Guideline for the Classification of Medical-Grade Polymers Used in Nonimplantable Applications

The next step toward an international standard begins with this review of previous publications for defining what constitutes a medical-grade material

Medical-Grade Materials Consortium

This document follows the path of recent publications by the Association of German Engineers (Verein Deutscher Ingenieure; VDI) and the North America Medical-Grade Materials Consortium (MGMC). The goal of those publications was to develop a consolidated guideline for defining what constitutes a medical-grade material.[1–3]

VDI guidelines emphasize compliance with a European regulatory regime, while MGMC's approach is closer to the requirements of the U.S. Food and Drug Administration (FDA). Where these differences in approach result in corresponding differences in recommendations or requirements, full harmonization may be difficult to achieve.

The purpose of this document is to formalize a preliminary review of the three previous publications and create a consolidated document with built-in regional differences that can serve as a soft guideline for immediate adoption, permitting materials suppliers to conduct business as approved in other regional markets (Figure 1).

TERMS AND DEFINITIONS

The VDI guidelines offer terms and definitions to assist regional users in interpreting and applying the recommendations of the document.[4] The selection of terms and definitions is geared toward the European market, with citations to European regulations or international standards. Many of the definitions are accompanied by notes that help to interpret or explain their practical use. The list of terms is divided into three groups: general information, materials, and participants (Table I).

According to VDI, the party that distributes a medical device is responsible for adherence to the relevant regulatory provisions.[5] This statement makes sense, because VDI's definitions treat the terms 'manufacturer' and 'distributor' as equivalent, which is the norm in the European Union. In the United States, however, distributors are often separate corporate entities that have no involvement in the design, manufacture, packaging, or labeling of particular products; their sole responsibility is to fulfill product orders by arranging for their distribution as required. FDA defines the terms 'manufacturer' (twice) and 'distributor' as follows:

> **Manufacturer** means any person who designs, manufactures, fabricates, assembles, or processes a finished device. Manufacturer includes but is not limited to those who perform the functions of contract sterilization, installation, relabeling, remanufacturing, repacking, or specification development, and initial distributors of foreign entities performing these functions.[6]
>
> **Manufacturer** means any person who manufactures, prepares, propagates, compounds, assembles, or processes a device by chemical, physical, biological, or other procedure. The term includes any person who either:
>
> (1) Repackages or otherwise changes the container, wrapper, or labeling of a device in furtherance of the distribution of the device from the original place of manufacture;
>
> (2) Initiates specifications for devices that are manufactured by a second party for subsequent distribution by the person initiating the specifications;
>
> (3) Manufactures components or accessories that are devices that are ready to be used and are intended to be commercially distributed and intended to be used as is, or are processed by a licensed practitioner or other qualified person to meet the needs of a particular patient; or
>
> (4) Is the U.S. agent of a foreign manufacturer.[7]
>
> **Distributor** means any person (other than the manufacturer or importer) who furthers the marketing of a device from the original place of manufacture to the person who makes final delivery or sale to the ultimate user, but who does not repackage or otherwise change the container, wrapper, or labeling of the device or device package. If you repackage or otherwise change the container, wrapper, or labeling, you are considered a manufacturer as defined in this section.[8]

The terms 'client,' 'end-user,' and 'supplier'—all of which are defined in the VDI guidelines—have no defined equivalent in the U.S. Federal Food, Drug, and Cosmetic Act.

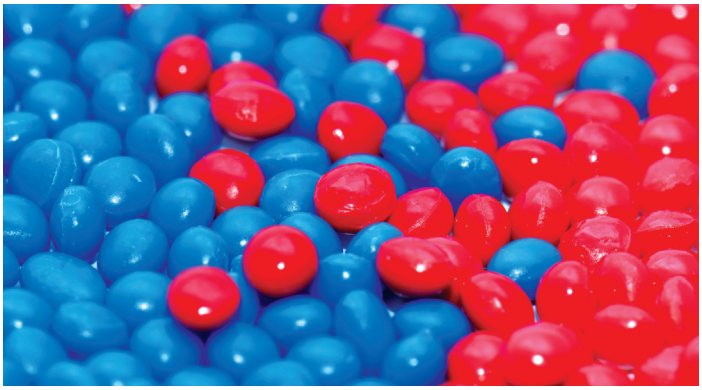


Figure 1. Following the lead of VDI and MGMC, this document serves as a soft guideline, permitting materials suppliers to conduct business across a variety of regional markets. Image courtesy Dreamstime (ID 35363447) © Xxlphoto.

REGULATORY REQUIREMENTS

Medical product manufacturers are subject to governmental and other regulations that influence nearly every aspect of their 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 (Figure 2).

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. Manufacturers may adopt sections of this document as a guideline for the selection and use of appropriate materials across the globe.

VDI's discussion of regulatory requirements for medical-grade plastics (MGPs) is rooted in European Union practices, including the use of voluntary standards and conformity assessments. This approach may be different for other non-EU regulatory authorities.

VDI's guidelines cite a wide variety of regulatory sources that may apply to the manufacture of medical devices and in vitro diagnostics (IVDs), and include general information about regulatory compliance in a European Union context.[9] VDI specifies that "medical devices, including IVDs and primary pharmaceutical packaging . . . must be assessed by the manufacturer with regard to conformity for the dedicated application."[10] Manufacturer testing recommended by VDI—and applicable across the EU and other regional markets—include the following:

- Biocompatibility testing "in accordance with the relevant sections in the DIN EN ISO 10993 series of standards or USP 87/88 (USP Plastics Class VI)."
- Tests relating to chemical requirements, "such as permissible limits for metal ions, which are laid down in the relevant product standard."
- Tests relating to the requirement for sterilization of the product (e.g., resistance to radiation, ethylene oxide, or steam sterilization).
- Physical and technical tests that arise from client requirements or are stipulated by the relevant product standard.
- Testing on the extraction and migration behavior of plastics used in pharmaceutical packaging, in accordance with the Guideline on Plastic Immediate Packaging Materials, published by the European Medicines Agency.
- Tests conducted in accordance with requirements of the European Pharmacopoeia or U.S. Pharmacopeia.
- Conformity assessments for materials that come into contact with foods.

Figure 2. Medtech manufacturers expect that their suppliers will provide testing and other data as needed to support regulatory submissions. Image courtesy Dreamstime (ID 321278153) © Yuri Arcurs.

General Information	
Combination product	Pharmaceutical packaging
In vitro diagnostics (IVDs)	Primary packaging
Medical device	Quality assurance agreement
Materials	
Blend (polymer blend)	Polymer
Compound (compounding)	Raw material
Elastomer	Thermoplastic
Macromolecule	Thermoplastic elastomer (TPE)
Masterbatch	Thermoset (duromer, duroplast)
Plastic	
Participants	
Client	Manufacturer (distributor)
Converter	Supplier
End-user (consumer)	

Table I. List of terms defined in the VDI guidelines.[4]

VDI also recommends the production and use of a drug master file (DMF), which is "a collection of information, including on the formulation, on properties and structure, on the manufacture, suppliers, and quality control."[11]

This master data collection is compiled by the manufacturer of the MGP and filed with the regulatory authorities, more specifically with the FDA for the North American market, and is updated at regular intervals. The authority uses it for authorization purposes, it is confidential, shared only between the manufacturer and the authority, and may not be accessed by third parties.[11]

VDI's guidelines include notes for conformity assessment of materials that come into contact with foods, which are outside MGMC's scope.

For its part, MGMC identifies 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 (Table II).[12] While many regulations and standards may apply broadly, others may have relevance only to specific medical applications. MGMC's discussion describes some of the key organizations and standards that apply to the definition of medical-grade plastics, with notes about how they may be used in real-world settings.[12]

MGMC's recommendations include an option for materials suppliers to submit regulatory information directly to various regulatory authorities, or to submit information for a targeted market region by way of the device manufacturer's regulatory affairs organization.

CONSISTENCY OF FORMULATIONS

VDI's guideline describes an approach whereby suppliers may assess materials, and manufacturers must assess finished products, for conformity with regulatory and customer requirements.[13] Examples of common testing include all of the biocompatibility, chemical, physical, and technical tests recommended by VDI (see above, Regulatory Requirements).

When it comes to consistency of formulations, VDI states that raw materials suppliers must define and assess the consistency of their materials' primary and secondary components, including supplier sources.[14] VDI defines primary components as:

> constituents that make up the basic matrix of the MGP and are usually present in the overall matrix at a mass fraction in the multi-digit percentage range.[15]

By contrast, secondary components are:

> added to modify the formulation, to adjust a desired property in a targeted fashion. A secondary component is usually present in the overall formulation at a mass fraction in the single-digit percentage range, or less.[15]

Additionally, the materials supplier should document characteristics of their materials and inform manufacturers of changes.[16] The following elements should be documented:

- Composition of the formulation, listing primary and secondary components, with their contents and tolerances.
- Sources and specifications for the components.
- Technical data sheet for the formulation and inspection certificate.
- Description of the process and the critical parameters for ensuring the product properties.
- Naming of the production site.
- Information about the test methods used to characterize the material.
- Data associated with production controls related to consistency of the formulation.
- Assessment of formulation consistency, taking into account the properties of the formulation.

In furtherance of the above recommendations, MGMC defines specific ingredients requirements that apply, with variations, to medical-grade, pharmaceutical packaging grade, and skin-contact grade materials.[17] MGMC also lists requirements for locked-down grade materials, which differ slightly from the requirements for medical-grade materials. Key requirements identified by MGMC include the following:

- Materials suppliers must establish and issue policies on the ingredients of medical-grade materials and pharmaceutical packaging grade materials. No equivalent requirement applies to skin-contact grade materials.
- Suppliers of medical-grade and pharmaceutical packaging grade materials must offer single-source base materials; any substitution requires customer notification. Suppliers of skin-contact grade materials can change the source of their base materials if the new material meets biocompatibility requirements and the change does not affect product performance.
- Suppliers of medical-grade and pharmaceutical packaging grade materials must offer single-source additives and

Aerospace Standard (AS) 9100 Certification
ASTM International (www.astm.org)
European Union (EU)
- EU In Vitro Diagnostics Regulation (IVDR)
- EU Medical Device Regulation (MDR)
- EU Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH) Regulation
- EU Restriction of Hazardous Substances in Electrical and Electronic Equipment (RoHS) Directive
- EU Substances of Concern in Products (SCIP) database
- EU Substances of Very High Concern (SVHC) list
- EU Waste Framework Directive (WFD)
- EU Waste from Electrical and Electronic Equipment (WEEE) Directive

International Organization for Standardization (www.iso.org)
- ISO 9001
- ISO 10993
- ISO 13485

U.S. Food and Drug Administration (www.fda.gov)
- FDA Quality Management System Regulation

U.S. Pharmacopeial Convention (www.usp.org)
- USP Class VI Certification
- USP Test Methods for Plastic Materials of Construction (USP 661.1)
- USP Test Methods for Plastic Packaging Systems for Pharmaceutical Use (USP 661.2)

Table II. List of agencies, voluntary standards organizations, and schemes for regulating the development, production, and distribution of medical products, as described by MGMC.[12]

colorants; any substitution requires customer notification. No equivalent requirement applies to skin-contact grade materials.

- Suppliers of medical-grade and pharmaceutical packaging grade materials must offer polymer and colorant formulas free of animal-derived components (ADCs). No equivalent restriction on ADCs applies to skin-contact grade materials.
- Suppliers of medical-grade, pharmaceutical packaging grade, and skin-contact grade materials must offer polymer and colorant formulas free of latex.
- Suppliers of medical-grade materials should avoid formulas that include substances deemed carcinogenic, mutagenic, or toxic for reproduction (CMR 1A and 1B substances) and endocrine-disrupting chemicals (EDCs). No equivalent requirement applies to pharmaceutical packaging grade or skin-contact grade materials.
- Suppliers of medical-grade, pharmaceutical packaging grade, and skin-contact grade materials must offer formulas free of heavy metal chemistries.
- Suppliers of medical-grade and skin-contact grade materials must define specifications and ranges for the following properties; medical grade is typically narrower than industrial grade; skin-contact grade is typically similar to industrial grade. No equivalent requirement applies to pharmaceutical packaging grade materials.
    - Black specks
    - Clarity
    - Customization options
    - Pellet size control
    - Viscosity
    - Yellow index
- Suppliers of medical-grade, pharmaceutical packaging grade, and skin-contact grade materials must conduct analytical testing for purity control of each lot or unit of delivery, as appropriate.
- Biocompatibility of medical-grade, pharmaceutical packaging grade, and skin-contact grade materials must be demonstrated via testing to ISO 10993 (sections 5, 10, 11, 23 required; other sections as appropriate) or USP Class VI.
- Pharmaceutical packaging grade materials must comply with USP standards 661.1 and 661.2. No equivalent requirement applies to medical-grade and skin-contact grade materials.
- Medical-grade, pharmaceutical packaging grade, and skin-contact grade polymers and additives (e.g., fillers, pigments) must comply with FDA and EU requirements. No equivalent requirement applies to locked-down grade materials.
- Medical-grade, pharmaceutical packaging grade, and skin-contact grade polymers and additives (e.g., fillers, pigments) must comply with the EU REACH regulation and RoHS directive.

Figure 3. Suppliers should ensure that their materials meet the specifications necessary for onward manufacturing with equipment such as this extruder. Image courtesy Dreamstime (ID 198034404) © Forance.

MANUFACTURING PROCESSES

In its definition of 'medical-grade plastics,' VDI notes that such materials must comply with minimum requirements, including "specific quality management regarding the development, production, and handling of MGPs."[18]

Additionally, VDI's discussion includes several recommendations about the materials manufacturing process, with an emphasis on the potential for inconsistencies when changes in the sites or methods of processing are implemented. Key points in VDI's discussion include the following:

- The plants used in the manufacture of the formulation must be clearly defined within the scope of consistency of the formulation.[19]
- The use of different production plants for the manufacture of the formulation is only possible if this has no effect on the final properties of the formulation.[19]
- A change in the manufacturing process or the supplier of the raw material can "result in a significant change to the properties of the formulation for the polymer, and must be equated to a change in the formulation."[19]

MGMC's publications include limited comments focused on the manufacturing processes for medical-grade materials. Key points from MGMC's publications include the following:

- Suppliers of medical-grade, pharmaceutical packaging grade, and skin-contact grade materials must comply with FDA requirements.[20]
- Suppliers of medical-grade, pharmaceutical packaging grade, and skin-contact grade materials must perform process validation and provide documentation at the correct level (1–4).[20]
- Where applicable, suppliers of medical-grade, pharmaceutical packaging grade, and skin-contact grade

materials should comply with 21 CFR Ch. 1, Sub. C, Part 211, current good manufacturing practices, at levels 1 and 2 (quality manual, company policies).[20]

- Suppliers of medical-grade and pharmaceutical packaging grade materials should consider requirements for the following additional manufacturing criteria (Figure 3). No such recommendation applies to suppliers of skin-contact grade materials.
    - AS 9100 certification
    - Batch or lot traceability
    - Cleanroom validation
    - Machine parameter validation
    - Regrind control
    - Retain control and traceability
    - Routine audits
    - Routine healthcare inspections
    - Screw cleaning[20]

SECURITY OF SUPPLY

VDI's guidelines include a distinct section dedicated to security of supply.[21] Key points in this section include the following:

- Materials suppliers should create a plan for ensuring material supply in the case of emergencies or unplanned losses. Potential measures may include operation of an additional production plant, maintenance of safety stocks, or other alternatives.[22]
- Materials suppliers should account for their material's shelf life when creating a plan for ensuring material supply in the case of emergencies or unplanned losses.[23]
- Materials suppliers must guarantee availability of their materials for an agreed term (typically 2 years) after a notification of change.[21]

In MGMC's view, recommendations for notifications to manufacturer-clients, supplier notifications of change, handling

Figure 4. Raw material suppliers and their manufacturer-clients should adopt practices to protect medical-grade plastics from being contaminated during transport and filling processes. Image courtesy Dreamstime (ID 261335522) © Jerd Nakata.

of last order calls, and exceptions due to technical or regulatory limitations are all mandatory requirements. MGMC's publications offer the following specifics:

- Suppliers of medical-grade and pharmaceutical packaging grade materials must offer long-term supply assurance without change of formulation (formulation lock). Suppliers of skin-contact grade materials are not required to offer long-term supply assurance without change of formulation.[20]
- Suppliers of medical-grade, pharmaceutical packaging grade, and skin-contact grade materials must establish and issue a policy on shelf life for their materials.[24]
- Contracts with suppliers of medical-grade and pharmaceutical packaging grade materials must include an agreed term for advance notification of formulation change (e.g., 2 years). Contracts with suppliers of skin-contact grade materials are not required to include an agreed term for advance notification of formulation change.[20]

CHANGE MANAGEMENT

In its section defining 'medical-grade plastics,' VDI lists change management as the first of several areas where compliance with "specific minimum requirements" is necessary for a material to be considered medical grade.[18] VDI's definition states that medical-grade plastics must satisfy such requirements in relation to

> rigorous change management with regard to potential planned changes in the materials specification or composition, the manufacturing site, as well as the manufacturing technology and changes in regulatory status.[18]

In its section on security of supply, VDI states that materials suppliers must guarantee availability of their materials for an agreed term (typically 2 years) after a notification of change.[21] VDI adds further information about the notification of change as part of its section on the consistency of formulations, noting that:

- Raw materials suppliers must notify manufacturers of any changes to the formulation of their materials, unless the changes have no discernible effects.[14]
- A change in the manufacturing process can "result in a significant change to the properties of the formulation for the polymer, and must be equated to a change in the formulation."[19]
- Raw materials suppliers must assess the effects of changes in production facilities or manufacturing methods, and notify the manufacturer.[19]
- To assess the effects of changes in components or manufacturing processes on their materials, raw materials suppliers should consider the following:
    - Biocompatibility (cytotoxicity, extractable and leachable substances)
    - Chemical properties (resistance, solubility)
    - Mechanical properties (elasticity, rigidity, creep properties, impact properties)

- Morphological properties (structure and homogenization, capacity for crystallization, degree of branching)
- Optical properties (transparency, color)
- Processing properties (viscosity, gelation, shrinkage, granulate form)
- Thermal properties (heat distortion resistance)[25]

After providing information about change management in its earlier sections on defining medical-grade plastics, security of supply, and consistency of formulations, VDI's guidelines include a further section dedicated entirely to change management.[26] Key points in this section include the following:

- The materials supplier must establish a change management process within its quality management system.[27] The process must document changes to the following:
  - Changes affecting the consistency of the material's formulation, components, or manufacturing process
  - Changes affecting security of supply
  - Changes that pertain to declarations of conformity in the drug master file, in relation to pharmacopeial representations, or in stating compliance with the REACH regulations or RoHS Directive
- The material supplier's change management process must cover the following points:[28]
  - Supplier assessment of the effects of changes on the material
  - An information chain to ensure that change requests from the supplier are conveyed to all relevant organizations, and ultimately to the finished product manufacturer; information should include a timetable for planned changes, and available alternatives
  - Information for the manufacturer about the effects of changes on the material, and how to distinguish new and old materials during all transition phases
  - Manufacturer assessment of the effects of the planned change, with approval of timing

MGMC's white papers offer direction related to change management in several sections of its criteria for medical-grade, pharmaceutical packaging grade, and skin-contact grade materials.

- Under the heading of ingredients, MGMC writes that supplier change management for medical-grade, pharmaceutical packaging grade, and skin-contact grade materials must follow current good manufacturing practices (cGMPs).[20]
- Also under the heading of ingredients, MGMC writes that contracts with the suppliers of medical-grade and pharmaceutical packaging grade materials must include an agreed term for advance notification of formulation change (e.g., 2 years). Suppliers of skin-contact grade materials are not required to include an agreed term for advance notification of formulation change.[20]
- Under the heading of manufacturing processes, MGMC writes that the suppliers of medical-grade and pharmaceutical packaging grade materials must offer the option of single-location manufacturing (location lock), with advance notification of change required. Suppliers of skin-contact grade materials are required to offer advance notification of change only if the site change affects product performance.[20]

PACKAGING, STORAGE, AND LOGISTICS

VDI's guidelines include an extensive discussion of issues related to packaging, storage, and logistics concerns for medical-grade plastics.[29] MGMC has previously assessed VDI's comments, and has published a summary of the areas of agreement and disagreement on these topics.[30] That discussion is substantially reproduced here as a basis for further consideration.

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 (Figure 4). Raw material suppliers and their manufacturer-clients should adopt practices to protect medical-grade plastics from being mixed with or contaminated by 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

Figure 5. Plastic pallets used during transportation of raw materials. When wooden pallets are used, they should not be chemically treated. Image courtesy Dreamstime (ID 150567487) © Artinun Prekmoung.

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.[31]

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 (e.g., 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.[32] MGMC recommends that labeling for medical-grade plastics include the following information, at a minimum.[33]

From:
Supplier name and address
Supplier product number
Supplier lot number
Other identifying information (e.g., 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 (e.g., 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.[34]

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.

Figure 6. Device manufacturers are responsible for validating their products to the cleaning, disinfection, and sterilization methods dictated by their bill of materials. Here, a steam autoclave. Image courtesy Dreamstime (ID 169613542) © Yury Tabolin.

- 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.[35]

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 (Figure 5).

END-USER CLEANING, DISINFECTION, STERILIZATION

In several passages, VDI's guidelines acknowledge the need for testing to validate terminal sterilization methods used to treat medical devices before they are distributed to healthcare professionals for use in patient procedures. VDI states that manufacturers are responsible for conducting "tests relating to the requirement for sterilization of the product, e.g. resistance to radiation, ethylene oxide, or steam sterilization."[10]

When assessing the biocompatibility of a material, manufacturers should be aware that "the biocompatibility may change again due to processing or sterilization."[36] Consequently, "risk assessment is to be carried out by the manufacturer on subsequent processing methods," including sterilization processes."[37] Device manufacturers are responsible for validating their products to the cleaning, disinfection, and sterilization methods dictated by their bill of materials, as appropriate to the type of device (Figure 6).

MGMC offers a detailed discussion on end-user cleaning, disinfection, and sterilization.[38] Portions of that discussion are reproduced here to provide a basis for further consideration.

MGMC states that 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 III).[39,40]

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.

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 III. FDA-listed sterilants and high-level disinfectants.[39,40]

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.

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.[41]

SUPPLIER-CLIENT RELATIONSHIPS

To ensure a successful relationship between materials suppliers and their device manufacturer-clients, VDI advises that material specifications and related working arrangements must be coordinated in advance.

> These agreements cover all information relevant to the client on the properties of the MGP, including the required documents and tests that are to be guaranteed by the supplier.[42]

In its section on the client-supplier relationship, VDI offers the following examples of such agreements:

- A quality assurance agreement.
- Technical specifications for the material.
- Declarations of conformity.
- Test certificates (test reports and certificates of compliance, inspection certificates) in accordance with DIN EN 10204.
- Agreements on transport, logistics, and packaging.
- Risk assessment on the use of the MGP in the product.

MGMC's take on supplier-client relationships focuses especially on the obligations that suppliers have to provide detailed characterization of the materials they sell, as well as ongoing support for business and regulatory requirements.[43] According to MGMC, the use of supplier-client contracts or nondisclosure agreements may be required for transparent data exchange and submission for product registration.[44] Manufacturers of medical-grade plastics should expect to be asked for any or all of the following:

- Business support, including
  - Use of a standard medical/healthcare approval form defined by contract, or the harmonized questionnaire developed by MGMC (Figure 7).
  - Notice of change (NOC) for formulation discontinuity, with 2-year notice and options for last-time buys.
- Support for laboratory testing, including the results of testing for
  - Animal-derived materials that may act as endocrine-disrupting compounds.
  - Certificate of analysis following WHO Annex 4 or MGMC harmonized certificate (Figure 8).[44]
  - ISO 10993, parts 5, 10, 11, and 23.
  - USP Class VI.
- Regulatory affairs support, including
  - Data to support instructions for cleaning, disinfection, and sterilization.
  - Mitigation of quality systems risk.
  - Mitigation of risk in supply chain.
  - Quality systems investigative support (e.g., CAPA).
  - Use of color additives (per 21 CFR 73 or 74).

QUALITY MANAGEMENT SYSTEMS

In its definition of 'medical-grade plastics' VDI observes that "a common characteristic of MGPs is compliance with specific minimum requirements" in relation to:

- Rigorous change management for a product's materials, manufacturing site, and manufacturing technology.
- Specific quality management for the development, production, and handling of materials.
- Guarantees for security of supply and logistics requirements.
- Support for fulfilling the manufacturer's binding regulatory requirements.[18]

Notable in this section of the VDI guidelines is the assertion that the development, production, and handling of MGPs are subject to specific quality management requirements.

Similarly, this section of the VDI guidelines states that MGPs must meet minimum requirements for "support when fulfilling the manufacturer's binding regulatory specifications, such as tests for contact with foods or biocompatibility."[18]

VDI writes that "the quality assurance agreement shall contain information and arrangements on the essential points" described in its standard, including:

- Information on the formulation for the MGP.
- Information on the manufacturing process.
- Agreements on the consistency of the formulation and the manufacturing process.
- Arrangements and agreements on the security of supply.
- Agreements on the change management process.[42]

In addition to these required elements, VDI writes that a quality assurance agreement may be extended to include other elements, such as:

- Declarations of conformity arising from regulatory requirements.
- Additional agreements on packaging, storage, and logistics.
- The supplier risk assessment.
- Agreements on the scope of incoming goods inspections.

VDI's commentary implies that suppliers and manufacturers should establish and maintain a quality management system at their

designated locations. Materials suppliers are required to provide support as needed to address quality-related issues at any point in the development of finished products. The following passage conveys VDI's approach to quality issues:

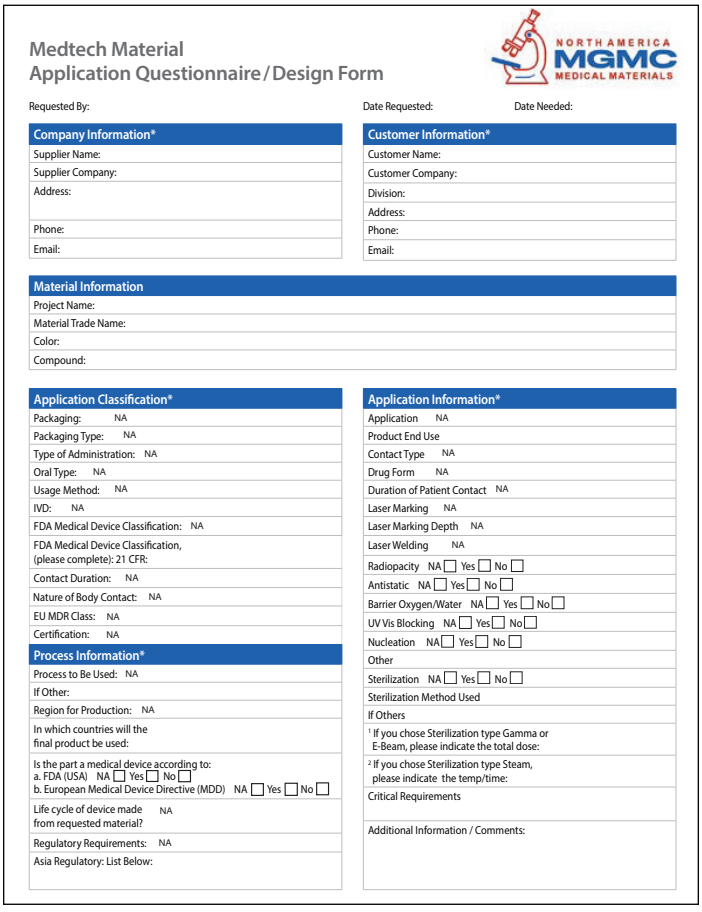
> The conformity assessment is ultimately carried out on the final product by the manufacturer. However, the manufacturer or supplier of MGPs can already conduct tests on the material that relate to the conformity assessment. The knowledge that, over the course of their processing into final products, plastics will be subject to further thermal, mechanical, and radiation stresses that can affect the properties of the plastic … constitutes an aid to the manufacturer when evaluating the material with reference to its suitability and use in a product.[45]

In short, VDI's approach recommends that suppliers may usefully assess materials for conformity with regulatory and customer requirements, but that manufacturers bear the ultimate responsibility for assessing the conformity of finished products with those requirements.

In its publications, MGMC is only slightly more direct in its discussion of quality management systems requirements. Under the heading of 'manufacturing processes,' MGMC states that the supplier is required to maintain a quality management system (QMS), and that clear notification of change (NOC) is required for both medical devices and pharmaceutical-grade packaging. For skin-contact devices, those requirements apply "only if the change affects product performance."[20]

FDA currently requires that device manufacturers comply with the agency's quality system regulation (QSR). However, the agency recently published a new rule to replace the QSR with a harmonized version of ISO 13485—renamed as the quality management system regulation (QMSR)—and manufacturers will be required to comply with this new regulation by 2 February 2026.[46,47]

While FDA does not require materials suppliers to establish or maintain a quality management system, MGMC advises that vendors seeking to market materials as medical-grade or pharmaceutical packaging grade should have such a system in place. In its section on manufacturing processes, MGMC advises that certification to ISO 9001 is the minimum requirement for a quality system, and that suppliers with quality systems certified to ISO 13485 should be granted preferred status. Suppliers of skin contact grade materials must comply with FDA current good manufacturing practices (cGMPs); certification to ISO 13485 is not required.[20]



Medtech Material
Application Questionnaire / Design Form

NORTH AMERICA MGMC MEDICAL MATERIALS

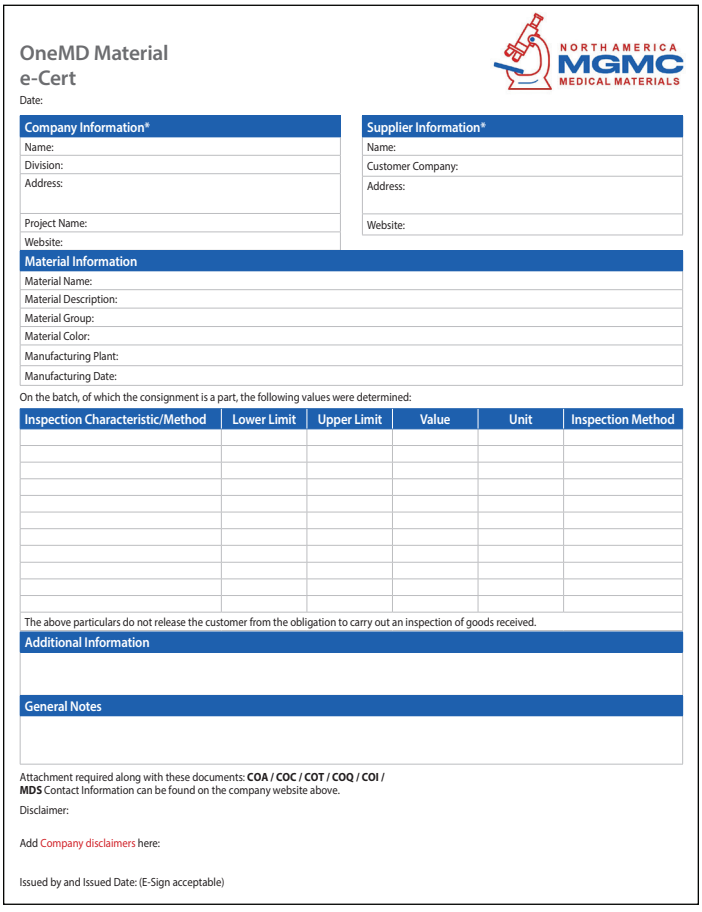
Requested By: Date Requested: Date Needed:

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

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

Application Classification*	Application Information*
Packaging: NA	Application NA
Packaging Type: NA	Product End Use
Type of Administration: NA	Contact Type NA
Oral Type: NA	Drug Form NA
Usage Method: NA	Duration of Patient Contact NA
IVD: NA	Laser Marking NA
FDA Medical Device Classification: NA	Laser Marking Depth NA
FDA Medical Device Classification, (please complete): 21 CFR:	Laser Welding NA
Contact Duration: NA	Radiopacity NA ☐ Yes ☐ No ☐
Nature of Body Contact: NA	Antistatic NA ☐ Yes ☐ No ☐
EU MDR Class: NA	Barrier Oxygen/Water NA ☐ Yes ☐ No ☐
Certification: NA	UV Vis Blocking NA ☐ Yes ☐ No ☐
Process Information*	Nucleation NA ☐ Yes ☐ No ☐
Process to Be Used: NA	Other
If Other:	Sterilization NA ☐ Yes ☐ No ☐
Region for Production: NA	Sterilization Method Used
In which countries will the final product be used:	If Others
Is the part a medical device according to: a. FDA (USA) NA ☐ Yes ☐ No ☐ b. European Medical Device Directive (MDD) NA ☐ Yes ☐ No ☐	[1] If you chose Sterilization type Gamma or E-Beam, please indicate the total dose:
Life cycle of device made from requested material? NA	[2] If you chose Sterilization type Steam, please indicate the temp/time:
Regulatory Requirements: NA	Critical Requirements
Asia Regulatory: List Below:	Additional Information / Comments:

Figure 7. 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*	Supplier Information*
Name:	Name:
Division:	Customer Company:
Address:	Address:
Project Name:	Website:
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 8. A harmonized certificate of analysis developed by MGMC (available online at www.namgmc.org/tools).

In its list of quality assurance requirements, MGMC includes five items that may have implications for a supplier seeking to meet quality management system requirements:

- Suppliers of medical-grade, pharmaceutical packaging grade, and skin-contact grade materials (but not locked-down grade materials) must use product design methods compliant with the EU Medical Device Regulation (MDR).
- On request, suppliers must disclose additives and residual chemicals present in polymers.
- Suppliers must issue certificates of analysis (COAs) for testing performed according to accepted test regimes (e.g., ASTM, EUP, ISO, USP).
- On request, suppliers must issue letters of support for a material's regulatory compliance, including EU voluntary declarations of conformity.
- Suppliers with certification to ISO 13485 should be granted preferred status. For suppliers of skin contact grade materials, certification to ISO 13485 is not required.[20]

CONCLUSION

This proposed guideline provides information to align the expectations of materials suppliers and their clients—specifically medical device OEMs—with regard to the essential requirements for polymers used in the manufacture of nonimplantable medical devices, in vitro diagnostics, and pharmaceutical packaging.

Establishing a universally adopted standard for defining medical-grade materials will strengthen compliance, improve quality and safety, and enhance transparency regarding the ingredients in medical products.

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5. VDI, p3.
6. 21 CFR 820.3(o).
7. 21 CFR 803.3(l).
8. 21 CFR 803.3(e).
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13. VDI, pp11, 12, 32, 33.
14. VDI, p15.
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19. VDI, p16.
20. MGMC1v2, pp5, 6, 7.
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