PROPOSED DOCUMENT

International Medical Device Regulators Forum

Title: Personalized Medical Devices – Regulatory Pathways

Authoring Group: IMDRF Personalized Medical Devices

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Table of Contents

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 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 category of personalized medical device. The adoption of consistent, harmonized requirements for such medical devices will underpin a harmonized regulatory approach for controls on these devices and offer significant benefits to the manufacturer, user, patient, and to Regulatory Authorities. Eliminating differences between jurisdictions supports global convergence, decreases the cost of gaining regulatory compliance and allows patients earlier access to new technologies and treatments. This document overviews some of the considerations and concepts that may be relevant in developing a harmonised 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, for example, using additive manufacturing (3D printing) methods based on patient CT scans, on a commercial rather than artisanal scale. The original GHTF documentation does not adequately address 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 to cover special cases where commercially available mass produced products are inadequate for the needs and requirements of a particular patient. 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 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. Technology has made “custom-made” devices, including implantable devices for particular patients, within reach on a much greater scale. Consequently, some jurisdictions are noticing questionable use of custom-made device exemptions; with growing numbers of patients receiving higher risk classification medical devices to meet their particular needs, under these exemptions.

2.0 Scope

This document applies to all personalized medical devices, 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*.

Note: The regulatory recommendations in this document represent a best practice model for harmonizing the regulation of personalized medical devices across international jurisdictions. Individual jurisdictions may have particular requirements in place, which pre-date this guidance or are more specific than this guidance, for some or all of the device categories represented.

3.0 References

GHTF/SG1/N68:2012 *Essential Principles of Safety and Performance of Medical Devices*

GHTF/SG1/N78:2012 *Principles of Conformity Assessment for Medical Devices.*

GHTF/SG1/N70:2011 *Label and Instructions for Use for Medical Devices.*

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

GHTF/SC/N4:2012 *Glossary and definition of terms used in GHTF documents*

IMDRF/SaMD WG/ N10 FINAL:2013 *Software as a medical device (SaMD): Key Definitions*

ISO/ASTM 52900:2015 Additive manufacturing — General principles — Terminology

IMDRF/PMD WG/N49 FINAL:2018 *Definitions for Personalized Medical Devices*

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[1]

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 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.

[1] For further information, including examples for these definitions see: IMDRF/PMD WG/N49 FINAL:2018 *Definitions for Personalized Medical Devices*

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
- 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.

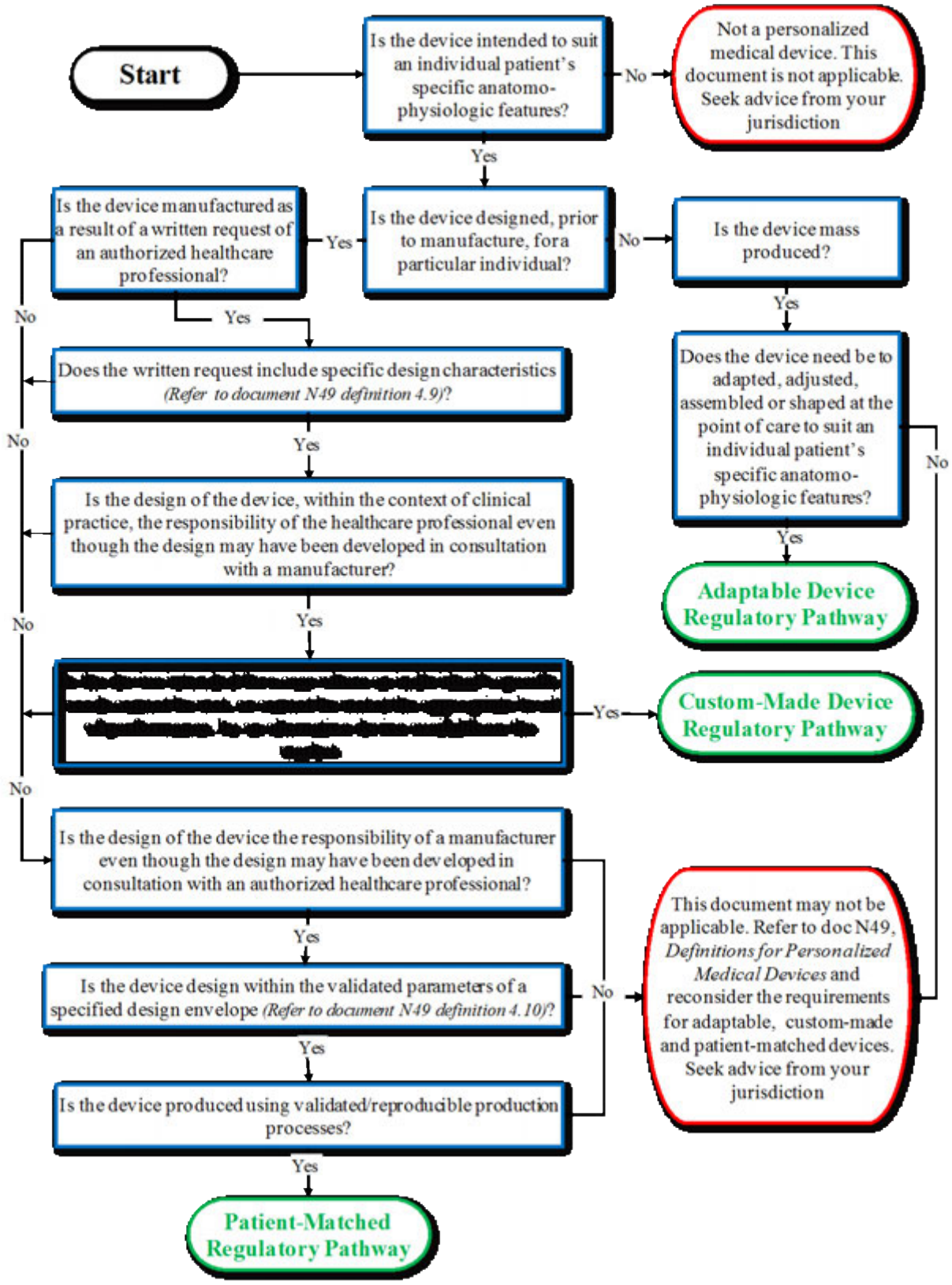
Note 2: The number and type of design inputs in consultation with a healthcare professional may vary depending on the medical devices to be manufactured.

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.

5.0 Decision Tree



6.0 Custom-made Medical Devices

General requirements

The manufacturer of a custom-made medical device should determine the classification the device would have were it not custom-made. The manufacturer should consider applying the equivalent safety and performance requirements, according to the device classification, of the jurisdiction in which it is supplied.

The safety and performance requirements are not intended to interfere in any way with the professional and clinical responsibilities of the requesting healthcare professional in the design and use of a custom-made device. These responsibilities do not fall within the scope of the relevant medical device legislation.

Manufacturing and record keeping

For higher risk custom-made devices, for example - permanent implants, it is recommended that the manufacturing is undertaken in a facility that is subject to third party oversight.

The manufacturer should consider whether the following are relevant for their custom-made medical devices:

- chemical, physical and biological properties of the device,
- infection and microbial contamination,
- method of sterilization,
- construction and environmental properties,
- protection against radiation,
- requirements for medical devices connected to or equipped with an energy source,
- information supplied by the manufacturer, including labels.

The manufacturer should review the requirements regarding information that is to be supplied with the device and determine what is appropriate for their products in the jurisdictions where they will be supplied.

It is recommended that the manufacturer should provide a statement with the custom-made device.
This statement should include:

- data allowing identification of the device in question, i.e. description, serial number, order number, generic name
- a statement that the device is intended for exclusive use by a particular patient, together with the name of the patient (this may be an identification number if patient confidentiality needs to be maintained, provided it can be traced through records to the named patient)
- 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 statement that the device in question conforms to all the relevant safety and performance requirements; and, where it does not, the grounds for believing it is safe for use
- the name and address of the manufacturer.

Additionally, it is recommended that the manufacturer should:

- retain and, upon request, make documentation, including a copy of the written request, available to the regulatory authority. The documentation should allow an understanding of the design, manufacture and performances of the product - including the expected performances - so as to allow assessment of conformity with regulatory requirements. The documentation for all implantable custom-made medical devices should be kept for a period of at least 15 years from the date of manufacture. For all other custom-made medical devices the period should be at least 5 years
- make the statement available to the named patient for whom the device has been manufactured.

Registration

It is recommended that custom-made medical devices and their manufacturers or local representatives are registered or notified to the regulatory authority in the jurisdiction in which they are supplied.

Post-market surveillance, corrective action and vigilance procedure

Manufacturers of custom-made devices should review and document experience gained in the post-production phase and set up a post-market vigilance system of reporting to authorities. Specifically, manufacturers should follow reporting requirements in the jurisdiction where their devices are supplied; for example reporting adverse events associated with the device, or field safety corrective action (e.g. a recall).
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 produced for a particular individual by a manufacturer within validated parameters of a specified design envelope. The variables within the design envelope are predetermined by the manufacturer and not the healthcare provider. As such, they can be considered to be mass-produced devices, with dimensional variations within a specified range. For this reason, the manufacturer of a patient-matched medical device must ensure the device is correctly classified, and must follow the usual regulatory requirements, according to the risk classification, in the jurisdiction in which the devices are supplied. These requirements include, for example, clinical performance, compliance with safety and performance standards,

manufacturing standards, the provision of labels and information, registration, and post market surveillance.

Manufacturing and record keeping

In order to demonstrate safety and performance for patient-matched medical devices, a manufacturer must identify the worst-case configurations, in terms of both device geometries and manufacturing variables, for the device. This is often done using simulation methods such as finite element analysis for the device geometry, and through standard methods of process validation for the manufacturing variables. The manufacturer must then perform appropriate validation and/or verification testing on physical samples that represent the worst-case, from both a design and manufacturing perspective, and bracket the intended design envelope to be supplied. This is to ensure that the full range of products 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.
The manufacturer should ensure that the technical documentation for patient-matched medical devices includes records for the design envelope validation process.

Additionally, it is recommended that the manufacturer should:

- maintain a copy of the written request or other specification document that includes the patient matching information. For all implantable patient-matched medical devices, this information should be kept for a period of at least 15 years from the date of manufacture. For all other patient-matched medical devices the period should be at least 5 years,
- make this 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, according to their risk classification, in the jurisdiction in which they are supplied. These requirements include, for example, clinical performance, compliance with safety and performance standards, manufacturing standards, the provision of labels and information, registration, and post market surveillance.

In addition to the usual requirements, validated instruction must be provided by the manufacturer of the device which explain how to adapt, adjust, assemble or shape the device. The validation must ensure that the permissible point-of-care changes to the device do not negatively impact the device’s safety or performance.

Appendix 1 – Considerations for personalized devices produced using additive manufacturing

Raw materials for additive manufacture

According to the GHTF definition of medical device[2], a 'material' can be a medical device. An example of a 'material' regulated as a medical device in some jurisdictions is dental resin material 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 original manufacturer. This means the resin manufacturer will have tested the safety and performance of samples of its device, when adapted or assembled according to its instructions. The original 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.

On the other hand, raw material for additive manufacture, as with any other manufacturing raw material, is not a medical device as it is not directly used for treating[3] a patient. Furthermore, the same approach that is applied to regulating dental resin material should not be applied to raw materials for additive manufacture. This is because regulating the raw material for a 3D printer will not ensure that the final devices it produces will comply with safety and performance requirements. Additive 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. Instructions for use provided by the manufacturer of the raw material for additive manufacture could not adequately specify control over all of the variables in an additive manufacturing process for all of the different types of devices it may produce.

Additive manufacturing system

If control over an additive manufacturing process outside of a regulated facility is needed, jurisdictions may consider defining and regulating a 'medical device production system' on the basis of the device it is intended to produce including the intended use for the device validated by the manufacturer of the medical device production system. In this case, and if appropriate to the applicable jurisdiction, the 'medical device production system' would not be regulated as a tool to allow universal printing of any medical device outside of a regulated facility.

For example:

[2] GHTF/SG1/N071:2012 *Definition of the Terms 'Medical Device' and 'In Vitro Diagnostic (IVD) Medical Device'*
[3] or any of the other medical device purposes in the GHTF definition of medical device

A *medical device production system* (MDPS) is a collection of the raw materials, software and digital files, and main production and post-processing (if applicable) equipment intended to be used by a healthcare provider, or healthcare facility, to produce a specific type of medical device at the point of care, for treating their patients.

- A MDPS includes the 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.
- The 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 intended medical device with the use of the supplied instructions.

Jurisdictions may introduce limits on the types of devices accepted for manufacture by a MDPS such as limiting them to low risk products only.

The manufacturer of a MDPS is regulated in a similar manner to the manufacturer of an adaptable medical device. The responsibility for the medical device safety and performance is with the manufacturer of the MDPS, along with the other responsibilities placed on a manufacturer in the jurisdiction where the MDPS is used.

Appendix 2 – Considerations for point-of-care production of personalized medical devices

Health institutions may be involved in manufacturing of medical devices for use in treating their patients. There may be different expectations for such medical device manufacturing in different jurisdictions compared with requirements placed on industrial manufacturing.

When certain exemptions or special requirements apply to manufacturing medical devices in health institutions, these only apply to devices intended to address indispensable clinical needs within that institution or its network of subsidiary or partner institutions.

Any exemptions for manufacturing within a healthcare institute 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.

Health institutions designing and/or manufacturing personalized medical devices at the point-of-care should consider the following to protect patient safety and ensure appropriate performance of the device:

(a) manufacture and use of the devices occurs under appropriate quality management systems,

(b) the health institution should have on file, and provide information upon request on the use of such devices to its competent authority, which should include a justification of the indispensable clinical needs and of their manufacturing, including appropriate quality management validation documentation, device designs or modifications and intended use;

(c) the health institution makes available to the patient receiving the device, the following information:

  (i) the name and address of the manufacturing health institution;

  (ii) the details necessary to identify the devices;

  (iii) a declaration that the devices meet the general safety and, where applicable, information on which requirements are not fully met with a reasoned justification therefor,

(d) the health institution draws up documentation under its quality management system that makes it possible to have an understanding of the manufacturing facility, the manufacturing process, 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 are met;

(e) the health institution takes all necessary measures to ensure that all devices are manufactured in accordance with the documentation referred to in point (d), and

(f) the health institution reviews experience gained from clinical use of the devices and takes all necessary corrective actions.

(g) the health institution will allow the regulatory authority to inspect the manufacturing processes when appropriate.