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Updating Your Device In The EU? It Isn't Always Clear When You Need To Tell The Notified Body

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Innovation in the medical devices sector is as much tied to incremental changes in product design as it is to groundbreaking new technologies.

But when does a change to an already marketed product, sometimes known as a line extension, need to go through the extra burden of being reviewed by a notified body before being placed on the market? And, on the other hand, when can manufacturers go ahead and market that product without prior notification to a notified body or prior review and just mention the change at the next audit?

It seems that the answers to these questions are highly subjective, with high costs at stake on the one hand, and the threat of being in violation of EU requirements on the other.

Indeed, because of the weight of uncertainty, some are starting to ask whether there might be a better way of setting conditions under which manufacturers have to inform their notified bodies. The new Medical Device Regulation, which entered into force last month and takes full effect in 2020, provided some additional clarity on the question, but still leaves the final decision in the hands of the manufacturer and notified body.

RISK-RELATED

For changes to high-risk class III or active implantable devices, the requirements of EU directives' requirements are clear: The manufacturer needs to inform the notified body and get approval from the notified body before placing the updates devices on the market, the UK's Medicines and Healthcare products Regulatory Agency (MHRA) confirmed to *Medtech Insight*.

But for other products, the requirements are not so clear; the Medical Devices Directive (MDD) states that the manufacturer must inform the notified body that approved the quality system/European Community (EC) type examination of any plan for "substantial changes."

If the notified body, following discussion with the manufacturer, considers these changes to be substantial (or "significant"), it must then assess the changes proposed and verify whether, after these changes, that the product and its quality system/EC type examination still meets the necessary requirements or whether a new certificate is required.

GUIDANCE ON "SUBSTANTIAL CHANGES"

But what are substantial changes? This is where there is potentially a high degree

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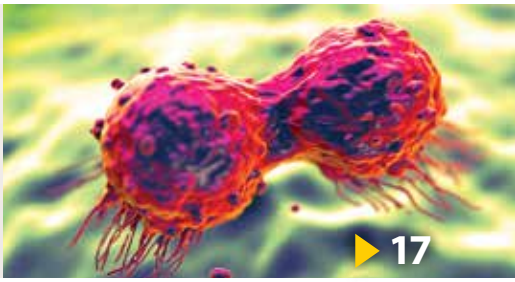
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21st Century Cures Act device provisions with actions to formalize an expansion of the Humanitarian Device Exemption program to include devices treating conditions that affect up to 8,000 patients, increase flexibility for the institutional review board process and specify validation requirements for certain reusable devices.

COMMERCIAL

R&D

START-UP SPOTLIGHT

GE Taps Healthcare Again For New Group Head

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John Flannery, current president and CEO of **GE Healthcare**, will succeed Jeff Immelt as chairman and CEO of GE. Flannery will assume the CEO role officially on Aug 1, and then take the additional position of chairman on Jan. 1, 2018.

Taking the helm of the health care business is Kieran Murphy, who has been overseeing the life sciences unit until now. In addition to these changes, Jeff Bornstein, current CFO, has been promoted to vice-chair of GE.

Kieran Murphy: new GE Healthcare CEO

Flannery has been with GE for 20 years, but, for most of that, he was not focused on health care. He joined GE in 1987, where he started at GE Capital and went on to lead GE Equity. During this period, working for GE's finance-related businesses, much of his focus was on growing operations in South America and Asia.

In 1997, he moved to Argentina where he successfully led GE's Equity business in Latin America and the overall GE Capital business for Argentina and Chile. In 2005, he moved to Asia where he was responsible for the Asia-Pacific region for GE Capital, and while there, he grew earnings in Japan by 100%, in Korea by 30% and in Australia by 25%. In 2009, he moved to India to lead the country for GE.

He became head of GE Healthcare in 2014 and is credited for turning around the business, succeeding in growing organic revenue by 5% and margins by 100 basis points in 2016.

Like Flannery, Immelt first joined GE in the late 1980s and established a diverse track record working across the group's different businesses, including Healthcare. He took on the role as GE CEO and chairman in September 2001, just before the 9/11 tragedy, and led the conglomerate through a time of political and financial turmoil. Nonetheless, he is leaving behind an impressive legacy, having succeeded in transforming its portfolio. During Immelt's tenure, GE nearly doubled its industrial profit and operating EPS was up by around 50%. Investors also benefitted from $143bn in dividends from GE with Immelt at the helm, more than in the entire prior history of the company.

Murphy, Flannery's successor as head of GE Healthcare, joined the division through the 2008 acquisition of the company he was leading at that time, Whatman PLC, the UK-headquartered supplier of filters and membranes for lab research, life sciences and medical diagnostic applications. *(Also see "GE completes Whatman acquisition:" - Medtech Insight, 1 May, 2008.)*. He then became head of GE Healthcare Life Sciences in April 201; this unit provides drug discover, preclinical and clinical development and biopharma manufacturing, as well as molecular tools for diagnostics, therapy selection and treatment monitoring in patient care.

GE said that the leadership appointments are the result of a succession plan that has been overseen by the company's board of directors since 2011.

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US Homeland Security-Funded Project Aims To Solve Medtech Cybersecurity Problem

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A project to develop software that allows medical devices to separate their functions and reduce cybersecurity vulnerabilities may be one answer to recent cases of device hacking and hospital ransomware attacks.

In February 2016, the Department of Homeland Security (DHS) awarded $2.2m to Adventium Labs, a Minnesota-based cybersecurity research company, to develop the *Intrinsically Secure, Open, and Safe Control of Essential LayErS (ISOSCELES)* architecture for medical devices, which is intended to align with US FDA guidelines and security requirements. The project's goal is to build a separation-kernel software program that allows medical devices to split up operations and keep critical functions of the devices safely away from other functions that may become compromised by malware or hackers.

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A year and a half into the project, the company's chief engineer and a co-owner, Todd Carpenter, says they have working prototypes of the separation-kernel that they are using to run mechanical infusion pumps.

"Now we're working on requirements and design for a hardened, essentially phase two, design," he told *Medtech Insight*. "Next year, phase three, is focusing more on final versions of code and working examples at the end as well as tools."

If all goes well, they hope to publically release their hardware requirements and the separation-kernel by the end of 2018 so that companies can use it as a standard when filing product submissions to FDA.

"What we're doing with the ISOSCELES program is we're developing a safe and secure platform. Think of it as building-codes, building-blocks, with the idea that any small medical device company can pick those up and build their own special medical therapies on top of this box," said Carpenter. "You're starting from an assured solid base so you can actually build from this, and expect that you can claim some safety and security properties once you actually release the device."

THE HAVES AND HAVE NOTS

There is a huge disparity in terms of cybersecurity capabilities between small and large medical device manufacturers, Carpenter says. Big companies typically do have adequate staff and cybersecurity skillsets, but companies with 50 or fewer employees, which make up the bulk of the medtech industry, often don't have the necessary expertise on staff.

He also points out that the smaller companies typically hire security personnel from the information technology industry, who tend to be more focused on patient and data confidentiality rather than cyber-physical system safety.

A solution like ISOSCELES is supposed to bridge the industry gap. It would provide another safe option to larger companies developing connected devices, but, perhaps more significantly, give smaller companies a means of making products with better security features.

Once the firm has developed the separation-kernel software and figured out requirements necessary to maintain a reasonable level of protection for medical devices, depending on their size and operation, the plan is to release the information for anyone to pick up and build on, Carpenter said.

"We want to foster innovation," he explained. "The idea is companies can pick up this overall approach and run with it and they're not going to have to pay a license fee for the work that DHS is funding along these lines."

While it would be good for companies to adopt ISOSCELES because it ensures stronger cybersecurity, Carpenter says they hope companies will also see the potential of getting through FDA review faster due to the use of a recognized and preferred architecture as a tangible incentive.

HYPERVISORS TO THE RESCUE?

Systems that separated functions on a device to minimize cybersecurity risks – known as hypervisors or virtual machine monitors – have been used in other industries. In such systems, computers have hardware that include hypervisor software, allowing the machine to simultaneously run multiple operating systems that share the hardware but don't interact with each other. the US Department of Defense's Defense Advanced Research Projects Agency, for instance, uses hypervisors to prevent hacking of US drones.

"What we want to do is bring that same type of capability down into the smaller embedded devices," said Carpenter. "We are providing the hypervisor-like functionality to run these different operating system images on it."

One of the problems with medical device and hospital cybersecurity is many of the products run older *Windows* operating systems that Microsoft no longer supports. The advantage of Windows is it is very easy to develop other software on top of it and create graphical interfaces, but it is not always the safest option if not patched properly.

"[Windows-like operating systems] are not the same environment I would want to run a safety monitor that controls the rate at which a drug pump is pumping," said Carpenter. "I might want to use a different operating system or potentially no operating system."

Over the past few years, DHS has been funding research into cyber-physical system security in various sectors such as cars, building controls and now medical devices.

A fundamental cybersecurity risk factor for medical devices, as with many other products with connectivity, has been that manufacturers did not consider the security issue when the products were first developed.

"Why would anybody attack a medical device, it's there for good things, we're increasing quality of life and we're extending life?" asks Carpenter. "The problem is the attackers don't care, they have no ethics, they have no morals, they're going to attack anything that moves."

GROWING THREAT OF DEVICE HACKS

The threat of hackers causing harm to patients has captured the attention of many, including US DHS, which is closely watching Carpenter and his team's work.

"DHS says this is a big risk because we have all these physical things now connected by networks... [The department] is very interested in results of this program getting deployed and used," said Carpenter. "DHS isn't in the business of doing basic research to write up a paper; they want these developments actually moved out into industry and applied and used."

Carpenter predicts there will be more and more attacks on medical devices and hospital systems in the foreseeable future. On top of that, he notes, market forces are driving devices to store patient data on cloud servers.

"A lot of these questions about what happens when the network goes down, that's going to get a lot more complicated," he said. "We definitely need solutions once that [network] is restored, whether virtual or physical – how do you regain access to that external storage and securely talk with it?"

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CONTINUED FROM PAGE 1

of subjectivity among manufacturers and among notified bodies. So how do you know whether your product needs prior review?

The most useful source of information to manufacturers in attempting to answer these questions is - NBOG 2014-3 Guidance for manufacturers and notified bodies on reporting of design changes and changes of the quality system.

But even this lengthy document – which provides examples – needs a degree of interpretation.

The document says: "It is recommended that manufacturers contact and discuss with their Notified Body about any questions related to the substantial or not substantial characteristic of the change in order to get a common understanding."

But not all notified bodies use this guidance consistently, Gert Bos, executive director and partner at Qserve Group, told *Medtech Insight*. Most, he said, have defined their own processes and provide clients with their own guidance.

WHY NO BLACK-AND-WHITE ANSWERS?

Another reason why this is such a complex issue is that there is a myriad of different possibilities when it comes to types of line extensions, and the answer depends, to a very large extent, on the notified body's opinion.

It is worth pointing out here, too, that a line extension is not a term mentioned nor recognized in the EU device directives – which makes the situation particularly open to interpretation, Mika Reinikainen, managing director of Abnovo consultancy, said in an interview. Instead the directives simply talk of "changes."

There are many ways in which extensions to product lines can introduce new risks. So companies should be careful to assess whether the extension could result in a product with a different scope to that mentioned in the conformity assessment certificate of the originally CE-marked product. If so, the notified body would need to be informed before the product is marketed.

In cases such as these and where the extension to the product may no longer be covered by the already-issued certificate, companies would require either a certificate extension or a new certificate from the notified body. One of these must be available *before* placing such a product on the market.

Companies should also be aware that even if the product may look as if it would be covered by the already-issued certificate for an existing product line, if the extension can be considered as a "substantial" or "significant" change to the product or to the quality management system, then an implementation of such change will also require prior involvement of the notified body.

ANNEX II DEVICES LESS LIKELY TO REQUIRE CHANGE REVIEW

A UK MHRA representative told *Medtech Insight* that, when it comes to products that are not among the highest-risk categories, many extensions to an existing product line, such as adding a new size offering, do not need to be communicated to the notified body, as the update should be picked up at the next audit.

Bos delivered a similar overall message. He said that, in principle, the manufacturer may add a product within the scope of its Annex II (quality system) certificate, provided it is not class III device. But, he

Key Points On Line Extensions Under EU Directives

- Changes comes in many different varieties – from adding a new size of product without any other design changes, to adding a completely new product to an existing product family.
- The manufacturer must report to the notified body any plan of "substantial" changes before implementation (NBOG 2014-3).
- The word substantial is sometimes replaced by the word "significant." Both these terms are open to interpretation.
- The response is different according to the risk class of the medical device – if it is a class III or active implantable, then the notified body needs to give approval before they are placed on the market.
- While the case is clear for high-risk devices, there is the opportunity for proportionate interpretation of the directives and rules for other classes of device.
- With minor changes, it may be possible to not inform the notified body before the product is put on the market, but you need to be sure and the NBOG 2014-3 guidance should help.
- Where a product has been certified through the quality management system route, Annex II, meaning the company has a design control system, the likelihood of not having to report a minor change increases.
- If it is just an extension to an existing products line that would not introduce any additional clinical risks, then it seems that the manufacturer does not need to inform the notified body as this will be picked up in the next audit.
- Whenever the change is related to the design or material or intended use, the manufacturer has to get approval from the notified body before the product is placed on the market. This is also the case if a change raises questions concerning safety or performance.
- Carrying out a risk assessment on the change should help the manufacturer determine whether a change is a "substantial" or "significant" one.
- The decision may depend on the routine approach and understanding that a company has with its notified body.
- If you make a wrong judgment about informing the notified body in the case of line extensions, you could be in violation of the directives.

stressed, that a list of added products should be kept for retrospective review during audits by the notified body based on sampling. The change control process will have been reviewed by the notified body anyway, he explained, prior to issuance of a certificate.

Bos agreed that a change notice should be provided for notified-body upfront review for all active implantables and class III products. Upfront review is also needed, he confirmed, for a line extension when it goes outside of what is the scope of the certificate. Companies have tried to minimize the need for upfront reviews, he suggested. "Hence the scopes have gradually become more detailed, including in terms of technology and clinical use," Bos said.

Mika Reinikainen of Abnovo also confirmed that for companies who have been certified under Annex II – meaning that they have a design control system – the likelihood of not having to report a minor change increases.

Daniel Shoukier, who is a lead auditor at notified body SQS, in Switzerland, observed that whenever the change is related to the design, or material, or the intended use, the manufacturer has to get approval by the notified body before the product is placed onto the market. This is also the case if the change raises new questions related to safety or performance, he said.

WHAT THE NEW MDR SAYS ABOUT PRODUCT CHANGES

The new MDR, is more detailed than the current MDD when it comes to requirements around line extensions. The focus in the MDR is on notified body oversight in this regard.

The MDR, requires notified bodies to have an established process for change control (Annex VII (Notified Bodies) Article 4.9), Bos explained, and that should be part of the contractual arrangement with the manufacturer.

Moreover, the conformity assessment annexes in the new MDR, he added, also require manufacturers to inform the notified body on significant changes specifically related to

- The approved quality management system or systems or to the product-range covered;
- The approved design of a device;
- The intended use of or claims made for the device;
- The approved type of a device; and
- Any substance incorporated in or utilized for the manufacturing of a device (i.e., tissues or cells or animal origin) and being subject to the specific procedures.

Importantly, it states that the procedures and contractual arrangements must include measures for checking the significance of the changes. Once the notified body has this information, the MDR states, the entity must:

- Ensure that manufacturers submit prior-approval plans for changes referred to above and relevant information related to such changes,
- Assess the changes proposed and verify whether, after these changes, the quality management system, or the design of a device or type of a device, still meets the requirements of the regulation; and
- Notify the manufacturer of its decision and provide a report or, as applicable, a supplementary report, which shall contain the justified conclusions of its assessment.

The regulation also states that when a manufacturer is applying for re-certification, it must submit a summary of changes in addition to scientific findings for the device(s) in question – this means all changes to the originally approved device, including changes not yet notified as well as changes to the components of a device.

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And In The US?

Similar to the EU, questions over how to handle product modifications or line extensions for low- or moderate-risk products in the US can be vexing. US FDA and industry have long relied on a 1997 guidance document, including detailed flowcharts, to map out when a modification to a 510(k)-cleared device qualifies as a "major change to intended use" or a "change that could significantly affect safety and effectiveness," which determines if a new FDA submission is necessary or not.

Despite the detail, the process is considered confusing: It's not unusual for companies to be cited for marketing a modified device without a 510(k) in FDA warning letters and there has been some public controversy raised over individual company decisions to simply record a modification to a product file rather than submit a new 510(k) *(Also see "FDA Policy For Device Modifications Faces Mounting Scrutiny" - Medtech Insight, 6 Jul, 2009.)* The agency attempted to revise the guidance in 2011, but was met with severe opposition from industry. *(Also see "A "Disastrous" Draft? Device Firms Take Issue With 510(k) Modifications Guidance" - Medtech Insight, 5 Dec, 2011.)* FDA issued a new draft 510(k) modifications guidance last August, which it is now working to finalize. *(Also see "FDA Calls For Full Risk Reviews For Device Changes In 510(k) Modifications Draft" - Medtech Insight, 5 Aug, 2016.)*

MedTech Europe's Bernasconi Urges EU Stakeholder Committee, Discusses The New Regulatory Landscape

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The medtech sector needs to set up some form of high-level committee to oversee the implementation of the new EU medical device regulations, and be nimble in assessing progress and making changes where necessary.

That is the view of Serge Bernasconi, CEO of the EU's largest medtech trade association, MedTech Europe. He confirmed during a recent interview with *Medtech Insight* that initial discussions related to such a committee have already taken place.

"We should not wait 10 to 15 years to suddenly change the regulations. We need to monitor them on a permanent basis," Bernasconi said. He added that all stakeholders should be represented on this committee, including regulators, patient representatives and industry.

Each party should have the opportunity to observe and monitor the impact of the implementation of these regulations. Stakeholders should be able to forward recommendations over time on how to make sure the regulations remain up-to-date, he said. And, if there are issues, the committee can help to better anticipate them.

Bernasconi also spoke to *Medtech Insight* about which companies and products MedTech Europe thinks are going to be most affected by the new regulations, why the organization has initiated an impact assessment, and what are its current priorities. That conversation is below.

Medtech Insight: What impact do you think the regulations will have on the medical device and IVD industry overall?

Serge Bernasconi: We should be in no doubt that we needed new solid regulations to demonstrate that products are approved effectively. We knew that the sector needed to raise standards – but now we need to understand the impact of the measures that were introduced to do this.

We have initiated an impact assessment with our members to look in detail at the impact of these new rules. We began it a couple of months ago because we needed to wait until the basic texts were finalized. This is an extensive and complex piece of work, and we expect the results in the fourth quarter of 2017. At that point, we should have a better vision of the impact, the costs and people needed, and potential expected delays, et cetera.

What impact do you think the regulations will have in terms of companies that will choose to leave the sector because of the much tougher environment, and companies that will survive? Is it likely that we will lose many SMEs?

Bernasconi: I am not sure that companies would chose to leave the sector because of the regulations themselves. I think it is more about their products – and if they have good devices or IVDs, then there is no reason to leave.

What counts is whether a device is significant, and offers significant innovation for patients.

Somebody in a more generic business may consider that managing this complex new environment is not worth it, however.

When it comes to the question of whether we will possibly lose SMEs, this is a difficult question to answer. Yes, there may be a risk that we may lose some or that they may go elsewhere to develop their products. But we hope this will not be the case and that we will be able to help them find solutions.

What about the impact of the regulations on the rate and volume of innovation?

Bernasconi: The regulations are more complex – for good reason. This will not reduce the volume of innovation – although it may delay it. But the positive side is that the regulations are clearer and more pragmatic, and we are likely to see more solid dossiers submitted in future, which will be in everyone's interests.

What about the impact of the regulations on the choice of market in which companies choose to do their clinical investigations? Will the EU continue to be a first target, before the US?

Bernasconi: Companies have often chosen the EU first to do their clinical work to support rapid CE-marking. If anything, the new regulations will most probably make companies look again at this question.

The new regulations allow for a single clinical investigation applicable to several markets, which is positive. So, I think that companies will question what works best for their situation and rethink their strategies in terms of product introduction and product development.

That does not mean that companies will turn away from Europe at this stage. We should not forget that other regions' clinical requirements come with their own set of complexities.

What about the impact of the regulations on the choice of market in which companies choose to launch high-risk products?

Bernasconi: In the EU, in the future, when it comes to high-risk devices, I think companies will have to run larger assessments than before and provide a larger clinical demonstration of the benefits of their device. But this is not just the case in the EU – regulations for high-risk devices are not that simple anywhere and rules are constantly changing.

I think it makes sense that companies reevaluate where is best for them, but we should not forget that if companies were coming to Europe because it was an easier market due to easier regulations, then that was sending out the wrong message.

What about the impact of the regulations on the types of products that are on the market now and will continue to remain available? What types of products are most likely to be withdrawn?

Bernasconi: When it comes to the question of which products companies will decide to withdraw, replace or retire, this is difficult to answer at present as there is still a good deal of secondary legislation awaited, including the delegated and implementing acts, for example.

We need to be careful that the market does not lose product choice and that we do not make things more complicated than they need to be.

There is also another factor that we should consider – and that is the capacity of notified bodies to handle all the potential work. I am not sure people understand that there is a risk some products will have to leave the market if there are bottlenecks at notified bodies and they do not have the capacity, nor time to assess all the necessary products in time.

In all, and under the new regulations, we are talking of hundreds of thousands of medtech files that need to be reviewed. We need to make sure that notified bodies have the capacity to deal with these.

It is fine to demand more clinical evidence – but notified bodies need to be able to evaluate it and come up with the necessary decisions. They need to be able to acquire the expertise. Without all this in place, there are going to be problems.

The number of EU medtech notified bodies continues to drop. How much of a concern is this to Medtech Europe and what are you doing about it?

Bernasconi: The fact that the numbers of notified bodies is decreasing is actually good news since it confirms that the European Commission's 2012 action plan, which aimed to improve standards among notified bodies, is working and that there has been a significant upgrade in performance among notified bodies.

This should mean that the ones that remain are solid and not vulnerable to being discredited as some of have been in the past.

It is a tough environment for those that are left. They are not only having to cope with more work, but also with trying to recruit experts when not so many are available. Because of this, we are already seeing and hearing of potential auditing delays. That is a concern for everyone, particularly given the challenges for notified bodies and manufacturers alike of getting up to speed in implementing the new regulations, and particularly for SMEs who have less resources to manage delays.

We are prioritizing discussions with the Commission and notified bodies to help things move in the right direction. We have been constantly reminding the European Commission that if the main actors under this regulation are not ready in time, that this is even more likely to create a bottleneck and problems with products being available on the market.

To what extent is MedTech Europe involved now in discussions on setting up governance and other structures such as Eudamed, and secondary legislation?

Bernasconi: We have always had a good relationship with the Commission and competent authorities and are very optimistic this will continue into the future and be important in terms of discussions on secondary legislation. We are pleased that they invite our input and want to help move now towards pragmatic and practical solutions, especially as there are issues around the whole governance of the system, such as setting up expert panels for example, which will play a critical role in reviewing some high-risk devices.

We have a good deal of work ahead to ensure that the whole regulations can work. We now need clarification and guidance on how we implement these complex texts.

What news is there of the readiness of the European Commission's implementation roadmap?

Bernasconi: We expect it to come out over the next few days. We need it to get down to work now.

Finally, what are you doing in terms of replacing John Brennan as director of regulations and industrial policy at MedTech Europe?

Bernasconi: Medtech Europe is hoping name later this month the person who will replace John Brennan. That person will have responsibility for regulatory oversight of both areas.

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US FDA Safety Alert Points To Questions Over Copycat Device Accessories

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A recent FDA safety alert suggests some discord between the agency and **Medtronic PLC** over the use of third-party accessories for a Medtronic device.

The FDA alert, dated May 3, reports that patients had experienced several major or minor adverse events, including two deaths, following procedures in which instruments made by certain third parties were used with Medtronic's *NavLock Tracker*. The tracker enables navigation during spinal procedures on the firm's *StealthStation* surgical navigation system.

The agency communication came several days after Medtronic circulated a letter to health-care providers about the issue, and specifically stating that the firm has updated the Navlock indications for use and warning statements so they explicitly say NavLock Trackers should only be used with Medtronic instruments. Medtronic says the third-party accessories present an extra risk because Medtronic did not assist in their design or development.

The revised warning reads, "The NavLock Tracker is designed and tested for use only with Medtronic instruments. The use of non-Medtronic instruments with NavLock Tracker may result in inaccuracy, leading to serious injury or death."

FDA's subsequent alert doesn't take the same hard stance. Specifically, the agency points out that it has cleared instruments from several manufacturers other than Medtronic for use with the NavLock Tracker, including tools manufactured by **Alphatec Spine Inc.**, **Globus Medical Inc.**, and **Orthofix Inc.**, and that the deaths weren't tied to those products.

FDA collected a total of 196 adverse-event reports associated with the use of the NavLock Tracker between Jan. 1, 2013, and March 22, 2017. Most of these injuries involve spinal injury caused by misaligned screws, the agency said.

The agency's data does not include the manufacturers of surgical instruments used with NavLock, making it difficult to estimate the exact scope of the risk. But FDA could confirm that in both cases where patients hemorrhaged and died after NavLock spinal surgery, third-party surgical stereotaxic navigation instruments that FDA *hadn't* cleared for use with Medtronic's NavLock Tracker on Medtronic's StealthStation were used.

For now, FDA is recommending that the NavLock be used only with cleared accessories, but isn't specifying particular manufacturers. The agency can't comment on pending a 510(k) submission or modification because they are considered confidential, spokeswoman Stephanie Caccomo said.

Mark DuVal, an attorney with DuVal & Associates who specializes in FDA device law, suggests the smaller companies are likely trying to take advantage of a market opportunity.

"One of the luxuries of being the size of Medtronic is that you have these problems," he said. "Medtronic was selling accessories, and when the accessories get popular enough you're going to start to see copycat products coming in through the 510(k) process."

"It's true to say that Medtronic wasn't involved in the design of third-party accessories, but it's not fair to suggest there may be risks involved in using them once they've been cleared by FDA," says Mark DuVal, DuVal & Associates.

In the past, manufacturers like Medtronic have tried to preserve market share by saying warranties on their products were void if used with accessories made by other manufacturers, Duval said. But FDA still vouches for the compatibility of accessories it clears.

"Ultimately, FDA doesn't want to get into the middle of a skirmish, but it also doesn't want anyone to misrepresent that an accessory can't be use if it's been cleared," he said. "It's true to say that Medtronic wasn't involved in the design of third-party accessories, but it's not fair to suggest there may be risks involved in using them once they've been cleared by FDA."

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FDA Moves On HDE, IRB, Reprocessing 'Cures' Provisions

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US FDA moved this week to enact multiple provisions of the 21st Century Cures Act, to expand the Humanitarian Device Exemption (HDE) program, streamline clinical-trial requirements and detail which reusable devices are subject to validation data requirements for some reusable devices.

The actions may reflect a pickup in policymaking from the agency now that Scott Gottlieb is in place as a permanent commissioner.

A technical amendments to the HDE rule that was published June 7, and immediately takes effect, follows the Cures Act mandate to allows HDEs for devices that treat or diagnose a disease or condition that affects "not more than 8,000" individuals in the US. This is an increase from the previous, fewer-than-4,000-individuals limit for the review pathway, which only requires proof of safety and probable benefit. Some companies are already in discussions with FDA about leveraging the HDE process under the expanded limit. *(Also see "Inside The Spinal Cord: InVivo Therapeutics Looks To Reverse Injury, Leverage Regulatory Reforms" - Medtech Insight, 17 Apr, 2017.)*

A technical amendments to the HDE rule allows HDEs for devices that treat or diagnose a disease or condition that affects "not more than 8,000" individuals in the US.

The amendment also implements the Cures Act reform that device companies can run clinical trials after sign off by a national institutional review board (IRBs), rather than having to rely on approval by local hospital IRBs.

The usual notice and comment period wasn't required for the changes because they simply update regulations to implement the legislation, FDA says. Similarly, the agency said there was no need for a delayed effectiveness date because the new rules were already in place as a matter of law.

Meanwhile, FDA issued an additional notice, which publishes June 9, follows the Cures mandate to list which reusable medical devices must submit, as part of a 510(k), validation data that addresses cleaning, disinfection, and sterilization, as well as validated instructions for use. I

Device types for which the validated information must be provided include bronchoscopes; ear, nose and throat endoscopes and accessories; gastroenterology and urology endoscopes that have elevator channels; automated device reprocessors; water-based heater-cooler systems; arthroscopes; and electrosurgical instruments and accessories. The notice also lists specific design features, such as crevices, small internal parts, rough surfaces, movable internal cables or lumens, that may make devices more difficult to properly reprocess, leading to a greater infection risk.

If FDA doesn't find the validation information adequate, the 510(k) may be turned down as not substantially equivalent, the Cures Act states.

The provision is needed, FDA says in the notice, because, "in recent years, there have been significant changes in knowledge and technology involved in reprocessing reusable medical devices. Additionally, there has been an evolution towards more complex reusable medical device designs that are more difficult to clean, disinfect, and sterilize." The agency believes that most manufacturers of affected products are already validating their instructions for use due to previous FDA recommendations.

Several infection outbreaks in recent years have been tied to improperly reprocessed endoscopes. Most recently, Sen. Patty Murray, D-Wash., asked **Olympus Corp.** officials for copies of all adverse event reports related to two *TJF-Q180V*-model duodenoscopes. The scopes had been linked to an outbreak of *Klebselia pneumonia* at a European hospital last year that killed one patient and sickened four others. FDA had released a guidance document on reprocessing duodenoscopes in March 2015, and held a public meeting on the issue that May. *(Also see "Outbreak Triggers Senator's Renewed Probe Of Olympus Duodenoscope" - Medtech Insight, 6 Apr, 2017.)*

The validation requirements for the specified devices will take effect Aug. 8.

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M&A ANALYSIS:

Grail's Chinese Merger Wraps Up Busy May

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May proved to be a robust month for medtech M&A activity, with a total of 17 transactions that were signed and/or completed. Deal-making beat the 16 deals recorded in May last year and was also up from the 14 deals in April.

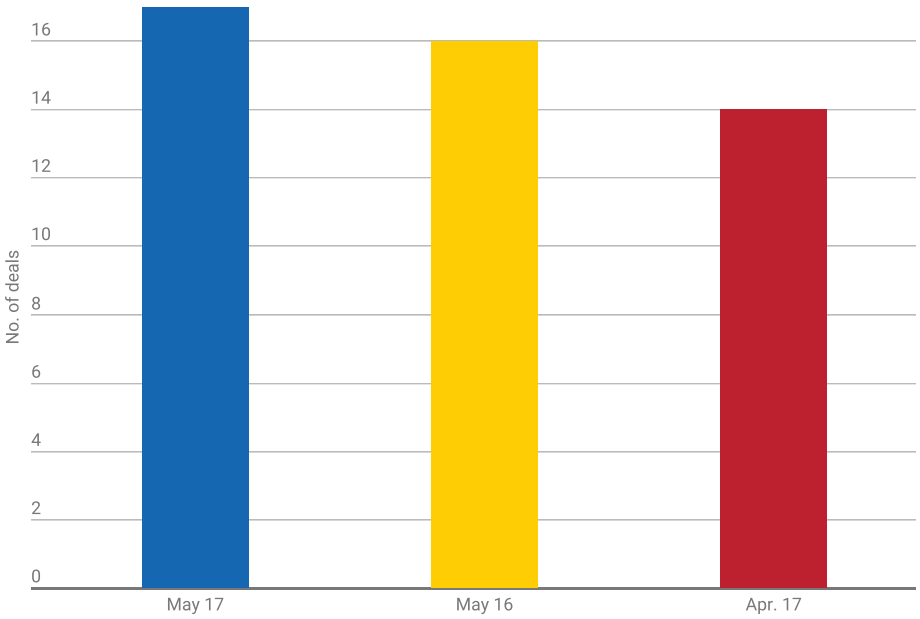
One of the last – but definitely not least – deals that made it into the month's list was the merger between cancer diagnostics company **Grail Inc.** and privately-held, Hong Kong-based business **Cirina Inc.,** which is also focused on early-stage cancer detection using blood-based biomarkers. The agreement, announced on May 31, will expand Grail's reach in the Asian markets and Western markets, as well as tapping into Cirina's leading expertise in molecular cancer diagnostics. The company was founded by Dennis Lo, a pioneer in the field of blood-based diagnostics, who led the team that discovered fetal DNA circulates in the mother's blood. Financial terms of the agreement were not disclosed.

In a statement, Grail CEO Jeff Huber said: "By combining our scientific expertise and resources, we will greatly enhance our ability to achieve our goal of reducing global cancer mortality through the early detection of cancer." Earlier this year, Grail, a spin-out from next generation sequencing specialist Illumina, raised more than $1bn in the first tranche of a Series B round. The investment came from major backers, including Johnson & Johnson, Bristol-Myers Squibb, Merck, Amazon and Varian Medical Systems. *(Also see "Big Pharma Helps Pour $900m Into Grail" - Medtech Insight, 1 Mar, 2017.)*

The deal is yet another indicator of the growing appetite among Chinese investors for genomics-based assets. *(Also see "China VC Watch: Genome, Diagnostics Ventures Attract New Funding" - Medtech Insight, 23 Sep, 2016.)* The wave of interest has been sparked by the success of **BGI,** China's largest genome testing company *(Also see "A Bubble Fit To Burst? China Genome Testing Firms Soar To New Heights" - Medtech Insight, 22 Nov, 2016.)* which is currently seeking to be listed on the Shenzhen stock exchange with a proposed target of raising $250m. The company has been a hotbed of financing and received investment from Alibaba billionaire Jack Ma's Yunfeng Capital fund, China Life Insurance Co., Ltd., Citic's Goldstone Investment and SoftBank China Capital. However, BGI has experienced a number of failed attempts to file for a successful foreign IPO due to restrictions from China's foreign-investment regulations.

FIGURE 1

M&A Deal Volume May 17 vs May 16 vs Apr. 17



Source: Medtech Insight M&A deal tracker

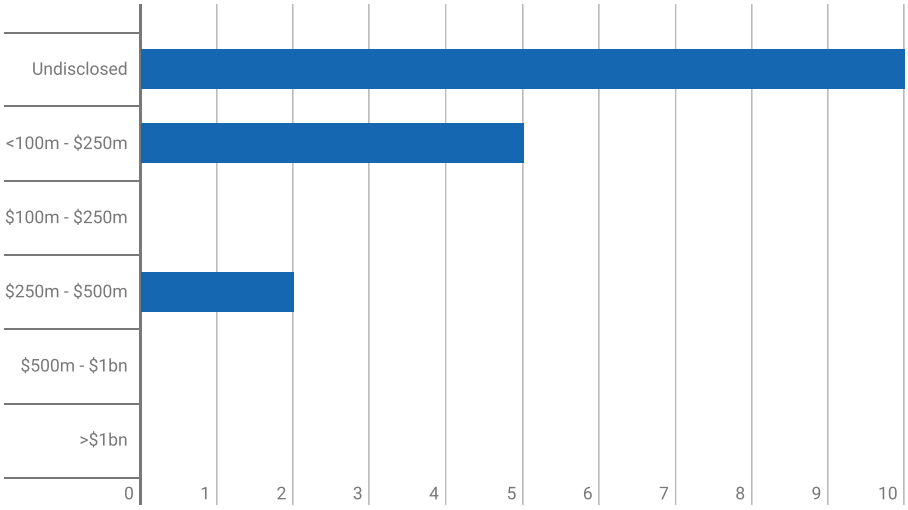
Of the 17 deals announced in the month, only seven disclosed financial terms. In the biggest value deal of the month, healthcare logistics company **Owens & Minor Inc.** picked up **Byram Healthcare**, a distributor of medical supplies sold directly to patient's homes, for $380m in cash. Byram's principal product lines include supplies for ostomy, wound care, urology, diabetes, and incontinence. In a statement, Cody Phipps, president & CEO of Owens & Minor said: "With the addition of Byram to the Owens & Minor family, we can quickly advance our strategic agenda with providers and manufacturers by expanding our reach beyond the hospital setting all the way to the patient's home."

Another significant deal is the closing of Varex Imaging's $276m acquisition of PerkinElmer's medical imaging business. The agreement was first announced in December last year. The acquisition is the first deal for Varex, which was spun out from cancer therapy specialist Varian Medical Systems to focus on commercializing X-ray imaging components. The addition of PerkinElmer's medical imaging business is expected to boost Varex's top line by $140m annually and scale up its digital detector operations.

In terms of bolt-on acquisitions, **Medtronic** agreed to acquire an option on the Chocolate PTA non-drug-coated balloon made by Singapore stock exchange-listed **QT Vascular** to treat peripheral vascular disease for $28m. In February, QT Vascular signed an agreement with Medtronic for the worldwide distribution of the Chocolate PTA catheter for five years. In a statement,

FIGURE 2

Mergers & Acquisitions By Value, May 2017



Source: Medtech Insight M&A deal tracker

Eitan Konstantino, CEO of QT Vascular said he expected Medtronic's global commercial capabilities will further "expand the reach of the device both inside and outside the US."

Philips Healthcare signed an agreement to acquire **Respiratory Technologies Inc.** (RespirTech), a US-based provider of an electronic pulsating vest therapy for patients with chronic respiratory conditions. The vests inflate and deflate rhythmically so patients can clear their lungs and is designed as a low-cost alternative to extended hospital stays. John Frank, Philips' Business Leader, Sleep & Respiratory Care, "With this transaction, we will broaden our portfolio with a proven therapy to enable patients with chronic respiratory disorders manage their condition and receive the care they need in the home." Financial details of the transaction were not disclosed.

London-based company **LivaNova PLC** signed a deal to pick up **Caisson Interventional LLC**, a privately held, clinical stage medical device company developing a novel transcatheter mitral valve replacement (TMVR) implant. The TMVR implant is designed entirely for use via a transseptal approach. LivaNova has been a strategic investor in Caisson since 2012 and will pay up to $72m, net of $6m of debt forgiveness, to acquire the remaining 51% of the company.

In a statement, LivaNova's CEO Damien McDonald said: "We intend to invest in the clinical studies, regulatory approvals, product enhancements and other steps needed to launch this mitral valve replacement system commercially. We expect it will become a strategic complement to our heart valve portfolio for heart team physicians, allowing us to offer patients the most advanced, minimally invasive mitral valve replacement option."

Caisson initiated human trials of the implant in June 2016 through a 20-patient FDA early feasibility study in the US. The company presented results for six patients enrolled in the study at the Third Annual Zurich Mitral Valve Meeting in February. Results showed five of the patients were successfully implanted. Patient enrolment for a CE mark study named INTERLUDE is due to begin later this year. The study has already been approved in Canada.

In its first quarter earnings call, LivaNova said it is aiming to achieve CE mark in late 2018 or 2019 with US FDA approval to come several years later. McDonald said: "We believe this market will develop comparably to the transcatheter aortic valve replacement or TAVR market with a vast majority of procedures taking place through a transseptal route which is our approach. This acquisition places LivaNova in a strong position to set the benchmark for TMVR systems and to be a leading player in the market."

Diagnostics manufacturer **Quidel Corp.** closed a $14m cash acquisition for two diagnostic businesses from RPS Diagnostics. The diagnostic products it's acquiring are rapid, lateral-flow based, point-of-care tests to detect infectious and inflammatory diseases and conditions of the eye. *InflammaDry* detects elevated levels of MMP-9, a key inflammatory marker for dry eye and *AdenoPlus* is a test that differentiates between a viral and bacterial infection of acute conjunctivitis. Quidel CEO Douglas Bryant said the two products are a "solid growth opportunity in adjacent markets for Quidel." The company said both products are CE marked, FDA-cleared, CLIA-waived, and "complement Quidel's existing rapid diagnostic testing solutions."

Berlin-based company **Eckert & Ziegler Strahlen und Medizintechnik AG** acquired competitor **Gamma-Service**, a specialist in isotope technology for $10.3m. The Gamma-Service Group manufactures isotope products for medicine and industry, as well as offering disposal services. The businesses being acquired include a manufacturer of blood irradiation devices, a specialty construction firm for laboratory and handling equipment, and a producer of industrial radiation sources. In a statement, Andreas Eckert, CEO of Eckert & Ziegler AG said the purchase of the businesses strengthened the company's market position.

Urological device company **MedicaMetrix Inc** announced it will merge into **Cardiff International** as the latter's subsidiary, in an all-stock transaction valued at approximately $6m. MedicaMetrix is the creator of *ProstaMetric*, a medical device for prostate cancer diagnosis and monitoring. The device enables physicians to measure the palpable surface of the prostate through the rectal wall using a physical measurement methodology, this measure is then used to determine prostate volume. The device was CE marked in October 2016.

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For more details about M&A deals in 2017 and previous years, go to *Medtech Insight*'s M&A deal tracker: https://medtech.pharmamedtechbi.com/datasets/mna

VC DEALS ANALYSIS:

From Famine To Feast, 2017 Bloats With May Haul

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May signaled a complete turnaround in the levels of venture financing activity after a weak April, with 29 deals of $1m and over recorded by *Medtech Insight*'s VC deal tracker that month. While this represents the biggest deal volume to date, even more notable was the quality of deals that were coming through, including one nine-figure transaction and a good handful of meaty rounds in the higher-value range.

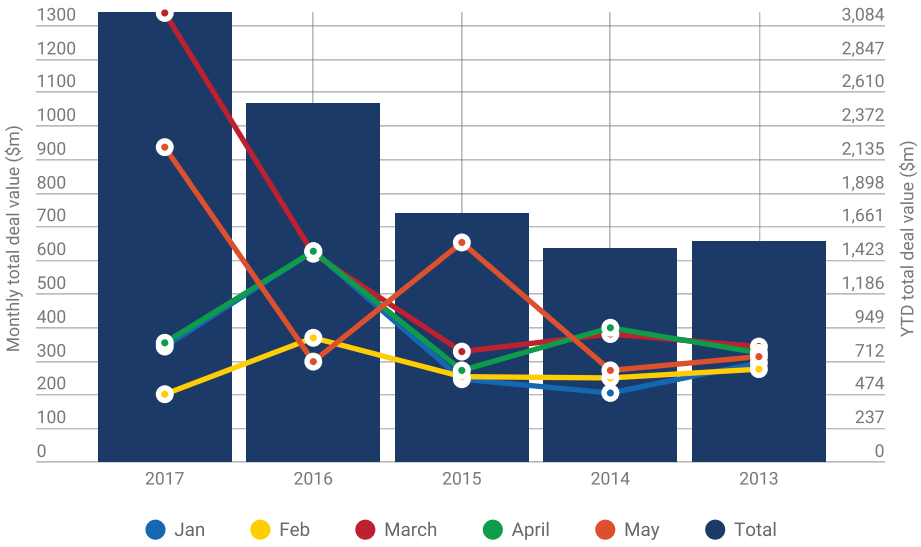
In total, around $935m was raised in May from the 28 deals that disclosed financial details. This did not beat March's unusually high $1.3bn, but is still streets ahead of the deal value seen in other months this year, and also when compared to the same month over the last five years. (See Figure 1.)

Giving May's deal value a big leg-up was a $360m round raised by **Guardant Health Inc.**, the Californian developer of the *Guardant360* blood test for patients with advanced cancer. The test is designed to identify individual genomic alterations of the tumor that could guide doctor's treatment-making decisions. This is Guardant's biggest round to date, as it brings the total investment in the company to over $500m, and highlights continued and growing investor interest in technologies for precision medicine.

Additionally, May surpassed April and the same period last year in the number of higher-value deals. For example, May had twice as many deals in the $30m-40m range vs April and four times as many vs May 2016. Looking at the Top 5 transactions in May, the total raised from these five deals came up to an impressive $601.5m (excluding No. 5 as there were two joint No.4s). (See Figure 2 and Table 1.) In contrast, April's Top 5 raked in a paltry $172.2m. *(Also see "VC Deals Analysis: Variety In Volume, But Lackluster Value In April" - Medtech Insight, 8 May, 2017.)*

FIGURE 1

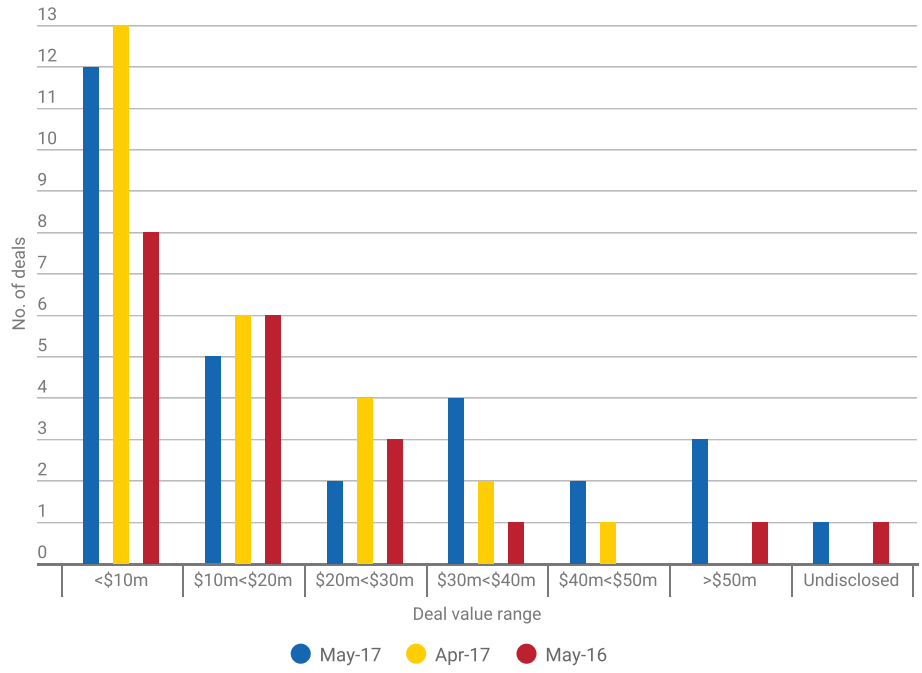
5-Yr Trend: Total Deal Value By Month And Year, 2013-2017



Source: Medtech Insight's VC deal tracker

FIGURE 2

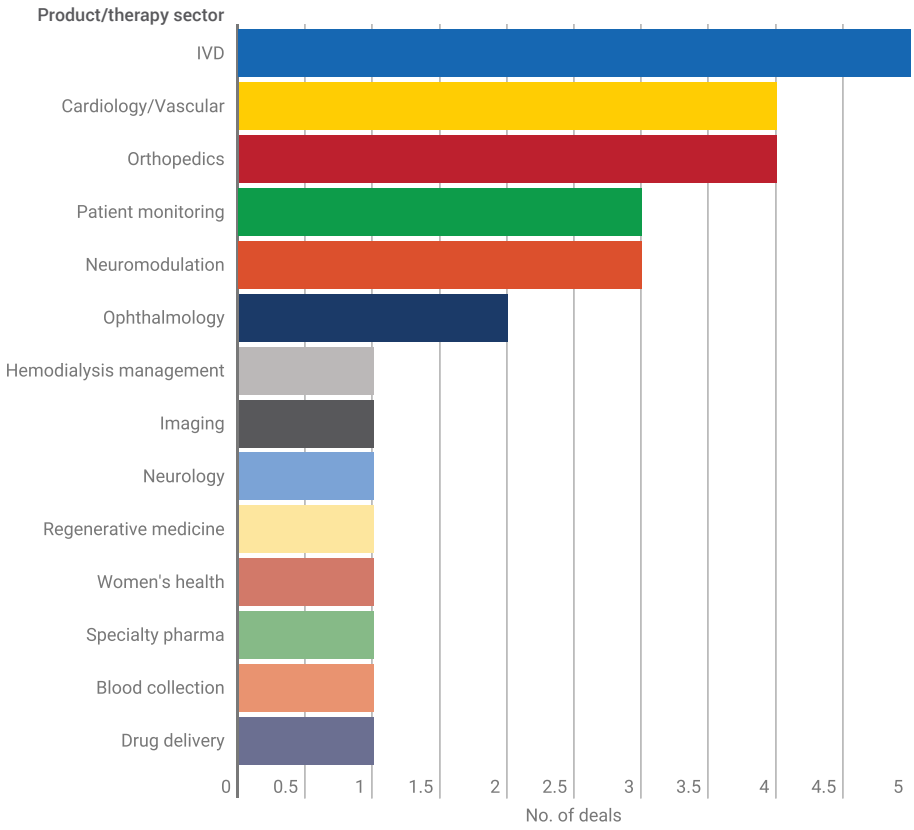
No. Of Deals By Amount Raised, May 2017 vs April 2017 vs May 2016



Source: Medtech Insight's VC deal tracker

FIGURE 3

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



Source: Medtech Insight's VC deal tracker

The Guardant Health round is the second transaction to surpass the $100m-mark this year to date, the first being Grail's whopping $900m in March, and still lags behind 2016 which recorded three $100m-plus rounds between January and May. 2016 also saw this bull run of nine-figure transactions continue into the second half of the year - September recorded a $215m round and December bagged a double-whammy with one deal raising $206m and the other $126m. Whether the rest of 2017 will be able to keep up the pace remains to be seen.

The second largest fundraising came from **Outset Medical Inc.**, a company whose CE-marked and US FDA-cleared hemodialysis system, *Tablo*, is designed as a consumer product. The automated systems run off tap water and does not require the industrial water-treatment equipment used in a traditional dialysis clinic, which means it could be used by patients independently in their own home as well as in an in-center setting. *Medtech Insight* had noted that February saw an unusual level of interest in hemodialysis management, with investments made in three companies targeting this space. *(Also see "VC Deals Analysis: Hemodialysis Stands Out In Feb 5-Year Famine" - Medtech*

TABLE 1

Top 5 Medtech VC Deals, May 2017

RANKING	COMPANY	BASED IN	PRODUCT/ THERAPY SECTOR	AMOUNT RAISED	FINANCING ROUND	TOTAL INVESTMENT
1	Guardant Health	CA, US	IVD	$360m	Undisclosed	More than $500m
2	Outset Medical	CA, US	Hemodialysis management	$76.5m	Series C	Undisclosed
3	WuXi NextCODE	Shanghai, China	IVD	$75m	Series B	Undisclosed
4=	Advanced Cardiac Therapeutics	CA, US	Cardiology	$45m	Undisclosed	Undisclosed
4=	Impulse Dynamics	Stuttgart, Germany	Cardiology	$45m	Undisclosed	Undisclosed
5	Saluda Medical	Artarmon, Australia	Neuromodulation	Aus$53m ($40m)	Series D	Undisclosed

Source: Medtech Insight's VC deal tracker

Insight, 7 Mar, 2017.) Investors' appetite for assets in the hemodialysis market could very well be whetted by the fact that this sector – which has not seen much innovation for some time – represent a potential $75bn opportunity in improving the effectiveness of dialysis and expanding renal disease patients' access to this therapy by moving it from clinic to home.

INVESTORS SPREADING BETS?

Aside from hemodialysis, investors appear to be spreading their bets across a diverse range of product and therapy sectors. While IVD, cardiology, orthopedics continues to feature near the top of the list of popular investment spaces, the big lead they used to have is narrowing as areas like neuromodulation, ophthalmology and patient monitoring continue to close in and grab more investor dollars. (See Figure 3.)

The likely factors for driving this diversity in investments is the fast pace of innovation that is happening in those particular areas. For example, in neuromodulation, the recent International Neuromodulation Society congress in Edinburgh, Scotland showed how previous early-stage technologies are now proving their mettle in clinical studies and gaining increasing recognition from the medical community. *(Also see "INS 2017: Saluda's Closed-Loop Spinal Cord Stim Tech Sparks GSK-VC Interest; Solid Preliminary Data" - Medtech Insight, 1 Jun, 2017.)(Also see "INS 2017: Positive Initial Data Put Axonics On Next Big Wave Of Sacral Neuromodulation Growth" - Medtech Insight, 30 May, 2017.)* While in patient monitoring, the application of digital technologies is creating more connected and effective systems that can help to reduce the cost burden, a benefit which health care payors are appreciating more. Should investors continue to expand their investment horizon like they have been doing this year so far, it is likely the venture financing landscape would be a more varied one at the end of 2017.

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ASCO 2017:

Myriad's MyRisk; Nanobiotix' NBTXR3; Chronix' CNI Test; Sirtex SIR-Spheres; ANGLE's Parsortix CTC Harvester

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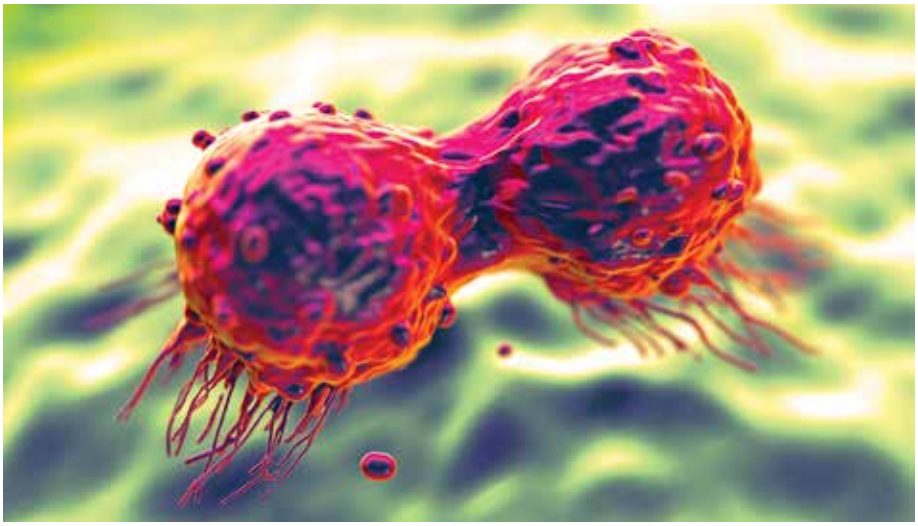
Although the scientific sessions at the 2017 American Society of Clinical Oncology annual meeting were dominated by basic research and drug trials, the meeting also featured many presentations on novel drug-delivery, radiation, and diagnostics technology. Here are some of the highlights of this year's meeting, which was held in Chicago June 2-6.



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MYRIAD'S MYRISK TEST UNCOVERS PATIENTS AT GENETIC RISK FOR CANCER

Results from Study 005, a 2,000-patient prospective study of **Myriad Genetics Inc.**'s *MyRisk* hereditary cancer test, showed that more than 50% of the cancer-related mutations identified by the tests were found in patients who do meet the criteria for genetic panel testing under current professional guidelines and 34% of mutations were identified in unexpected genes, which confirms the clinical utility of multi-gene panel testing to improve hereditary cancer-risk assessment, according to the company.

The results of the study led by Gregory Idos, University of Southern California, were the subject of three poster presentations at the ASCO meeting on June 5 and the abstracts are published in the *Journal of Clinical Oncology*.

All of the patients enrolled in the study met either the standard clinical criteria for genetic testing or were predicted to have at least a 2.5% probability of inherited cancer susceptibility using validated prediction models

and assessed them for 25 known cancer-related genetic markers using the MyRisk system. Among the 241 (12.1%) patients who tested positive for a pathogenic mutation, 31.5% had either a BRCA1 or BRCA2 mutation and of those, 68.4% patients had a BRCApro carrier probability greater than 5%. 15.8% patients had a pathogenic mutation in an MMR gene: 19 (50.0%) had an MMRpro carrier probability greater than 5%, while 34.2% had a PREMM1,2,6 carrier probability greater than 5%.

"In a diverse cohort of patients undergoing 25-gene multiple-gene panel testing, half or more carriers of BRCA1/2 or MMR mutations had a CP of < 5%, the consensus guideline-recommended cut-off for genetic testing," Idos et al conclude. "These results support a lower threshold for genetic testing guidelines."

Commenting on this study, Myriad's Chief Medical Officer Johnathan Lancaster, told *Medtech Insight*:"Panel testing, despite what many payers would like us to believe, is safe and efficacious, and it's for both of those reasons that it has become the standard of care."

"If we continue to use [the existing predictive models] as gatekeepers to access genetic testing, 50% of the mutation carriers are going to be missed," Lancaster said.

Before the patients were tested with MyRisk, experts predicted which inherited cancer syndromes they expected each patient to have, ranking the top eight most likely, in their estimation. However, 35% of the patients carried pathogenic mutations in genes the experts did not suspect, "suggesting a significant contribution of expanded multiplex testing to clinical cancer risk assessment," Idos et al. wrote. "The identification of off-target mutations broadens our understanding of cancer risk and genotype-phenotype correlations." The study authors are continuing to follow these patients to assess the clinical utility of multiplex gene panel testing.

"You need to use a pan-cancer panel test to maximally identify these mutations," Lancaster said. "The experts in the field [already] realize that you can't predict it. You need to use a panel to identify the optimal number of patients who are carrying these genes."

A separate analysis of Study 005 led by Allison Kurian of Stanford University looked at the potential harm of multiplex testing for cancer risk, such as unwarranted surgery or adverse psychological effects. The analysis found that few of the patients who underwent the multiplex testing in the study had preventative surgery within the next three months and the patients whose tests yielded a so-called "variant of uncertain significance" had no more distress, regret, or uncertainty than patients whose test results were negative for the cancer-related variants. Patients with positive test results most often advised their relatives to undergo similar testing, "suggesting that participants understood the implications of test results," Kurian et al. report.

> "If we continue to use [the clinical guidelines] as gatekeepers to access genetic testing, 50% of the mutation carriers are going to be missed," Myriad's Johnathan Lancaster.

NANOBIOTIX' NBTXR3 NANOPARTICLES PROVES SAFE IN EARLY TRIAL

Results of a small phase I trial presented at ASCO show **Nanobiotix SA**'s *NBTXR3* functionalized hafnium oxide nanoparticle radioenchancers are safe while results of another trial, also presented at the conference, indicate NBTXR3 injections combined with radiation therapy can help turn a "cold" tumor into a "hot" tumor and help kill the cancer.

NBTXR3's high-electron density of the nanoparticles allows for the absorption and deposition of a high radiation dose within tumor cells undergoing radiation, which Nanobiotix expects will help to kill tumor cells and improve patient outcomes.

On June 5, Christophe Le Tourneau of the Institut Curie in Paris and colleagues presented a poster with results from a phase I trial of NBTXR3-injections and radiation to treat locally advanced head and neck squamous cell carcinoma in 12 patients older than 65 years who could not receive chemotherapy with cisplatin.

There were no serious adverse events or early dose-limiting toxicities. The results showed that a single injection of NBTXR3 provides adequate bioavailability of the nanoparticles over seven weeks of radiation therapy, with no leakage of NBTXR3 to the adjoining healthy tissues. So far, 10 of the patients showed complete or partial response to the therapy.

Seven of the nine patients who received a dose of NBTXR3 equal to at least 10% of the tumor volume showed a complete response and the tumor response suggests a dose dependent effect, Le Tourneau et al. report. The patients treated with dose levels of 15% or 22% have shown a prolongated response with no relapses after a median follow-up of one year. Most of the complete responses were observed three to 10 months after the end of the radiation treatment, but late appearance of tumor complete response as well as "an unusual case of Pseudo Disease Progression" followed by tumor complete response have been observed in the study, according to Nanobiotix.

In May, Nanobiotix announced early results from 26 patients in a randomized trial comparing radiation therapy with or without intratumor injections of NBTRXR3 to treat in soft tissue sarcoma. The study is led by Jerome Galon of the French National Institute of Health and Medical Research in Paris.

Galon et al. collected tumor tissues both before and after the treatment from 14 soft-sarcoma patients who received NBTXR3 and radiation therapy and 12 soft-sarcoma patients who were treated with radiation alone. They also analyzed the immunohistochemistry and digital pathology of the patients for immune biomarkers as well as the patients' gene-expression profile and pre-optimized immune-gene signatures.

Galon et al found that the patients treated with NBTXR3 showed significant in-

crease of T cells and a marked increase of CD103+ immune cell infiltration after the treatment, while no such differences were seen for in the radiation-alone group. The NBTXR3 group also showed increased CD3 + CD8 cell densities after the treatment compared to radiation only group. The up-regulation of pan-immune genes expression, including the expression of adaptive immunity genes between the pre- and post-treatment tests, was more pronounced in the NBTXR3 patients than the radiation-only group, and functional analysis of genes up-regulated in the NBTXR3 group showed an enrichment of cytokine activity adaptive immunity and T cell receptor signaling pathway.

These findings suggest that the NBTXR3 nanoparticle injection "induces a specific adaptive immune pattern," Galon et al. conclude. "As such, it may contribute to convert "cold" tumor into "hot" tumor and be effectively combined with immunotherapeutic agents across oncology."

CHRONIX' CNI SCORE OUT-PREDICTS CURRENT METHOD FOR HEAD AND NECK CANCER RECURRENCE

Results of a 54-patient trial presented at the ASCO meeting show **Chronix Biomedical Inc.**'s copy number instability (CNI) test can be a more accurate predictor of time to cancer progression in patients with head and neck cancer than conventional cancer staging based on clinical parameters.

Given predicted time to progression is an important factor in the therapeutic decision post-surgery, such a test has the potential to improve outcomes in this cancer. "Given predicted-time-to-progression is an important factor in the therapeutic decision post-surgery, such a test has the potential to improve outcomes in this cancer," said lead investigator Julia Beck, a senior scientist with the company.

Chronix believes this test could be used to monitor adjuvant therapy patients at risk for recurrence of head and neck cancer.

Chronix' liquid biopsy system measures copy number instability signatures of cancers with next-generation sequencing of plasma cell-free DNA (cfDNA). Instead of detecting single mutations or rearrangements in the gene, Chronix's test measures the gains and losses of chromosomal regions in the genome. *(Also see "New Chronix Liquid Biopsy Test Could Save Doctors On Immunotherapy Costs" - Medtech Insight, 22 Mar, 2017.)*

Currently, human papilloma virus detected in oropharyngeal carcinomas is currently the only prognostic biomarker for this type of tumor, Beck et al. explain in their poster presentation at ASCO on June 5.

> The addition of selective internal radiotherapy with Sirtex Medical's SIR-Spheres Y-90 microspheres to first-line chemotherapy did not improve survival of metastatic colorectal cancer patients in the FOXFIRE Combined Analysis.

The investigators extracted cfDNA from 132 plasma samples from 54 patients with head and neck cancer and calculated CNI scores for each. After unblinding, the investigators evaluated the CNI scores as diagnostic parameter for association with disease characteristics and progression.

The study found that the 29 patients with tumors at stage three or worse and 11 out of 12 patients with stage four tumors had CNI scores over 31, with significantly higher CNI scores seen in patients with stage four tumors. Higher CNI scores were also found in patients with tumor lymph node invasion compared to negative lymph nodes. There was a steep decline of CNI scores after surgical resection and increasing CNI scores in later disease progression.

Also, pre-operative CNI scores proved to be a stronger predictor of time to recurrence than the lymph-node status. Baseline CNIs over 31 strongly correlated with time to recurrence with a median of 20 months and median overall survival of 30 months in the high CNI group. There was no recurrence in the low CNI-score group after five years of follow-up.

SIRTEX' SIR-SPHERES MISSES PRIMARY ENDPOINT

Results of the FOXFIRE Combined Analysis, a composite of three studies, showed that the addition of selective internal radiotherapy with **Sirtex Medical**'s SIR-Spheres Y-90 microspheres to first-line chemotherapy did not improve overall survival or progression-free survival in patients with metastatic colorectal cancer.

Ricky Sharma from University College London presented the results, which combine the data from the SIRFLOX, FOXFIRE, and FOXFIRE-Global studies, at the ASCO meeting on June 5. The combined analysis of 1,103 patients is the largest cancer study ever conducted to investigate the combination of chemotherapy with an interventional radiology procedure, Sharma said. *(Also see " CLINICAL CORNER: SIR-Spheres Improve Liver Chemotherapy; REVISE Supports Viabahn AV Endoprosthesis over PTA" - Medtech Insight, 4 Jul, 2016.)*

All three studies enrolled patients with metastatic colorectal cancer with liver metastases not suitable for curative resection/ablation who never had chemotherapy before. The combined analysis had two arms: Patients treated with either oxaliplatin-based chemotherapy with or without an investigator-chosen biologically targeted agent; and patients treated with the same systemic therapy plus a single treatment with SIR-Spheres and one or two cycles of chemotherapy. Median follow-up 43.3 months.

There were a total of 844 deaths and no difference in overall survival or progression-free survival between the two arms of the study, but the response rate and liver-specific progression were significantly more favorable in the arm treated with SIR-Spheres, but that group had higher risk of non-liver progression as the first event and severe or life-threatening ad-

verse events were slightly more common in the SIR-Spheres-treated group than the chemotherapy-alone group. There were no differences in patient health status questionnaire scores between the groups.

An exploratory subgroup analysis of the studies showed a strong signal indicating that the addition of SIR-Spheres may have improved overall survival in patients with right-sided primary colon tumors, which would increase the median overall survival by 4.9 months and reducing the risk of death in this group at any timepoint by 36%.

"This unexpected finding may prove to be clinically meaningful, as patients with right-sided primary colon tumors represent more than a third of all colon cancer patients," Sharma said. "They have a very poor prognosis compared to patients with other colorectal cancers, which represents a major unmet medical need and an important focus of cancer research today." A more detailed analysis of the primary tumor location in the SIRFLOX and FOXFIRE Global studies will be available at the European Society for Medical Oncology World Congress of Gastrointestinal Cancer, June 28 to July 1 in Barcelona, according to Sirtex.

ANGLE'S PARSORTIX SYSTEM ISLOATES CTCS FROM METASTATIC COLORECTAL CANCER

ANGLE PLC's *Parsortix* circulating tumor cell (CTC) harvesting system successfully analyzed CTCs for the presence or absence of arginine methylation of the epidermal growth factor receptor (meEGFR) in the first study of meEGFR-status across a population of circulating tumor cells isolated from colorectal cancer patients being treated with epidermal growth factor receptor (EGFR) inhibitors.

Krittiya Korphaisarn of the University of Texas MD Anderson Cancer Center in Houston and colleagues presented results of the 47-patient study as a poster on June 3 at the ASCO meeting.

Previous research has already established meEGFR-status as a predictor of a patient's response to EGFR- inhibitors, so this study was designed to see if the presence of meEGFR biomarker in CTCs could predict an adverse duration of progression-free survival in the treatment group.

The study found that the total number of CTCs harvested was not correlated to progression free survival, but that the proportion of those CTCs that had the meEGFR marker was predictive. The patients whose CTCs harvested by Parsortix had a higher proportion of meEGFR positive CTCs had significantly shorter progression free survival than the patients whose CTCs had lower levels of meEGFR. "Assessment of meEGFR-CTCs may provide a 'liquid biopsy' biomarker for reduced efficacy from anti-EGFR drugs," Korphaisarn et al. conclude.

"This study is a further demonstration of the effectiveness of Parsortix in enabling liquid biopsy analysis of patients' cancer through a simple blood test with the potential to provide clinically relevant information to advise treatment decisions," ANGLE says.

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LensGen, Eye On The Presbyopia Prize

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Most patients who undergo cataract surgery with the implantation of an intraocular lens achieve better distance vision, but are not corrected for near vision or presbyopia.

Hoping to shift this paradigm is **LensGen Inc.**, which has a permanent accommodating intraocular lens (IOL) in development designed to treat presbyopia. However, unlike many other standard monofocal IOLs that are single-piece lenses, *Juvene* is a modular, two-piece IOL design that combines both a standard monofocal lens optic (the base lens) with a fluid lens optic. The fluid lens optic changes shape on demand by the brain via the eye muscles when focusing on an object anywhere from near to distance automatically.

The base lens is inserted into the capsular bag first and is similar to a traditional

LensGen's two-piece *Juvene* accommodating intraocular lens

Photo credit: LensGen, Inc

IOL with haptics that surround the optic to securely position and hold the lens in place. The fluid lens optic is then inserted through the same small incision and tucked inside the base lens and held in place by three tabs.

"Juvene is implanted with a surgical procedure that is identical to standard cataract surgery," says company founder and CEO Ramgopal Rao. "In a sense, Juvene restores the youthful vision people lose starting in their 40s."

LensGen is initially targeting the cataract market, representing about 27 million cataract surgeries worldwide annually, for a yearly market opportunity approaching $4bn for Juvene. The company expects CE mark for the lens in 2019, followed by premarket approval 2021.

Rao was sparked to start the company after his own disappointing cataract surgery in 2011, which was unable to address his presbyopia and resulted in him needing to wear reading glasses. The serial entrepreneur was determined to create an IOL with clear optics and a sufficient amount of accommodation. This led him and his team to create a lens that could mimic the eye's natural lens by changing shape for various visual distances.

"We had to find the muscular forces in the eye that could be manipulated to change the shape of the fluid lens," Rao explains. "Fortunately, we had cutting-edge materials and came up with a design to amplify those tiny muscular forces."

Moreover, to be able to insert the new IOL though an incision less than 3 mm in diameter, the lens became modular, with each piece made of foldable silicone. "Silicones are generally more malleable compared to other optical materials," says Rao, whose ophthalmic background includes co-founder of Tomey Technologies Inc. (corneal topography imaging) in 1990; a co-founder of AcuFocus Inc. (a corneal implant device for presbyopia) in 2002; and CEO of 2C Tech Corp. (nanotechnology for treating age-related macular edema and retinitis pigmentosa) from 2010 – 2016, for which he became chairman of the board last November.

Advanced engineering and analysis tools were used to design and fabricate Juvene, including optical ray tracing, finite element analysis and state-of-the-art reaction cast molding. "A smaller incision is also highly desirable for cataract surgery because it reduces trauma, requires no sutures and can be performed under topical anesthetic," Rao says.

LensGen has one issued and 10 pending patents, and does not share any royalties/revenues with another entity.

An ophthalmic surgeon who mostly specializes in anterior segment surgery (front of the eye) uses a stereo microscope to first remove the cataract through the top of the capsular bag by creating a small incision near the cornea, followed by a technique called phacoemulsification, which fragments the cataract lens with ultrasound energy, then aspirates the fragments. Cataract extraction takes a maximum of 5 minutes and is performed under topical anesthesia.

The base lens of Juvene is then folded and placed in an injector, which inserts the lens into the back of the empty capsular bag, where the lens unfolds. "The lens nearly automatically positions itself, but the surgeon may need to manipulate the lens slightly," Rao conveys.

A different injector is used to position the fluid lens, where it sits snuggly on a shelf inside the base lens, like a jigsaw puzzle.

No further adjustments are needed for the IOL to be permanently fixated, and the two lenses are surrounded by the eye's natural saline fluid (aqueous).

In addition, the top of the capsular bag is left open because the bag is avascular (lacking blood vessels), so there is no healing process, per se. The initial small incision is also self-sealing and there is no patient downtime.

The entire surgical procedure, including lens extraction, takes about 15 minutes.

Michael Landreville, chief operating officer for LensGen, says the surgeon learning curve to implant Juvene is minimal. "The only difference is that with a standard cataract procedure, only one lens is inserted, whereas we insert two lenses," he says.

The Juvene fluid lens is slightly different than the base lens because it is designed to fit inside the base lens, therefore the fluid lens is slightly smaller and flatter. "It looks almost like a disc," Landreville notes. The amount of silicone fluid contained in the lens is a fraction of a drop of water. "One surface of the fluid lens moves slightly," he says. "However, the movement is almost imperceptible."

The base lens of the IOL will likely come in three sizes, with one size around 9.2 mm in diameter and the other two, 0.5 mm smaller and 0.5 mm larger. The fluid lens, though, will be available in one size only, around 6.6 mm in diameter.

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Contact: Michael Landreville, COO

Industry Segment: Ophthalmology

Business: Modular, fluid-optic accommodating IOL fully compatible with small-incision cataract surgery

Founded: February 2012

Founder: Ramgopal Rao, CEO

Employees: 6

Financing to Date: $28m

Funding: The Hoya Group; Relativity Health Care Partners; Angel Investors; Grant from the Johnson and Johnson Corporate Office of Science and Technology

Board of Directors: Ramgopal Rao; Michael Colaco (Gems Holding LLC);Akiteru Furukawa (The Hoya Group)

Scientific Advisory Board: Roger Steinert, MD (University of California, Irvine); Uday Devgan, MD (University of California, Los Angeles School of Medicine); Thomas Kohnen, FEBO (Goethe-University, Frankfurt, Germany); Kerry Assil, MD (Assil Eye Institute, Beverly Hills, CA); Eric Donnenfeld, MD (Ophthalmic Consultants of Long Island, NY); Rosa Braga-Mele, MD (University of Toronto, Canada); Kerry Solomon, MD (Medical University of South Carolina, Charleston)

The company has an ongoing clinical pilot study of Juvene that started two years ago, with 20 eyes of 20 patients (ranging in age from 55 to 75) treated to date. All patients were candidates for standard cataract surgery. "Juvene has been found to be safe," Landreville reports. "Most patients are also achieving objective and subjective accommodation."

Landreville worked at 3M Vision Care from 1984-1993, departing as international business manager of the surgical division for the Asia region, after 3M divested its ophthalmic franchise to Alcon. In addition, he served in various operating roles, including category leader for the refractive franchise, at Bausch + Lomb from 1996-2003; and director of medical marketing for the cardiac rhythm management division at St. Jude Medical from 2008-2012 (now part of Abbott Laboratories Inc.).

LensGen's closest competitor in this new classification of shape-changing, fluid-optic accommodating IOLs is *FluidVision* from **PowerVision Inc**. "FluidVision pumps fluid (silicone oil) from their haptics that look like tiny pontoons into the lens optic to create the shape change when the eye muscles and capsule contract," Landreville explains. "The fluid then returns to the pontoon like haptics when the eye muscles relax. In contrast, Juvene's mechanism is direct and relies on the direct forces of the capsule contraction on our haptic to generate the shape change on our fluid lens."

Likewise, FluidVision is single-piece design, not a two-piece like Juvene. "Because of its bulk, the [FluidVison] lens requires a larger incision," Landreville says. Maintaining the smallest possible incision in cataract surgery is important, including no induced astigmatism, faster healing and visual recovery, and usually better outcomes."

Multifocal IOLs from major ophthalmic companies like **Alcon** (a division of Novartis AG), **Johnson & Johnson Vision** and **Carl Zeiss Meditec AG** are also competitors.

"These lenses are more similar to bifocal glasses," Landreville observes. "Some people have difficulty adjusting to multifocals. They can create optical issues like glare, halo and night-vision problems because you are splitting light, which reduces contrast. Juvene, on the other hand, does not compromise quality of vision because it works in a continuous manner, like the natural lens. Instead of splitting light, Juvene changes curvature to produce the power change. This way, the optics are preserved."

Another disadvantage of multifocal IOLs is that it is challenging to predict which patients will encounter problems and which patients will adapt well to the lenses, according to Landreville. "Screening patients is not a perfect science; therefore, some surgeons have opted to avoid using multifocal IOLs all together," he says.

Juvene is expected to start selling in Europe and Asia in either 2019 or 2020, at a price of roughly $1,000, through a hybrid direct/distributor sales force. The IOL will be partially reimbursable.

US sales are planned for 2021 through a direct sales force, with the lens also partially covered by insurance.

The $28m secured by LensGen to date represents three phases of financing: about a $250,000 grant from the Johnson and Johnson Corporate Office of Science and Technology, which was received in 2012; approximately $6.5m in several early seed rounds, mostly from angel investors, which concluded the end of 2016; and a $21m Series A round, led by The Hoya Group, which closed in May.

A $5m extension of the same Series A will be decided by early next year, either funded by Hoya or a third party. Furthermore, a Series B in the amount of nearly $50m is scheduled for 2019, relying on large venture capital firms, strategic partners like Johnson & Johnson, and existing investors.

"However, we would prefer not to commercialize our IOL," Rao says. "We would rather be bought out by a major IOL manufacturer in 2019."

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