POLICY & REGULATION
China exemptions, p. 6

COMMERCIAL
Medtronic works with Aetna, p. 18

R&D
RepliCel poised to partner on dermal injector, p. 20

Medtech Insight
Issue 50
medtech.pharmamedtechbi.com

Pharma Intelligence Informa

July 3, 2017

Photo credit: Ferdous Al-Faruque

Hisani Madison speaks May 31 during FDA's Science Forum at the agency's Maryland headquarters

Q&A: FDA Dx Reviewer's Tips For Next-Gen Sequencing Sponsors

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

Next-generation sequencing, or NGS, has been touted as a potential game-changer in health care, but it is still in early stages and not many NGS products have passed through US FDA yet. But, even with its limited experience, the agency has noticed some repeat issues in NGS submissions that it hopes future sponsors can learn from.

A significant promise of NGS lies in its potential to help personalize treatments to patients based on their genetic makeup. It is the foundation of bold research projects, including some supported by the federal government's Precision Medicine Initiative, and companies are starting to develop companion NGS diagnostic tests to better target drug therapies. (Also see "Thermo Fisher Makes Final Push For 'Universal' Lung-Cancer Companion Dx" - Medtech Insight, 14 Nov, 2016.)

In November 2013, FDA cleared the first NGS in-vitro diagnostic, **Illumina Inc.'s** *MiSeqDx* Cystic Fibrosis test (*Also see "FDA Approves First Next-Generation DNA Sequencing Platforms" - Medtech Insight, 20 Nov, 2013.*) and late last year the agency approved **Foundation Medicine Inc.'s** *FoundationFocusCDxBRCA* NGS test. (*Also see "Clovis Transitions To Commercial Stage On Rubraca Approval" - Medtech Insight, 19 Dec, 2016.*) Based on their discussions with industry at conferences and vendor shows, the agency says they expect to see an increase in NGS products coming up for review.

In the meantime, FDA has published draft guidances on NGS technology and is working on several more. (*Also see "US FDA's Next-Gen Sequencing Guidances: One Stop On A Pathway" - Medtech Insight, 26 Jul, 2016.*) The agency also recently launched a platform called PrecisionFDA to help scientists share data and new NGS-based tests. However, the novelty and complexity of the tests means sponsors are still struggling with narrowing their focus on what the tests can measure, and showing there's a relationship between known markers and diseases. (*Also see "'App-A-Thon' Aims To Create PrecisionFDA Software Library To Advance Next-Gen Sequencing" - Medtech Insight, 6 Oct, 2016.*)

Hisani Madison, a scientific reviewer in FDA's Office of In Vitro Diagnostics and Radiological Health, says the most common error sponsors make in NGS submissions is they don't provide an appropriately refined intended use, which, she says, is critical to how FDA reviews the products. Madison submitted responses to an interview with Medtech Insight over email, in which she explains some NGS submission shortcomings that she has observed and provides tips on how to avoid them.

CONTINUED ON PAGE 5

Over 100 event types

Over 100 catalyst types

Over 5,000 products

Meddevicetracker
Pharma intelligence | informa

Double **the Power**

Meddevicetracker with Medtech Insight reports is a new interactive real-time source of in-depth medical technology market intelligence

Meddevicetracker brings you closer to the medtech market, helping you to:

- Identify upcoming device regulatory events/filings
- Search for medtech clinical trial starts and data
- Find historical and forecasted procedure volumes data
- Monitor drug delivery technologies and identify partnership opportunities
- Quantify the market size for devices or diseases
- Discover forecasted market share of devices by type
- Understand the device competitive landscape and identify unmet clinical needs

Request your free demo today:
please visit - **www.meddevicetracker.com**

6


13

20

explore more:

exclusive online content

New game in mental health
http://bit.ly/2s24PM3

Virtual reality is seeing an upsurge in use by mental health practitioners for treating conditions such as post-traumatic stress disorder, panic disorders, and anxiety in a safe and controlled manner.

Competing concerns
http://bit.ly/2tkZqDD

Deep controversies tied to the Senate bill to repeal and replace the Affordable Care Act are holding up movement by Congress to pass US FDA user-fee reauthorization, a top medtech industry priority.

Compliance Corner
http://bit.ly/2tYtkej

When inspecting a device manufacturing facility, US FDA investigators will check a company's quality data to make sure it's Attributable, Legible, Contemporaneous, Original and Accurate – or "ALCOA."

Stents and trade
http://bit.ly/2shzDg7

US President Trump met with India Prime Minister Modi June 26, and trade barrier were on the agenda. In particular, US lawmakers pressed Trump to bring up price caps on coronary stents that have been imposed by the Indian government.

Device Week
http://bit.ly/2r2fg5N

Our weekly podcast, where *Medtech Insight* journalists discuss topics they are covering that impact the device and diagnostics sector.

medtech.pharmamedtechbi.com

inside:

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

▶ join the conversation

We are tweeting, chatting, liking and sharing the latest industry news and insights from our global team of editors and analysts — join us!

@Medtech_Insight

CONTINUED FROM PAGE 1

Medtech Insight: What are the most common errors NGS sponsors make and how they can avoid making them, so that the application process goes smoother?

Hisani Madison: With regard to the application process, the FDA's top tip to sponsors is to provide a refined intended use that succinctly describes how the device will be used, the markers detected and the intended population/indication. A well-developed intended use is an important aspect of the application, since the FDA uses the proposed intended use statement to guide the device review process.

What advice would you give sponsors to avoid such errors when submitting an application, whether in combination with a drug or a stand-alone NGS test?

Madison: When sponsors are submitting applications for complementary or companion diagnostic devices, the FDA recommends that sponsors plan ahead to ensure that the timing for the device submission is in line with the therapeutic submission.

We recommend that sponsors take the time to think critically through the entire analytical and clinical validation process prior to submitting their applications to the FDA.

Given that NGS is a complex technology with multiple potential sources of error, the agency advises sponsors to consider the entire assay process when planning their validation strategy. For example, if the assay is intended to be used on samples that require unique pre-processing steps (i.e., bone metastases), it would be helpful for the sponsor's application to give consideration to the pre-analytical steps. The FDA considers the test system from sample collection all the way through to variant reporting (i.e., results); it would be in the sponsor's interest to appropriately validate this entire process.

Communication between the FDA and sponsors, as well as between device and drug sponsors, is critical to ensure that timelines for approval are aligned and that all of the pertinent information is relayed to the necessary parties. For those seeking contemporaneous approval of a device and therapeutic, one tip to help facilitate communication would be to invite the drug or device sponsors to their meetings with the FDA in the respective Centers (i.e., CDER or CDRH).

Sponsors would also benefit from reviewing the previously published summary of safety and effectiveness data (SSED) to get an expectation of what the FDA may require for device validation in a marketing application. Reviewing this data can be useful tool for the sponsor when beginning their device development plans.

You say "NGS is a complex technology with multiple potential sources of error." Could you give me a list of the most common sources of error that sponsors should look out for?

Madison: At the FDA we have a great team of scientists that spend a lot of time thinking critically about our review of NGS devices and how to tackle this complex and emerging technology.

One colleague in particular, Dr. You Li, has been an invaluable resource in helping to chart the various sources of error that may be of particular interest when understanding the performance characteristics of an NGS device.

Different components of the NGS workflow will have unique error profiles. For example, sample preparation steps like DNA/RNA extraction may have different sources of error (i.e., DNA quality/quantity) than the library construction step (i.e., appropriate target enrichment).

The FDA recommends that error models for each component of the NGS workflow, including sample preparation, library construction, sequencing and data analysis, are characterized separately.

Are there any other tips you can think of that could help sponsors better prepare their submissions?

Madison: When submitting an application, the FDA recommends planning ahead and beginning discussions with the agency early through the pre-submission process.

When planning a device validation strategy, consider how validation data will support the intended use of the device and how the sample set you choose to include in your validation strategy are reflective of the intended use population.

Use the output from your NGS quality metrics (i.e., sequencing metrics, mapping metrics and variant calling metrics) as a guide to assist with refining the validation strategy. Since different variant types detected using NGS may have different error profiles, for example, the assay sensitivity and specificity for detecting SNVs (single nucleotide variations) will be different from the detection of gene fusions, the sponsor should consider developing a validation plan that is tailored to the range of variant types, sizes and genomic contexts the device is intended to detect.

For class III devices, when submitting a premarket application (PMA), the FDA advises sponsors to consider submitting the application as a modular PMA. The modular PMA allows sponsors to submit preclinical and manufacturing information while still collecting and analyzing the clinical data. This submission type can provide a more efficient review process and give sponsors an opportunity to respond to any issues that may be noted by the FDA early in the review timeline.

Published online 06/22/17

China Proposes Local Trial Exemptions For Another 130 IVDs, 27 Devices

VIBHA SHARMA vibha.sharma@informa.com

Shutterstock: Kisan

The China Food and Drug Administration has proposed exempting another 130 *in vitro* diagnostics and 27 medical devices from local clinical trial requirements, which could save companies seeking registration for affected products at least several months, according to Jeff Sun of consultancy firm Brandwood Biomedical.

While it could take a few months for the CFDA's proposal to be finalized, once in place it would mean that applications to register exempted products would no longer need to contain local clinical trial data. In cases where local trials of exempted IVDs and medical devices have already commenced, it will be up to the manufacturer to weigh up the benefits of whether to complete the ongoing trial.

"Trial data have other uses including supporting market acceptance, and can be useful outside of China, so we would not expect to see many trials, which have already commenced, being abandoned," Sun, senior consultant at Brandwood Biomedical's Beijing office, told *Medtech Insight*.

Data from local clinical trials "would certainly strengthen a registration submission and support a clinical evaluation report – so we would expect to see at least some manufacturers complete their trial and file the data anyway," Sun said. On the other hand, "some manufacturers may choose to hold off on planned trials pending the finalisation of the exemption list, probably later this year."

IVDS: SECOND WAVE

The CFDA's latest proposal with respect to IVDs lists several Class II and Class III products, such as blood chemistry and protein assays, troponin tests for myocardial infarction, IgG/A/M and IgG subtypes used in inflammatory disease diagnosis and fecal occult blood assays.

This is the second time that the CFDA has proposed local trial exemptions for IVDs. The first list, issued in September 2016, exempted only 15 IVDs comprising immunoassay analyzers and a range of lower risk reagents, Sun said.

As a result, to date, almost all Class II and III diagnostics have had to be supported by Chinese clinical data. The proposal to exempt 130 IVDs was long awaited by the industry. It is being viewed as a "substantial move forwards and promises to dramatically curtail regulatory approval times and costs in China for a wide range of IVDs," said Lily Chen, also of Brandwood Biomedical. Related guidance issued with the latest list "points to the acceptability of comparative analytical validation against a suitable predicate device already marketed in China," Chen added.

The CFDA is expected to publish further exemption lists, especially for Class II IVDs. "We would also expect some of the [more] lower risk Class III IVDs to be exempted at some stage. But the [agency's] reform agenda is a very busy one, so it's not clear when CFDA will get around to the next lists," Sun added.

Class I IVDs do not need undergo clinical trial in China; their registration can be supported with just clinical evaluation reports.

MEDICAL DEVICES: THIRD WAVE

The CFDA has also proposed exemptions in relation to 21 Class II medical devices (such as, dental instruments and materials, endoscopic surgical instruments, insulin pen injectors, gynecology devices and electronic endoscopic image processor) and six Class III devices (such as orthopedics devices including bone screws, acetabular cups and fracture plates (3D printed devices are not on the exemption list) and needleless connectors for indwelling catheter).

The proposal represents the third wave of exemptions for medical devices. The CFDA has already exempted 755 Class II devices and 171 Class III devices from local clinical trial requirements under second (in September 2016) and first waves (in August 2014), said Sun. *(Also see "China Confirms Second Batch Of Device Clinical Trial Exemptions" - Medtech Insight, 28 Oct, 2016.)*

Devices proposed in the latest exemption list are those that are safely used and have a low risk in clinical use, so there are "no surprises here". The proposal can save several months of registration time for the products concerned. In the case of devices where clinical trials are lengthy, "time savings could approach a year or more," Sun added.

Published online 06/23/17

South African Medtech Reg: Pieces Coming Together As August Deadline Approaches

ASHLEY YEO ashley.yeo@informa.com

In February 2017, the South African Government Gazette published a notice that gave companies until August 24 to submit applications for licenses to manufacture, export, import and distribute medtech products. As part of the application, companies had to list all products they currently have on the market.

The establishment license rule was first announced in July 2016, at an industry workshop. *(Also see "South Africa Finally Gets Medtech Regulations Over The Start Line" - Medtech Insight, 21 Sep, 2016.)* But the South Africa Medical Technology Industry Association (SAMED) raised concerns about the wisdom, and, indeed, legality of launching a nationally applicable instrument in a closed forum. How would non-members of SAMED comply, for instance?

When new overarching South African medtech regulations finally came out in December 2016, the rule indicated a requirement for a license call and deadline to be published in a government gazette notice, explained Tanya Vogt, SAMED's executive officer. "It would appear they heeded our concerns and made the call-up official," she said. The regulations also refer to a second, separate call-up, for products. This must also be published in the gazette. That notification has yet to be published.

Vogt spoke to *Medtech Insight* last month from the Global MedTech Compliance Conference (GMTCC) in Amsterdam, Netherlands.

Shutterstock: niroworld

"This is a process and a learning curve for both industry and the regulator, and it's essential that we work closely together," SAMED's Tanya Vogt says.

FEES, QMS CHALLENGES

But while transparency has improved, concerns remain, particularly with the licensing fees that the government plans to charge. Local medtech players say the fee rates are the same charged to pharmaceutical companies, which they say is inappropriate, considering the size differences between companies in the two sectors.

"We hoped that they would have taken into account that most device companies in South Africa are SMEs," Vogt said.

The fees that apply to medicines, and, thus, to devices, are:

- Manufacturing: R21,800 (about $1,700);
- Distribution: R13,000;
- Wholesale: R13,000;
- Import: R13,000 (for holders of certificate of registrations); and
- Export: R13,000 (for holders of certificates of registration).

In addition, companies must start to put into place a quality management system (QMS). Its currently expected that ISO 13485:2016 will be the applicable version of the required QMS standard in South Africa. Companies can prepare themselves for that, but they cannot yet be accredited to the South African version of ISO 13485:2016 until the South African National Accreditation System (SANAS) is able to audit the conformity assessment bodies (CABs). These, in turn, must then accredit device companies to the ISO standard. That process hasn't started, although SANAS has set up a working group and has advertised for technical experts who will be trained up as auditors.

The implementation and indeed impact of the new South African medtech regulations will thus be phased in: first, establishment licensing; then SANAS is made ready to accredit CABs; and meanwhile companies must investigate putting QMS in place.

PUZZLE PIECES DROPPING INTO PLACE

Current developments mean that there is a growing list of tasks for industry, but

Key Next Steps

- Device establishments gain licensure (Aug. 24 deadline)
- South African National Accreditation System readies to accredit conformity assessment bodies
- Companies put quality management systems in place, likely based on ISO 13485:2016

it does appear that the necessary parts of the South African medtech regulatory ecosystem are finally dropping into place.

In particular, after a long wait, the South African Health Products Regulatory Agency (SAHPRA) has finally been established as the new oversight organization, as of June 1. *(Also see "South Africa Medtech Reg: As New System Nears Finish Line, Device-Drug Distinctions Still Need Highlighting" - Medtech Insight, 20 Jun, 2017.)* SAHPRA will replace the Medicines Control Council (MCC).

The proposal has always been for SAHPRA to have a dedicated medtech regulatory organization, Vogt said, but there is still work to be done on that front. "We still wish to have a separate medical devices department, and I think it *will* happen, but we are noticing that the people who have been in the [MCC] department all along are those who are beginning to manage the local applications and respond to questions from the medtech sector," she noted. "We do hope that SAHPRA will have dedicated medtech people in a separate department."

SAMED has also requested that MCC hold workshops with industry, and plans are being made for a session in Johannesburg on July 13-14. SAMED has also hosted several sessions for its members, but, as with any new regulation or piece of legislation, Vogt observes that there can be many interpretations. Thus, she suggests, there is a need for clarity.

"This is a process and a learning curve for both industry and the regulator, and it's essential that we work closely together," says Vogt. She stressed the value of SAMED as a partner and as a platform for industry engagement with the regulator. One forum for that engagement will be MCC's quarterly task force meetings that involve pharma and complementary medicines representatives, as well those from IVDs and device associations. These meetings offer an opportunity for stakeholders to gain insight on a range of issues, including seemingly routine matters such as application formats.

"We're hoping that the product registration fees won't be a deterrent and that, with SAHPRA, processes around decision-making will be more efficient with quicker turnaround times," Vogt says.

REGULATORY CHANGE: COSTLY BUT NECESSARY

Overall, Vogt believes South Africa is moving in the right direction on medical devices, but the impact of the reforms must be closely monitored, she said.

"I do believe that the regulatory changes are absolutely necessary, but we can't underestimate the impact that these are having on industry, given the new costs of getting a license or appointing an authorized representative (AR)," she said.

For instance, all sites – even storage sites – will need a license. "That will be very expensive for a small company, and in addition they now have to prepare for getting trained up for ISO 13485." In time, product registration fees will likely be layered on top of the fees to get companies listed as medical device establishments.

But what effect will this have on the availability of products and new brands coming onto the market? As it stands, if a company were not already in existence as of December 9, 2016, it cannot start operating until it gets a license to do so. This means that as of that date, completely innovative medical devices cannot be put on the market until there is a call-up for that type of device; the health ministry would have the right to stop products at ports of entry.

SAMED has asked the head regulator, Joey Gouws, who took over from Mandisa Hela last year, for more clarity on transition schedules. Transitional arrangements prescribed in the regulation need to be amended to avoid the unintended consequences of barring access to new medical devices and establishments, SAMED argues.

The reality of the new regulations may be that some suppliers will exit the market as it becomes too expensive to do business or too onerous to meet the new requirements. "We're hoping that the product registration fees won't be a deterrent and that, with SAHPRA, processes around decision-making will be more efficient with quicker turnaround times."

It is clear that by the end of this year, companies without a license to sell medical devices will be conducting their business unlawfully in South Africa. This time next year, the picture should be clearer, but the detail is in the implementation, Vogt says. "You can create a fabulous policy that has borrowed from best practices around the world, but unless you have the people, processes and the understanding of industry, smooth implementation may not be possible."

She adds, "Our industry might need additional support from the regulator to help us gear up for and abide by the regulations. We need more workshops and guidelines, and we need more opportunities to engage with the regulator."

Published online 06/21/17

CLICK

To read more on the upcoming medical device regulations in South Africa, based on our interview with SAMED Executive Officer Tanya Vogt, go online: http://bit.ly/2udLybb.

EU'S MDR:

When Three Plus Four Does Not Necessarily Make Seven

AMANDA MAXWELL amanda.maxwell@informa.com

The EU's recently adopted Medical Devices Regulation will fully apply starting May 26, 2020. Nonetheless, the provisions of the MDR allow current certificates that were issued by notified bodies under the current directives to remain valid well after that date, until May 27, 2024. At least, that is the theory.

In reality, this late deadline is only going to work for a select few. EU regulatory experts emphasized this point during Knect 365's MedTech Summit held earlier this month in Amsterdam.

Much confusion has surfaced surrounding the clauses in the regulation that reference the May 26, 2024, extension date for products that are CE marked under the current directives. In particular, Article 120.2 of the MDR states that, in general, certificates will remain valid until the end of the period indicated on the certificate, which shall not exceed five years from the date the certificate is issued. But it adds that certificates will be void, at the latest, by May 26. 2024.

Additional details surrounding this clause and some practical realities mean that this is not the give-away that some may think at first glance. Regulatory staff at medtech firms must be ready with solid arguments to explain to company management why planning to comply with the new regulation as soon as possible, rather than waiting for the 2024 deadline, is a must. This message was voiced repeatedly by speakers June 19, during the first day of the five-day MedTech Summit.

Sabina Hoekstra-van den Bosch of Philips, lead for European regulation, global regulations and standards at **Philips Healthcare**, stressed that the 2024 deadline can only be relied upon for products where no significant changes to the design or intended purpose are made. This means, she said, that a product has to be "frozen" and cannot change if it is to benefit from the additional time.

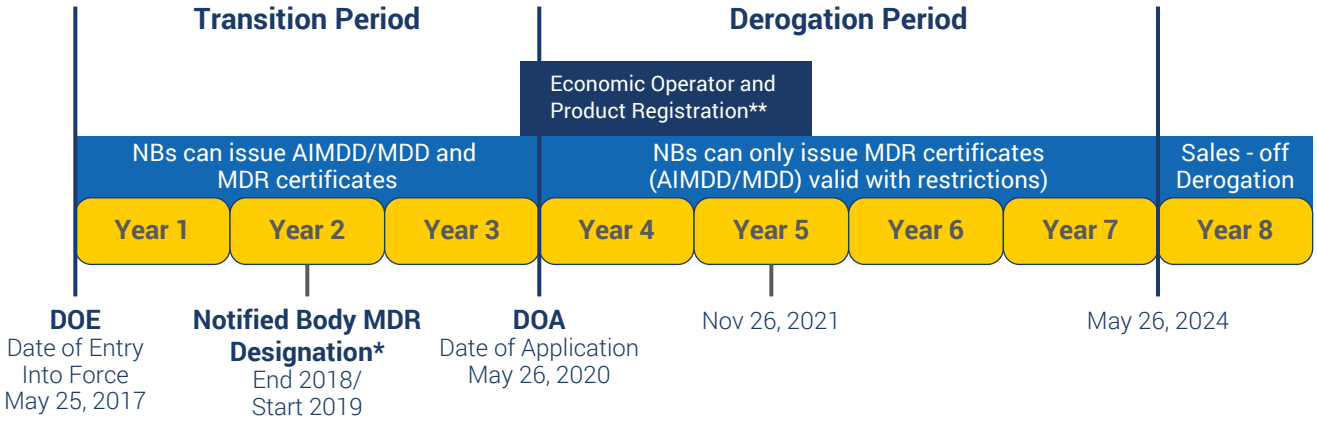
Although it is difficult to know the precise meaning of "significant," there are likely to be few devices where the technology can remain static. The historically accepted average iteration of a device is just three years. In addition, a company's post-market surveillance and risk management obligations compel it to respond by implementing changes where improvements can be made.

Hoekstra-van den Bosch also warned that if a company's notified body subsequently decides not to continue its designation under the MDR, then its clients will not be able to make use of the 2024 "soft deadline" for affected products either.

The Philips executive also noted that the relevant MDR clause only applies to devices with notified body certificates. It does not apply, therefore, to low-risk, class I products.

Nor does it apply to those products that will come under the scope of the MDR for the first time but that were not regulated as devices previously under the Medical Devices Directive (MDD) or the Active Implantable Medical Devices Directive (AIMD) – such as many aesthetic products under the new Annex XVI.

EU MDR Transition Provisions



*Expected
**If EUDAMED is functional at DOA

UDI Labeling

a. Class III +Implants:	1 year after DOA
b. Class IIb/IIa:	3 years after DOA
C. Class I:	5 years after DOA

Direct UDI Labeling of reusable devices 2 years after the relevant date for the respecitve product class.

Joachim Wilke, Medtronic

What is more, she and other speakers advised, any company which finds that it has products that can benefit from the late deadline will still have to comply with the MDR obligations for market surveillance, post-market surveillance, vigilance and registration of economic operators and devices. So whatever position a company finds its products in, there is no reason at all to be complacent or to delay.

Gert Bos, executive director and partner at Qserve consultancy, agreed. "We don't have seven years of transition, we have three years", he stressed.

"My advice to industry is to be MDR-ready three years from now," he said. And for those products that are key to a company's survival, a company has to be "fully ready" and try to convince its notified body to prioritize this part of its portfolio, he said.

He advised delegates to be cautious if they hear notified bodies advising them to wait. "I have heard that some notified bodies are telling companies that having their dossier ready in 2021 is soon enough," Bos said. "But if they are saying that, it is because they will not have time to review it before," he warned summit attendees.

He also advised companies not to be complacent over r renewal of certificates that will run out before 2024. If a firm's certificate is valid until, say 2022, well into the soft transition period, but not valid until the May 26, 2024, soft transition deadline, companies should not rely on getting an extra review from their notified body in time under the medical device directives. By this time, Bos asserted, notified bodies will be too busy with the work they have following their designation under the new MDR.

Even if the notified bodies did have time, they would likely advise a company to do half of the assessment under the MDR at that date, because there simply will not be time for the notified body to carry out full assessments for every company under the MDD (or AIMD) and MDR (similarly, for the IVD Directive and IVDR). Bos emphasized this as the smart approach to a situation where bottlenecks are already likely to develop.

A 2025 DEADLINE?

A timeline presented at the meeting by Joachim Wilke, European director of regulatory affairs and policy at Medtronic GmbH, illustrates year-by-year expectations for companies, and also includes a "year eight" that goes into 2025. (See figure, "EU MDR Transition Provisions," p. 9.)

This is a selling-off period, when products already on the market that are certified under the directives can be made available, typically by a distributor, and put into service by the end user. So, if a device is placed on the market on May 26, 2024, it still can be made available to the end customer and put into service for one additional year, as long as it remains within its shelf life.

NOTIFIED BODY PLANS CRITICAL FOR DECIDING TIMELINES

The other big issue that companies need to be mindful of is that some notified bodies currently assessing products under the MDD may decide to stop operating at some point, deciding not to transition to the MDR. As a result, notified body staff may start leaving to do other jobs. Any company whose notified body suddenly decides to stop operating while it has already made the decision to go through the full four-year soft transition period will face big challenges.

"In theory, another notified body can take care of your medical device directives certificates in the transition. That could happen," Bos said. "But I have not seen it done by any notified body in the recent four or five years, and it seems unlikely because of liability issues."

Additional matters, that companies should consider when deciding whether to wait for the soft transition are what the position will be in face of competitors who already have MDR certificates, Bos said.

Hospitals and other procurers may prefer MDR-compliant devices, and there will be potential repercussions for devices with CE marking when it represents a passport to other markets outside Europe, Bos said, as we do not know how soon countries in South and Latin America, and those in Asia, will insist on MDR-compliant devices. Once the first MDR certificates have been received in one of these countries, local authorities may well start turning devices with older certificates away. In the worst-case scenario, they may not accept old certificates after May 26, 2020.

CONVINCE YOUR MANAGEMENT

All of these potential pitfalls mean it is vital for regulatory experts within companies to explain their rationale for proper timing of compliance with the MDR to management and to all impacted departments.

Some worry that smaller companies will face the biggest challenges in managing to comply with the new stricter and more complex EU requirements. But in some ways, smaller companies may have an advantage, summit speakers agreed. Not only will they have fewer products for which they need to decide future strategies, but their management may be more accessible to reach and potentially influence.

What's Does The MDR Say?

Article 120.3 of the MDR says, from the date the regulation is fully applicable – May 26, 2020 – products may still be placed on the market or put into service as long as their certificates remain valid, they still comply with the legacy directives and there are no significant changes in the design and intended purpose of the product. Also, the notified body must continue to be responsible for appropriate surveillance under the applicable requirements relating to the devices it has certified. In these cases, the MDR requirements apply in place of the directives' requirements for post-market surveillance, market surveillance, vigilance, and registration of economic operators and of devices. *(Also see "EU's New Medical Device Regulation: A Timetable To Kickstart Planning" - Medtech Insight, 9 May, 2017.)*

Published online 06/23/17

MEDTECH SUMMIT:

The Three Biggest Challenges Of The EU MDR

AMANDA MAXWELL amanda.maxwell@informa.com

The three most challenging aspects of the EU Medical Devices Regulation for the medtech sector concern the need for companies to have sufficient clinical evaluation, the timely redesignation of notified bodies and the much-disputed matter of how much time companies will really have to comply with the regulations.

These topics came up again and again June 19 during the annual MedTech Summit, held this year in Amsterdam, The Netherlands.

During this first of a five-day conference covering all aspects of the new Medical Device and IVD Regulations, delegates heard how the text of the regulations is considered "disruptive" because of the extent it forces companies to change their ways of working.

The MDR was published on May 5 and entered into force on May 25. That should provide some regulatory certainty and transparency, but stakeholders are currently searching for answers to many fundamental questions surrounding implementation.

There is not enough official guidance yet available but a significant amount awaited, speakers complained June 19. This includes the delegated and implementing acts (about 14 of which are urgently needed), and the implementation roadmap being developed by the European Commission and the Competent Authorities for Medical Devices group, which was due in early June, but may not be available until shortly before the traditional EU summer break in about a month's time.

A major unknown is how the various interrelated elements of the MDR will synchronize. Experts pointed out at the summit that there are so many structures still needed, including redesignated notified bodies, an updated Eudamed database, and the expert panels to help with evaluating high-risk products, among others. Speakers asked: How can companies prepare to meet the new regulations and plan with any certainty when they do not know when these essential elements will be ready?

It's a complicated moment for those highly engaged in these reforms. It will be even tougher to try and explain the new requirements to management and to other departments within companies, such as sales or quality management, summit panelists noted. But those stakeholders will need to understand why the changes were made, the consequences of the new regulations and the likely costs, timelines and impact on the future availability of current products.

Changing the whole culture of a company is going to be an uphill struggle, summit attendees heard, but everyone will need to be brought on board through education and a consistent message.

A key issue that will need to be communicated how long companies will have to CE-mark their products under the new regulations. The challenge with that is there is still much confusion surrounding the clauses in the regulation that address that issue. At face value, the regulation allows products CE-marked under the current directives with ongoing certificates to remain on the market until May 26, 2024, four years beyond the date the MDR is fully applicable.

But experts emphasized on June 19 that it would be precarious for any company to rely on this route – due to the "small print," they would risk having to prematurely withdraw their products from the market.

Published online 06/20/17

COMPLIANCE CORNER:

US FDA Wants Device Firms To Fully Consider Risks To Consumers, Agency Expert Says

SHAWN M. SCHMITT shawn.schmitt@informa.com

Some device firms are falling down when conducting risk management activities by not fully considering the possible dangers their products pose to consumers and by failing to put their best foot forward when using risk assessment tools, US FDA's national expert on devices says.

"With risk management comes this concept of, which risk are you really trying to minimize? The risk to the producer, or the risk to the consumer?" said Phil Pontikos, who is also an agency investigator. "As a device manufacturer, you are in the business of making money, so there's risk to the producer about doing what you do. No doubt about it. But from the FDA perspective, it's about risk to the consumer, too."

When conducting a facility inspection, FDA investigator "questions are most typically driven from the risk-to-the-consumer perspective in terms of how you applied your risk management principles when you do things like, for example, develop sampling plans, or you identify upper and lower confidence limits," Pontikos said.

Investigators "are also trying to understand whether [risk assessments] are static or dynamic in nature, and whether you react to them as new information is obtained by you," he added. "So, those are areas we see where firms can do better. We don't see firms characterizing risk-to-consumer as well as we would like."

Risk management is required by FDA's Quality System Regulation under Sec. 820.30(g), "Design Validation." Good risk analysis is started during the beginning stages of device design and should continue throughout the life of the product.

"Frequently we see firms not using post-market data to update their risk documents," FDA investigator Ben Dastoli says.

"Risk" is defined as the severity of harm that could come to a patient or user of a device and the probability of that harm actually occurring, either by way of use error, environmental conditions or problems with the device itself.

Although experts agree that it is next to impossible to create a device that is 100% safe, they say firms can reduce recalls and shore up public confidence in their products by putting in place a strong risk program.

Yet there is no consensus – either among regulators or within industry – on what constitutes an acceptable level of risk in a device. Various regulations and standards leave it up to each device company to make that determination for itself, and firms vary in their tolerance of hazards.

"When you develop rating systems for identifying a problem in an FMEA, for example, or a PFMEA, or if you're identifying a category for a complaint, you really want to have your rating systems be definable," Pontikos said at MedCon 2017 in Cincinnati.

FMEA is Failure Modes and Effects Analysis, a tool to help provide information for a firm's risk analysis and risk management plan; a PFMEA is used to review processes. Other risk management tools can include a Hazard Analysis and Critical Control Points (HACCP) analysis or a fault tree analysis.

"'Likely' or 'possible' are ambiguous terms that folks use in FMEAs to denote if something problematic could happen to a device," Pontikos said. "So, when we see that [as investigators inspecting a facility], we quickly try to understand what you mean by 'likely' and 'possible,' and whether you consistently and uniformly can apply that when you're working in your cross-functional teams."

Instead, "try to put 'likely' and 'possible' into terms that are easily understood by the folks doing [risk assessments], and make sure the terms are well defined, and can be consistently and uniformly applied. That's really what we're looking for," he said.

CLICK

For a Compliance Corner column on quality data integrity, go online: http://bit.ly/2tYtkej.

Risk Management: US & Beyond

Although FDA's QSR makes only brief mention of risk analysis, the agency maintains that the overall concept should be applied by companies throughout their manufacturing activities. The agency strongly endorses risk management guidelines outlined in the international standard ISO 14971:2007, "Medical Devices – Application of Risk Management to Medical Devices."

Outside the US, risk management is required by the EU's Medical Devices Directives (and upcoming Medical Devices and IVD Regulations), and ISO 13485, the international quality standard to ensure quality systems compliance with regulators in different countries, including Canada, Japan, Australia and the 28 member states of the European Union.

For guidance on how to perform risk management, ISO 13485:2003 and its new 2016 version refers manufacturers to ISO 14971. *(Also see "It's A Green Light For ISO 13485: Revised Global Quality Systems Standard Finally Published" - Medtech Insight, 26 Feb, 2016.)*

A 'LIVING DOCUMENT'

Meanwhile, FDA investigator Ben Dastoli is reminding manufacturers to keep risk files current by keeping an eye on post-market data.

"Remember, your risk management is a living document that is continuously updated. It's never stagnant," Dastoli said at MedCon. "Frequently we see firms not using post-market data to update their risk documents. Sometimes I wish I could talk to compliance officers across the country to see how many times we keep finding this problem."

Post-market data can include complaints, service records, installation records and other customer-based feedback.

"And, does your firm have a system in place to update and review these documents?" he asked.

For example, "when you're validating your complaints, do you indicate the link to your risk documents to help support your decisions? Have you identified a new failure mode?" Dastoli said. "When I'm inspecting your firm, I'm looking to say, 'Hey, is there a new failure mode? Has the frequency changed? Has the severity changed?'

"So, this is all something you should be doing, and if you make it really easy right in your complaint files and post-market data to show that link, you're probably not going to miss it, either."

Published online 06/20/17

US FDA Works To Finalize 3D Printing Guidance; Industry Asks For More

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

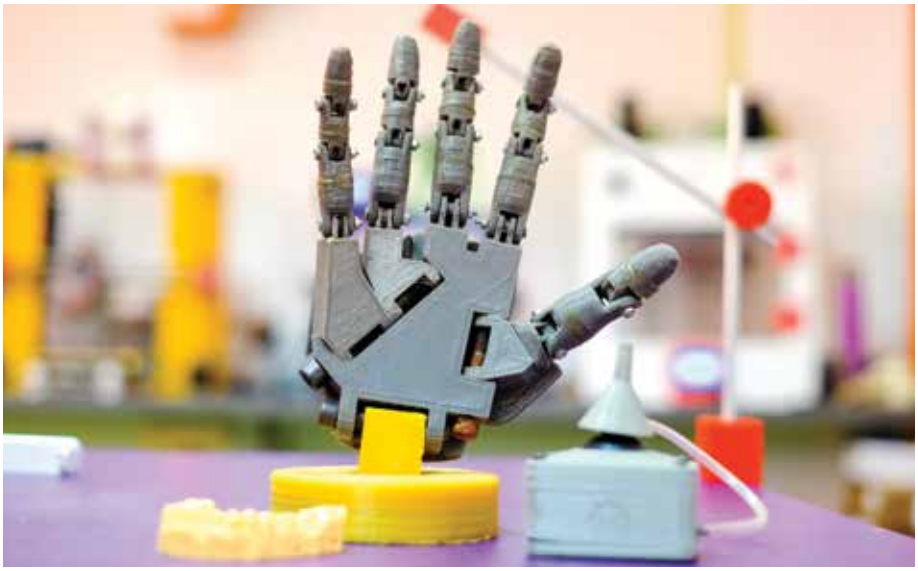
US FDA is hoping to finalize a leap-frog guidance on 3D printing of medical devices this year, but industry groups want the agency put greater detail and attention on the issue of patient-specific devices in a standalone document on that topic.

Speaking to *Medtech Insight* at FDA's Science Forum on May 31, James Coburn, a senior engineer at the device center, emphasized the timeline goal for the guidance, which focuses on "technical considerations for additive manufactured devices." The agency describes additive manufacturing as a broad category that encompasses 3D printing.

The additive manufacturing (AM) guidance is already listed on the agency's B-List of guidances to finalize this year. While Coburn did not provide a more specific timeframe he was optimistic, while acknowledging that progress will depend on available resources.

The draft guidance was issued in May 2016 and specifically is labeled as a leap-frog guidance, one of only a few documents that have been released by the agency in this category, signifying it is the agency's initial thinking on an early-stage, emerging technology of public health significance.

According to FDA, additive manufacturing encompasses a range of techniques that can be used to construct an object by iteratively building two-dimensional layers and joining each layer together. The techniques, which is being applied in a range of industries, allow device manufacturers to rapidly alter designs without the need for retooling and to build complex devices as a single piece. This can simply serve as a cost-effective and more precise manufacturing tool. But, more significantly, it can potentially be used to make patient-matched, made-to-order devices, a growing segment of the orthopedics industry in particular. *(Also see "At AAOS, Makers Of Large Joint Implants Make It Personal" - Medtech Insight, 27 Feb, 2012.)*



Shutterstock: Axel Alvarez

"Patient-matched device considerations are distributed throughout the current draft and, in places, it is unclear whether the considerations being addressed are specific to patient-matched devices or [additive manufacturing] in general," J&J says.

Companies are already applying these tools, and dozens of devices that rely on additive manufacturing have passed through FDA. *(Also see "3-D Printed Implants Hit The Market, Pave The Way For More Personalized Devices" - Medtech Insight, 4 Nov, 2013.)* Most recently, **SI-Bone Inc.** announced June 13 FDA clearance and US commercial launch of *iFuse-3D* Implant, which it says is the first-ever 3D-printed titanium implant for use in the sacroiliac (SI) joint.

But current products are considered early-stage efforts, particularly in the realm of customized implants.

INDUSTRY WANTS PATIENT-MATCHED-FOCUSED GUIDELINE

The public comment period for the draft guidance closed in August. The agency has received 28 comments, including from several trade organizations and device companies. *(Also see "FDA Tackles 3-D Printing Considerations In Draft Guidance" - Medtech Insight, 12 May, 2016.)*

A common request from the device industry, including trade group AdvaMed was for FDA to produce a separate, standalone companion guidance document specifically addressing patient-matched devices, which, commenters point out, can be made using both additive and tra-

ditional manufacturing techniques. But reference to patient-matched products in the additive manufacturing guidance without more detail might lead to confusion, industry stakeholders suggest.

"We request that CDRH clarify in the draft guidance which recommendations apply to patient-matched devices (also referred to as patient-specific, personalized and/or customized) by separating Patient-Matched Products into its own stand-alone guidance that would cross-reference this draft guidance as applicable," AdvaMed wrote.

Device-makers including **Zimmer Biomet Holdings Inc.**, and **Smith & Nephew Inc.** submitted letters affirming support for AdvaMed's statements.

In its own comments, **Johnson & Johnson** argues that while the guidance addresses some of the concerns related to patient-matched devices, there is "significant benefit" to creating a separate guidance on the topic.

"Patient-matched device considerations are distributed throughout the current draft and, in places, it is unclear whether the considerations being addressed are specific to patient-matched devices or AM in general," J&J says. "AM is not the only method for producing patient-matched devices; such devices are on the market today produced by traditional manufacturing methods (for example, computer-controlled milling machines). Traditional (non-additive) manufacturing technology has advanced to the point that it is possible to create affordable, high-quality patient-matched products. However, as this guidance notes, 'AM, is a rapidly growing technology' that can be used to achieve this end while having many advantages."

Another industry group, the 510(k) Coalition, is explicitly asking FDA to take out all mentions of patient-specific manufacturing from the AM guidance, stating it is outside its scope.

"How custom devices rules fit AM procedures is something that should be addressed within custom device rules, not within manufacturing process draft guidances," the industry group said.

The 510(k) Coalition also says language in the guidance stating that patient-matched accessories need to be identical to patient anatomy is incorrect.

"FDA is going to be increasingly pressured to find ways to allow commercial 3D manufacturing to migrate from stand-alone FDA regulated establishments to health-care settings," says attorney Kevin Madagan, Reed Smith.

"This may not be medically required and it is often impossible for something to be 'identical,'" they said. "The key is whether the accessory meets its intended function. As such, the coalition suggests using the term 'sufficiently similar' in place of the word identical."

Companies have previously asked FDA for guidance in the patient-matched device space, specifically focusing on orthopedics, where companies are employing software and imaging capabilities to fashion individually tailored surgical tools. Questions have circulated over the proper regulatory approach to the software used to design patient-matched instruments versus the instruments themselves, among other issues. *(Also see "Ortho Companies Emphasize Software For Patient-Matched Instrumentation Guidance" - Medtech Insight, 6 Apr, 2015.)*

FDA's Coburn affirmed that the agency is planning on releasing a draft guidance on patient-matched instrumentation for orthopedic devices, but would not elaborate on whether a broader guidance on patient-matched devices is under consideration.

POINT OF CARE AND BIOPRINTING

Kevin Madagan, an attorney with Reed Smith, also advocates for a stand-alone guidance for patient-specific manufacturing. He says the AM draft guidance, in its current form, is limited in scope, arguing that there remains a long list of legal and regulatory issues associated with 3D printing that need to be resolved.

"By way of example, we need guidance about point-of-care manufacturing," he told *Medtech Insight*. "FDA is going to be increasingly pressured to find ways to allow commercial 3D manufacturing to migrate from stand-alone FDA regulated establishments to health-care settings."

AdvaMed backs the sentiment and states that, in the interest of public safety, the agency should consider adding language making it explicit that point-of-care establishments that install 3D printers and use them routinely are subject to FDA's oversight, including pre-market review, post-market controls, and adverse-event reporting. The trade group acknowledges there are likely to be exceptions, such as cases where additive manufactured devices are used for underserved populations with unmet needs, where FDA could use its enforcement discretion.

Madagan recommends the agency could take a risk-based approach to point-of-care additive manufactured devices, similar to its approach to mobile health applications. Under such an approach, FDA would use its enforcement discretion to refrain from regulating low-risk devices that are printed at health-care facilities, as long as they meet the agency's criterion.

The AM guidance explicitly states that it does not apply to biological, cellular or tissue-based products manufactured with these techniques, but Madagan and other stakeholders said industry needs a guidance from FDA on bioprinting.

Overall, Madagan says the guidance has been well-received by industry, except for the push for companion guidance documents that cross reference the AM guidance, such as for patient-matched devices and bioprinting.

Coburn refused to comment on whether the agency is looking into potentially developing other guidances related to the AM guidance but did state that the agency is constantly assessing the technology landscape based on interactions with stakeholders at workshops, conferences and scientific meetings.

While FDA is directing all AM questions regarding biologics to their biologics cen-

ter, the 510(k) Coalition says CDRH may still need to be involved with the issue, especially for combination products.

AdvaMed similarly states that there needs to be cross-center collaboration on AM devices, but it says CDRH should take a leadership role in molding FDA's policies.

"We suggest that, in addition to moving forward with this guidance, that CDRH take the lead to work with its counterparts within the agency to facilitate discussions on best practices throughout the agency," said the group. "For instance, this issue may be appropriate to present to the Combination Products Policy Council." *(Also see "US FDA: No Timeframe On Combo Products Council Response To Industry Feedback" - Medtech Insight, 9 May, 2017.)*

"This discussion and leadership by CDRH will be especially helpful, not only to manufacturers, but FDA field compliance officers as the move to a product-type inspection program moves forward," added AdvaMed. ( )

The 510(k) Coalition also asked the agency how it intends to handle scenarios where part of a device relies on AM. The group wants to know if in such a situation the device would fall under the AM guidance or traditional regulatory oversight.

"Within the document, it is regularly mentioned that this applies to AM manufacturing processes, but the coalition believes there is an open question as to whether or not design and post-market fall in to the scope of the draft guidance," the group said.

Coburn says dozens of devices that rely on AM have been cleared or approved for marketing, but the agency doesn't keep track of the exact numbers, and wouldn't divulge how many such devices are currently under FDA review.

As of now, FDA's device-center has yet to release a new draft or final guidance document since the start of the Trump administration in January. It's not clear to what extent that resulted from staff transitions, the absence, until last month, of a permanent FDA commissioner, or specific orders from the White House, including its executive order to remove two regulations for every new one issued.

Published online 06/14/17

US FDA Faces Down Complex Combo Products, Fires Up Oncology Center Of Excellence

BRENDA SANDBURG Brenda.Sandburg@informa.com

Photo credit: Brenda Sandburg

FDA officials chat at the DIA meeting in Chicago

US FDA is struggling to come up with solutions to deal with complex combination products and has not ruled out a potential legislative fix.

Agency officials highlighted the challenges of dealing with these products during a panel discussion at the Drug Information Association's annual meeting in Chicago on June 22.

The law and FDA regulations "never envisioned some of the products that we are starting to see or some of the complexities we are starting to see, such as a biologic administered with a device where the device that's used to administer that biologic could actually physically transform that biologic so that it has a different activity," said Center for Biologics Evaluation and Research (CBER) Director Peter Marks.

"How you actually start to work with these things, whether you take cross labeling pathways or have some other type of combination pathway that you follow, gets to be complicated," he said.

Marks also pointed to the complications manufacturers face as device makers want to use drugs that don't belong to them and a drug or biologic manufacturer must label their product for use with a device. He noted that the agency's Combination Products Policy Council is trying to work toward a solution, adding that he does not know if a proposed legislative fix will be needed.

FDA formed the Combination Products Policy Council in April 2016 to have a senior-level group deal with cross-cutting combination policy issues. In August, the agency also initiated an intercenter consult request pilot program, which includes deadlines for an office to complete and issue a consult on a combination product. *(Also see "Companies Want New US FDA Council To Help Resolve Inter-Agency Combo Product Disputes" - Medtech Insigh, 3 May, 2017.)*

The 21st Century Cures Act also included provisions on combination products. The statute established mandatory meetings between FDA and combination product developers and clarified the process for resolving disputes between FDA product centers.

Douglas Throckmorton, deputy director of regulatory programs in the Center for Drug Evaluation and Research (CDER), said there are both cultural and legal complexities around this issue. He noted that, historically, centers could address f combination products like metered dose inhalers on their own.

"Now that the stakes have become more complicated we don't have that luxury. We've got to make sure that the standards CDRH [Center for Devices and Radiological Health] has for the device are applied appropriately for the combi-

nation product. So, a new, different kind of coordination needs to happen," he said.

WILL CENTERS BE RESTRUCTURED?

Panelists also discussed the activities of the Oncology Center of Excellence (OCE), which was established in January. It was first announced prior to the Cures Act, but the OCE aligns with a provision in the new statute to create cross-center groupings to coordinate handling of major diseases.

While, OCE on its own satisfies the minimum mandate of the Cures act for inter-center institutes, signs suggest the agency is moving towards expanding its approach to other diseases. For instance, in a recent blog post from FDA Commissioner Scott Gottlieb that primarily focused in digital health oversight, the agency head signaled plans for broader cross-center efforts.

"FDA will soon be putting forward a broad initiative that is focused on fostering new innovation across our medical product centers," Gottlieb wrote June 15. "I will have more to say on many elements of this initiative soon."

At DIA, Paul Kluetz, OCE's acting associate director of patient outcomes, explained that the first center of excellence targeted oncology, in part, because the agency was already addressing the issues it is supposed to tackle. He noted that *in vitro* diagnostic-drug combinations are very common and there is now potential for combinations of IVDs, therapeutic devices and a drug or biologic product.

"My guess would be for the next OCE, you want to look at a therapeutic area that already has a lot of combination product activity," and is producing exciting science, he said.

Kluetz rattled off several focus areas for the Oncology Center of Excellence. In the area of real-world data, he said the center is investigating how to develop "synthetic" clinical-trial control arms to help with targeted populations that are difficult to randomize because they are so small. "We would like to understand how to create endpoints out of real-world data so that we can take real-world data and understand it enough to make it into real-world evidence that we can use for regulatory decision-making," he said.

Photo credit: Brenda Sandburg

FDA regulations "never envisioned some of the products that we are starting to see," says Peter Marks, director, Center for Biologics Evaluation and Research.

Photo credit: Brenda Sandburg

"A new, different kind of coordination needs to happen," says Douglas Throckmorton, deputy director for regulatory programs, Center for Drug Evaluation and Research.

OCE is also looking at pediatric drug development and the development of pediatric clinical outcome assessment tools. Kleutz noted that children sometimes cannot provide patient-reported outcomes so other ways to get their perspective must be identified. The center is also seeking to aggregate and standardize FDA's clinical trial data sets and to set up a patient-focused development program.

DIA panel moderator John Weiner, associate director for policy in the Office of Combination Products, questioned if there should be a paradigm shift, given the more complicated products coming into the agency. "Is the Center for Excellence enough? Are the [product] centers here for the long term?" he asked.

CBER's Marks replied that they would have to see how things evolve over time. He said that while medical products are getting more complicated, at least for now, "we can say there might be a need for buckets." He noted that CDRH has experts in engineering issues that impact most devices, while CDER has expertise in small molecule and protein drugs and CBER has expertise in gene and cell-based therapies, manufacturing challenges, and vaccines.

And Throckmorton pointed out that the new complex products represent a small portion of the agency's workload. "If you pull back to a million feet, 90 plus percent of business centers do does not touch this world," he said.

PROMOTING INDUSTRY COLLABORATION

A member of the audience noted that drug and device manufacturers that work together on a product are not always a good match and suggested that FDA give companies advice on who to partner with.

Weiner noted that this issue comes up quite a bit and asked the panelists for their views. Throckmorton said that CDER and CDRH have at times worked together to get trials conducted in specific areas, but that it would be much harder to work together on product development. For example, he cited his experience in the opioid space, where companies have been required to work together to develop Risk Evaluation and Mitigation Strategies.

"I would be telling a fib if I told you that convincing them to work together has been without its challenges," Throckmorton said.

Kluetz noted that some of his group's biggest successes have been getting competitors to come to consensus on a topic at a public workshop. He referred to an Oncologic Drugs Advisory Committee meeting on development of products to treat patients with non-metastatic castration-resistant prostate cancer. He said the meeting, which was held in 2011, led to the establishment of a special protocol assessment and critical drug development processes. Kluetz said the agency is probably going to hold a workshop on real-world data.

Tamy Kim, associate director for regulatory affairs, Office of Hematology & Oncology Products in the Office of New Drugs, agreed that workshops have been beneficial in getting industry to collaborate. She noted that the agency held a safety reporting workshop in conjunction with the American Society of Clinical Oncology's recent annual meeting to increase awareness of how industry should be using safety reports.

Kim said one company did an outstanding job and shared its best practices with other companies. She said the company was willing to do so because it realized the submission of safety reports to FDA was also affecting institutional review boards.

A representative from **Janssen Pharmaceutical Cos.** asked what FDA is doing in response to President Trump's executive order requiring that two regulations be eliminated for every new one issued. She noted that the White House has asked trade groups for information on this issue and they have been trying to come up with lists of guidances or other regulations that could either be eliminated or modified.

The Office of Management and Budget issued a memo that the order only applies to what are defined as significant regulations, meaning those that would have an annual adverse effect on the economy of $100m or more. *(Also see "US FDA Likely Not 'Significant', Could Be Mostly Spared From Trump's Regulation-Slashing Order" - Medtech Insigh, 10 Feb, 2017.)*

Marks said the agency must interpret what a "significant effect" on industry means. "So, it's been a process of teasing this out," he said. He added that any guidance that need to get out because of public health concerns will get out.

Published online 06/26/17

CMS Proposes High Payment Score For Use Of Imaging Appropriate-Use Criteria

SUE DARCEY sue.darcey@informa.com

Radiologists and imaging firms touted a Medicare proposal to highly value health-care provider use of appropriate-use criteria for imaging in performance-based payment calculations.

Under a CMS rule proposed June 20, clinicians that consult appropriate-use criteria (AUC) through a clinical decision support mechanism to order advanced imaging for their patients could count that choice as a "high-weighted improvement activity" to enhance reimbursement through the Medicare Merit-based Incentive Payment System (MIPS).

The MIPS pathway was developed under the Medicare Access and CHIP Reauthorization Act of 2015 (MACRA) to allow providers to earn a performance-based payment adjustment to the usual Medicare reimbursement. Based on their performance in 2017, physicians, physician assistants, nurse practitioners and other providers can earn a positive, neutral or negative adjustment of up to 4% starting in calendar year 2019.

The June 20 proposal would update details on quality payment programs such as MIPS for 2018 and future years, CMS says. One of these specifications to help providers win bonuses, under the subcategory of "patient safety and practice assessment," would be a new activity – employment of AUC for advanced imaging orders. *(Also see "CMS Administrator Seema Verma: What Industry Can Expect" - Medtech Insight, 20 Mar, 2017.)* The agency scores its improvement activities as high, medium, or low, and it is proposing to make the AUC advanced imaging consultation using clinical decision support a high-scored activity.

CMS says that "this activity is for clinicians that are early adopters of the Medicare AUC program (e.g., 2018 performance year) and for clinicians that begin the program in future years." The agency adds that qualified clinical-decision support mechanisms will provide a report that the ordering clinician can use to assess her patterns of image-ordering, and improve upon those patterns, "to ensure that patients are receiving the most appropriate imaging for their individual condition."

"The proposal underscores the importance of the AUC's role in clinical decision support to ensure patients receive the appropriate imaging service at the appropriate time," said Tim Trysla, executive director of the Access to Medical Imaging Coalition. AMIC is made up of physicians, medical provider groups, patient groups, and representatives of advanced imaging equipment makers, including the Medical Imaging Technology Alliance (MITA).

Comments on the proposed rule are due Aug. 21, and should bear docket number CMS-5522-P.

Published online 06/23/17

Zimmer: Surprised By Biomet Quality Problems, But Responded Before FDA Arrived

ELIZABETH ORR elizabeth.orr@informa.com

Zimmer Biomet Holdings Inc. acknowledged major compliance weaknesses in pre-merger Biomet's quality control processes that Zimmer only learned about after its 2015 $13bn acquisition of the firm. But the orthopedic giant said it was well into fixing the issues before US FDA investigators came knocking in the fall of 2016.

Those details came out in a 282-page response letter from Zimmer Biomet to an unfavorable, late-2016 agency inspection. FDA inspected the Warsaw facility from September to November 2016, and issued a Form-483 with 14 observations that attracted investor attention. *(Also see "Zimmer Biomet Inspection Finds Extensive GMP Woes" - Medtech Insight, 15 Dec, 2016.)* Zimmer's response letter was dated Dec. 21, 2016, and was recently posted online by FDA.

In its letter, Zimmer Biomet said it had already started audits and an overhaul of quality systems at Biomet's Warsaw, Ind., facility before FDA initiated the inspection.

The company said it had been largely unaware of "major compliance-related issues" at the orthopedics manufacturing plant before the 2015 Zimmer Biomet merger. *(Also see " BUSINESS BITES: Zimmer becomes Zimmer Biomet; Amendia grows spine portfolio; Mindray MBO gathers pace" - Medtech Insight, 25 Jun, 2015.)* Pre-merger information had suggested to Zimmer that the plant's "quality system was in substantial compliance."

"Once the merger was completed, the new Zimmer Biomet corporate management team conducted audits, learned of issues through the audits, and promptly initiated corrective actions," the letter states. "Improvements were well underway when FDA started the inspection and will continue with strong support, oversight and resources." Specifically, these corrective actions focused on design controls, sterile packaging complaint handling, nonconforming material, and corrective and preventive actions.

In July 2016, Zimmer Biomet launched a remediation program that targeted seven observations and six discussion points that would later be listed in the FDA-483. But the firm's program was just getting started at the time of the agency inspection, the company said. Further, the company was in the first year of a global quality initiative launched after the merger had been finalized.

Zimmer Biomet had performed three audits of the Warsaw facility in 2016, focusing on the complaints process, design control, and general quality systems, the letter states. In total, these audits identified four critical observations; 36 major observations; and seven minor observations. The company is also developing a plan for a corporate audit of all Zimmer Biomet plants that will focus on issues identified by the FDA inspection.

Further, the company replaced five managers as part of the efforts to address the "quality culture" at the facility, including the senior VP of global operations, as well as four quality system and compliance directors responsible for the Warsaw plant's operations. Zimmer Biomet also changed the reporting structure of its Warsaw Operations Group, though its response letter redacts details of the new system.

In addition, the company placed a hold on all final products from the Warsaw plant for a month during the inspection. The products were released only after product safety had been established, Zimmer states.

The heavily redacted letter further explains steps Zimmer Biomet is taking to improve its performance in areas such as process validation, environmental control procedures and design control.

Some observers speculated the inspection would lead to a warning letter, but none has yet been publicly issued. Zimmer Biomet acknowledged the FDA-483 in a December 2016 filing with the US Securities & Exchange Commission.

Published online 06/26/17

Medtronic Enters New Outcomes-Based Insulin Pump Deal With Aetna

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

In a show of the growing emphasis on value-based care, **Medtronic PLC** has entered into an agreement for its products to be reimbursed by **Aetna Inc.** based on how well patients do on their self-adjusting insulin pump systems. The device-maker says patients on their pumps manage their disease better, which reduces cost to the insurer. Ultimately, Medtronic wants to expand incentives for patients currently treated with daily insulin injections to adopt the pump systems.

"The agreement will measure health outcomes for those patients that choose to transition to pump therapy using a Medtronic insulin pump featuring *SmartGuard* Technology, including the new *MiniMed 670G* system – the first and only system that constantly self-adjusts to keep patients' blood sugar levels in range based on their personalized needs," Medtronic said.

The deal is the first phase of a plan to move patients who take daily insulin injections to Medtronic insulin pumps, according

to company spokeswoman Janet Kim. Under the agreement, Kim tells *Medtech Insight*, Medtronic intends to use A1C measures, which reflect average blood glucose levels, to determine whether patients using the Medtronic pumps are maintained within an acceptable blood-sugar range. If patients fall outside of that range, the company will pay Aetna a rebate.

Kim would not provide details phase two of the agreement, but she says the ultimate goal is to expanded number of patients using Medtronics' products.

"We are committed to expanding this agreement with Aetna as we work together to expand the reach of this to their broader member population," Kim said.

Medtronic entered into a similar four-year deal with **UnitedHealthCare** a year ago, and if all goes well, the company is hoping to work with other insurance providers as well.

The deals with insurers parallel other types of partnerships and acquisitions intended by the company to position insulin pumps and continuous glucose monitor systems as more routine tools for type 2 diabetes, which represents a much larger population than type 1 diabetes, for which these systems are mostly used. *(Also see "Medtronic Builds Toward Integrated Care With A String Of Diabetes Deals" - Medtech Insight, 23 Apr, 2015.)*

The deal with Aetna covers both type 1 and type 2 diabetes. While MiniMed 670G is only indicated for type 1 diabetes, the *MiniMed 630G* insulin pump has a broader indication.

"This agreement reinforces our shift toward value-based health care. We know technology alone isn't enough and ultimately, improved outcomes are what matter," said Hooman Hakami, president of the Diabetes Group at Medtronic. "We have the only insulin delivery systems in the world that take action based on sensor values. The growing body of clinical evidence demonstrating the benefits of our proprietary SmartGuard Technology is compelling and we are pleased to work with Aetna to drive awareness and align incentives around the technologies that make the biggest difference for patients and for the health system."

There have been some references to MiniMed 670G system as the first artificial pancreas, but Kim says the Medtronic prefers to call it a hybrid closed-loop system. She says the Smartguard algorithm used in the systems are intended to prevent hypoglycemia. *(Also see "Advent Of Artificial Pancreas Tech To Galvanize Fast-Growing Diabetes Market" - Medtech Insight, 26 Apr, 2017.)*

When patients have to manually measure their blood glucose levels and inject themselves with insulin throughout the day, there is a higher risk for user error, which can lead to over- or under-dosing and severe health consequences. Kim says that Medtronic's trial data and real-world evidence from patients using their MiniMed 670G system demonstrate much better ability to control glucose levels.

"There is a broader trend where Medtronic is moving towards a value-based approach to managing patients with diabetes and overall Medtronic PLC is very committed to value-based care," Kim said. " Our confidence in the outcomes that we've seen delivered by our systems really signaled to us that these kinds of deals make sense because of the strength of our clinical data."

Published online 06/26/17

Philips Completes M&A Hat Trick With Neurodiagnostic Buy

TINA TAN tina.tan@informa.com

Philips has inked a deal to acquire Electrical Geodesics, Inc. (EGI), a US firm specializing in noninvasive technology for monitoring and interpreting brain activity.

The deal marks Philips' third acquisition so far this year. In March, the Dutch group acquired Australia Pharmacy Sleep Services, a sleep testing services provider, and last month, it acquired RespirTech, a US firm that markets airway clearance therapy vests.

The deal marks Philips' third acquisition so far this year, also including Australia Sleep Services and RespirTech.

In 2016, EGI generated $14.3m in revenue through sales of its electroencephalogram (EEG) hardware, software and acquisition sensors. The products feature the firm's proprietary dense array EEG technology, which gathers brain activity data from significantly more electrodes than conventional EEG products. This, says Philips, allows for significantly higher quality and more precise levels of information to be acquired.

Eugene, Oregon-based EGI's products will sit alongside Philips' existing portfolio of MRI and PET-CT imaging technologies and advanced informatics platforms for neurological applications. Philips says the combined portfolios will offer more comprehensive insight into a patient's neurological health. The suite could help support more personalized treatments for disorders such as stroke, epilepsy, traumatic brain injury and Parkinson's disease.

EGI is listed on the UK AIM market. Under the terms of the acquisition agreement, EGI stockholders will receive, in cash, 105.4 pence per EGI share, which constitutes a 36% premium to EGI's closing price on June 21, for a total equity value of £29m ($36.7m). The transaction is expected to close in the third quarter of 2017.

Published online 06/22/17

Bonesupport Cements Funding With SEK 500m IPO

CATHERINE LONGWORTH catherine.longworth@informa.com

Swedish orthobiologics company, Bonesupport, has completed its IPO on the Nasdaq Stockholm and raised SEK500m ($57m) in total. The firm issues over 17.2 million new shares in the offering, at a final price of SEK29 per share, the midpoint of the price range it had set when it first announced its intention to float earlier this month. *(Also see "Bonesupport Primed For Nasdaq Stockholm Flotation" - Medtech Insight, 13 Jun, 2017.)*.

Bonesupport's ticker symbol is BONEX.

The company has also issued an over-allotment option of 2,586,206 new shares which will bring the total number of shares in Bonesupport to 48,838,806 if the option is fully utilized. The total number of shares after the offering will amount to 46,252,600 shares if the over-allotment option is not utilized.

Bonesupport's largest shareholders will include Stockholm-based venture capital firm HealthCap, with a 13.5% share, Stiftelsen Industrifonden (9.8 %), Lundbeckfond Invest A/S (9.8%), Swedbank Robur Fonder AB (9.2%), Tredje AP-fonden (8.3%), Carl Westin (5.5%) and Tellacq AB (5.3%).

The funds will be used to grow sales of Bonesupport's drug-eluting bone scaffolds based on its *Cerament* technology platform. The injectable bioceramic bone scaffold acts as a substitute by providing targeted drug elution directly into the bone void and remodelling the host bone in six to twelve months. The company is looking at a 2019/2020 timeframe for a US launch of Cerament G – its gentamicin-eluting drug filler.

Bonesupport's is aiming to achieve revenue exceeding SEK500m in the financial year 2020, with a gross margin exceeding 85 percent and a positive operating profit.

Published online 06/22/17

RepliCel Poised To Partner Up For Precision-Control Dermal Injector

TINA TAN tina.tan@informa.com

Having already bagged a partnership with **Shiseido Co.**, the world's fourth largest cosmetics company, for its clinical-stage cell-based therapy for pattern baldness, RepliCel is now looking to forge more alliances with industry players in the aesthetics and dermatology arena for its novel dermal injector it has developed.

RepliCel CEO Lee Buckler told *Medtech Insight* that the company will have the first functioning prototype of *RCI-02*, its dermal injector , in July, ready to be tested in preparation for a CE mark submission in July. "We anticipate submitting our CE mark application in the first half of 2018," he said.

The device was originally designed to support the injection of the firm's cell-based therapies for pattern baldness, *RCH-01* (which this is the therapy that RepliCel has licensed Asian commercial rights to Shiseido), and for ageing or sun-damaged skin, *RCS-01*.

"We were convinced there were a couple of attributes [in an injector] which are important for delivering these cell therapies to the skin and which didn't exist in current dermal injectors," said Buckler. "One attribute we wanted was to have absolute control over the depth and dose of delivery. Cells are very sensitive injectable products and they can be killed by unnecessary sheer force – for example, if you push a plunger too hard or you push too many cells into a small area; any number of things can do damage to the cells.

"We wanted to delegate the skill of the delivery – the protocol of the delivery – to electronic precision," he continued. The injector device – which has a small electronic docking station and a touch screen display (see Figure 1) – can be programmed to deliver injections to a specific depth and volume. Additionally, the injector head is designed to take 1-16 needles and be configured specifically to the treatment area.

Another feature of RCI-02 is a patented cooling element at the injector head, which "reduces significantly, if not eliminates, the need for local anesthetic," the firm says. "Many of today's aesthetic procedures are preceded by a number of local anesthetic into the area to be treated. With local anesthetic, not only does it have cost and time implications, but there is also the pain associated with the needle," said Buckler. The element embedded into RCI-02 cools and numbs the skin to remove sensation, so the needle can deliver the dose without pain.

FIGURE 1

Replicel's *RCI-02* injector

The needles, together with the prefilled cartridge of injectable substance that is loaded into the injector device, make up the disposable part of the RCI-02. (See Figure 2.)

RepliCel believes RCI-02's injector features will help to further broaden out what is already a lucrative market. "There are around

$3bn worth of products being injected into people's skin for aesthetic purposes each year; about $2bn of that are hyaluronic acid-based dermal fillers and all of those are currently being injected by a device driven by manual pressure asserted on the plunger," Buckler told *Medtech Insight*.

RCI-02 not only brings "absolute precision and control, and therefore reproducibility to injections," it also means that "for the first time, you can do very even and broad dispersion of the [injectable substance], as well as shallow controlled delivery," he added.

The injector is ideal for delivering dermal fillers to treat fine, shallow wrinkles, which, the CEO said, remains an untapped opportunity. "Right now, the dermal filler market is largely reserved for deeper wrinkles. For the kind of fine wrinkles that appear in areas like the expanse of cheek, the décolleté, the tops of hands, you cannot adequately inject dermal filler [using current injector technologies]. They are able to put a lot of filler under the skin to stretch it, but they cannot deliver injectables to fine wrinkles and this is what our injector promises to do. RCI-02 would be able to deliver already-approved dermal filler products in a novel, non-surgical manner that will help to address fine wrinkles."

While RepliCel's cell therapies, RCH-01, and RCS-01, are currently in clinical trials and some way off to being approved for commercialization (*See box, "Hair, Skin, Tendon: Cell Replication Therapies"*), the company still intends to use RCI-02 on patients taking part in the clinical studies. In the meantime, Buckler said that the firm is already in discussion with "a number of big multinationals that are well-positioned in the aesthetics market. "They have been very interested in the technology, anticipating the delivery of the functioning prototype to get the [licensing] deal done."

The patented technologies behind RCI-02 will ultimately lead to various iterations of the device that can be used for different purposes, said Buckler. These patents include those around micro-aspiration, the delivery of drugs and enzymes, among other things. And aside from delivering substances intradermally, RCI-02 could potentially be used to deliver injectables subcutaneously and intramuscularly.

FIGURE 2

Prefilled cartridge of injectable loaded into the RCI-02 injector

For now, though, RepliCel's focus will be firmly on the dermal filler market and solidifying a partnership that will move the company into its next phase of growth. "We expect the injector to be market-ready next year, to have a partnership secured on the device also at some point next year and then to launch the product in concert with our partner – that will transition us into a revenue-generating company."

Published online 06/23/17

Calcivis Ready To Sink Teeth Into UK Market With Imaging Device

CATHERINE LONGWORTH catherine.longworth@informa.com

Dental device developer **Calcivis** is gearing up for a full commercial launch in the UK for its preventive tooth imaging system. The company is conducting beta tests for the *Caries Activity Imaging* System in 20 UK dental practices, with a planned launch in the second half of 2017.

Calcivis' handheld imaging device combines an intraoral camera and an applicator that delivers a small amount of photo protein solution which detects active lesions on the tooth surface that are likely to progress to cavities. The photo protein solution uses as a marker of early demineralization free calcium ions, such as those found on actively demineralizing tooth surfaces. A very short, low-level flash of light (luminescence) is created which is undetectable by the naked eye and captured by the intraoral camera.

Calcivis will cut its teeth in the UK market ahead of a planned 2019 launch in the US. "Our business plan is all about proving [commercial] success by selling the product in the way we think we can, delivering the type of revenues we think we can make and getting access to the US market," Adam Christie, CEO of Calcivis told *Medtech Insight*.

"If you want to practice dentistry preventatively you need to be able to work out where you have an active disease on the tooth surface before you actually get to the cavitation stage," said Christie. "There was a frustration in the cariology community that there were no tools out there to help dentists predict which tooth surfaces were going to progress to cavitation so this device acts as a solution."

The handheld imaging device combines an intraoral camera and an applicator.

Christie said the device's ability to identify active lesions was attracting attention from across the dental community in the UK, who believe it can provide explanation and justification for preventive management treatments. "One of our working assumptions is that at launch this would be sold to the private/fee-for-service sector, but the feedback we've got from UK dentists is that they are very interested

in the prospect of the NHS using this because of its potential to reduce long-term costs of treatment."

Calcivis aims to prove the value of the system in home territories before targeting the massive US market. In June 2017, it completed patient recruitment of its premarket approval clinical study to assess the safety, performance and usefulness of the device. The study data will be used to support the planned PMA for the imaging system in the second half of 2017 with the first data readout from the study expected next month.

"The regulatory status of this is quite tricky as it's a biologic [combined with] a medical device so we've had to agree a pathway with the FDA," said Christie. The FDA directed Calcivis down the PMA pathway and is treating it as a combination product of "device and non-therapeutic biologic." The device has already been CE marked as Class IIa medical device. "We've made a number of pre-submissions to get the FDA to agree to the clinical study design and the quality standards for the protein so we hope that when we submit our PMA later this year it will go through relatively cleanly so we can launch the product in 2019 in the US."

Calcivis said it is looking to raise "significant funds" in the next six months to support commercialization of the device. To date, Calcivis has raised £8m in equity and grant funding.

Published online 06/23/17

Sophia Genetics' AI Brings In More Standardization To Liquid Biopsies

CATHERINE LONGWORTH catherine.longworth@informa.com

Shutterstock/Sashkin

Sophia Genetics has developed a new artificial intelligence clinical application for clinicians to use when analyzing liquid biopsy results. The new application utilizes the AI analytical platform *SOPHiA* to help clinicians diagnose cancer early by offering a standardized approach to DNA analysis in liquid biopsy testing; this approach was built on data mined from the network of hospitals already using Sophia Genetics' AI technology for genomic data analysis.

SOPHiA analyzes circulating tumor DNA (ctDNA), contained in patients' liquid samples such as blood, urine, and cerebral spinal fluid and is currently used by 305 hospitals in over 50 countries. The system continuously learns from thousands of patients' genomic profiles and clinicians' knowledge to improve patients diagnoses and treatments.

"Once you can build a network of hospitals that are sharing knowledge, you can leverage machine learning techniques and improve the outcome of analytics. So this brings us today to the huge potential SOPHiA represents for liquid biopsy," Jurgi Camblong, CEO and co-founder of Sophia Genetics told *Medtech Insight*.

From a blood test, clinicians can use SOPHiA to monitor the progression of a tumor and identify the best treatment option. Patient blood samples are first processed using a DNA sequencer and the data yielded from the genomic sequencing is then entered into the company's online analytical platform *SOPHiA DDM* which uses AI algorithms to identify mutations in the patient's genome. The results are then logged in the company's OncoPortal, an interface dedicated to solid tumors and haematological malignancies, which flags associations between human gene alterations, disease causality, progression, drug efficacy, and clinical trials to help provide personalized care to patients.

The system will present clinicians with a faster, less invasive and cost-effective alternative way to regularly check the status of cancer patients which is not available today with tumor biopsies. "The Human Genome Project paved the way for data driven medicine where for the first time we are able to leverage digital results for better diagnosing and treating patients," said Camblong. "For many years we've been focusing, within health care, on eliminating infectious disorders and this was achieved by antibiotics and now we move to an era where we have to better manage chronic disorders and cancer, which are both disorders of DNA."

Camblong said the technology is paving the way for the "democratization," of cancer detection and will improve both the accuracy of diagnoses and the care that patients receive. "Liquid biopsy is a promise of better monitoring of the efficiency of cancer treatment, as well as – eventually – the hope of screening for cancer regularly," he said. "This is where the magic of SOPHiA happens, the technology enables clinicians to perform analysis of solid tumors and haematological malignancies at various time points to detect tumor progression and monitor treatments' effectiveness."

The first clinical user of the application, Prof. Léa Payen-Gay, co-investigator of the CIRCAN ("CIRculating CANcer") program at the Hospices Civils de Lyon Laboratory in Lyon, France, said that SOPHiA helped save "precious time and resources" and served as an "excellent benchmark" for the laboratory as it detects and validates a more comprehensive list of variants.

Camblong said: "We launched [the technology] in 2014 and since then we have been growing 300% year on year and so the number of patients we are analyzing is increasing rapidly. We have new hospitals adopting our technology all the time and these hospitals trust us so we are seeing the volume of analysis they do increase year on year and we expect many more to follow."

Published online 06/26/17

Medtech Insight
Pharma intelligence | informa

advertise with us and take your business to the next level.

you won't believe the transformation

Contact our sales executive to learn about our various advertising opportunities available to you!

Christopher Keeling
+44 203 377 3183
christopher.keeling@informa.com
Customer Care: +1 888-670-8900 (USA)

medtech.pharmamedtechbi.com

Pharma intelligence

informa

Intelligence with a Global Perspective

The Premier Resource In The Life Sciences Industry

- Biomedtracker
- Datamonitor Healthcare
- In Vivo
- Meddevicetracker
- Medtrack
- Medtech Insight
- Pink Sheet
- Pharmaprojects
- RxScorecard
- Scrip
- Sitetrove
- Trialtrove

Pharmaintelligence.informa.com