The Regulatory Aspects of 3d Printing: Implications for Pharmaceuticals

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Abstract

Like any other trend, the growth of three-dimensional (3D) printing in design and production is the result of foresight and action taken by those with the courage to make it happen. It is a type of additive manufacturing technology that has revolutionized engineering, product design, and manufacturing and holds enormous promise for doing the same for medicine. The Food and Drug Administration (FDA) of the United States has set the bar for an industrial revolution in pharmaceutical manufacturing by approving the first three-dimensional (3D) printed drug product. Nevertheless, according to regulatory standards, every product in every batch must meet certain requirements for quality, purity, and impurities. However, because the manufacturing, distribution, and compounding of medicinal products are governed by different legal frameworks in different nations, on-demand and industrial pharmaceutical 3D printing must take these differences into account. The purpose of this article is to discuss the current regulatory environment for 3D printing, as well as the regulatory gaps and challenges that must be addressed in order to advance the modern manufacture of medicines.

Keywords: *3D-Printing (3DP), Additive manufacturing, Point of Care (PoC), Health Care Facility (HCF)*

1. Introduction:

The newest cutting-edge technology, three-dimensional (3D) printing, has revolutionised engineering, product design, and manufacturing and holds enormous promise for doing the same for medicine [1]. The last ten years have seen a surge in interest in 3D printing (3DP), and it has been quickly embraced by sectors like biomedicine, aviation, pharmaceuticals, and automobiles. Although numerous traditional dosage forms and formulations were evolved over the years, they fail to cater to the desires of the affected person or a cohort [2]. The American Society for Testing and Materials (ASTM) defines 3DP as the "fabrication of objects through the deposition of materials using a print head, nozzle, or another printing technology" [3]. 3D printing makes it possible to quickly create actual objects from information in digital 3D models [4]. 3DP generation addresses those problems and contributes to the upgrading and improving of traditional pharmaceutical system techniques. Three-dimensional (3D) printing is a quick prototyping method that enables the manufacturing an object that was previously created using computer software, layer by layer [5]. Three-dimensional (3D) printing is a type of additive manufacturing technology that has opened up new possibilities for rethinking manufacturing paradigms in various industries that need the design and fabrication of items. [6]. Subtractive manufacturing, as used in conventional production, refers to frequently removing material from a solid block through milling. In contrast, 3D printing is a general word that refers to several techniques for building items layer by layer (for this reason, it is often called additive manufacturing). The initial idea of "powder bed printing," which entailed printing a liquid binder onto a thin powder bed, was invented at MIT in the United States. As a result of recent technological advancements, there are currently various sorts of 3D printers that might all be used to create pharmaceutical items. In every case, a computer-aided design (CAD) software programme is used to generate the object to be printed, which is then exported as a file for printing. The 3D model is divided into a number of layers in the exported file, which is subsequently printed one layer at a time. [7].

It has the potential to be a game-changing technology, reshaping the pharmaceutical industry's focus from mass production of fixed-dosage units to flexible manufacturing of individual units with dose or other characteristics customised for the patient (personalised medicine) [6]. Last year, the FDA approved the world's first 3D-printed drug, "Spritam", which contains levetiracetam, to treat seizures. This printed pill is excellently porous, which allows rapid dissolution (<4s) and makes the tablet easy to take. 3D printing has made it possible to create high-dose, fast-dissolving tablets, offering doctors reliable customisation and complete control over the speed and strength of the administered dose [8]. 3D printed medicines are often made consistent with individual preferences, with customised dose strength, pill size, flavours, and colours, which is particularly helpful once making ready doses for patients with difficulty swallowing, comparable to infants or physically impaired individuals [8]. 3-D printing strategies are appropriately mounted in different areas, including regenerative medicinal drug, however have no longer been extensively implemented for the fabrication of unit dosage forms, regardless of the apparent potential [9]. Partly that is due to the fact that it has to be commercially viable, a 3-D printed medicinal drug has to be able to bulk

manufacture in a time scale and of a unit cost similar to present methods, or it has to provide specific properties simplest and conceivable with the aid of using printing.

2. 3-D printing regulations:

Utilizing 3D printing to create formulations has its own special obstacles, some of which the healthcare sector may have never faced before, just like any other new technology [10]. However, despite its enormous potential and importance for the digital economy, it lacks a global policy. Some nations, like India, have primarily eluded appropriate regulation; yet, in others, the focus is only on specific industries, such as medical devices. Most significantly, there are a number of regulatory and technical issues that must be resolved before 3D printed products are incorporated into traditional clinical and drug development procedures [10]. Governments must concentrate on regulating 3DP as a whole and sector-by-sector whenever the need arises because industries worldwide are now looking to 3DP to determine the future of technology. This is especially important because the adoption of 3D technology varies widely by country and industry [11].

2.1 China:

China, the U.S., and the EU are the nations that are setting the pace for 3DP implementation and regulation [12]. China has invested a lot of time and effort into creating rules regulating its 3DP sector [13]. It created the "Additive Manufacturing Industry Development Action Plan (2017-2020)" in 2017 as an action plan for the growth of the 3DP industry. A year later, China's Center for Medical Device Evolution published rules for licencing and regulating 3DP medical devices, including those made to order via additive manufacturing [14]. China has since produced multiple standards for various 3DP medical devices, including a 2020 technical guidance for 3D printed replacement vertebrae and an acetabular cup [15].

2.2United States:

The US government is likewise progressing. In 2017, the Food and Drug Administration (FDA) released regulations for medical devices produced using additive manufacturing [16]. These recommendations advise assessing devices that contain at least one additive manufacturing technique or component. A roadmap covering manufacturing and certification criteria has been developed by the Federal Aviation Administration (FAA) for additive manufacturing in the aerospace industry for the next eight years. The FAA has also given its approval for the fabrication of 3D-printed engine components. By putting a series of bills before Congress, the US has made an effort to limit and control the misuse of 3D-printed weaponry. However, none of these have been made public yet. Today, medical devices are the most common category of 3D-printed products. A range of medical devices, including those with intricate geometry or features that precisely match a patient's individual anatomy, are produced using 3D printers [17]. Many identical replicas of the same device can be produced by printing some devices from a common design. Other devices, known as patient-matched or patient-specific devices, are produced using imaging data from a particular patient.

Commercially available 3D printed medical devices include:

- Instrumentation (e.g., guides to assist with proper surgical placement of a device),
- Implants (e.g., cranial plates or hip joints), and
- External prostheses (e.g., hands).

Although this research is still in its early stages, scientists are investigating how to produce biological organs like the heart or liver using the 3D printing technology. Several alternative technologies can be used to carry out the 3D printing process [18]. Numerous considerations, such as the intended purpose of the finished output and how user-friendly the printer is, might influence the technology chosen. Powder bed fusion is the most popular technology for 3D printing medical items [19]. Because it functions with a number of materials used in medical equipment, including titanium and nylon, powder bed fusion is frequently employed. In the powder bed fusion technique, very fine metal or plastic powder that has been meticulously levelled onto a platform is used to create three-dimensional products. The material it contacts is then melted as a laser or electron beam passes across the powder layer. A solid is created when melted material fuses with the powder surrounding it and the layer underneath it. When one layer is finished, the platform descends and another layer of meticulously levelled powder is added on top. The FDA has a number of 3D printers that aid in our understanding of the possibilities of 3D printing medical equipment as well as the advantages this technology offers for the general public's health [20]. For instance, the FDA has printers that use various printing methods, such as powder bed fusion, to assess which steps in the workflows and printing processes are crucial for ensuring the quality of the final medical device.

2.2.1 Patient-matched devices

While identical replicas of the same device are frequently produced using 3D printers, same technologies can also be utilised to produce devices that are individual to a single patient [21]. Devices that are patient-matched (or patient-specific) are made individually for the patient based on unique characteristics like anatomy. They might be built using a template model that has been matched with a patient utilising imaging technology. Techniques like scaling the device using one or more anatomic features from patient data can be used to match patients.

Similar to traditional medical devices, 3D printed medical devices are regulated by the FDA, and as such, they are assessed in accordance with the manufacturer's safety and efficacy data. While typically produced medical devices come in discrete sizes, patient-matched devices can be constructed in a continuous range of forms with pre-defined minimum and maximum parameters that we can use to examine the devices in the same way as standard sized devices. For instance, the specification can specify the minimum and maximum wall thickness or the maximum allowable curve sharpness for a device to function as intended. 'Custom' medical devices are free from FDA inspection under a federal law clause, however patient-matched devices are not always compliant with the standards.

2.2.2 Other uses of 3D printing:

Medical device manufacturing is not the only application for 3D printing. Its application is also appealing to other business sectors and government agencies [22]. For instance, the U.S. Department of Energy (DOE) is spending money to research 3D printing and how it might be utilised to reduce waste by utilising fewer raw materials and necessitating fewer manufacturing

stages. The numerous types of printers, their uses, and how 3D printing functions have all been compiled by DOE.

2.2.3 3-D printed medical devices:

Over the past ten years, the use of 3D printing in medical devices has grown significantly as print costs have reduced and print quality has improved. In the past, 3D printing could only create hard materials that were a good approximation of things created traditionally [23]. More recently, soft materials and those that resemble organic or physiological materials have started to match the quality and accessibility of their hard equivalents, allowing 3D printing to be applied in novel ways.

The primary classes of 3-D printing technology consist of powder bed fusion (selective laser sintering), stereolithography, extrusion (fused filament modelling), and inkjet. All these kinds of printing had been used for 3-D printing medical devices or biological materials supposed for regenerative medicine [9]. Differences in producing strategies between 3D printing and ancient manufacturing approaches have specific superimposed technical issues for 3-D printed products in U.S. Food and Drug Administration (FDA) scientific analysis. To date, marketed medical products manufactured using AM are reviewed and regulated below the premarket notification [510(k)] (9) and new drug application (NDA) (10) pathways within the United States [24]. As extra complicated additive manufactured products are developed, different regulatory pathways, which include premarket approval (PMA) will also be used.

Table 1: Common FDA pathways for regulating additive manufactured medical products

COMMON FDA PATHWAYS FOR REGULATING ADDITIVE MANUFACTURED MEDICAL PRODUCTS	
PATHWAY	**DESCRIPTION**
Premarket Notification (510K)	Request for permission to market a device by demonstrating that the device to be marketed is at least as safe and effective as, that is , substantially equivalent to, a legally marketed device [21 CFR §807.92(a)(3)] that is not subject to premarket approval.
Premarket approval (PMA)	Request for permission to market a class III device that poses a significant risk of illness or injury, or devices found not substantially equivalent through the 510(k) process by demonstrating the safety and effectiveness of the device.
New drug application (NDA)	Request for permission to approve a drug for sale and marketing in the United States by demonstrating the drug is safe and effective.

Biologics license application (BLA)	Request for permission to introduce, or deliver for introduction, a biological product into interstate commerce (21 CFR § 601.2) by demonstrating the biologic is safe and effective.
Master file	Submission to the FDA to provide confidential detailed information about facilities, processes, or articles in the manufacture of a device, drug, or biologic. A Master File can be referenced in a regulatory file submitted for approval or clearance of a medical product.

2.2.4 FDA'S ROLE IN 3D- PRINTING:

Manufacturers, repackagers, relabelers, and/or importers of medical devices for sale in the US are subject to regulation by the FDA's Center for Devices and Radiological Health (CDRH). The Center for Devices and Radiological Health (CDRH) is devoted to ensuring that patients and providers have prompt and ongoing access to safe, efficient, and high-quality medical devices and safe radiation-emitting products [25]. In order to provide this assurance, CDRH acknowledges that advancements in product design and delivery are equally as significant as advancements in manufacturing processes. Since a long time ago, CDRH has promoted advanced manufacturing, including the use of novel and developing production and distribution techniques that incorporate automation, computing, software, sensing, and networking. By enabling quick and flexible fabrication of equipment, such as patient-specific devices and anatomical models for surgical planning, 3D printing at the point of care (PoC) may significantly advance public health [26]. This technology may enable a healthcare facility (HCF) to respond to patient demands swiftly, provide prompt, individualised care to patients, and inspire new developments in patient care and treatment. Depending on a variety of variables, such as the HCF's capacity to engage in 3D printing activities and the intricacy of the product or its printing, 3D printing at the PoC may take numerous forms. The majority of PoC 3D printing scenarios will include special considerations, and an HCF's abilities, knowledge, and experience affect which devices are suitably 3D printed at the PoC. FDA is aware that HCFs might not be as experienced with or knowledgeable about the FDA's regulatory framework for medical devices as traditional manufacturers are. However, an HCF should guarantee that any medical equipment 3D printed at the PoC are of a high standard, work as intended, and do not put patients at a disproportionate risk of illness or harm. At the PoC, there are several conceivable scenarios in which an HCF could use 3D printing, each of which raises significant issues and challenges.

The application of 3D printing throughout the Coronavirus Disease 2019 (COVID-19) pandemic demonstrates both the adaptability and difficulties of 3D printing at the PoC [27]. Batch production is the foundation of traditional manufacturing, which relies on efficient supply chains to deliver enough raw materials and other components. During the COVID-19 pandemic, the supply chains of numerous American businesses were disrupted [28]. As a result of the COVID-19 pandemic's medical device shortages, individuals and facilities worked with

3D printer producers to create face shields, face mask holders, nasopharyngeal swabs, and ventilator pieces using locally accessible materials.

Before and during the COVID-19 epidemic, there were problems with 3D printed medical equipment at the point of care, including the following:

- **Assuring devices 3D printed at the PoC are safe and effective**: FDA regulation is designed to provide a reasonable assurance that devices are safe and effective; this assurance applies regardless of where and how a product is manufactured.
- **Assuring appropriate control of devices 3D printed at the PoC:** Appropriate controls during product design and manufacturing help assure that product specifications are met; these approaches are well-defined for traditional manufacturing but are less defined for 3D printing at the PoC.
- **Clarifying the responsible entity:** Under the Federal Food, Drug, and Cosmetic (FD&C) Act, specific requirements apply depending on the activities an entity conducts across a device's life cycle. There may be uncertainty regarding responsibilities for activities related to 3D printing at the PoC, including device design, testing, FDA premarket submissions, manufacturing, quality control, complaint handling, adverse event reporting, and corrective actions. The entities responsible for 3D printing at the PoC should understand the requirements related to these activities.
- **PoC training and capabilities:** Many 3D printing technologies are available; each has strengths and weaknesses for different clinical applications. Under many circumstances, the PoC facility could be responsible for complex processes, such as patient-matching or post-processing activities, to generate a final finished device. Additionally, devices can vary in risk depending on their intended use and technological characteristics. Therefore, the entities responsible for 3D printing at the PoC should have the requisite knowledge and expertise to conduct these activities.

  Devices produced using 3D printing technology are governed by regulations just like those applied to products produced using conventional manufacturing techniques [29]. Premarket requirements are regulations that apply to medical devices before they are marketed, whereas postmarket requirements are requirements for medical devices after they are marketed (postmarket requirements). Class I, II, and III medical equipment are the different classifications. From Class I to Class III, the level of regulation increases. The device categorization regulation outlines the legal specifications for a certain type of device. Premarket Notification 510(k) is not required for the majority of Class I devices, Class II devices must submit Premarket Notification 510(k), and Class III devices must get Premarket Approval [30]. At Classification of Medical Devices, you can read more about device classification and find a link to the Product Classification Database.

  To assist manufacturers that are creating devices using 3D printing technology, the FDA published a draft guidance document in 2016 titled "Technical Considerations for Additive Manufactured Devices." This proposed guidance is not yet final or in effect and has only been made public to solicit public feedback. New 3D-printed medical device submissions are now being assessed by the FDA for their usefulness and safety [31]. The proposed guidance offers suggestions for device design, manufacturing, and testing concerns to manufacturers when

creating 3D printed devices. A device's regulatory classification still dictates the kind of premarket filing that is necessary.

This draft guidance is broadly organized into two topic areas:

- **Design and Manufacturing Considerations:** This section of the guidance provides technical considerations that should be addressed as part of fulfilling Quality System (QS) requirements for a device, as determined by its regulatory classification or regulation to which it is subject, if applicable. While this draft guidance includes manufacturing considerations, it is not intended to comprehensively address all considerations or regulatory requirements to establish a quality system for the manufacturing of a device.
- **Device Testing Considerations:** This section of the guidance describes the type of information that should be provided in premarket notification submissions [510(k)], premarket approval (PMA) applications, humanitarian device exemption (HDE) applications, de novo requests and investigational device exemption (IDE) applications for a 3D printed device.

2.2.5 CDRH Regulating 3D-Printing:

FDA does not control all 3D printing operations, although it typically does so when those activities result in devices, or items used for medical reasons, such as image segmentation systems and software interfaces [32]. For general, non-medical uses like those in education, building, art, and jewellery, among other non-medical ones, 3D printers may be commercially marketed to the general population. Because they don't fit the definition of a device when used for these general, non-medical uses, manufacturers of these goods are exempt from all other device requirements of the FD&C Act and do not need to obtain FDA device marketing authorization. Manufacturers of general purpose manufacturing machinery, such as general purpose 3D printers, mills, or lathes, are typically not needed to register with the FDA or receive marketing authorisation [33]. When devices are covered by the QS Regulation, FDA generally regulates the processes, facilities, and controls utilised in their manufacture. At the PoC, 3D printing systems—also known as MDPS—could be commercially marketed with the express purpose of producing particular kinds of medical devices. In this instance, the MDPS is categorised as a device under the FD&C Act as a system of items that collectively accomplish an intended medical purpose. The duties of the organisations creating and commercially disseminating the 3D printing MDPS for usage at the PoC would typically be governed by the regulatory requirements for the devices 3D printed using the MDPS.

PoC 3D printing facilities might have a variety of 3D printing tools and experience, which means they might have different capacities for producing devices. A PoC 3D printing facility might be able to use already-existing procedures from their HCF when producing devices there. HCFs might, for instance, adhere to or conform to:

- internal processes;
- accreditations (e.g., Joint Commission, Utilization Review Accreditation Commission);
- state regulations;
- voluntary consensus standards; and
- clinical practice guidelines.

A single HCF PoC 3D printing facility might be able to 3D print some devices but not others since devices differ in complexity and danger. Based on the technology and skills at hand, other gadgets might not be suitable to produce at the PoC.

2.3 EUROPE:

Special laws in the EU govern using 3DP to produce medical devices [34]. It published specific instructions on employing 3D printing to provide COVID-19 alleviation around that time. The importance and adoption of 3DP have increased due to the pandemic. To quickly address a supply constraint caused by increased demand for respiratory valves in a hospital, an Italian start-up called Issinova deployed 3D printing in March of this year. These were produced in accordance with the EU COVID-19 standards for 3DP medical devices. Ventilator tubes and other accessories can now be manufactured in 3D by the US FDA[35]. The U.K. acted similarly.With 3DP set to dominate the future of manufacturing, standardisation is a crucial concern. Therefore, the International Standards Organization (ISO) is currently developing a standard for 3D printing: IEC CD 23510. ASTM International and ISO set up a working group in 2016 recommending standards for additive manufacturing. It has created a framework on 3DP called the Additive Manufacturing Standards Structure. ISO already has various standards for additive manufacturing, some of which have been developed while others are under development [36].

2.4 INDIAN SCENARIO:

At the moment, India only has a few industry-specific regulations, like those in medicine, which can be interpreted to cover 3DP. In the medical/ pharmaceutical field, where 3DP is most used, 3D-printed objects include:

- the anatomical components of the human body (organs, bones, glands, etc.);
- pharmaceutical, immunological, or metabolic in nature (e.g., medicines like tablets, capsules, etc.); and
- those that aid in the treatment, monitoring, alleviation, etc. of various medical conditions (eg. ventilators, scanning machines, medical instruments like forceps, scalpels, protective gear, etc.).

However, the Ministry of Health and Family Welfare expanded the definition of "drugs" under the Act in February 2020 to include devices whose function is diagnosing, preventing, or treating a disease [37]. The Drugs and Cosmetics Act, 1940, of India does not specifically mention such 3D-printed objects. However, it's unclear if this law applies to objects made using 3D printing. Additionally, while the Transplantation of Human Organs and Tissues Act, 1994 addresses the transplantation of organs from person-donors, the transplantation of a 3D-printed organ or gland is outside the purview of this law. These rules must be changed to encompass organs and equipment made via 3D printing, or new policy guidelines must be formed specifically for these. The time is right for India to think through a 3DP policy or perhaps the guiding principles for 3D printing. It could serve as the template for universal rules.

The comprehensive policy should address:

a) purchase of 3D printers and scanners;

b) manufacturing processes using 3D printers;

c) quality of input material and final product;

d) classification of computer-aided design (CAD)/digital file, and whether it is a good or a service, which will determine its sale, distribution and taxation;
e) product sale and distribution, including intermediary liability;
f) Governing body and single window clearance for businesses;
g) Standardisation:

- The Bureau of Indian Standards (BIS), the country's central standards organisation, should include 3DP in its mandatory printer registration scheme.
- In addition to standards for the finished result, BIS should think about creating distinct standards for the input units used in 3DP.
- The Central Drugs Standard Control Organization, which establishes standards for medicines produced in and imported into India, should do the same for 3D-printed pharmaceuticals and medical devices.

While standards and policy will establish a favourable environment for the controlled expansion of 3DP in India, the administration must also provide financial and tax incentives to encourage the adoption of 3DP by businesses. There are examples that might be used, for instance, Australia built an ecosystem that comprised various funding for R&D and financial investments in emerging tech companies, as well as innovation laboratories that encourage new initiatives in this industry to boost sophisticated manufacturing, including 3DP. India recently offered incentives tied to production for the domestic production of medical supplies, pharmaceuticals, and electronics manufacturing. The government is also exploring similar programmes for other industries, such as auto parts. All sectors should take into account such incentives for 3D printing.

3. Conclusion:

With increased recognition, curiosity, and understanding of 3D printing's capabilities, we are on the verge of a digital fabrication revolution that has the potential to disrupt how future products are made. 3DP has applications in nearly every aspect of healthcare, including pharmaceuticals, diagnosis, surgery, and devices. This progress is being driven by exponential advancements in 3D printers and their application in almost all areas of manufacturing and personalisation, including aeronautics, engineering, architecture, and pharmaceutics. However, there are several unanswered questions, primarily in terms of regulatory perspectives, which are expected to be addressed with the confirmation of different product categories and the evolution of regulatory guidelines. The following article provides a comprehensive overview of potential benefits and drawbacks, as well as a detailed description of the new and exciting possibilities that can emerge simply by implementing rapid prototyping techniques.

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Conflict of Interest

Authors declare no conflict of interest.

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