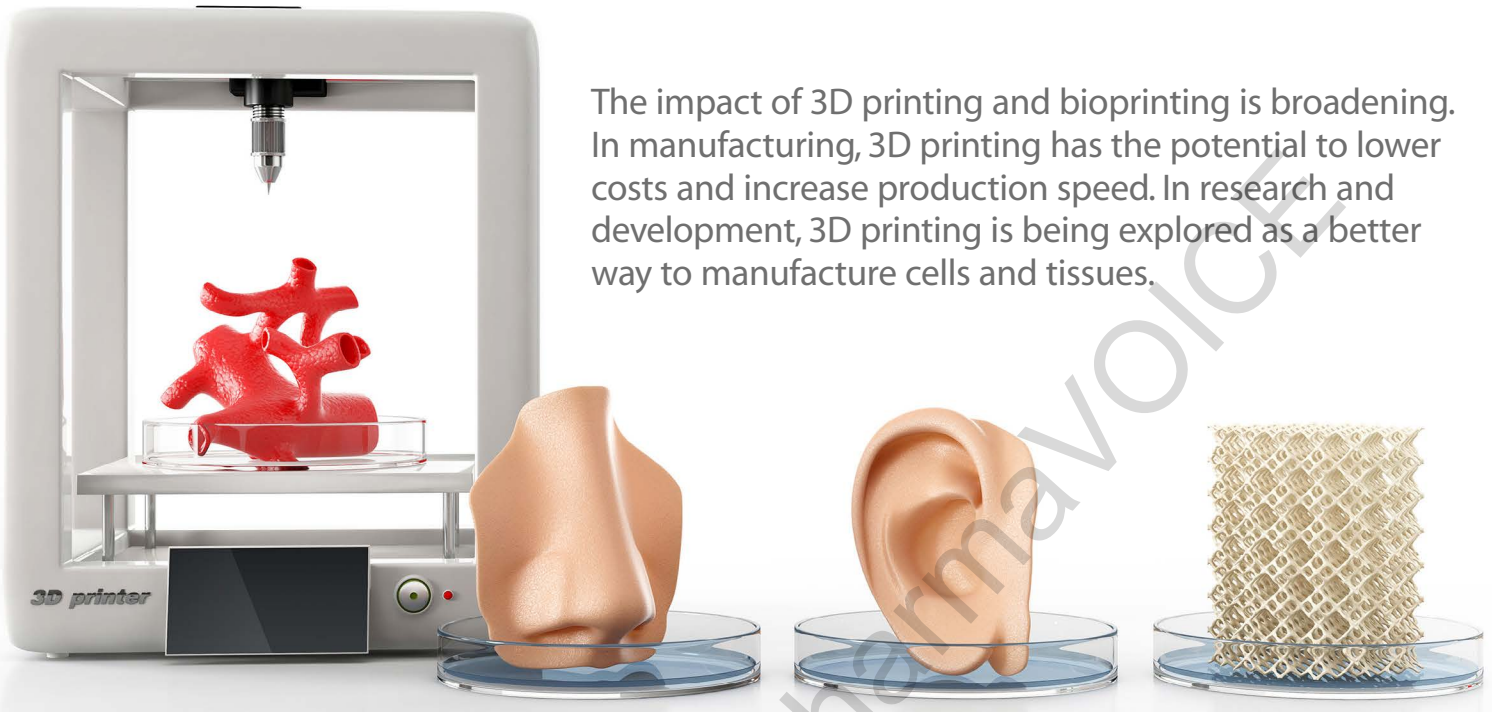
By Denise Myshko



The impact of 3D printing and bioprinting is broadening. In manufacturing, 3D printing has the potential to lower costs and increase production speed. In research and development, 3D printing is being explored as a better way to manufacture cells and tissues.

Trend: 3D and Bioprinting

The bioprinting field continues to grow and mature. With the evolution of the technology, experts believe even broader applications are on the horizon, providing patients with fully functioning cells — and even organs — that have been created through bioprinting processes.

"All of us can envision a day when bioprinting technologies will allow us to 3D bioprint solutions that provide a supportive or a structural solution to the body," says Taylor Crouch, CEO and president, Organovo. "Ultimately, the goal is to be able to print fully functioning organs, and that, of course, is the science fiction and future that we hope to achieve, but we are still a few decades from this becoming a reality."

Many large healthcare and life-sciences companies are investing in 3D bioprinting, or exploring how 3D printing can be used, recognizing that these technologies are an important part of drug development in the future.

The Food and Drug Administration has called 3D printing a tantalizing step toward changing manufacturing processes and has been actively supporting the adoption of 3D printing technology in the biomedical and dental industry. Last year, the agency made a statement regarding its commitment to the technology releasing guidelines for manufacturers submitting 3D printed implants and other medical devices. The FDA has also awarded grants to five research institutes for the study and improvement of biomanufacturing, including 3D bioprinting.

Bioprinters deposit layers of biomaterial, which may include living cells that need food, water, and oxygen, to build complex structures like blood vessels or skin tissue. Companies in this space are working to create conditions that foster the fastest and most efficient cell growth. Some companies are creating bioinks — multi-cellular building blocks — that are loaded into a printer. Other researchers are implanting cells around 3D scaffolds made of biodegradable polymers or collagen so they can grow into a fully functional tissue.

Through these processes, living tissues, such as blood vessels, bones, heart, or skin can be created. In the short term, industry experts say the biggest impact of 3D and bioprinting will be in the in vitro testing area, helping to bring promising drugs quickly to the clinic and to the market.

P&S Intelligence predicts that the 3D bioprinting market size will reach $792.5 million by 2022, growing at a CAGR of 35.9%

Bioprinting offers the potential to predict how drugs may perform in humans, eliminating some animal testing and helping to avoid potential trial failures. Having the ability to conduct drugs and disease model testing on 3D-printed tissues instead of on animals or humans, opens up new platforms in the drug discovery and development process. Many drugs are withdrawn or are not approved by the regulatory authority due to their toxicity in certain organs such as the liver, which could not be predicted during the preclinical trial process. By using 3D bioprinted liver tissues, researchers have the potential to better evaluate drug toxicity and improve drug efficacy.

Printing Human Tissue

Organovo has already had some success in 3D printing parts of liver, kidney, and gut tissues. The company designs and creates functional human tissues using a proprietary 3D bioprinting technology. The goal is to build living human tissues that are proven to function like native tissues. The first step is to develop the bioprocess protocols required to generate bioink from the cells that will be used to build the target tissue.

The bioink building blocks are then dispensed from a bioprinter, using a layer-by-layer approach. Bio-inert hydrogel components may be used as supports, as tissues are built up vertically to achieve three dimensionality, or as

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ERIK GATENHOLM
Cellink

fillers to create channels or void spaces within tissues to mimic features of native tissue.

"Our approach to 3D bioprinting tissues is to mimic human function in a number of ways," Mr. Crouch says. "We use these tissues in the laboratory to study how promising new drugs perform in a human tissue-like system in vitro. The hope is to better predict how a drug may ultimately perform in human testing."

In April, Organovo announced that it, along with its collaborators, had achieved several breakthrough capabilities for its 3D bioprinted tissues. The company demonstrated that it was able to create functional human liver tissue, produce a spectrum of non-alcoholic steatohepatitis (NASH) disease conditions, and then treat that disease successfully with a client's development stage NASH drug.

Organovo and Merck also jointly published a peer-reviewed study describing the company's bioprinted human intestinal model, which exhibits compelling architecture, barrier, and metabolic functions, while also being able to model key aspects of toxicity and inflammation.

Organovo's goal is to take these functioning tissues, scale them to a reasonable size, and implant them into humans to help supplement or replace a missing function in an otherwise defective or severely diseased liver.

"We are moving toward an IND track with our liver patch program to address a range of life-threatening diseases typically resulting from genetic deficiencies, which prohibit a patient's liver from handling certain proteins or enzymes resulting in cascading and severe effects on the body," Mr. Crouch says. "Often, patients with these types of liver diseases need a transplant shortly after birth."

Organovo's animal studies have shown that the cell patches have exhibited function for up to 90 days, sometimes for as long as four months.

For patients on a transplant list, where every day or week is crucial, Organovo hopes that its patch can bridge the time gap and perhaps even reduce the need for a transplant.

"Once our patches are in a human environment, we hope that our cells will begin to replicate in a healthy pattern and provide a longer-term benefit," Mr. Couch says. "We are able to generate synthetic enzymes that are critical to regulating liver function and provide some support, and this could and should be enough to provide a meaningful benefit to patients in a number of settings."

Organovo plans to submit an IND for this application with liver tissue in 2020. Mr. Crouch says the company is funding this research, but may consider a partnership for other therapeutic areas.

The company has also done proof-of-concept studies with kidney tissue and several other organs.

Another company working in this area is Cellink. Founded in early 2016, Cellink offers 3D printable bioink, a liquid that enables life and growth of human cells. Currently, the company is bioprinting parts of the body — noses and ears — mainly for testing drugs and cosmetics. It also prints cubes enabling researchers to "play" with cells from human organs such as livers.

"The bioprinted tissues are behaving and doing the things we would expect human tissue to do," says Erik Gatenholm, CEO of Cellink.

The company's universal bioink combines nano-fibrillar cellulose and alginate. Both components are derived from natural sources and are produced under stringent quality control. In October, Cellink announced that it is launching several new bioinks, including a bioink series that uses collagen as its primary component. Collagen is the main structural component found in many tissues and is the most abundant protein in mammals, and Cellink even offers collagen bioinks. Potential applications include research in tissue development, cell migration, and drug screening.

Cellink has also expanded its existing GelMA-series and Alginate-series to include more variety in molecular weight, methacrylation degree, and formulation. Additionally, the company has released its Additive-series to allow collaborators to better tailor and customize bioinks toward their specific applications. These additives can be blended into existing bioinks, combined with kits, or mixed with the researchers' own bioinks.

"Our focus is on novel biomaterials that can be used in tissue engineering applications," Mr. Gatenholm says. "We are good at making materials look like tissue, and when we put human cells in those materials, they thrive and they do the things they are supposed to do inside the human body." He adds that the company's vision for this technology is to replace animal studies.

Cellink recently partnered with CTI Biotech, a French medtech company specializing in producing cancer tissues, to advance the area of cancer research and drug discovery. The company's platform users include J&J, Merck, Novartis, and Roche, and the company has academic partnerships with Harvard and Yale.

Mr. Gatenholm says his company has been able to lower the price of 3D bioprinters to make it possible for greater access to the technology.

FAST FACT

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Source: P&S Intelligence

Other 3D Printing Applications

Today, 3D printing is able to positively impact and increase efficiencies for fixtures on the production line, tooling for molded fiber packaging, and general prototyping. And 3D printed drugs are already being made available to patients. Spritam (levetiracetam), an oral

3D Printed Pills

The Food and Drug Administration approved Aprecia Pharmaceuticals' Spritam in 2015 for oral use as a prescription adjunctive therapy in the treatment of partial onset seizures, myoclonic seizures, and primary generalized tonic-clonic seizures in adults and children with epilepsy. Spritam was the first and remains the only 3D printed product to be approved.

Spritam uses the proprietary ZipDose Technology platform, a three-dimensional printing platform to produce a porous formulation that rapidly disintegrates with a sip of liquid.

The process involves the use of print fluids that bind layers of API-containing powder together into porous structures or dosage forms. The ZipDose formulation platform is ready and immediately available to develop and manufacture advanced fast melt dosage forms that accommodate large drug loads yet disperse quickly with a sip of liquid. Today, ZipDose technology is opening possibilities in new therapeutic areas for drug manufacturers and is helping patients who need easy-to-take medicines and caregivers who want medicines that are easy to administer.

Industry leaders say 3D printing manufacturing will enable pharmaceutical companies to tailor the dose, release profile, size, and shape of a drug to meet the unique or changing medical needs of special populations.

As Aprecia evolves its 3DP manufacturing systems, equipment assemblies, and processes, it may be possible to develop additional applications for the technology, such as anti-counterfeiting properties. This application of the technology involves the printing of a company mark (e.g., name, brand, etc.) within the inner layers of the dosage form.

Source: Aprecia Pharmaceuticals

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TAYLOR CROUCH
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drug for epilepsy patients suffering from seizures manufactured by Aprecia Pharmaceutical, became the first 3D bioprinted medication to gain FDA approval in 2015. (See sidebar for more information.)

Unlike conventional production techniques, the 3D printing process for Spritam does not rely on compression forces, punches, or dies. Instead, it binds layers of powdered medication together with an aqueous fluid. This forms medicine that is solid, yet very porous.

"Someday, 3D printing of pills could have an immense impact on custom dosages, compounding, or even timed-release formulations," says Lee Dockstader, director of vertical market development, 3D printing, HP.

HP is working with the Centers for Disease Control on a pilot program using its Biohacker technology to "print" and test antibiotics in an effort to catch antimicrobial resistant strains from spreading faster. The HP D300e Digital Dispenser BioPrinter technology works by using the same set up as a regular ink printer, but instead dispenses any combination of drugs in volumes from picoliters to microliters for research purposes. The CDC will use these printers in four regional areas within the Antibiotic Resistance (AR) Lab Network to develop antimicrobial susceptibility test methods for new drugs, according to HP.

The HP BioPrinter also is currently being used by labs and pharmaceutical companies, such as Gilead, which is testing drugs against the Ebola virus. It is also being used in various CRISPR applications.

3D printing is widely accepted across the health and medical industry as one of the most effective and efficient means of production, Mr. Dockstader says. "The biggest trend we're seeing is the continued expansion of 3D printing of medical devices and anatomical models across practices and disciplines."

3D printing of unique medical devices is the largest application; more than 450,000 unique parts are printed every day, including hearing aids, molds for clear dental aligners, and a wide range of other dental devices. More than 90% of the global hearing aid production is 3D printed and has been for more than 10 years.

Mr. Dockstader says there are a vast amount of 3D applications currently being used in the marketplace. For example, 3D printed surgical guides being used for better-fitting joint replacements, custom hip sockets, and titanium plate fixtures for complex fractures.

In the United States alone, there are more than 600,000 full knee replacements per year, and more than 100,000 of those surgeries are now carried out using 3D printed surgical guides.

"These types of applications shorten operation times and result in less initial pain for patients, fewer surgical revisions, and better long-term outcomes for patients," Mr. Dockstader says. "For pharmatech customers, 3D printing is critical to producing complex parts, new applications, and geometries not possible with conventional metal fabrication technologies. In the plastic space, companies such as Invent Medical for example are using 3D printing to produce helmets for babies to remove naturally occurring skull dents created while in the womb." PV

We thought "holding company" meant having some people over.

In our opinion, the only thing holding companies hold is you back. We much prefer the flexibility fierce independence offers to dream and deliver for our clients alone.

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