ETHICON
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Guidelines for Defining Medical-Grade Materials

Part 1: What Is a Medical-Grade Material?

Medical-Grade Materials Consortium

The numerous and varied criteria that have traditionally been used to define medical-grade materials are somewhat confusing and ambiguous, depending largely on the defining source and how that source relates to a specific aspect or role in the global healthcare sector. Nevertheless, the medical device industry, regulatory agencies, and standards-writing organizations often rely on such ambiguous definitions of medical-grade materials as the foundation and critical components for creating their own policies, procedures, and standards.

Such standards are critical for optimizing patient care, but as they currently exist there is little continuity or agreement among them. Basically, each organization uses a definition derived by consensus, interpretation, or manufacturing convenience. This absence of a single, universal definition for medical-grade materials has resulted in an array of ambiguous standards, subjecting patients to unknown and possibly lethal risks. The need to identify such potential risks has created a critical demand for defining what constitutes a medical-grade material in order to create a foundation for compliance in the selection and use of such materials.

It is absolutely imperative that the resulting definition be applied unilaterally and universally among companies and standards organizations across all international borders. For example, the definition should inform the reports of companies operating in or selling into the European Union (EU), where new data reporting requirements have recently been established under the EU waste framework directive.[1] Similarly, companies importing into the EU articles containing substances of very high concern (SVHCs) above the EU threshold must submit data to the new substances of concern in products (SCIP) database by the 5 January 2021 deadline.[2] Companies should also apply the definition when considering how to comply with the voluntary standards and regulations of relevant national and international agencies, including the American Society for Testing and Materials (ASTM International), the EU, the European Pharmacopoeia (EUP), FDA, the International Organization for Standardization (ISO), and the United States Pharmacopeial Convention (USP).

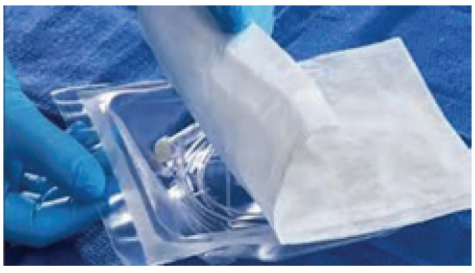
MEDICAL-GRADE CRITERIA

The acceptability of specific materials for medical device applications is typically determined not by testing individual ingredients but by bench and bedside testing of finished products. Such testing is intended to take into account the effects of all relevant manufacturing processes, including every step from equipment qualification through packaging, sterilization, and distribution.

When testing a medical device for biocompatibility, manufacturers should also consider the effects of materials compatibility, environmental factors, handling and storage, use-related requirements such as cleaning and disinfection, and any other characteristics that might affect the device at any time during the product life cycle. Specific requirements for biocompatibility testing are determined in part by the nature and duration of the product's contact with different tissue types. For most national and international device regulatory systems, the testing requirements explained in ISO 10993-1 are considered a good starting point.[3]

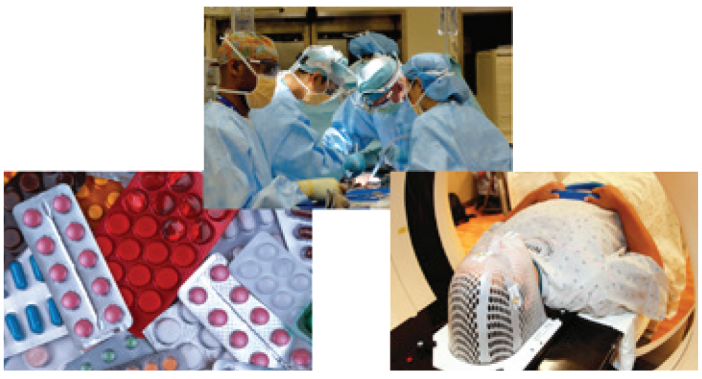
In a 2018 blog post, "Everything You Need to Know about Medical-Grade Materials," a leading manufacturer of medical-grade elastomeric O-rings and seals lists biocompatibility as one of the most important criteria when choosing materials for a medical application.[4] Biocompatibility means that the material must not react harmfully with other materials and must be biologically compatible with living tissue. The authoring company's medical-grade elastomers are designed to exhibit strong chemical resistance, excellent heat resistance, and low permeability to gas. The company tests its medical-grade materials to ISO 10993, the internationally accepted standard for biocompatibility.[3] Additionally, the company's medical-grade components are tested and evaluated following USP standards for food ingredients, dietary supplements, medicines, and medical materials.[5] Based on these criteria, the company certifies its materials as safe and durable for any medical application.

In another recent blog post, "What Makes a Material Medical Grade?," a leading contract design and manufacturing organization focuses on devices implanted into the body, noting that in the United States such products are regulated by the FDA Center for Devices and Radiological Health.[6] FDA requirements for demonstrating patient safety drive the careful selection of additives such as plasticizers and antioxidants, as



well as the adoption of manufacturing processes that minimize potentially harmful polymerization residues. Like the previously discussed blog post, this post emphasizes the importance of biocompatibility testing to meet applicable ISO 10993 or USP requirements, but adds that voluntary consensus standards developed by ASTM International may also be considered relevant. The post also goes beyond biocompatibility to list toughness, transparency, sterility, transportability, and flexibility as desirable attributes for plastics used in medical settings.

In a 2018 article in *Medical Plastics News*, "Defining the Standard for Medical-Grade Polymers," a specialty medical polymer distributor observes that in spite of all the regulations, qualifications, certifications, and long-term testing regimes that apply to medical devices, the device industry has yet to answer the seemingly simple question of what constitutes a medical-grade polymer.[7] The article suggests that some motion toward resolving this question is now under way, as the Association of German Engineers (VDI), has undertaken the task of defining a standard for medical-grade polymers. A first draft of the standard was presented at a VDI symposium in 2018, and a reviewable German and English draft was published earlier this year.[8]



These and many other publications demonstrate that the term 'medical-grade material' is far from clearly defined or universally understood. Adding to the confusion, raw materials suppliers frequently seek to differentiate their medical-grade offerings through the use of distinctive brand or category names, including care grade, dental grade, implant grade, healthcare grade, medical grade, medical technology grade, pharmaceutical grade, and many other terms.

A U.S. INITIATIVE TO DEFINE MEDICAL-GRADE MATERIALS

Plastics designated as 'medical grade' are used in the manufacture of many types of medical devices and equipment. They are usually selected on the basis of characteristics and capabilities that make them especially suited to applications where patient safety is involved.

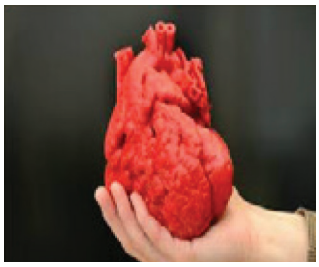
Notable characteristics that lend themselves to performance criteria include biocompatibility, chemical properties, color/pigment/filler additives, mechanical and physical properties, surface properties, and stability in finished device applications. For some medical applications, materials must withstand hundreds of sterilization cycles—typically using ethylene oxide, gamma radiation, or steam autoclaving—without degradation.

A Call to Action. The fact that it is necessary to reference the guidelines and regulations of multiple national and international agencies and organizations when classifying a material, process, or finished device as 'medical grade' illustrates the importance of establishing a comprehensive, universal definition of this term. To further this goal, Ethicon (a member of the Johnson & Johnson family of companies) issued a call to action at the 2017 Medical Design & Manufacturing Conference & Exposition in New York

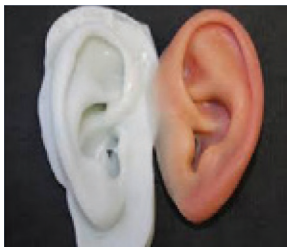
City. This call led to creation of the North America Medical-Grade Materials Consortium (NAMGMC) and an initial conference hosted by Ethicon in August 2019. A summary of the conference was released in November 2019.[9]

Participants in the 2019 conference included polymer suppliers, compounders, color and master batchers, makers of 3D printing materials, distributors, and a leading silicone manufacturer. Attendees set a deadline of November 2019 for creating a draft of industry guidelines to define medical-grade materials, with a goal of March 2020 for circulating a prerelease draft for review.

In discussions at the conference, participants noted that component suppliers and finished device manufacturers often market their products as suitable for medical applications based solely on the assumption that using materials claimed to be 'medical grade' results in a product that is safe for medical uses. But manufacturing and packaging processes can expose such 'medical-grade' materials to lubricants, release agents, natural rubber latex gloves, and other variables that can reduce their suitability for medical applications. Such considerations led conference participants to suggest that it may be necessary to require compliance with an established quality assurance protocol, which may include cleaning and additional analysis of finished products.



Participants at the 2019 conference were aware of the efforts of the Association of German Engineers (VDI) to publish a draft standard for medical-grade plastics.[8] It was noted that while the German efforts were similar to the U.S. initiative, the two were not identical, as NAMGMC's work would include relevant adhesives, cellulosic materials, colorants, composites, elastomers, fluoropolymers, inks, lubricants, masterbatches, silicones, thermoplastics, and thermosets. Examples of materials outside the scope of the NAMGMC initiative include ceramics, chemicals, finished components, metals, solvents, and spun-bonded polyolefin.



Mold Release Agents and Lubricants. The 2019 conference did not specifically address criteria related to mold release agents or device lubricants. Nevertheless, attendee comments made it clear that such agents would be required to meet certain agreed-upon requirements if used in the production of 'medical-grade' components or finished medical devices. Lubricants intended to remain on or within a finished product—such as agents used to improve ease-of-use for devices used in hospital environments—must also meet requirements for medical applications (see Sidebars 1 and 2).

Additionally, even when manufactured with qualified materials and processes, components and finished devices that have been painted or labeled may require subsequent cleaning and inspection to ensure that potentially harmful residues are thoroughly removed and have not been absorbed in any way. If not removed, such residues can compromise the performance of both components and finished products.

Additive Manufacturing. Often called 'three-dimensional (3D) printing,' additive manufacturing has rapidly penetrated the medical device industry, enabling manufacturers to create novel products with unique composition, structure, and customizability. The fabrication processes for 3D-printed components and finished medical devices pose unique challenges for meeting regulatory requirements. At present, academic researchers and manufacturing consortiums around the world follow a variety of different procedures when developing 3D-printed products intended for medical applications.

FDA recently released a guidance document on technical considerations for additive-manufactured medical devices.[10] In addition to requiring material controls—including controls on the chemical, mechanical, and biocompatibility properties of starter materials—the guidance initiates discussion of several key issues encountered when using 3D printing to manufacture medical

A Biocompatible Mold Release Agent

Specifically for the manufacture of silicone rubber products used in medical applications, Chem-Trend has developed a new biocompatible release agent. Mono-Coat 1989W is especially well suited for the molding of products such as medical tubes, protective caps, and closures. The semipermanent, water-based release agent is certified in accordance with the USP Class VI panel of tests, and is therefore suited for use in the medical rubber molding industry. [Adapted from *Medical Plastics News*.[11]]

Mold Release Agents for Medical Applications

Products used in the medical industry need to be formed correctly with as little flawing in their surface and functionality as possible. Since the medical device industry uses a high amount of polymer material for the production of lifesaving tools and devices, device manufacturers also require mold release agents for proper forming and release. Plastic and rubber are staple materials for laboratory and medical use because they have high versatility. [Adapted from W.N. Shaw and Co.[12]]

devices. To ensure that 3D printed output is comparable to parts produced using traditional molding processes, 3D printable substrates must adhere to the product's approved stoichiometry—effectively, the proportions of component raw materials used to create the printable polymer. Both starter materials and additives must satisfy any criteria necessary to qualify the 3D-printed item as suitable for medical applications. And the finished device must meet all regulatory requirements and applicable quality system standards.

Conference Outcomes. Attendees at the 2019 conference determined that the scope of their initiative should focus on defining the basic criteria for medical-grade, locked-down grade, pharmaceutical packaging grade, and skin-contact grade materials. Nonmedical and implant-grade materials were specifically excluded from the scope of the initiative.

Conference attendees further agreed that their initiative to define medical and related material grades should target most of the common types of medical applications, including the following.

- Drug delivery systems
- Imaging systems (eg, CT, MRI, PET, and x-ray scanners)
- In vitro diagnostics and related tools
- Medical devices
- Pharmaceutical packaging
- Robotic surgery instruments and consoles

To communicate the outcomes of the conference, attendees recommended the compilation of one or more white papers describing the following elements to be included in the definition of medical and related material grades.

- Ingredients (eg, colorants, pigments, polymers, solvents)
- Manufacturing processes
- Quality assurance
- Regulatory compliance
- Shipping and logistics
- Customer expectations

The initial working groups of the 2019 conference focused on the first three of these elements, leaving the criteria for regulatory compliance, shipping and logistics, and customer expectations to be considered at a future conference. At the conclusion of the conference, the working groups approved a comprehensive list of criteria to be evaluated as part of the definition of medical-grade materials. With modifications as necessary, it was determined that this list could be used as the basis for preparing criteria applicable to each of the focus areas adopted by the conference attendees.

The sections below present the list of criteria compiled by the initial conference working groups, covering the criteria that should be considered for the ingredients, manufacturing, and quality assurance of medical and related material grades.

PROPOSED CRITERIA FOR MEDICAL-GRADE AND LOCKED-DOWN GRADE MATERIALS

Following the recommendations of the 2019 NAMGMC conference, the lists below cover the criteria that should be considered for the ingredients, manufacturing, and quality assurance of medical-grade and locked-down grade materials. The criteria for these two grades are similar, but items marked with an asterisk (*) are not required for locked-down grade materials.

Ingredients

a. Supplier to establish and issue policies for medical-grade materials.

b. Supplier to establish and issue policy on shelf life for medical-grade materials.

c. Polymer and colorant formulas free of animal-derived components (ADCs).

d. Formula should avoid substances deemed carcinogenic, mutagenic, or toxic for reproduction (CMR 1A and 1B substances) and endocrine-disrupting chemicals (EDCs).

e. Formula free of heavy metal chemistries.

f. Polymer and colorant formulas free of latex.

g. Define specifications and ranges for the following properties; medical grade is typically narrower than industrial grade:
   - Black specks
   - Clarity
   - Customization options
   - Pellet size control
   - Viscosity
   - Yellow index

h. Supplier to conduct analytical testing for purity control of each lot or unit of delivery, as appropriate.

i. Supplier to offer expanded certificate of inspection or analysis (COA).

j. *Supplier must register polymer in FDA master access file (MAF) or drug master file (DMF) and provide letter to authorize use and ensure support for device submissions.

k. Biocompatibility must be demonstrated via testing to ISO 10993 (sections 5, 10, 11 required; other sections as appropriate) or USP Class VI.

l. —

m.*Polymers and additives (eg, fillers, pigments) must comply with FDA and EU requirements.

n. Polymers and additives (eg, fillers, pigments) must comply with EU REACH regulation and RoHS directive.

o. Supplier change management to follow current good manufacturing practices (cGMPs).

p. Supplier to offer single-source base materials; any substitution requires customer notification.

q. Supplier to offer single-source additives and colorants; any substitution requires customer notification.

r. Supplier to offer long-term supply assurance without change of formulation (formulation lock).

s. Supplier contract to include agreed term for advance notification of formulation change (eg, 2 years).

Manufacturing Processes

a. Supplier to perform process validation and provide documentation at correct level (1–4).

b. Supplier to offer single-location manufacturing (location lock); advance notification of change (NOC) required.

c. Supplier to comply with FDA requirements.

d. Supplier to maintain a quality management system (QMS); clear notification of change (NOC) required.

e. Where applicable supplier should comply with 21 CFR Ch. 1, Sub. C, Part 211, current good manufacturing practices, at levels 1 and 2 (quality manual, company policies).

f. Suppliers with quality systems certified to ISO 13485 should be granted preferred status; certification to ISO 9001 is the minimum requirement for a quality system.

g. Supplier should consider requirements for the following additional manufacturing criteria:

- 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

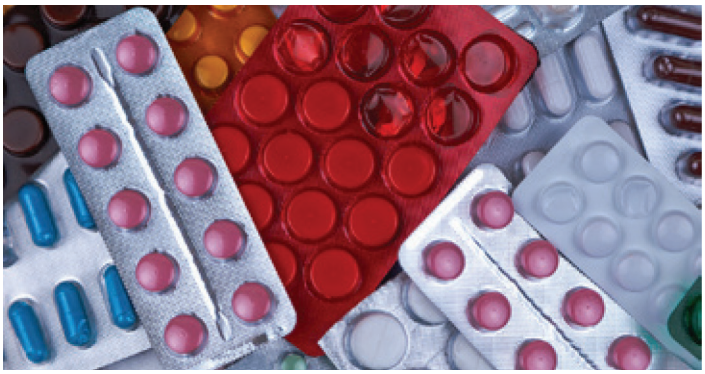
Quality Assurance

a. Supplier to issue certificates of analysis (COAs) for testing performed according to accepted test regimes (eg, ASTM, EUP, ISO, USP).

b. On request, supplier to issue letter of support for a material's regulatory compliance, including EU voluntary declarations of conformity.

c. On request, supplier to disclose additives and residual chemicals present in polymers.

d. *Supplier to use product design methods compliant with the EU Medical Device Regulation (MDR).



PROPOSED CRITERIA FOR PHARMACEUTICAL PACKAGING GRADE MATERIALS

Materials that meet the requirements for use in pharmaceutical packaging applications are a breed apart. They are widely used to package a wide range of medical products, from robotic surgery accessories to home-use thermometers. But they are also held to higher standards of biocompatibility because of their use for packaging medications in many formats, where plasticizer leachables and extractables could be harmful. Testing to USP Class VI requirements is typical, but is often supplemented with additional tests as needed. The lists below cover the criteria that should be considered for the ingredients, manufacturing, and quality assurance of pharmaceutical packaging grade materials.

Ingredients

a. Supplier to establish and issue policies for pharmaceutical packaging grade materials.

b. Supplier to establish and issue policy on shelf life for pharmaceutical packaging grade materials.

c. Polymer and colorant formulas free of animal-derived components (ADCs).

d. —

e. Formula free of heavy metal chemistries.

f. Polymer and colorant formulas free of latex.

g. —

h. Supplier to conduct analytical testing for purity control of each lot or unit of delivery, as appropriate.

i. Supplier to offer expanded certificate of inspection or analysis (COA).

j. Supplier must register polymer in FDA master access file (MAF) or drug master file (DMF) and provide letter to authorize use and ensure support for device submissions.

k. Biocompatibility must be demonstrated via testing to ISO 10993 (sections 5, 10, 11 required; other sections as appropriate) or USP Class VI.

l. Pharmaceutical packaging grade materials must comply with USP standards 661.1 and 661.2.

m. Polymers and additives (eg, fillers, pigments) must comply with FDA and EU requirements.

n. Polymers and additives (eg, fillers, pigments) must comply with EU REACH regulation and RoHS directive.

o. Supplier change management to follow current good manufacturing practices (cGMPs).

p. Supplier to offer single-source base materials; any substitution requires customer notification.

q. Supplier to offer single-source additives and colorants; any substitution requires customer notification.

r. Supplier to offer long-term supply assurance without change of formulation (formulation lock).

s. Supplier contract to include agreed term for advance notification of formulation change (eg, 2 years).

Manufacturing Processes

a. Supplier to perform process validation and provide documentation at correct level (1–4).

b. Supplier to offer single-location manufacturing (location lock); advance notification of change (NOC) required.

c. Supplier to comply with FDA requirements.

d. Supplier to maintain a quality management system (QMS); clear notification of change (NOC) required.

e. Where applicable supplier should comply with 21 CFR Ch. 1, Sub. C, Part 211, current good manufacturing practices, at levels 1 and 2 (quality manual, company policies).

f. Suppliers with quality systems certified to ISO 13485 should be granted preferred status; certification to ISO 9001 is the minimum requirement for a quality system.

g. Supplier should consider requirements for the following additional manufacturing criteria:
- 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

Quality Assurance

a. Supplier to issue certificates of analysis (COAs) for testing performed according to accepted test regimes (eg, ASTM, EUP, ISO, USP).

b. On request, supplier to issue letter of support for a material's regulatory compliance, including EU voluntary declarations of conformity.

c. On request, supplier to disclose additives and residual chemicals present in polymers.

d. Supplier to use product design methods compliant with the EU Medical Device Regulation (MDR).

PROPOSED CRITERIA FOR SKIN-CONTACT GRADE MATERIALS

Skin-contact grade materials are commonly used in medical equipment whose proper functioning requires direct patient contact, such as continuous positive airway pressure (CPAP) devices, continuous glucose monitors, infusion pumps, oxygen machines, and wearable devices. In many cases, skin-contact grade materials are the same as industrial-grade materials, except that skin-contact grade materials meet the pertinent biocompatibility requirements of ISO 10993. Listed below are proposed criteria applicable to ingredients, manufacturing, and quality assurance for skin-contact grade materials.

Ingredients

a. —

b. Supplier to establish and issue policy on shelf life for skin-contact grade materials.

c. No restriction on animal-derived components (ADCs).

d. —

e. Formula free of heavy metal chemistries.

f. Polymer and colorant formulas free of latex.

g. Define specifications and ranges for the following properties; skin-contact grade is typically similar to industrial grade:
- Black specks
- Clarity
- Customization options
- Pellet size control
- Viscosity
- Yellow index

h. Supplier to conduct analytical testing for purity control of each lot or unit of delivery, as appropriate.

i. Supplier to offer standard certificate of analysis (COA).
j. Supplier not required to register polymer in FDA master access file (MAF) or drug master file (DMF).
k. Biocompatibility must be demonstrated via testing to ISO 10993 (sections 5, 10, 11 required; other sections as appropriate) or USP Class VI.
l. —
m. Polymers and additives (eg, fillers, pigments) must comply with FDA and EU requirements.
n. Polymers and additives (eg, fillers, pigments) must comply with EU REACH regulation and RoHS directive.
o. Supplier change management to follow current good manufacturing practices (cGMPs).
p. Supplier can change source of base materials if the new material meets biocompatibility requirements and the change does not affect product performance.
q. —
r. Supplier not required to offer long-term supply assurance without change of formulation (formulation lock).
s. Supplier contract not required to include agreed term for advance notification of formulation change.

Manufacturing Processes

a. Supplier to perform process validation and provide documentation at correct level (1–4).
b. Supplier required to offer advance notification of change (NOC) only if the site change affects product performance.
c. Supplier to comply with FDA requirements.
d. Supplier to maintain a quality management system (QMS); notification of change (NOC) required only if the change affects product performance.
e. Where applicable supplier should comply with 21 CFR Ch. 1, Sub. C, Part 211, current good manufacturing practices, at levels 1 and 2 (quality manual, company policies).
f. Suppliers to manufacture in compliance with FDA current good manufacturing practices (cGMPs); certification to ISO 13485 not required.
g. —

Quality Assurance

a. Supplier to issue certificates of analysis (COAs) for testing performed according to accepted test regimes (eg, ASTM, EUP, ISO, USP).
b. On request, supplier to issue letter of support for a material's regulatory compliance, including EU voluntary declarations of conformity.
c. On request, supplier to disclose additives and residual chemicals present in polymers.
d. Supplier to use product design methods compliant with the EU Medical Device Regulation (MDR). MDR requirements are applicable to patient contact devices.

CONCLUSION

Across the globe, there is growing public concern about the use of plastics. People are becoming increasingly insistent about knowing what potentially harmful chemistries they are being exposed to or having contact with. Of particular concern are products made using plastics containing BPA and products containing recycled plastics, but there are many other ingredients that are also worthy of some attention.

Plastics used in medical products were long exempt from regulations that applied to other industries, but that is no longer the case. Plastics used in medical products and pharmaceutical packaging are now being subjected to far greater scrutiny than ever before.

The European Union is attempting to address the issue of plastic waste with adoption of the EU waste framework directive.[1] Under this directive, development of the centralized public database of substances of concern in products (SCIP) will provide a foundation for transparency about product ingredients.[2] The availability of such information may help to inform regulatory requirements worldwide. When applied to the development of medical products, detailed information about product ingredients may help to reduce biocompatibility risks for both patients and clinicians.

NAMGMC's initiative to develop universally adopted criteria for defining what constitutes a medical-grade material has set in motion an effort with potentially wide-ranging effects for the manufacturers and users of medical products. When fully harmonized and adopted for use, a standard for defining medical-grade materials will strengthen compliance in the selection and use of such materials, improving both the quality and safety of medical products worldwide.

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