ETHICON
Johnson & Johnson SURGICAL TECHNOLOGIES

Guidelines for Medical Grade Material Definition

Part 2: Regulatory Compliance, Shipping and Logistics, End-User Disinfection, and Customer Expectations

Medical-Grade Materials Consortium (MGMC)

The first part of this white paper series described the genesis and evolution of an ongoing initiative to establish a comprehensive definition of medical-grade materials, with an emphasis on polymers used in four broad application categories:[1,2]

- Medical-grade materials
- Locked-down grade materials
- Pharmaceutical packaging materials
- Skin-contact grade materials

For each of these categories, the previous paper defined the properties and testing requirements for the types of ingredients, manufacturing, and quality assurance activities that would permit a material to be classified within a particular category. Although the four categories share many areas of testing and evaluation, particular requirements may vary from category to category, as appropriate for its applications.

Below, the second installment of this series continues the discussion by looking at how elements of regulatory compliance; shipping and logistics; end-user cleaning, disinfection, and sterilization; and customer expectations may interact to help shape usable definitions of medical-grade materials.

REGULATORY COMPLIANCE

The single trait that best defines and characterizes the global medical technology sector is the fact that it is regulated. Wherever in the world a medtech manufacturer may decide to design, develop, produce, or sell its products, it is sure to be subject to governmental and other regulations that govern nearly every aspect of the company's business.

Companies that supply raw materials or components to medtech manufacturers may not be directly subject to such regulations, but they are nevertheless constrained by contractual agreements that nearly always impose strict requirements for periodic reporting and vendor audits. Medtech manufacturers typically expect that their suppliers will provide testing and other data as needed to support regulatory submissions in the United States and around the world.

Establishing a uniform set of criteria for defining 'medical-grade' materials is an important step in helping manufacturers and regulators ensure that the materials used in manufacturing medical products meet their required specifications. When fully harmonized, such criteria will simplify the selection and use of appropriate materials across the globe (Figure 1).

In Part 1 of this white paper series MGMC identified a wide range of regulatory bodies and voluntary standards organizations whose operations bear directly on the task of defining what constitutes a medical-grade plastic. While many regulations and standards may apply broadly, others may have relevance only to specific medical applications. The sections below describe some of the key organizations and standards that apply to a definition of medical-grade plastics, with notes about how they may be used in real-world settings.

Aerospace Standard (AS) 9100 Certification.[3] AS 9100 (1999) is a widely adopted and harmonized quality management system for the aerospace industry developed by the Society of Automotive Engineers and the European Association of Aerospace Industries, and published by the International Aerospace Quality Group (IAQG). It is based on the internationally recognized ISO 9001 quality systems standard. While ISO 9001 calls for test reports and similar quality information to be provided by external providers of components, AS 9100 requires manufacturers to actually verify that information through their own testing, inspection, and audits.

Figure 1. There is currently no definition of what constitutes a medical-grade plastic. MGMC aims to change that. Image courtesy Dreamstime (ID 99742785) © Ekkamol Eksarunchai.

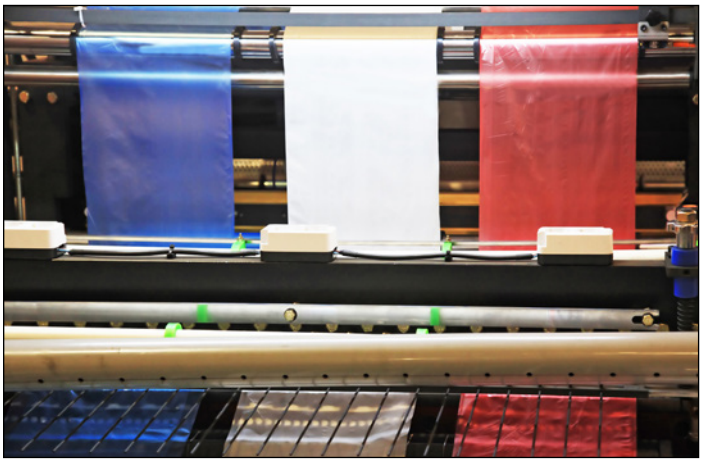


Figure 2. Polyethylene sheeting on its way to becoming plastic bags. Manufacturing of medical-grade plastics must be performed under rigorous quality control. Image courtesy Dreamstime (ID 138966817) © Stepan Popov.

MGMC recommends that certification to AS 9100 be considered among the additional standards used to monitor the manufacturing of medical-grade plastics and pharmaceutical packaging.

ASTM International. Online at www.astm.org. Originally known as the American Society for Testing and Materials, ASTM is now an international standards-writing organization that develops and publishes voluntary consensus technical standards for a wide range of materials, products, systems, and services. Mechanical properties and functional capabilities of medical-grade plastics may be measured according to ASTM criteria.

European Union (EU). The original schema for regulating health technologies in the EU was based on three directives that member nations were required to translate into national laws and regulations: the Medical Device Directive (MDD; 1994), the Active Implantable Medical Devices Directive (AIMDD; 1990), and the In Vitro Diagnostics Directive (IVDD; 1998). The MDD and AIMDD were due to be replaced by the EU Medical Device Regulation (MDR) by 2024. However, it has been proposed to extend these deadlines to December 2027 for implantable devices and to December 2028 for low-risk medical devices.[4] The IVDD was replaced by the In Vitro Diagnostics Regulation (IVDR; 2017) effective 26 May 2022.[5]

Companies operating in or selling into the EU are subject to new data reporting requirements under the EU Waste Framework Directive (WFD; 2008). Companies importing articles containing substances of very high concern (SVHCs) above the EU threshold have been required to submit data to the Substances of Concern in Products (SCIP) database since 5 January 2021.

International Organization for Standardization (ISO). Online at www.iso.org. An independent, nongovernmental organization that develops and publishes international standards in all technical and nontechnical fields other than electrical and electronic engineering. FDA recognizes many ISO standards that apply to health technologies, most notably the quality systems standard for medical devices (ISO 13485) which will soon replace FDA's quality systems regulation.

ISO 9001.[6] The oldest internationally recognized quality systems standard, ISO 9001 is the basis for both ISO 13485—the quality systems standard for medical devices—and FDA's Quality Systems Regulation. In modern medical device contracting, certification to the current version of this standard (ISO 9001:2015) is typically considered the minimum acceptable level of quality systems compliance. Vendors seeking to do business with medical device OEMs may be required to have certification to ISO 13485 (Figures 2,3).

ISO 10993.[7] The ISO standard on the biological evaluation of medical devices (ISO 10993) provides the internationally accepted criteria for demonstrating the biocompatibility of medical-grade materials and finished products (Table I). At a minimum, medical-grade materials, pharmaceutical packaging materials, and skin-contact grade materials should be evaluated using tests outlined in parts 5, 10, and 11, as described below. Depending on the clinical

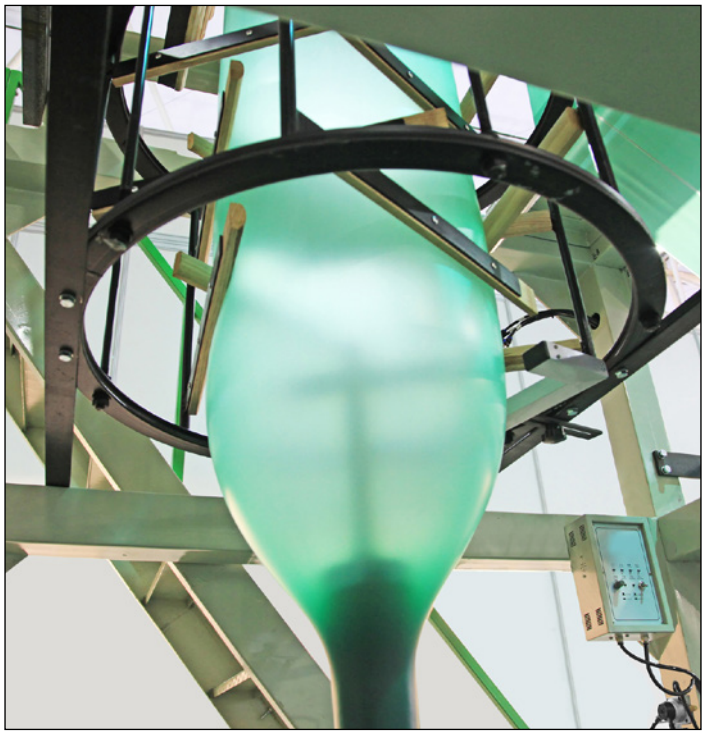


Figure 3. Blown extrusion of polyethylene for plastic bags. Image courtesy Dreamstime (ID 91210874) © Stepan Popov.

application of the finished product, testing as described under other sections of ISO 10993 may also be required.

- ISO 10993-5: In vitro cytotoxicity. This standard describes test methods to assess the in vitro cytotoxicity of medical devices. The methods specify the incubation of cultured cells in contact with a device and/or extracts of a device either directly or through diffusion. The methods are designed to determine the biological response of mammalian cells in vitro, using appropriate biological parameters.
- ISO 10993-10: Skin sensitization. This standard specifies the procedure for assessing medical devices and their constituent materials with regard to their potential to induce skin sensitization. The document includes details of in vivo skin sensitization test procedures and key factors for interpreting test results.
- ISO 10993-11: Tests for systemic toxicity. This standard specifies requirements and provides guidance on procedures to be followed in evaluating the potential for medical device materials to cause adverse systemic reactions.

ISO 10993 identifies the following as best practices for applying the standard to particular medical devices.

1. Identify device and surgical procedure
2. Categorize device and identify endpoints
3. Collect information
   a) Physical and chemical information
   b) Secondary processes/materials: life cycle, including packaging, cleaning/disinfection/sterilization, storage, etc.
   c) Particulate
   d) Review of literature, similar devices, and bench/clinical data
4. Identify gaps and open risks
5. Select endpoint testing
6. Perform testing
7. Assess final biological safety and any residual risks
8. Update regularly based on new evidence

ISO 13485.[8] The internationally recognized standard for quality management systems in medical device manufacturing, ISO 13485 is the standard that most medical device companies follow to

Part Number	Testing Topic
ISO 10993-1	Evaluation and testing in the risk management process
ISO 10993-2	Animal welfare requirements
ISO 10993-3	Genotoxicity, carcinogenicity, and reproductive and developmental toxicity
ISO 10993-4	Tests for interactions with blood
ISO 10993-5	In vitro cytotoxicity
ISO 10993-6	Tests for local effects after implantation
ISO 10993-7	Ethylene oxide sterilization residuals
ISO 10993-8	Selection and qualification of reference materials for biological tests
ISO 10993-9	Framework for identification and quantification of potential degradation products
ISO 10993-10	Skin sensitization
ISO 10993-11	Tests for systemic toxicity
ISO 10993-12	Sample preparation and reference materials
ISO 10993-13	Identification and quantification of degradation products from polymeric medical devices
ISO 10993-14	Identification and quantification of degradation products from ceramics
ISO 10993-15	Identification and quantification of degradation products from metals and alloys
ISO 10993-16	Toxicokinetic study design for degradation products and leachables
ISO 10993-17	Establishment of allowable limits for leachable substances
ISO 10993-18	Chemical characterization of materials
ISO 10993-19	Physicochemical, morphological, and topographical characterization of materials
ISO 10993-20	Principles and methods for immunotoxicology testing of medical devices
ISO 10993-22	Guidance on nanomaterials
ISO 10993-23	Tests for irritation

Table I. ISO 10993 is a 22-part standard that provides the internationally accepted criteria for demonstrating the biocompatibility of medical-grade materials and finished products.

Figure 4. Cleanroom molding of biomedical products—a common setting among medical product manufacturers. Image courtesy Dreamstime (ID 48273907) © Moreno Soppelsa.

satisfy their quality management requirements. FDA has announced plans to harmonize the current version of this standard (ISO 13485:2016) with its Quality System Regulation (21 CFR 820)—creating a new Quality Management System Regulation—but no date for implementation of this change has been assigned.

ISO 13485 can be used by organizations involved in one or more stages of the product life cycle, including design and development, production, storage and distribution, installation, or servicing of a medical device and design and development or provision of associated activities (eg, technical support). The standard can also be used by suppliers or external parties that provide product, including quality management system-related services to such organizations (Figure 4).

Requirements of ISO 13485:2016 are applicable to organizations regardless of their size and regardless of their type except where explicitly stated. Wherever requirements are specified as applying to medical devices, the requirements apply equally to associated services as supplied by the organization.

Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH) Regulation.[9] This EU legislation addresses the production and use of chemical substances and their potential impacts on both human health and the environment. The regulation divides substances into three lists that are typically updated every six months. Manufacturers—including medical device manufacturers—are required to reassess the compliance of their devices each time the lists are updated, and are expected to be no more than six months behind in their compliance with any applicable updates. The three lists encompassed by the regulation include the following:

- Substances of Very High Concern (SVHC) list. These are chemicals for which the harms to human health or the environment are thought to outweigh the benefits, but that haven't been fully assessed yet. Items on the SVHC list can be thought of as "in the queue" to possibly be in one of the next two lists while the European Chemicals Agency (ECHA) and the public make their cases for and against.
- Authorization list. These are chemicals known to be harmful to human health or the environment, but manufacturers can apply for authorization to use them anyway. A manufacturer must show that there are no safer alternatives, and it's better overall for the public to use that chemical for a certain application than not to be allowed to use it at all. All authorizations are application-specific and are posted publicly. Medical devices need not address REACH-driven risks to human health when applying for authorization (this is presumably because risks to human health must be considered as part of the medical device regulatory process anyway).
- Restricted list. These are chemicals known to be harmful to human health or the environment. The opposite of authorized, they are restricted for certain applications but are permissible for applications not addressed.[10]

Restriction of Hazardous Substances in Electrical and Electronic Equipment (RoHS) Directive.[11] This EU directive and related national laws restrict the use of certain hazardous substances in electrical and electronic equipment. Increasing use of such products has resulted in a growing volume of electrical and electronic waste. During the use, collection, treatment, and disposal of such waste, products may release harmful substances that can cause major environmental and health problems.

The RoHS Directive currently restricts the use of ten substances: bis(2-ethylhexyl) phthalate (DEHP), butyl benzyl phthalate (BBP), cadmium, dibutyl phthalate (DBP), diisobutyl phthalate (DIBP), hexavalent chromium, lead, mercury, polybrominated biphenyls (PBB), and polybrominated diphenyl ethers (PBDE).

In parallel, the Waste from Electrical and Electronic Equipment (WEEE) Directive promotes the collection and recycling of such equipment.[12]

U.S. Food and Drug Administration (FDA). Online at www.fda.gov. The regulatory agency for health technologies in the United States, FDA is widely admired and often considered the global gold

standard for health product and service regulation. Nevertheless, FDA does not have a uniform definition for what constitutes a medical-grade material (plastic or otherwise), but instead requires manufacturers to test materials for suitability in their proposed applications and settings. FDA has published more than 600 guidance documents, and accepts certifications to scores of national and international voluntary standards.

In the broadest terms, FDA regulations divide medical devices and diagnostics into three groups, based on whether they are substantially equivalent to predicate devices already on the market (Class I, Class II) or represent novel technologies (Class III). Class I and Class II devices may be cleared via the agency's premarket notification (510(k)) process. Class III devices must undergo more rigorous testing, and are approved via the agency's premarket approval (PMA) process. (International regulatory agencies also divide products into separate categories, but often use four classes instead of three).

Resins used in medical devices are often split in a similar way, according to the risk represented by their application: non-patient contacting materials; materials expected to be in patient contact for less than 24 hours; and materials intended for contact greater than 24 hours, including implantable devices.

Regulatory agencies typically care more about endpoint testing of finished devices than about testing of resins or components. However, there are exceptions to such agency interests, especially in the case of changes to a previously cleared or approved patient-contacting device, which may require testing of any new materials brought into play.

FDA recently released a guidance document on technical considerations for additive manufactured medical devices.[13] In addition to material controls—including chemical, mechanical, and biocompatibility properties of starter materials—the document initiates discussion regarding several aspects of the 3D-printing process used when manufacturing medical devices (Figure 5).

U.S. Pharmacopeial Convention (USP). Online at www.usp.org. Sets standards for food ingredients, dietary supplements, medicines, and medical materials. USP also tests medical-grade materials for conformity with ISO 10993, the international standard for biocompatibility and toxicity testing.

USP has designated six testing regimes for certifying the performance of plastics used in pharmaceutical and other applications. Each regime incorporates a set of tests for determining basic safety, together with guidelines on how to test and certify a material to a specific USP class. Class VI is the most rigorous of the regimes, and requires materials to undergo the following tests:

- Extract of sample in NaCl, systemic injection test in mouse (intravenous)
- Extract of sample in NaCl, intracutaneous test in rabbit
- Extract of sample in 1:20 solution of alcohol in NaCl, systemic injection test in mouse (intravenous)
- Extract of sample in 1:20 solution of alcohol in NaCl, intracutaneous test in rabbit
- Extract of sample in polyethylene glycol 400, systemic injection test in mouse (intraperitoneal)
- Extract of sample in polyethylene glycol 400, intracutaneous test in rabbit
- Extract of sample in vegetable oil, systemic injection test in mouse (intraperitoneal)
- Extract of sample in vegetable oil, intracutaneous test in rabbit
- Extract of sample in vegetable oil, systemic injection test in mouse (intraperitoneal)
- Extract of sample in vegetable oil, intracutaneous test in rabbit
- Implant strip of sample in rabbit
- Implant sample in rat

A material that has been granted Class VI certification is considered likely to produce favorable biocompatibility results.

USP 661.1 and USP 661.2.[14,15] USP has established analytical standards to ensure that polymer materials do not

Figure 5. FDA recently released a guidance document on technical considerations for additive-manufactured medical devices.[13] Here, the gantry with x-carriage and printhead of a fused deposition modeling (FDM) 3D printer producing white helical gears. Image courtesy Dreamstime (ID 241350887) © Roman Boettcher.

affect human health regardless of how or when those materials come into contact with a pharmaceutical product. Plastics may contain residues from the polymerization process or additives of concern such as antioxidants, stabilizers, lubricants, plasticizers, and colorants. To assess the safety of plastics used in pharmaceutical applications, in-depth analytical investigations are required.[16]

In 2016, USP expanded its testing standards for Plastic Packaging Systems and Their Materials of Construction (USP 661) to identify analytical methods that would further support package safety testing. The new sections specify test methods for Plastic Materials of Construction (USP 661.1) and Plastic Packaging Systems for Pharmaceutical Use (USP 661.2). Both standards are set to become official on 1 December 2025, but early adoption is encouraged.

USP 661.1 introduces standards and testing to demonstrate that the polymer raw material is well-characterized and suitable for its intended use. Testing includes:

- Identification and characterization tests (infrared spectroscopy, differential scanning calorimetry)
- Physicochemical tests (water extraction, UV absorbance, acidity/alkalinity using indicators, total organic carbon)
- Biological testing for high-risk applications (per USP 87)
- Material-specific tests for plastic additives or related substances

USP 661.2 provides analytical methods for testing plastic packaging components and systems used for packaging final drug products. Testing includes:

- Physicochemical tests (water extraction, appearance [color, clarity of extraction], UV absorbance, acidity/alkalinity using indicators, total organic carbon)
- Biological testing for high-risk applications (per USP 87)
- Spectral transmission if light protection is necessary
- Two additional tests for PET and PETG
- Chemical suitability assessment (extractables per USP 1663, leachables per USP 1664)

MGMC recommends that testing according to USP 661.1 and USP 661.2 be adopted as appropriate for medical-grade plastics used in pharmaceutical packaging applications, recognizing that USP 661.1 is currently limited in scope as material chemistries such as polyether ether ketone (PEEK) are not included.

For cases where a material has previously been tested to the USP 661 standard, USP does not require testing to the new USP 661.1 standard. Nevertheless, other regulatory bodies may require recertification according to the revised test methods.

SHIPPING AND LOGISTICS

Arrangements for the packaging, labeling, handling, transport, and storage of medical-grade plastics should be subjected to risk assessment, and appropriate mitigations should be developed to protect the materials from all anticipated hazards. Raw material suppliers and their manufacturer clients should adopt practices to protect medical-grade plastics from being mixed or contaminated with other materials and substances during transport and filling processes.

Shipping and logistics requirements for medical-grade plastics should be regularly communicated to all personnel who carry out any aspect of such operations. MGMC agrees with VDI recommendations that:

- Personnel who are employed in the packaging, storage, and transport of MGPs are to undergo regular training on the stated requirements of MGPs—especially in relation to the possible risks of contamination.
- This training should also address contamination prevention pertaining to equipment that comes into direct contact with the MGP or that is to prevent contact between the MGP and the environment, as well as handling of this equipment.
- Such training should take place at regular intervals, but at least every three years. This requirement for training applies equally to contractors who are employed in these fields.
- Every effort should also be made to ensure that transport companies (logistics partners) and their members of staff receive regular training on the stated requirements of MGPs.[17]

Packaging and Labeling. Raw material suppliers of medical-grade plastics should carry out packaging operations in a controlled environment that will protect the materials from contaminants and harmful environmental conditions (eg, extremes of temperature, humidity, or light exposure). To reduce the potential for exposure to contaminants, automated filling and packaging systems are preferable to manual operations.

Incomplete or improper labeling of medical-grade plastics during storage or transport can result in confusion over what materials are being selected for delivery and use in product manufacturing. VDI recommends that raw material suppliers and their manufacturer clients should frame an agreement about required labeling as part of their quality assurance agreement.[17] MGMC recommends that labeling for medical-grade plastics include the following information, at a minimum.

From:
Supplier name and address
Supplier product number
Supplier lot number
Other identifying information (eg, color)

To:

Manufacturer name and address

Manufacturer part number

Manufacturer purchase order number

Each quantity to be shipped or placed in storage should also be accompanied by paperwork that defines the material and grade of the shipment, including:

Supplier name, product number, lot number

Manufacturer name, product number, specification number

Certificate of Analysis

Safety Data Sheet

Handling. Raw materials suppliers and manufacturers should avoid all unnecessary handling of medical-grade plastics, including decanting the materials or changing their packaging or containers. When it is necessary to handle medical-grade plastics, operators should ensure that the working environment is clean and free of contaminants, and that all equipment has been thoroughly cleaned before use. MGMC agrees with VDI recommendations that:

- Any decanting or changes to packaging are to be documented for each batch within the scope of quality assurance.
- Potential risks of contamination must be checked, and the client must be informed of any concerns if the client requests individual packaging or transport solutions (eg, delivery in an octabin as special packaging for an MGP).
- It is at the discretion of the manufacturer of an MGP to decline the request for special packaging in the event of an increased risk of contamination or to demand a countersignature for a corresponding legal disclaimer when the client's request for packaging is fulfilled.[17]

Storage. The shelf life of medical-grade plastics depends on the formulation of the materials, their packaging, and the conditions under which they are stored. Compromised storage conditions can cause materials to undergo blooming, degradation, and other instabilities, making them unsuitable for use. Storage of medical-grade plastics by the supplier and manufacturer should seek to minimize adverse environmental effects from variations in temperature, exposure to sunlight or ultraviolet light, humidity, and so on.

Suppliers of medical-grade plastics should be prepared to offer informed recommendations and information about the conditions and duration of storage permitted for a particular product. To encourage compliance with such recommendations, they may be included in contractual agreements between raw materials suppliers and finished product manufacturers. Suppliers should not be held responsible for damage to raw materials resulting from inadequate downstream storage conditions.

MGMC agrees with VDI recommendations that:

- Raw materials suppliers must identify any materials that require storage in a temperature-controlled environment, and must provide validated parameters for such storage.
- Bagged goods and other forms of packed loose goods must only be stored in clean, roofed, and closed storage depots.
- Storage in outdoor areas is permitted in exceptional cases, after a corresponding risk assessment.
- Relevant measures for pest control must be in place.
- Relevant and safe cleaning measures must be established and documented for the different forms of storage.[17]

Transport and Logistics. Medical-grade plastics should only be transported under controlled conditions designed to prevent adverse mechanical, thermal, chemical, or other events that could affect the properties of the materials.

To ensure that medical-grade resin pellets are not contaminated during transport, MGMC recommends that box liners be used for all materials to be shipped. Wooden pallets used during transportation should not be chemically treated.

END-USER CLEANING, DISINFECTION, STERILIZATION

Before they are distributed to healthcare professionals for use in patient procedures, most medical devices undergo some form of terminal sterilization. Commonly used methods include exposure to ethylene oxide (EtO), gamma radiation, or steam, but a variety of other chemistries are also employed. The U.S. Environmental Protection Agency has recently proposed rigorous rules for the continued use of EtO sterilization in medical applications, leading to industry concern that some terminal sterilization suppliers may be forced to cease operations.[18–21]

Some agents used in terminal sterilization may be suitable for products made entirely of metal, but wholly unsuitable when applied to products that have plastic components. Exposure to plasma chemistries, radiation, or high heat can cause some plastics to deteriorate rapidly, making their devices unusable for patient applications.

Reusable devices add an extra level of complexity, as they require healthcare professionals to undertake specific steps to clean, disinfect, and sterilize the devices before they can be used for the next patient. Materials used in such devices may be expected to withstand hundreds of cycles of sterilization via ethylene oxide (EtO), gamma radiation, or steam autoclaving. Hospital settings typically do not lend themselves to the use of all terminal sterilization technologies, so the methods employed for sterilization in clinical settings may be less effective against

microbial contamination (Table II).

To ensure that medical-grade plastics can undergo both terminal sterilization and reprocessing as intended, raw material suppliers should be prepared to offer study data demonstrating the compatibility of their materials with common cleaning, disinfecting, and sterilizing agents and related protocols. Where particular agents are known to cause adverse effects on a plastic, suppliers should make certain to advise their manufacturer customers of such limitations.[21]

In their turn, manufacturers must also conduct testing to validate the use of recommended cleaning, disinfecting, and sterilizing agents on their finished products. Such testing should inform the manufacturer's instructions for use, which are used to guide cleaning, disinfecting, and sterilization operations in clinical settings.

The American Institute for Ultrasound in Medicine (AIUM) has recently updated its guidelines on the cleaning and disinfection of ultrasound transducers, noting that many disinfecting chemicals now in use can cause device malfunctions and incorrect patient diagnoses. The institute encourages ultrasound practitioners to follow the manufacturer instructions for use with regard to cleaning and disinfection—making it critically important that manufacturers provide fully validated information.[22,23]

Although medical device manufacturers are required to validate their selection of materials and to test finished products for biocompatibility in their intended applications, FDA does not currently require manufacturers to demonstrate compatibility with particular methods for cleaning, disinfection, or sterilization. The Healthcare Surfaces Institute has recently undertaken development of a credentialing program that will enable raw material suppliers and finished device manufacturers to certify the compatibility of their products with certain disinfectants. Rollout of the program is expected in 2023.[24]

CUSTOMER EXPECTATIONS

In many industries, raw material suppliers are not expected to provide very much in the way of sales support. Materials that are treated as commodities rarely require detailed characterization or instructions for use, and the suppliers of such materials are typically not prepared to provide such information.

But that is hardly the case for healthcare products, whose manufacturers expect their suppliers to provide a wide range of information and ongoing support. Manufacturers of medical-grade plastics should expect to be asked for any or all of the following:

- Business support, including
  - o Use of a standard medical/healthcare approval form defined by contract, or the harmonized questionnaire developed by MGMC (Figure 6).
  - o Notice of change (NOC) for formulation discontinuity, with 24-month notice and options for last-time buys.
- Support for laboratory testing, including the results of testing for
  - o Animal-derived materials that may act as endocrine-disrupting

Name	Composition/Action
Chlorine dioxide	Inorganic chemical compound (ClO_2) Antimicrobial (an oxidizing biocide that deactivates microorganisms by penetrating their cell walls, disrupting the transport of nutrients across the cell wall by inhibiting protein synthesis)
Glutaraldehyde	Organic compound ($CH_2(CH_2CHO)_2$) Antimicrobial (induces cell death by cross-linking cellular proteins; usually used alone or mixed with formaldehyde)
Hibidil	Chlorhexidine gluconate ($C_{22}H_{30}Cl_2N_{10}$) Antiseptic
Hydrogen peroxide	Inorganic compound (H_2O_2) Antiseptic and antibacterial (a very strong oxidizer with oxidation potential of 1.8 V)
Hypochlorite/ hypochlorous acid	Inorganic compound ($HClO$) Antimicrobial (myeloperoxidase-mediated peroxidation of chloride ions)
Ortho-phthalaldehyde	Organic compound ($C_6H_4(CHO)_2$) Antimicrobial (strong binding to outer cell wall of contaminant organisms)
Peracetic acid	Organic compound (CH_3CO_3H) Antimicrobial (high oxidation potential)
Phenol/phenolate	Organic compound (C_6H_5OH) Antimicrobial

Table II. FDA-listed sterilants and high-level disinfectants.[26,27]

compounds.
- o Certificate of analysis following WHO Annex 4 or MGMC harmonized certificate (Figure 7).[25]
- o ISO 10993, parts 5, 10, and 11.
- o USP Class VI.

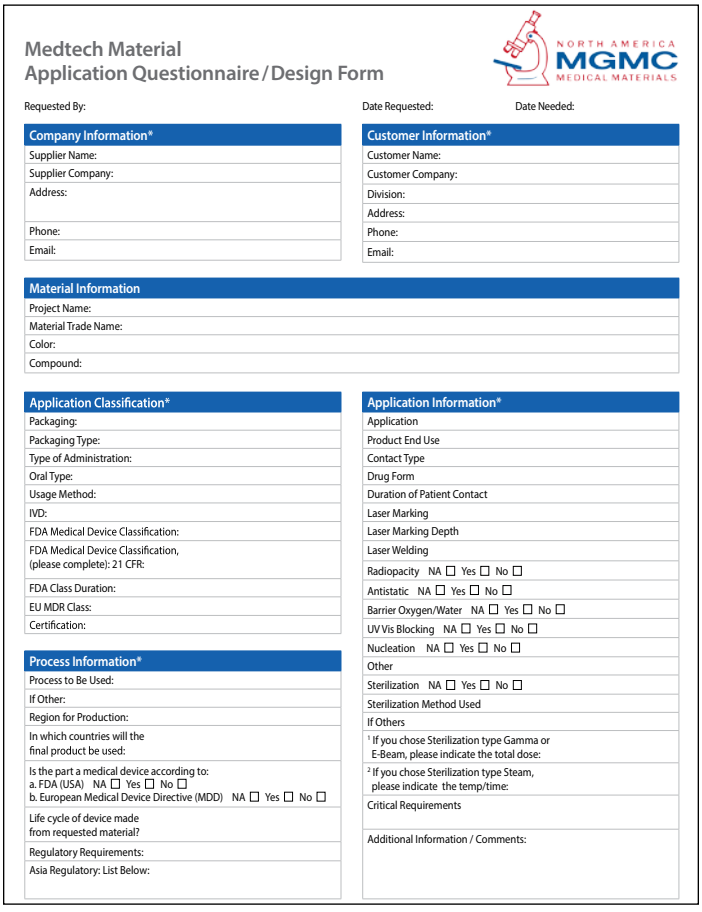
• Regulatory affairs support, including
- o Data to support instructions for cleaning, disinfection, and sterilization.
- o Mitigation of quality systems risk.
- o Mitigation of risk in supply chain.
- o Quality systems investigative support (eg, CAPA).
- o Use of color additives (per 21 CFR 73 or 74).

CONCLUSION

Considering the many government bodies and voluntary standards organizations relevant to the regulation of materials used in medical products, it is understandable that no unified definition of medical-grade plastics has previously been attempted. Efforts to create such a definition now offer hope for simplified selection and application of such materials worldwide. Nevertheless, evolving regulations are a moving target, and it should not be expected that a harmonized definition will be easy to achieve.

Although raw material suppliers may play an important role in helping to define what constitutes a medical-grade plastic, finished device manufacturers will likely remain responsible for ensuring the biological safety of their devices. But having a validated menu of medical-grade plastics will provide manufacturers with confidence that their devices will pass biocompatibility testing following ISO 10993 or other standards.

This new approach will prevent labeling surprises by reducing the unknown factors related to the selection of materials for healthcare applications. Careful selection and application of medical-grade materials will minimize potential use of chemicals that could be carcinogenic, mutagenic, or reprotoxic (CMRs), or endocrine-disrupting compounds (EDCs).



Medtech Material
Application Questionnaire / Design Form

NORTH AMERICA MGMC MEDICAL MATERIALS

Requested By: Date Requested: Date Needed:

Company Information*
Supplier Name:
Supplier Company:
Address:
Phone:
Email:

Customer Information*
Customer Name:
Customer Company:
Division:
Address:
Phone:
Email:

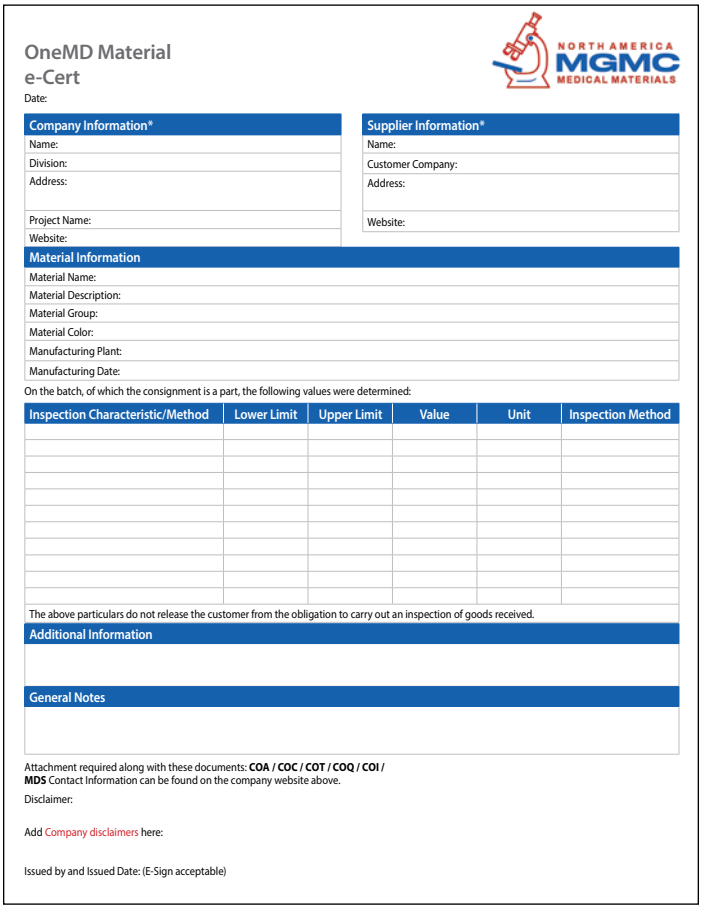
Material Information
Project Name:
Material Trade Name:
Color:
Compound:

Application Classification*
Packaging:
Packaging Type:
Type of Administration:
Oral Type:
Usage Method:
IVD:
FDA Medical Device Classification:
FDA Medical Device Classification, (please complete): 21 CFR:
FDA Class Duration:
EU MDR Class:
Certification:

Application Information*
Application
Product End Use
Contact Type
Drug Form
Duration of Patient Contact
Laser Marking
Laser Marking Depth
Laser Welding
Radiopacity NA ☐ Yes ☐ No ☐
Antistatic NA ☐ Yes ☐ No ☐
Barrier Oxygen/Water NA ☐ Yes ☐ No ☐
UV Vis Blocking NA ☐ Yes ☐ No ☐
Nucleation NA ☐ Yes ☐ No ☐
Other
Sterilization NA ☐ Yes ☐ No ☐
Sterilization Method Used
If Others
[1] If you chose Sterilization type Gamma or E-Beam, please indicate the total dose:
[2] If you chose Sterilization type Steam, please indicate the temp/time:
Critical Requirements
Additional Information / Comments:

Process Information*
Process to Be Used:
If Other:
Region for Production:
In which countries will the final product be used:
Is the part a medical device according to: a. FDA (USA) NA ☐ Yes ☐ No ☐ b. European Medical Device Directive (MDD) NA ☐ Yes ☐ No ☐
Life cycle of device made from requested material?
Regulatory Requirements:
Asia Regulatory: List Below:

Figure 6. A harmonized medical/healthcare materials questionnaire developed by MGMC (available online at www.namgmc.org/tools).



OneMD Material
e-Cert

NORTH AMERICA MGMC MEDICAL MATERIALS

Date:

Company Information*
Name:
Division:
Address:
Project Name:
Website:

Supplier Information*
Name:
Customer Company:
Address:
Website:

Material Information
Material Name:
Material Description:
Material Group:
Material Color:
Manufacturing Plant:
Manufacturing Date:

On the batch, of which the consignment is a part, the following values were determined:

Inspection Characteristic/Method	Lower Limit	Upper Limit	Value	Unit	Inspection Method

The above particulars do not release the customer from the obligation to carry out an inspection of goods received.

Additional Information

General Notes

Attachment required along with these documents: **COA / COC / COT / COQ / COI / MDS** Contact Information can be found on the company website above.

Disclaimer:

Add Company disclaimers here:

Issued by and Issued Date: (E-Sign acceptable)

Figure 7. A harmonized certificate of analysis developed by MGMC (available online at www.namgma.org/tools).

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Next Up . . .

In August 2023, the Medical-Grade Plastics Consortium (MGMC) will hold a mini-conference to discuss the issues raised in parts 1 and 2 of this white paper series, together with the recommendations of the 2019 draft standard compiled by the association of German engineers (Verein Deutscher Ingenieure). It is expected that this discussion will lead in the direction of a harmonized set of guidelines to define the elements that constitute a medical-grade material, including their ingredients, manufacturing processes, and required quality assurance activities.