changes are coming in the near future

• MDMs will need to:
  - Update their technical files
  - Recognize changes may have an impact on existing validations and packaging designs
  - Adapt labeling
Tools to Help You with Packaging Design and Regulatory Submissions
We Are Applying Key Learnings from MPTP

• Collaboration with medical device manufacturers (MDMs) during the Tyvek® Medical Packaging Transition Project (MPTP) gave us:
  - A better understanding of the kind of data you need
  
  and

  - Insights of how best to present that data

• New documents and online tools developed based on:
  - Vast amount of data and key learnings from MPTP
  combined with

  - Our in-depth knowledge of industry regulations

• We actively seek suggestions from MDMs for continuous improvement
A Selection of Major Tools from DuPont™ Tyvek®

• Technical Reference Guides
  - For Transition Tyvek® 1073B, Transition Tyvek® 1059B and Tyvek® 2FS™
  - For Legacy Tyvek® 1073B, Legacy Tyvek® 1059B and Tyvek® 2FS™ (Updated June 2017)

• Compliance Documents—Materials Portion of ISO 11607-1 Standard
  - For Transition Tyvek® 1073B & Transition Tyvek® 1059B (June 2017)
  - For Legacy Tyvek® 1073B, Legacy Tyvek® 1059B and Tyvek® 2FS™

• Where you can find these and other tools:
  - medicalpackaging.dupont.com
  - medicalpackaging.dupont.com/knowledge
  - Medical Packaging Reference Library — Technical and Regulatory
  - transitiondata.tyvek.com

Metric Units

English Units

- Contains **newest data** and information for:
  - Transition Tyvek® 1073B
  - Transition Tyvek® 1059B
  - Tyvek® 2FS™
- Includes **extensive application guidance and troubleshooting guidelines**
- Features reorganized chapters to help **simplify data research**
- **Is interactive**, including cross-links and links to useful external information

*Designed to help you develop and validate the most appropriate packaging solutions with Tyvek®*
Color-Coded Sections of the New Technical Reference Guide

1. Why is DuPont™ Tyvek® the preferred choice for sterile barrier systems?
2. DuPont™ Tyvek® — Properties
3. Biocompatibility, food contact, pharmacopeia and bioburden
4. Sterilization compatibility
5. Stability testing
6. Package system performance testing
7. Application guidance
Comparison of Properties—Tyvek® vs. Medical-Grade Papers

This is one of many figures showing comparison of properties

Figure 7. DuPont™ Tyvek® vs. medical-grade papers: a comparison of properties—microbial barrier (ASTM F2638), Mullen burst (ISO 2758), Elmendorf tear (ASTM D1424 and EN 21974), elongation (EN ISO 1924-2) and hydrostatic head (AATCC TM 127 and EN 20811).

Due to the smaller sampling populations used for these material comparisons, the Tyvek® data presented in this section may differ slightly from the specification and miscellaneous properties tables.
New Particle Generation Data—Gelbo Flex Testing Method

Figure 14. Particles generated by Transition Tyvek® 1073B, Transition Tyvek® 1059B and two commonly used medical-grade papers (Gelbo Flex testing method, ISO 9073-10).
Gelbo Flex Test Method ISO 9073-10

- Principle: tube made from test material twisted and compressed
- Test chamber with particle counter
- Results corrected based on count of empty chamber
- “Dynamic” with movement or “Static” without movement
- Well-established test method for cleanroom fabrics
- Can be applied to packaging
- Measures 3-µm to 25-µm particles

*Photos provided courtesy of Nelson Laboratories.*
Why We Chose Gelbo Flex Testing for Particulate Measurements

• Particulate testing is increasingly important as pharmaceutical and medical regulations and standards become more stringent

• There are many types of methods, ranging from dry to wet, such as:
  - Visual inspection
  - Wet solvent extraction

• We chose Gelbo Flex method because:
  - Dry test methods are most representative of typical package conditions
  - We advise that wet packages be considered damaged
  - DuPont has experience with Gelbo particulate testing and has found it reliable and repeatable
  - Can be applied to all packaging materials
  - Widely available throughout the world
DuPont™ Tyvek®—Properties Shown in Tables, Figures or Links

- Specification properties
- Miscellaneous properties
- Differential Scanning Calorimetry (DSC) curves
- Infrared Spectrum “Fingerprinting” via ATR-FTIR curves
- Dimensional stability study results
- Coefficient of Friction (COF) study results
- Chemical resistance information

Figure 15. DSC curves for Transition Tyvek® 1073B and Transition Tyvek® 1059B. Individual DSC plots—offset for clarity.
Note: Slight differences in crystallinity are consistent with normal DSC sampling and lot-to-lot variability.
## Biological Evaluation Results

**Table II. Biocompatibility, food contact, pharmacopeia and bioburden testing results for Transition Tyvek® 1073B and Transition Tyvek® 1059B**

<table>
<thead>
<tr>
<th><strong>BIOCOMPATIBILITY</strong></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Cytotoxicity (ISO 10993-5:2009)</td>
<td>PASS:</td>
</tr>
<tr>
<td></td>
<td>• Pre-sterilization</td>
</tr>
<tr>
<td></td>
<td>• Post-sterilization and 5- and 10-year accelerated aging (EO, 100 kGy gamma, 100 kGy electron-beam, STERRAD® 100S, vapor hydrogen peroxide, steam)</td>
</tr>
<tr>
<td>Cytotoxicity (USP &lt;87&gt;)</td>
<td>PASS (pre-sterilization)</td>
</tr>
<tr>
<td>USP &lt;88&gt; Class VI Biological Reactivity Tests, in vivo</td>
<td>PASS (pre-sterilization)</td>
</tr>
<tr>
<td>Skin irritation and sensitization (ISO 10993-10:2010)</td>
<td>PASS (pre-sterilization)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Extractables and leachables (ISO 10993-18:2005: Infrared spectroscopy; ICP-MS; GC-MS; UPLC-MS)</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-sterilization:</td>
<td></td>
</tr>
<tr>
<td>• No major bands of interest (Infrared spectroscopy)</td>
<td></td>
</tr>
<tr>
<td>• No quantifiable extractables above a concentration of 1.0 µg/mL detected by ICP-MS; GC-MS; UPLC-MS</td>
<td></td>
</tr>
<tr>
<td>Post-sterilization (EO, 100 kGy gamma, 100 kGy electron-beam, STERRAD® 100S, vapor hydrogen peroxide, steam):</td>
<td></td>
</tr>
<tr>
<td>• No major bands of interest (Infrared spectroscopy)</td>
<td></td>
</tr>
<tr>
<td>• No quantifiable extractables above a concentration of 1.0 µg/mL detected by ICP-MS; GC-MS; UPLC-MS</td>
<td></td>
</tr>
<tr>
<td>• UPLC-MS testing—see*</td>
<td></td>
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<table>
<thead>
<tr>
<th><strong>ENDOTOXINS</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Endotoxins (USP &lt;85&gt;)</td>
<td>PASS (pre-sterilization)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>BIOBURDEN</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioburden (ISO 11737-1:2006)</td>
<td>&lt;100 cfu/ft²**</td>
</tr>
</tbody>
</table>
Sterilization Compatibility of Tyvek®—Details and Data

- Ethylene oxide (EO)
- Gamma radiation
- Electron-beam radiation
- Steam sterilization
- Low-temperature oxidative sterilization

Figure 20. Results of shrinkage tests and Gurley Hill porosity measurements conducted on Transition Tyvek® 1073B and Transition Tyvek® 1059B after steam sterilization.
Effects of Sterilization on DuPont™ Tyvek® Properties

- Tensile strength (MD and CD)
- Elongation (MD and CD)
- Puncture strength
- Microbial barrier
- Material color (L,a,b)

Figure 21. Effects of sterilization on material tensile strength (MD) for Transition Tyvek® 1073B, Transition Tyvek® 1059B and Tyvek® 2FS™ (ASTM D5034—in newtons [N]/10.16 cm). MD = machine direction
*No results available for Tyvek® 2FS™.

MD = machine direction; CD = cross direction
Performance of DuPont™ Tyvek® After Aging

- 5-year shelf-life
- 5-year real-time aging after EO sterilization
- 1- and 7-year real-time aging after gamma and electron beam radiation

- 1-, 3-, 5-, 7- and 10-year accelerated aging after different sterilization methods
- 1-year real-time aging after different sterilization methods

Figure 36. Effects of sterilization and 1-year real-time aging on material tensile strength (CD) for Transition Tyvek® 1073B and Transition Tyvek® 1059B (ASTM D5034—in newtons [N]/10.16 cm). CD = cross direction
Package System Performance Testing

• Mechanical properties
• Transport simulation and subsequent testing
• Storage requirements
• Packaging exposed to liquid
• This section includes links to extensive package performance studies, including several White Papers
Extensive Application Guidance

- Guidelines for printing
- Labeling
- Heat sealing guidelines
- The unique structure of Tyvek®
- Determining the rough vs. smooth side of Tyvek®
- Package quality evaluation
- Slitting of Tyvek®
- Processing/troubleshooting guidelines
- Recycling of Tyvek®

Figure 44. Microscopic view of the smooth side of DuPont™ Tyvek® (25x magnification).

Figure 45. Microscopic view of the rough side of DuPont™ Tyvek® (25x magnification).
Guidelines for Printing

- Flexographic printing
- Lithographic printing
- Variable information printing
  - Thermal transfer
  - Ink jet
  - Laser (electrostatic)
- Barcode readability test results
## Barcode Readability Test Results

<table>
<thead>
<tr>
<th>FLEXOGRAPHIC PRINTING</th>
<th>EAN 13</th>
<th>GS1 128</th>
<th>GS1 DATAMATRIX</th>
<th>GS1 DATAMATRIX</th>
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</thead>
<tbody>
<tr>
<td>1D Barcode</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Size: 21 x 8 mm</td>
<td></td>
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<td></td>
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<tr>
<td>1D Barcode</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Size: 37 x 13 mm</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2D Barcode</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symbol size: 18 x 18</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Data region size: 9 x 9 mm</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Symbol size: 18 x 18</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Data region size: 4.5 x 4.5 mm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barcode readability with handheld barcode scanner</td>
<td>Transition Tyvek® 1073B</td>
<td>Transition Tyvek® 1073B</td>
<td>Transition Tyvek® 1073B</td>
<td>Transition Tyvek® 1073B</td>
</tr>
<tr>
<td>Regular 1D laser scanner</td>
<td>6P/6</td>
<td>0P/6</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>2D barcode imager</td>
<td>6P/6</td>
<td>5P/6</td>
<td>6P/6</td>
<td>5P/6</td>
</tr>
<tr>
<td>2D DPM reader</td>
<td>6P/6</td>
<td>0P/6</td>
<td>6P/6</td>
<td>5P/6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>THERMAL TRANSFER PRINTING</th>
<th>GS1 128</th>
<th>GS1 DATAMATRIX</th>
</tr>
</thead>
<tbody>
<tr>
<td>1D Barcode</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Size: 55 x 12 mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2D Barcode</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symbol size: 12 x 12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Data region size: 9 x 9 mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barcode readability with handheld barcode scanner</td>
<td>Transition Tyvek® 1073B</td>
<td>Transition Tyvek® 1073B</td>
</tr>
<tr>
<td>Regular 1D laser scanner</td>
<td>6P/6</td>
<td>N/A</td>
</tr>
<tr>
<td>2D barcode imager</td>
<td>6P/6</td>
<td>6P/6</td>
</tr>
<tr>
<td>2D DPM reader</td>
<td>6P/6</td>
<td>6P/6</td>
</tr>
</tbody>
</table>

**Figure 41. Barcode readability results for Transition Tyvek® 1073B.**
Processing/Troubleshooting Guidelines

• Avoiding fold problems
• Over sealing or no seal transfer
• Fiber tear
• Controlling static charges during converting operations

Figure 46. Pictorial representation of DuPont™ Tyvek® during package opening.
Tyvek®, a monolayer material, acts like a multilayer material represented by the green/yellow/green layers.

Figure 47. Pictorial representation of DuPont™ Tyvek® during opening at an extreme angle.
An extreme fold or bend puts the exterior surface in tension and the interior surface in compression, causing the interior of the sheet to buckle.

- Get the data you need to help speed up your compliance process
- Find valuable design and application guidance, as well as troubleshooting guidelines
- Choose metric unit or English unit version

Coming soon to Medical Packaging Reference Library / Technical Library
We Provide Regulatory and Packaging Science Support

• DuPont Regulatory Affairs Experts are available globally to assist you with the support you need to:
  - Meet worldwide regulations and packaging standards
  - Accelerate your product regulatory submissions and certifications

• DuPont Packaging Engineers are available globally to support you with knowledge about:
  - Materials
  - Packaging design
  - Processing

We are focused on helping you develop and validate the most appropriate packaging solutions with Tyvek®
We’re Here to Help

• Attend a DuPont™ Tyvek® Seminar near you:
  - Costa Rica—January 2018
  - New Jersey—Spring 2018
  - Germany—Spring 2018
  - California—Fall 2018

• Visit us at:
  - Compamed/MEDICA in Düsseldorf—November 13-16, 2017
  - MD&M West in Anaheim, CA—February 6-8, 2018
  - MD&M East in New York, NY—June 12-14, 2018

• Global webcasts—available on-demand for up to a year via UBM, slide decks are available in the Medical Packaging Knowledge Center

• Tyvek® Rx eNewsletter

• medicalpackaging.dupont.com

• Follow us on LinkedIn
Questions?
Thank you

Today’s webcast will be archived for one year for on-demand viewing.

For any additional questions, please contact us:

• Daphne Allen, Editor, Pharmaceutical & Medical Packaging News at daphne.allen@ubm.com

• Or a member of the DuPont team at medicalpackaging.dupont.com
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Appendix
The New MDR vs. the MDD—In Relation to Sterile Packaging

Annex 1 – GENERAL SAFETY AND PERFORMANCE REQUIREMENTS - Chapter II Requirements regarding design and manufacture

<table>
<thead>
<tr>
<th>Medical Device Regulation</th>
<th>Medical Device Directive</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>11. Infection and microbial contamination</strong></td>
<td><strong>8. Infection and microbial contamination</strong></td>
<td><strong>Added requirements a, b, c, d,</strong></td>
</tr>
<tr>
<td>11.1. Devices and manufacturing processes shall be designed in such a way as to eliminate or to reduce as far as possible the risk of infection to patients, users and, where applicable, other persons. The design shall:</td>
<td>8.1. The devices and manufacturing processes must be designed in such a way as to eliminate or reduce as far as possible the risk of infection to the patient, user and third parties. The design must allow easy handling and, where necessary, minimize contamination of the device by the patient or vice versa during use.</td>
<td><strong>New Requirement with impact on packaging:</strong></td>
</tr>
<tr>
<td>(a) reduce as far as possible and appropriate the risks from unintended cuts and pricks, such as needle stick injuries,</td>
<td></td>
<td>(c) easy and safe handling</td>
</tr>
<tr>
<td>(b) allow easy and safe handling,</td>
<td></td>
<td>(d) prevent microbial contamination of the device or its content such as specimens or fluids.</td>
</tr>
<tr>
<td>(c) reduce as far as possible any microbial leakage from the device and/or microbial exposure during use, and</td>
<td></td>
<td></td>
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</table>
Annex 1 – GENERAL SAFETY AND PERFORMANCE REQUIREMENTS - Chapter II Requirements regarding design and manufacture

<table>
<thead>
<tr>
<th>Medical Device Regulation</th>
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</table>
| 11.4. Devices delivered in a sterile state shall be designed, manufactured and packaged in accordance with appropriate procedures, to ensure that they are sterile when placed on the market and that, unless the packaging which is intended to maintain their sterile condition is damaged, they 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. | 8.3. Devices delivered in a sterile state must be designed, manufactured and packed in a non-reusable pack and/or according to appropriate procedures to ensure that they are sterile when placed on the market and remain sterile, under the storage and transport conditions laid down, until the protective packaging is damaged or opened. | Deleted “non-reusable pack”

Added “at the point of use”

Added requirement:

“It shall be ensured that the integrity of that packaging is clearly evident to the final user.” |
**Annex 1 – GENERAL SAFETY AND PERFORMANCE REQUIREMENTS - Chapter III Requirements regarding the information supplied with the device**

<table>
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<tr>
<th>Medical Device Regulation</th>
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</thead>
<tbody>
<tr>
<td><strong>23.3. Information on the packaging which maintains the sterile condition of a device ('sterile packaging')</strong></td>
<td>(b) → 13.3 (c)</td>
<td><strong>New specific requirement for sterile packaging labelling</strong></td>
</tr>
<tr>
<td>The following particulars shall appear on the sterile packaging:</td>
<td>(c) → 13.3 (m)</td>
<td></td>
</tr>
<tr>
<td>(a) an indication permitting the sterile packaging to be recognized as such,</td>
<td>(d) → 13.3 (a)</td>
<td></td>
</tr>
<tr>
<td>(b) a declaration that the device is in a sterile condition,</td>
<td>(e) → 13.3 (b)</td>
<td></td>
</tr>
<tr>
<td>(c) the method of sterilization,</td>
<td>(f) → 13.3 (h)</td>
<td></td>
</tr>
<tr>
<td>(d) the name and address of the manufacturer,</td>
<td>(g) → 13.3 (g)</td>
<td></td>
</tr>
<tr>
<td>(e) a description of the device,</td>
<td>(h) → 13.3 (l)</td>
<td>only for active devices</td>
</tr>
<tr>
<td>(f) if the device is intended for clinical investigations, the words:</td>
<td>(i) → 13.3 (f)</td>
<td>but changes to language</td>
</tr>
<tr>
<td>‘exclusively for clinical investigations’,</td>
<td>(j) → 13.3 (f)</td>
<td></td>
</tr>
<tr>
<td>(g) if the device is custom-made, the words ‘custom-made device’,</td>
<td>(j)</td>
<td></td>
</tr>
<tr>
<td>(h) the month and year of manufacture,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(i) an unambiguous indication of the time limit for using or implanting the device safely expressed at least in terms of year and month, and,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(j) an instruction to check the instructions for use for what to do if the sterile packaging is damaged or unintentionally opened before use.</td>
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Annex 1 – GENERAL SAFETY AND PERFORMANCE REQUIREMENTS - Chapter II Requirements regarding design and manufacture

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<tr>
<td>11.5. Devices labelled as sterile shall be processed, manufactured, <strong>packaged</strong> and, sterilized by means of appropriate, validated methods.</td>
<td>8.4. Devices delivered in a sterile state must have been manufactured and sterilized by an appropriate, validated method.</td>
<td>“<strong>packaged</strong>” has been added</td>
</tr>
<tr>
<td>11.6. Devices intended to be sterilized <strong>shall</strong> be manufactured and <strong>packaged</strong> in appropriate and controlled conditions <strong>and facilities</strong>.</td>
<td>8.5. Devices intended to be sterilized must be manufactured and <strong>packaged</strong> in appropriately controlled (e. g. environmental) conditions.</td>
<td>“<strong>Must</strong>” becomes “<strong>shall</strong>”, “<strong>facilities</strong>” added</td>
</tr>
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</table>
### Annex 1 – GENERAL SAFETY AND PERFORMANCE REQUIREMENTS - Chapter I General requirements

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</table>
| 7. 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. | 5. The devices must be designed, manufactured and **packed** in such a way that their characteristics and performances during their intended use will not be adversely affected during transport and storage taking account of the instructions and information provided by the manufacturer. | **“shall” statement**  
Adding example of fluctuations of temperature and humidity during transport and storage |
## Annex 1 – Essential Requirements

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| **23.4. Information in the instructions for use**  
(l) If the device is supplied sterile, instructions in the event of the **sterile packaging being damaged or unintentionally opened** before use.  
(m) If the device is supplied non-sterile with the intention that it is sterilised before use, the appropriate instructions for sterilisation.  
(n) If the device is reusable, information on the appropriate processes to allow reuse, including cleaning, disinfection, **packaging** and, where appropriate, the validated method of resterilisation **appropriate to the Member State(s) where 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. | **13.6. Where appropriate, the instructions for use must contain the following particulars:**  
(g) the necessary instructions in the event of damage to the sterile packaging and, where appropriate, details of appropriate methods of resterilization;  
h) if the device is reusable, information on the appropriate processes to allow reuse, including cleaning, disinfection, **packaging** and, where appropriate, the method of sterilization of the device to be resterilized, and any restriction on the number of reuses. | **Adding case of “unintentionally opened sterile packaging”**  
**Extended requirements in case device is supplied non-sterile for sterilization or for reusable devices**                                                                                                                                 |

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Annex 1 – GENERAL SAFETY AND PERFORMANCE REQUIREMENTS - Chapter II Requirements regarding design and manufacture

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<td>11.8. The labelling of the device shall distinguish between identical or similar devices placed on the market in both a sterile and a non-sterile condition <strong>additional to the symbol used</strong> to indicate that devices are sterile.</td>
<td>8.7. The packaging and/or label of the device must distinguish between identical or similar products sold in both sterile and non-sterile condition.</td>
<td><strong>Added requirement to include symbol and specific label</strong></td>
</tr>
</tbody>
</table>