

Medical Device White Paper Series

The impact and potential for 3D printing and bioprinting in the medical devices industry

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1. Introduction

3D printing refers to a set of manufacturing processes which all build components using an additive approach – commonly fabricating and joining layers of material together to create a 3D component. The first patent for a 3D printing system was granted over 30 years ago, presaging the emergence of a range of 3D printing processes over the following decade. Many of the most common 3D printing processes were, and still are, used initially to create prototype components, and the technologies have been described in a number of ways over the years (e.g. rapid prototyping, rapid manufacturing, additive manufacturing, freeform fabrication), but the most widely used label in terms of public understanding of the processes is 3D printing, and that collective name for the technologies will be applied throughout this report. As these new manufacturing processes emerged, researchers were quick to identify that the ability to create complex one-off components offered new tools for the manufacture of medical devices. There is now a near 20-year track record of the use of 3D printing processes for medical devices. Around 15 years ago bioprinting processes started to emerge through initial studies in printing cells and other biological materials, and these have now developed to the stage where the potential to use them in enhancing medical devices towards combination products is clear.

The aim of this whitepaper is to review the history of 3D printing of medical devices, identify the key characteristics of successful exploitation, and to examine the scope for bioprinting processes to enhance medical devices, bearing in mind the lessons learnt from the more established 3D printing industry.



2. 3D printing and additive manufacture

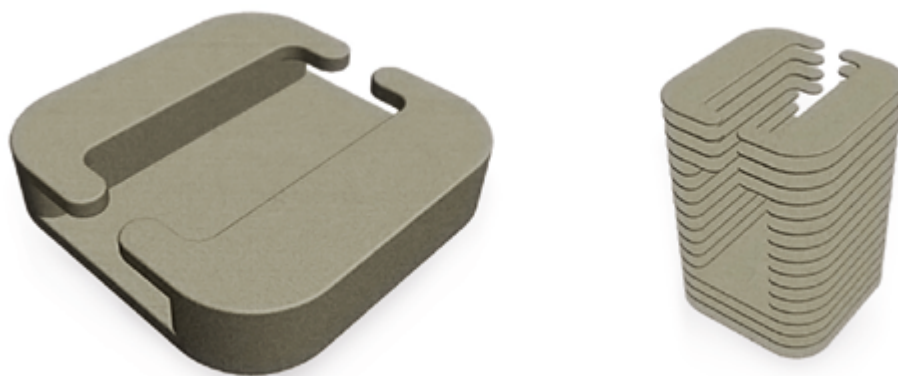
2.1 Principles

3D printing techniques are all, in effect, layer manufacture techniques. They all produce a series of 2D layers, which are bonded together to create a 3D component. The additive nature of the process means that they are also commonly, and more formally, known as additive manufacture processes. 3D printing processes all share some common characteristics, and commonly occur in four steps:

1. The production of a CAD (computer-aided design) model of the component to be manufactured, conversion of the CAD model to an .stl surface model file format, and transfer to the 3D printer.
2. 'Slicing' of the .stl file to create a series of 2D layers that represent the component, as illustrated in Figure 1.
3. Fabrication and bonding, using a wide range of materials processing techniques to be described in section 2.2 of the layers, normally in situ within the machine, in order to create the 3D structure.
4. Removal from the machine and finishing, where required.

Steps 1 and 2 are near universal (although they may be addressed as a single problem by some software systems), whereas steps 3 and 4 are specific to the 3D printing process being used.

Figure 1 – CAD file and 'slices' used to create the component



2.2 Common processes

3D printing is not a single process: it is a wide range of processes, which have a wide range of capabilities and which can cost from a few hundred pounds for a hobbyist's home 3D printer to hundreds of thousands of pounds for a large industrial 3D printer. A brief description of some of the more commonly applied processes is outlined in sections 2.2.1 to 2.2.4. This is by no means exhaustive: full details of all the processes on the market can be found in the sources indicated in the bibliography.

2.2.1 Stereolithography

Stereolithography was the first modern 3D printing process, patented in 1986. The stereolithography process is based on the use of light to polymerize a photocurable polymer, with the original process using a scanning laser to create 2D layers within a vat of liquid polymer resin, as shown in Figure 2. In order to hold the layers in place, a support structure is used to anchor the first layer in position, with a support structure also used to support downward facing free surfaces. Support structure removal is a required finishing process if they are used. In the last decade or so stereolithography systems based on the projection of whole layers of light have become available: these normally invert the build process to project light from underneath onto a build platform that rises as the layers are built. The recently launched Carbon3D process, illustrated in Figure 3, is an example of this approach. Stereolithography processes can be very high resolution, but are limited to photocurable materials, with epoxy, methacrylate, silicone and urethane materials typical of those used in the process.

Figure 2 – Stereolithography process

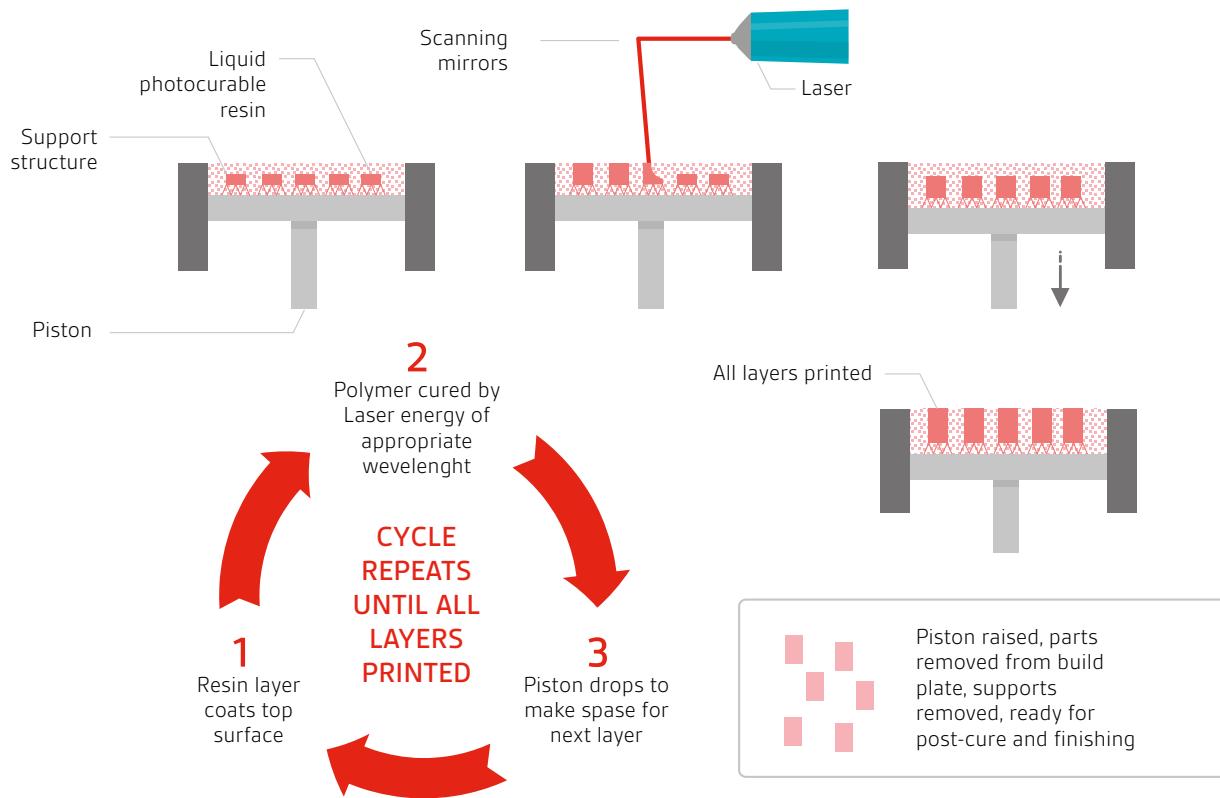
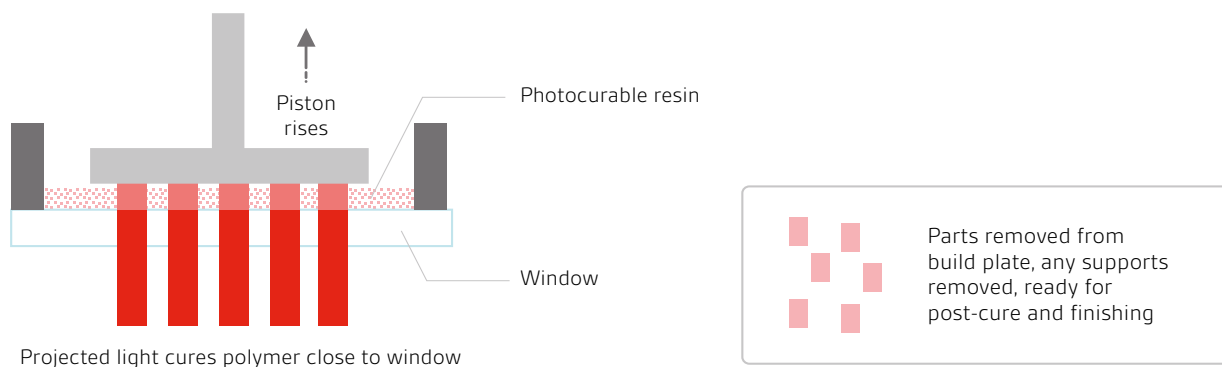


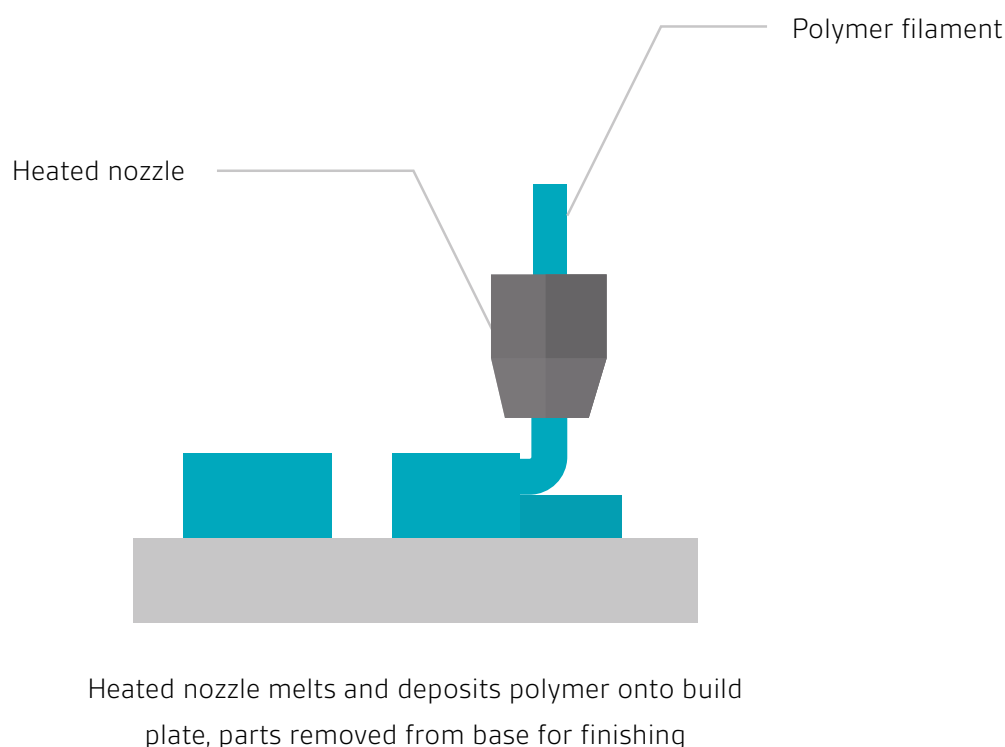
Figure 3 – Digital light projection stereolithography process



2.2.2 Fused filament fabrication

Fused filament fabrication (FFF) uses a heated nozzle to deposit polymer material onto a build plate, depositing lines of material in order to create layers, as shown in Figure 4. The processes typically use extruded filaments as feedstock and have seen significant growth as low-cost 3D printing processes, including open source, have emerged alongside industrial versions of the processes. Again, support structures can be required depending on the geometry. Common FFF materials are ABS (acrylonitrile butadiene styrene), PLA (polylactic acid) and TPU (thermoplastic polyurethane).

Figure 4 – Fused filament fabrication process



2.2.3 Binder or polymer jetting

Binder and polymer jetting systems in essence borrow technology from 2D printers in order to build 3D components. Binder jetting reached the market first and was a powder-bed-based process in which a binding liquid was printed onto a bed of powder in order to locally 'glue' the powder particles together, as shown schematically in Figure 5. This approach can be used with polymer, metal or ceramic powders, with post-processing (i) to remove the component from the powder bed and (ii) to develop strength. With metal and ceramic powders, the 3D printed component can be processed with conventional sintering techniques to remove the binder and create a consolidated metal or ceramic component. Polymer jetting was developed later and is conceptually simpler: droplets of polymer resin are jetted onto a build plate and UV cured in situ in order to create layers of material and bond them to layers below (Figure 6), with support structures required dependent on the geometry. Binder jetting systems have a wide range of possible materials based on the starting powder; polymer jetting materials are more limited, similar to those available for the stereolithography processes. A new variation on this type of processing is the HP Fusion Jet process, which jets a fusing agent into a powder bed, before applying radiant heat to the bed as a whole: where the fusing agent has been applied, the powder fuses to create a layer of material and bond it to the layer below.

Figure 5 – Binder jetting process

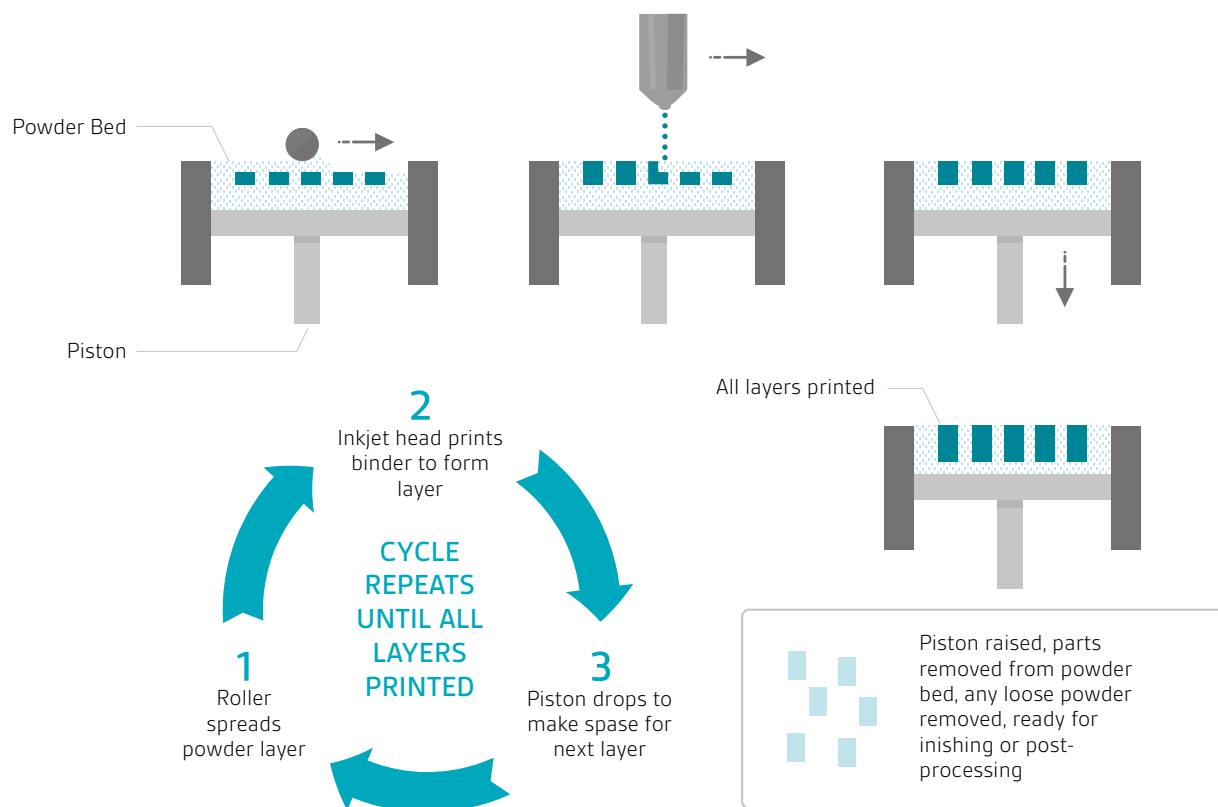
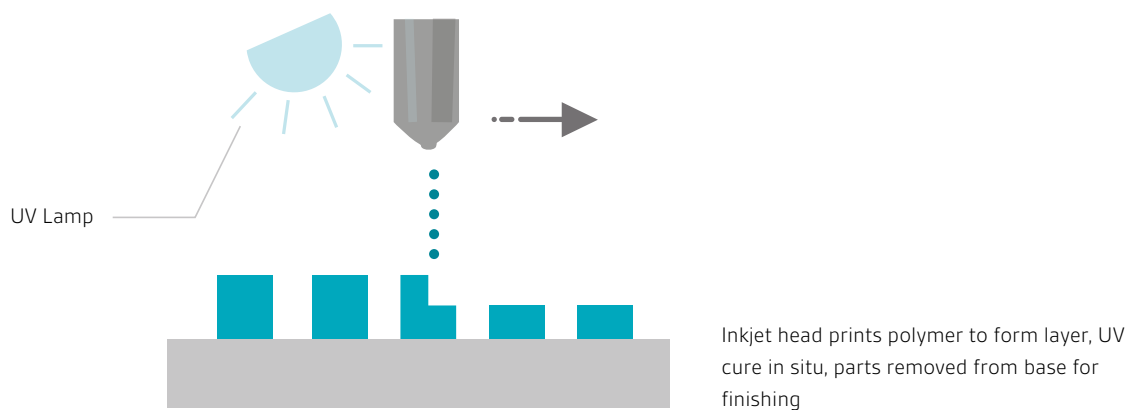


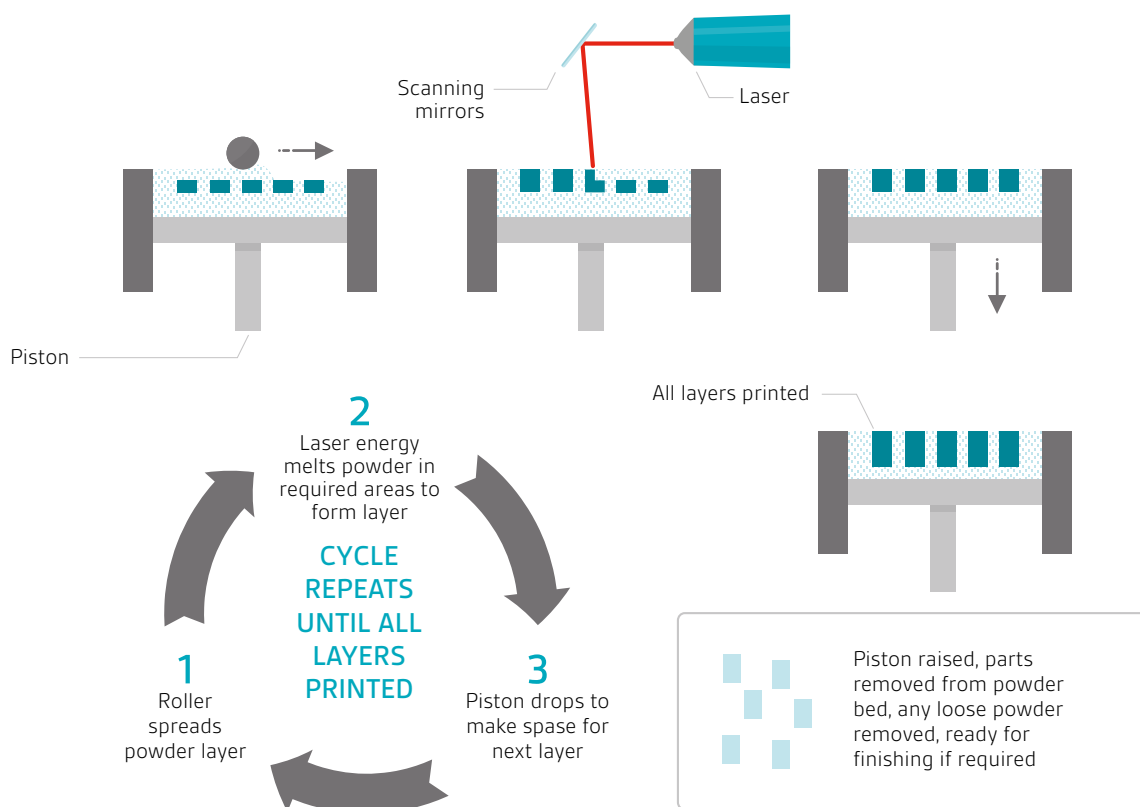
Figure 6 – Polymer jetting process



2.2.4 Powder bed fusion

Powder bed fusion covers a range of processes that start with a bed of powder material (which can be polymer, metal or ceramic) and uses a heat source to locally melt and consolidate the powder to create layers and bond them to previous layers in a single step, as illustrated in Figure 7. The original process was known as selective laser sintering and worked with a scanning laser as the heat source for melting polymer powders, most commonly Nylon, but recent growth has been on systems using metal powder and either a laser or an electron beam as the heat source. Polymer powder laser melting normally does not require support structures, but metal processes do, dependent on the geometry.

Figure 7 – Selective laser sintering process



2.3 Key features of 3D printing processes

- Digital: the input must be CAD, and the process from CAD to machine control is automated with limited process planning required. This allows the design and manufacture steps to be in different locations.
- The cost of component manufacture is mostly defined by the volume rather than the geometric complexity, although if significant finishing is required this is less true, and cost models generally favour small geometrically complex components. For biomedical applications the geometric complexity can embrace the manufacture of physiological shapes and porous structures.
- Customization/lot size of 1: it costs the same to make 100 one-offs as it does to make 100-off, if the component volume remains the same. However, the cost of designing 100 components is clearly greater than the cost of designing 1 component, and so for scalable customization some level of design automation is desirable.

2.4 Limitations of 3D printing processes

- When the whole process chain is considered, including design, finishing and quality assurance (QA), 3D printing of functional, load bearing components is not necessarily low lead time or low cost. However, 3D printing processes are still developing, getting quicker, cheaper and better, and so this is improving.

- Whilst the processes are generally automated, to get consistent high-quality output a trained specialist machine operator will normally be required.
- Each machine type will have a specific, sometimes quite limited, range of materials that it can use, with the material cost often significantly higher than the equivalent raw material for processing using more mass production techniques.

2.5 Choosing 3D printing processes

3D printing processes are manufacturing processes, and so choosing a 3D printer should be no different from choosing any manufacturing process. The key elements to consider are materials, accuracy, surface finish, productivity, lead time and cost. For most manufacturing applications this means that the choice can be not of a 3D printer in isolation, but a 3D printer plus finishing process and/or post-processing equipment. For medical devices choice of materials are key and this factor tends to play a large part in the choice of a process.

3. Biomedical applications of 3D printing

3D printing gives the ability to produce physiological shapes from 3D imaging techniques in a wide range of materials. This has opened up the ability to create medical devices in geometries which would be difficult to create using other manufacturing techniques, and the research literature offers many examples of innovative devices and associated clinical case studies. 3D printing is also extensively used for producing prototypes as part of product development, and applications of 3D printing to making models for surgical planning or to inform clinical or patient decision making, both of which are important and valuable applications. The major commercial application areas for 3D printing in biomedical applications have been surgical guides, musculoskeletal implants, hearing aids and orthotics, and these are described in sections 3.1 to 3.5. Again, this is not an exhaustive list, but an outline of the major application areas, with the bibliography providing pointers to further information.

3.1 Surgical guides

The utilization of medical imaging techniques to provide geometric information with which to design medical devices is a key feature of early medical applications. Materialise, a Belgian CAD/CAM company which produces the Mimics software package was a pioneer in making the link between medical applications and .stl files, and still maintain a significant market presence. Musculoskeletal surgical devices were one of the first commercial applications, allowing clinicians to define in silico where a hole or cut should be made as part of a surgical procedure, and then to have a device produced which would guide a drill or saw to the required position. The work flow is generally (i) to work from a CT or MRI scan and generate a 3D reconstruction of the bone, (ii) to define the holes or cuts relative to that scan and (iii) to define a device which would be uniquely located onto patient landmarks and also provide guidance to the surgical instrument. Once designed, an .stl for the device is produced and the device produced, normally in a polymer, with steel inserts used to reinforce the guide where the drill or saw would be deployed. Surgical guides for dental applications were one of the first applications, but the largest scale application has been guides for total joint replacement, in particular for the knee. The clinical value of guides in complex surgery is clear, with reduced operation times and improved outcomes, but for operations where clinicians are well practiced, the clinical evidence suggests the value is more marginal.

3.2 Dental

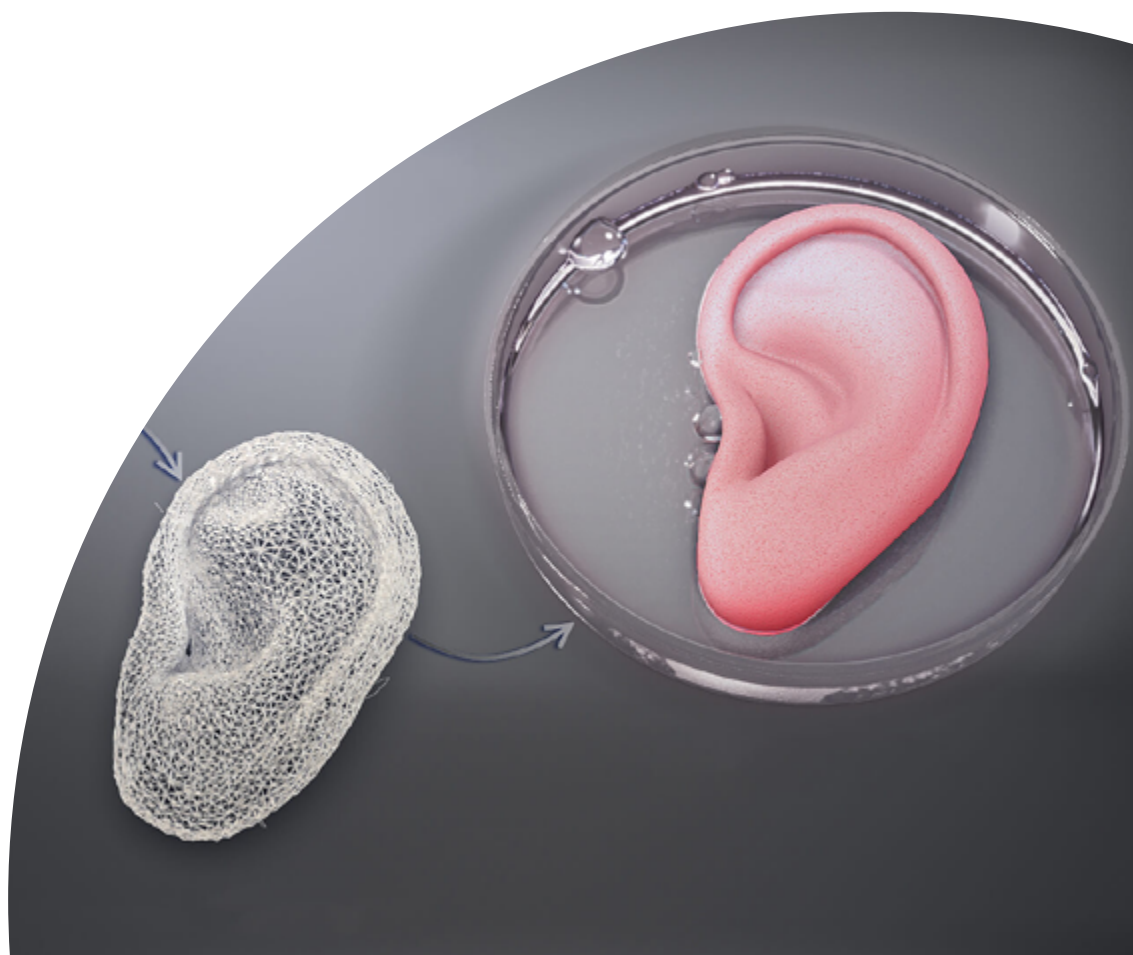
Dentistry has in general been an early adopter of new technologies and has embraced 3D printing not only for guides, but also for a range of dental devices, most notably in a commercial sense for bridges and crowns. This has been associated with increasing availability of intraoral 3D scanning techniques. Generally, the devices are produced in cobalt chrome alloy or medical grade titanium–aluminium–vanadium alloy, or through producing sacrificial models which can be used as patterns for casting.

3.3 Hearing aids

One area in which 3D printing techniques have almost completely displaced conventional manufacturing techniques is in the production of in-the-ear hearing aids. These are produced based on a laser scan of an impression of the inner ear, or on the basis of an intra-aural scan. From this a hollow shell is designed, with the internal space configured to accommodate the functional electronic hearing aid unit – in effect what is produced is packaging for the hearing aid which is a custom fit to the patient's ear.

3.4 Orthotics

A range of foot and ankle-foot orthoses have been researched and brought to the market. These are designed to re-align or provide pain relief to patients with a damaged or diseased lower limb. The design is based on an external scan of the foot and lower leg, with correction applied for re-alignment or cushioning and with polymer 3D printing then used to create a device. The geometric freedom offered by 3D printing can allow for the mechanical properties of the devices to be locally tailored, resulting in an orthosis which is flexible and accommodating in some areas, but rigid and supportive in others.



3.5 Prosthetics

Prosthetic applications of 3D printing fall into two categories: (i) using 3D printing to produce externally applied prosthetics and (ii) the manufacture of polymer or metallic musculoskeletal implants using 3D printing.

3D printing of externally applied prostheses has two alternative strands. The first is the creation of bespoke covers for prosthetic devices, generally with the aim of making devices more aesthetically pleasing, allowing personalization of both geometry and design. The second approach is to use 3D printing techniques to make functional elements of the prosthetic, and a number of open source projects have emerged over the years, offering designs for patients and their carers to manufacture devices at home. 3D printed prosthetic hands for children, for example, have the advantage that designs can be upgraded as the children grow, or in response to changes in motor skills.

3D printed implants have attracted significant public attention and have shown significant growth over the past decade. Two main strategies have emerged, one focussed on custom devices, and the other on enhancing non-custom devices. Much of the original work focussed on custom implants, normally in medical grade titanium alloy, with implants for large bone defects and joint replacement the most common. The alternative approach is to exploit the ability of 3D printing to create complex porous geometries, but within a standardised product, an approach that Stryker has used in its Triathlon® Tritanium® Knee and the Tritanium® Posterior Lumbar Cage products. For custom joint replacement the production of revision implants can offer a more compelling rationale: revision implants are generally more complex and can have a greater need for customization.

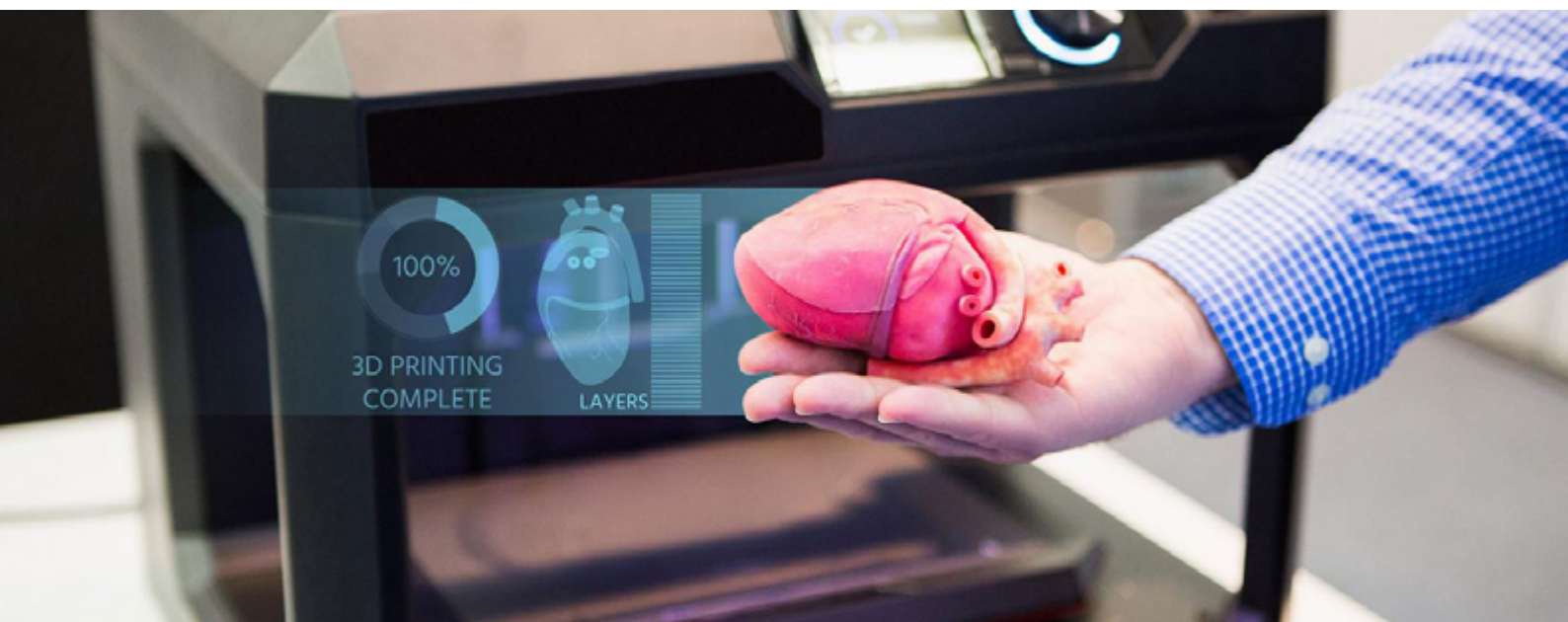
3.6 Key features of successful applications

There are three key features of successful applications of 3D printing of medical devices:

1. **Design for 3D Printing.** 3D printing techniques are manufacturing techniques, and each specific 3D printing process has its own set of design for manufacturing rules, and so device designs need to carefully consider process capabilities and the need for finishing processes in order to generate robust designs which meet product specifications.
2. **A very clear design and manufacture process chain.** Important for all applications, but of particular importance in the development of custom devices, is a clear understanding of how geometry data will be captured or defined, how designs will be generated, how parts will be orientated in a build and how they will be post-processed to produce the net shape part. At each stage the required accuracy and precision needs to be understood, and clearly the overall productivity of the process chain is set by the slowest element in the process chain.
3. **A clear understanding of the added value from 3D printing.** Again, important for all applications, but of particular importance in the development of custom devices, the value in terms of customization or process capabilities needs to be clearly understood, as only then can the cost of the design and manufacture process chain be justified.

To date 3D printing has been most successful when applied to small and/or customized devices. Small because of the cost and time of production and customized for the added value this can offer. However, as noted previously, 3D printing processes are getting quicker and, to some extent, cheaper, and so the size of components which can be created quickly enough and at a marketable cost is likely to increase.

The digital nature of 3D printing processes means that the design and manufacture steps can be separated, offering potential for the supply chain to be re-distributed to offer more flexibility of supply, with manufacture near the point of use. This potential has not been significantly exploited to date but could for some devices allow for point-of-care or near point-of-care manufacture.



4. Standards and medical device regulation

4.1 Key standards

The two key families of standards for 3D printing processes are ISO 17296 and ISO/ASTM 52900 series.

ISO 17296 defines standard terminology; provides an overview of process categories and feedstock, outlines the main characteristics and corresponding test methods, and gives an overview of data processing.

The ISO/ASTM 52900 series runs from ISO/ASTM 52900 to ISO/ASTM 52950, with a more specific range of standards, but many of these still under development. The series includes:

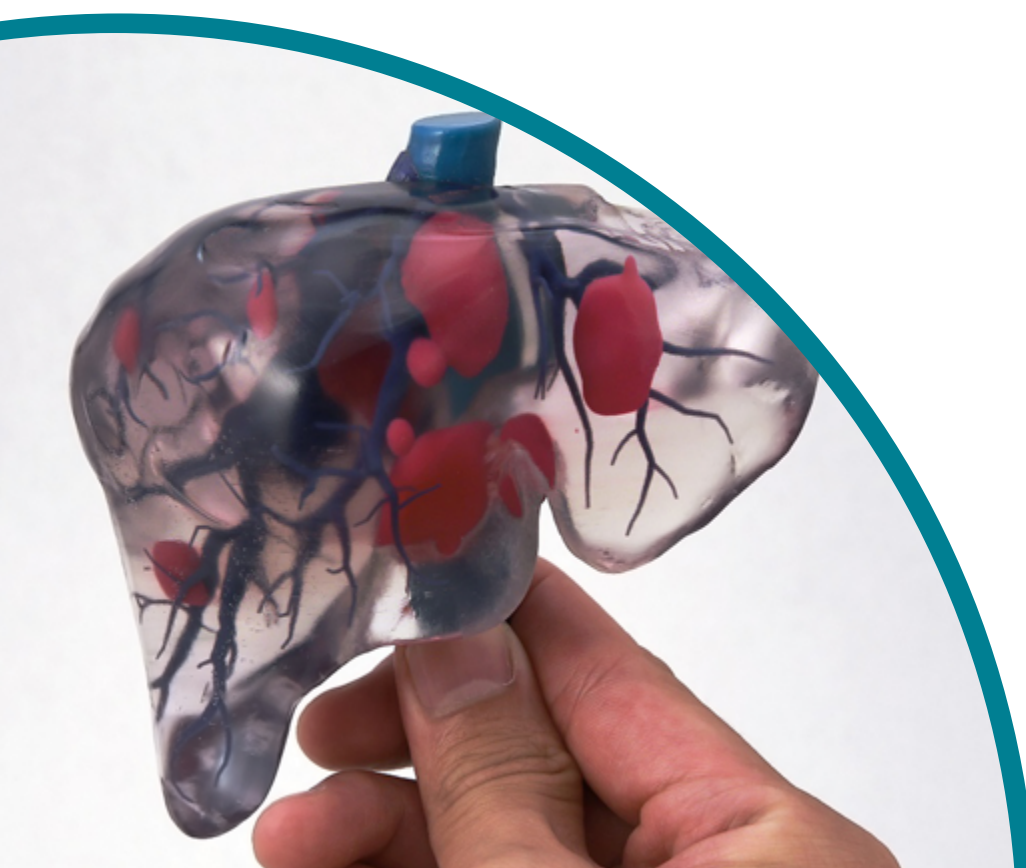
- [ISO/ASTM 52900 Standard Terminology for Additive Manufacturing – General Principles – Terminology;](#)
- [ISO/ASTM 52901:2017: Requirements for Purchased AM Parts;](#)
- [ISO/ASTM FDIS 52902 \(under development\): Geometric Capability Assessment of Additive Manufacturing Systems;](#)

- ISO/ASTM DIS 52903, parts 1–3 (under development): Standard Specification for Material Extrusion Based Additive Manufacturing of Plastic materials, Covering Feedstock, Equipment and Parts;
- ISO/ASTM FDIS 52904 (under development): Practice for Metal Powder Bed Fusion Process to Meet Critical Applications;
- ISO/ASTM DTR 52905 (under development): Non-destructive Testing of Additive Manufactured Products;
- ISO/ASTM FDIS 52907 (under development): Technical Specifications on Metal Powders;
- [ISO/ASTM 52910:2018: Design; Requirements, Guidelines and Recommendations;](#)
- ISO/ASTM DIS 52911, parts 1 and 2 (under development): Technical Design Guideline for Powder Bed Fusion, Covering Metals and Polymers;
- [ISO/ASTM 52915 Standard Specification for Additive Manufacturing File Format \(AMF\) Version 1.2;](#)
- [ISO/ASTM 52921:2013: Coordinate Systems and Test Methodologies; and](#)
- ISO/ASTM CD 52950 (under development): Overview of Data Processing.

Additionally, the ASTM committee F42 has developed standards for both material and process specific applications. These include the following:

- [ASTM F2924 Standard Specification for Additive Manufacturing Titanium-6 Aluminum-4 Vanadium With Powder Bed Fusion;](#)
- [ASTM F2971 Standard Practice for Reporting Data for Test Specimens Prepared by Additive Manufacturing;](#)
- [ASTM F3001 Standard Specification for Additive Manufacturing Titanium-6 Aluminum-4 Vanadium ELI \(Extra Low Interstitial\) With Powder Bed Fusion;](#)
- [ASTM F3049 Standard Guide for Characterizing Properties of Metal Powders Used for Additive Manufacturing Processes;](#)
- [ASTM F3055-14a Standard Specification for Additive Manufacturing Nickel Alloy \(UNS N07718\) with Powder Bed Fusion;](#)
- [ASTM F3056-14e1 Standard Specification for Additive Manufacturing Nickel Alloy \(UNS N06625\) with Powder Bed Fusion;](#)

- ASTM F3091/F3091M Standard Specification for Powder Bed Fusion of Plastic Materials;
- ASTM F3122 Standard Guide for Evaluating Mechanical Properties of Metal Materials Made via Additive Manufacturing Processes;
- ASTM F3213-17 Standard for Additive Manufacturing – Finished Part Properties – Standard Specification for Cobalt-28 Chromium-6 Molybdenum via Powder Bed Fusion;
- ASTM F3184-16 Standard Specification for Additive Manufacturing Stainless Steel Alloy (UNS S31603) with Powder Bed Fusion;
- ASTM F3187 Standard Guide for Directed Energy Deposition of Metals;
- ASTM F3301 Standard for Additive Manufacturing – Post Processing Methods – Standard Specification for Thermal Post-Processing Metal Parts Made Via Powder Bed Fusion;
- ASTM F3302-18 Standard for Additive Manufacturing – Finished Part Properties – Standard Specification for Titanium Alloys via Powder Bed Fusion;
- ASTM F3303-18 Standard for Additive Manufacturing – Process Characteristics and Performance: Practice for Metal Powder Bed Fusion Process to Meet Critical Applications; and
- ASTM F3318-18 Standard for Additive Manufacturing – Finished Part Properties – Specification for AlSi10Mg With Powder Bed Fusion – Laser Beam.



It is worth noting that there is no formal standard for .stl files, but these can be created using all major commercial CAD systems. There is a standard file format (AMF; defined by ISO/ASTM 52915) which allows for richer content than an .stl file (colour, lines, multiple materials), but .stl remains the file format used for most applications.

In the broader QA sense, the challenge that the use of 3D printing techniques can bring is that the properties of 3D printed parts can be different from those of the same material processed using an alternative manufacturing process (e.g. a 3D printed ABS component will have different mechanical properties to an injection moulded ABS component). In addition, the properties obtained depend on how well the 3D printer is maintained and operated, and even with good practice it is still possible for there to be variations in properties both within a build (so the properties of two nominally identical parts made at the same time in the same machine may differ) and between builds (variations in the properties achieved from nominally identical parts produced in the same machine but in different builds). Variations in properties are not unique to 3D printed parts, but the scale of the variations has acted as a spur for (i) the development of the ISO 17296 and the ISO/ASTM 52900 series to enable better process control and (ii) the development of 3D printers which are designed with a greater emphasis on ensuring consistent output.

Some variation in properties is inevitable however components are made, and the key thing is ensuring that components will meet their specification and establishing an effective QA system. For medical devices the standards designed to ensure that products are fit for purpose are:

- [BS EN ISO 13485 \(medical devices, quality management systems, requirements for regulatory purposes\) and BS EN ISO 9001 \(quality management\);](#)
- [BS EN ISO 14971 \(application of risk management to medical devices\); and](#)
- [BS EN ISO 10993 \(biological evaluation of medical devices\).](#)

Problems can arise when a 3D printing process is considered as a way of making an already established product, currently produced using a different manufacturing process. If the product specification and QA system have been developed and evolved around an established processing route, then the properties obtained by that method of production may be embedded within both the specification and the QA system. Considering a switch to a 3D printing process (or indeed any new manufacturing process) should always prompt a review of the specification, to ensure that both the new and existing processes are being assessed in terms of product fitness for purpose, rather than being abstractly compared to one another.

4.2 Medical device regulation

3D printed medical devices are subject to the same regulatory processes as other medical devices which entail the same degree of risk.

Within the EU medical devices are regulated by the 'The EU Regulation on Medical Devices 2017/745' (known as MDR) or 'The EU Regulation on In Vitro Diagnostic Medical Devices 2017/746' (known as IVDR). These regulations are being brought in over a transition period and by 2020 will have replaced European Council Directives 93/42/EEC (for medical devices, known as the MDD) and 90/385/EEC (for active medical devices), and by 2022 will have replaced 98/79/EC (for in vitro diagnostics), with both sets of regulations applicable over the transition period. These regulations classify devices by the risk inherent in their use, with medical devices classified as I (lowest risk, e.g. spectacles), IIa, IIb and III (highest risk, e.g. pacemaker). All medical devices require assessment to ensure that they are fit for purpose.

This ranges from self-assessment for low-risk devices to assessment by a notified body (an independent organization designated to carry out assessments) for high-risk devices, and assessment by a national competent authority (such as the MHRA in the UK) or expert panel for the highest risk devices. Mass produced devices which have been successfully assessed can be CE marked, and introduced to the market, in all cases with appropriate post-market surveillance.

The majority of 3D printed medical devices to date have been under MDD regulation and will in future fall under MDR regulation. In many cases, 3D printed devices are designed around the needs of a specific patient, and these are considered 'custom-made', defined as

specifically made in accordance with a written prescription of any person authorised by national law by virtue of that person's professional qualifications which gives, under that person's responsibility, specific design characteristics, and is intended for the sole use of a particular patient exclusively to meet their individual conditions and needs.

Under MDD custom-made devices do not require a CE mark but require a prescription from an appropriately qualified registered medical practitioner and must meet the same essential requirements indicated by the regulations in terms of fitness for purpose. For each custom-made device, a statement must be recorded which defines and uniquely identifies the device, names the patient and outlines conformity with general safety and performance requirements. Post-market surveillance is required.

MDR changes the definition of custom-made devices, as under MDR 'devices which are mass-produced by means of industrial manufacturing processes in accordance with the written prescriptions of any authorised person shall not be considered to be custom-made devices'. Since 3D printers are industrial manufacturing processes, this means that as part of the assessment of custom-made devices manufacturers could (depending on how the phrase "mass-produced" is interpreted) have to define how and why devices are customized and to show that the safety and performance of devices is assured across the range of the potential customization. The precise interpretation will need to be tested as MDR comes into force. However, what is clear is that from 2020 custom-made devices will be regulated in the EU in a similar way to standardised devices. Where there is any doubt regarding the regulatory requirements, consultation with a notified body is recommended

The MDR regulation is similar to the situation in the US, where for most classes of device 510(k) accreditation from the FDA is required. The 510(k) submission for patient specific devices also must define the extents of customization, such that fitness for purpose across the range of the potential customization can be evaluated, and the FDA have issued detailed advice on the use of 3D printing techniques to make medical devices (see bibliography). For rare conditions the FDA allows up to five devices a year to be produced with 'custom device exception', meaning that these devices can be produced without a 510(k) submission, but subject to all other regulatory requirements.

5. Bioprinting

Bioprinting techniques first emerged in 2003 with the first demonstrations of cell printing. Bioprinting can be considered a sub-set of biofabrication, which can be defined as the processing of biological materials (cells, proteins, pharmaceuticals) and materials to create structures which have a designed biological function. The intended application area may be for regenerative medicine, for diagnostic/theranostic tools (e.g. the creation of physiological micro-tissue models for drug testing or personalized medicine), or for non-medical applications (synthetic food or leather for instance). The aim of the bioprinting step is normally to produce a cell/material construct which will be further cultured or processed for the specific application.

In terms of differentiating between 3D printing and bioprinting, the key to this is normally in the material being deposited: if the material in whole or in part has a biological function, which is maintained through the process, then it would be considered to be 3D bioprinting. Depositing passive biomaterials would simply be considered 3D printing.

5.1 Principles

Whilst there are a range of biofabrication techniques, bioprinting techniques share a number of key characteristics with 3D printing, including an almost identical process flow: geometry acquisition from MRI/CT, design, manufacture, post-processing. Where biological materials are used hydration is key, and so materials are normally deposited in solution (often cell culture media) or in gels. Gels offer cells an aqueous environment, with the added benefit of having properties which can approximate those of a range of soft tissues.

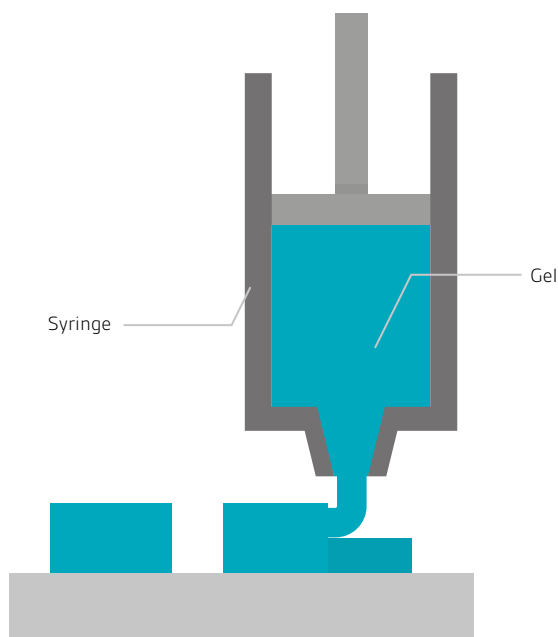
5.2 Common processes

Sections 5.2.1 to 5.2.3 outline some common approaches to bioprinting, and again sources of further information are outlined in the bibliography.

5.2.1 Gel extrusion

The most common bioprinting process is gel extrusion, which is conceptually similar to fused deposition modelling. A gel material is extruded through a nozzle or syringe to deposit a track of material on a substrate, as shown in Figure 8. Often the gel material is 'cell-filled' and so is prepared with cells dispersed through the gel. Mostly gel materials are prepared and extruded having been crosslinked, but the more viscous a gel is the more difficult it is to extrude, and higher extrusion pressures create both shear and direct stresses on cells within the gel, adversely affecting cell viability. To avoid this problem gels may be crosslinked during deposition (e.g. by introducing a crosslinking agent as part of the deposition, using a twin syringe system) or after deposition (e.g. by UV curing).

Figure 8 – Gel extrusion process



5.2.2 Inkjet deposition

Inkjet print heads can be used to print small volumes of cells in a solution. The size of droplets created by inkjet heads is small, so that this is effectively printing of a few cells per droplet and can give an average of one cell per droplet. The viscosity of fluid which can be jetted is quite low. Again, there is scope for post-deposition crosslinking reaction to be used to create a gel.

5.2.3 Micro-valve deposition

Micro-valve printing also uses low viscosity materials but can deposit larger droplets with hundreds or thousands of cells per droplet. Post-deposition crosslinking can be used, but more recently techniques which use multiple jets have been developed. These can be used to combine liquids in mid-air in order to create gel droplets, which are then deposited on a substrate. This approach has the benefit of creating high cell density gels, as the low viscosity fluids which are dispensed can have a heavier cell loading without affecting cell viability.

6. Bioprinting and medical devices

The potential impact of bioprinting on medical devices would be if bioprinting processes were used to enhance medical devices, for example through applying cells or biomolecules to a device prior to implantation. The device may be mass produced or custom-made, and bioprinting offers a potentially attractive route to biological enhancement of devices, with scope for that enhancement to be either personalized or stratified, through the use of cells harvested from the patient or the addition of pharmaceuticals based on a theranostic test. Given that the sterilization approaches and shelf life duration of medical devices are generally incompatible with the needs of biological materials, the most practical approach to combining medical devices with a medicinal product or substance may be for the medicinal product to be applied in clinic, immediately before the device was implanted.

The use of a medicinal product would change the regulatory environment. In the EU, medicinal products and substances are regulated either as:

- medicinal products, regulated by EC Directive 2001/83/EC and Regulation (EC) No 726/2004; or
- advanced therapeutic medicinal products, if the product is based on genes, tissues or cells, with regulation through EC Directive 726/2004.

Where a device is combined with a medicinal product it is known as a 'combination product'. The combination of a 3D printed medical device with a medicinal product will present its own set of regulatory challenges. Put simply:

- where the main therapeutic effect to the patient is via the medicinal product, the combination would need to be regulated as a medicine (EC Directive 2001/83/EC); although the device part would require a Notified Body Opinion under Article 117; and
- where the main therapeutic effect is from the device part, with the medicine having an ancillary action, the combination could be considered a Class III medical device.

Manufacturers will be required to demonstrate the principle action and ensure the correct regulatory path is followed.

The key elements in successfully using 3D printing were identified as design, process integration and clearly understanding value, and these factors will also be important in the exploitation of bioprinting processes for medical devices. The need to understand value in a product development process is not a surprise. The introduction of biological functionality will mean that the intended biological effect will be part of the design process, and integration will include cell and tissue culture processes as well as other design and manufacture steps. A further key element of product development is clarity regarding the regulatory process, and the combination product regulatory process would be a further consideration when seeking to exploit bioprinting to enhance a medical device.

7. Future developments

The 3D printing market overall continues to grow and develop, with new processes, which give faster, cheaper and more consistent output, continuing to be developed. Bioprinting is still commercially in its infancy, but again new machines and processing techniques with new levels of functionality are being developed and launched. As the machines develop, the range of potential products that can be economically produced also increases, but future developments will also need to address the overall process chain. The development of design automation systems is key to enabling the economic design of custom devices. These systems tend to work to a template and greatly simplify the generation of custom device designs given a set of specific needs. Addressing finishing times and costs also remains a challenge for some processes, with 'design for finishing' approaches being developed to ensure that the finishing step is as quick and easy as possible, and there is currently significant research effort being directed at automated approaches to finishing and QA.



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