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Guidelines for the application of 3D printing in the field of medical devices

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[Abstract] This paper briefly summarizes the regulatory laws and regulations for customized additive manufacturing medical devices in China, the United States, and Canada. There are still some differences in the clinical use and supervision of customized medical devices in different countries. The establishment of a scientific supervision model for customized medical devices can better promote its development. At the same time, in the process of supervision, it is necessary to conduct long-term observation of customized medical devices, assess their risks, and trace their sources. It is advisable to strengthen communication and cooperation between regulatory reviewers, technical employees, and medical staff to jointly guarantee the safety and effectiveness of products.

[Key words] 3D printing; Medical devices; Regulations

1 Introduction

Three dimension (3D) printing (3DP), also known as additive manufacturing, prototyping, or solid freeform fabrication, is the construction of an object from a digital model of computer-aided design (CAD), with material being printed and added together layer by layer[1]. By different working principles, 3D printing techniques are classified into laser printing, inkjet printing, and material extrusion. Inkjet printing may be continuous inkjet (CIJ) printing or drop-on-demand (DOD) printing. Laser printing is divided into stereolithography (SLA) printing with drop-on-powder bed deposition (DoP) and SLA printing with DOD deposition; the extrusion printing system includes fused deposition modeling and pressure-assisted microsyringe printing systems[2]. Well-known and accepted by the public as "an

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important mark of the Third Industrial Revolution", 3D printing is a cutting-edge technology with a huge potential for development. It can be used in combination with new materials and new energy as a powerful influence for innovation in the manufacturing industry. At present, 3D printing has been widely used in the fields of construction, aerospace, restoration of cultural relics, civil engineering, and medicine, etc[3].

2 Development of 3D printing in medical field

Levetiracetam Tablet, the first 3D printed drug was approved by the United States Food and Drug Administration (USFDA) in 2015[4]. With a special grid structure and large internal surface area, the tablet can be melted and dispersed in only a small amount of water, and takes effect quickly, which are huge advantages of levetiracetam (a drug for treating epilepsy). The birth of 3D-printed levetiracetam allows people to focus on the application of 3D printing in the field of medicine.

Since 3D printing can be individualized, it is suitable for high-volume manufacture of the medical devices that match patients' conditions. China Food and Drug Administration approved the use of 3D-printed artificial hip joints and 3D-printed artificial vertebrae in 2015 and 2016, respectively[5]. Many orthopedic surgeries require the insertion of implants in the patient's body. With standardized shape and size, the implants produced by traditional techniques often do not match well with the patient's affected part, which may cause the loosening and even dislocation of the prosthesis during use[6]. Moreover, if the prosthesis does not match the patient's affected part in size, the anatomical structure of the patient will be changed to adapt to the prosthesis, resulting in a situation similar to the situation of "trim the feet to fit the shoes[7]". 3D printing can instead customize the most suitable prosthesis for patients according to the particular situation of their affected part, and precisely control the microstructure of the printed object to ensure the manufactured implant matches the body[8], thus changing the current situation of "trim the feet to fit the shoes" in the field of medical devices to the situation of "make the dress to suit the figure". Moreover, a long-term implantable medical device made of 3D-printed orthopedic titanium alloy carries no risk for precipitation of particles in the body's fluid environment, dislodgement of material in a dynamic environment, or potential sub-chronic systemic toxicity[9].

At present, 3D printing is widely used in the manufacture of orthopedic prosthesis[10], orthodontic brackets[11], and maxillofacial defect repair[12]. The materials used in 3D printing are mostly metal, ceramics, photosensitive resin, engineering plastics, and plaster, as well as some organic and inorganic polymer materials[13-15]. In 2011, an 83-year-old Belgian woman was successfully implanted with a 3D-printed mandible, and in 2014 the People's Liberation Army No. 411 Hospital successfully implanted China's first 3D-printed mandible, which was made of a titanium alloy, with the implanted patient recovering well[16]. Xu Zhiqing et al.[17] applied the 3D printing technology to treat bilateral knee osteoarthritis for a patient with pseudo-achondroplasia. X-ray reexamination of the patient one year later showed that the prosthesis was in good position, and the patient was very satisfied with the surgery. Open reduction and internal fixation of fractures is a common type of surgery in orthopedics[18-20], and internal fixation is the crucial step to promote the reduction and healing of factures[21-22]. In traditional surgeries, a bone plate made of metal[23-25] is often used, but it usually needs to be removed in a second surgery, since it cannot perfectly match the affected part of the patient. Qi Dahu, et al.[26] adopted 3D printing technology using degradable polylactic acid-based composites to manufacture a bone plate, which can not only match the affected part perfectly, but also

degrade itself after healing without the need for a second surgery.

3 Existing laws and regulations on the application of 3D printing in the field of medical devices

While developing rapidly in the medical field, 3D printing has not been subjected to adequate laws or regulations, as described below.

3.1 Domestic regulations for 3D printing of medical devices

The first batch of five group standards for 3D printing medical devices were published on June 28, 2019 by the 3D Printing Medical Devices Committee of the China Association for Medical Devices Industry, and officially implemented since July 20, 2019. The five standards have respectively specified the quality management system of customized implantable and non-implantable medical devices, the evaluation indicators, and acceptance criteria of doctor-designer-manufacturing supervisor interaction process for customized medical devices, the evaluation of a mechanical-equivalent model for customized medical devices, the terminology and definition of realization process for 3D printing medical devices, and the design & quality control of patient-matched artificial temporo-mandibular joints. Details are shown in Table 1.

Table 1 First batch of group standards for 3D printing medical devices

Scope	Name	Content
Special requirements for quality system of customized medical devices	"Group Standard for Quality System of Customized Medical Devices: Special Requirements"	Custom medical devices, especially high-risk custom medical device quality system special requirements are specified. (The customized medical devices referred to in this standard exclude the 3D bioprinting medical devices.)
Quality system and process control of customized medical devices	"Group Standard for Monitoring & Evaluation Indicators, and Acceptance Criteria of Whole Doctor-Designer-Manufacturing Supervisor Interaction Process for Customized Medical Devices"	Establishment of good doctor-designer-manufacturing supervisor interaction mechanism for the quality system and process control of customized medical devices, including personnel, design and development, raw materials, production equipment, production process, device quality control, document management and traceability; implementation of the whole-process monitoring to ensure the safety and effectiveness of the clinical application of customized medical devices; monitoring & evaluation indicators and acceptance criteria of the whole doctor-designer-manufacturing supervisor interaction process for customized medical devices.
Mechanical analysis of customized medical devices	"Group Standard for Mechanical-Equivalent Model of Customized Medical Devices"	Requirements and precautions for development of the mechanical model to predict the loading condition of the mechanical-equivalent model in evaluation for customized medical devices. Procedures for model verification and validation are recommended, to help check whether the mechanical-equivalent model analysis follows the recommended guidelines and includes the content that should be included in the analysis report.
Internet conditions for realization of customized additive manufacturing medical devices	"Group standards on Internet conditions for realization of customized additive manufacturing medical devices: General requirements"	Terminology and definition, interested parties, and related responsibilities for production of customized additive manufacturing (3D printing) medical devices; implementation conditions, security requirements for development, and maintenance of a web-based information platform.
Requirements for design & quality control of patient-matched artificial temporo-mandibular joints	"Group standard for patient-matched artificial temporo-mandibular joints"	Product design and type, materials, design evaluation, test methods, quality control, manufacturing, sterilization, and packaging of the patient-matched artificial temporo-mandibular joint; requirements for the information provided by manufacturer. Applicable to patient-matched artificial temporo-mandibular joints.

The second batch of group standards for 3D printing medical devices were published on June 18, 2020 and officially implemented on July 1 of the same year. The second batch contains a total of 10 standards, three of which are quality standards for oral implants or dental implants; two are quality standards for tantalum metal, the raw material for 3D printing; two are quality management practices for 3D printing medical devices; one is the quality specification for customized orthopedic surgical guides; and the remaining two are related to the performance evaluation and the quality uniformity evaluation of 3D printed metal implants. Details are shown in Table 2.

Table 2 Second batch of group standards for 3D printing medical devices

Scope	Name	Content
3D printing oral implants	"Additive Manufacturing (3D Printing) Oral Metal Implants"	The terminology of product quality uniformity for 3D-printed metal implants is clarified, and the evaluation method and indicators of product quality uniformity for 3D-printed metal implants are specified.
	"Additive Manufacturing (3D Printing) Personalized Dental Implants"	Specification of product design, materials, quality evaluation, test methods, quality control, manufacturing, heat treatment, sterilization, packaging, and information requirements of the personalized dental implants mainly manufactured by 3D printing technology.
	"Additive Manufacturing (3D Printing) Surgical Guides for Oral Implants"	Definition of oral implant surgical guide based on 3D printing technology, specifying the design, manufacture, requirements, test methods, and information provided by the manufacturer of the oral implant surgical guide.
3D printing orthopedic implants	"Additive Manufacturing (3D Printing) Customized Orthopedic Surgical Guides"	Definition, requirements, design, manufacturing, inspection rules, sterilization and packaging of the additive manufacturing (3D printing) customized orthopedic surgical guides; requirements for the information provided by manufacturer.
Quality evaluation of 3D printing metal implants	"Quality Uniformity Evaluation Indicators for 3D Printing Metal Implants"	Terminology of quality uniformity of 3D printing metal implants; quality uniformity evaluation methods and indicators of 3D printing metal implants. The quality evaluation of the product includes the following contents: evaluation methods and indicators of chemical components, internal quality, microstructure, size, surface quality, surface roughness, porous structure, and mechanical properties.
Quality of the production of medical devices	"Special Requirements for Production Quality System of Bioprinting Medical Devices"	Special requirements for the whole process of bioprinting medical devices, including design and development, production, sales, and after-sales services.
	"Special Requirements for the Production Quality Management System of Metal Additive Manufacturing Medical Devices"	Special requirements for the quality management system of manufacturing of the metal additive for implantable and non-implantable medical devices.
Metal raw materials for medical 3D printing	"Medical Additive Manufacturing Tantalum Metal Powder"	Technical requirements, test rules, labeling, packaging, transportation, storage and quality certification of medical tantalum metal powder in the additive manufacturing process with laser or electron beam as the energy source.
	"Standard for Clinical Application of 3D Printing Tantalum Metal"	Quality management and specification requirements for the clinical application process of customized 3D printing porous tantalum metal (porous).
Performance evaluation of 3D printing metal implants	"Finite Element Analysis Method for 3D Printing Metal Implant"	References for mechanical properties, locomotor functions, biological functions, and other performances of 3D metal implants in product design and verification phases.

The "Provisions on the Supervision and Administration of Customized Medical Devices (Trial)" (hereinafter referred to as the "Provisions") was officially released on July 4, 2019 by the National Medical Products Administration of China, and officially implemented on January 1, 2020. The Provisions standardized the definition, registration, design, processing, use, supervision, and management of customized medical devices. Furthermore, the Provisions promoted the development of customized medical devices, and ensured a safe use of medical devices for patients, while meeting their individual needs.

3.2 Foreign regulations of 3D printing medical devices

In 2009, the American Society for Testing and Materials (ASTM) established the Additive Manufacturing Technical Committee ASTM F42, which comprises eight subcommittees and 15 working groups, to formulate the technical standard for additive manufacturing from the aspects of terminology, process, materials, and test methods of additive manufacturing. In 2011, the International Organization for Standardization (ISO) set up the Additive Manufacturing Technical Committee ISO/TC 261, which consists of the working groups of terminology, processes, systems and materials, test methods and quality specifications, data and design, environment, and health and safety. The ISO and ASTM International established a joint advisory group with divisions for aerospace application, plastic additive manufacturing, and medical implants. The European Union Organization for Standardization also established the Standardization Committee for Additive Manufacturing (CEN/TC438 Comité Européen de Normalisation) to provide the best guidance for existing and future standardized technologies in the field of additive manufacturing.

On December 5, 2017, the USFDA issued the "Technical Considerations for Additive Manufactured Medical Devices" (TCAMMD), which specifies the technical factors that need to be considered for additive manufacturing of medical devices, from the aspects of design, material control, post processing, and considerations for testing. The TCAMMD specifies the 3D printing process, and the technical factors that need to be considered for 3D printing medical devices in light of 3D printing design, material control, post processing, and considerations for testing. In terms of design, the precision and imaging accuracy of 3D printing equipment, and its interaction with the design model need to be considered. In terms of material control, the recycling process of raw materials and whether the recycling will bring adverse effects on the finished product need to be described. Impacts of the post-processing technique of raw material on performance of the finished product need to be recorded. Testing needs to consider mechanical testing, dimensional measurement, quality characterization, cleaning, and biocompatibility[27].

The Canadian regulatory authority for medical devices issued a guideline for customized medical devices (Guidance for health care professionals on special access and custom-made medical devices) on February 18, 2016, which mainly introduces the definition of customized medical devices, guides production according to the design feature instructions given by medical staff, and only applies to specific patients or to medical staff with special needs.

There are multiple working groups under the International Medical Device Regulators Forum, including the Personalized Medical Device Working Group, which is mainly responsible for the terminology and regulatory requirements of personalized medical devices. On November 7, 2018, this Working Group issued the "Guidance of personalized medical device terms", indicating the initial uniform international understanding of personalized medical devices[28]. This guidance

gives the definition of "custom-made medical device" as a broad category, and classifies the personalized medical devices from high to low degree of their personalization into the "custom-made medical device", "patient-matched medical device", and "adaptable medical device". The highest regulatory requirements for the marketing of customized medical devices are for the highest degree of personalization. In addition to meeting the regulatory requirements and basic requirements for safety and effectiveness for this category of non-specified medical devices, computer modeling, and simulation methods of validation, as well as physical and mechanical performance testing are also required.

3D printing customized medical devices has great potential for development, but the production faces tremendous pressure in terms of supervision. Different countries are actively formulating relevant regulations to regulate and promote the development of 3D printing in the medical field. In general, 3D printed medical devices have been regulated by laws and regulations of different countries in regards to their definition, supervision model, pre-marketing, and post-marketing requirements.

4 Summary and outlook

3D printing has become the most promising technology in the personalized medical field for its ability to accurately control the structure of printed products. The customized medical devices manufactured by 3D printing technology can better match the patient's affected part, but they are available in small quantities, so it is difficult to verify and evaluate them in a way similar to traditional products. Moreover, the production of 3D printed customized medical devices involves many aspects, such as doctor-designer-manufacturing supervisor interactions, raw materials, design software, 3D printing equipment, monitoring and inspection, and other uncertain factors. Therefore, the quality control of the production system is rather important for customized medical devices, especially for high-risk implants. Each step should be strictly controlled, with highly operable and predictable measures for risk prevention and control established to guarantee the quality of the product and control for the risks.

Customized medical devices are a relatively special and innovative type of medical devices that bring new requirements and challenges to the whole industry in product design and development, production and processing, post-marketing tracing, and monitoring. As 3D printing is flourishing in the medical field, the demand for customized medical devices is also increasing. However, there are relatively few data on clinical use of these products. The development of any new thing will experience the process from sprout to maturity, so will the improvement of laws and regulation systems. Nowadays, there is a growing demand for 3D printing customized medical devices. From preliminary exploration to accumulation of clinical experience and related data, we will improve the technical guidelines and regulatory requirements to standardize the industry development and maximize satisfaction of personalized medical needs for patients, while ensuring safety.

Since customized medical devices are used for special purposes, there are higher requirements for their physical and chemical properties, as well as for 3D printing materials, especially the biocompatibility of materials. Therefore, the relevant laws and regulations should not only be applicable to the improvement of general standards for materials and technical processes, they also need to develop the specific and targeted application standards according to the particularities of the medical industry.

The regulatory authorities of drugs and medical devices in China have been building an evaluation and supervision system that is based on precise risk control and suits innovative medical devices.

The design and processing of customized additive manufacturing medical devices have fully reflected the necessity of building a good doctor-designer-manufacturing supervisor interaction mechanism. The scientific supervision of such medical devices can be achieved if: (1) Always pay attention to adverse events and risks of customized medical devices, collect relevant clinical information, conduct long-term observations to explore the root cause of the risk, and trace back to the production process to find solutions. (2) Ensuring the safety and effectiveness of products is a responsibility shared by the supervisor, reviewer, researcher, and medical staff, who should strengthen mutual communication. The supervisor and reviewer ensure that the product is manufactured in accordance with laws, and that the review and approval procedures are justified and well-founded. As the main body of product development, the researcher and medical staff should listen to demands of patients, provide the products that suit patients better, fully consider and meet regulatory requirements during product development to ensure product safety.

The standard for 3D printing medical devices not only guides and regulates the development of the industry, but also provides an important support for the supervision of such medical devices. It is also an important guarantee to achieve mutual promotion and effective interaction between supervision and innovative development.

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