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VC DEALS ANALYSIS:

Liquid Biopsy Summons Yet Another Top A-Lister

TINA TAN tina.tan@informa.com

Venture financing activity levels did heat up in tandem with the summer temperatures, as May, June and July each surpassed the previous year's performance. However, August saw deal volume and value take a sharp drop with only 21 fundraisings and around $257m raised in total.

While August was only able to muster two thirds of the deal volume seen in July, this was on par with the level seen in August last year. (See Figure 1.) Additionally, August's deal value might have fallen significantly short of July's total takings of $398m, this is still in line with previous year's performance.

Indeed, looking at the five-year data from *Medtech Insight*'s VC Deal Tracker in Figure 2, August has always signaled a downturn in financing activity (with the exception of August 2015 which saw a big spike from not just one but two nine-figure financing rounds). The slowdown in August could likely be explained by the holiday period in both the US and Europe, when Congress and EU Parliament go into recess and industry also takes time for some R&R.

LIQUID BIOPSY GRABS TOP BUCKS

Notably, August's biggest deal is a $50m series A – the biggest series A this year to date – by **Karius Inc.**, a company developing a liquid biopsy test for infectious diseases. The *Karius Digital Culture* test uses a combination of machine learning, proprietary genomics algorithms and next-generation sequencing to detect cell-free DNA fragments left by bacteria, viruses, fungi, and other eukaryotic pathogens from a patient's blood sample. The test can detect over 1,250 pathogens within one business day, according to Karius.

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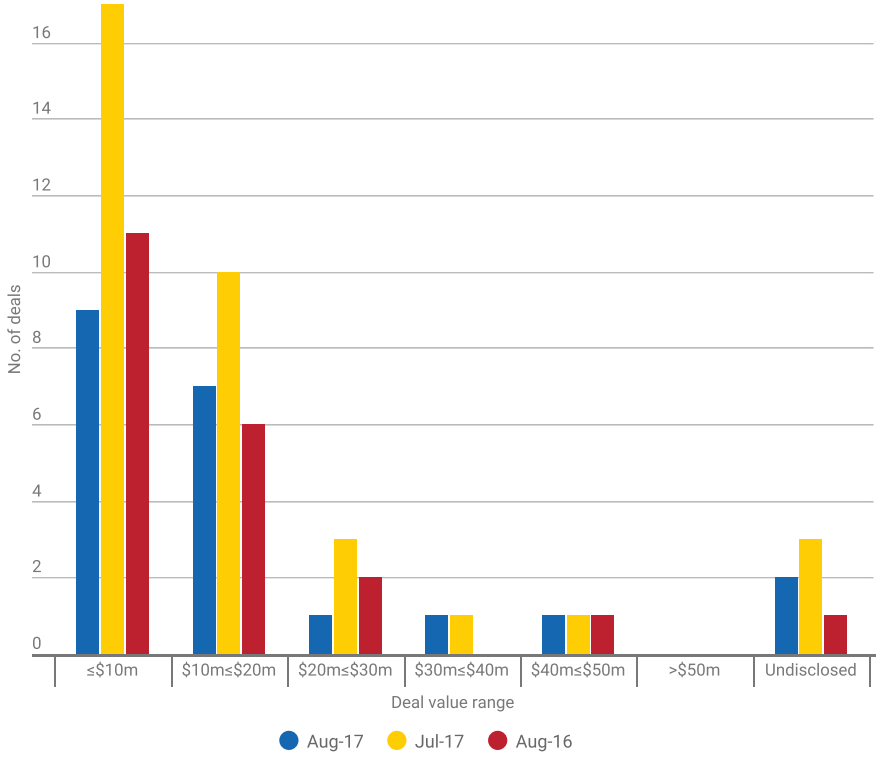
FIGURE 1

No. Of VC Deals By Amount Raised, Aug 2017 vs July 2017 vs Aug 2016



Source: Medtech Insight VC Deal Tracker

FROM THE EDITORS OF: **THE GRAY SHEET, CLINICA, START-UP** AND **MEDTECH INSIGHT NEWSLETTER**

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Nine manufacturers will be selected for US FDA's voluntary "Premarket Approval Application Critical to Quality" pilot program to assist the agency's review of the manufacturing section of a PMA and post-approval inspections, and qualify to swap a pre-approval inspection for a post-approval audit.

Abbott drops *Absorb*
http://bit.ly/2wWa5G3

Abbott will stop selling its first-generation bioabsorbable coronary stent, which failed to match the performance of contemporary metallic drug-eluting stents in clinical trials. The company says it will continue working on next-generation biosorbable stents.

J&J rethinks obesity
http://bit.ly/2gYeHlR

Johnson & Johnson subsidiary Ethicon launched a new initiative to significantly alter the treatment of obesity at this year's 22nd World Congress of the International Federation for the Surgery of Obesity and Metabolic Diseases.

Global guidance tracker
http://bit.ly/2xuQheh

Stay current on regulatory guidelines from around the world with the latest updates to *Medtech Insight*'s Guidance Tracker.

Device Week
http://bit.ly/2v0IJtS

Check our latest episodes of the Device Week podcast, where journalists discuss our analyses of recent US FDA 510(k) exemptions and both US and global device approval trends.

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Medtech insight

DAVID FILMORE @MEDTECHDAVID
david.filmore@informa.com
TINA TAN @MEDTECHTINATAN
tina.tan@informa.com
SHAWN M. SCHMITT @MEDTECHSHAWN
shawn.schmitt@informa.com
REED MILLER @MEDTECHREED
reed.miller@informa.com
AMANDA MAXWELL @MEDTECHAMANDA
amanda.maxwell@informa.com
MARION WEBB @MEDTECHMARION
marion.webb@informa.com
SUE DARCEY @MEDTECH_INSIGHT
sue.darcey@informa.com
FERDOUS AL-FARUQUE @MEDTECH_DANNY
danny.al-faruque@informausa.com
ELIZABETH ORR @ELIZABETHJORR
elizabeth.orr@informa.com
CATHERINE LONGWORTH @MEDTECHCATE
catherine.longworth@informa.com
ASHLEY YEO @ASHLEYPYEO
ashley.yeo@informa.com
MAUREEN KENNY @SCRIPREGMAUREEN
maureen.kenny@informa.com
NEENA BRIZMOHUN @SCRIPREGNEENA
neena.brizmohun@informa.com
VIBHA SHARMA @SCRIPREGVIBHA
vibha.sharma@informa.com
JANET HANIAK SENIOR DESIGNER
GAYLE REMBOLD FURBERT DESIGN SUPERVISOR
RICHARD FAINT HEAD OF MEDTECH
richard.faint@informa.com
PHIL JARVIS MANAGING DIRECTOR

Editorial office:
52 Vanderbilt Avenue, 11th Floor, New York, NY 10017
phone 240-221-4500, fax 240-221-2561

CUSTOMER CARE:
1-888-670-8900 OR 1-908-547-2200
FAX 646-666-9878
clientservices@pharmamedtechbi.com

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3D-printed, customized, lifesaving medical interventions. But aside from these niche markets for personalized medical devices, can 3D printing ever become mainstream in health care? Leaders at the Boston Consulting Group explore the issue in this guest column.

POLICY & REGULATION

DEVICE INTEROPERABILITY:

US FDA Details Expectations In Final Guidance

ELIZABETH ORR elizabeth.orr@informa.com

A newly finalized guidance document from US FDA urges firms to incorporate device interoperability design and assessment from the beginning stages of product design. Companies should pay close attention to electronic interface functionality, data-exchange factors and time synchronization, among other challenges, the agency states.

The 21-page document spells out several specific concerns related to devices' ability to safely exchange and use identifying information wirelessly or over ports such as USB, as well as strategies the agency expects manufacturers to use to mitigate any risks tied to interoperability. It also outlines how interoperability issues should be addressed in device submissions such as PMAs and 510(k)s.

Specifically, the agency recommends manufacturers of interoperable devices "perform a risk analysis and conduct appropriate testing that considers the risks associated with interoperability, the anticipated users, reasonably foreseeable misuse, and reasonably foreseeable combinations of events that can result in a hazardous situation." Device labeling should clearly explain an electronic interface's functional and performance requirements, as well as any limitations the device or its interface might have when used in an interoperable system.

Developers should begin by considering the purpose of the interface, the guidance states. The interface may be key to a device's intended use, or play a much smaller role, FDA says. But no matter how important or minimal its function, developers should consider a range of issues including the types of devices the interface will connect to; the type of data exchange taking place, such as sending, receiving, or issuing commands; the need for time synchronization; the data transmission method; the transmission of metadata such as Unique Device Identifiers (UDIs); and any warning or precautions needed for the use of the exchanged information.

Device design should keep with specific interoperability scenarios in mind, FDA says, using the example of a pulse oximeter that sends data to a computer system for eight hours to assess sleep in newborns, while the system is also gathering ECG data. "Therefore, the information from the pulse oximeter and ECG need to have their times synchronized and data collected at a specific rate. Knowing the scenario would demonstrate the need for specific features," the agency explained.

Time synchronization problems between devices and with other electronic systems has been a particular challenge in health-care settings. *(Also see "Lack Of Device Clock Synchronization Vexes Physicians, Hospitals" - Medtech Insight, 2 Jul, 2012.)*

Another key factor to consider is the intended users, as different audiences may need different risk management or usability information, FDA says. For example, clinicians need to know the clinical uses and potential clinical risks of the interface, while IT professionals need to understand any security risks and patients may need instructions to properly use the device in a home environment.

The agency also expects device developers to consider the potential for both intended and unintended access to the interface in its risk management calculations. Device interfaces should be protected against failures or malfunctions caused by invalid commands or erroneous data, FDA says.

The interface development process should also consider whether implementation or use of the interface could make the device's routine functioning less safe. The interoperable system "should maintain basic safety and essential performance during normal and fault conditions," FDA states. The agency expects manufacturers to have a process throughout the device lifecycle to systematically conduct risk evaluations and determine whether risks are acceptable or unacceptable.

In addition, the interface should be verified and validated for use throughout the device lifecycle, including before delivery, during set-up and installation, while in use, and during maintenance and software updates.

The guidance recommends developers use interoperability consensus standards in device development, but doesn't include a list of suggested standards. However, FDA issued recommendations on accepted interoperability standards in 2013.

The document will take full effect after a 60-day transition period. It finalizes a draft guidance issued Jan. 25, 2016. *(Also see "FDA Emphasizes Risk Analysis, Labeling Details In Interoperability Draft Guidance" - Medtech Insight, 25 Jan, 2016.)*

An FDA reviewer recommended the agency modify the draft guidance to incorporate a requirement that sponsors submit written commitments accepting responsibility for managing changes that may affect interoperability. However, the proposal was not incorporated in the final version.

In an FDA blog post, Bakul Patel, associate director for digital health in FDA's device center, made a case for its importance even while acknowledging interoperability is a somewhat arcane topic.

"It's not likely that medical device interoperability is a part of the everyday vocabulary of American consumers—and frankly, we hope it stays that way," Patel wrote. "We want patients and consumers to have confidence that medical devices work as intended without concern over how these devices operate together. But, in working with manufacturers to bring innovative medical devices to patients who need them, interoperability is an indispensable concept."

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Hindsight 20/20: Ian Gilham

TINA TAN tina.tan@informa.com

With a PhD in Biological Sciences, Ian Gilham started his career as a bench scientist but soon made the transition to commercial roles within the in vitro diagnostics sector, working for established names such as Abbott and GSK. The turn of the millennium marked a significant milestone when he joined Anglo-Nordic IVD firm, Axis-Shield, in 2001 as chief operating officer then took the helm seven years later. As CEO, he oversaw the acquisition of Axis-Shield by Alere Inc. in 2011. (Also see "Alere finally bags Axis-Shield with slightly increased offer" - Medtech Insight, 6 Oct, 2011.)

Following the acquisition, Gilham has been sharing his experience and knowledge with several diagnostics and biotech companies and is currently chairman of Horizon Discovery Group PLC, BioSurfit, genedrive and Multiplicom.

Ian Gilham, former CEO of Axis-Shield and IVD industry veteran

Medtech Insight: You come from a scientific background but managed to successfully expand into senior executive roles that focus on commercial growth. What advice would you give to founders of start-ups who have more scientific/academic, rather than commercial, backgrounds to help them grow their "baby"?

Ian Gilham: The key thing is to get a network of people who have done it properly to give you feedback. One of the keys to a company's success is knowing when a different skill-set is needed. People are good at different phases of the business and somebody who runs a $1bn-market cap company may not be someone who would ever sit in a garage with a computer and £5,000 and start a business. It's not very often where you have people who can transition to that later commercial stage – it's very, very rare and often that problem is recognized too late and businesses get into trouble without the correct leadership.

I think that's where the board comes in; having an independent board and a chairman who have done it before and can take the steps to renew the management team and get the right skills set in.

You made that transition, though. Where in your career, would you say, was the turning point for you that allowed you to make the switch and take on a more commercial/operational role?

I started doing my PhD in immunoassays and I started at Celltech, did a few years there in the labs then went to Amersham, who, scientifically, was the world leader in diagnostics at that stage. I was a bench scientist but I really wanted to do something different, get some commercial experience and I found that quite difficult, frankly, at Amersham, because people moved in very definite career paths and it was very hard to move between them.

So I got a position in Abbott Labs, then the world leader in commercial diagnostics, in technology licensing and acquisition, which bridged the gap between science and business. In tech licensing and acquisitions, you really get into patent acquisitions, understanding the IP, the strengths and weaknesses, prior art, etc. I really got a good grounding in IP [in that role], and it is important to understand this in a high-tech sector, as a lot of the value of the company is in the IP estate.

I really enjoyed the commercial side of technology acquisition and licensing and then moved on to a pure commercial role and ran Abbott's eastern European business. Abbott was a great business school generally; I learnt very quickly about country organization, finances, business planning, all that.

Financing is always an issue for companies, especially start-ups and SMEs with limited resources. In which area(s) would you advise companies absolutely not to skimp on with the budget and why?

As I said, IP is very important so you would want to invest in protecting it. But it's not just about owning the IP but understanding what IP you might be treading on with your product. Frankly, when you come to raising money, if you haven't done the due diligence on the IP yourself, the investors will do it and you'll find out the hard way that you have an IP problem or your competitors are ahead of that.

Invest in a strong team and a strong board. Having people who understand special areas, who you can go to and get advice is absolutely critical. You need to recognize you can't do it all yourself and that you need to get the best IP people, the best finance people, the best commercial people you can af-

ford to bring them in or have them consulting to help you build a strong business. And it's not just advice: with those kinds of people on board, you are much more likely to get funding. Because you have a very strong business case and tested it against people who have done it before.

As CEO of Axis-Shield, you led the acquisition of the company by Alere and now you are chair of a number of start-ups which, in all likelihood, are hoping for a trade sale exit. What advice would you give to venture-backed start-ups or more mature publicly-listed companies who are being approached by potential acquirers? Are there any attributes to look out for in an ideal suitor – or is it all about the money?

The biggest thing people do not take into account when considering an acquisition proposal is the objectives of their investors. Sometimes, founders of companies fail to understand that when they bring investors in, they don't own the company anymore. And it's the investors who will decide what a good offer is. So the first thing is to be aware of who you bring in as an investor and what their objectives are.

There might be those who are thinking that if they can sell the company and get X times more money in two years, they'll be thrilled. While there are others who might think this is a 10-year project for them, that they want to invest money in the company, make acquisitions, grow the business, set up offices in the US or in China, etc. So they want to invest in a longer period of time to get an outcome.

If you get an offer from somebody who says they want to offer so much, you as the founder might have views on that but ultimately the market/investors will decide what a good price is. You are not the decision-maker.

3 IN 30: Three quick-fire questions in 30 seconds

What do you do to help unwind from the stresses of your job?
I enjoy sport and am a member of the Great Britain age-group triathlon team.

Who, outside the medtech industry, do you see as a role model and why?
[Double Olympic champion triathlete] Alistair Brownlee – humble and dedicated with an unbelievable focus on achieving his goals and being the best athlete he can possibly be.

If you weren't a medtech executive, what would have been your career Plan B?
I'd probably like to be a medical doctor. Can't think of anything more satisfying than helping to make sick people well – which is probably why I'm so passionate about the medtech industry.

If you had to put together a dream team to help you take your company's disruptive, white space-targeting technology from bench to market, what attributes/skills/expertise would you be looking to recruit?

One of the key things is to build that support network by hiring people who have been very successful in their area, whether its commercial or regulatory or clinical. Not just those who have had a positive experience but also who have made mistakes and learnt from it and can advise the team not to make those same mistakes. It's critical to build as strong a team as possible and use that network.

There is a feeling that to be a CEO of a business, you need to be fiercely independent and successful and visionary; most people aren't like that and the good news is, you don't have to be. There are plenty of good people out there with a lot of experience and you can learn from it.

In terms of which functions to focus on more than others, all the functions are important. You'd need R&D expertise to manage the product development process, a regulatory person to oversee the requirements for registering the product in different markets, a commercial person to assess how you would want to sell the product whether to go direct or through a distributor, and then there is also the reimbursement aspects, how to get your product reimbursed, whether that is a one-year project or ten-year project. You would need all of those functions filled all the time, but the balance shifts as the company goes through the different phases of growth. It's important to understand which phase you're at and thinking ahead, and getting the resources to be prepared for that phase.

We learnt this lesson when Axis-Shield was plan to launch a point-of-care blood testing instrument in the US. In the early days, we would hire people from Europe to head a US operation and then have them spend one week in the US and one week back. This didn't work out for this product launch and we got it wrong twice. The third time, we got a VP of sales who was actually based in the US; it was a very expensive hire, but what I learnt was sometimes you need to bite the bullet and spend the money, because you're learning about the market and you need their knowledge. It's the same in China. We had an office in China and at first, we were running it from Europe but when we finally got a local to oversee the business there, suddenly we got product registration, suddenly we got sales, suddenly we understood the market.

So, at the appropriate phase of the business, you need to be prepared to invest properly in the right person.

Do you want to share with us another experience of a particular crisis that a company you were managing/or on the board of had encountered and a) if it did overcome this crisis, how

was it done b) if it didn't succeed in overcoming it, what would you have done differently?

There was a point when Axis-Shield had some field performance problems with a product which required fixing. We had some serious trouble shooting to do and so it comes back to having a really good management team with the experience and who have seen this before and knew what to do. The team we had was very proactive. We promptly informed the FDA, we spoke to the customers and that, frankly saved the business, because we were able to fix the problem without losing customers and too much negative publicity.

All companies run into problems – whether it's a product problem, a manufacturing problem, or competitor problem – but it's what you do about it that matters. Again, it's about putting your heads together during a crisis and having an experienced team that knows what to do so that there is minimal impact on the business. You learn from that and you put new quality controls to put in so it doesn't happen again.

Ultimately, it's about people. The success of a company is not so much about the technology itself but the quality of people who deliver that technology. It's all about the team you put in place, the support and the advice you get, recognizing when business is transforming from one phase to another and realizing the different skillsets you might need then and when you might need to refresh the team again.

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M&A ANALYSIS:

August Activity Cools As The Summer Closes

CATHERINE LONGWORTH catherine.longworth@informa.com

The surge of summer M&A deals finally began to slow in August, with 16 deals recorded on the *Medtech Insight* M&A Deal Tracker.

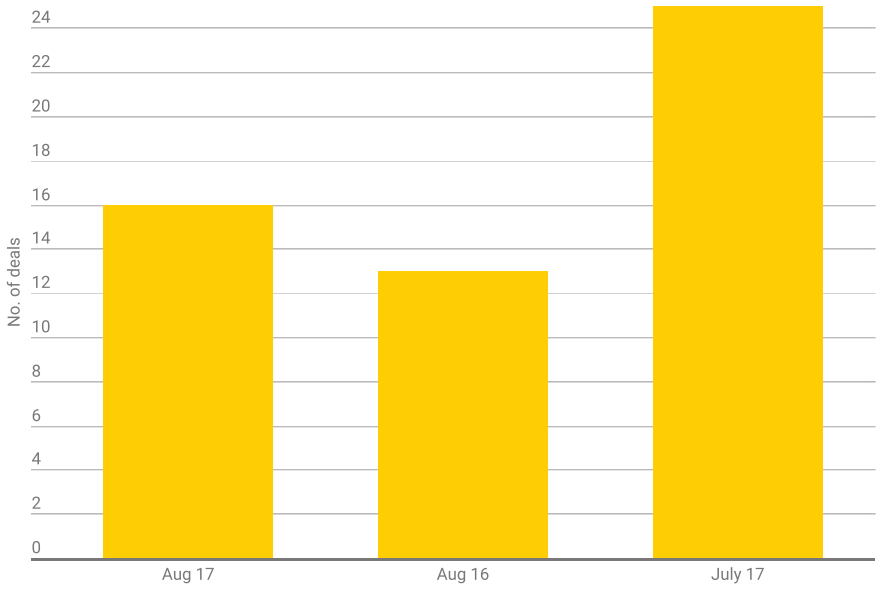
The fall in activity reversed a busy trend of medtech M&A deal-making over the summer months. August 2017 was unable to beat the 25 deals seen in July, but nonetheless was busier than August last year, which recorded 13 deals. (See Figure 1.) *(Also see "M&A Analysis: July M&A Levels Reach Fever Pitch" - Medtech Insight, 3 Aug, 2017.)*

Of the 16 deals recorded in August, only five disclosed financial terms. In the biggest acquisition of the month, **Fresenius Medical Care (FMC)** struck a $2bn deal to buy-US-basedhome dialysis equipment-maker **NxStage Medical.** The German health-care group is currently the world's largest provider of products and services for dialysis, and is looking to solidify its leadership position by expanding further into the home dialysis market. The company agreed to pay $30 for all of NxStage's shares – a 30% premium to the company's closing price on Friday Aug. 4. *(Also see "Fresenius Homes In On NxStage" - Medtech Insight, 7 Aug, 2017.)*

Rice Powell, chairman and CEO of Fresenius Medical Care, said the acquisition supported the company's 2020 goal of driving growth in the core business. "Combining our two companies would strengthen and diversify our business in the US, and help meet the evolving needs of our patients," he stated.

FIGURE 1

M&A Deal Volume Aug 17 vs Aug 16 vs July 17



Source: Medtech Insight M&A Deal Tracker

In the past, home dialysis has been a niche market, but the need is expected to increase substantially, driven by growing patient numbers and rising cost pressures. Expansion into the market has been a focus for FMC for some time. In 2007, the company acquired US company **Renal Solutions Inc.** and its SORB technology for $190m. "Home dialysis is a critical component of renal care, and this acquisition would help us accelerate growth and innovation in this important modality," said Bill Valle, CEO of Fresenius Medical Care North America, said about the latest NxStage acquisition.

In the ortho/dental arena, Swiss group **Straumann** paid $150m to buy **ClearCorrect**, a manufacturer of clear aligner orthodontic corrective devices. Straumann said the acquisition is part of its initiative to enter the orthodontic market and leverage digital technologies to deliver orthodontic solutions. In a statement, Marco Gadolo, CEO of Straumann said: "ClearCorrect provides us with technology, expertise and a strong footing in this field. In return, we offer a global distribution and marketing network, in addition to brand leverage. With some big changes expected in the clear aligner industry, our union with ClearCorrect has come together at exactly the right time."

Orthopedics firm **Globus Medical** acquired Swiss robotic surgical developer **KB Medical** for an undisclosed sum**.** Dave Demski, president of emerging technologies for Globus Medical said the acquisition of KB Medical will enable the company to accelerate, enhance and expand its product portfolio in Imaging, Navigation and Robotics. The news came as Globus Medical announced Q2 earnings and FDA clearance for its *Excelsius GPS*, a robotic guidance and navigation system for minimally invasive and traditional orthopedic and neurosurgical procedures.

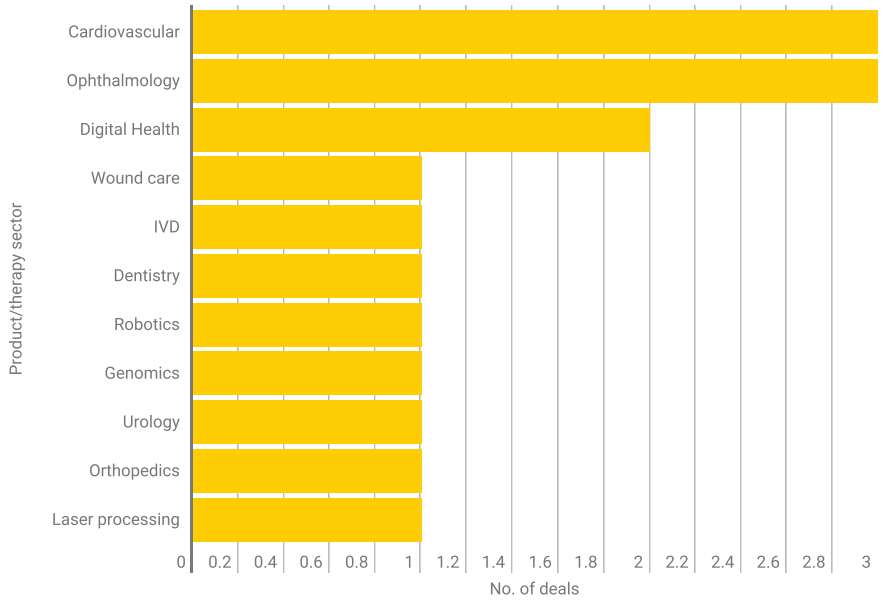
Another noteworthy deal is one from tech giant **Google**, which continued to show its interest in digital health care with the acquisition of **Senosis Health**, a Seattle-based startup that has been developing patient monitoring apps for collecting health metrics, and providing services such as diagnosing pulmonary function and hemoglobin counts. Terms of the deal were not disclosed by Google, but according to a report in Geekwire, Senosis will not be joining Google's Life Sciences branch Verily, and it's unclear how the company will fit within the structure of Alphabet, the parent company of Google.

EYES ON OPHTHALMOLOGY DEALS

Of the 16 recorded deals in August, three acquisitions were inked in the ophthalmologic sector. This is space that has had limited M&A activity so far this year but it shares the top spot with cardiovascular as the product sector with the most deals last month. (See Figure 2.)

FIGURE 2

M&A Deal Volume Aug 17 vs Aug 16 vs July 17



Source: Medtech Insight M&A Deal Tracker

Johnson & Johnson Vision announced it will acquire **TearScience**, a privately held medical device manufacturer focused on treating meibomian gland dysfunction, a leading cause of dry eye syndrome. In September last year, Terms of the TearScience deal were not disclosed. Johnson & Johnson made a big investment in its ophthalmology business with the acquisition of **Abbott Medical Optics** in an all-cash deal worth $4.3bn.

German optical manufacturer **Carl Zeiss AG** strengthened its cataract surgical offering by acquiring privately held **Veracity Innovations**, a developer of intelligent cloud-based data management platforms for helping ophthalmic surgeons plan and manage cataract surgery. The platform will complement other data management products currently offered by Zeiss, which includes *Forum*, a platform that connects diagnostics devices and integrates the data from multiple modalities to deliver the required information to physicians.

Ophthalmic devices is the largest of Carl Zeiss Meditec's two strategic business unit, the other unit being microsurgery. Earlier in August, the company reported an 8.3% year-over-year increase in revenue, at €864.7m, for the first nine months of 2016/2017. This was driven by the 9.2% growth in revenue for ophthalmic devices, at €639.9m. Microsurgery saw revenue grow 5.6% to €224.8m. *(Also see "Carl Zeiss Meditec Sees Data Management Potential In Cataract Surgery" - Medtech Insight, 22 Aug, 2017.)*

Further interest in the ophthalmic space came from Japanese device-maker, **Hoya Corp.**,which agreed to buy **Performance Optics**, a global ophthalmic lens manufacturer specializing in polycarbonate, photochromic, polarized and high index eyeglass lenses. The deal includes the acquisition of its subsidiaries Vision Ease and Daemyung Optical and production facilities in the US, Thailand, Indonesia, South Korea and China. "Performance Optics provides Hoya with additional capabilities and offerings in polycarbonate, photochromic and polarized lens technologies, and expands our global footprint in high index lens casting," Hoya Vision Care CEO Girts Cimermans said in a statement.

Hoya said by joining forces with Performance Optics, its global research & development capabilities would increase and lead to the creation of a new "technology center of excellence" outside of Thailand and Japan.

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Teleflex Adds Minimally Invasive BPH System With NeoTract Buy

REED MILLER reed.miller@informa.com

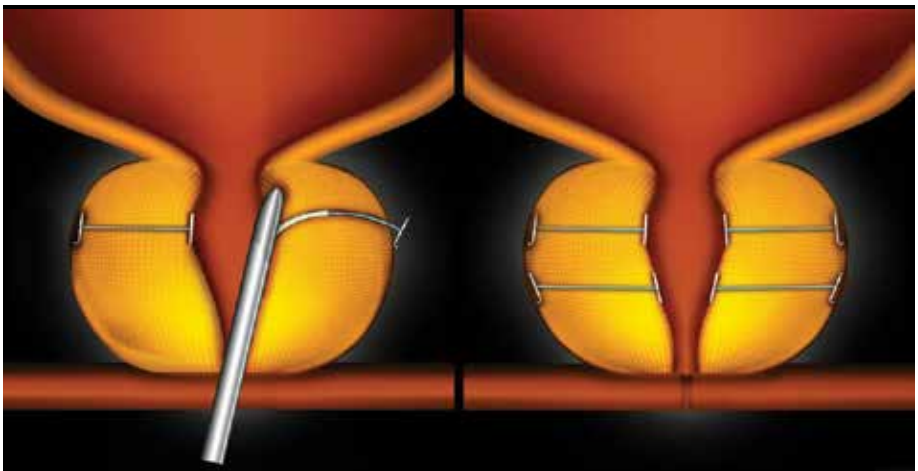
Teleflex Inc. is making another big investment in a novel product that it believes can boost the revenue growth of its broad product portfolio with the $1.1bn acquisition of privately held **NeoTract Inc.**, manufacturer of the *UroLift* system for minimally invasive treatment of benign prostate hyperplasia, the companies announced Sept. 5.

Teleflex has agreed to acquire NeoTract for $725m up front, and additional commercial milestone-linked payments of up to $375m over the next three years. The companies expect the deal to close in the next 30 days.

Teleflex expects the deal to be slightly dilutive to earnings in 2017, breakeven in 2018, and contribute $0.35 to $0.40 to earnings per share in 2019. NeoTract could add between one to two percentage points toward the Teleflex organic constant currency revenue growth rate over the next few years, according to Teleflex.

This is the latest in a series of major acquisitions for Philadelphia-based Teleflex this decade, as it has transformed from a diversified industrial company into a medical device company. Teleflex divested its marine and industrial instrumentation businesses in 2009, followed by a recreational marine business in 2011, and aerospace business in 2012. It became a major player in anesthesia and laryngeal face masks when it bought **LMA International NV** for $276m in 2012 and got into intraosseous – bone – access technology by paying $262.5m for **Vidacare Corp.** in 2013. In late 2016, Teleflex acquired **Vascular Solutions Inc.**for about $1bn. *(Also see "Teleflex Buys Vascular Solutions For $1bn To Improve Growth" - Medtech Insight, 6 Dec, 2016.)*

"Our strategic business unit structure … allows one business to integrate and manage an acquisition while our separate business unit can then evaluate and integrate a different acquisition opportunity," Teleflex CEO Benson Smith said during a Sept 5 teleconference. "Even when we were completing the acquisition of Vascular Solutions, we told our business-development group to continue to look for that next great asset. And it is our belief that we found it in NeoTract."



NeoTract's UroLift implant holds the enlarged prostate tissue out of the way to open-up the urethra

Photo credit: NeoTract Inc.

Teleflex offers a wide range of products for vascular and interventional access, surgical, anesthesia, cardiac care, urology, emergency medicine and respiratory care. It expects NeoTract to be a high-margin, high-growth addition to its urology business, which already includes the *Rüsch* line of intermittent and indwelling catheters, collection devices, and other operative urology and endourology products. Teleflex's 2016 net revenues were $1.868bn, representing a 3.2% year-over-year increase

"With a revenue growth profile that exceeds that of Vidacare, this acquisition accelerates Teleflex's near-term sales growth trajectory and provides us with a significant sales channel opportunity. This acquisition enhances Teleflex's long-term organic growth profile and solidifies our ability to substantially generate mid-single digit organic and constant currency revenue growth," Smith said. "This acquisition will enable us to improve our margin profile due to NeoTract's gross margins, which exceeds 70% today, as well as allow us to capitalize on a significant international infrastructure to drive further penetration of NeoTract's UroLift system outside of the United States."

NeoTract was founded in 2004 to develop and commercialize UroLift, a system of devices, including a delivery handle and implant cartridges, for transurethral delivery of a permanent implant to hold open the urethra in patients with urinary outflow obstructions secondary to benign prostatic hyperplasia. It first earned a CE mark in 2010 and a 510(k) from US FDA in 2013, but the company didn't begin commercializing the device until 2014.

Pleasanton, Calif.-based NeoTract reported revenues of approximately $51m in 2016, up 178% year-over-year. The company expects revenues in 2017 to be between $115m and $120m, and increase 40% in 2018.

NeoTract has 62 patents and 30 patents pending. Also, UroLift has been the subject of two randomized clinical trials, seven open-label studies and three meta-analyses. For example, results of the 206-patient LIFT trial, which randomized patients with symptomatic BPH to UroLift or a sham cystoscopy procedure, showed UroLift implants created rapid and dura-

ble improvements in symptoms and urinary flow without compromising sexual function, according to NeoTract.

"This helps to create a very wide competitive moat with significant barriers to entry," Smith said. "Two of the key tenets of Teleflex's M&A criteria is to acquire products that provide superior clinical benefit through existing alternatives and to find products that have long product lifecycles that benefit from patent protection."

During the conference call, Teleflex COO Liam Kelly explained that NeoTract has about 70 sales reps in the US, but very little market presence overseas except the UK and Japan. Teleflex expects to rapidly expand UroLift's international market reach, especially in countries like Japan where reimbursement is already in place for the UroLift procedure. "We have a solid urology business in Europe, and we have a global footprint obviously in Asia, and we think we'll be able to leverage that over time to take advantage of the countries where they have already got reimbursement registration," he said.

Kelly, who is set to succeed Smith as Teleflex CEO when the latter retires at the end of this year, said 40% of men in their 50s and about 90% of men in their 80s suffer with BPH. With the aging of the population in the US, Europe and Japan, the addressable market this patient population will grow. About 8.5 million men have tried a medication to treat BPH and within this group, approximately 1.5 million patients have BPH symptoms, tried a pharmaceutical solution, but dropped out of that therapy because it was not working well enough. This patient population is a $6bn market opportunity for UroLift, Kelly said.

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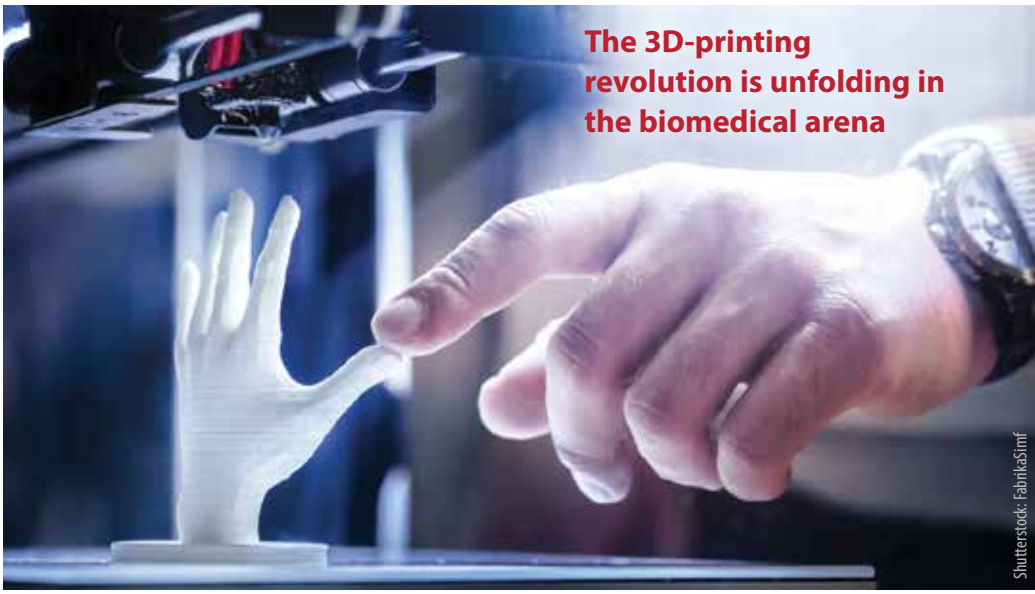
How 3D Printing Can Enhance And Expand Medtech Opportunities

CLEMENS MOELLER moeller.clemens@bcg.com
CHRISTOPHE DURAND durand.christophe@bcg.com
SCOTT RADER scott.rader@stratasys.com

The buzz around 3D printing is growing increasingly louder and the market opportunity this technology can bring to medtech manufacturers is certainly real. The global market for joint reconstruction and replacement is expected to increase to $16bn by 2018. The global market for prescription lenses is valued at approximately $13bn today. Spinal implants are a $9bn market. All of these clinical areas have the potential to be enhanced by 3D-printing technologies.

3D printing has already demonstrated its value across a wide range of industries beyond health care. Companies are using 3D printing to develop products with complex designs that are difficult or impossible to create using traditional manufacturing approaches. These companies better manage the cost of goods sold by eliminating post-processing and assembly steps. And they cost-effectively create "units of one" on demand, since 3D-printing costs remains relatively stable regardless of how many units are printed (unlike casting or injection molding). The ease of one-off printing has historically allowed many companies to use 3D printing for prototyping. In the biomedical field, these benefits (see Figure 1) translate into the following specific value drivers:

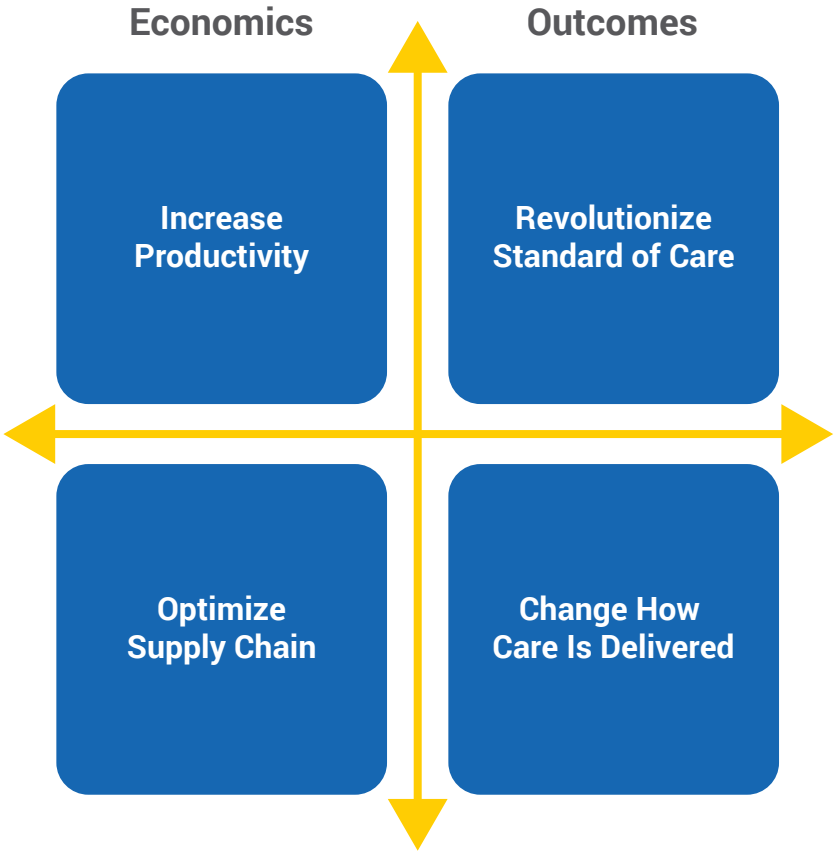


Increase productivity. With 3D printers, companies can perform rapid prototyping to create new designs more quickly and enable faster decision-making; the technology makes it much easier to engage "end users" earlier in the product development process. 3D printing also enables novel tools that can make testing more effective and lower costs. Bioprinted cell culture and tissue assays for research and drug testing offer an exciting example of the ways prototyping with 3D printers can help biomedical companies get products to market more quickly.

FIGURE 1

Value Drivers Of 3D Printing

Biomedical 3D printing has the power to reduce the cost and increase medical benefit.



Source: Boston Consulting Group

Optimize supply chain. Because products are custom-made with 3D printing, the process reduces waste and scrap material (as opposed to subtractive approaches, like milling). 3D printing can also lower labor costs by reducing the amount of assembly retooling or pre- and post-processing required. The availability of "onsite printing" may also help reduce inventory and simplify logistics. If medical equipment and devices are printed directly in a hospital, for example, it reduces the need for routing from a central facility (which involves field reps, in many instances) and storing inventory onsite. However, foolproof onsite printing solutions will be required to overcome regulatory concerns about patient safety.

Revolutionize standard of care. By making products that cannot be manufactured in any other way, 3D printing has the potential to revolutionize the standard of care by addressing previously unmet needs. Take hearing-aid shells, for example. Introduced in 2004, customized hearing aid shells were one of the first commercially relevant 3D-printed end-use parts, and they are now incorporated in most hearing aids sold each year. Because they can be customized, and therefore provide a much better fit, they offer a compelling value proposition for patients.

Change how care is delivered. With 3D printing we will see more products being made directly at the point-of-care, possibly accelerating treatment and reducing the number of visits for patients. 3D printing can also offer less costly alternatives to standard treatments, making advanced medical treatment more widely accessible. 3D-printed prescription glasses for example, could eventually be printed on-demand in a store, at low cost, and in any style imaginable, whether as a fashion statement for customers who want one-of-a-kind designs or as a low-cost option in emerging markets.

STEADY FLOW, NOT FLOOD, OF PRODUCTS

While we are seeing a steady flow of new 3D-printed biomedical products entering the market, the absolute number is still relatively low: more likely in the dozens, rather than in the hundreds or thousands. Many have only recently gained regulatory approval and their uptake in the medical community has not yet been established.

For a 3D-printing application to be successful in the medical domain, it needs to provide value in multiple areas. For example, dental clear aligners are a prime example of what we would call a 3D-enabled "killer app." It's a patient-customized product ("unit of one"); it needs to be regularly replaced over an extended period of time (multiple units per patient drive up overall volumes); it is a substitute for a costly and painful incumbent solution (metal braces that require an orthodontist's skills to be inserted and maintained) with a more pleasant treatment for the patient, both clinically and aesthetically; and it can be cost-effectively achieved with 3D printing, and only with 3D printing.

There is a simple reason why we have not seen equally compelling examples to date; it is quite difficult to come up with a 3D-printed product or solution that effectively addresses a significant unmet clinical need, and does so in a cost-effective fashion. However, with 3D technology rapidly advancing, the playing field is getting steadily bigger, and more products approach the sweet spot of 3D printing.

Each new 3D-printed application enters the market with a very specific value proposition; therefore, we expect 3D printing to transform health care one application at a time (rather than transforming an entire manufacturing ecosystem broadly and fundamentally, like the steam engine or conveyor belt).

While hundreds of applications are in the early development and pilot stage, they are not yet commercially available. This is an important distinction that is too often blurred. It's important to take

stock of what's "real" in the biomedical industry. In this article, a "real" biomedical application is defined as one that has been approved or cleared by US FDA (or equivalent bodies in Europe and around the globe) and is commercially available.

Figure 2 highlights the commercially viable applications for 3D printing that exist in health care today, and assess their current level of maturity and adoption, the market opportunity, and barriers to entry.

TOP 4 HIGH-POTENTIAL APPLICATIONS

Of all biomedical applications in use today, we expect 3D printing to make the biggest impact in following four areas over the next five to ten years: orthopedic products, dental products, cranial and facial implants, and patient-specific surgical guides and medical models (the models, custom-made from medical images, serve as highly accurate reproductions of a patient's anatomy).

Orthopedic products. In orthopedics, 3D printing is currently used primarily for hip implants, spinal implants, customized knee replacement, orthotics and prosthetics.

Hip implants: Hip implants are among the more established 3D-printed biomedical products available today. They have been commercially available from several manufacturers, including Lima Corporate, Adler Ortho and Exactech, for almost a decade. 3D-printed hip implants have an important advantage over conventional cups. While conventional cups require the costly step of applying a porous coating to promote bone in-growth, a cup manufactured through 3D printing can include porous surface structures without requiring a special coating, which significantly decreases unit production costs.

Spine implants: Like hip implants, 3D-printed spine implants offer a unique value proposition because they include a porous structure that stimulates bone growth (without requiring a special coating). They also offer improved radiographic visibility, implant stability, and surgical outcomes, though it has not yet been established how they perform over the long term. Several new products have gained regulatory approval, including implants from 4WEB, joimax, K2M, Medicrea, Renovis and Stryker. A 3D-printed titanium device targeted at the cervical spine recently gained publicity after being used for lifesaving surgeries through FDA's emergency use authorization program.

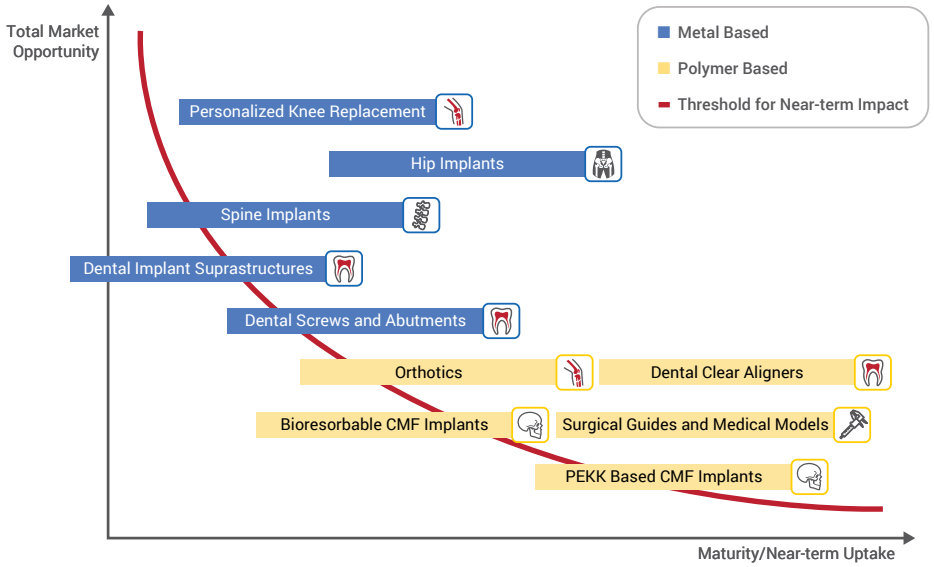
Personalized knee replacement: Close to 700,000 knee replacements are now performed in the US each year – and this number is projected to grow to 3.5 million by 2030. Approximately 90% of the knee-replacement market is controlled by established medtech players. While these companies' products are not fully customized, the implants are offered in different sizes. A fully patient-customized, 3D-printed knee has been available for several years from ConforMIS, but it has gained limited traction thus far. Many manufacturers and clinicians report that existing knee implants are "good enough" for the majority of patients, and the long-term cost-benefit equation of a fully customized system has yet to be established. We expect the debate about the clinical advantages of custom versus non-custom knee replacements to continue.

Orthotics: Over-the-counter foot insoles are already highly commoditized, but 3D-printed prescription orthotics may have some growth potential. Start-up companies already offer 3D-polymer insoles online. The foot can be assessed via smartphone photo, and 3D-printed custom orthotics are produced and delivered quickly. As of now, 3D-printed orthotics only serve simple indications, such as plantar fasciitis and bunions. However, the strong growth areas in the orthotics market come from other medical indications, such as diabetes, rheumatoid arthritis, and ankle foot orthotics for indications such as drop foot. Because these more complex indications typically require a prescription, they are currently still handled by more established players rather than 3D-printing providers.

Prosthetics: A small number of 3D-printing players are active in the prosthetics market. It is hard to estimate the specific market for prosthetics since the actual prosthetic (the hardware) is typically bundled in combination with patient treatment (such as fitting, rehabilitation and physical therapy), and therefore its market value cannot be easily calculated as a standalone product. The demand for prosthetics will likely drop in the coming years as medical advancements in vascular disease (which cause more than 50% of amputations) continue to emerge. Further, people who need a prosthetic are typically primarily interested in features

FIGURE 2

Existing Biomedical Applications Of 3D-Printing, And Those With The Highest Near-Term Potential



Source: Boston Consulting Group

such as myoelectric control and limb sensation (that is, the hardware and electronics in prosthetics), and less concerned with whether the prosthetic is 3D-printed or not.

Dental products. The dental segment represents the greatest breakout success for biomedical 3D printing to date. Millions of clear aligners from companies like Invisalign and ClearCorrect are created with the help of 3D printers each year and they are expected to continue to be a major area of growth. In addition to clear aligners, 3D printing is also used for dental implant suprastructures, screws, and abutments. Dental labs are also using 3D printing to make stone models for dental caps, crowns, and bridges; this will remain an important application for 3D printing, but further growth from stone models will be limited in the near term. Some first movers have begun to experiment – not just with models – but with 3D printing dental caps, crowns and bridges directly, and this has potential to go mainstream. For example, it is already possible to 3D-print the metal copings for dental caps and bridges, or entire crowns and bridges for temporary use. However, matching the durability and aesthetics of existing products across the spectrum of dental restoration will remain a challenge for 3D-printed products for some time to come.

Cranial and facial implants. Two platforms are commercially relevant for cranio-maxillofacial (CMF) implants: polyetherketoneketone (PEKK)-based implants used for skull or facial reconstruction, and bioresorbable implants used as bone fillers for skeletal reconstruction and bone regeneration.

PEKK-based CMF implants: The US-based company, Oxford Performance Materials (OPM), developed a proprietary process to create customized 3D-printed implants for cranial, facial and spinal reconstruction. The 3D-printing process offers biocompatibility, radiolucency and bonelike mechanics and behavior. Studies have also shown superior bone in-growth due to the product's microtextured surface.

Bioresorbable CMF implants: Two products are currently available on the market: 3D-printed bioresorbable implants used to cover burr holes and repair fractures and 3D-printed bone filler used to repair neurosurgical burr holes. These 3D-printed implants are designed to be porous in order to facilitate bone healing, and they don't require metal plating as reinforcement, which means they can be used as an alternative to bone harvested from the patient for complex skeletal reconstruction. The implants can also be customized to fit a patient's anatomy. We do see long-term potential for 3D-printed bioscaffolds beyond CMF applications and we address advances in this area in the "implantable organs" section (below).

Surgical guides and medical models. 3D printing enables physicians to visualize a patient's unique anatomical details and create personalized, patient-specific guides for complex surgical procedures. These surgical guides can help surgeons better identify entry points, screw trajectories and implant specifications in order to improve accuracy, efficiency and outcomes. The primary application for surgical guides is in orthopedics. In addition, 3D-printed medical models can be used in place of animal models, cadavers and mannequins to test new biomedical products and train physicians. It can also be used in surgical preplanning, which represents an exciting opportunity that could enhance many surgical interventions. The primary use cases for medical models today are:

Product validation and verification: 3D-printed products can be used to simulate a clinical environment, allowing medical companies to test products on realistic patient anatomy before clinical trials and better understand how the product performs. This helps companies validate concepts quickly and get products to market faster.

Physician training and education: Physician training is severely limited by the drawbacks of working with animal models, cadavers and mannequins. These models can be expensive, difficult to obtain, and not sufficiently representative of human anatomy. The 3D-printed models, on the other hand, are based on real human anatomy, readily available, modifiable to simulate a range of anatomies and pathologies, and usable in any environment.

Surgical preplanning: Medical models created through 3D printing allow physicians to optimize the therapeutic approach before ever stepping foot in the operating room. 3D-printed surgical models simulate live tissues, provide an unobstructed view of a patient's unique anatomy, and offer physical, spatial and tactile orientations that can't be matched by computer models. (See box.)

LOOKING AHEAD

As 3D-printing technologies become more sophisticated, new materials become available, and prices fall, we will see even more novel applications emerge – and some of them could be groundbreaking. Bioprinted assays for research and drug testing, complex implantable organs, and 3D-printed drugs and drug delivery devices offer just three examples of the ways 3D printing have the potential to dramatically change the future of medicine in the long-term:

Bioprinted assays for research and drug testing: In 2014, the US-based company Organovo commercialized the ExVive 3D Bioprinted Human Liver Tissues – the first such assay on the market. Companies worldwide are building proprietary bioprinting platforms to create 3D cell cultures and tissues that mimic elements of human organs. In the long term these will serve as valuable tools to complement *in vitro* testing, animal testing and clinical studies. However, there likely won't be a broad impact right away, since it is very difficult to meet the high standards for validation and reproducibility when dealing with living materials. Also, biologic structures can take days or weeks to generate, and require specific skill and infrastructure to keep them alive and functional. In the absence of suitable standardization and automation technology, bioprinted products will not be easily mass-produced in the near-term.

Complex implantable organs: Several research centers have successfully created bioprinted organ tissues, including skin, bladders, tendons, and heart valves. Since 2012, 3D-printed tracheal splints have been successfully implanted and research is being conducted to use these tracheal

splints as scaffolds combined with human stem cells. In addition, the solid-organ transplant market is tremendous. In the US alone, approximately 100,000 patients await kidney transplants, while only approximately 17,000 transplants are performed each year. Organovo claims they are three to five years away from clinical trials for 3D-bioprinted human liver tissue for direct transplantation to patients. That said, there are major technological barriers in the development of entire transplantable organs and it may take decades before these become available.

3D-printed drugs and drug delivery devices: FDA has already approved a 3D-printed prescription pill for consumer use: Spritam, a medication used to treat certain types of seizures caused by epilepsy. The pill disintegrates easily when added to liquid and is therefore easier to swallow – an important benefit for patients who have difficulty swallowing hard pills (such as infants or stroke victims). The long-term potential for 3D-printed drugs is extremely promising as it opens the door for personalized medicine. Instead of a one-size-fits-all pill, companies can readily manufacture patient-specific doses or a single bespoke pill to replace difficult combination therapies. It's even conceivable that consumers could one day print their own medicines at home. Regulatory approval will undoubtedly present a hurdle that will slow the commercialization process for 3D-printed drugs.

The Transformative Potential of 3D-Printed Medical Models for Surgical Procedures

Cost remains a major concern in health care today, and patients, hospitals and payers have almost zero tolerance for high-cost solutions. The reimbursement landscape is continuing to shift toward a value-based environment where positive outcomes are rewarded, and sub-optimal outcomes and inefficiencies are penalized. To make a strong impact in the marketplace, innovations need to deliver improved outcomes at the same (or less) cost than existing products and solutions.

For 3D-printed biomedical products to gain acceptance, they need to deliver superior results in one or more of these areas: provide medical benefits to patients that lead to better health outcomes, reduce procedure cost (while maintaining or improving outcomes), and provide benefits to clinicians by reducing treatment time (which frees up time to treat more patients) and minimizing risk of errors or complications. Another often undervalued benefit is communication with patients; the model can be used to obtain informed consent, for example.

Anatomical medical models created through 3D printing have tremendous potential to assist clinicians in planning successful surgeries. They can help surgeons make the right decisions up front by determining the viability of a procedure and selecting the appropriate surgical approach. They also allow surgeons to better prepare for and even practice the surgery before actually working on the patient. This is particularly valuable when multi-disciplinary coordination is required for complex procedures. In this way, medical models can help speed up procedures, increase the level of precision, and minimize the risk for unforeseen complications.

From a patient perspective, this can translate into an accelerated recovery and better outcomes. Providers benefit from cost savings through reduced operating room time and hospital bed utilization, which has a direct impact on profit margins where reimbursement rates are fixed for a given procedure. A recent study shows that patients who experience surgical complications have 119% higher hospital costs than patients without complications, and payers' reimbursement costs are 106% higher.

As a patient-customized, on-demand solution, 3D-printed medical models can lead to mutual benefits for patients, providers and payers. What's more, they represent an opportunity for medtech companies to move away from standalone products and shift toward a business model based around end-to-end solutions that deliver greater value and improved outcomes.

3D-printed medical models require cost and effort to make, and it takes time for clinicians to learn how to use them; therefore, they will be most impactful when used for procedures that are particularly costly or come with higher risk. Surgical domains where 3D printing could make a real difference include cardiac surgery, orthopedic surgery, surgical oncology and neurosurgery, to name just a few.

To achieve their potential, medical models need to transition easily from scan to product, ideally with the push of a button. New automated solutions are just now coming on the market, which will enable 3D-printed medical models to be readily developed for use in the clinical setting. Anecdotal evidence of improved outcomes through 3D-printed modules will need to be supplemented by large-scale, controlled trials to pave the way for broader acceptance and uptake.

There are a number of other applications of 3D printing that may be relevant in niche markets, as well as many additional examples that we have not yet even imagined.

The 3D printing revolution in health care is happening – one application at a time. While dental clear aligners may have been the first killer app in health care, they won't be the last. Health care companies need to keep their eyes open and be prepared to act swiftly when opportunity knocks.

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About The Authors

Clemens Moeller is a partner and managing director in The Boston Consulting Group's Boston office. He is a core member of the firm's health-care practice and leads the biomedical 3D-printing topic area.
Christophe Durand is a senior partner and managing director in BCG's New York office. He is a core member of the health-care practice, serving medical device/technology and biopharma companies and leads the firm's medtech innovation topic area.
Scott Rader founded and leads the Medical Solutions team at Stratasys, bringing 20-plus years of industry experience that ranges from medical center professor to leading successful venture-funded companies.

CONTINUED FROM PAGE 1

The Redwood City, California firm raised the funds from its existing investors – Data Collective, Lightspeed Venture Partners (these two co-led the round), Innovation Endeavors and Spectrum 28 – and also welcomed new investors, Chinese tech group Tencent and Khosla Ventures, the VC started up by co-founder of Sun Microsystems, Vinod Khosla.

Karius said it will use the proceeds for ongoing and new clinical trials to validate the technology, scale up laboratory capacity, and advance commercialization.

The $50m round may be the largest series A this year to date, but it still lags some distance behind the $100m series A that went into **Grail**, also in liquid biopsy. Grail was spun out of Illumina and is working to develop a single blood test that can screen for different types of cancer.

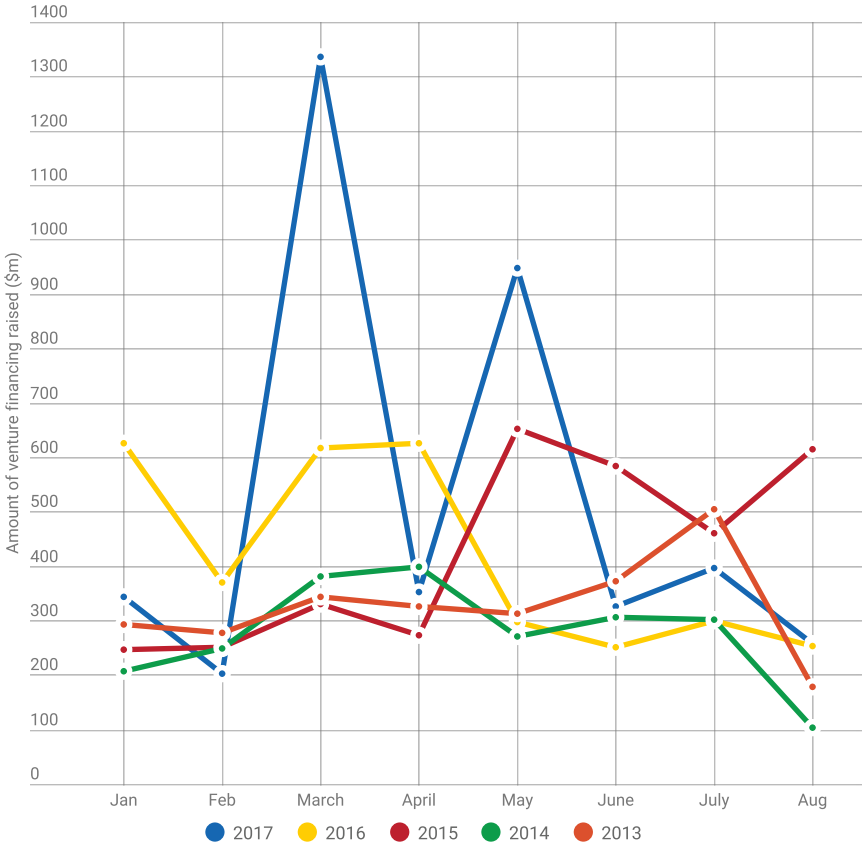
Liquid biopsy might be a hot investment area but aside from Karius, the other deals that made it to August's top 5 were not IVD-related. (See Table 1.)

NEUROMODULATION KEEPS DIVERSIFYING

Two of the three neuromodulation deals in August were among the top 5 biggest rounds: **SetPoint Medical**, which raised $30m in series D financing, and **Neuros Medical**, which raised $20m in series AA funds. These two companies might be in the area of neuromodulation but their technologies and target indications could not be more different. While SetPoint is developing a vagus nerve stimulation system for treating inflammation diseases like rheumatoid arthritis, Neuros' Electrical Nerve Block uses a cuff electrode coiled around a peripheral nerve to block post-amputation pain.

FIGURE 2

Total VC Deal Value, Jan-Aug 2013-2017



Source: Medtech Insight VC Deal Tracker

The third neuromodulation company that also caught investors' interest in August – although not enough to make it to the top 5 – was **NeoSync**, which raised $13m in series C funds to support trials of its transcranial magnetic stimulation therapy for treatment-resistant depression.

TABLE 1

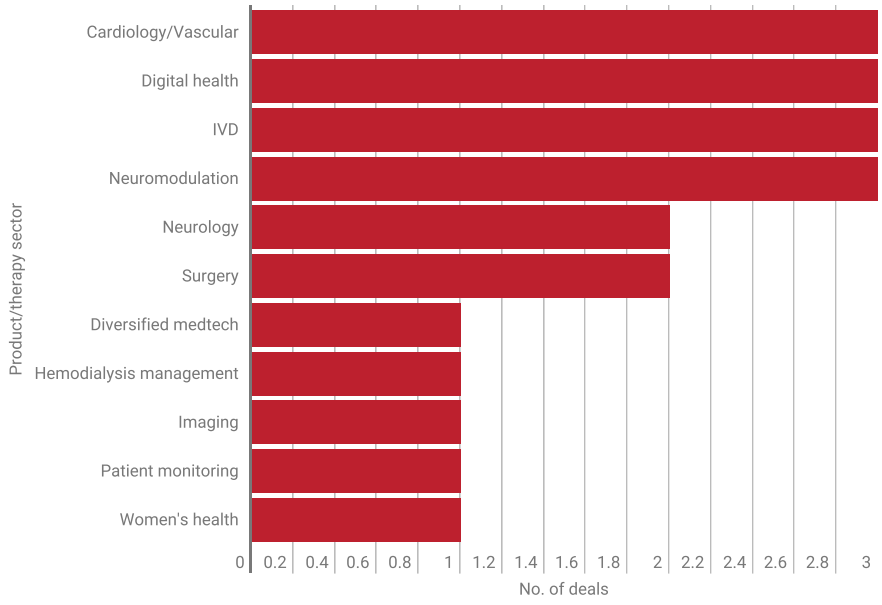
August's Top 5 VC Financing Deals

RANKING	COMPANY	BASED IN	PRODUCT/ THERAPY SECTOR	AMOUNT RAISED	FINANCING ROUND	TOTAL INVESTMENT
1	Karius	CA, US	IVD	$50m	Series A	Undisclosed
2	AbleTo	NY, US	Digital health	$36.6m	Series D	$57.4m
3	SetPoint Medical	CA, US	Neuromodulation	$30m	Series D	$90m
4	Neuros Medical	OH, US	Neuromodulation	$20m	Series AA	Undisclosed
5	Shape Memory Medical	CA, US	Neurology/Vascular	$18m	Part of an expected $25m Series B	Undisclosed

Source: Medtech Insight VC Deal Tracker

FIGURE 3

No. Of VC Deals By Product/Therapy Sector, Aug 2017



Source: Medtech Insight VC Deal Tracker

The diversity of these three companies underline how neuromodulation is moving into increasingly diverse applications and, more importantly, investors' growing belief that "bioelectronic medicine" offer a new form of therapy for conditions traditionally treated with drugs. For other evidence of how attractive this space is becoming, one only has to look at the uptick in interest from non-medtech players like **GSK**, which set up a bioelectronic medicines-focused fund (Action Potential Venture Capital) and **Verily**. Both have spent the last couple of years laying down the groundwork through investments and partnerships to ensure they have a secure footing in this market. *(Also see "GSK Venture Fund Selects Neurostim Device Maker SetPoint Medical As First Investment" - Medtech Insight, 27 Sep, 2013.)(Also see "New GSK-Verily JV Aims For Smart, 'Grain Of Rice' Neuromod Tech" - Medtech Insight, 2 Aug, 2016.)*

Overall, August saw the financing deals spread relatively evenly across different product/therapy sectors. There was not one sector that had the most number of deals: instead, four sectors – cardiovascular, digital health, IVD and neuromodulation – each got no more than three deals and the remainder were spread across seven other sectors. (See Figure 3.)

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For more details about VC deals in 2017 and previous years, go to Medtech Insight's VC deal tracker: https://medtech.pharmamedtechbi.com/datasets/vc-funding

UK Industry Targets Best Outcome From Life Science Strategy

ASHLEY YEO ashley.yeo@informa.com

It was a short summer for the UK health-care products industries, whose leaders were hauled back to work early with the August release of the UK government's life sciences strategy. *(Also see "Moonshot Projects In Life Sciences Strategy Can Lift UK Over Brexit Hurdle" - Medtech Insight, 30 Aug, 2017.)* This document contains multiple recommendations on how the UK should adjust, post-Brexit, to maximize its industrial, research and innovation and academic strengths.

Brexit, of course will dominate daily news coverage in the UK well into the future – and long after the UK's scheduled March 2019 departure from the EU. More's the pity, say many. But the pragmatists of the health-care industry now insist on forward motion as a priority – never mind the consistent misjudgments and ongoing mishandling of the withdrawal negotiations by the UK's Brexit secretary.

The Association of British Healthcare Industries (ABHI), for all its desire to remain inside the EU, is determined to secure a "good" Brexit for the UK medtech industry. The association's reactions to the Life Science Strategy will doubtless be debated fully at its annual UK market conference on September 14. Brexit will also never be far from the surface at the NHS Health & Care Innovation Expo (September 11-12), where the UK health minister and NHS chief executive among others will give their views on how best to shape public sector health-care delivery while keeping health and wealth uppermost in mind.

ABHI REACTION TO LIFE SCIENCE STRATEGY

The ABHI said it was pleased that a significant number of medtech recommendations in the Life Science Strategy report had been incorporated as a direct consequence of the medtech industry's input into the process. Neil Mesher, CEO of Philips UK and Ireland and a member of the Life Science Industrial Strategy board, considered the document to represent a "collaborative framework that will allow the development and adoption of effective new technologies for NHS patients."

Furthermore, the industry sees opportunities for medtech in the strategy's stated focus on digitalization and AI as tools to transform pathology and imaging. It has welcomed the opportunities that the strategy offers in terms of funding high-risk projects. The proposed Accelerated Access Pathway will be important for strategically-important, transformative products, the ABHI stresses. The pathway is a recommendation of the Accelerated Access Review (AAR).

There is much to commend in the report, seen through the ABHI's eyes, including its repeated stress on the value of the NHS and the need for it to be an active partner in the strategy as it unfolds. Another element to draw industry praise is the strategy's understanding that the existing medtech clusters should work together, and with government, to promote a "single front door" to the UK for research collaboration, partnership and investment.

But the strategy's recommendations on how to provide more favorable conditions for medtech SMEs, while welcomed, do not go far enough, in the ABHI's view. NHS procurement and the current systems for setting reimbursement tariffs, among other things, "can make it very difficult for SMEs to find a route to market," the report acknowledges. Nevertheless, the ABHI wants stronger language and intent than the strategy's recommendation that these elements should merely be "reconsidered," if the NHS is to be a "good customer" for SMEs.

However, the recognition of the *impact* that SMEs have is welcomed by industry, although it stresses that NICE's proposed funding models for technology evaluation should be set up in a way that does not stifle SMEs' engagement in the evaluation process. And on the question of NICE fees, the ABHI wants to ensure they do not have negative, unintended consequences.

Accelerated Access Review – Benefits For Medtech

With the broad approval of the UK medtech industry, the AAR makes a big case for speedier adoption of innovative medtech in the UK, proposing;

- A transformative designation for innovations that have the potential for greatest impact.
- A single set of clear, national and local routes to get medical technologies, diagnostics, pharmaceuticals and digital products to patients.
- Evolution of the process for assessing emerging technologies, so that it is fit for the future.
- A range of incentives to support the local uptake and spread of innovation.
- An enhanced horizon-scanning process to enable joint planning between industry, the NHS and the government.

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[**Editors' note:** *The ABHI's annual UK Market Conference will be held on September 14 at Simmons and Simmons (London), and will be addressed by parliamentary under-secretary of state for health Lord O'Shaughnessy, the chief executive of NHS Providers Chris Hopson, and ABHI chief executive peter Ellingworth, among others.*]

Multiple Hacking Risks Found In Another Infusion Pump

FERDOUS AL-FARUQUE danny.al-faruque@informa.com

Cybersecurity vulnerabilities discovered in several versions of **Smiths Medical**'s *Medfusion 4000* wireless syringe infusion pumps could allow malicious hackers to change their functionality and disable communications capability, the US Department of Homeland Security (DHS) said in an advisory issued late last week.

According to Smiths, the vulnerabilities were first discovered and reported to them by Scott Gayou, a security engineer at Garmin International in Kansas City, Mo. In response, the company contacted US FDA and DHS' Industrial Control Systems Cyber Emergency Response Team, or ICS-CERT, to investigate the extent of the vulnerabilities and potential remediation.

Gayou specifically discovered eight vulnerabilities that could allow someone to remotely cause the communication system on the pumps to crash, or to launch a "man-in-the-middle" (MITM) attack, and could allow access to some user passwords stored in the devices, according to ICS-CERT's investigation.

"Successful exploitation of these vulnerabilities may allow a remote attacker to gain unauthorized access and impact the intended operation of the pump," warns ICS-CERT. "Despite the segmented design, it may be possible for an attacker to compromise the communications module and the therapeutic module of the pump."

The agency says the impact on individual organizations will depend on factors unique to the entity and it recommends that all organizations using the devices evaluate the level of risk they face based on their clinical environment and product usage.

For its part, Smiths says it is working to issue a software update by January, but, for now, the company recommends users take specific precautionary measures that the company and ICS-CERT developed together.

"The possibility of this exploit taking place in a clinical setting is highly unlikely, as it requires a complex and an unlikely series of conditions," said Smiths in a statement. "In partnership with ICS-CERT, we have released the technical details of this exploit and actions that you should take to protect against it."

Among the mitigation actions recommended are:

- Assigning static IP addresses to the pumps;
- Monitoring network activity for rogue DNS and DHCP servers;
- Ensuring network segments connected to the pumps are segmented from other hospital and clinical information technology infrastructure;
- Considering use of network virtual local area networks (VLANs) for the segmentation of the pumps; and
- Using proper password hygiene standards.

FDA APPLAUDS RESEARCHER-COMPANY COORDINATION

This is just the latest in a growing number of cybersecurity vulnerabilities publicly identified for specific medical devices, in addition to several cases of malware attacks on hospitals potentially putting patient privacy and health at risk. So far, US FDA notes it has not recorded any incidents where a patient was harmed or killed by an exploit.

Smiths says it is working to issue a software update by January, but, for now, the company recommends users take specific precautionary measures that the company and ICS-CERT developed together.

This is not the first time an infusion pump has been singled out for risk. FDA, for instance, issued an alert in 2015 warning of cybersecurity vulnerabilities with **Hospira Inc.**'s *Symbiq* infusion pumps. *(Also see "FDA Warns Of Hacking Threat From Hospira's Symbiq" - Medtech Insight, 3 Aug, 2015.)*

Cybersecurity vulnerabilities have also been a frequent topic of discussion within industry. FDA has held workshops to hash out best practices with device-makers and other stakeholders, and the agency has also issued several guidances spelling out how companies should develop and maintain cybersecurity integrity for wireless products. *(Also see "'Sharing' Organizations Stay In Final Post-Market Cybersecurity Guidance" - Medtech Insight, 29 Dec, 2016.)*

Another high-profile medical device cybersecurity case is the vulnerabilities that have been discovered in **St. Jude Medical Inc.** implantable cardiac devices. So far, FDA has issued two alerts warning patients about the devices and asked them to download software updates. *(Also see "Despite US FDA Alert, Abbott-Muddy Waters Lawsuit Continues" - Medtech Insight, 8 Sep, 2017.)*

But that case has one important difference from the recent Smiths alert. For the St. Jude devices, investment firm Muddy Waters Research, working with security firm MedSec, brought discoveries about the device vulnerabilities directly to FDA and the public without cooperation from St. Jude.

FDA says it prefers that security researchers collaborate with manufacturers to fix problems, rather than Muddy Waters' approach. *(Also see "St. Jude Hacking-Risk Allegations: US FDA Continues Assessment, As Firm Files Lawsuit" - Medtech Insight, 8 Sep, 2016.)* The agency was more positive in its response to how Smiths' infusion pumps have been handled. According to FDA spokeswoman Angela Stark, the agency first became aware of the vulnerability when Smiths and Gayou approached them using a coordinated disclosure process.

"This is the proactive behavior the FDA has been looking to see from the medical device manufacturer and research community and demonstrates the collaborative manner in which vulner-

abilities can be addressed in a way that best protects patients," she said. "The FDA applauds these efforts and will continue to encourage this type of coordinated disclosure moving forward."

The procedure followed by Smiths and Gayou is similar to **Johnson & Johnson**'s recent work with a hacker who discovered a security loophole on the firm's **Animas Corp.** *OneTouch Ping* insulin pump to mitigate the problem. *(Also see "J&J, Hacker Work Together To Fix Insulin Pump Vulnerability" - Medtech Insight, 12 Oct, 2016.)*

Stark says the coordinated disclosure process applied by Smiths follows the basic principles set out by the agency in its final guidance on "Postmarket Management of Cybersecurity in Medical Devices." In the guidance, FDA states that device manufacturers and cybersecurity researchers should work together openly to identify, assess and remediate potential cybersecurity vulnerabilities. Then the manufacturer should asses the vulnerabilities to determine the actual level of risk to patients. Finally, the device-maker should be transparent and timely in communicating the risks and remediation to patients and health-care providers.

Gordon Morrison, director of government relations at the cybersecurity firm McAfee, says health organizations are facing "unprecedented pressure" due to cybersecurity challenges. He says there needs to be a new approach to how connected devices are developed and managed.

"It is essential to ensure these devices are not introduced at the expense of the safety of the patient and their data," he said. "Achieving this will be twofold: ensuring that the devices are built securely by design and with the necessary security controls in place; as well as a security policy for connected devices in hospitals, to ensure that they can't access sensitive data and are regularly patched against newly-discovered vulnerabilities."

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US FDA: Calling All Digital Health Gurus

FERDOUS AL-FARUQUE danny.al-faruque@informa.com

When US FDA's device center is faced with a particularly sensitive and difficult regulatory issue, it tends to ask outside experts to help figure out how to deal with it. In that spirit, the agency is asking experts with industry experience to spend six months working for it on a part-time basis to help develop a new pathway to speed digital-health products to market.

On Sept. 6, the agency announced an Entrepreneur-in-Residence program to help it develop the newly announced Digital Health Software Precertification Program. The Pre-Cert Program which is currently being evaluated in a pilot project would allow trusted device manufacturers to get their products through FDA's review process faster and, in some cases, allow them to skip the pre-market submission process altogether. *(Also see "Industry Praise US FDA Software Pilot Program" - Medtech Insight, 31 Jul, 2017.)*

FDA says those picked for the EIR program would work for a minimum of three days a week at FDA's headquarters in Silver Spring, Md., for a span of six months. They would be tasked with analyzing software industry business processes as well as key indicators to help the agency figure out how to predict product quality and organizational performance, among other tasks.

FDA says it is looking for " creative problem-solvers, innovators, and entrepreneurs " who have five years of experience in six categories including software design, business process modeling, business metrics development, clinical trial design, decision analysis, and investment and business valuation.

"We are launching this Entrepreneurs-in-Residence program to take advantage of input from thought leaders and others with real experience in software development to build and structure the digital health function within FDA," said FDA spokeswoman Stephanie Caccomo. "The entrepreneurs will be an integral part of our digital health precertification pilot program."

The program will be funded by revenue collected from the new user fees and headed by Bakul Patel, associate center director for digital health at FDA, who has been championing the Pre-Cert Program to industry. *(Also see "FDA Pitches Novel Pathway For Software" - Medtech Insight, 9 Mar, 2017.)*

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"EIR Fellows may be hired by FDA as contractors or term employees, dependent on qualifications and type of expertise," adds FDA. "If selected, candidates will be required to undergo a background check, and may be subject to ethics clearance and divestment requirements."

The agency will be accepting resumes for Digital Health EIR candidates until Sept. 29.

This isn't the first time FDA has relied on entrepreneurs in residence to develop creative regulatory programs. A previous group of EIRs spawn the idea for a program launched last year to let device companies invite private payers to FDA pre-submission meetings to help meet reimbursement requirements. *(Also see "Bringing Private Payers To The Regulatory Table: FDA Reaches Out To Insurers" - Medtech Insight, 23 Feb, 2016.)* Another EIR group originated the concept behind the current Expedited Access Pathway for devices.

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US Congress Extends Funds For FDA, NIH, To Dec. 8 In Bill Linked To Hurricane Relief

SUE DARCEY sue.darcey@informa.com

The two chambers of Congress swiftly passed a measure Thursday and Friday to provide disaster relief for Hurricanes Harvey and Irma victims, extend the debt limit and continue funding for federal agencies, including FDA, from Oct. 1 to Dec. 8, at slightly below current, FY 2017, levels.

President Trump will almost certainly sign the disaster relief/debt ceiling/continuing resolution package.

Congressional appropriators decided earlier this year to increase FY 2018 funding at FDA only slightly more than in FY 2017, which would give the agency's device center $329.7m in budget authority. *(Also see "House Budgeters Give FDA Device Center Slight Bump In 2018" - Medtech Insight, 30 Jun, 2017.)*

Adding in user fees of about $158m – as slated under the MDUFA IV agreement enacted Aug. 18 – would have given the Center for Devices a total budget of $487.8m for FY 2018, beginning Oct. 1. *(Also see "MDUFA IV (And More) Is Law: Trump Signs A Health-Care Bill" - Medtech Insight, 18 Aug, 2017.)*

Although funding through early December will not reach that level the pace of work at the agency is likely to stay on a steady course.

"With a CR in place, the FDA – along with other government agencies – should be able to operate smoothly for the 10 weeks starting Oct. 1," commented Steven Grossman, deputy executive director of the Alliance for a Stronger FDA.

Grossman and the Alliance warned, however, that instead of supplying dollars to domestic agencies at the current FY 2017 level, the CR shaves 0.68% from that amount, which will cost FDA and all its divisions – covering device, drug, food safety etc. – roughly $3m in budget authority funds.

TWO-FISTED HURRICANE PUNCH PUSHES CONGRESS TO ACT FAST

Approved by the Senate Sept. 7 and by the House Sept. 8, the twin CR bills were able to quickly move through the Congress after President Trump reached an agreement Sept. 6 with Senate Minority Leader Chuck Schumer, D-N.Y., and House Minority Leader Nancy Pelosi, D-Calif., in a White House meeting on how to handle the looming fiscal deadlines. These included both a potential shutdown of the government minus a budget agreement, and default on the national debt by Sept. 30, if no spending/debt-ceiling agreement was reach by then by legislators.

The deal surprised Republican leadership, but lawmakers nonetheless supported the measure. Republican congressional appropriators said they worried that disaster relief funds at FEMA, the Federal Emergency Management Agency, had been exhausted by Hurricane Harvey cleanup efforts in Houston, and would soon run out, while residents of Florida and the southeast coast faced a fresh storm assault from Hurricane Irma mid-day Friday.

"The serious nature of the natural disasters and fiscal commitments before us demand the Senate and House act without delay," said Senate Appropriations Committee Chairman Thad Cochran. He added, "Congress has a duty to ensure that government operations are maintained, and that our country's financial obligations are met."

"This is a responsible approach to ensure that we address the needs of our Nation at this pivotal time," agreed Senate Appropriations Committee ranking member Patrick Leahy, D-Vermont.

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Ex-FDA Device Compliance Chief Joins AdvaMed

SUE DARCEY sue.darcey@informa.com

Former FDA device center Office of Compliance Director Steve Silverman joined AdvaMed as VP of technology and regulatory affairs, effective Sept. 5.

Silverman moves to the role from his post as a senior expert for McKinsey & Co., where he advised clients in the medical device and pharmaceutical fields on regulatory strategies, compliance, and quality initiatives. At AdvaMed, Silverman will focus on the joint FDA/Medical Device Innovation Consortium Case for Quality initiative, inspections, combination products and the ophthalmic sector.

Silverman's career at FDA spanned 13 years.

He took over as compliance director within FDA's Center for Devices and Radiological Health in 2010. While there, he was a key player in launching the agency's Case for Quality initiative in 2011, an overarching program designed to encourage quality-improvement practices by companies and enhance collaboration between FDA and manufacturers on quality issues. *(Also see "Root Cause Analysis A Key Element Of FDA's 'Case For Quality'" - Medtech Insight, 12 Jul, 2012.)*

Now administered jointly by FDA and MDIC, Case for Quality has spawned multiple initiatives and pilot programs.

Silverman also oversaw a reorganization of the Office of Compliance in 2013 to more of a function-based structure. *(Also see "CDRH Office Of Compliance Shifts To "Function-Based Structure"" - Medtech Insight, 20 Sep, 2013.)*

Prior to moving to the FDA device center, Silverman served in FDA's drug center Office of Compliance and in the agency's Office of Chief Counsel.

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US FDA To Public: Help Us Streamline Our Regs

FERDOUS AL-FARUQUE danny.al-faruque@informa.com

More than seven months after President Trump issued an executive order requiring federal agencies to remove two regulations for every regulation they implement, known as the two-for-one rule, US FDA is asking stakeholders for input on which regulations to withdraw.

In separate notices addressing each product center of FDA, the agency issued identical request for broad stakeholder input on how to reduce regulatory burdens in accordance with the president's orders. *(Also see "Trump's Two-For-One Reg Order Needs Agency Interpretation, Medtech Reg Experts Say" - Medtech Insight, 30 Jan, 2017.)*

"As part of the implementation of Executive Order 13771 entitled, 'Reducing Regulation and Controlling Regulatory Costs,' and Executive Order 13777 entitled, 'Enforcing the Regulatory Reform Agenda,' the Food and Drug Administration … is seeking comments and information from interested parties to help FDA identify existing regulations and related paperwork requirements that could be modified, repealed or replaced, consistent with the law, to achieve meaningful burden reduction while allowing us to achieve our public-health mission and fulfill statutory obligations," said the agency.

Besides commenting on which regulations should be removed, the agency is also asking for supporting technical, scientific, economic or other data to support the reasoning for removing those regulations.

In making their determination, FDA says it will be asking whether a regulation considered for withdrawal is outdated or unnecessary, whether industry has had difficulty adhering to the regulation, whether third-party organizations already cover the regulation through voluntary or consensus standards, whether the regulation requires unnecessary recordkeeping, whether there are potentially cheaper alternatives to achieving its goal, and which factors the agency should consider in selecting and prioritizing regulations and reporting requirements for reform.

Anna Abram, the agency's recently appointed deputy commissioner for policy, planning, legislation and analysis, announced the new effort in an agency blog post.

Abrams was formerly health policy director and senior adviser on the Senate Committee on Health, Education, Labor and Pensions, and has also worked for Sen. Richard Burr, R-NC. She was also part of President Trump's transition team, responsible for staffing the Department of Health and Human Services, and helping develop broader policy approaches.

THE VOICE OF TRUMP

Abrams, known for her policy positions calling for regulatory flexibility, says the US is in a "moment of extraordinary opportunity," and is calling on removing burdens to advancing public health.

"As part of my commitment to help oversee the development and implementation of key policy issues, and to help advance these broader policy efforts, I've been working closely with FDA

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Commissioner Scott Gottlieb and other senior agency colleagues to explore ways to modernize our regulations in a manner that will benefit all Americans," she said. "To achieve this, we're not only looking at what new regulations or policies we need in order to be most effective in fulfilling our public health responsibilities. We're also taking a closer look to see if we need to revise, update and in some cases eliminate existing regulations to help us better keep pace with scientific advancement and the people that we serve. We need policies that are as modern as the products that we're being asked to evaluate, and a regulatory framework that uses efficient tools to achieve our vital consumer protection role."

Abrams noted that FDA has more than a hundred years of accumulated regulations.

"We have a lot of ground to cover. Today, FDA's regulations comprise more than 4,000 pages in the Code of Federal Regulations. Some regulations may not adequately reflect advances in science, technology or changes in industry practice," she said. "Others may be geared toward products and practices that have largely ceased to exist."

To address the changing world, Abrams says the agency needs to adopt a risk-based approach in everything it does.to ensure it is using its resources efficiently.

"Our goal is to have regulations that reflect modern risks and opportunities, and use the full scope of our authorities to achieve our consumer protection mission," she added.

Written comments are due Dec. 6 under docket No. FDA-2017-N-5105.

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