IMDRF International Medical Device Regulators Forum

FINAL WORKING DRAFT

Title: Personalized Medical Devices – Regulatory Pathways

Authoring Group: IMDRF Personalized Medical Devices

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Preface

The document herein was produced by the International Medical Device Regulators Forum (IMDRF), a voluntary group of medical device regulators from around the world. The document has been subject to consultation throughout its development.

1.0 Introduction

The primary purpose of this IMDRF guidance is to recommend a harmonized approach for the application of existing regulatory pathways to medical devices that are intended for a particular individual, and to identify special considerations for the regulation of each identified category of personalized medical device (PMD). The adoption of consistent, harmonized requirements for such medical devices will underpin a harmonized regulatory approach for controls on these types of medical devices and offer significant benefits to the manufacturer, user, patient, and to Regulatory Authorities (RAs). Eliminating differences between jurisdictions supports global convergence, reduces the cost of gaining regulatory compliance and allows patients and healthcare professionals earlier access to new treatments and technologies. This document includes an overview of some of the considerations and concepts that may be relevant in developing a harmonized assessment approach in future.

Technology has progressed from the time the original Global Harmonization Task Force (GHTF) foundation documents were published. It is now possible to produce medical devices that are individualized on a commercial rather than artisanal scale. Manufacturing technologies used to create these PMDs include computer-controlled additive and subtractive manufacturing methods based on patient images. The original GHTF documentation does not adequately address medical devices of this nature.

Many jurisdictions already define the term *custom-made device* and have introduced exemption provisions for regulating custom-made medical devices, with the intention of covering special cases where commercially available products or alternative therapies are inadequate for the needs and requirements of a particular individual. In some jurisdictions the exemption provisions were based on the premise that affected devices would largely comprise low-risk products or limited use of higher-risk implantable devices. In other jurisdictions the exemption provisions were established with the intention that numbers of manufactured custom-made devices would necessarily be small due to the requirement for them to be used only in special cases.

Now regulators are faced with a very different environment. Technologies such as additive and subtractive manufacturing (see Appendix 1), especially when combined with digital patient data, have made “custom-made” devices, including implantable devices, within reach on a much greater scale. Furthermore, advancing technology has also enabled a shift to near or at point-of-care manufacturing (collectively referred to as POC manufacturing throughout this document) for manufacturing a broad range of medical devices not limited to PMDs only.

Existing regulations and guidance were not necessarily designed to address this form of manufacturing and, consequently, present challenges for RAs to ensure that the medical devices produced at POC manufacturing facilities meet the same requirements of quality, safety and performance as medical devices produced at traditional manufacturing facilities. A secondary purpose of this IMDRF guidance is to provide some considerations for how the current regulatory frameworks can be adapted to address this evolution in manufacturing practices.

Note: This document is intended to provide a best-practice model for suitable regulatory pathways for different types of medical devices and is primarily intended to assist with harmonizing the regulation of PMDs across international jurisdictions.

Individual jurisdictions may have particular requirements in place, which pre-date this guidance or that are more specific than this guidance, for some or all of the device categories represented.

2.0 Scope

This document applies to all personalized medical devices (PMDs) and is intended to identify and describe different regulatory pathways and their requirements for the different categories of personalized devices that are defined in the IMDRF document N49, *Definitions for Personalized Medical Devices*. This document should be read in conjunction with N49.

Note that the concepts and regulatory approaches described in this document in relation to Medical Device Production Systems (MDPS) and POC manufacturing of medical devices, may also apply to a broad range of medical devices, and are not restricted to PMDs.

Excluded from the scope are *in vitro* diagnostic medical devices[1] (IVD MDs).

3.0 References

ISO/ASTM 52900:2015	Additive manufacturing — General principles — Terminology
GHTF/SG1/N071:2012	Definition of the Terms 'Medical Device' and 'In Vitro Diagnostic (IVD) Medical Device'
IMDRF/PMD WG/N49 FINAL:2018	Definitions for Personalized Medical Devices
GHTF/SG1/N55:2009	Definitions of the Terms Manufacturer, Authorised Representative, Distributor and Importer
IMDRF/GRRP WG/N47 FINAL:2018	Essential Principles of Safety and Performance of Medical Devices and IVD Medical Devices
GHTF/SC/N4:2012	Glossary and definition of terms used in GHTF documents
IMDRF/GRRP WG/N52 FINAL:2019	Principles of Labelling for Medical Devices and IVD Medical Devices
GHTF/SG1/N78:2012	Principles of Conformity Assessment for Medical Devices
IMDRF/SaMD WG/ N10 FINAL:2013	Software as a medical device (SaMD): Key Definitions

[1] See *Definition of the Terms 'Medical Device' and 'In Vitro Diagnostic (IVD) Medical Device'* (GHTF/SG1/N071:2012)

Note: Regulations and Guidance documents from the organizations represented by all working group members were considered in the drafting of this document. For example:

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

USFDA CDRH, Technical Considerations for Additive Manufactured Devices - Guidance for Industry and Food and Drug Administration Staff, 5 Dec 2017

USFDA CDRH, Custom Device Exemption - Guidance for Industry and Food and Drug Administration Staff, 24 Sept 2014

4.0 Definitions[2]

4.1 custom-made medical device—a medical device that, at a minimum, meets the following requirements:

- it is intended for the sole use of a particular individual (which could be a patient or healthcare professional); and
- it is specifically made in accordance with a written request of an authorized healthcare professional, which gives, under their responsibility, specific design characteristics; even though the design may be developed in consultation with a manufacturer; and
- it is intended to address the specific anatomo-physiological features or pathological condition of the individual for whom it is intended.

Note 1: Medical devices that are patient-matched, adaptable or mass-produced shall not be considered to be custom-made.

Note 2: A custom made device is intended for a case where an individual's specific needs cannot be met, or cannot be met at the appropriate level of performance, by an alternative device available on the market.

4.2 **patient-matched medical device—**a medical device that meets the following requirements:

- it is matched to a patient's anatomy within a specified design envelope using techniques such as scaling of the device based on anatomic references, or by using the full anatomic features from patient imaging; and
- it is typically produced in a batch through a process that is capable of being validated and reproduced; and

[2] For further information on personalized medical devices, including examples for definitions included in this document, and supporting definitions, see: IMDRF/PMD WG/N49 FINAL:2018 *Definitions for Personalized Medical Devices*

- it is designed and produced under the responsibility of a manufacturer even though the design may be developed in consultation with an authorized healthcare professional.

Note 1: A written request from an authorized healthcare professional may be present; but is not mandatory.

Note 2: The number and type of design inputs in consultation with a healthcare professional may vary depending on the medical devices to be manufactured.

Note 3: The design must remain within the validated parameters of the specified design envelope.

4.3 adaptable medical device—a medical device that meets the following requirements:

- it is mass-produced; and
- it is adapted, adjusted, assembled or shaped at the point of care, in accordance with the manufacturer's validated instructions, to suit an individual patient's specific anatomo-physiologic features prior to use.

4.4 Manufacturer[3]

"Manufacturer" means any natural or legal person[4] with responsibility for design and/or manufacture of a medical device with the intention of making the medical device available for use, under his name; whether or not such a medical device is designed and/or manufactured by that person himself or on his behalf by another person(s).

NOTES:

1. This 'natural or legal person' has ultimate legal responsibility for ensuring compliance with all applicable regulatory requirements for the medical device in the countries or jurisdictions where it is intended to be made available or sold, unless this responsibility is specifically imposed on another person by the Regulatory Authority (RA) within that jurisdiction.
2. The manufacturer's responsibilities are described in other GHTF guidance documents. These responsibilities include meeting both pre-market requirements and post-market requirements, such as adverse event reporting and notification of corrective actions.
3. 'Design and/or manufacture', as referred to in the above definition, may include specification development, production, fabrication, assembly, processing, packaging,

[3] GHTF/SG1/N55:2009 *Definitions of the Terms Manufacturer, Authorised Representative, Distributor and Importer*

[4] The term "person" that appears here and in the other definitions of this document, includes legal entities such as a corporation, a partnership, or an association.

repackaging, labelling, relabelling, sterilization, installation, or remanufacturing of a medical device; or putting a collection of devices, and possibly other products, together for a medical purpose.

4. Any person who assembles or adapts a medical device that has already been supplied by another person for an individual patient, in accordance with the instructions for use, is not the manufacturer, provided the assembly or adaptation does not change the intended use of the medical device.

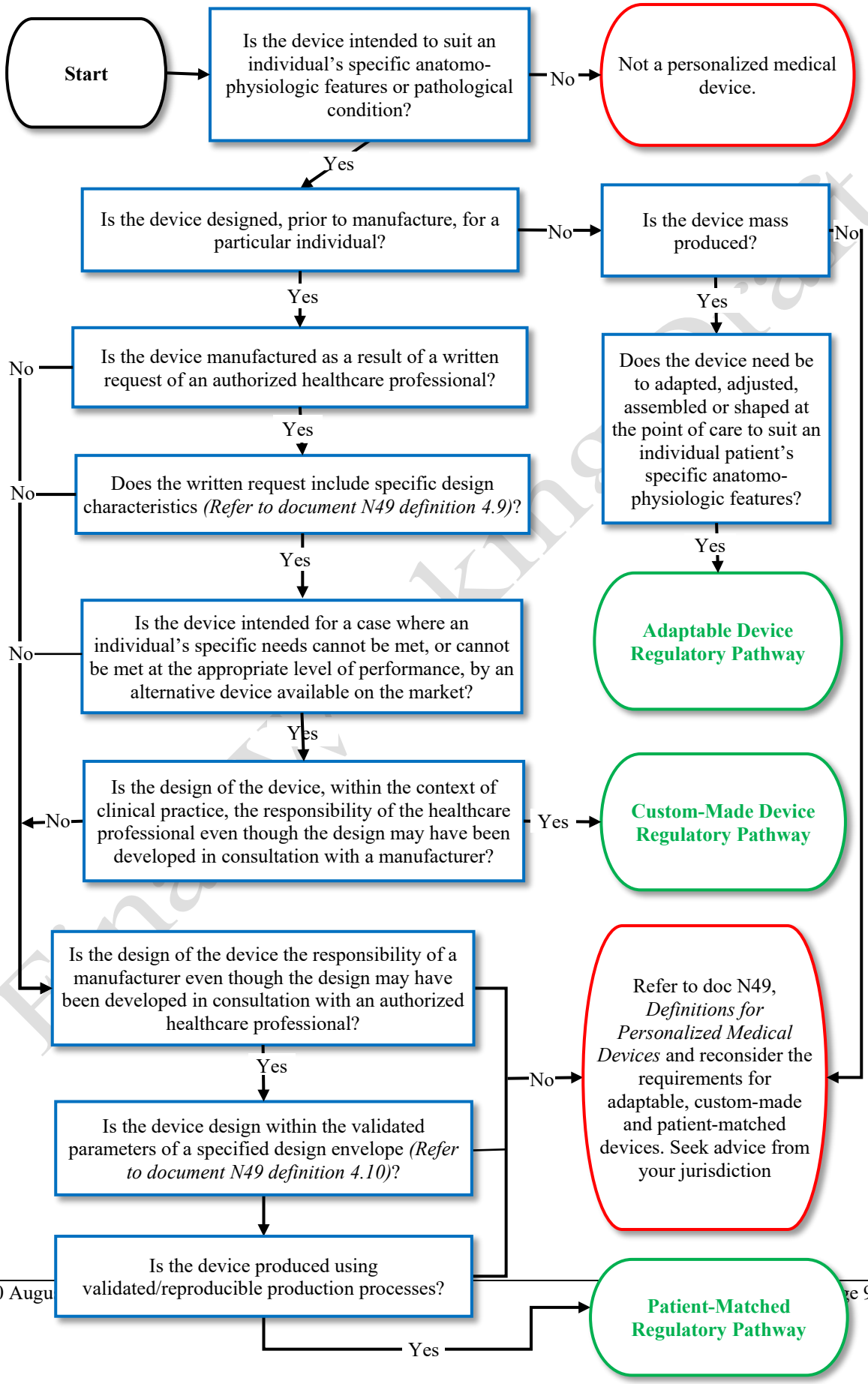
5. Any person who changes the intended use of, or modifies, a medical device without acting on behalf of the original manufacturer and who makes it available for use under his own name, should be considered the manufacturer of the modified medical device.

6. An authorised representative, distributor or importer who only adds its own address and contact details to the medical device or the packaging, without covering or changing the existing labelling, is not considered a manufacturer.

7. To the extent that an accessory is subject to the regulatory requirements of a medical device[5], the person responsible for the design and/or manufacture of that accessory is considered to be a manufacturer.

[5] See GHTF/SG1/N29 *Information Document Concerning the Definition of the Term "Medical Device"*

5.0 Decision Tree



6.0 Custom-made Medical Devices

Introduction

Custom-made medical devices are intended to cover special cases where commercially available products or alternative therapies are inadequate for meeting the needs and requirements of particular individuals.

Many jurisdictions have addressed this challenge by implementing special regulatory pathways for custom-made medical devices, which generally includes some exemptions from the usual regulatory requirements to ensure that the specific needs of individuals are able to be met. The pathways typically involve a requirement for an authorized healthcare professional to provide design input and to take some of the responsibility normally placed on manufacturers for the safety and performance of the finished medical devices.

The special regulatory pathways that many jurisdictions have for custom-made medical devices are not intended for trialing new technologies—most jurisdictions have experimental and investigation pathways for this purpose.

General requirements

The manufacturer of a custom-made medical device should first ensure that all elements of the custom-made medical device definition are met; this includes obtaining the documented request and specific design characteristics from an authorized healthcare professional[6].

The manufacturer should then determine the classification the device would have were it not custom-made and consider applying the equivalent regulatory requirements, according to the device classification, of the jurisdiction in which it is to be supplied. All custom-made devices should meet safety and performance requirements[7].

Validated computational modelling and simulation methods, including reproducing the patient-matched conditions to which the custom-made device will be exposed, may be one way to assess the safety and performance of custom-made devices. Physical testing may also be appropriate. The manufacturer should conduct a risk-analysis to determine the most appropriate methods to employ.

Although professional and clinical responsibilities on the authorized healthcare professional do not fall within the scope of this guidance document, in accordance with good medical practice, it is expected that the authorized healthcare professional will be fully aware of the health-related risks and benefits of the requested device in comparison to conventional therapies or alternative

[6] An *authorized healthcare professional* is a person legally entitled to provide health services in the applicable jurisdiction.

[7] IMDRF/GRRP WG/N47 FINAL:2018 *Essential Principles of Safety and Performance of Medical Devices and IVD Medical Devices*

devices available on the market. They should also be knowledgeable about the available safety and performance information in respect of the requested device.

The meeting of the individual's specific needs, as translated by the specific design characteristics provided by the authorized healthcare professional to the manufacturer, may lead to the production of a custom-made medical device that does not fully comply with the usual safety and performance requirements. The manufacturer should be required to document and justify such non-compliance.

Note: It is expected that manufacturers will raise any concerns they may hold about the implementation of the specific design characteristics with the authorized healthcare professional.

Manufacturing and record keeping

It is recommended that manufacturers be required to manufacture custom-made devices under a quality management system (QMS). For higher risk custom-made devices, for example, permanent implants, it is recommended that the QMS be subject to third-party oversight (e.g., an auditing organization or regulatory agency).

The manufacturer should review the requirements and determine what is appropriate for their custom-made devices in the jurisdictions where they will be supplied. Some important considerations (by no means exhaustive) include:

- manufacturing impact on chemical, physical, and biological properties of the device;
- infection and microbial contamination control;
- method of sterilization;
- infrastructure and environment of manufacture;
- requirements for medical devices connected to or equipped with an energy source;
- maintenance of technical documentation and manufacturing records; and
- information supplied by the manufacturer, including labels and instructions for use.

It is recommended that the manufacturer be required to provide a statement with the custom-made device; this statement should include:

- data allowing identification of the device, i.e., description, serial number, order number, generic name;
- a section that indicates that the device is intended for exclusive use for a particular individual, together with the name of the individual (this may be an identification number if confidentiality needs to be maintained, provided it can be traced through records to the named individual);
- the name of the authorized healthcare professional who requested the device, and, where applicable, their place of work;
- the particular features of the device as specified in the relevant written request;
- a section that indicates that the device conforms to the relevant safety and performance requirements; and, where it does not, which requirements are not fully met and the grounds for believing that the device is nevertheless safe for use; and
- the name and address of the manufacturer.

Additionally, it is recommended that the manufacturer be required to:

- upon request, make documentation, including a copy of the written request and statement to the regulatory authority. The documentation should allow an understanding of the design, manufacture, and intended purpose of the custom-made device—so as to allow assessment of conformity with regulatory requirements.
- retain the documentation for all implantable custom-made medical devices for a period of at least 15 years or for the projected useful lifespan of the device, whichever is longer, from the date of manufacture. For all other custom-made medical devices, the period should be at least 5 years or for the projected useful lifespan of the device, whichever is longer; and
- make the statement available to the requesting authorized healthcare professional and the individual for whom the device has been manufactured.

Registration or notification to regulatory authorities

It is recommended that custom-made medical devices and their manufacturers or local representatives be required to be registered or notified to the regulatory authority in the jurisdiction in which they are supplied. Regulatory authorities should provide guidance on registration or notification requirements, if any.

Post-market surveillance, corrective action, and adverse-event reporting

Manufacturers of custom-made devices should be required to review and document experience gained in the post-production phase and set up a post-market surveillance system, including reporting of adverse-events to authorities.

Responsible parties (for example, manufacturers, local representatives, or authorized healthcare professionals) should follow applicable post-market requirements in their respective jurisdictions; for example, reporting adverse events associated with the device, or conducting field safety corrective actions (e.g., recalls).

Manufacturers should be required to investigate adverse-event reports, with the results of investigations of any adverse-event reports that identify causes linked to the specific design characteristics being fed back to the authorized healthcare professional who provided them.

Note: Ordinary return of devices to manufacturers for adjustment or fitting would not need to be reported.

7.0 Patient-matched Medical Devices

General requirements

Patient-matched medical devices are designed and produced for a particular individual by a manufacturer within validated parameters of a specified design envelope[8]. The variables within the design envelope are predetermined by the manufacturer and not the authorized healthcare professional.

Although design inputs, such as medical imaging or anatomic references, may be provided to the manufacturer (e.g., by an individual or authorized healthcare professional), it is the manufacturer that is responsible for matching the design of the device to the individual's anatomy, within the design envelope, based on techniques such as scaling.

Patient-matched medical devices can be considered to be mass-produced devices, with dimensional or other variations within a specified range.

The manufacturer of a patient-matched medical device must ensure the device is correctly classified and must follow the usual regulatory requirements to obtain pre-market approval, according to the risk classification, in the jurisdiction in which the devices are supplied.

The manufacturer must meet both pre- and post-market regulatory requirements in the jurisdiction where the device is supplied; these might include, for example, clinical performance; compliance with safety and performance standards; manufacturing standards; the provision of labels and information; registration; and post-market surveillance, corrective action, and adverse-event reporting.

Note: Relevant GHTF/IMDRF guidance documents are included in the references section above.

Manufacturing and record keeping

In order to demonstrate safety and performance for patient-matched medical devices, a manufacturer must identify the maximum performance limits and limiting configurations in terms of both parameters and manufacturing variables, for example, related to device geometry, mechanical stress concentrations, energy power envelopes, material properties, or computational power of the device. This is to ensure that any medical devices produced within the specified design envelope comply with the relevant essential principles. This is a similar process used to demonstrate safety and performance for mass-produced medical devices that are supplied in different sizes.

Maximum performance limits and limiting configurations are commonly identified through the manufacturer's risk-analysis process. Simulation and modelling methods, such as finite element analysis, are sometimes useful for investigating the maximum performance limits and limiting configurations.

[8] The term 'specified design envelope' is defined in N49.

Standard methods of process validation and/or verification can also usually be applied for determining performance limits and limiting configurations for manufacturing and design variables; for example, testing of physical samples that represent worst-case scenarios (or boundaries) within which the device will operate as intended.

The manufacturer should ensure that the technical documentation for patient-matched medical devices includes records for the design envelope identification and validation process.

Additionally, it is recommended that the manufacturer be required to:

- maintain a copy of any written request(s) and other specification documentation that includes the patient-matching information. For all implantable patient-matched medical devices, the requirement should be for this information to be kept for a period of at least 15 years or for the projected useful lifespan of the device, whichever is longer, from the date of manufacture. For all other patient-matched medical devices the period should be at least 5 years or for the projected useful lifespan of the device, whichever is longer; and
- make the patient-matching information available to the named patient for whom the device has been manufactured.

8.0 Adaptable Medical Devices

Adaptable medical devices are mass-produced and must follow the usual regulatory requirements to obtain pre-market approval, according to their risk classification, in the jurisdiction in which they are supplied.

The manufacturer must meet both pre- and post-market regulatory requirements in the jurisdiction where the device is supplied; these might include, for example, clinical performance; compliance with safety and performance standards; manufacturing standards; the provision of labels and information; registration; and post-market surveillance, corrective action, and adverse-event reporting. Note: Relevant GHTF/IMDRF guidance documents are included in the references section above.

In addition to the usual requirements, the manufacturer of the adaptable medical device should be required to provide *validated* instructions that explain how to adapt, adjust, assemble, or shape the device. Development of the instructions should include suitable human factors considerations in order to minimize safety issues that might result from the adaptation process.

The manufacturer's validation should:

- ensure that the permissible POC[9] changes to the adaptable medical device do not negatively affect the device's safety or performance;
- include, where applicable, analysis of allowable multi-component or multi-device configurations; and

[9] Note: It is acknowledged that the definition references 'POC'; however, in some jurisdictions, changes might be conducted after supply but prior to the point of care, for example, by a dispensing contractor. The adaptation might also be conducted by a patient or care giver.

- include consideration of human factors, particularly around an adapting entity's ability to suitably adapt, adjust, assemble, or shape the adaptable medical device.

The manufacturer may place requirements on the individual or entity who will be undertaking the adaptation (the adapting entity), for example, requiring that verification testing be conducted and that records be maintained. Records required to be maintained by the individual or entity might include:

- identification of the device;
- where applicable, identification of the patient for whom the device was adapted;
- results of any verification testing; and
- any additional components or materials used as part of the adaptation.

The manufacturer may also consider the need for training of the adapting entity.

Note: it remains the manufacturer's responsibility to ensure safety and performance of the adaptable medical device.

Appendix 1—Some considerations for medical devices produced using additive or subtractive manufacturing

Introduction

Additive and subtractive manufacturing are manufacturing methods that have existed for many years; however, digital, and data-handling capabilities combined with increased availability of affordable equipment, such as 3D printers, have resulted in the advent of technologies for the ready production of a broad range of medical devices, including PMDs, by healthcare professionals at POC manufacturing facilities or by traditional manufacturers.

This has raised questions about the suitability of these manufacturing methods for the production of safe medical devices, particularly with respect to the validation of their design and production methods; and the sufficiency of the quality control over any and all components, equipment, and raw materials used for production purposes. Accordingly, a new concept is introduced—the *medical device production system* (MDPS). Additionally, some considerations and guidance are provided herein on:

- raw materials used for manufacture; and
- materials that are medical devices in their own right

Medical device production systems

If control over a manufacturing process, such as additive or subtractive manufacturing, outside of a regulated manufacturing facility is needed, for example, for production of medical devices above Class A[10], jurisdictions may consider defining and regulating a 'medical device production system' on the basis of the resultant medical device the system is intended to produce, and any additional risks resulting from the POC production methods.

The manufacturer of an MDPS should be considered as a medical device manufacturer and will be responsible for validating the intended use, the safety and performance of the devices which can be produced at the POC using the MDPS. This includes validation of the design envelope for patient-matched medical devices.

We define an MDPS as:

> A *medical device production system* (MDPS) is a combination of the resultant medical device and the medical device production process (MDPP) elements. The elements of an MDPP includes the raw materials, software[11] and digital files, main production, and post-processing (if applicable) equipment, and operating instructions intended to be used by specific end users at a healthcare facility (HCF), to produce a specific type of medical device for treating the patients of the HCF.

[10]2012 GHTF SG1 *Principles of Medical Devices Classification*

[11] Software used as part of production rather than software that meets the definition of a medical device in its own right.

- An MDPS includes the resultant medical device it is intended to produce and the intended use for the device validated in accordance with safety and performance requirements in the relevant regulatory jurisdiction.
- An MDPS classification should be determined by the risk-based classification of the resultant medical device it is intended to produce, which may include consideration of any additional or likely foreseeable risks that may arise as a result of the operation of the MDPS.
- An MDPS may require the use of ancillary equipment, human factors considerations, technical capability requirements, or other specified input and design limit controls; however, all components must be validated as a production process to consistently produce the resultant medical device with the use of the supplied operating instructions.

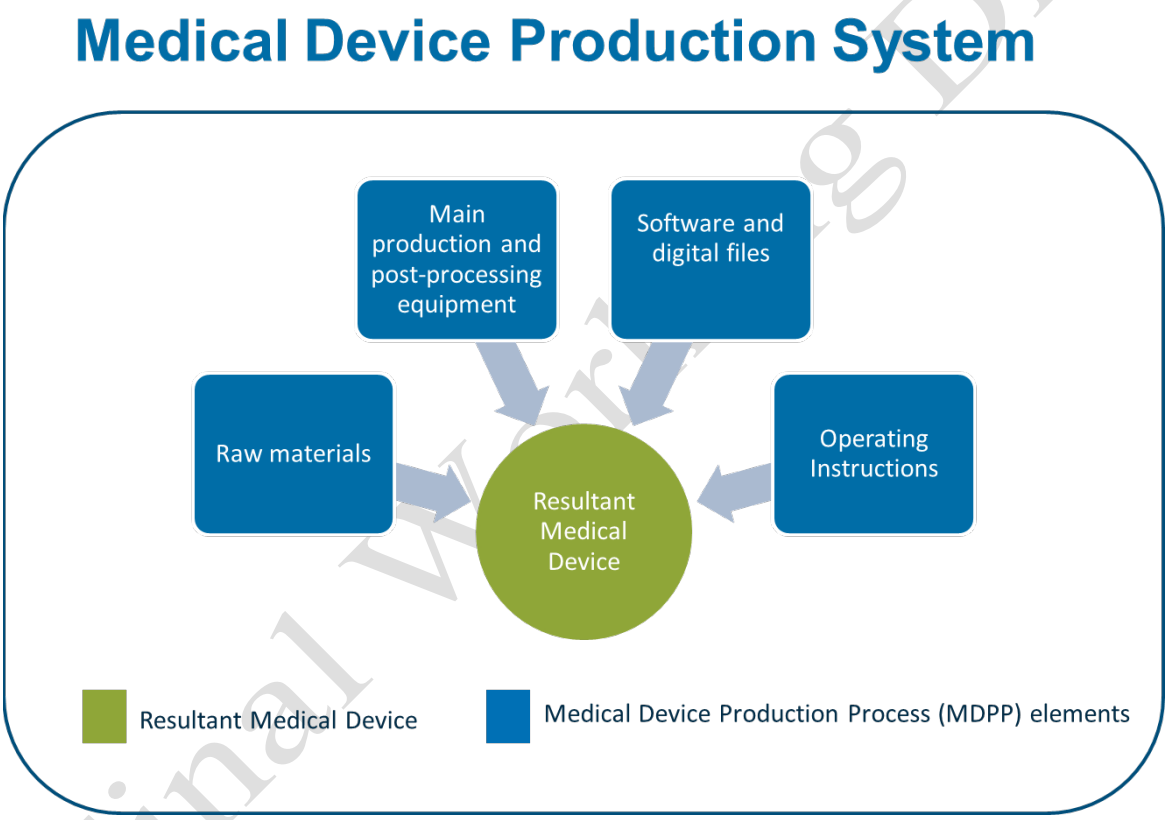


Figure 1. An illustration of the constituent parts of a medical device production system (MDPS).

As shown in Figure 1, an MDPS has two primary constituents:

i. Medical Device Production Process (MDPP) elements: which may include raw materials, main production and post-processing equipment, software and digital files, and the operating instructions supplied by the MDPS manufacturer to produce a specific medical device; and
ii. Resultant Medical Device: the specific medical device that the MDPP produces using the operating instructions supplied by the MDPS manufacturer.

RAs having jurisdiction may consider an MDPS in accordance with the concept of a kit [12] or system. That is, a group of products that together achieve a stated intended use —and as such, can be considered a medical device in its own right.[13] Consequently, all applicable elements of the medical devices framework then apply to it. In this case, and if appropriate to the applicable jurisdiction, the 'medical device production system' is not intended to be regulated as a production tool for universal manufacture of medical devices as it would be if it were used for production in a regulated manufacturing facility.

Jurisdictions may choose to introduce limits on the types of devices accepted for manufacture by an MDPS, such as limiting them to low-risk products only; and they may also choose to impose credentialing requirements for the use of an MDPS[14].

The GHTF/IMDRF definition of 'manufacturer' applies to the manufacturer of an MDPS. This allows for multiple OEMs and outsourcing to component manufacturers while one legal manufacturer takes responsibility for MDPS. However, following the pre-market approval, and as determined by the RA having jurisdiction, there may be different models under which an MDPS manufacturer may supply its MDPS to an HCF:

a) Build, Own, Operate model: the MDPS manufacturer takes the responsibility for the installation, ongoing maintenance including (but not limited to) supply of spare parts and raw materials, and execution of the MDPP at the HCF. The MDPS manufacturer takes the ongoing responsibility for the resultant medical devices that the MDPP produces.
b) Build, Own, Operate, and Transfer model: the MDPS manufacturer takes the responsibility for the installation, ongoing maintenance including (but not limited to) supply of spare parts and raw materials to the HCF. The MDPS manufacturer executes the MDPP for a period of time during which they take responsibility for the resultant medical devices that the MDPP produces. At the predetermined time and conditions, the ongoing responsibility for the resultant medical devices produced by the MDPP thereafter is transferred to the HCF. Separate pre-market approval for the resultant medical device may be required when the HCF assumes the responsibility; however, depending on the jurisdictional requirements, an abridged assessment could be undertaken leveraging the pre-market approval status of the MDPS.
c) Build, Own, Transfer: the MDPS manufacturer takes the responsibility for the installation, ongoing maintenance including (but not limited to) supply of spare parts and raw materials to the HCF. The HCF takes the responsibility for the resultant medical devices that the MDPP produces. The HCF may require separate pre-market approval for the resultant medical device; however, depending on the

[12] GHTF/SC/N4:2012 *Glossary and definition of terms used in GHTF documents*
[13] Jurisdictions not considering an MDPS (which includes the intended resulting medical devices) as a medical device, should introduce requirements for MDPS manufacturers on the quality, safety, and performance of the MDPS. Such requirements should include the obligation of the manufacturer to validate the MDPS and ensure conformity of the intended resultant medical devices with the Essential Principles.
[14] Further information is provided in *Appendix 2(2)—Using Medical Device Production Systems*

jurisdictional requirements, an abridged assessment could be undertaken leveraging the pre-market approval status of the MDPS.

As with all other medical devices, the manufacturer of an MDPS must identify and document any necessary requirements regarding use of the MDPS. These might include, for instance, environment controls; staff training and certification; conduction of verification testing; and maintenance of records. Manufacturers should also establish methods for ensuring that the necessary controls are implemented and that they remain effective over the lifetime of the MDPP.

If the HCF or healthcare professional uses the MDPP to produce a device outside the original manufacturer's intended use of the MDPS, then the user would take on all regulatory responsibilities associated with the new intended use. In such instances, the user could be considered a manufacturer in their own right and, consequently, all the requirements for manufacturers would then apply to them.

Raw materials for manufacture

Raw materials for additive or subtractive manufacture, as with any other manufacturing raw material, is not a medical device as it is not directly used for treating[15] a patient, with limited exceptions[16]. This is because regulating the raw material for a 3D-printer or CAD/CAM system (for example) will not ensure that the final devices the system produces will comply with applicable safety and performance requirements.

Additive and subtractive manufacture involves more than assembling or adapting a device for a particular patient; it is a complex multifactorial process that has an impact on the finished device's compliance with the essential principles. Consequently, instructions for use provided by the manufacturer of a raw material for additive or subtractive manufacture cannot adequately specify sufficient means of control over all of the variables in an additive or subtractive manufacturing process.

Materials that are medical devices

According to the GHTF definition of medical device[17], a 'material' can be a medical device in its own right. An example of a 'material' regulated as a medical device in some jurisdictions is dental resin materials used for restorations in the repair of teeth. A dentist assembles and/or adapts the resin material for an individual patient, as intended by the manufacturer of the resin, in accordance with the instructions for mixing, forming, curing, etc. the resin.

The assurance that the final assembled or adapted resin medical device will perform as intended comes from the validated instructions provided by the manufacturer. This means that the resin

[15] or any of the other medical device purposes in the GHTF definition of medical device
[16] IMDRF/PMD WG/N58 Appendix 1 - Materials that are medical devices
[17] GHTF/SG1/N071:2012 *Definition of the Terms 'Medical Device' and 'In Vitro Diagnostic (IVD) Medical Device'*

manufacturer will have tested the safety and performance of samples of its device, when adapted or assembled according to its instructions. The manufacturer makes certain specifications for the use of its product, such as the mixing constituents, the mixing ratio, the type and size of defect to which the resin should be applied and how long it needs to cure. When the dentist follows these instructions, the dental resin restoration will perform as intended by the manufacturer of the resin. It is important to note that the material regulated as a medical device is only to be used for the specific intended use identified and not for unlimited intended uses for other medical devices that have not been validated for safety and performance.

Appendix 2—Considerations for point-of-care manufacture of medical devices

Introduction

HCFs or healthcare professionals may be involved in manufacturing of medical devices, including PMDs, for use in treating their patients. Medical device manufacturing usually occurs under appropriate quality management systems, and in regulated manufacturing facilities. Under the GHTF model, it is recognized that appropriate regulatory oversight of medical device manufacturers is an important factor in ensuring safety and performance of medical devices. For this reason, there should also be an oversight of manufacturing that is occurring in alternative locations such as at the POC.

Traditionally, POC manufacturing has been limited in scope; however, advances in technology have enabled the manufacture of more complex, higher-risk medical devices including PMDs by healthcare professionals (on a routine basis) without the usual requirements and oversight that traditional manufacturers are typically subject to.

Oversight of HCFs and healthcare professionals varies in different jurisdictions around the world, from full regulation of them as regulated entities (as traditional manufacturers), through to pathways that allow for exemption under certain criteria (for example, when medical devices including PMDs are manufactured at HCFs or by recognized healthcare professionals).

The following sub-sections in this Appendix include recommendations for three possible approaches that regulators might choose to implement for regulatory oversight of medical device manufacturing at or near the POC. These are:

1. Manufacturing under special arrangements
2. Using Medical Device Production Systems
3. Fully regulated manufacturing (as per the GHTF/IMDRF model)

1. Manufacturing under special arrangements

Introduction

Some jurisdictions apply different regulatory frameworks (such as exemptions or special provisions) for medical device manufacturing undertaken in HCF, or by healthcare professionals, as compared to manufacturing undertaken by traditional manufacturers. The different frameworks tend to be limited to medical devices intended to address indispensable clinical needs within specific institutions or their network of subsidiary or partner institutions.

Any exemptions for manufacturing within a HCF should not apply to establishments primarily claiming to pursue health interests or healthy lifestyles, such as gyms, spas, wellness, and fitness centers, or to establishments focused on beauty treatments such as cosmetic clinics.

Protection of safety and performance

When HCFs or healthcare professionals design and/or manufacture a medical device under special arrangements, including at the POC, it is recommended that they be required to protect patient safety, and ensure appropriate performance of the medical device, by meeting certain imposed requirements that include the following:

a) the manufacture and use of the devices to be undertaken under an appropriate quality management system;

b) the HCF or healthcare professional to be required to have on file, and to provide information upon request, on the use of devices it has manufactured to its regulatory authority. The information should include a justification of the indispensable clinical needs warranting manufacture of the device and details of their manufacture, including appropriate quality management validation documentation, device designs or modifications, and the intended use;

c) the HCF or healthcare professional to be required to make available to the RA having jurisdiction or the patient receiving the device the following information:

   i. the name and address of the manufacturing HCF or healthcare professional;

   ii. the details necessary to identify the device;

   iii. a declaration that the device meets general safety principles and, where applicable, information on which principles have not been fully met together with a reasoned justification thereof;

d) the HCF or healthcare professional to be required to draw up documentation under its quality management system that makes it possible to have an understanding of the manufacturing facility; the manufacturing process; and the design and data providing confidence that the device will function as intended, including the intended purpose, and that is sufficiently detailed to enable the regulatory authority to ascertain that the general safety and performance requirements have been met;

e) the HCF or healthcare professional to be required to take all necessary measures to ensure that all devices it manufactures are manufactured in accordance with the documentation referred to in point (d);

f) the HCF or healthcare professional to be required to review experience gained from clinical use of all devices it manufactures, report any adverse events to the regulatory authority, and take all necessary corrective and preventive actions; and

g) the HCF will allow the regulatory authority to inspect the manufacturing processes when appropriate.

Regulators who apply special frameworks for the manufacture of medical devices within a HCF, or by healthcare professionals, should consider including regulatory oversight commensurate with that of the equivalent frameworks in place for traditional manufacturers. For instance, a hospital may be required to operate under a quality management system certified by a competent 3rd party and be required to meet, and be assessed against, appropriate safety and other technical standards that are equivalent to the essential principles of safety and performance.

2. Using Medical Device Production Systems[18]

The manufacturer of an MDPS is responsible for conducting validation activities and maintaining relevant documentation in relation to the MDPP and the resultant medical device.

[18] This is introduced in Appendix 1

The MDPS manufacturer is further responsible for all pre-market approval activities, and depending on the jurisdictional requirements, the manufacturer may be required to register the MDPS and the resultant medical device separately. Following the pre-market approval, the RA having jurisdiction may consider placing additional responsibilities on the MDPS manufacturer, including (but not limited to) systematically collecting post-market user data for the MDPP, post-market adverse-event reporting for the resultant medical device, advertisement compliance, and maintaining production and supply records.

Following pre-market approval, the supply of an MDPS to the HCF may occur under different arrangements (as explained in Appendix 1) depending on the contractual agreements between the manufacturer and the HCF.

In some regulatory jurisdictions, when the HCF takes the responsibility for the resultant medical device that an MDPP is intended to produce, the HCF may be required to obtain separate pre-market approval for the resultant medical device before the device can be supplied for use in the patients of the HCF. Depending on the requirements of the RA having jurisdiction, an abridged assessment for the resultant medical device may be undertaken leveraging the pre-market approval status of the MDPS. Following the pre-market approval, the HCF could have ongoing regulatory obligations to meet, including (but not limited to) supplying devices with appropriate labelling, post-market adverse-event reporting, advertisement compliance, and maintaining production and supply records.

3. Fully regulated manufacturing (as per the GHTF/IMDRF model)

In this case, the regulator treats HCFs and healthcare professionals that/who undertake manufacturing the same way they treat traditional manufacturers.

These 'POC manufacturers' need to ensure their medical devices are correctly classified and follow the usual regulatory requirements to obtain pre-market approval according to the risk classification in the jurisdiction in which the devices are supplied.

Manufacturers are required to meet both pre- and post-market regulatory requirements in the jurisdiction where their medical devices are supplied; these might include, for example, implementation of appropriate quality management systems; generation of clinical evidence; compliance with safety and performance standards; design; testing; manufacturing standards; undertake supplier control (including outsourcing[19] of different elements of manufacture); the provision of labels and information; registration; and post-market surveillance, corrective action, and adverse-event reporting.

Note: Relevant GHTF/IMDRF guidance documents are included in the references section above.

[19] The GHTF/IMDRF definition of 'manufacturer' allows for outsourcing of different manufacturing steps (including testing, validation, and sterilization) to third parties while the 'manufacturer', in this case the HCF or healthcare professional, takes legal responsibility for the entire quality management system and the medical devices manufactured under it.