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Review Article

An outlook on regulatory aspects of 3D printing in pharmaceutical and medical sectors

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ABSTRACT

Background: Since the time of origin, three-dimensional printing has not only mesmerizing the researchers also health professionals too. Even though the process is exciting, it involves fussy coordination and selection process to get a desirable product. Still the manufactures are in confusion state that to follow which regulations and guidelines to gets an approval for their product of 3d printing.
Materials and Methods: The importance of 3D printing has laid to recognize the best suitable product and ways to prevent its misuse. FDA approved more than 100 3D printed medical devices and it includes Orthopedic, Cranial implants, Dental restorations such as crowns and external prosthetics, surgical instruments. It also approved one 3D printed drug product using Zip Dose technique for the treatment of Epilepsy called SPRITAM (levetiracetam).
Conclusion: The objective of this review article is to give a brief introduction, history, evolution of 3D printers, their development process, FDA role and guidelines.

1. Introduction

3D Printing is a type of additive manufacturing and it has several types of additive manufacturing. The terms 3D printing and additive manufacturing are often used interchangeable, but we will refer to both as 3D printing for simplicity. 3D Printing is a process, it develops a three-dimensional object by building successive layers of raw material and every new layer is attached to the previous one until the object is complete. Objects are produced from a digital 3D file, such as computer-aided design (CAD) drawing or a Magnetic Resonance Image (MRI). The flexibility of 3D printing enables designers to make changes easily without the need to set up additional requirements like equipment or tools. It also enables manufactures to create devices matched to a Patients anatomy (Patient Specific Devices) or devices with very complex internal structures. These capabilities have interest in 3D printing of medical devices and other products including food, household items, and automotive parts.[1] In some 3D Printing processes, 98% of the raw material is used in the finished part.3D Printing allows manufacturers to create new shapes and lighter parts by using fewer raw materials and requires fewer manufacturing steps than conventional manufacturing processes. Though, the possibilities for additive manufacturing are endless. Today 3D Printing is widely used to build small, relatively costly components using plastics and metal powders. So far, the desktop 3D printer's price continues to drop, while some innovators are experimenting with the different materials like chocolate and some food items, ceramics, wax and biomaterial which are similar to human cells.[2] FDA approved or cleared more than 100 Medical devices and it includes Orthopedic, Cranial implants, Dental restorations such as crowns and

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external prosthetics, surgical instruments. In August 2015, Aprecia Pharmaceuticals introduced the first drug product using the ZipDose technique for the treatment of Epilepsy. FDA approved the drug product SPRITAM (levetiracetam) for oral use for the treatment of partial seizures, primary generalized Tonic-Clonic seizures, Myoclonic seizures in Adults and Children.[3]

2. History

Charles Hull was a founder of 3D systems and he invents "Stereolithography" in 1984, which is patented in 1987.[4] Hull was an Engineer and Physicist and he was working for a company that manufactured ultraviolet lamps into a layer of plastic to put on surfaces used for household use. He thought an idea to use the UV light in a new way; to turn parts created by computer-aided design software into 3-D objects and he given permission to use their laboratories at night and on the weekends. Hull discovered with photopolymers, which are acrylic substances that harden when they are exposed to UV light. Once he discovered this, he built a machine that had a UV laser to engrave the layers of acrylic into shapes and stacked the layers up to form an object. One of the main tasks for Hull was writing the code to tell the printer and how to engrave the acrylic layers, so he stuck to mostly simple shapes. After so many years of research and experimentation, Hull sold his first 3D Printer for $100,000 in 1988.[5]

The basic idea behind an additive manufacturing was found in rock formations which are under deep underground (dripping water deposits thin layers of minerals to form Stalactites and Stalagmites). But the modern example is a common desktop printer. It was just like an inkjet printer adds individual dots of ink to form an image a 3D Printer only adds material where it is needed based on a digital file. In comparison, many conventional manufacturing processes which have recently been termed as "Subtractive Manufacturing". It requires cutting away excess materials to make the desired part. It means to say that, for every one pound of useful material in some parts is going to waste up to 30 pounds, according to finding from the Energy Departments Oak Ridge National Lab.

3D Printing technology was foremost used for medical purposes as dental implants and custom prosthetics in the 1990's. In due period, scientists were able to grow organs from patient's cells and used a 3D printed scaffold to support them. As the technology improves even more a miniature kidney and the doctors start to aim for making full functioning organ without a scaffold for support. In 2008, scientists were able to produce the first prosthetic leg. As recently as 2012, there was a 3D Printed Jaw in Holland by a manufacturing company as Layer wise. Now, the 3D printers have become fairly inexpensive and a common use in hospitals. 3D Printers was unfolded to make things such as vital to human life as organs.[2]

3. Regulatory Authorities

1. Drugs regulated by FDA's Center for Drug Evaluation and Research (Drugs/UCM2018538)
2. Medical devices regulated by FDA's Center for Devices and Radiological Health (CDRH), (Medical Devices/UCM2005076)
3. Blood vaccines regulated by FDA's Center for Biologics Evaluation and Research (Biologics Blood Vaccines/UCM2018586)[1]

3.1. Overview of device regulation

The basic regulatory requirements that manufacturers of medical devices distributed in the U.S. must comply with are:

1. Establishment registration – 21 CFR Part 807
2. Medical Device Listing – 21 CFR Part 807
3. Premarket Notification 510(k) – 21 CFR Part 807 Subpart E
4. Premarket Approval (PMA) - 21 CFR Part 814
5. Investigational Device Exemption (IDE) for clinical studies – 21 CFR Part 812
6. Quality System (QS) regulation – 21 CFR Part 820
7. Labeling requirements – 21 CFR Part 801
8. Medical Device Reporting (MDR) – 21 CFR Part 803[6]

4. FDA Role in 3D Printing

The FDA center for Devices and Radiological Health (CDRH) regulates firms who manufacture, repackage, re-label and import of medical devices sold in the United States.

Like the other medical devices using the manufacturing process and regulatory requirements for getting approval are subject to same as for the 3D printing medical devices. Some regulatory requirements for apply to medical devices before they are marketed ("Premarket requirements") and other requirements for apply to medical devices after they are marketed ("Post-market requirements"). Medical devices are classifies into Class I, II, and III. Regulatory control increases from Class I to III and also it defines the classification of regulations related to the regulatory requirements for a general device type. Class I devices are exempt from Pre-market Notification 510(k); Class II devices requires the Pre-market Notification 510(k); and Class III devices requires the Pre-market Approval.[7]

Before the regulatory entity grants a license to manufacture or distribute a medical device which is classified under Class C or D, the manufacturing site will be inspected within a period of 60 days from the date of marketing application by the regulatory entities to verify the conformance with quality management system. After that, an inspection report will be completed by the inspection team. Once, the inspection report has been received, the

government will have 45 days to either grant a license or reject the application to manufacture or distribute a medical device.[8]

5. Common Patient-specific Devices

5.1. Medium and high risk

Orthopedic implants, heart valves and dental implants devices are the examples of medium and high risk of 3D printing medical devices. The bespoke implants of 3D printing devices has created based on the anthropometric characteristics of the patient. In that situation, the 3D printed implant is sold by a healthcare service provider to the patient. For example, "3D printed hip joint" is a class III medical device that possesses high risk. Sometimes failure may occur due to poor design, manufacturing of the implant. So, the entire device including the material and manufacturing process needs to be regulated.

5.2. Low risk medical devices

Assistive aids such as 3D printed grabber, custom-made tooth brushes etc., low risk to the patient. While manufacturing these devices require to follow good manufacturing processes. These devices are exempted from regulation due to the low risk level of the patient.

5.3. Humanitarian and custom device exemption

In 2013, a 6-week-old baby was integrated with a 3D printed artificial windpipe to help in breathing. The devices which needs patient immediately for survival, for those devices doesn't require to go through any regulation process due to humanitarian exemption which allows a device to bypass the lengthy regulatory process. In the same way, devices which are used to treat patients who suffer from exceptionally rare diseases are often granted exemption and to conduct trails are also impossible due to the absence of sufficient sample size to make a conclusion on whether the device is suitable for the market.[9]

The USFDA will verify the medical devices based on their classification and this has been shown in Figure 1.[10]

5.4. Patient-matched device

Although, 3D printers are frequently used to create identical copies of the same device, they can also be used to create devices unique to a specific patient. Patient-matched devices are produced specifically for the patient based on individual features such as anatomy. It can be based on a template model that is matched to a patient using medical imaging. Patient-matching can be completed by techniques such as scaling of the device using one or more anatomic features from patient data.

The FDA regulates 3D printed medical devices through the similar pathways as traditional medical devices; then they are evaluated according to the safety and effectiveness information which is submitted by the manufacturer. The traditionally manufactured medical devices can be prepared in discrete sizes and the patient-matched devices (3D medical devices) can be prepared in a continuous range of shapes with pre-defined minimum and maximum specifications. So, we can use those specifications to review the devices and compile with the standard sized devices. For example, the specification may define a minimum and maximum wall thickness or how sharp a curve can be to maintain device performance for its intentional use. There is a stipulation in federal law that exempts "custom" medical devices from FDA review; however patient-matched devices could not meet all the requirements automatically. For further information on custom device exemptions, please refer to the Custom Device Exemptions guidance.

Table 1: Few examples of FDA approved 3D printed materials.

S. No	Name	Year of approval
1	DENTCA Receives FDA approval for world's first material for 3D printed Denture Bases Figure 1	Aug 10,2015
2	GRiTT 3D creating custom 3D Printed Sports Mouth guards Figure 2	Feb 23, 2015
3	OssDsign AB Figure 3	Jan 27, 2017
4	E-Denture Figure 4	Jul 4, 2017

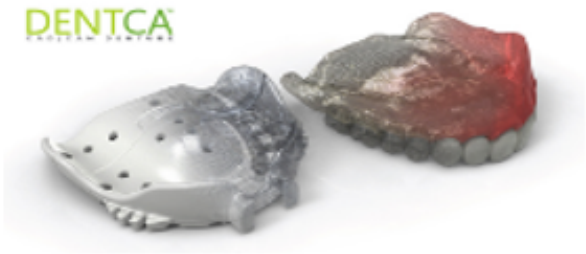

Fig. 1: DENTCA eeceives FDA approval for world's first material for 3D printed denture bases.

6. FDA approach to 3D Printed Drugs and Medical devices

The FDA has approved 3D printed products via traditional drug and device approval pathways. FDA will approve a New Drug application (NDA) based on its adequate and well-controlled clinical investigations and also if it determines the new drug is safe and effective under the conditions of use in its proposed labeling. Likewise, the

Fig. 2: GRiTT 3D creating custom 3D printed sports mouth guards.

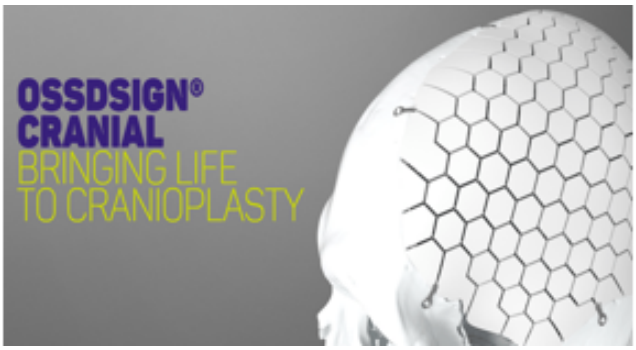

Fig. 3: OssDsign AB

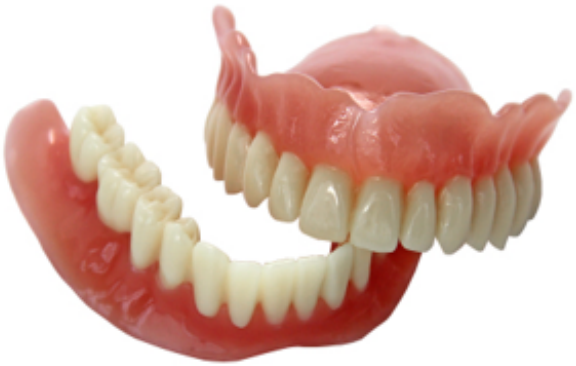

Fig. 4: E-Denture

FDA will "clear" the approval pathway of medical devices based on their risk classification for marketing, if it is substantially equivalent (i.e., safe and effective) as the legally marketed or predicate device. The new device must have the same intended use as that of predicate device and also it may have either same technological characteristic or different technological characteristic that does not raised any new issues of safety or effectiveness.

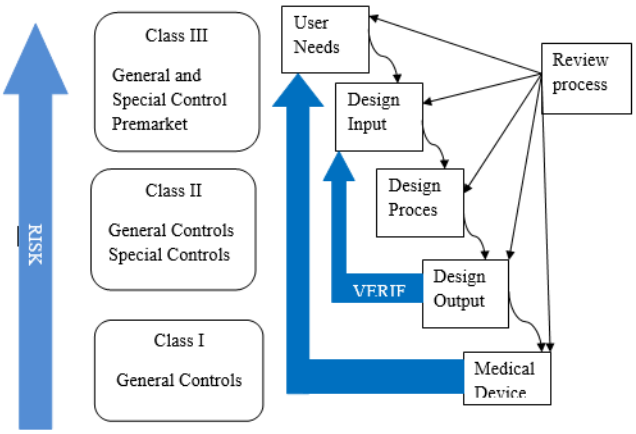

Fig. 5: Medical devices classification as per USFDA.

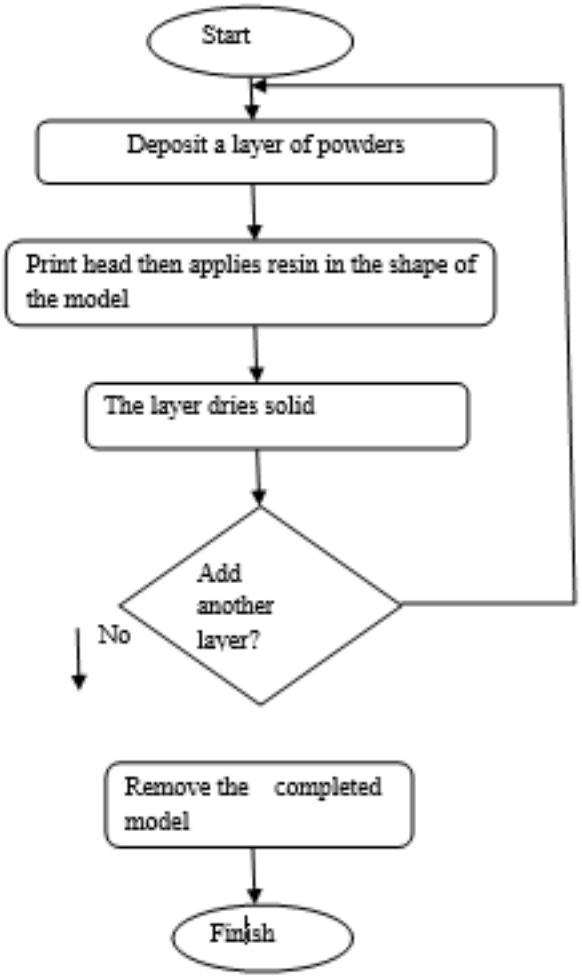

Fig. 6: 3D printing manufacturing process.

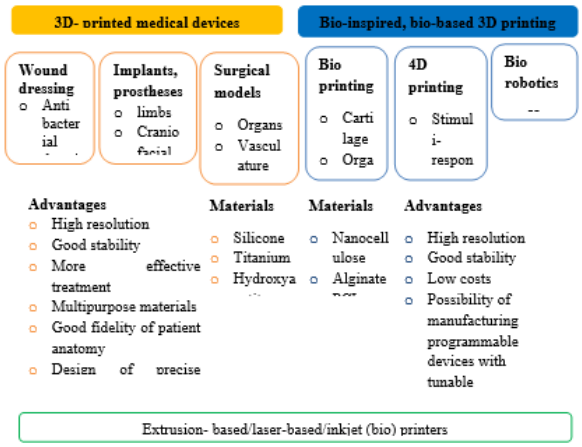

Fig. 7: Advantages of 3D printing medical devices and Bioprinting materials.

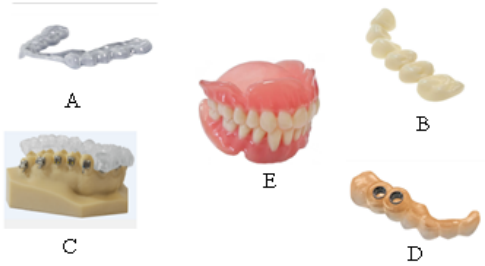

Fig. 8: Dental 3D printing devices of envision tec's.

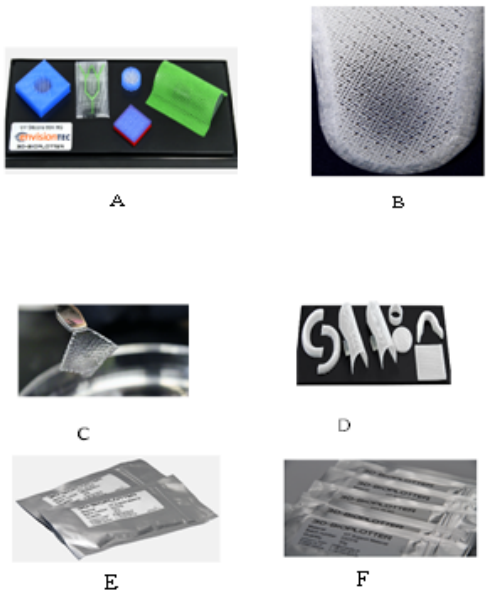

Fig. 9: 3D Bio printing materials of envision Tec's.

Gottlieb also said that FDA has now reviewed more than 100 3D printed medical device applications including knee replacements and implants used for facial reconstruction, up from the 85 reviewed at that time the draft was released. In 2015, the US FDA granted the approval process of a 3D Drug called "Spritam" which is used for the treatment of "Epilepsy". It was found that 3D printing allows the creation of thin layers of drug thereby assisting in the faster dissolution of the pill. It melts in mouth only a sip of water. So, it improves the efficacy of the drug and its chemical reaction owing to the composition of the drug that finally causes the required effect. Hence, in this scenario both the chemical composition and manufacturing process plays a major role in maintaining the efficacy of the drug. So, instead of regulating the chemical composition and manufacturing process of fabrication of the final product that is 3D printed "Spritam" is bought under the regulatory framework as a drug.

Similarly, the cells and the other active components are regulated as biologics owing to the mechanism of action which is in biological nature.[11]

6.1. Guidance document

The guidance is nothing but a full document to tackle all regulatory requirements, it highlights the technical considerations and recommendations for design, manufacturing and testing of medical devices that comprise at least one fabrication step using 3D printing.

In 2017, the US FDA provide a draft guidance document on the "Technical Considerations for Additive Manufactured Devices" for guiding the manufacturers who are expanding or developing devices through 3D printing techniques. This guidance has been published to get a public feedback and this is not final or in effect at this time. So, the FDA is currently evaluating submission process for new 3D printed medical devices to determine their safety and effectiveness. And also it will give glance to the manufactures with recommendations for device design, manufacturing and testing considerations to develop 3D printed devices and also the type of Pre-market submission required for a device by its regulatory classification. This draft guidance is broadly organized into two topics areas:

7. Design and Manufacturing Considerations

In this section, it provides the guidance on technical considerations and it should be addressed as part of fulfilling Quality System (QS) requirements for a medical device based on its regulatory classification. It also includes manufacturing considerations which is not deliberate to broadly address of all regulatory requirements to establish the quality system for the manufacturing of a device.

8. Device Testing Considerations

In this section, it provides guidance on the type of information is needed in Pre-market Notification submissions [510(k)]; Pre-market Approval (PMA) applications; Humanitarian Device Exemption (HDE) applications; De novo application and Investigational Device Exemption (IDE) applications for a 3D printed device.

FDA describes the guidance document as "Leap-Frog" Guidance. It meant to provide the manufacturers about its initial thinking and how to characterize and validate on manufactured 3D printing devices. The final guidance also focus on recommendations which has done, it will not be applicable to all 3D printed devices because of the wide array of available information on additive manufacturing technologies and materials. Some changes were included in the final guidance document as new considerations for handling of complex design files and cyber security for Patient-Matched devices.[7]

9. Medical Applications of 3D Printing

3D printer technology is used to manufacture a variety of medical devices, with their complex geometry or features that match a patient's unique anatomy. Some devices are printed from a standard design to create multiple identical copies of the same device. Other devices called "Patient-Matched Devices" are created from specific patients imaging data.

Commercially available 3D Printed medical devices include:

1. Instrumentation (e.g., guides to assist with accurate surgical placement of a device).
2. External prostheses (e.g., Hands).
3. Implants (e.g., cranial plates or hip joints).
4. Bioprinting tissues and organs.

Scientists are researching that how to use the 3D printing process to manufacture living organs such as a heart or liver, but this research is in early stages of development.

9.1. ASTM standards

In 2009, ASTM Committee F42 formed an Additive Manufacturing Technologies. F42 meets twice a year, frequently in the Spring and Fall (US and Non-US respectively) with about 150+ members attending two days of technical meetings. The committee with an existing membership in excess of 725, has 8 technical sub-committees; all standards developed by F42 are published in the Annual Book of ASTM Standards, vol-10.04. Knowledge on F42 sub-committee structure, portfolio of approved standards and Work Items under development is available in the List of Sub-committees, standards and work items. These standards will play an excellent role in all aspects of additive manufacturing technologies.

Developing one set of 3D printing standards and test methods is helpful because it provides continuity and ensures that devices are safe, reliable and of good quality and these standards can be applicable to 3D printed medical devices all over the world. In 2009, the American Society of the International Association for Testing and Materials (ASTM) implemented an international committee on "Additive Manufacturing" technologies which goes by its committee name: F42. The committee's membership has gradually increased since that time and now approximately 400 members. These standards focus on several different categories including general standards (such as terminology, test methods, safety), feedstock material standards, application-specific standards (including medical uses), process and equipment standards and finished part standards. The standards for 3D printing are built off existing standards to the extent possible and modified for 3D printing when necessary.

The International Organization for Standardization (ISO) also has a committee stanch to 3D printing in 2011: Technical Committee 261 Additive Manufacturing (ISO/TC 261). Twenty two countries partake in this initiative including the United States and the nine countries observe the developments. ISO and ASTM united to develop a common roadmap, organization structure for 3D printing standards, with the eventual goal of creating one set of worldwide standards. The American National Standards Institute (ANSI) which is the U.S representative to the ISO, has partake with America and makes to organize the development of 3D printing standards, industry wide in the U.S. This data will be helpful in creating the ISO standards.[12]

9.2. Working of 3D printing

Additive manufacturing technology has come up with many sizes and shapes, but no matter that which type of 3D printer or material you are using. The 3D printing process follows the some basic steps:

1. First it will starts with creating a 3D blueprint by using the computer-aided design (CAD) software. It is only limited by the imaginations of creators. For example; 3D printers have been used to manufacture everything from Robots, Musical instruments and Prosthetic limbs to custom shoes. Once, the 3D blueprint is created and then the printer needs to be prepared. It includes the refilling raw materials like as metal powders or binding solutions, plastics. Then prepare the build platform. In some cases, you might have to clean it or can apply any adhesive materials to prevent movement and warping from the heat during the printing process.

2. Once you hit print, the machine will takes it and then it will automatically build the desired object. But the printing process is different & it depends upon the type of 3D printing technology, material extrusion (which involves the different types of process such as fused deposition modeling) and it is the commonly used process in desktop 3D printers.
3. Actually the material extrusion works like a "Glue Gun". The printing material is a plastic filament and it should be heated until it liquefies and extruded through print nozzle. By the information using from the digital file, the design should be divide into thin 2D cross sections. Then only the printer knows exactly where has to put the material and then the nozzle deposits the polymer in to the thin layers of 0.1 millimeter thick. The polymer get solidifies quickly and it will binds to the layer before the print head adds another layer. The entire process can take time from minutes to days due to its depending up on their size and complexity of the object.
4. Once the printing is finished, every object requires a bit of post-processing. It can range from unstuck the object from build platform to remove a support structures (which support the printed material temporarily and overhangs on the object) to brushing off excess powders.

10. Types of 3D Printers

As soon as the 3D printing industry has grown drastically and created different new technologies (a new language which describes the different additive manufacturing process). For simplification of this language, ASTM International releases the standard terminology in 2012, which classifies the additive manufacturing technologies into seven broad categories. These categories of summary mentioned below:

1. *Material Jetting:* It is same as the standard desktop printer. It extrudes the material through an inkjet printer head. In this process, photopolymer use as a plastic that requires light to harden it and it can also print waxes and other materials. Material jetting can produce accurate parts and incorporate multiple materials by using additional inkjet printer nozzles. The machines are relatively high cost and build times can be slow.
2. *Binder Jetting:* In this process, a thin layer of powder (which might be prepared from plastics or metals or sand or glass) is spread across the build platform. Then the printer head sprays a binding solution (which is similar to a glue) to mix the powder properly only in the specified places of the digital file. Then repeat this process again until the desired object is finished printing and the excess powder which is used to support the object during the build is removed keep it safe and use later. Binder jetting can be used to create relatively larger parts, but it is more expensive for larger systems.
3. *Powder Bed Fusion:* It is same as binder jetting, except the layers of powder mixed together (any Melted or Sintered; In this process heat or pressure is using to form a solid mass of material without melting it) by using heat as a source, for example, laser or electron beam. Whereas powder bed process can produce high quality, solid metal parts, strong polymer and raw materials choice are limited in this type of additive manufacturing.
4. *Directed Energy Deposition:* It can come in any forms however they all will follow a basic process. By using laser as a high-energy source, wire or powder material is deposited into thin layers and it be melted. This system is commonly used to darn existing parts and build very large parts. But with this technology, these parts frequently require more extensive post processing.
5. *Sheet Lamination:* This system connected with thin sheets of material (might be paper or metals) mutually using adhesives, low temperature heat sources or other forms of energy to develop a 3D object. This system also enables to manufactures to print the materials which are sensitive to heat (such as paper and electronics) and they tender the lowest cost of materials of any additive process. Although, this process may be slightly less accurate than other types of additive manufacturing systems.
6. *Vat Photo polymerization:* It is an oldest type of 3D printer. In this system liquid resin is used to cure using special lights to create a 3D object. Depending on the type of printer it uses either laser or projector to elicit a chemical reaction and harden thin layers of resin. The machines are very expensive and the choices of materials are limited, but this process can build very accurate parts with fine point.[2]
7. *Stereo-lithographic Technique:* It is one of the best and first 3D printing technologies. By this technique, 3D structures are built by solidifying resins and curative with ultraviolet rays. In this process photo-initiators helps in converting light energy to chemical energy.
8. *Selective laser sintering:* In this process, powdered materials are sintered with the use of laser beam. To create a 3D structure, the optimal conditions of heating and storage should maintain the geometry.
9. *Fused Deposition Modeling:* FDM technology was invented in the year 1990s by "Scott Crump". Mainly in the FDM technology, thermoplastic filament and two kinds of materials such as modeling material and support material were used. Through the print head, the solid polymer filaments are heated to melting

temperature (predefined in the computer file) by a heating block which is deposited on to the build platform as per predefined coordinates (as defined in the computer-based design file usually STL file). Repeat this procedure until a layered structure can be formed. The other similar technology is FFF. Another similar technology is PAM-Syringe technique, which involves layer by layer deposition of semisolid or paste like materials on a build plate through nozzle.[13]

10. *Zip dose method:* This technique was developed by MIT. It is used for formulating a tablet with high dose and rapid disintegration. In this process, aqueous fluid is used to bind the layers of powder. If a layer of powder is deposited as a substrate, a liquid or binding fluid is applied to form interaction between the powder and the liquid binder. Repeat this process until desired product of optimal size and shape is produced. It leads to formation of highly porous dosage form and with high drug loading.[3]
11. *Pen based 3D printing method:* In this method, the layer by layer is manually controlled with handheld device.[14]

11. Development Process of 3D Printing Medical Devices

The process undergoes several steps to develop a 3D printing of an end product. These steps depend up on several factors such as the environment where the product will be used, material to be used and complexity of the product, cost and size of the product. The following sequence of steps is one of the examples of the process.

11.1. Device design

First create the design according to a patient's anatomy and validated by using digital models with pre-specified sizes or digital models. A computer model is generated with CAD and computer-aided simulation studies can be done if required.

11.2. Software workflow

The CAD model is converted to a buildable file and it sent to the printer. This file again will divide the design into layers; it includes additional support material to aid printing and let to know the printer where to build the device on the printer platform and prepare it for printing. 3D printer often requires some preparation to build different designs by changing settings for the material, type of design and deliberate use, sometimes it incorporates instructions for any scaffolding material is required.

11.3. Material controls

Like other manufacturing process, 3D printing requires high quality materials to meet their consistent specifications to build reliable high-quality devices. To ensure every batch of material, procedures, requirements, material controls of suppliers, purchasers and end-users of the material are verified. It can print objects as transparent, plastic, opaque, rubber-like, glass, wooden, metallic and color of one's choice. The choice of material depends on the final properties of desired product. E.g., A Good choice of biodegradable material is Poly-lactic acid (PLA) and if you want a strength, flexibility and durability: Nylon and Acrylonitrile butadiene styrene (ABS) is the best choice. The material used classified as:

1. *Thermoplastics:* It is the most commonly used material in various combinations. It is used in powder form in sintering and filament form in FFF/FDM process. The widely used materials are ABS, Nylon a polyamide used for heat resistant properties; PLA is a biodegradable product, used as a resin in SLA and acrylic also called PMMA; Poly-ether-ether-ketone (PEEK); Polyethersulfone; Polycarbonate; Polyethylene (PE), especially ultrahigh molecular weight PE; Polyetherimide; Polybenzimidazole; Polyphenylene oxide; Polyphenylene sulfide, Polystyrene; Polypropylene and Polyvinyl chloride.
2. *Ceramics:* The using of ceramics has being increased but need to be followed by firing and glazing steps. Gypsum is commonly used.
3. *Paper:* Standard A4 paper is used by the proprietary SDL process and the main advantage is easy availability of A4 paper.
4. *Wood:* It is commonly used in filament form in wood/polymer combination known as WPC.
5. *Glass:* MIT-mediated matter group and Micron 3DP has been used for 3D printing mainly soda lime and borosilicate.
6. *3.2.3.6 Metal:* The most commonly used metals are aluminum and cobalt. Gold, silver, brass, stainless steel are also used. Titanium is also being used in powder form.
7. *3.2.3.7 Food:* Chocolate is being widely used for making food items by 3D printing. Sugar, pasta and meat also used.
8. *3.2.3.8 Combinations:* Carbon fibers, elastomeric polyurethane and thermoplastic polyurethane combinations have been used. Stratasys has a proprietary (Object Connex) combination of over 140 types of materials has been used in various combinations by mixing of popular materials.[15]
9. *Printing:* The object is printed by using the design specifications which is included in the file.
10. *Post-Processing:* After the printing is complete, one or more post-processing steps may be performed on

the device or component. In this process, cleaning should be done to remove residual debris, controlled cooling (called "Annealing") and or additional steps will require such as cutting, drilling, polishing and sterilization.

11. *Process Validation and Verification:* Check individual device or component characteristics after they produced desired design and to make sure that they had functioned properly and meet adequate specifications. This process is specially used for accurate of geometric features which can be checked quickly properly and non-destructively. While other functional features such as mechanical strength can't be checked individually due to the test could damage the object or is impractical. Manufacturers validate their processes proceeding to production. Process validation ensures that a manufacturing process will produce a product that is within the specifications and parameters are controlled and monitored.
12. *Testing:* Each device or type of device has its own set of testing methods that may be based on Guidance documents, international standards or internal process controls. Devices which are manufactured by 3D printing technology are usually subject to the same regulatory requirements as more traditionally manufactured medical devices. Device testing methods and their results are submitted to the FDA and it proves that the device meets regulatory requirements and is safe and effective for its intended use. A simple example of one possible 3D printing manufacturing process has mentioned in Figure 6.

12. Materials used in 3D Printed Devices

FDA normally clears or approves finished medical devices and not as specific materials which are use in the manufacturing of medical devices, as well as the materials which may be used in the manufacturing of 3D printed devices. For example, FDA has approved spinal implants which are made by titanium alloy, but the FDA does not review or provide blanket approval for the use of titanium in medical devices. Materials used in formulating medical products are evaluated within the context of FDA's evaluation of the safety and effectiveness of the medical product for its intended use. Examples and its advantages of 3D printing medical devices and Bioprinting materials has shown in Figure 7

FDA evaluates a material as part of the finished device and its intentional use and it also determines if the device purpose of use and technological characteristics (including the materials) are reasonably safe and effective of a legally marketed device. So the FDA approves or clearance to individual device with its intentional use. But it does not approves or clearance for the manufacturer to use these same materials in the other devices. Devices containing new materials, does not necessity require the FDA's more meticulous premarket review process known as PMA review. Actually, devices with new materials may be cleared through the 510(k) Premarket Notification process provides that new materials does not elevate different questions of safety and effectiveness and the submission describes that the new materials is at least as safe and effective as similar to the legally marketed device.

13. Materials Used in 3D Printed Dental Devices

For the manufactured 3D dental devices, the FDA clears some engineered materials for a specific intentional use as a device. These specific materials are considered as finished devices that are suitable for use by health care professionals and are patient-matched or fitted at the point of care. Examples are dental restorative and prosthetic devices such as direct filling resins, denture resins, night guards, crowns, dental cements, orthodontic retainers, inlays and onlays. While clearing or approving these devices, the FDA usually requires performance testing on the material in its finished form to make obvious that the material has the appropriate physical and material properties for its intentional use.

It is important to note that the FDA has cleared or approved these device materials only for that specific purpose of use such as "to fabricate a denture base" or "to restore a structural defect in teeth. The FDA does not approves or clear materials for unlimited intentional uses. Each engineered material is cleared to make specific device with specific physical properties and its intentional use. For example, a device material cleared for specific intended use such as "tooth shade resin material" is not automatically FDA cleared to be used for other purposes such as an "End osseous dental implant abutment". A few examples of FDA approved 3D printed materials have shown in. Table 1 [16] In some cases, manufacturer would like to use the same material for a new intentional use. FDA would evaluate information regarding to the material properties and for the new intended use. If the new intentional use falls under a different classification regulation, the manufacturer could be required to satisfy any regulatory requirements for that classification regulation. [17]

14. Cranial Device

The FDA accepted the first 510(k) clearance of Oxford Performance Materials (OPM) for their polymer of additive manufacturing OsteoFab^{TM} Patient Specific Cranial Device (OPSCD). The customizable implant is designed by plastic material PEKK to restore voids in the skull caused by trauma or disease. It is manufactured a matter of hours with additive technology by EOS, and its use has seen in just a few days later when the device was successfully implanted in a patient lost a significant portion of cranial bone. Yet, PEKK has a high melting point compare to other polymers.

The EOSINT P 800 is only the industrial 3D printing system in the world which can produce the high-temperature polymer by means of additive layer manufacturing.

15. Envision Tec's for Dental 3D printing devices

1. *E-Guard:* For the invention of exact bite guards and night guards on the Perfactory® line of 3D Printers, E-Guard is the best choice and it is a transparent biocompatible material. The results formed by combining E-Guard with Envision TEC technology are superior to traditional methods of built-up bite guards and night guards. It is a clear material and allows for maximum visibility.
2. *E-Dent:* E-Dent 400 MFH printing material is an FDA approved solution for the accurate 3D printing of crowns and bridges for long-term temporary use as well as dentures.
3. *E-IDB:* It is a 3D printing material allowing for the manufacture of indirect bonding trays for the exact placement and release of orthodontic brackets.
4. *E-Guide Tint:* It is a biocompatible certified class I material, developed for the production of high precision surgical drill guides for use in implant surgery. The results produced by combining E-Guide Tint with Envision TEC are superior to traditional methods of manufacturing implant placement guides.
5. *E-Denture:* E-Denture 3D + material is an FDA approved, biocompatible, Class IIa material suitable for 3D-printing of all types of denture bases. Envision TEC for Dental 3D printed medical devices has shown in Figure 4. [18]

16. Bioprinting Materials

Even though Envision TEC has been selling the world's largest bioprinter as its founding in 2002, the first official 3D-Bioplotter materials weren't launched awaiting 2017. The Envision TEC is only open-source material printer for 3D-Bioplotter: a quality design to give medical researches and manufacturers the flexibility to develop their own materials for exceptional research or a specific patient. For above 15 years, our users have been liability just that: Printing silicones, Ceramic, Metal pastes, Thermoplastics, Hydrogels and more frequently on living cells.

3D-Bioplotter has become more popular with more than 200 citations in peer-reviewed journals and demand also has been increasing on standard printing materials. That's been especially accurate for routine functions, such as printing supports for tissue engineering applications or structures for soft implants. Today, Envision TEC offers bioprinting materials are biocompatible and cell-friendly for a variety of those functions. In order of purity; three grades of materials are now offered.

1. Technical Grade (TG)
2. Research Grade (RG)
3. Medical Grade (MG)

Many of Envision TEC's standard bioprinting materials has come up with low temperature (LT) or high temperature (HT) designations to meet different printing needs. For instance, Envision TEC offers LT and HT versions of its support RG material. This Research-Grade material can be used to produce sacrificial supports that are dissolved in distilled water after the support is no longer needed. The LT version is cellulose-based and it can be processed at 23ºC or 73ºF and the HT version is sugar-based and it can be processed at 150ºC or 302ºF.

Envision TEC is the world leader and still using in bioprinting solutions and it continuously develop their bioprinting materials with its global partners as the field of regenerative medicine and we can see our line of bioprinting materials mounting in the coming years as research moves into clinical trials and manufacturing production.

17. Envision TEC's for 3D Bioprinting Materials

1. *3D-Bioplotter UV Silicone 60A MG:* Silicone 60A UV MG is a biocompatible, bio-inert and non-biodegradable. Liquid silicone rubber is cured with a UV light and delivers a Shore A hardness of 60. A transparent material is also mixed with pigments. Approved to use in the body as a short-term (29 days or less) and it is suitable for micro-fluidics, bio-sensor housings, wound dressings and prototyping.
2. *3D-Bioplotter Silicone TG:* The flexible material can be used for numerous demo applications, for making new shapes and patterns by the use of cheap material through technical parts(e.g: Gaskets) to medical device casings.
3. *3D-Bioplotter LT Support RG:* The Research Grade material is biocompatible and cell friendly, ensures that residue materials does not negatively affect the biological properties of final object. LT Support RG can be easily processed as a hydro-gel in short to medium long jobs.
4. *3D-Bioplotter HT PCL 120K MG:* Medical grade Polycaprolactone (PCL) is biodegradable thermoplastic polyester and it can be processed at high temperatures. It is approved for both short-term and long-term use in the body (longer than 29 days) and perfect for applications such as drug release, hybrid scaffolds, bone regeneration and cartilage regeneration.
5. *3D-Bioplotter PCL 45K RG:* Polycaprolactone (PCL) is one of the most flexible thermoplastic materials for Tissue Engineering Applications. With little thermal degradation, it is an excellent material for large and time-consuming parts.

6. *3D-Bioplotter HT Support RG:* The Research Grade material is biocompatible and cell friendly, ensuring that residual material does not negatively affect the biological properties of final object. This sugar-based derivative can be easily processed as a melt in prolonged jobs with no measurable degradation. Envision TEC for 3D bioprinting materials has shown in.Figure 5

18. Conclusion

3D Printing technology is a manufacturing technique for medical devices, drugs and biologics. The outcome of the process depends upon the material and the ability of the person operating the process. For this reason, it is an importance to optimize and improve the 3D Printing process in order to accomplish the best possible outcomes for the patient. In this manner, may reduce the need for quality assurance and testing post-manufacturing. Regulations, standards and best practices for 3D Printed medical devices will be slow to develop and achieve consensuses. 3D printing medical device manufacturers should be aware of inadequacies and suspicions in the manufacturing process and regulations will help assuage potential problems before they develop.

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20. Conflict of Interest

None.

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