MEDICAL POLYMERS:

NAVIGATING THE REGULATORY PROCESS

HEALTH

In specifying polymers for medical devices, consideration needs to be given not just to product performance attributes but also to regulatory and compliance support, which includes the material supplier's quality management system and the level of support they are able provide over the full product lifecycle. These factors are sometimes overlooked during initial material selection activities.

LUBRIZOL LIFE SCIENCE HEALTH CREATED THIS E-BOOK TO PROVIDE MORE INSIGHT INTO THESE MATTERS.

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INTRODUCTION TO THE FDA APPROVAL PROCESS

Newcomers to the process of bringing a new medical device to market in the United States should familiarize themselves with the basic elements of U.S. Food and Drug Administration (FDA) requirements. This regulatory framework is used by medical device companies to determine compliance requirements and applicable regulatory pathways to market their products in the United States. The European Union (EU) and other geographies have their own requirements, which Lubrizol also monitors on an ongoing basis. The content covered in this section is solely intended to provide high level regulatory information and is NOT intended to be comprehensive.

The FDA categorizes medical devices intended for human use into three classes – Class I, II, or III – based on the device's risks and the regulatory controls necessary to provide a reasonable assurance of safety and effectiveness. Class I includes devices with the lowest risk and Class III includes those with the greatest risk. Class III devices are those that are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury due to their application. Manufacturers (both domestic and foreign) and initial distributors (importers) of medical devices must register their establishments with the FDA. All organizations intending to market a medical device in the United States need to officially list their product with the FDA. The device classification determines the regulatory pathway required for FDA clearance and/or approval to market the product.

There are two primary regulatory pathways in the United States: 510(k) Premarket Notification and Premarket Approval (PMA).

Premarket notification procedures are described in the Code of Federal Regulations 21 CFR Part 807 Subpart E. A 510(k) submission must demonstrate that the device is substantially equivalent to one legally in commercial distribution in the United States: (1) before May 28, 1976; or (2) to a device that has been determined by FDA to be substantially equivalent. Detail on requirements and applicability is available on the FDA website: 510(k) Submission Programs | FDA.

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PMAs are described in the Code of Federal Regulations 21 CFR Part 814. PMAs are typically required for devices that pose a significant risk of illness or injury, or devices found not substantially equivalent to a Class I or Class II predicate through the 510(k) process. The PMA process is more involved and includes the submission of clinical data to support claims made for the device. Details on PMA is available on the FDA website: Premarket Approval (PMA) | FDA.

MASTER FILES. Device makers are required to provide detailed information in a 510(k) or PMA submission about the materials the device is made from, including raw materials, product formulations, manufacturing processes, and biological testing. Material formulation and certain other information is often regarded by suppliers as confidential intellectual property, which they are not willing to disclose to the applicant. This can make it problematic for device makers to answer FDA analysts' material-related questions.

To help preserve the trade secrets and facilitate the approval process, the FDA established the Device Master File (MAF) system. The applicant can request a Letter of Access from the supplier in order to reference the supplier's MAF in the application. In this way, well-documented MAFs reduce the possibility of the material being the cause of any delay. Materials suppliers are not required to establish MAFs, but many do so in order to support their customers' decision to use their materials for medical device applications. Lubrizol has MAFs established with the FDA for many of our medical polymer products.

Medical device regulatory compliance is a complex process that requires constant monitoring. The proceeding discussion has only considered the United States. The EU, as well as other independent nations, each have their own regulatory framework. This review article explains the different ways the United States and the EU approach the challenges of balancing the competing goals of assuring safety and efficacy while providing rapid movement of innovative therapies through the investigative and regulatory processes as quickly as possible. In May 2021, the EU initiated a four-year-long process of implementing the new EU Medical Device Regulation (EUMDR).

Medical device regulatory compliance is a complex process that requires constant monitoring.

MATERIAL SELECTION CONSIDERATIONS

Choosing the manufacturing materials for a medical device should be one of the earlier decisions in the product development process. It is often crucial to regulatory approval of the device. Formulators of medical grade materials, like Lubrizol, are well qualified to recommend candidate materials for your device. They should be able to provide a summary of manufacturing, quality, and compliance information about the material as well as provide guidance on application end use in the public domain where the materials may serve a similar function.

The selection of component materials may be based on many regulatory-related considerations including but not limited to:

- Biological performance: biocompatibility, biostability, hemocompatibility and infection risk
- Chemical resistance: cleaning-product resistance, drug resistance, sterilization stability
- Processability: compatibility with other materials within the device
- Regulatory and compliance requirements such as:
  - Does the material contain EU REACH (Registration, Evaluation and Authorisation of Chemicals) Substances of Very High Concern (SVHC)?
  - Is it fully compliant with EU RoHS (Restriction of Hazardous Substances)?
  - Are there any other substances of concern or impurities?

For more information on regulatory and compliance terminology, see the FAQ section of our Regulatory Page.

Device makers should assess the toxicity of the materials and chemical substances they want to use as early as possible. In addition to assessments of individual component materials, the FDA requires chemical and biological assessment. For Class II and III devices, this may include testing for extractables, leachables and impurities. Typically, device makers hire an independent laboratory to conduct such a study. The lab should be experienced in testing devices that include the particular manufactured materials used in the device. It might be important for the lab to be able to interpret the extractable substances and provide suggestions for potential sources based on the materials of construction of the device. Your materials supplier may be able to recommend qualified labs and help interpret the results.

MEDICAL GRADE POLYMERS

What is a medical grade polymer? The question seems simple enough, but it may surprise you that a globally accepted, agreed-upon definition and standard does not exist. The short answer is that while non-medical grade polymers are of high quality and performance, in most cases, medical grade polymers are best positioned to address both the immediate and long-term requirements for high performing sustainable medical devices. Here is what you need to know:

Globally, the vast majority of polymers production is used in industrial and consumer products, with only a small percentage being used in medical devices. In order to differentiate grades supplied into the medical device market, raw material suppliers distinguish these materials as medical grade.

"Medical device development requires rigorous testing, quality control systems and regulatory compliance. As the need for new devices grows, so does the need for medical grade polymers to support device development."

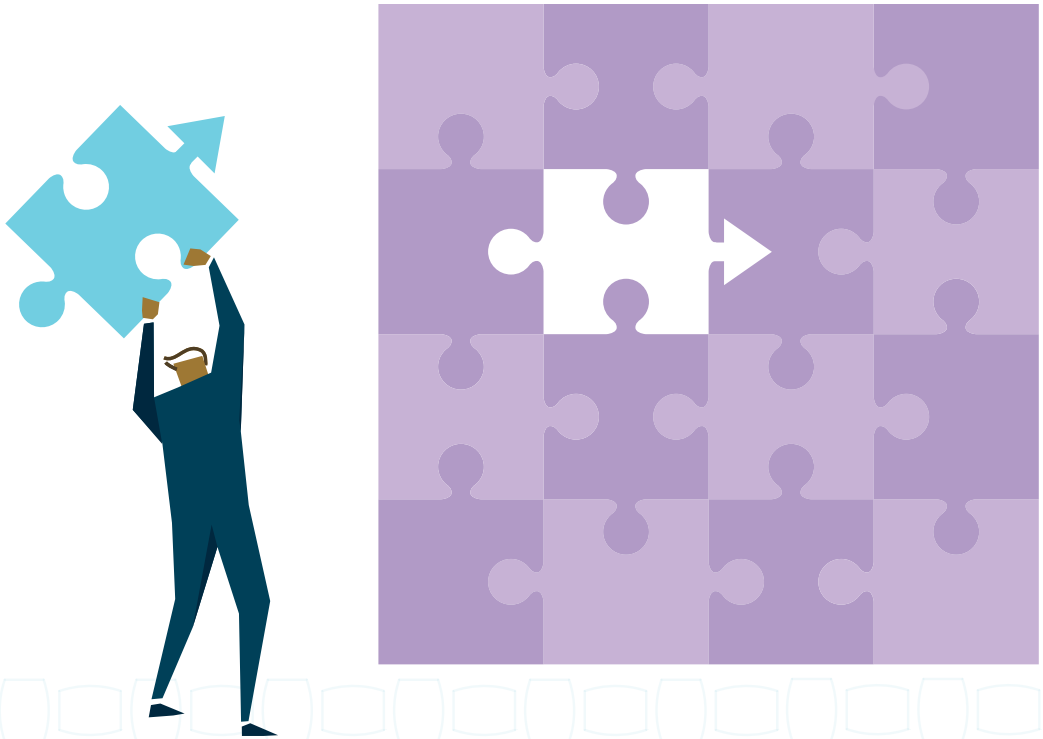
– JENNIFER GREEN, Technical Marketing Manager, Medical Polymers, Lubrizol Life Science Health | Medical Device

Currently, there is no regulatory definition of a medical grade polymer and no prescriptive regulatory requirements for raw materials used in medical devices, so material suppliers and others in the medical device industry have assigned their own meaning to "medical grade polymer." Consequently, polymers designated as medical grade from different suppliers are not necessarily equivalent in performance, quality or associated support. This situation can create confusion for the OEM or device designer when selecting materials.

In some cases, a non-medical grade polymer may seem attractive from a perceived cost and efficiency perspective, especially when the OEM plans to conduct its own biocompatibility evaluations. In such cases, it can be easy to overlook the value of change control and notification for materials specifically designed for medical applications. Medical polymer materials from Lubrizol are under strict change management systems (MOC requirements).

In other cases, a non-medical grade polymer may have been used in a device for decades, as it was evaluated prior to the availability of medical grade materials, and the validation cost to the device maker to change materials is significant.

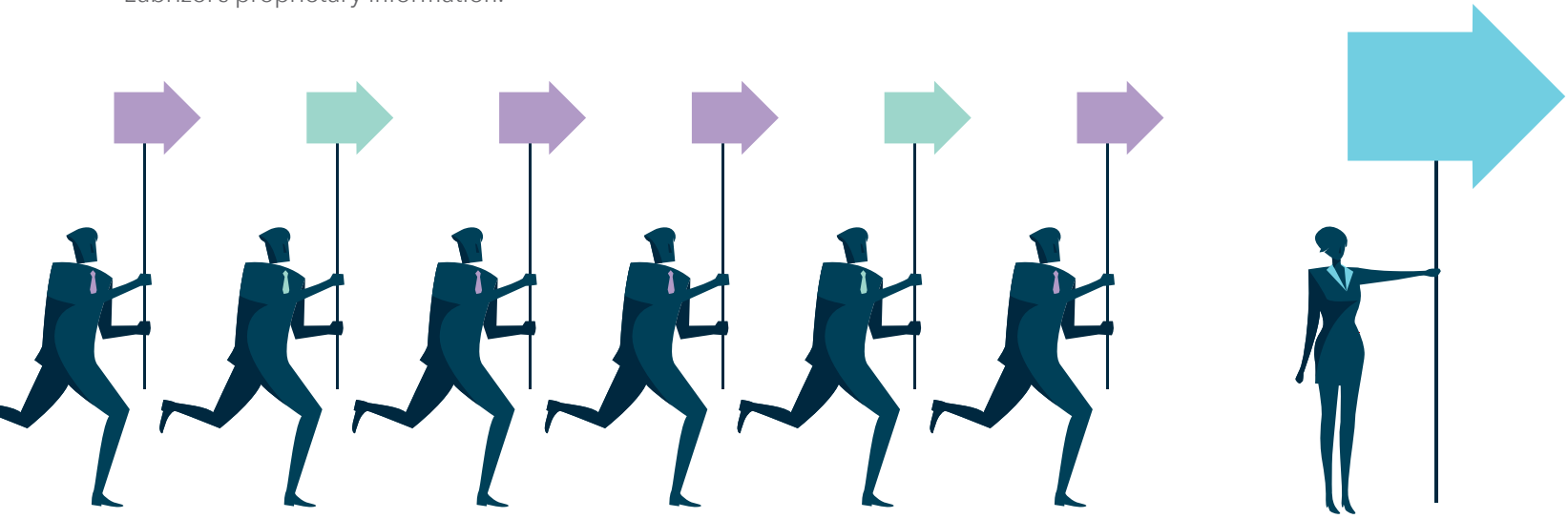
Often, however, any efficiencies accrued by selecting a non-medical grade polymer are more than negated when changes or discontinuations are made. Non-medical grade polymers are designed for applications that do not require evaluation of impact on biocompatibility and medical device regulatory and compliance status. These situations can leave OEMs in danger of getting stuck in a constant and costly re-validation loop without the benefit of supporting material biological and medical regulatory information.



ADDRESSING REGULATORY CHALLENGES

Lubrizol's team of product, regulatory and technical experts pride themselves on being proactive and readily available to help medical device OEMs navigate through the complex and challenging regulatory landscape and material selection needs as they arise. Some examples of our support are highlighted below.

- We closely monitor the EU's REACH Substances of Very High Concern list and proactively take steps to communicate potential product impact to avoid any surprises.
- When it is a matter of urgency, we will communicate directly with regulatory agencies to provide additional or supplemental information related to a device filing. In one recent case, an OEM was filing updates to their device to change the grade of Lubrizol's Thermoplastic Polyurethane (TPU) material. Their regulatory body unexpectedly requested additional clarification around the material manufacturing process that involved Lubrizol's proprietary information.
- When appropriate, we review the bench/lab and in-vitro analysis information for a device to provide guidance to the OEM on the interpretation of results. One customer had been working with a lab for the chemical and biological assessment for their device submission, including extractables and leachables. Unfortunately, the lab they selected was not experienced in testing devices that included TPUs, and our team of specialists were able to step in and provide the additional insight the customer needed to move along in the process.
- Recently, we were able to help a segment of device designers and manufacturers in a geographic region of the world through a broad, multi-year regulatory advocacy effort. Vascular device OEMs were facing a high level of regulatory scrutiny, causing delays around the use of TPU in specific infusion devices. We successfully educated the associated regulatory agency on the rigorous quality and manufacturing controls in place to make our medical grade materials. This allowed the OEMs to move forward because the regulatory agency then understood that the risk of adverse events was negligible.



ROBUST REGULATORY AND COMPLIANCE SUPPORT

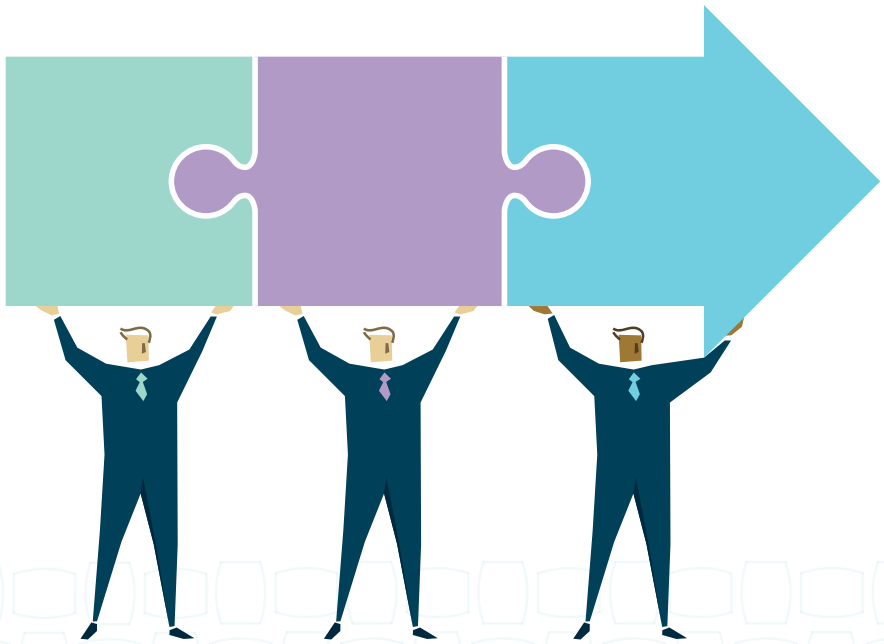
When it comes to selecting materials for development of a medical device, device makers have many options and factors to consider. With over 30 years of experience as a leading materials supplier to the healthcare industry, we understand the technical and regulatory support device makers need to select medical-grade polymers with confidence. At Lubrizol, the support begins in the early stages of device design and continues through the provision of MAFs to support your device submission and throughout the device's product lifecycle.

Our medical grade TPUs are specifically formulated for superior biostability, biocompatibility and processing versatility, and are utilized by global leaders throughout the industry. They are backed by a high level of quality control and regulatory support. We maintain comprehensive quality systems with manufacturing and quality record retention. Our manufacturing plants are ISO 9001 certified, with plant audits or audit packets available upon approval.

Our rigorous quality standards throughout the device development process help facilitate prompt regulatory approvals and, ultimately, help device OEMs achieve consistent product performance at the point of care. We have change-management processes in place to ensure that changes are not made to process, procedures or composition without review and approval by the key product design groups. If a change to a product composition, specification, manufacturing location, or other significant aspect is necessary, Lubrizol will provide notification prior to implementing the change, and documentation of the change will be provided as far in advance as possible. Every effort is made to ensure minimal impact of any change to the material end user or processor.

A 65-person corporate product safety and compliance group monitors regulatory and legislative developments across the globe. Our product stewards help translate the technical and legal information into meaningful guidance and put it into perspective. For example, here are some important trends we are monitoring on behalf of our customers:

BIOCOMPATIBILITY TESTING. The FDA has issued guidance related to material characterization in lieu of animal testing for biocompatibility. This may lead to increased requirements for understanding extractable/leachable profiles of widely used medical materials as well as how the profile may be impacted in a device manufacturing, assembly and sterilization process.



STERILIZATION METHODS. It is important to select a sterilization method which is compatible with the device's materials of construction, design, and packaging and does not negatively influence the device's ultimate safety or performance. For many medical devices, ethylene oxide (EtO) sterilization is the best choice to meet these demands. However, due to recent safety and environmental concerns around EtO sterilization, the FDA and others are actively seeking alternative sterilization methods and investigating their compatibility with existing medical device materials.

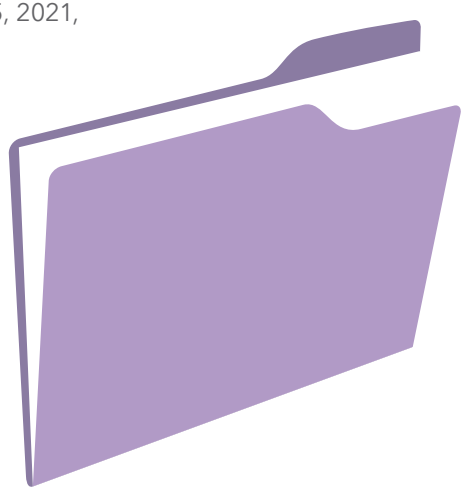
EU MDR. The European Union represents the second largest medical device market in the world after the United States. After four years in development and being postponed for a year due to the Covid-19 pandemic, the new EU MDR went into effect on May 26, 2021. One major change is in chemical compliance requirements for directly or indirectly invasive medical devices. To have your device certified for use in Europe, you not only need to be aware of all the chemicals in your device, but you may need to also ensure that these chemicals don't include even minuscule amounts of other base chemicals in their formulation. Europe is taking the lead in this area, but virtually every major country is increasing its scrutiny of low-level chemicals.

EU SVHC. The number of chemicals on the EU REACH SVHC list continues to grow. If a substance is added to SVHC candidate list, that does not mean it is banned. However, if the substance is further added to REACH authorization list, it cannot be placed on the EU market or used after a given date, unless an authorization is granted for its specific use, or the use is exempted from authorization. If a substance added to the candidate list is present in a material or product, suppliers are obliged to update the safety data sheet, communicate on safe use, and investigate alternative solutions (if present >0.1%). Effective January 5, 2021, manufacturers of articles entering EU Member States need to notify the European Chemicals Agency if the substance is present in those articles above a concentration of 0.1% (w/w).

On a routine basis, we continually update our safety data sheets as needed, and we proactively address frequently asked compliance-related product questions through Material Information Packages that we maintain on our TPU polymers. These documents are available to customers with pre-approval from your account manager.

For more information and to view additional resources on the regulatory process, visit our Regulatory Page.

To discuss a specific inquiry or project need, please contact us to get in touch with one of our regulatory experts.



WHY LUBRIZOL?

If you focus on development of novel and innovative medical devices, Lubrizol Life Science Health should be on your preferred provider list. We offer full finished medical device design, development and manufacturing – plus engineering, quality management, and regulatory and compliance support. But what truly makes us unique is our polymer chemistry and customization expertise. This total package of integrated technologies and capabilities is designed to provide truly differentiated solutions for medical device makers like you.

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