MiniReview Article

Transfiguring Healthcare: Three-Dimensional Printing in Pharmaceutical Sciences; Trends During Covid-19: A Review

Three-dimensional(3D) printing is a unique technique that allows for a high degree of customization in pharmacy, dentistry, and the designing of medical devices. 3D printing satiates the increasing necessity for consumer personalization in these fields as custom-made medicines catering to the patients' requirements are novel advancements in drug therapy. Current research in 3D printing indicates reproducing an organ in the form of a chip, paving the way for more studies and opportunities to perfect the existing technique. In addition, we will also attempt to shed light on the impact of 3D printing in the COVID-19 pandemic.

ABSTRACT:

Keywords: 3D Printing, Additive manufacturing, 3D Printing in Pharmaceutical sciences, 3D Printed Drugs, Personalised medicine, and COVID-19 impact on 3D printing.

INTRODUCTION:

Three-dimensional printing or 3D printing is a technique of additive manufacturing, where a three-dimensional structure is obtained either by deposition or solidifying many layers successively[1,2][3]. The material extruded in many layers can be a polymer, hydrogel, photosensitive resin, and many more. This technology finds applications in a wide variety of fields such as aerospace research[4,5], automotive industry, consumer goods industry[6][7]. The extraordinary features of this method are accuracy, repeatability, and reliability. [8][9]

Recent studies have led to the introduction of a novel application of this technique in the fields of regenerative medicine[10][11–18], which utilizes cell-based materials[19] and stem cells[20][21], medical device development[22–28], dentistry and especially 3D printing of drugs in pharmaceutical sciences and printing of organs. [29]

Some of the most recent achievements using 3DP in pharmacy are drug delivery systems with multifunctionality, personalized medicines, adjustable dosage forms, accelerated drug release delivery systems, customized implants suitable for a specific patient body anatomy.

3D printing technique has garnered substantial attention from all over the world for being a helpful tool in precision placement of biologics such as live cells, nucleic acids, growth factors, and proteins to imitate natural anatomy, biology, and physiology of tissues. The research has shown the potential of precision placement of drug particles, kindling interest in personalized medicine. [30]

As the medical field is pressing forward, it is inevitable to accept that tailor-made formulas won't work because of the overwhelming differences in the physiological action from one individual to another. Personalized medicine is the future to upsurge the efficiency of drug delivery systems and decrease toxicity[31], and this is where 3D printing finds its applications. With the help of this technique, manufacturing complex pharmaceuticals, the on-demand manufacture of drugs becomes easier[6]. The ability to fabricate pharmaceutical products during pandemics, emergency operations, military, and healthcare units where time and resources are limited poses an interesting pharmaceutical application of 3D printing.[8] [32]

As of dentistry, 3DBP has emerged as an exciting technique in the regenerative aspect. The printing of cellularized scaffolds has allowed the precise positioning on demand [33]. The stands play an essential role in obtaining functional tissues, as the support they give helps stimulate attachment, proliferation, and differentiation. 3DBP is a prospective, helpful tool to help investigate the application of scaffolds in dentistry to enhance the regeneration tissue and alveolar bone.[34]

After the coronavirus disease, 2019 (COVID-19) started as an outbreak in Wuhan, China, the demand for N95 respirator masks, face shields, ventilator valves, testing kits, and other personal protective equipment (PPE) are on the rise, but the supply limited worldwide. 3DP is an exciting approach to address this issue, which poses the effect of this pandemic on design innovation and prototyping during a pandemic.[35]

2. 3D PRINTING IN PHARMACEUTICAL SCIENCES- CURRENT ADVANCES [36]

In line with the advances, there are also specific challenges in using traditional methodologies in drug discovery. Figures 1 and 1A below are a schematic representation of challenges and the application of 3D printing to overcome the obstacles.

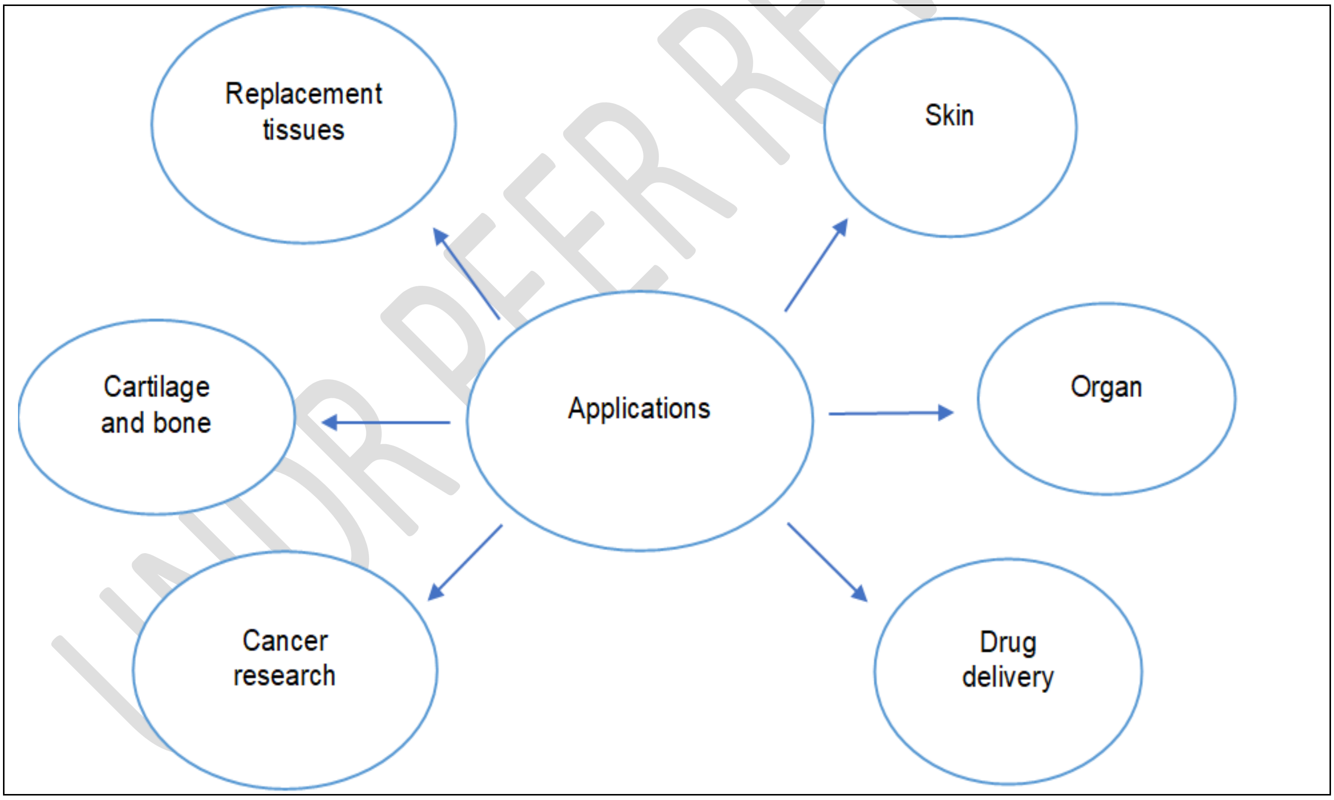

Figure 1: Applications of 3D printing

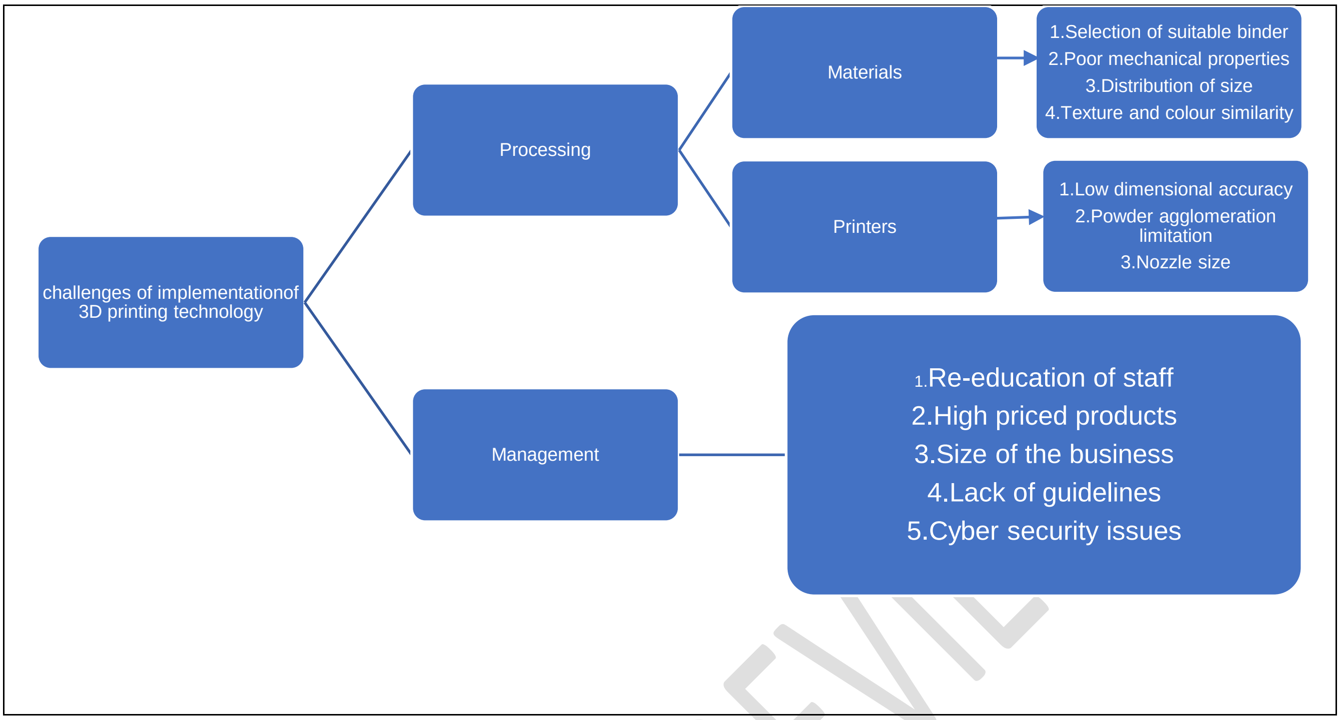

Figure 1A: Challenges of implementation of 3D printing technology

The applications of 3D printing use of various techniques in pharmaceuticals are present in Table 1. Table 1 below shows the diverse 3D printing techniques used in pharmaceutical sciences and their principles.

Table 1: Various 3D Printing techniques used in Pharmaceutical Sciences.

Sl no	**Name of the technique**	**Principle**	**Dosage form prepared using the technique**	**Ref**
1	Binder jetting	• Powder solidification. • Selective deposition of the binder.	Levetiracetam tablets for oral suspension, Chlorpheniramine maleate and fluorescein tablets.	[48] [49] [50]
2	Drop on solid deposition	• Powder solidification • Liquid binding of powdered material .	Isoniazid sustained release implant, Captopril rapidly disperses tablets.	[19]
3	Drop on drop disposition	• Solidification of liquid • Solidification of droplets.	Ropinirole HCL tablets, Fenofibrate tablets.	[19]
4	Stereolithography	• Liquid solidification. • Solidification of photosensitive resin	Paracetamol tablets	[19]

5	Inkjet printers	• Droplet based printing, drop-on-demand printing • Thermal, piezo, or acoustic forcefully expels the droplets onto the supporting substrate, later solidified by mechanisms like crosslinking agents, pH, and ultraviolet (UV) radiation.	Folic acid nanosuspension, Rifampicin nanoparticle, Salbutamol sulfate solution, Levofloxacin implant.	[49]
6	Fused deposition modeling	• Extrusion based • Solidification of melted material.	Aripiprazole orodispersible films, Theophylline tablets, Budesonide caplet, Prednisolone tablet.	[19] [51] [52]
7	Pressure assisted Syringe	• Layer-by-layer disposition • A multi-syringe system with a single nozzle.	Guaifenesin bilayered tablet, Tablet 'polypill' with captopril, glipizide and nifedipine.	[53] [51]
8	Laser-assisted printing/ Laser direct-write	• Laser-based • Laser-centered on the substrates absorbs shock waves.	4-aminosalicylic acid, paracetamol tablet.	[54]
9	Selective laser sintering	• Laser based, powder solidification. • Hardening of powdered material.	Paracetamol orodispersible tablets.	[19]
10	Acoustic ink printing	• Drop-on-demand • Droplets of ink are created and expelled underneath the effect of an acoustic field. The acoustic beam is targeted on a free liquid surface to eject distinct ink droplets of measured diameter.	Engineering of microenvironments with stem cells	[55] [56] [52]
11	Microvalve-based systems.	• Drop-on-demand. • Microvalves are attached to separate gas regulators that give pneumatic pressure and valve opening time through the solenoid coil and plunger. The bio-ink placed after the pneumatic pressure overpowers the fluid viscosity and surface tension at the opened orifice.	Gastro-floating tablets with hydroxypropyl methylcellulose-based dipyridamole paste.	[57] [56] [58]
12	Pneumatic/ Mechanical (piston or screw-based)	• Extrusion based. • A wide variety of drive forces allows the deposition of various biological substances with different rheological	Tissue printing substitutes or scaffolds of soft tissues, as well as the manufacture	[59]

		properties.	of complex drug delivery systems	

Advantages of exploiting 3d printing in pharmaceutical sciences:

- Drug discovery is a very time-consuming, costly process that adjures a considerable investment and human resources. Some recent efforts in 3D *in vitro* assay systems have shown potential in becoming an ideal solution for improving the prediction of efficacy and toxicity of drug candidates, thus speeding up the process of conversion on novel drugs to clinics. Researches done by many researchers shed a positive light on 3D printing being an effective tool in drug discovery.[30]
- 3D printing is considered the future of personalized medicine. With the current technologies of commercial methods of drug manufacture, it is impossible to cater to the need of customizing the medication.
- Because tissue models are fabricated in microarrays using 3D printing, they resemble and closely mimic the native tissues, thus can be used in high-throughput assays and toxicology studies[37].
- Printing is superior in microarchitecture, decreased risk of cross-contamination and size controllability[38].
- Generation of co-culture and single-cell array with precision in controlling cell density is an advantage for 3D printing. [30]
- 3D printing helps fabricate geometrically complex structures, enables architectural intricacy, simplistic construction of multi-layer drug delivery systems, and assists numerous controlled release mechanisms. [29][19]
- It enables the printing of custom-made multi-dose and multi-drug-containing dosage forms, designed based on the patient's weight and lifestyle, and help adjust dose and dosage form as essential for individual patients, which would prevent the risk of over or off underdosing. [19][29][8]
- The sheer ability of scalability and relatively low cost of production of drugs, especially for orphan drugs with a small demographic of patients, makes 3D printing more attractive.[19]
- The bioavailability of drugs is tweaked by fabricating multiple separate chambers loaded with different substances.
- 3D Pharming (the direct printing of pharmaceutical dosage forms) signifies an innovative process for engineering controlled release drug delivery systems. [8]
- An effective drug metabolism with the help of a micro-liver chamber fabricated with the help of soft elastomer lithography united with a micro-molding technique designed by the investigators of Sun's group. The drug used is a prodrug named 7-ethoxy-4-trifluoromethyl coumarin (EFC).[30]
- Tumor models used in cancer research are usually two-dimensional. However, 3D printing offers an accurate representation of the cancer microenvironment.[30]

Limitations of 3d printing in pharmaceutical sciences:

- To use the 3D printer at home, the patient needs special training. They might not identify and correct the deformities in design, which could highly likely alter the bioavailability and other aspects of the drug.[30]
- Polymers pose a challenge in printing a clinically significant tissue as the polymers widely used in various traditional tissue engineering processes might not be most appropriate biologically. Many of them are biologically too active, potentially causing unwanted effects on 3D printed tissues. [39]
- The shortcomings associated with the usage of conventional polymers have led to the invention of more biologically appropriate polymers and hydrogels. Still, these are not compatible with currently available 3D printing technologies as they lack structural integrity. [39]
- The mechanical forces used by the printer can cause an alteration in the geometry of the cell, and signal pathways even could potentially cause cell death.
- Current technologies of 3D printing are generally inefficient and take a lot of time to complete the whole process. There is a need to improve the efficiency. [39]

The limitations of applying 3D printing in the pharmaceutical sciences schematically represented in Fig 2 below

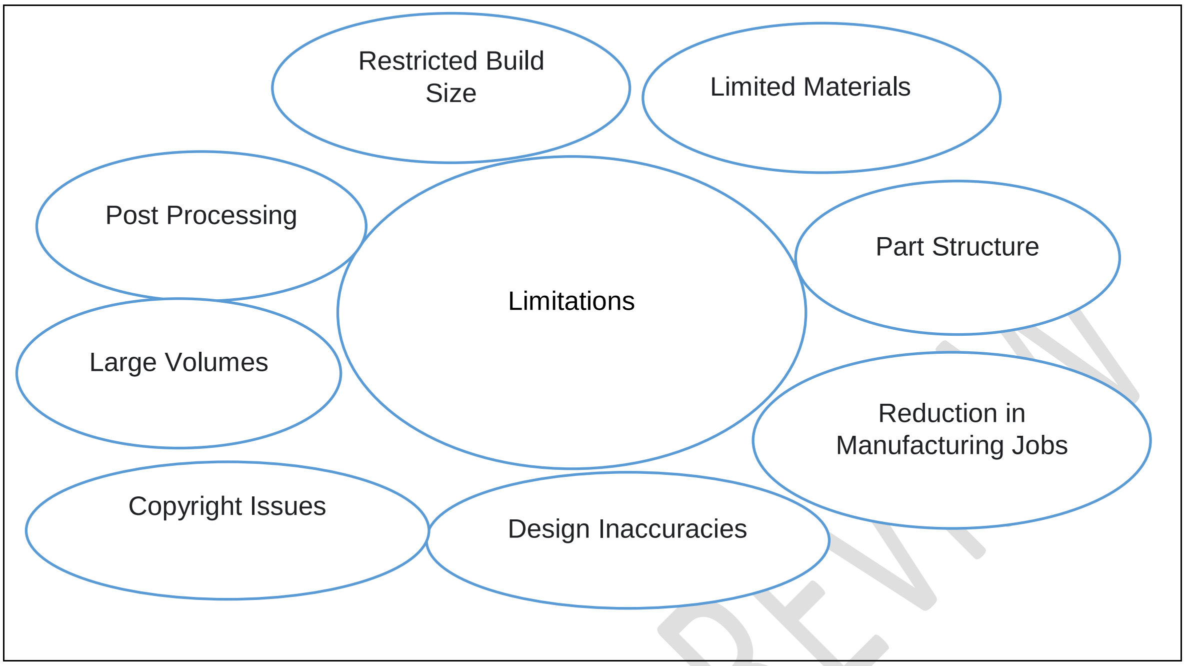

Figure 2. Limitations of applying 3D printing in the pharmaceutical sciences

4. COVID-19: EFFECTS ON 3D PRINTING DESIGN INNOVATIONS AND PROTOTYPING:

The official records regarding the outburst of coronavirus disease 2019 (COVID-19), identifies Wuhan, China, as the point of initiation; where the first case was on December 8, 2019[35][40]. With this being a virulent and highly contagious disease, the epidemic soon became a global pandemic when definitive information about this disease being spread across all continents was made available to the world. According to WHO, the death toll is rising exponentially worldwide, with 79,232,555 confirmed cases on December 27, 2020.

The patients affected with the novel coronavirus also have symptoms like fever, cough, myalgia, or fatigue. Some patients have shown headaches and hemoptysis. Comorbid patients are likely to experience respiratory failure. Some experience organ failure which would sometimes lead to death. Many are known to show no known symptoms (asymptomatic).[41]

This pandemic has caused a worldwide shortage of personal protective equipment (PPE) such as N95 masks, face shields, respirator masks, testing kits, and so on. 3D printing, among numerous other applications, is being researched to find its potential use to overcome the said shortage and fill in the critical gap in supply chains[35][42]. Many efforts made to look for alternative, cheaper ways to mitigate this void caused by the pandemic, and 3D printing is an exciting and potential approach.

3D printing-innovations due to the drive, that is; the pandemic:

- In a research article by Cavallo and others, they talk about expanding the use of CAD/CAM technology and 3D printing technologies used in dentistry to print plastic valves with the help of dentists in the hopes of helping mitigate the shortage of respiratory devices.[43]
- Due to the pandemic, many companies are experiencing a delay in shipping, forced turndown of an order, or delay taking new orders. The ability to virtually print anything anywhere has governments, universities, 3D printing enthusiasts; professionals readily volunteer to find innovative ways to overcome this problem. [42]

- The European Association for Additive Manufacturing has urged its member states to help manufacture medical equipment and other personal protection kits by lending the equipment in their AM industries.
- The colleges under the University of Idaho have teamed up and had 3D successfully printed the components of PPE kits for the usage of healthcare workers.
- Researchers of RMIT University, Australia, have produced a "clip-on" filter that can turn standard cameras of smartphones into a dominant microscope with the help of 3D printing technology.
- 3D printing firms have been volunteering in producing ventilator components, facemasks, test kits. An innovation of a 3D printed add-on, allowing the user to open the modern doors without coming in contact with the door handles by 'Materialize.'
- A company in China has mass-produced 3D printed safety goggles for healthcare workers in China. Another company of architectural basis, Winsun, has produced around 15 3D printed quarantine booths.[42]
- As efforts are going on to develop a vaccine for the virus, new measures to make a novel drug delivery system are being researched. It was identified that with the help of 3D printing, it is possible to dispense low volumes of drugs with precise exceptional control and very high accuracy.[40]

Figure 3 below is a schematic representation of the effects of covid-19 on 3d printing.

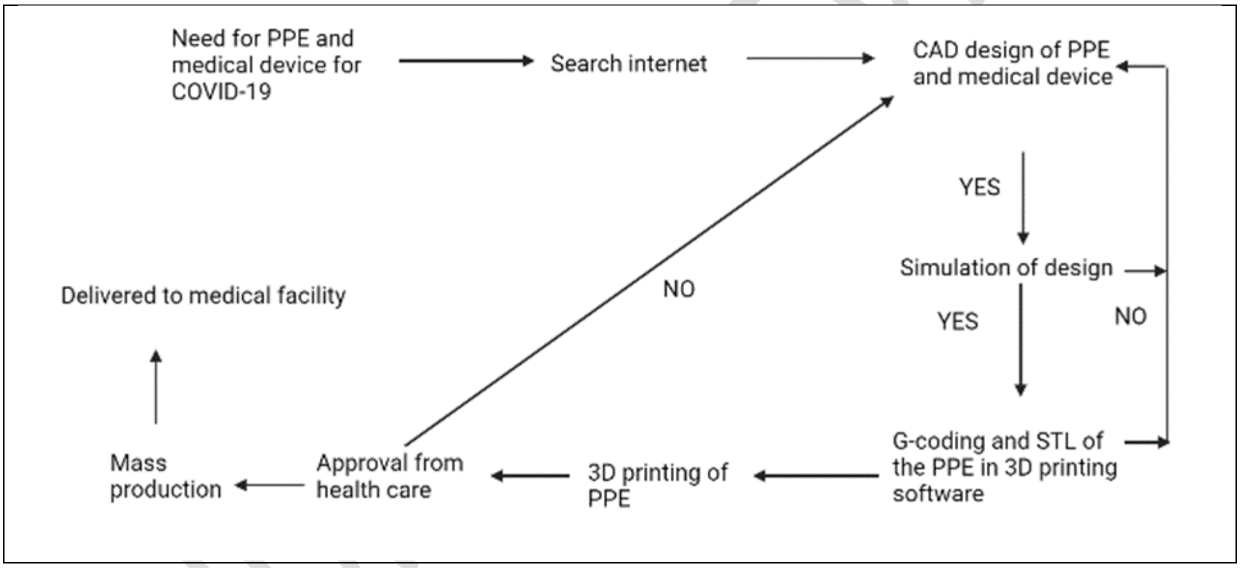

Figure 3: Schematic representation of effects of COVID-19 on 3D printing.

Table 2 below shows the compilation of the US patents, which indicate the use of 3D printing in either the whole process or at least one processor step relevant to pharmaceutical sciences and dentistry.

Table 2: Some patents regarding the usage of 3D printing in Pharmaceutical Sciences and Dentistry.

SL no	Patent heading	Inventors	US Patent no	Year of filing	Field of application
1	Medical devices including medicaments and methods of making and using same including enhancing comfort, enhancing drug penetration, and	Doshi; Praful	10,632,068	July 27, 2019	Pharmaceutical sciences, Medical devices.

	treatment of myopia				
2	Expandable gastroretentive dosage form	Menachem, et al.	10,485,758	June 2, 2015	Pharmaceutical sciences
3	3-D printed packaging	Divine, et al.	10,435,185	February 2, 2016	Pharmaceutical sciences and dentistry.
4	Dental implant system	Hertz; Paul	10,779,912	December 19, 2015	dentistry
5	Robotic ophthalmology	Gerrans; Lawrence J.	10,194,799	March 9, 2015	Prosthetics

5. REGULATORY ASPECT OF 3D PRINTING IN PHARMACEUTICAL SCIENCES AND DENTISTRY:

Legal aspect:

The increasing use of additive manufacturing in pharmaceutical, dentistry, and medicinal sectors have pointed towards the need for various legal considerations. According to Kririkos[44], grouped as:

- The aspect of data protection;
- Intellectual property rights (IPRs);
- The legal classification of 3D printing;
- Liability;
- Issues regarding safety;
- Security difficulties; and
- Socio-ethical planning.

Concerns and gaps in the current regulatory aspects regarding the use of 3d printing in pharmaceutical sciences:

Till today, there are no clear regulatory guidelines in any country that defines the apparent differences between bulk manufactured medicine and personalized medicine. According to the current regulatory and cGMP guidelines, it is possible to use 3D printing technology on an industrial scale based on the "one size fits all" ideology. The real problem arises when the idea of fabricating the products in a doctor's office, hospital, pharmacy, or even for personal use [45].

Currently, the regulatory structure that controls the manufacture, distribution, and compounding of pharmaceuticals using 3D printing differs from country to country, which adds to the issue.[46][45]

In the US, drugs compounded with 3D printing technology don't come under bulk manufactured drugs' compounding regulations; it is essential to include this under the existing compounding regulations.

The main concerns with printing at clinical study sites, hospitals, and pharmacies are health threats and safety features that arise from the usage of raw materials, organic solvents, and possible toxic degraded products that might be unknown. 3D printing involves the portability aspect, from where the concerns about robustness during shipping and changes in environmental conditions arise.

Protecting a CAD file is challenging as the final product under claim is a physical object. A CAD file is just a set of instructions based on the reproduction of material development with the assistance of a 3D printer.[47]

As for printing in a doctor's workplace or home, there are no guidelines for that yet.[45]

Intellectual property rights- For most IPRs, it is a given that they give the ability to prevent any third party from doing or undertaking specific actions. The IPRs are territory-based, meaning governed by a national basis, which slightly differs from jurisdiction-to-jurisdiction.[46]

3D printing products- European Union (EU) regulations: [44]

The new rules, i.e., 'The new Medical Devices Regulation (2017/745/European Union (EU)) (MDR) and the *in vitro Diagnostic* Medical Devises regulation (2017/746/EU) (IVDR) help in creating a robust, transparent and workable regulatory framework thus helping to lessen the risk of inconsistencies in explanation across the EU market.
Figure 4 below is the schematic representation of key points of the EU regulatory framework.

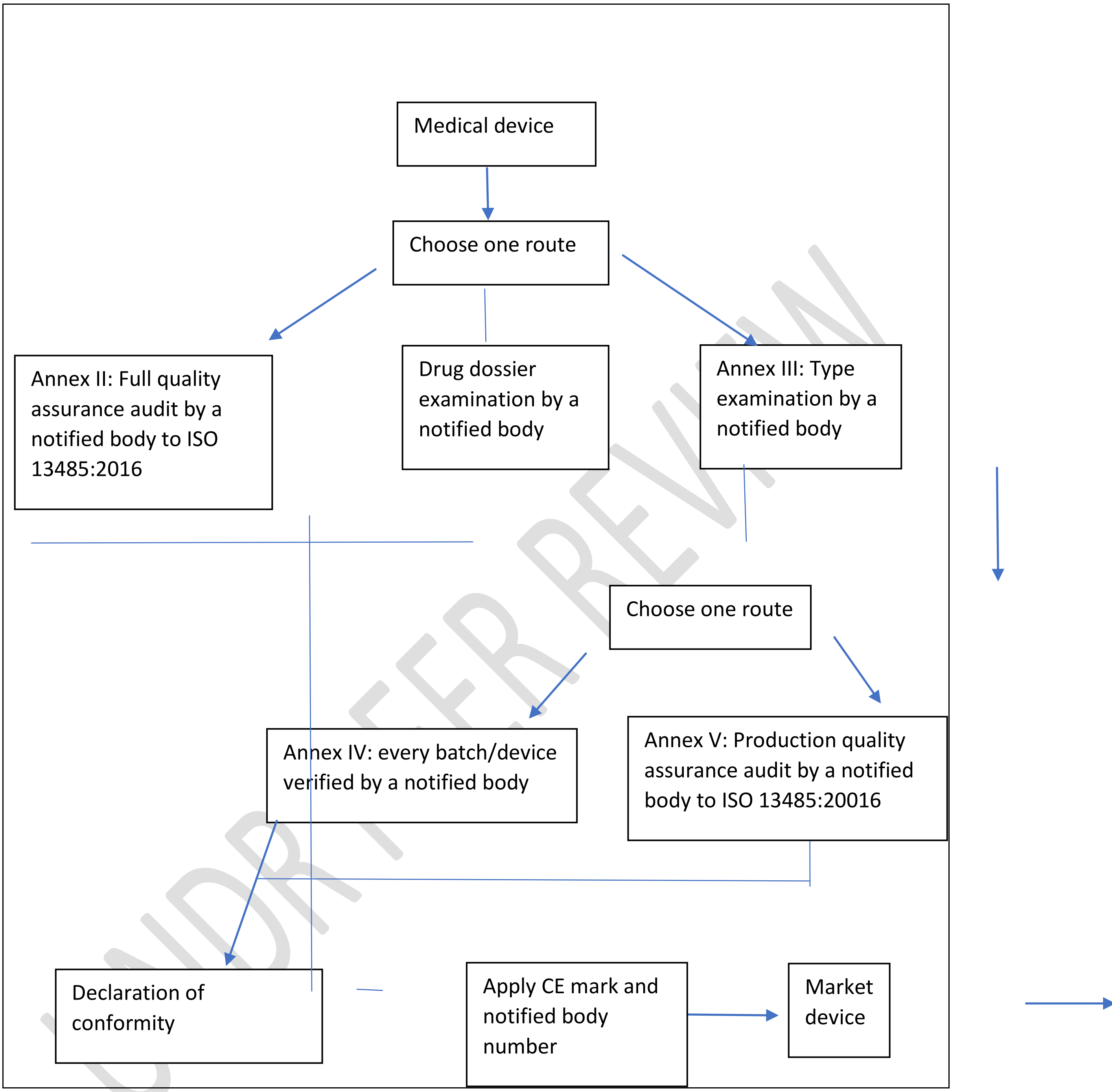

Figure 4: Schematic representation of key points of EU regulatory framework

6. CONCLUSION:

3D printing is an attractive tool for the customized production of medical devices, pharmaceuticals with personalized bioavailability. Dentistry has a fair share in using 3D printing techniques for various purposes, such as 3D printing on surgical tools with accurate grooves, dentures, crowns, implants, and many more. The COVID-19 pandemic, though it has affected thousands of lives, has provided the 3D printing enthusiasts with opportunities to innovate and prototype newer techniques to help the lack of availability of personal protection equipment. This article briefly summarises the abovementioned aspects, based on the data obtained from recently published works in the relevant areas.

7. CONFLICT OF INTEREST:

The authors reported no conflict of interest in the current work.

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