IFPW FOCUS IFPW

Vol. 22 No. 12 International Federation of Pharmaceutical Wholesalers June 11, 2015

3D Printing and Its Pharmaceutical Application

(Sources: An article prepared by Katharine Sanderson and published by The Pharmaceutical Journal, Alvaro Goyanes, Niklas Sandler and the British Association of Pharmaceutical Wholesalers)

As the pharmaceutical industry shifts from mass manufacture towards personalized medicine, 3D printing could become part of the drug production line. 3D printing promises a future of drugs printed on demand, to custom doses, and the possibility that cost may no longer be a barrier to making niche medicines. Children could be among the patients to benefit most. "This technology could revolutionize the way we look at children's medicines, both in terms of what they take and the ability to keep changing the dose as they grow," says Steve Tomlin, consultant pharmacist at Evelina London Children's Hospital, UK. Having a 3D printer in a hospital pharmacy could make weekly medication changes simple, personalized, and even fun.

A 3D printer works by adding materials layer by layer until a 3D shape emerges. So far, different 'inks' have been used to print everything from pizza to heart valves. If a 3D printer ink that is laced with a drug can be developed, then why not print tablets as well? This is an idea that has caught the imagination of a number of academics and pharmaceutical companies, who intend to develop not just the technology but the quality control needed to bring 3D printing to pharmacies.

"The potential of 3D printing is about being able to deliver what you want when you want," says engineer Ricky Wildman from University of Nottingham in the UK. Wildman is trying to find the right materials that can be used as inks to make tablets with varying doses of drugs. In particular, Wildman is looking at inkjet 3D printing. Wildman has replaced coloured inks with polymers, drugs and other materials used in pill manufacture. The tablet is then printed layer by layer, by squirting out these ingredients into the desired shape and letting them set. Wildman is looking closely at the materials he prints with. "In inkjet we're exploring the way you can create suspensions and liquid-based materials that can be triggered to make solids," he says. But he acknowledges that real-world applications are some years off, perhaps 5, 10 or even 15 years hence.

Other groups are also looking at applying 3D printing to drug manufacturing. Simon Gaisford, a pharmaceutical scientist at University College London, is combining 3D printing and hot-melt extrusion (HME) — a technique already used in the pharmaceutical industry to make polymer blends of drugs that are not very soluble. When HME is used, a drug and polymer are heated, mixed and squeezed through a small aperture. This disperses the drug in the polymer, and this polymer can then be shaped into a tablet. By combining the ability, conferred by HME, to work with drugs that are not very soluble with the possibility of making tailored shapes using 3D printing, Gaisford hopes to manufacture a variety of drugs with different doses and configurations. Eventually, he sees

(continued on page 2)

In Brief . . .

- **Cardinal Health** (US) is acquiring US pharmaceutical distributor **The Harvard Drug Group** for approximately US$1.12 billion in a deal that aims to build its generic and over-the-counter drug businesses. Purchasing the privately-held company based in Michigan, will provide Cardinal with specialized packaging to help supply hospitals and other institutions. The Harvard Drug Group had revenues of about US$450 million last year, has 450 employees and operates 2 distribution centers. The deal comes after Johnson & Johnson's acceptance of Cardinal's US$1.94 billion offer to buy the former's Cordis heart devices unit.
- Finland-based wholesaler/retailer **Oriola-KD** opened an online pharmacy **(InternetAptieka.lv)** and acquired a pharmacy in Latvia late last year, which has now been rebranded and is open for customers.The new concept of InternetAptieka pharmacy utilizes the layout and design of Oriola's successful Swedish retail pharmacy chain **Kronans Apotek**. The physical pharmacy represents the product assortment of online pharmacy internetaptieka.lv, and has the same attractive online prices, while serving as a pickup point for products ordered online.
- **AmerisourceBergen** (US) plans to build 3 new distribution centers in Mississippi, Minnesota and New York as part of an overall plan to continuously improve its pharmaceutical supply chain delivery ability. The three DCs are currently in the design phase but promise to feature state-of-the-art automation, warehouse management, and advanced communications technologies.
- *Ken Suzuki*, president of the **Federation of Japan Pharmaceutical Wholesalers Associations** (JPWA), was re-elected to a second 2-year term at a general meeting of the JPWA. Mr. Suzuki pledged his renewed resolve to forge ahead with what is called "single product single price" transactions, where drugs are traded between wholesalers and healthcare institutions at prices that reflect their actual value as opposed to the bundling practice of setting the total price for a cocktail of products. "We must achieve a distribution reform in the true sense by promoting the single product single price transactions," he said. Mr. Suzuki also serves as a Director of IFPW.
- **CVS Health** (US) is acquiring **Omnicare** (US), the leading provider of pharmacy services to long term care facilities, for approximately US$12.7 billion, including US$2.3 billion in debt. According to CVS, the acquisition of Omnicare will significantly expand its ability to dispense prescriptions in assisted living and long term care facilities, serving the senior patient population, and will expand its presence in the rapidly growing specialty pharmacy business. Omnicare's complementary specialty pharmacy platform and clinical expertise will augment CVS Health's capabilities and enable CVS Health to continue to provide innovative and cost-effective solutions to patients and payors.

(Sources: Cardinal Health, CVS, Drug Store News, Oriola-KD)

3D Printing (cont.) . . .

this technology developing so that pharmacists can tailor-make drugs for each patient.

Polymers are already used by pharmaceutical companies, and Gaisford suggests that in the future pharmacists could purchase polymer inks pre-loaded with a drug and then print out pills at a local dispensary. This approach of 'mixing up' medicines for each individual patient echoes the way drugs used to be dispensed many years ago. So far, Gaisford and his team have tested their printing prowess on two aminosalicylate drugs used to treat inflammatory bowel disease. They applied a process related to HME called fused-deposition modelling, in which a heated polymer is squeezed out of the printer tip and then solidifies. They printed tablets in a range of shapes and found that the different shapes affected the speed at which the drug was released in the body — for example, a pill with a hollow middle dissolved at a different rate to one in which more of the middle was filled in.

The trouble with this technology is finding the right materials, says Mohamed Albed Alhnan, a pharmaceutical scientist at the University of Central Lancashire in Preston, UK, who is looking at a similar approach. So far Alhnan has printed the steroid prednisolone in differing doses, and an anti-asthmatic drug theophylline. Any polymer used in drug manufacture needs to be biocompatible but also able to withstand the high temperatures used during the printing process, Alhnan says. He has had some success in finding polymers that can be processed at high temperatures, although still lower than the typical 220–255 °C used in non-pharmaceutical 3D printing applications. With a patent pending on the technology and a paper on the way, Alhnan is reluctant to say more.

3D printing is often considered to be at the forefront of the 'democratisation of technology' — the idea that technology can bring anything to anyone. For Lee Cronin, a chemist at the University of Glasgow in Scotland, the developing world is where 3D drug-printing would be most useful. "Personalisation is the 'sexy' driver but I think distribution and reach are the winners here — especially in the developing world," Cronin says. He has his own take on 3D printing — he is developing a system called reactionware, in which a 3D printer prints out the necessary kit to perform the entire synthesis of any molecule. "I would get away from 3D printing as a concept and more look at the 3D printer as a cheap configurable chemical and formulation robot," he says. In Cronin's reactionware, the chemical starting materials are printed, as is the equipment needed to mix, transfer, analyse and purify the molecule. "We are making big strides in combining chemical synthesis, purification and control within the devices," Cronin says. Without the need for specialized equipment (the printer does everything), reactionware has the potential to enable poor and remote communities to manufacture any drug they need. Wildman is also excited about the idea of using 3D printing to increase access to medicines. "You could create mini-factories distributed and set up for the most frequent type of drugs used," he says. In remote locations, the 'factory' would be the local pharmacy, he suggests.

But getting 3D drug-printing off the ground first requires some interest from industrial partners. This could take time: "The pharmaceutical industry is a conservative one," says Wildman. There is some progress in this area, though. Aprecia Pharmaceuticals, based in Langhorne, Pennsylvania, filed its first 3D-printed product for approval to the US Food and Drug Administration

(continued on page 3)

Japan's Drug Wholesalers' Financial Reporting for FY2014

(Source: PharmaJapan)

The top four Japanese drug wholesalers reported an average operating profit rate of 0.82% in their core drug wholesaling business for the fiscal year ended March 2015, according to data compiled by Jiho. With posting an average operating profit rate of 0.52% in the first half of the fiscal year (April - September 2014), these four wholesalers showed profit growth in the second half of the fiscal year. Market growth was negative due to factors including a slump in demand following an increase in purchasing prior to the increase in the consumption tax, NHI price revision, and declining sales of long-listed drugs. The four wholesalers posted combined sales of ¥7,228,603 million (US$58.2 billion), a decrease of 2.7% from the previous year. While the four wholesalers' average operating profit rate was less than 1%, which is considered reasonable, they were able to secure minimal profit despite decreases in sales.

Alfresa Holdings, Medipal Holdings, and Toho Holdings reported larger declines in sales than the market average, while Suzuken's sales fell just 1.0%. "We continued working steadily to meet customers' needs," explained Hiroshi Ota, president of Suzuken.

The four wholesalers reported combined operating profit of ¥59,604 million (US$479.8 million), down 21.2%. This reflects the decline in sales of high profit long-listed drugs resulting from the "category shift" from long-listed drugs to generic drugs in the ethical drug market.

Selling, general and administrative (SGA) expenses fell at all four companies, but since their sales fell as well, the four companies' average SGA cost ratio rose 0.08 points to 5.62%. Medipal Holdings was able to control its costs and personnel expenditures, and its SGA cost ratio declined. Many companies reported profits that exceed their revised forecasts on a consolidated basis. They revised their full year forecasts before or after announcing their first-half results, but their profits did not decline more than expected. Selling prices fell in the first half due to increased efforts to settle prices earlier following the introduction of the medical fee cut rule for low price settlement rates, but price levels seem to have improved in the second half. At the end of March, price settlement rates stood at 97.7% for Alfresa Holdings, 98.1% for Medipal Holdings, 96.3% for Suzuken, and 97.1% for Toho Holdings.

The four wholesalers forecast combined sales of ¥8,736 billion (US$70.3 billion) for the fiscal year ending March 2016, which would represent a 3.7% increase over the previous year. They expect the market to recover due to the launch of major new drugs including Gilead Sciences's oral chronic hepatitis C treatment Sovaldi. The four companies also forecast a 6.7% increase in combined operating profit to ¥91 billion (US$732.7 million). Three expect increases in operating profits, but Suzuken anticipates decreases due to an increase in SGA costs in its drug manufacturing business.

Since price negotiations in the second year after an NHI price revision are usually based on the prices agreed to the year before, price levels tend to decline. All four wholesalers agree that "prices agreed on so far are already at the second year level." FY2015 price negotiations have already started with a view to avoid medical fee cuts for low price settlement rates at the end of September. However, wholesalers will need to reach price agreements quickly without cutting prices in order to secure their profits.

3D Printing (cont.) . . .

(FDA) in October 2014. The company is developing a system that can print large doses of drugs in a formulation that makes them easy to swallow. Aprecia's product, called *ZipDose*, is built up from layer upon layer of powders of the drug bound together by droplets of liquid. When the pill is taken with water it disintegrates very quickly, which makes taking high doses a breeze, Aprecia claims.

Jennifer Zieverink, Aprecia's senior director of alliance management, explains that the key drivers for using this method of manufacture are the ability to be more precise and to make drugs more patient-friendly. "We hope to ultimately improve adherence by alleviating medication avoidance issues related to hard-to-swallow or hard-to administer dosage forms," she says.

The company has invested in facilities, and is gearing up to create 150 jobs in its manufacturing plant in Blue Ash, Ohio. Elsewhere, Gaisford has started a company based in Ashford, UK, to commercialise his technology, called FabRx. And pharmaceutical giant GlaxoSmithKline (GSK) is running a research and development project looking at 3D printing of drugs in its Upper Merion, Pennsylvania site. The project is at an early stage and is more about assessing whether GSK should be investing in 3D printing of drugs than doing it for now. Firstly, GSK wants to determine whether there are certain types of drugs that might benefit from being manufactured using this method, and, if so, what materials and systems they might need to start a 3D printing programme.

Niklas Sandler is investigating hyperspectral imaging as a way of building quality control into printing drugs. Of course, any commercial effort to produce drugs using 3D printing will have to comply with regulations, an issue that will require some serious thought. "One wouldn't want to place a pharmaceuticals factory in someone's home that wasn't regulated," says Wildman. Alhnan speculates that it may make sense to regulate the finished, printed product but suggests that printed medicines would also need to be manufactured under the supervision of someone with a lisence to operate a 3D printer to dispense drugs. And for regulators to be confident in any licences they grant, they need to know that the printers will give the same product each time. This will require validation, says Wildman. "The challenge is to ensure that you are creating what you said you were going to create," he says. To do this, a portfolio of safe materials that can be regulated and used as standard will need to be established.

Niklas Sandler, professor in pharmaceutical technology at Åbo Akademi University in Turku, Finland, is focusing his 3D printing efforts on building quality control into the process. Sandler is exploring with lots of proof-of-concept ideas for printing drugs with different doses, layer by layer. To check that each layer contains the correct amount of drug, Sandler is looking at a technique called hyperspectral imaging. This method takes tens of thousands of spectral images at one time across an entire sample, with each spectrum becoming a pixel in an overall image of what the sample contains, chemically, at each point. Sandler has shown that the technique works in inkjet 3D printing of drugs, using theophylline as a model compound. He is confident that hyperspectral imaging can be integrated into the printing process in the future. As well as clinicians being able to control doses accurately, regulators should also benefit from this kind of in-line monitoring, says Sandler. "You can build in the quality in your system if you're able to monitor every single thing," he says. High quality control should give regulators the confidence that patients will get what it says on the label.

So will 3D printing completely replace drug manufacturing as we know it? Or is it more likely that 3D printing's future lies alongside traditional ways of making pills? It depends who you talk to. "You wouldn't want to make ibuprofen with a 3D printer," says Wildman, who thinks the technology will be used for niche drugs that might not be manufactured otherwise, even if they had been discovered and tested in the clinic. Cronin is more ambitious for the technology: "In the end it will replace big plant [drug manufacturing] all together. That's my vision, anyway."

IFPW Foundation Adds New Resource Library to Web Site

IFPW Foundation has added a new resource library to its web site (www.IFPWfoundation.org) which includes reports on Global Health issues, particularly those with supply chain needs and/or applicability.

Visit the site to access this content and to keep abreast of the opportunities IFPW Foundation and the industry are presented with and to keep informed on the organization's current activities.

The library can be found at www.IFPWfoundation.org/library.htm.