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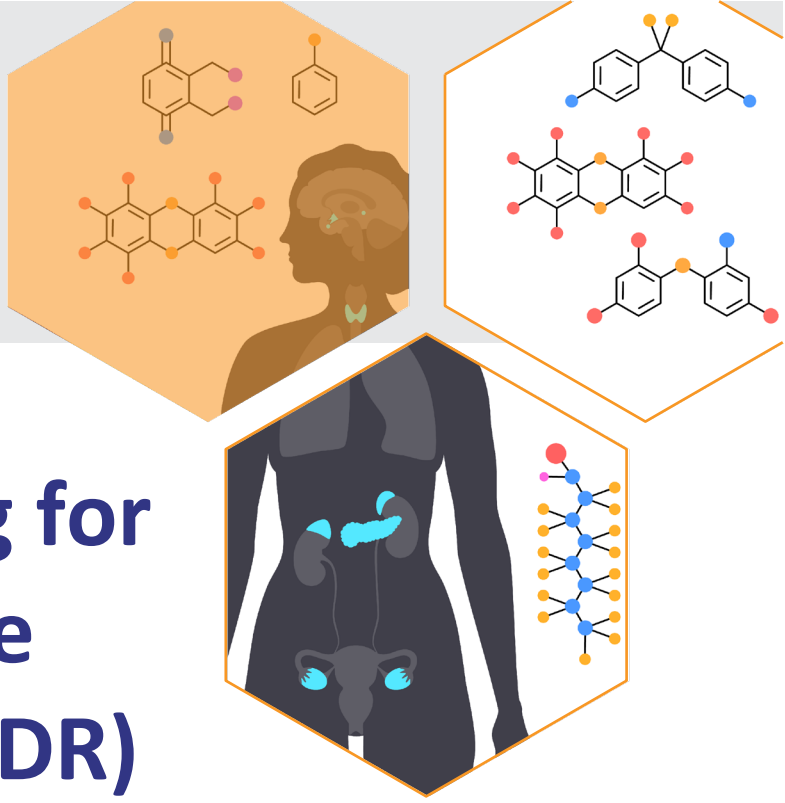

CMR & ED Testing for EU Medical Device Regulation (EU MDR)

By Dr. Rebecca Bader

Summary

In May 2021, the Medical Devices Directive (MDD) was replaced by the Medical Device Regulation (MDR) to improve the safety and efficacy of medical devices marketed in the EU[1]. Medical device manufacturers are now within a transition period whereby existing products must be submitted for certification. These changes have had a profound effect on the medical device industry, but as part of MDR remediation, manufacturers are carefully examining the requirements with regards to the allowed quantities of specific compounds in devices. In some cases, this is on historical devices, with known clinical history.

This application note covers one small portion of the changes and describes screening of medical devices or medical device components for two specific families of compounds, namely diisocyanates and phthalates. Phthalates are commonly used as plasticizers within PVC, while diisocyanates are starting materials used in the production of polyurethanes. Both groups of compounds have been commonly used within medical devices but are now coming under increasing safety scrutiny.

Introduction

With reference to Section 10.4.1 of Annex I General Safety and Performance Requirements of the EU Medical Device Regulation, medical devices should not contain substances that are carcinogenic, mutagenic, or toxic by reproduction (CMRs) and endocrine disruptors (EDs) at a concentration above 0.1% weight by weight unless adequately justified. Per Section 10.4.2, the justification of higher levels necessitates consideration of patient risk due to exposure, including nature and duration of contact. The justification would also require a discussion of possible alternatives and an explanation as to why substitutes, if feasible, are inappropriate in relation to maintaining the functionality of the device (in other words, a description of the cost/benefit of the inclusion of these materials).

Along with the justification, devices that contain CMRs require labelling that provides a list of such substances and instructions for use that include a description of residual risks to patient groups that are particularly vulnerable, e.g. children and pregnant or breastfeeding women (Figure 1).

[1] Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices

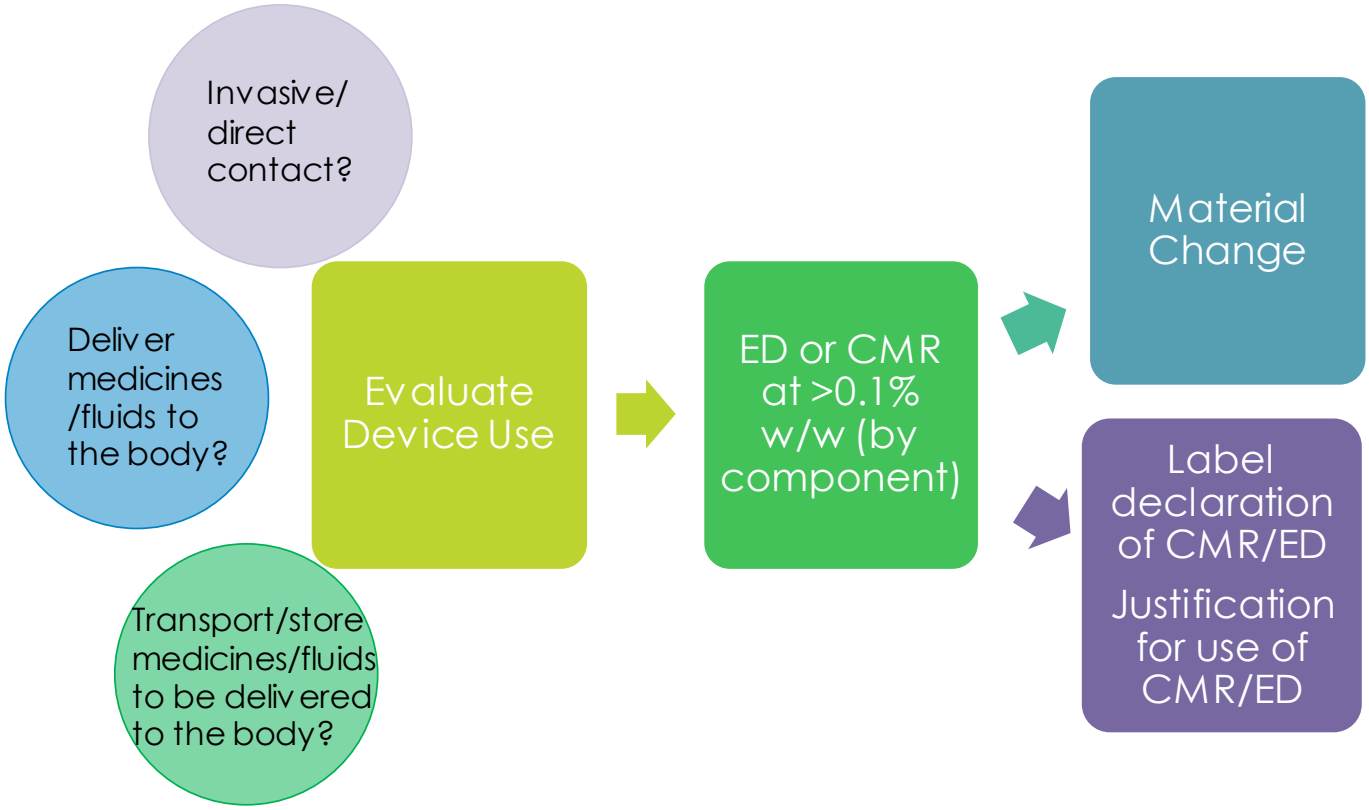

Figure 1: Considerations for CMRs and EDs in medical devices for MDR.

For MDR, there is no so-called grandfathering of legacy devices that were previously on the market. In the absence of grandfathering, which contrasts to MDD, where devices with a known clinical history were largely considered safe irrespective of composition, devices that have been on the market for long periods without additional scrutiny with regards to safety and effectiveness are now required to conform to current standards and regulations. Although Section 10.4.1 requires in-depth material knowledge for identification and quantitation of CMRs, most manufacturers are using chemical characterization per ISO 10993-18:2020 as a starting point for identification of compounds that may pose a toxicological risk to patients. As a result, for legacy devices, non-targeted screening during chemical characterization can point to potential CMRs and EDs that then necessitate a more targeted analysis that would perhaps not have been considered required in the past.

Polyurethane is used in numerous medical devices, including catheters, drug delivery systems, and oral devices. This material is typically produced via reaction of diisocyanates, such as toluene diisocyanate (TDI) and methylene diphenyl diisocyanate (MD), with diol. Upon exposure to moisture (including physiological conditions), diisocyanates are rapidly hydrolyzed to form the corresponding diamine and carbon dioxide. Because the diisocyanates and diamines are reported to be CMRs, detection of residual monomers in polyurethanes during chemical characterization requires further investigation. Of note, the diamines will typically react with residual diisocyanate to generate polyurea oligomers that do not present as much of a toxicological risk.

Likewise, PVC was heavily used historically and is still widely used in numerous medical applications, including blood bags, tubing, breathing circuits, nasal cannulas, and oxygen masks. Flexible PVC medical devices are often plasticized with phthalate additives. Phthalates are known EDs that are associated with reduced fertility, diabetes, and pregnancy loss. Although non-phthalate plasticizer alternatives are available, numerous suppliers continue to produce raw materials and device components that contain phthalates, necessitating screening to ensure that phthalate levels are below the threshold set by MDR.

Case Studies

In a recent exhaustive chemical characterization for an MDR submission study, a medical device exhibited diisocyanates following extraction in hexanes. As part of the analytical workflow the polyurethane component of the device was cryoground and extracted with methylene chloride at 60ºC overnight with gentle agitation. A feature of diisocyanate compounds is that they are not easily analyzed in conventional chromatographic techniques therefore an additional analytical step is required. The extracted diisocyanates were reacted with dibutyl amine as a derivatization agent to yield a compound that was readily detectable by ESI+ LC-QTOF-MS. Extracted ion chromatograms were then used to determine if 2,4 toluene diisocyanate (2,4-TDI), 2,6 toluene diisocyanate (2,6-TDI), or methylene diphenyl diisocyanate (MDI) was present in the samples. 2,4-TDI was used for semi-quantitation.

Of the diisocyanates that were targeted, only 2,6-TDI yielded a detectable peak within the extracted ion chromatogram (Figure 2). This compound was quantitated and provided to toxicologists for a toxicological risk assessment based on the clinical application.

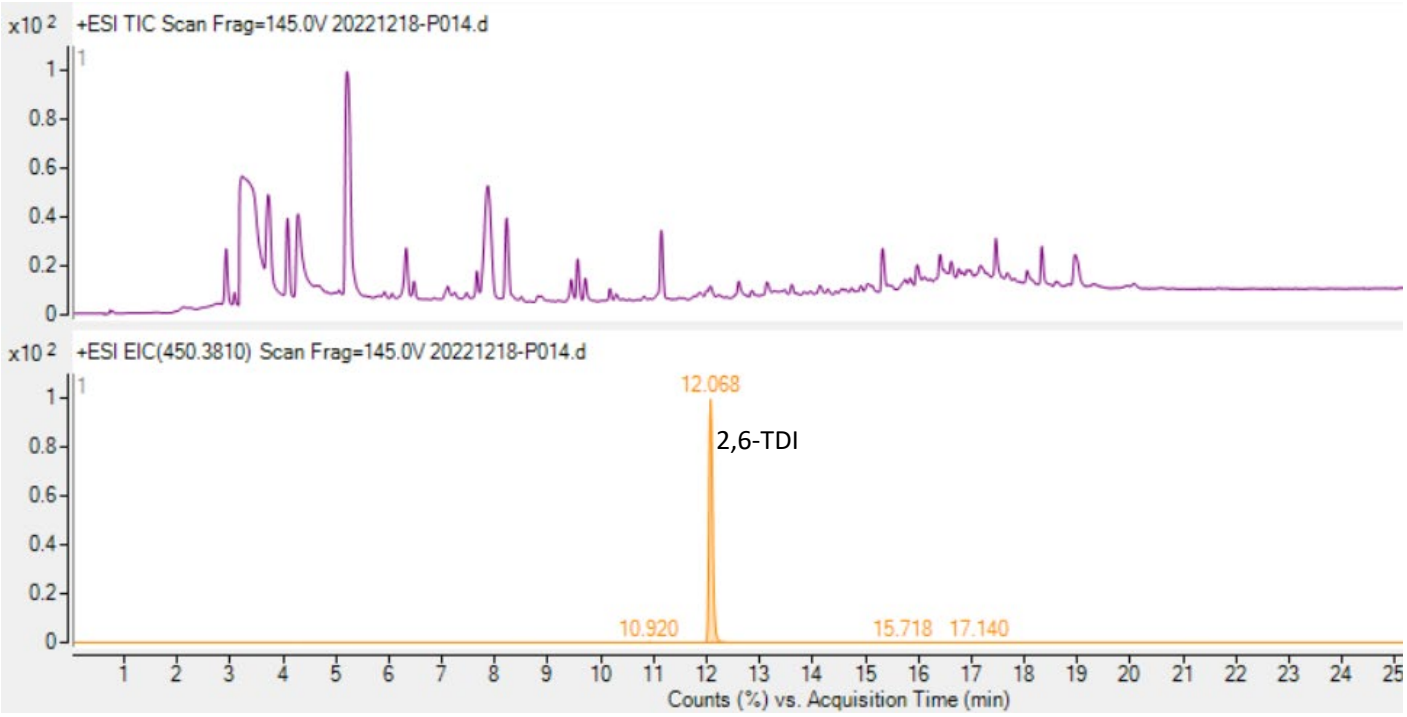

Figure 2: + ESI ionization mode LC-QTOF-MS total ion chromatogram (top) and extracted ion for 2,6-TDI m/z 450.381) bottom.

In a similar study, a medical device that showed phthalates during chemical characterization was cryoground and dissolved in THF. Following precipitation of the polymer with hexanes, the supernatant was analyzed directly by GC-MS. Diisononyl phthalate (DINP) was detected and semi-quantitated with di(2-ethylhexyl)phthalate (DEHP). Diisononyl phthalate yielded several isomeric peaks within the extracted ion chromatogram (Figure 3). The amounts of TDI and DINP, as determined via semi-quantitation, were substantially below 0.1% weight by weight, as specified by MDR. As a result, this device did not require additional biocompatibility assessment or specific hazard warnings for these compounds if sold in the EU.

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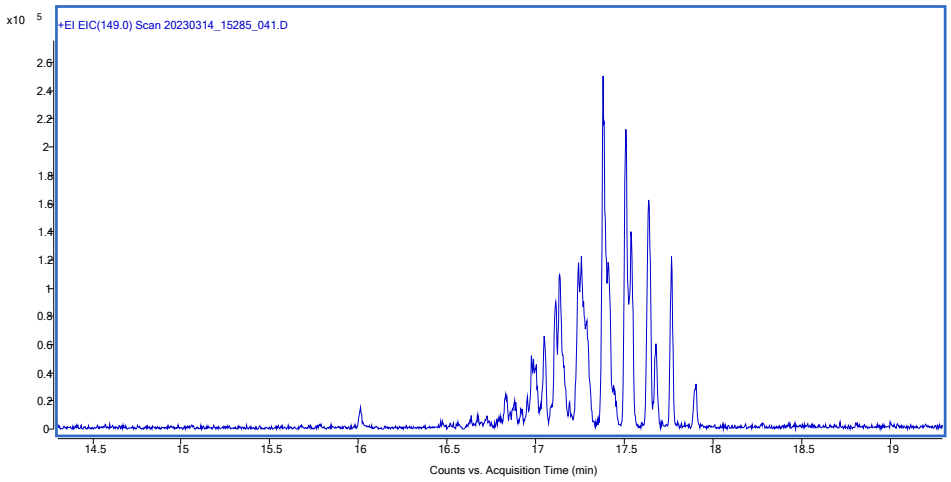

Figure 3: GC-MS total ion chromatogram for DINP (m/z 149.0)

Conclusions

Although general screening chemical characterization indicated the presence of CMRs and EDs within medical devices, targeted screening showed that the CMRs and EDs are present at thresholds lower than that specified by MDR. Consequently, this material should not present a regulatory hurdle based on the presence of restricted substances. The increasing complexity of medical devices made with multiple material types can challenge reliable characterization of restricted chemical substances. A robust sample preparation approach coupled with validated high resolution chromatography can ensure reliable data that meets regulatory requirements and will support the development of safe medical devices in a timely and cost-efficient manner.

Contact CPG for more information on how targeted approaches can be used to mitigate risk from CMRs during the MDR application process.

About Dr. Rebecca Bader

Dr. Rebecca (Becky) Bader is the Associate Director of Chromatography and biocompatibility specialist at Cambridge Polymer Group. Prior to returning in 2023 after initially working for Cambridge Polymer Group from 2017-2020, Becky was Biocompatibility Engineering Manager at ZOLL Medical Corporation where she ensured biocompatibility and material compliance with harmonized standards and global regulatory requirements. Becky has over 20 years of experience in polymeric materials, drug delivery, medical device, and analytical chemistry. She is currently advancing analytical techniques for materials characterization at Cambridge Polymer Group.

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