Savitha Bhat et al /J. Pharm. Sci. & Res. Vol. 11(7), 2019, 2515-2520

ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

Comparison of 3D Printing in USA, Europe and Australia and IPR

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Abstract:

3D (3-dimensional) printing is a promising technology which is emerging rapidly in the field of life sciences. U.S., E.U. and few countries have the rules on 3D printing for pharmaceutical product. 3D printing is employed in both additive manufacturing and prototyping. The objective of this study is to delve in the regulative parameters of 3D printing in US, Europe and Australia. Food and Drug Administration has established a guidance to deliver the Agency's initial thinking on technical considerations specific to devices using additive manufacturing and the general category of manufacturing encircling 3D printing and also the IPR concerned in 3D printing. The purpose of change to existing regulative framework in Australia is confirm acceptable regulations of customized medical device like those being allowed by 3D printing. European medical devices law is presently being redrafted with the intention of introducing a novel Medical Devices Regulation. The comparison is made by user need, design input, performance requirement, design process, functional requirements, design output, verification and validation, bio printing law regulative prospective, standardization and certification. With the technological advance in additive manufacturing, 3D bio printing technologies have arisen as an efficient tool for regenerative medicine and tissue engineering by adopting computer aided manufacturing into health care delivery. The novelty of 3 D printing is safeguarded by intellectual property rights. The applications for 3D printing in the healthcare field, and the technology make it possible to create and administer patient-specific solutions too.

Keywords: Additive manufacturing, 3D printing, Bio printing, IPR, Personalized medical device

INTRODUCTION:

3D printing is any numerous processes in which material is connected or coagulated under computer control to produce a three - dimensional object, with the material being added together; 3D printing is used in both additive manufacturing (AM) and rapid prototyping. Articles can be of any shape or geometry, and are typically created by digital model data from a 3Dimentional model or alternative electronic data source.

Devices prepared by 3D printing technology are subject to regulatory requirements similar to devices made by other manufacturing process. Medical devices may require pre-market requirements and post market requirements.

The objective of the study is to compare the regulative parameters of 3D printing in United States, Europe and Australia and the IPR involved in 3D printing and their application in health care system. [1]

DISCUSSION

3D printing is a technology that has remodelled numerous areas of human activity over a previous couple of decades, being one in all the support of the fourth technological revolution. In current years, the practice of this technology in drug analysis has incontestable such potential. Professionals around the world entail that the pharmaceutical field has finally been given, once in two centuries, the chance to form a crucial scientific jump.

In the few last years, 3D printing of medical devices has gained universal consideration; specifically, merchandise like bone implants, artificial knees, and spine prosthetic device, that are customised for every patient. In 2017, the FDA released guidelines for producing medical devices and implants; but, there are currently no regulative guidelines on the 3D printing of different products. **Figure I** depict the process involved in 3D printing and **Figure II** describes the steps involved in 3D printing.

FDA introduced the principal 3D printed drug product, Spritam® (levetiracetam) in 2015. This unlimited technological step leads to the expansion of analysis on 3D printing technology to supply drug delivery devices. [2]

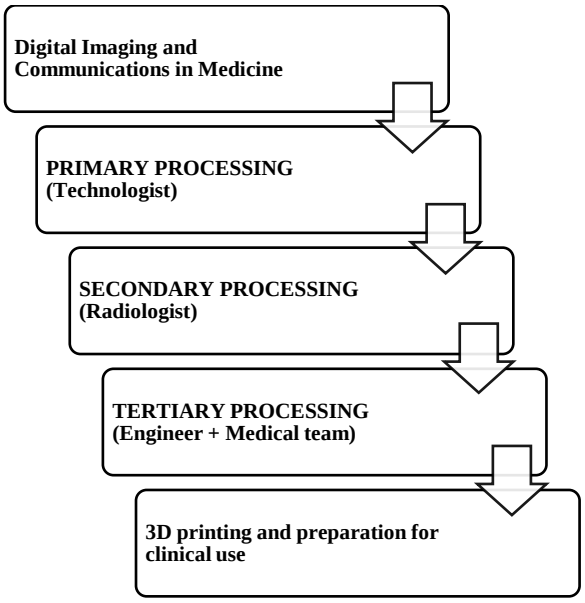

Figure I: Process involved in 3D printing

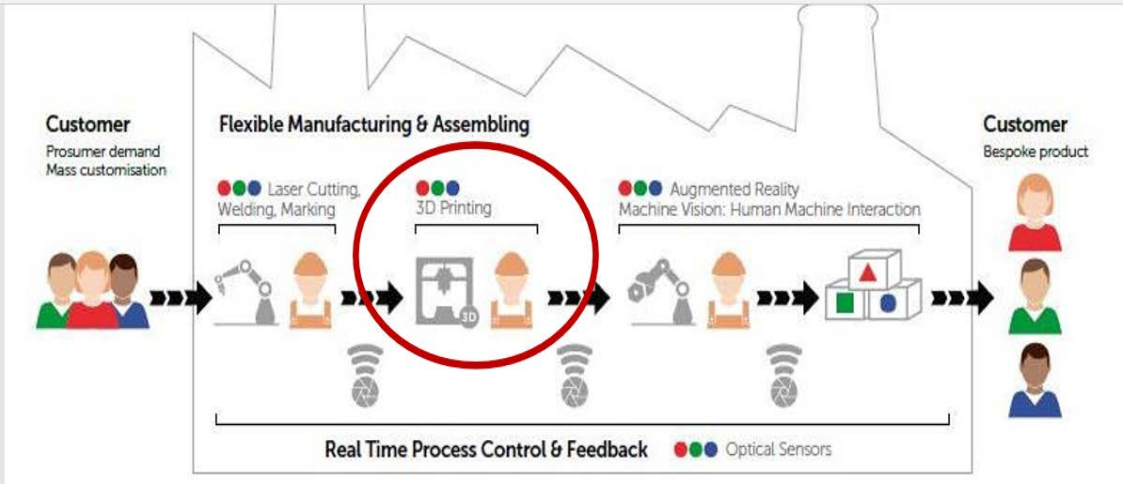

Figure II: Steps involved in 3D printing

UNITED STATES:

FDA role in 3D printing:

The FDA's CDRH controls companies who manufacture, repackage, re-label, and/or import medical devices oversubscribed within the US.

Technical Considerations for Additive Manufactured Devices was issued by FDA in 2016. This guides the manufacturer to produce devices through 3D printing techniques. The FDA is presently assessing submissions for new 3D printed medical devices to regulate efficacy and safety. This guidance is divided into two areas:

- **Design and Manufacturing Considerations** accomplishes the Quality System (QS) requirements for a device, are addressed as portion of accomplishing Quality System (QS) necessities for a device, as determined by its regulatory classification to which it belongs. While the guidance contains manufacturing considerations, it is not intended to methodically address all considerations or regulatory requirements to create a quality system for the manufacturing of a device.
- **Device Testing Considerations:** Designates the type of material that should be delivered in humanitarian device exemption (HDE) applications, de novo requests, investigational device exemption (IDE) applications, premarket notification submissions [510(k)] and premarket approval (PMA) applications, for a 3D printed device. [3]

Overview of medical device regulation: *[4]*

Annual registration with FDA – 21 CFR 807

- Fees structure:

Year	FY 2018	FY 2019
Fees	$ 4,624	$4,884

- Registration and listing of information submitted electronically
- Pre-market approval : 21 CFR 814
  Submission of clinical data to support claims made for the device.
- Quality system regulation: Control of designing, packaging, labelling, storing, installing of device
- Labelling requirement for medical device is according to 21 CFR 801

***Regulatory aspects*:** [5]

- Quality System (QS) requirements for a regulated device
- Recommends proper management of personally identifiable information (PII) and protected health information (PHI) in accordance with U.S. Health and Human Services (HHS) Guidance through appropriate cyber security measures.
- Software workflow includes file format conversions in the guidance, noting that file critical attributes and performance criteria should be verified as part of the software workflow validation to ensure expected performance, particularly for PMDs.
- Validation of the materials contains: Risk-based determinations for appropriate validation activities generally and on process validation activities specifically, recommendations for which have been articulated throughout the guidance.
- Quality data: To recognise existing and potential reasons of nonconforming product, or other quality problems is an important part of any quality system.
- Labelling: Device-specific guidance documents and consensus standards.

Application of Medical device in US: [6]

Customized devices are formed precisely for the patient, based on individual features, such as anatomy.

Powder bed fusion: It is method used to build a 3D product from plastic powder or very fine powder, which is transferred onto a platform and smoothed carefully. FDA Powder Bed Fusion printer is showed as **figure III.** An electron beam or laser then travels through the

powder layer and softens the material it touches. Molten material fuses to the layer below it and to the powder around it to make a solid. [7]

1. FDA-approved 3D-printed pharmaceutical on the market is Spritam (Anti – Epileptic Drug)
2. 3D-printing technology developed in surgical manufacturing, particularly in research and development.
3. Using 3D printing, hearing aid company Sonova is capable to mass-produce hundreds of thousands of custom-made products per year.

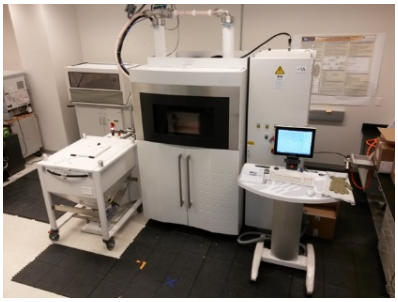

Figure III: FDA Powder Bed Fusion printer

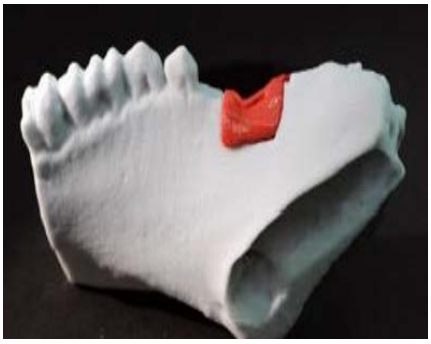

Figure IV: Regenerated tissues of mouth

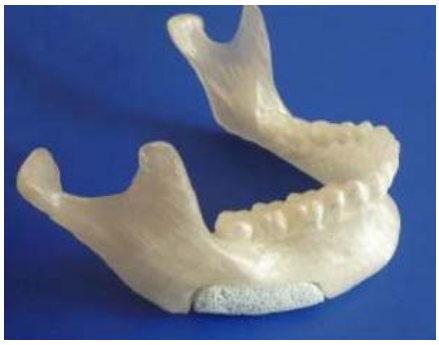

Figure V: 3D printed tooth

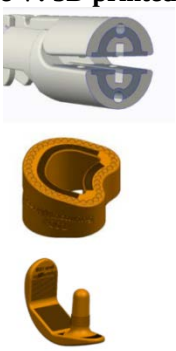

Figure VI: Cross sectional view of micro surgical tool

Future of 3D printing:

A paediatrician can adjust everyday dose of steroids to a 4 year old child who is diagnosed with Duchenne muscular dystrophy. The paediatrician will prepare a tablet according to the taste of the child by noting on the computer and the tablets will be 3D printed in the hospital pharmacy.

EUROPE:

As per European Commission´s study on categorising, present 3D printing industrial value chains in the EU (2016) classifies medical devices into the five subsequent groups: Bio manufacturing, Inert implants, Medical aids, supportive guides, Models for preoperative planning, instruments, Tools and parts for medical devices, splints and prostheses,

3D-printed medical devices offer several benefits when correlating them with their traditional equivalents, safeguarding unique customisation to patients. Additive manufacturing (AM) technology enables the manufacture of complex structures, permitting medical devices to match the needs of the human body precisely. [8]

Regulatory aspects:

- **Regulatory framework and barriers for AM**

1. ISO/ASTM TC 261 - ASTM F42 - CEN/TC 438 : Standardisation
2. Digital Single Market EC Communications

- **Certification**

1. Regular medical device: CE-marking
2. Customized implants : No CE-marking

- **Approval of 3D printed implants for surgery**

a) Surgeon has to request for manufacturing an implants via AM
b) Approval by the Ethical Commission of the hospital
c) The patient has to agree with the use of 3D-printed implants for surgery.

The process has to also comply with the ISO 13485 standards (or equivalent) which specifies “requirements for a quality management system where an organization needs to demonstrate its ability to provide medical devices and related services that consistently meet customer requirements and regulatory requirements applicable to medical devices and related services”.

Growth of Additive Manufacturing in research and development in the year 2010 & 2016 is shown in the **Figure VII & VIII.**

Applications:

Bio-Scaffolds: Bone - forming cells

Cell encapsulating bio- silica alginate hydrogels is a novel oestrogenic customized scaffolds for tissue regeneration. **Figure IV & V** depicts the images of Regenerated tissues of mouth & 3D printed tooth respectively.

Ceramic AM Personalized medical products

Ceramic is used in additive manufacturing (AM) of Implants Suspension and also the Micro surgical tools. Refer **Figure VI**

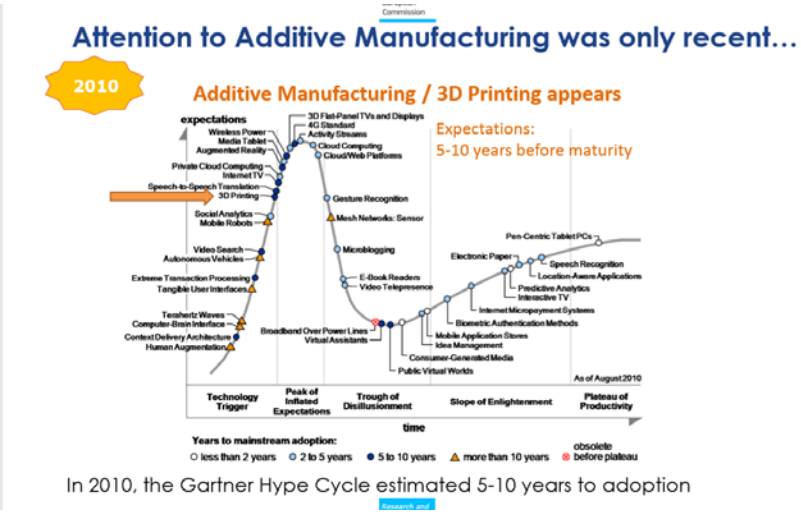

Figure VII: Growth of 3D printing in 2010

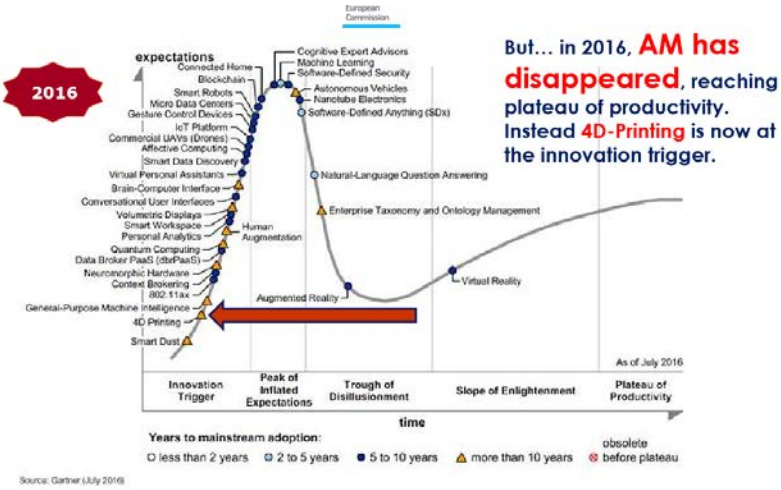

Figure VIII: Status of 3D printing in 2016

AUSTRALIA:

In Australia, the medical device regulatory framework was advanced before 3D printed medical devices were in clinical use. Under the present framework any articles that meet the definition of a Medical device, with those that are manufactured with the use of 3D printing, are subject to regulation. For mass produced 3D printed devices there is no change in regulatory requirements compared with predictably manufactured devices.

The custom made conformity assessment process needs a manufacturer of a custom made medical device to undertake four activities.

A producer must:

- Make a declaration about the device and its submission with the essential principles
- Get ready with a certification for the device in relation to its intended performance and design production;
- Check that the industrial procedure results in the device fulfilling with its proposed performance and design of the device ;
- Inform the secretary of possible adverse reaction, or recalls of the device.

Regulatory aspects:

A 3D printed medical device should be regulated as one of the following:

- **Custom-made devices**
  - As per custom-made device in the EU MDR, they are not 'mass produced'.
  - Custom-made devices should continue to be exempt from inclusion in the ARTG (Australian Register of Therapeutic Goods).
  - ARTG inclusion - will remain a condition for obtaining reimbursement using the standard health technology assessment (HTA) processes.
- **Patient matched or patient specific devices**
  - Mass production based on a standard device template model that is matched to a patient's anatomy.
  - Patient matched/ specific devices are included in the ARTG and should

qualify for reimbursement, like any other medical devices.

Standards applicable to 3D printed medical devices

- MTAA (Medical Technology Association of Australia) agrees that state-of-the-art standards that are relevant to medical devices in general should be valid to 3D printed medical devices
- Demonstrating the compliance with the Essential Principles of performance and safety.[10]

Bio printing:

Complete biological part, including the cells, the extracellular matrix and other components that make up the bone and gum tissue can be produced by bio-printing technology.

Bio-printing has ethical, legal and regulatory aspects. Struggles are emerging in the area of intellectual property over 3D printing, additive manufacturing and bio-printing. Product liability is the greater issue in 3D printing. [9]

Applications of 3D printing in Australia:

- Anatomical models
- Surgical tools
- Dental devices
- Bio printing
- Implantable orthopaedic devices

Table I summarizes the comparison of 3 D printing in US, EU and Australia

INTELLECTUAL PROPERTY RIGHTS:

Shielding an object from being printed in 3D without authorization does not raise any specific IP issues as such. Copyright will shield the innovation of work and the creator's right to replicate it. The copyright law can assist the innovator if the original object is 3D printed without authorization. Similarly, industrial design rights guard an attractive and artistic presence – its shape and form - while a patent shields its technical function, and a three – dimensional trademark permits inventers to differentiate their products from those of their competitors.

Gaps in IP laws:

- Who owns an article when it is first considered by one individual, digitally modelled by another, and printed by third?

The individual who designed the work and the person who is digitally modelled it is considered co-authors of collaborative work under copyright law?

The objects qualify for patent protection, would be the same individuals be considered co-inventors?

- The type of protection available for the owners of 3D printing: Because of financial investment producers can enjoy the rights

Table 1: Comparison of 3 D printing in US, EU and Australia

PARAMETERS	UNITED STATES	EUROPE	AUSTRALIA
Regulatory Authority	USFDA (CDER)	EMA	TGA
Classification	Class iii	Class iii	Class iii
Law/ directive	Technical Considerations for Additive Manufactured Medical Devices	3D-printed medical devices Report on promising key enabling technology- based product	Consultation: Proposed regulatory changes related to personalized and 3D printed devices
Design input	Patient matched device designed from patient own medical image	Esthetical preferences of the patients	Patient-matched medical device
Functional requirements	Operational qualification	Operational qualification (follow the FDA)	Realistic anatomical geometries
Performance requirements	Additive Manufacturing and Hot Isostatic Process	Additive manufacturing	Safety
Design process	Standard design	NA	NA
Design output	Development and documentation	NA	NA
Verification	Non-destructive evaluations	Non-destructive evaluations	Safety, performance and clarification
Validation	Quality	Quality	Quality management system
Bio printing law regulatory perspective	IP, regulation of distribution, premarket restrictions, control mechanism	Protecting human health and safety	Regulated as per biological framework
Standardization	ISO/ASTM 52915	ISO/ASTM TC 261 - ASTM F42 - CEN/TC 438 Digital Single Market EC Communications, 2016	ISO 31485
Certification	QMS certification	CE marking	QMS certification

***NA: Not Available**

Measures to control unauthorized use:

The objects can be safeguarded by copyright, such as: to mark an object and its correlated 3D print folder with a unique identifier to monitor use.

Cooperation between 3D printer manufacturers and right holders, in applying these measures to models proposed for 3D printers could be advantageous. Likewise, partnerships with sharing platforms that create 3D files publically obtainable could support control unauthorized use.

3D printing is deeply embedded in daily life because of regenerative medicine to prosthetics and gathers pace and digital transformation continues to gain momentum. [10]

Regulatory issues:

Spritam® is an oral, fast disintegrating pill, approved by current legislation for large-scale industrial manufacture. The 3D printing procedure developed upon a disintegrating methodology, providing the drug contained a best-known active pharmaceutical ingredient (levetiracetam), in an allowed dose (up to a thousand mg) to treat an established condition (epilepsy). 3D printing in an industrial scale presents profits, because the plan of compound geometries, when related to different technologies, like tableting, isn't as inexpensive. Custom-made formulations, 'polypills' and orphan medications made in tiny batches can spread places the pharmaceutical business cannot envisage.

Many 3D printing technologies have lost their patents over the last decade; that was conclusive; consider creating this machinery more available to the general public and to the pharmaceutical business. The patentability procedure, especially with reference to intellectual property rights linking 3D printed drug product, ought to be organized to innovative processes or product. The patent owner has clannishness on the merchandise or method until the concession expires; within the meanwhile, different manufactures might not produce, use, or sell without the owner's authorization. [11]

CONCLUSION:

Currently, devices created by the 3D method are regulated equally to devices created through ancient producing strategies. The regulative framework that must be applied in 3D printing is comparable to it of the conventionally manufactured device, apart from the fact that 3D printed device is employed nearly instantly after fabrication, thereby not allowing for prolonged quality assurance process. Food and Drug Administration has updated the initial guidance document on 3D printing. TGA has better laws, but the regulations within the EU need to be updated. The analysis is going on in the field of 3D printing and also the amended laws may be proposed in close to future. IP law will defend each 3D files and people mistreatment 3D printing technologies for non-commercial functions. The possibility of 3D printing for the development of personalized drug products is undeniable; however, machine diversification are basic for proper pharmaceutical use. Additionally, a viable production method desires the co-participation of the pharmaceutical business (to produce filaments on an oversized scale), and digital pharmacies (to print medicine according to patient-specific prescriptions). Finally, regulative and patent agencies ought to work along with firms to carve a solid path into the market.

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