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Digital Health – The Next Gold Rush Of Opportunities, Says Kaiser Permanente Ventures

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Digital health venture investing reached an all-time high in 2015. According to CB Insights, the convergent space reached a deal volume of 891 venture transactions during the year totaling nearly $5.8bn. Already in 2016, investor tone has noticeably softened based on sentiment at large gatherings like HIMSS 2016 and JP Morgan. Despite the weaker attitudes, Startup Health, a New York-based accelerator, summarized Q1 2016 investing activity at an all-time high.

Matt Gardner, founder and CEO of the California Technology Council, spoke to Jordan Kramer of Kaiser Permanente Ventures, the venture arm of health giant Kaiser Permanente, to find out what is driving digital health investment, the opportunities and challenges as the sector grows and the healthcare provider's approach to investing in this sector.

Why has investment in digital health grown so dramatically in the last five years?

Jordan Kramer: I think there are several reasons why there has been great enthusiasm for digital health. What makes digital health exciting is the promise of delivering greater value and patient satisfaction while reducing unnecessary costs. Kaiser Permanente is very excited about meeting our members where they are, whether it is care delivered in the traditional setting, remotely or in the member's home. The recent ubiquity of smart phones has enabled a proliferation of apps that have the promise to be able to reduce unnecessary costs and better manage patients. Essentially, you're filling in the blanks between episodic meetings with your physician. Instead of having snapshots of a patient's health, the idea is to get a much broader picture.

The second reason [for the growth in digital health] is a shift away from more traditional medical device and diagnostics investing. The third reason digital health or healthcare IT in general has become a hot area is because we have new entrants outside of the traditional healthcare venture capital investors moving from IT investing, looking at healthcare IT as the next gold rush of opportunities.

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Top Johnson & Johnson executives sat down with *Medtech Insight* at AdvaMed 2016 to talk about the company's new Center for Device Innovation in Texas, the company's strategic goals in the US and globally, and why they think the US leads in medical device innovation.

Earnings season descends
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Medical device and IVD industry leaders including Johnson & Johnson, Roche, Abbott, St. Jude and more have released their latest quarterly earnings season. Find out what how they've done and their predictions for the full year.

Medtech in politics
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J&J Pledges To Stop Animal Use In Sales Training

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Following protests from an animal rights group, **Johnson & Johnson** has promised to stop using live animals in device training exercises.

The controversy came to light after the People for the Ethical Treatment of Animals (PETA) released an action alert urging the group's supporters to contact Johnson & Johnson to protest a planned Oct. 27 demonstration in which pigs would have been killed following the demonstration of an unidentified surgical device manufactured by J&J subsidiary **Ethicon Inc.**

But J&J spokesperson Samantha Lucas said on Oct. 20 that the company has now discontinued live animal use in sales training throughout the North America region, and is working to discontinue live animal use in sales training globally by Dec. 31. And the company is working to find alternatives to animal testing wherever possible, Lucas said.

"At Ethicon and **Ethicon Endo-Surgery Inc.**, we have implemented new computer simulations that enhance the training of health-care professionals," she stated. "As a result, we have significantly reduced live animal use as we deliver on the Johnson & Johnson commitment to explore alternative testing methods and reduce the use of animals."

"PETA welcomes Johnson & Johnson to the modern scientific era," said Kathy Guillermo, PETA senior VP of laboratory investigations. "Pigs are wonderful, sensitive beings, not training tools, and there are far better ways for sales reps to learn how medical devices work in human patients."

PETA has been trying to get J&J to stop using animals in medical device sales rep training since 2009, the group says.

"As far back as 2009, a J&J marketing intern publicly reported on her LinkedIn profile that she cut out a live pig's spleen and uterus and cut into a pig's rectum during a sales training program," explained Shalin Gala, a senior laboratory methods specialist in PETA's laboratory investigations department.

> "In some rare cases, a surgical demonstration might need a live animal so surgeons can see the blood flow and tissue reactions, but for sales staff there's no need," says Richard Bianco, a University of Minnesota surgical professor.

PETA had previously worked with **Covidien Ltd.** to help that company stop using pigs in training, so PETA put J&J staff in touch with Covidien employees. J&J confirmed to PETA that it was discussing the subject internally, Gala said.

Other PETA efforts to encourage J&J to stop using animals included protests, private negotiations with the company and introducing a shareholder resolution in 2012 urging the company to switch to non-animal methods used by competitors.

Johnson & Johnson was out of step with its industry peers in using live animals, some industry observers say. Other manufacturers have moved on to high-tech substitutes, such as advanced human-patient simulators, "living" human-cadaver models and synthetic soft-tissue models.

Most device-makers now use simulations or models in place of live animals in training demonstrations, said Richard Bianco, an associate professor of surgery at the University of Minnesota who researches ethics in animal use during device trials. Bianco said in an interview he was surprised to hear Ethicon still demonstrated some devices for sales reps via live-animal demonstrations. Even medical students at the University of Minnesota train via high-quality stimulations, he said.

"There's really no reason to do this anymore," he said. "In some rare cases a surgical demonstration might need a live animal so surgeons can see the blood flow and tissue reactions, but for sales staff there's no need. They aren't trying to be doctors."

US FDA has released a draft guidance on the design of animal trials for medical devices. However, the document doesn't discuss use of animals outside the lab, as in sales-rep training.

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EU'S EUDAMED DATABASE:

Crucial To New Regs, But Will It Be Ready in Time?

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Concern persists in the EU that the new Eudamed medical device database, which will underpin the forthcoming Medical Device and IVD Regulations, will not be up and running smoothly by the time the regulations start to operate.

The new database is supposed to go fully live in early 2020 if the current timetable proceeds as planned. But many questions remain unanswered, including whether registration of manufacturers might be possible before the database is fully live, and what will happen if Eudamed, which is the centerpiece on which oversight and transparency rests under the pending regulations, is delayed.

Several speakers at last month's ABHI's Annual Regulatory Conference 2016 were keen to promote stakeholder involvement to help the European Commission create a Eudamed system that works, is ready on time, and is compatible with other systems around the globe, including with the US system.

John Wilkinson, head of devices at the UK's Medicines and Healthcare Regulatory Agency (MHRA), told the meeting that he shared concerns over the usability of Eudamed. "If you get it wrong, it will be wrong all along" he said, describing it as "a critical issue that we're tracking closely."

Industry, meanwhile, wants to support implementation of the system by engaging in dialogue with the European Commission and member states to provide input on the management and governance of the system. Companies say they want something better than the current EU medical device database, which some say does not work effectively. John Brennan, director regulations and industrial policy, Medtech Europe, has already confirmed that industry is involved in discussions with the European Commission and member states on Eudamed.

The current Eudamed database doesn't function very well, but with "the future one, we hope it will," said Celine Bourguignon, chair of the EU industry's Eudamed working group.

Bourguignon said a joint European Diagnostics Manufacturers Association-Eucomed industry task force on Eudamed aims to:

- Give input on the management/governance of the whole system;
- Promote a single, central European database based on Unique Device Identification, and better explain the link between UDI database and Eudamed; and
- Provide support to implementation of Eudamed by engaging in a collaborative partnership with the European Commission and member states.

In terms of readiness of the new database, Phil Brown, director, technical and regulatory at the UK's Association of British Healthcare Industries, said that if the new Eudamed is not up and running by the time the regulations are in place that "we could have some issues."

> "If you can't get the single registration number" for your device, then "you can't process anything," J&J's Celine Bourguignon says.

Having "some issues" could be an understatement, as the Eudamed system is fundamental to the new regulations working. But the European Commission has already anticipated a potential delay. Indeed, because of the possible delay in the availability of Unique Device Identifiers and Eudamed, there is leeway built into the registrations of economic operators and certificates. Any delays will mean that current registration requirements will continue to apply.

EIGHT PILLARS AND TWO-PART ROLL OUT

Bourguignon, who is also director of medical device and diagnostics government affairs and policy, Johnson & Johnson, explained to meeting attendees that obtaining a registration number is a first and pivotal step for economic operators to operate within the future EU system. "If you can't get the single registration number" for your device, then "you can't process anything," she explained.

This registration number is needed to officially register products in the database in the registration section of the database, as well as to then get a Unique Device Identifier from the UDI section.

Bourguignon reminded the audience of the eight pillars, or sections, of the future Eudamed database:

- Registration of economic operators;
- Registration of devices;
- UDI;
- Notified bodies;
- Information on applications for conformity assessments and on certificates;
- Clinical investigations;
- Vigilance and post-market surveillance; and
- Market surveillance.

She reported that the database will be rolled out in two tranches. The first will cover economic operator and device registration, UDI and certificates, and the second will cover clinical investigations, vigilance and market surveillance. Some elements of the database will be more accessible to different stakeholders than with the current Eudamed, with a significant amount of information available to the public, whereas no information in the current database is available to the public.

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ANTICIPATED TIMELINE FOR ESTABLISHING EUDAMED	
Q1 2017	Adoption of MDR & IVDR
Q4 2017	Architecture & design in place
Q2 2018	Acceptance testing of first set of modules: economic operator registration; device & UDI registration; and notified bodies & certificates
Q4 2018	Acceptance testing of second set of modules: vigilance; market surveillance; and clinical investigation/performance studies
Q2 2019	Audit
Q2/3 2019	EUDAMED complete
Q1 2020	EUDAMED goes live

COMPATIBILITY WITH OTHER DATABASES

When it comes to compatibility, the Commission will need to ensure that the new database is compatible with existing databases and with the EU database for clinical trials on medicinal products, as well as the US FDA's Global Unique Device Identifier Database (GUDID), where all UDI information is stored.

The EU regulations also leave open the possiblity for member states to keep national databases in operation, but this creates potential problems surrounding submissions to both national and EU databases, including the risk of duplication or diverging information circulating from different sources.

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French Medtechs Demand Attention To Ongoing Reimbursement Delays

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A year ago, Stéphane Regnault, president of the French medical device industry manufacturers' association (SNITEM), alerted all public health-care reimbursement decision-makers to the fact that the reimbursement of medical devices by the CEPS (Comité économique des produits de santé), the executive body in charge of the activity, was taking excessively long.

The statutory limit of 180 days was being flouted, Regnault said, claiming that 420-480 days was nearer to the actual time that medtech files were taking to get through CEPS to be added to the LPPr list (the sickness insurance system's list of reimbursable products and services).

A year on, nothing has changed, he complained this week. Matters have possibly worsened, even, given the recent levels of staff turnover and absences at CEPS.

On top of this, Regnault added that the industry is also having to sustain price reductions and is living under the "constant threat of heavy tariff reductions."

Last week his frustration apparently boiled over as he called on ministers to address the problems in a statement circulated by SNITEM. "Is it so complicated?" Regnault asked.

In raising the issue, he has refocused attention on joint ministerial efforts already launched in August to improve the performance of the CEPS for both pharmaceuticals and devices. Health minister Marisol Touraine was one of four signatories to a letter addressed to CEPS president Maurice-Pierre Planel, setting out plans for a new framework agreement on reimbursement.

The letter, dated Aug. 17, effectively requests Planel to improve CEPS' performance while keeping spending within the limits set by ONDAM, which is the French social security law's mechanism for limiting spending to within annual agreed increases for primary, secondary and health-center settings.

The ministerial quartet (public accounts minister Michel Sapin, economy minister Emmanuel Macron – who resigned from that role in late August – and budget responsibility minister Christian Eckert, alongside Touraine) have tasked Planel with making substantial progress in processing of medtech dossiers. Some of the ministers' recommendations include:

- Clawing back the average delay times on files by prioritizing human-resource needs, and thereby speeding patient access to innovations, while pursuing sound economic management. A series of performance management tools is envisaged for CEPS; "reducing the delays is a priority," the ministers contend;
- Establishing better links with other health-care stakeholders so CEPS can secure better knowledge and understanding of the market's needs, as well as of issues such as competitiveness and growth, which are at present described as "patchy";
- Setting pricing limits for products that do not yet have them to make reimbursement tariffs clear and transparent; and
- Establishing a detailed, multi-year plan of work to determine generic product descriptions and undertake a systematic review of their prices and tariffs.

These actions might go some way toward placating the industry, the majority of which are classified as small-to-medium enterprises (SME) and very small enterprises (TPE – Très Petites Entreprises).

SNITEM, for its part, is demanding more human and IT resources at CEPS to reverse a situation that has become "unacceptable"; the establishment of better monitoring of CEPS' dossier handling times; and a fixed schedule of actions to rectify the identified problems.

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UK Accelerated Access Review Can Create A Post-Brexit 'Medtech Powerhouse'

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The long-awaited final report of the UK government-commissioned Accelerated Access Review (AAR), published Oct. 24, has been welcomed by the medical device industry as an important step in promoting the rapid uptake and spread of medical technology innovation in the UK and the creation of an "attractive market" in the country.

Implementation of the AAR's recommendations, which had full input from the wider medical technology industry, can help make the UK a global medical technology innovation "powerhouse," Association of British Healthcare Industries (ABHI) chief executive Peter Ellingworth said in a statement.

The ABHI now looks forward to the development of an "effective industrial strategy" to support a more favorable commercial environment for the UK industry, and says it will also work with the national provider, NHS England, on appropriate payment systems for innovative medtech.

Ellingworth adds that the upcoming "autumn statement" (a planned, Nov. 23 budget statement by the UK chancellor of the exchequer) is an opportunity for the government to publicly put its weight behind the AAR and allow clinical commissioning groups and health service trusts to invest in "wealth-creating, impactful innovations."

The AAR was launched in 2014 by the then-minister for life sciences, George Freeman. Independently chaired by Sir Hugh Taylor, the AAR was asked to make recommendations on how to speed access for NHS patients to innovative medicines, medical technologies, diagnostics and digital products. Another aim was to make the UK the best place in the world to design and develop innovations.

The final report, Accelerated Access Review: Final Report – Review of innovative medicines and medical technologies, runs 70 pages. It recommends that an Accelerated Access Partnership should be set up so that the collective leadership can be effective in 2016-17. It supports some actions already underway (via the Vanguards and Academic Health Science Networks, or AHSNs) as examples of new care models that can deliver change.

POST-BREXIT BOOST

The AAR gives a fillip to a UK industry sent spinning on an uncertain course by the Brexit vote of June 23. It says the UK's exit from the EU gives the country "a chance to look afresh at systems and identify steps to improve our its international competitiveness in life sciences." It also comes at a time of acute financial pressures on the NHS.

As an initiative, it shows that the new government has sought to be inclusive and to listen to stakeholders. Turning words into deeds is another matter, of course. But the ABHI, which provided input throughout the review process, says it finds much to applaud in the document. In particular, the industry group says it supports:

- Its pledge for a renewed focus by the UK National Institute for Health and Care Excellence (NICE) on medtech, which could lead to an effective route to market for key technologies;
- Its proposed alignment of national evaluation processes, potentially meaning that evaluations are conducted once only. There is also a renewed focus on "real world evidence" and support for "commissioning through evaluation";
- Its aim to use the full potential of the AHSNs to promote innovation adoption, using local networks for local implementation; and
- Its plan to identify impactful medtech innovations through enhanced horizon scanning.

UK junior heath minister Lord Prior of Brampton says that the report is a blueprint for coordinated action – not a complete solution on its own – as it sets out the important practical steps to support a systems-based approach to a whole life sciences ecosystem, improving uptake of innovations. In a statement, he said, "As the government develops its industrial strategy following the vote to leave the EU, the report highlights the opportunities to attract inward investment and secure its position as a global leader in medical innovation."

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Promoting Your 510(k)-Pending Device: 5 Questions About FDA's Policy

For almost 40 years FDA has allowed firms to advertise and display medical devices after a 510(k) has been submitted, but prior to clearance. This policy was set forth in a short compliance policy guide (CPG 300.600) issued in 1978, which says: "Although a firm may advertise or display a device that is the subject of a pending 510(k) … a firm may not take orders, or be prepared to take orders, that might result in contracts of sale for the device unless limited to research or investigational use."

It is remarkable how durable the policy has been over the decades. Nonetheless, there are several questions that arise periodically as device companies attempt to comply. It is unfortunate that FDA has not provided any additional guidance. This article is my attempt to clarify some of the most pressing issues.

About The Author

Jeffrey K. Shapiro is a director with Hyman, Phelps & McNamara specializing in medical device law. He has advised and represented start-ups, mid-sized and large medical device companies before FDA for more than 20 years on issues including product clearances and approvals, Medical Device Reporting and Part 806 reporting requirements, labeling and advertising, recalls, and responding to Form 483s and warning letters.

If a manufacturer communicates to the public that it is not willing to accept orders, and it does not in fact accept orders, that should be sufficient to satisfy CPG 300.600.

'FIRM MAY NOT … BE PREPARED TO TAKE ORDERS'

One question that frequently arises is what FDA means by saying a firm may not "be prepared" to take orders. Are there launch-preparation activities that are not permissible while a 510(k) is pending? For example, what about synchronization with the computer systems of potential hospital customers or group purchasing organizations (GPOs)? If a firm must wait until after clearance to engage with customer ordering and billing systems, there could be significant delays because this electronic infrastructure requires time to set up.

The phrase "be prepared" is best analyzed in context. CPG 300.600 was issued shortly after the Medical Device Amendments of 1976 (MDA) had created a complex new regulatory scheme for medical devices. To ease the transition, the MDA had decreed that devices already in "commercial distribution" as of May 28, 1976, would be allowed to remain on the market for the time being. The purpose of CPG 300.600 was to explain how FDA would determine whether a device would be considered in "commercial distribution" as of May 28 of that year.

Naturally, if a manufacturer had sold at least one unit of a device prior to May 28, it would be obvious that the device was in commercial distribution before the cutoff date. But what if a manufacturer had *offered* the device for sale but no orders had ever been placed? Could the device still be considered to have entered commercial distribution?

FDA answers with a qualified "yes." In CPG 300.600, FDA indicates that it would consider a device as having been in commercial distribution prior to May 28 if: (1) it was "displayed, advertised, or otherwise offered for sale before May 28, 1976, for a specific intended purpose or purposes" (and it was not being offered for research or investigational use) *and* (2) the manufacturer had "accepted, or been prepared to accept, at least one order to purchase the device that resulted, or would have resulted, in a contract of sale."

Almost as an afterthought, FDA applied this reasoning to the situation when a firm has submitted a 510(k) and, while it is pending, proceeds to advertise the device. Would advertising the device constitute unlawful "commercial distribution" prior to 510(k) clearance? The answer in CPG 300.600 is a qualified "no." FDA said it would not consider advertising a device prior to 510(k) clearance to be sufficient by itself to constitute commercial distribution, just as FDA would not consider advertising a device prior to May 28 to be sufficient by itself to constitute commercial distribution. In both cases, the missing ingredient to create commercial distribution was acceptance of orders or at least being "prepared" to do so.

But what does "prepared" mean in this context? FDA has never commented on what it means. In most dictionaries, "prepared" has a dual meaning. It can mean that one is *ready* and *able* from a logistics standpoint. However, it also can mean that one is *willing* from an intent standpoint. The most natural reading of CPG 300.600 is that FDA was using "prepared" in the sense of "willing" rather than "ready" and "able." Realistically, it is easiest for FDA to determine whether a firm is willing to accept orders based on whether the firm

has actually accepted orders or has made public statements indicating an intent or "willingness" to do so.

Conversely, it is difficult to see how FDA could draw lines around the degree of readiness that would be permissible in the logistical sense. Drawing these lines would require fact-intensive investigation into a firm's operational activities to determine when it truly became ready and able to accept orders. Furthermore, even if a firm makes itself ready and able to accept orders, there is no danger that it will accept orders unless it has the requisite intent to do so. It would make sense, therefore, to conclude that FDA was focused on preparedness in terms of willingness. In short, if a manufacturer communicates to the public that it is not willing to accept orders, and it does not in fact accept orders, that should be sufficient to satisfy CPG 300.600, regardless of additional logistical steps taken to get ready to sell a device.

NEW INTENDED USE?

It is well established under Federal Food, Drug and Cosmetic Act (FDCA) that FDA grants 510(k) clearance or PMA approval to medical devices based upon the concept of "intended use." When a 510(k) clearance or PMA approval is granted, it is based upon a specific intended use. If the manufacturer wishes to offer it for a new intended use, it generally must submit a new 510(k) or PMA.

An FDA labeling regulation, 21 C.F.R. § 801.4, defines "intended use" to refer to the "objective intent" of persons labeling the device based upon labeling, advertising, other "expressions" or "the circumstances surrounding the distribution of the article." If a manufacturer promotes a device for a new intended use outside the scope of clearance or approval, FDA may conclude that the manufacturer has altered the intended use. Because the device does not have clearance or approval for the new use, FDA deems it misbranded or adulterated.

What does intended use have to do with CPG 300.600? The issue can be illustrated with a hypothetical. Suppose a device has received 510(k) clearance for "Use A" and is regularly being sold and shipped for Use A. Now suppose the manufacturer files a 510(k) for "Use B," and the 510(k) is pending. May the manufacturer start advertising Use B prior to clearance? We already know from CPG 300.600 that it is lawful to advertise the device for Use B while a 510(k) is pending (so long as the manufacturer does not accept orders and is not prepared to do so). But could FDA still allege that advertisements for Use B effectively alter the intended use of the ongoing sales for *Use A*, causing the device to be "intended" for Use B as well? If so, then FDA could allege that the devices as shipped while the 510(k) is pending are adulterated and/or misbranded due to the lack of clearance for Use B.

If devices being shipped for Use A cannot be used off-label for the new Use B without physical modification (e.g., a software upgrade is needed), it is difficult to see how FDA could credibly argue that advertising Use B alters the intended use of the devices being shipped for Use A. In the more common case, in which devices shipped for Use A are physically capable of Use B, it is easy to imagine FDA taking the position that the advertisement for Use B alters the intended use of the devices currently being shipped. Because the definition of intended use (21 C.F.R. § 801.4) is broad and subjective, that is certainly a position FDA could take.

> The vagueness of the intended-use regulation tends to empower the agency, because many firms will err on the side of caution rather than risk enforcement action.

On the other hand, if the determination of intended use is based on a manufacturer's labeling and advertising, it ought to be possible to guard against the unintentional creation of a new intended use by using appropriate language in advertising for Use B. For example, a manufacturer might create a separate model for Use B (with different colors and branding) and make clear that it is "not available for sale" and is "under review by FDA, 510(k) pending." The firm might even add language to the labeling and advertising of the device for Use A, making it clear that it is intended only for Use A and not Use B.

If steps like these were taken, FDA would find it much more difficult to argue that the intended use of the devices being shipped had been altered to include Use B. But the vagueness of the intended-use regulation means that a manufacturer adopting this approach risks an enforcement fight with FDA. Most firms understandably do not want to take on this risk, and so they refrain from advertising a device for a new use if it is already on the market for another use. Like so much else in FDA regulation, the vagueness of the intended-use regulation tends to empower the agency, because many firms will err on the side of caution rather than risk enforcement action.

ORDERS CONTINGENT UPON CLEARANCE

Another question that arises from time to time is whether it is acceptable under CPG 300.600 to take sales orders if they are contingent upon receipt of 510(k) clearance. Although CPG 300.600 does not expressly address this question, FDA officials over the years have consistently indicated that contingent orders are *not* permissible.

This conclusion makes sense. The purpose of CPG 300.600 is to prevent commercial distribution prior to 510(k) clearance. FDA's position in CPG 300.600 is that accepting orders that might result in contracts of sale is the essence of commercial distribution. That conclusion would hold even if the parties agree to a contingency, *i.e.*, that failure to obtain clearance will

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excuse delivery. Hence, orders contingent upon 510(k) clearance should be seen as engaging in commercial distribution, which is permissible only after 510(k) clearance is obtained.

WHAT ABOUT ADVERTISING PRIOR TO SUBMITTING A 510(K)?

A puzzling aspect of CPG 300.600 is that it permits advertising only for a device with a *510(k) pending*. FDA officials have over the years publicly indicated that the advertising is not permitted until a 510(k) is pending. It is not uncommon for firms to work very hard to get a 510(k) submission filed and pending just before a major trade show so that advertising will be permitted.

But what gives FDA authority to ban advertising before a 510(k) is filed? Certainly, if a firm is taking orders prior to filing a 510(k), FDA may reasonably take the position that the firm is placing the device into commerce. But what if the firm is not accepting orders and is not prepared to do so? In that case, under the test of CPG 300.600, the device cannot be deemed to have entered commercial distribution under FDA's own test. There is no obvious reason that advertising should not be equally lawful *before* a 510(k) is filed, so long as no orders are taken and the firm is not prepared to accept orders.

WHAT IF A 510(K)-PENDING DEVICE HAS SUPPORTING CLINICAL DATA?

At the time CPG 300.600 was issued, 510(k) submissions were not accompanied by clinical data. In 1990, the Safe Medical Devices Act (SMDA) amended the FDCA, authorizing FDA to require clinical data during a substantial equivalence review. In 1980, FDA had issued regulations prohibiting sponsors from promoting an investigational device or representing it as safe or effective for its investigational use. Today, FDA routinely may request clinical data, albeit in something less than 10% of 510(k) submissions.

Is it permissible to advertise 510(k) submissions with clinical data under CPG 300.600? In the quarter century since the SMDA, FDA has never issued guidance to answer this question. I wrote an article in 1997 taking the view that a regulation trumps a compliance policy guide. I still take that position, but it is disappointing that FDA has never addressed this obvious conflict between the regulations and CPG 300.600.

The short statement in the CPG 300.600 policy has served reasonably well for decades, despite little effort by FDA to elaborate. But this discussion suggests the agency should thoroughly review the policy, along with its other labeling and advertising regulations and policies to ensure that its regulatory objectives are appropriately met in the decades ahead.

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FCA Liability After Escobar: Challenges And Opportunities For Device Companies

The federal False Claims Act (FCA) is the government's primary tool for policing alleged health-care fraud and abuse. For many medical device companies, the risks and costs associated with the FCA are all too familiar: recent years have seen a steady stream of blockbuster FCA lawsuits and hefty recoveries from device companies.

But a recent Supreme Court decision on the FCA may have a significant impact on how courts apply the statute in cases against device manufacturers. In June, the court decided *Universal Health Services Inc. v. United States ex rel. Escobar* (136 S. Ct. 1989, 1997 [2016]), a case testing the validity of a theory of FCA liability known as "implied certification." That theory is one that the government and private whistleblowers, who may bring suit on the government's behalf, have relied on heavily in recent years to exact huge settlements or sanctions for alleged violations of health-care regulations. The court concluded that a company can be liable (at least in some circumstances) for submitting a claim for government reimbursement that falsely *implies* that the company has complied with an important statutory, regulatory, or contractual requirement. For medical device companies, which are subject to numerous complex and ever-evolving legal requirements, the Escobar court's ratification of FCA liability based on representations relating to regulatory requirements has potentially far-reaching consequences.

In this article, we summarize Escobar's teachings and then consider the key legal arguments for device companies in the post-Escobar era, focusing on FCA cases alleging "off-label" promotion, violations of Medical Device Reporting (MDR) and Quality System Regulation (QSR) requirements, and kickbacks. We also address the government health program reimbursement framework for medical devices, which may provide some ammunition for device companies to challenge the government's or whistleblowers' efforts to impose expansive FCA liability.

THE ESCOBAR DECISION

Escobar involved allegations that a mental health hospital provided inadequate care to a teenage patient by using counselors whose qualifications did not meet regulatory requirements. The patient's parents filed suit under the FCA alleging that the hospital submitted false claims for payment by Medicaid by "impliedly certifying" that the services were provided by specific types of professionals (in accordance with state regulations), when in fact, they were not.

Before Escobar, some lower courts relied on the "implied certification" theory to hold that claims for payment could be false or misleading, even if they said *nothing* about a defendant's compliance with underlying laws, rules or regulations. The Supreme Court did not go that far. Rather, the court held that the implied false certification theory can provide a basis for liability under the FCA "at least" where (1) a "claim does not merely request payment, but also makes *specific representations about the goods or services provided,*" and (2) "the defendant's failure to disclose noncompliance with material statutory, regulatory, or contractual requirements makes those representations *misleading half-truths*." (Emphasis added.)

The court did not stop there. It also required that "a misrep-

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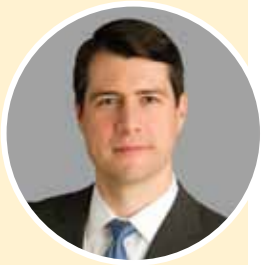

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resentation about compliance with a statutory, regulatory, or contractual requirement must be *material* to the government's payment decision." The court rejected the notion that materiality hinges on whether a statutory, regulatory, or contractual requirement is expressly identified as a "condition of payment." According to the court, such labels are relevant to, but not dispositive of, the issue of *materiality* – that is, whether the misrepresentation would be important to the government's decision to reimburse the services in question.

The court then dug into the FCA's "rigorous" materiality requirement, explaining "how [it] should be enforced." The relevant question is not merely whether the alleged underlying legal violation allows the government the *option* to deny payment, but whether the government actually would not have reimbursed the claims if it knew that it was billed for services performed in violation of the statute or regulation at issue. Courts applying the standard must assess whether the defendant's noncompliance with the requirement, if disclosed, would have affected either a reasonable person's decision or the actual, subjective decision of the government agent. But, in any event, materiality "cannot be found where noncompliance is minor or insubstantial."

> The Supreme Court's recent decision returns the focus of the FCA to fraud, as informed by common law principles of fraud.

Key Takeaways

- Escobar is one of the most significant Supreme Court decisions on the False Claims Act in decades, with broad implications for medical device companies' risk and liability.
- The legal theory at issue in Escobar – implied false certification – is often used to target medical device companies – and the Supreme Court concluded that the theory is viable, at least in certain circumstances.
- But device companies are uniquely situated to use some helpful aspects of the Escobar opinion to argue against FCA liability in some cases.

WHAT ESCOBAR MEANS FOR MEDICAL DEVICE COMPANIES

Because medical device companies typically do not seek reimbursement of their products directly from government health programs, the government and whistleblowers tend to allege that device companies are liable under the FCA for *causing* another entity – e.g., a health-care provider that prescribes a device – to submit false claims. In many – if not most – cases, the government and whistleblowers contend that the provider's claim is false because of a "certification" of compliance with some regulatory, statutory or contractual obligation. That means that Escobar's "implied certification" liability implicates a host of FCA claims against device companies.

So what type of requirements give rise to the type of alleged "certifications" in cases against medical device companies? According to the government and whistleblowers in the most common types of FCA suits, providers certify that (1) the device is reimbursable for a specific use, which may be an issue if the device is used for an off-label purpose, (2) the device company complied with various regulatory requirements (e.g., MDR or QSR requirements), and (3) a claim for reimbursement was not the result of an illegal kickback.

OFF-LABEL PROMOTION

Medicare regulations do not categorically bar reimbursement of devices supplied for off-label use, but rather limit reimbursement to cases where the device is "reasonable and necessary." FCA complaints against device manufacturers often try to thread the needle and allege that claims for off-label uses are false because the device was not FDA-approved, or reasonable and necessary, for that specific use, and therefore that the device company *caused* improper reimbursement claims by promoting the device for such uses.

After Escobar, FCA plaintiffs proceeding on off-label theories may have to show, somehow, that the "specific representations" in claims for reimbursement for the device in question were either facially false or that they were rendered misleading by some material omission. This will be particularly challenging where providers seek reimbursement under a diagnosis-related group (DRG) code for a bundle of services and items (including the device) involved in a particular patient's treatment.

Indeed, by and large, claims for payment for a device – whether as part of a DRG or otherwise – contain only true statements about the device used and the patient's condition (even if that condition is not an approved indication). As a result, FCA plaintiffs should have a difficult time proving a "half-truth" in the claim, especially because the government typically knows – or should know – from the codes submitted that the device is being used off-label when it pays the claim. This disclosure to the government also may cause FCA plaintiffs to struggle to show that omissions regarding marketing are material – indeed, some courts had already begun to reject that argument. Further, defendants will continue to challenge whether an off-label use

of a device is material when reimbursement for the device is sought as part of a DRG rather than for the device alone.

QSR, MDR REGULATORY VIOLATIONS

At first glance, Escobar's endorsement of FCA liability for regulatory violations is eye-opening for device-makers, given the many FDA regulations that pertain to medical devices. But, on closer examination, Escobar seems to have ratified prior courts' efforts to rein in such far-reaching theories.

Let's consider two important areas for medical device companies as examples. In both, courts have refused to recognize FCA liability based on alleged violations of adverse-event reporting and manufacturing quality regulations. Escobar reinforces those decisions.

> Medical device companies often face theories of FCA liability based on "implied certifications" that are particularly vulnerable after Escobar.

First, in a case with clear parallels to MDR compliance cases, a federal court rejected a whistleblower's allegation that a pharmaceutical manufacturer defrauded the government by failing to comply with adverse event reporting (AER) requirements (*United States ex rel. Ge v. Takeda Pharmaceutical Co. Ltd.* [D. Mass. 2012]). According to the court, AER compliance was not a "material precondition of payment" because FDA exercises enforcement discretion in that area and the whistleblower had not shown that FDA would have withdrawn approval for the drugs because of the alleged compliance issues. Although Escobar refused to base FCA liability on whether a regulation is an express "precondition of payment," the Supreme Court confirmed the high bar set by the Ge case for establishing materiality, especially given FDA's enforcement discretion. After Escobar, FCA plaintiffs cannot just say that the regulatory requirement at issue *could* have led to nonpayment of a medical device; they must establish with evidence that the government *would have* refused to pay based on the alleged noncompliance.

Second, in a case of particular interest to device companies because of their QSR obligations, a federal court refused to recognize a theory of fraud liability based on a defendant's alleged failure to comply with Good Manufacturing Practice (GMP) rules (*United States ex rel. Campie v. Gilead Sciences, Inc.* [N.D. Cal. 2015]). In the Campie case, the whistleblowers alleged that a drug manufacturer falsely promised FDA that it would comply with manufacturing regulations, particularly FDA's GMP provisions, and then fraudulently sought government reimbursement while failing to comply with those rules. The Campie court rejected those allegations, observing that the FCA was not meant as a "sweeping mechanism to promote regulatory compliance." The court concluded that the whistleblowers' theory was not viable because there was no representation of compliance to CMS – as opposed to FDA – in the course of requesting payment. By focusing on material "specific representations" about the products in question as part of the claim for government payment, Escobar appears to have confirmed the crucial distinction in Campie between representations of compliance made to *FDA* and representations made to CMS. Representations to FDA are an important compliance issue, of course, but Escobar indicates that they do not amount to a violation of the FCA. Whistleblowers alleging fraud based on QSR noncompliance should face an uphill climb after Escobar.

ANTI-KICKBACK STATUTE

Another major theory of liability under the FCA for medical device companies focuses on purported violations of the Anti-Kickback Statute (AKS). Sales representatives and marketing personnel at device companies should be familiar with the AKS and its broad prohibitions against offering or paying any "remuneration" to induce providers to use a company's devices. Because the government interprets "remuneration" expansively, AKS cases can be premised on a broad array of arrangements between device companies and providers – from the obvious (cash payments and luxury vacations) to the not-so-obvious (speaking fees, consulting arrangements, patient care information and educational materials).

After the enactment of Patient Protection and Affordable Care Act, a medical claim that results from a violation of the AKS is false for purposes of the FCA. For cases based on conduct after the Act's effective date, the Escobar decision may not offer much in the way of new arguments.

But in FCA cases arising from alleged misconduct before 2010 – and there are still *plenty* lingering in the court system – plaintiffs must establish that claims obtained through kickbacks were false because the provider *certified* compliance with the AKS. To the extent that Escobar limits certification liability to cases where there is a "half-truth" made about the "services or goods provided," it is hard to see how pre-Affordable Care Act kickback cases can move forward.

STRENGTHENED ARGUMENTS FOR FUTURE CASES

In conclusion, Escobar provides device companies with unique new arguments to level against new and pending FCA lawsuits. Although FCA exposure will remain a major risk, companies can—and should—think about ways to fight back against meritless FCA suits using the arguments newly strengthened by the Supreme Court.

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As you mentioned, some dollars may be moving away from other spaces. Why is the investment climate in device and diagnostic spaces tougher?

Kramer: I think it's cyclical. When I started ten years ago, medical device [investing] was hot. Then there was a period when molecular diagnostics was hot. We've had an evolution toward more healthcare IT and services. Kaiser Permanente Ventures has followed that trend and spearheaded that trend.

The main factors leading to a relative exodus of early-stage medical device investing are two-fold: one is the US FDA and regulatory environment has become less predictable, and secondly, the reimbursement environment has changed. You have two major risks for an early-stage company that venture capitalists feel less competent to predict accurately.

So in health IT, the customer and payment pathway are easier to understand?

Kramer: Yes, it's both. For the most part, they're unregulated. You don't need FDA approval for most digital health products and services. Secondly, they're building a premise for return on investment that hopefully is easier for their customers to understand, whether they are payers, providers, or individuals.

Your earlier points related to where Big Data is taking us. You're sitting at the venture arm of Kaiser Permanente, which has a unique legacy of accumulating data and doing so for a long time. How has Big Data influenced your investment decisions?

Kramer: Clearly, being an integrated delivery network, we see the value in long-term patient data. We're fairly prolific in publishing our findings to the community at large.

We definitely feel that being both the payer and provider gives us great insights. We not only know the expense of providing care, but we also know the clinical outcomes. We've always been an extremely data-driven organization. The multitude of data has blossomed recently. Kaiser Permanente has positioned itself as an innovator in healthcare IT, as evidenced by our company's record of HIMSS awards and reputation.

Digital health is a much more natural extension of that within Kaiser Permanente than maybe other organizations a little behind on the IT evolution curve.

We've seen start-ups like M2Gen spin out of Moffitt Cancer Center, using all their data to drive a business outside of an institution. How has Kaiser's approach differed?

Kramer: Fundamentally, Kaiser Permanente thinks of member-generated data as just that - the member's data. I don't think we naturally think of this as an asset to be monetized in a for-profit sense. It's not that we don't see the value in that data, it's just that we're not likely to spin out a for-profit that would utilize our patients' data. We have our members' trust and they believe we're going to do the best for them in terms of care delivery and use the data for that purpose, not for generating profits.

Is digital health a new category, or is this all really healthcare IT with encroaching consumer products? With companies like Apple and Google making more investments, how has the definition of digital health changed?

Kramer: I see digital health more as an evolution of telemedicine and healthcare IT in general. Companies like Apple are in the business of selling hardware, not in the business of delivering affordable care, so the incentives are different. We see digital health as just another tool in our arsenal to deliver care.

Digital health in my mind spans two categories. There are the patient-facing, headline-gathering companies that have a lot of buzz and enthusiasm. Then there are the less sexy back office IT investments. Kaiser Permanente Ventures has split amongst those.

Some things are, like Omada Health, very visible and focus on the end user. Others like KitCheck or Validic are more back office[-oriented], helping us be more efficient at managing data and making better decisions using that data.

"One of the challenges for digital health is that, particularly at the seed and Series A stage, there are too many companies all claiming to do unique things, but not necessarily aware of each other's existence."

Could you tell us more about those portfolio companies and their approaches?

Kramer: I'm a board member of Validic Health. The premise there is that there is a huge proliferation of sensing devices whether they are fitness, wellness, or activity devices or more clinical-grade glucometer or blood pressure devices. There's a huge amount of data out there that currently is not being used or not being used efficiently in the management of patients.

The bet on Validic is a bet on the ecosystem as opposed to a bet on any particular device. We believe member-generated data will be valuable. Validic is going to become the de facto standard API aggregator for that data. They will make it easy for customers to connect to them, to then connect to the universe of connected devices, as opposed to having to build separate APIs to all these devices.

We've seen even the most traditional companies shifting their behavior recently. Companies like Novartis have hosted code-

a-thons. How is this shift making startups faster and lighter?

Kramer: I certainly think a code-a-thon is a great way to solicit new ideas and enthusiasm for the space. Unfortunately, I think anything that can be developed in a 72-hour hackathon may not be inimitable. There is an inherent tension between investing more time and labor in understanding the marketplace better and making sure that you're meeting the needs of all the constituents, versus doing something fast and dirty and just trying to get an application out there.

One of the challenges for digital health is that, particularly at the seed and Series A stage, there are too many companies all claiming to do unique things, but not necessarily aware of each other's existence.

What differentiates Kaiser Permanente Ventures' investments in digital health is we're picking companies that have already generated clinical data that validates their premise. Take Omada Health. They are based on years of research of the Diabetes Prevention Program and turning this brick-and-mortar program into a digital asset using social media. They have real clinical data and can do that very efficiently. That's why that sort of investment makes sense to us.

> "People assume that whatever product they're designing is going to be embraced by physicians because it's wonderful...What we've found is anything that adds even a modest amount of time to their schedule is really hard to get enthusiastic about."

We're trying to differentiate the signal from noise by finding those companies that have a clinically rigorous approach to proving not only are they sticky and appealing apps getting lots of page views, but are also producing the behavior modifications they purport to influence.

Is this increase in capital toward digital health a permanent shift in venture dollars, or is this a one-time investment?

Kramer: I think the jury is still out. It's all going to be determined by whether people can actually make money in the space. There have been some exits. What we have yet to see is many companies going out of business in this space. Right now, everyone is betting that they'll be the winner. I think that there will be some rationalization of, not only valuations in the space, but also the number of players. Only those that actually deliver on the promise should survive and should be valuable assets to own.

Is there still opportunity in the app layer or interoperability or new spaces?

Kramer: Without a doubt, interoperability is a challenge for most organizations. At Kaiser Permanente, we're certainly blessed by having a uniform Epic EMR system. Most have multiple systems and they have to figure out some way to transfer data to and from those systems. That definitely will be a challenge and an opportunity.

When we talk about the application layer and member-generated data, traditional EMR systems don't really have a vehicle to write member-generated data into their health records. There's a question of 'what data is valuable', and ensuring the data is secure and accurate, and ensuring the right data is getting to the right place. Those are all opportunities and challenges.

What areas will go through the most growth over the next couple of years?

Kramer: Anything in behavior modification space is very intriguing. In terms of medication management and medication adherence, these are huge opportunities. Whoever can crack that nut with the right set of tools will be very successful. It's arguably described as digital therapeutics. That's an area we're looking at.

There are definitely opportunities for software to sit as an adjunct to installed EMR systems. The areas I think are exciting are decision support tools, predictive analytic tools, better charge recapture tools and billing code extraction tools. There's a lot of opportunity in going from the combination of free text and fixed text to extracting a signal from all that data.

Has the average physician's practice converted to all these systems yet?

Kramer: People assume that whatever product they're designing is going to be embraced by physicians because it's wonderful. We have the advantage of having over 18,000 physicians and when we do our diligence, we're going to talk to those physicians. What we've found is anything that adds even a modest amount of time to their schedule is really hard to get enthusiastic about.

You have a lot of innovators coming from the SaaS (software as a service) world and traditional IT world thinking that what they've learned is easily applicable to healthcare. The stakeholders and realities of the healthcare work environment are different and you have to understand those nuances to find those products that will resonate.

Matt Gardner is co-founder of BioCalifornia, a California coalition of innovators, investors, and industry leaders in human health, the environment, and sustainability.

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China Precision Medicine Push Boosting Genomic Business Forays

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Aiming to become a global superpower in the area, China is strongly pushing a homegrown precision medicine initiative and has officially declared that therapies derived from next-generation sequencing (NGS) technology will be viewed as one of the nation's foremost science and technology projects under the 13th Five-Year Plan for 2016-2020.

The Ministry of Science and Technology has already said that the central government plans to spend CNY20bn ($2.97bn) to support precision medicine research over the period to 2030, and the National Health and Family Planning Commission is currently drafting a strategic plan for promoting the sector's development nationwide.

In recent years, NGS has evolved rapidly and is widely regarded as an essential technology for enabling precision medicine, particularly in cancer therapy. In the future, treatments based on individual genomic and biological characteristics could become the mainstream of cancer therapy, bringing new opportunities to pharmaceutical companies.

China had 4.29 million new cancer cases and 2.81 million deaths from various forms of the disease in 2015. Based on these statistics, the market size for NGS-related products for cancer in China could be worth more than CNY100bn, while the market for cancer precision medicine could reach more than CNY10bn, predicts Jiaxin Li, senior investment manager at Fosun Tonghao Capital.

The Chinese genomic sequencing market is already the fastest-growing globally, with a compound annual growth rate of 20%-25% in recent years. After NGS, the hottest area of investment in the genomics space in China is expected to be tumor liquid biopsies, with Guosen Securities Research predicting that the potential market for such products could be worth some CNY20bn.

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"We can jointly research and develop genetic testing with pharmaceutical companies, and through big data from research, we could discover possible gene mutations as potential treatment targets, in order to help pharma firms to develop new drugs," CSCO president Yilong Wu says.

FORMING A FRAMEWORK

In May, the China Society of Clinical Oncology (CSCO) held a conference in Beijing for the diagnosis and treatment guidelines of lung cancer. At the meeting, CSCO and the China Actionable Genome Consortium (CAGC) released China's first consensus on the use of NGS in clinical oncology, which is expected to lead to the development of NGS in clinical genetic testing for cancer, and to also provide guidelines to standardize clinical practice.

The CAGC was formed in September 2015 to initiate genetic analyses for five cancer types in China: lung, liver, colon, stomach and breast.

For its part, the CSCO plans to conduct NGS technology-driven genome analysis for six types of malignant solid tumors (lung, breast, liver, stomach, and colorectal cancer and hematologic forms such as leukemia), aiming to provide clinical oncology practices suitable for China.

Through these studies, the society aims to be able to regulate NGS testing technology, material for analysis, and to formulate diagnosis and treatment models, processes and standards.

After releasing the consensus, the next phase of the project is to conduct multigene analysis to verify the feasibility of NGS in China, which will lead to the final step of carrying out clinical trials for new drugs based on multi-gene biomarkers.

Both the CSCO and CAGC plan to invite selected companies to participate in the development program with the aim of helping enterprises better understand what type of genomic testing has most clinical significance for Chinese patients.

"We can jointly research and develop genetic testing with pharmaceutical companies, and through big data from research, we could discover possible gene mutations as potential treatment targets, in order to help pharma firms to develop new drugs," said Yilong Wu, president of CSCO and chairman of the Chinese Society of Lung Cancer.

Burning Rock Biotech, a Chinese venture, is one of the participants in formulating the consensus in China on the role of NGS, and its founder and CEO Yusheng Han noted that currently there are more than 200 NGS companies in China. But without guidelines and standards in place, some patients are at risk of buying uncertified cancer testing products and services, he cautioned.

ACTIVE SINGLERA RAISES FUNDS

A number of major Investments have been made in the field in China this year, fueled by venture capital and strategic investors including Lilly Asia Venture and Beijing Genomics Institute, aimed at discovering better preventative and targeted therapies for cancer.

From mid-September 2015 to the end of last year, there was a boom in China's A-share market for biologics and genomic sequencing stocks, particularly for genomic testing linked to the pharma sector. The sector had an overall increase of more than 20%.

Singlera Genomics Inc., based in La Jolla, Calif., and Shanghai, has been among the most active firms, raising $20m in a recent Series A financing led by Lilly Asia Ventures together with Green Pine Capital Partners and CDBI Partners.

The round will be used mainly for R&D and commercialization of non-invasive genomic sequencing products for cancer and other genetic diseases, with a focus on tumor liquid biopsies, the company told Scrip. Singlera has proprietary technologies in single-cell sequencing, DNA methylation and bioinformatics, and its main products and services include tumor diagnosis, personalized treatment and noninvasive prenatal diagnosis.

The company's major competitors include Burning Rock Biotech, Novogene and Geneseeq Technology. "Compared with competitors, our products have higher sensitivity and accuracy, and our unique technology for next-generation sequencing library preparation and fully automatic analysis software for bioinformatics can make the whole NGS detection process simpler and more repeatable to ensure a higher detection success rate," the company said.

> "We are looking for collaborative partners who are willing to work with Singlera to promote technology innovation, and to lead the industrial development" – Singlera Genomics

Tumor heterogeneity is the main reason for cancer therapy failure, and precision medicine has been proved significantly more effective in treatment, as the slow launch of new targeted cancer drugs is not meeting patients' needs, Singlera noted.

Singlera's main product lines include gene mutation detection kits for lung, breast and ovarian cancer. It has already established partnerships with several multinational companies, while collaborating with domestic partners including pharmaceutical companies, research institutes and industrial associations.

Singlera has been highly active in partnering in China. In June, it signed a strategic agreement with the Taizhou Institute of Health Sciences of Fudan University and Singlera to identify biomarkers for early stage cancer detection from samples of a 200,000-patient cohort. The joint research team will adopt Singlera's proprietary technology to analyze biofluids collected prior to disease onset in order to identify specific biomarkers for early cancer detection for esophageal, gastric, colorectal, lung and breast cancer.

Earlier in March, Singlera and Shanghai-based Genor Biopharma entered into a strategic collaboration agreement to jointly develop targeted immune-oncology drugs and related companion diagnostic products. Genor will also use Singlera's patented sequencing technology and bioinformatics analysis to conduct research on PD-1 and PD-L1 to discover novel tumor antigens and immunotherapies for personalized treatment.

"We are looking for collaborative partners who are willing to work with Singlera to promote technology innovation, and to lead the industrial development," Singlera said. Its business plan for the second quarter of this year is to seek a wider range of partners and recruit more R&D and marketing talent, while speeding up new product launches, especially of tumor liquid biopsy products, the company disclosed.

Last year, Burning Rock and Illumina Inc. collaborated to develop molecular diagnostics in oncology for the China market based on Illumina's NGS technology after completing a $23m fundraising in support of diagnostics for solid tumor cancers from Jifeng Capital, Sequoia Capital and Legend Star.

STRING OF DEALS

Amid the national push into precision medicine, there has been a string of deals and investments in related areas including therapeutic, companion diagnostics, and related technology.

Shenzhen-listed Beijing Beilu Pharmaceutical and Beijing D.Z Capital in June increased by CNY60m their investment in precision cancer-care provider Nanjing Geneseeq Technology. Beilu said the investment is part of its oncology business strategy and may bring in new profit growth.

With operations in the US and Canada, Geneseeq provides treatment solutions

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based on the comprehensive systematic analyses of patients' genomic mutations through the combination of NGS and up-to-date cancer knowledge databases.

Genetron Health, a Beijing-based cancer genomics solutions start-up, announced in September that its Series B round had raised hundreds of millions of yuan from Chinese biotech firm Vcanbio Cell & Gene Engineering and New Horizon Capital, Shenzhen Share Capital Partners, and Yueyin Venture.

Shenzhen HaploX Biotechnology, a returnee run company specialized in genomic mutation detection, received CNY50m in Series A round funding in June. With the aim of establishing a foundation to actualize precision medicine, HaploX and Shenzhen Peoples' Hospital launched the Chinese Cancer Sequencing Project in 2015, which was the first large-scale cancer precision medicine project in China.

This project covers early screening, prognosis monitoring and individualized medication for more than 10,000 individuals from diagnosed and high-risk groups, mainly targeting carcinoma of the lung, breast, colon/rectum, stomach and liver.

Meanwhile, Shanghai-listed Ningbo Medicalsystem Biotechnology announced in September that it had signed a cooperation framework agreement with the Chinese National Human Genome Center in Shanghai, Shanghai Huaguan Biochip and Shanghai Shenyou Biotechnology to acquire 70% of shares in the biochip and diagnostics developer Shanghai Huaguan.

Upon completion of the investment, Ningbo Medicalsystem will have the priority right of the research achievements from Shanghai Human Genome Center, which backs Shanghai Huaguan. The acquisition and cooperation will enhance Medicalsystem's R&D capability in genetic diagnosis and enrich its molecular diagnostic products.

In another September deal, Beijing Genomics Institute (BGI) invested in a cancer genetic testing startup Geneplus-Beijing, leading a $30m Series A funding round together with venture capital firms Green Pine Capital Partners and Shanghai Huoshanshi Capital. BGI will support the company strategically in its development of liquid biopsy technologies and related clinical applications.

In addition, China National GeneBank, a nonprofit research institute cofounded by BGI and the Chinese government, officially opened a 47,500 square meter facility in Shenzhen, equipped with NGS instruments developed by BGI. The institute has an approved NGS-based non-invasive prenatal test and last year also received approval from China's National Health and Family Planning Commission to conduct clinical sequencing services for cancer.

In September, **Thermo Fisher Scientific Inc.** disclosed in the *Shanghai Daily* that it might bring precision medicine technologies to China. The firm has already formed local alliances including with Fu Wai Hospital in Beijing, West China Hospital, and Sun Yat-sen University.

Chinese pharmaceutical companies are also starting to acquire overseas genomic technologies. In July, Jilin Zixin Pharmaceutical Industrial bought a majority stake in US genome firm Nabsys 2.0 for $42m.

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Merit Faces Subpoena Over Marketing

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Merit Medical Systems Inc.' marketing practices are under federal scrutiny, the company revealed in an Oct. 21 filing with the US Securities & Exchange Commission.

According to the filing, Merit received a subpoena on Oct. 19 requesting "documents and other information regarding certain marketing and promotional practices relating to the company's products."

The company is in the process of responding to the subpoena and plans to cooperate, the filing says.

The announcement doesn't mention what specific marketing issues caused the DoJ's concerns. Originally, a disposable medical device company, South Jordan, Utah-based Merit Medical has recently made acquisitions allowing it to diversify further into cardiac intervention, peripheral intervention, spinal and endoscopy products.

Most recently, in July, Merit paid $97.5mm for spinal device company **DFINE Inc.**, maker of the *StabiliT* bone cement injector and *Star* spine tumor ablation system. And in March, Merit paid $18.5mm in cash for **CryoLife Inc.** 's HeRO (Hemodialysis Reliable Outflow) subcutaneous arteriovenous access graft assets, including global marketing rights, customers, intellectual property, equipment, and inventory.

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New Clinical Trial Approach For Urgently Needed Therapies Could Be On Horizon

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The Medical Device Innovation Consortium has chosen the Michael J. Fox Foundation for Parkinson's Research to help it create a new statistical methodology for incorporating patients' preferences into the design of clinical trials. Its decision was driven largely by the foundation's large network of patients willing to share their experiences through the Fox Insight network.

MDIC is a Minneapolis-based non-profit collaboration of researchers from the device industry and US and Canadian federal agencies. On Oct. 18, it announced the start of the pilot collaboration with MJFF, FDA, research and consulting firm RTI Health Solutions, and researchers at the Massachusetts Institute of Technology Sloan School of Management.

MDIC vice-president for technology innovation, Dawn Bardot, explained to *Medtech Insight* why MJFF was asked to collaborate on the project, which will hopefully yield statistical tools that can be applied to clinical trials of drugs and devices for a variety of conditions, not just Parkinson's disease. "As we were putting together this project, we were looking for a patient partner that was really savvy with their patient network and the Michael J. Fox Foundation has invested in being a leader in engaging with their patients with a digital platform," Bardot said.

Fox Insight began as MJFF's online portal to help Parkinson's patients get into clinical trials of novel therapies, and it has evolved into a system for patients to share their experiences with the disease and their treatment through regular confidential surveys. Fox Insight already has about 3,000 active patients and could eventually be collecting regular survey data from as many as 10,000 patients. "For medical devices, that's easily an order of magnitude or two more than what we're able to engage with in the typical medical device clinical trial," Bardot explained. "We're able to gather patient preference information from a really robust set of patients and places and demographics."

Bardot explained that in order to operationalize the new statistical method that the group is creating, they had to be able ask the patients meaningful and detailed questions that would show how the patients weigh the risks and benefits of unproven therapies. So the researchers will ask the patients about a hypothetical neuromodulation device to treat Parkinson's disease that has been proven safe, but not yet proven effective.

> "We're trying to incorporate patient preferences to figure out what that level is, but still balance the desire to make sure that we don't approve therapies that don't really work"
> – MIT Economist Andrew Lo

"The nice thing is that we can do this in a hypothetical context and the hypothetical context exists because we have a group of patients who have preferences for improvements in their disease that are currently not available," Andrew Lo, the Director of the Laboratory for Financial Engineering at MIT, who is helping MDIC develop this new statistical methodology, told *Medtech Insight*. "So what we want to understand is what does matter, and if we had the opportunity to design a trial to test a device that would actually address those needs, what would it look like [and] I could also see this informing a future clinical trial in Parkinson's disease very readily."

Although this project is focused on Parkinson's disease, Bardot emphasized: "The beauty of this methodology is that it's extensible to a variety of patient groups, a variety of disease states, to devices and drugs." For example, the researchers have already tested their approach on a retrospective data set of patients being treated for obesity.

GETTING BEYOND P VALUES

In its press release announcing the collaboration with MJFF, MDIC explained that it wants to "move clinical trials from generic p-values of 0.05 to therapy-specific patient-values." Generally speaking, small p-values in statistical analysis of clinical trial result indicate that the apparent effects of the therapy being tested are real, rather than just an illusion created by random chance, and that the therapy would prove effective again if it were tested in a different sample of similar patients. Usually, a result with a p-value below 0.05 is considered "statistically significant" but, that cut-off is largely arbitrary.

"A p value is a measure of statistical significance, but it doesn't incorporate how significant a particular therapy is from the patient's perspective," Lo said. "The idea behind [this collaboration] is to reflect patients' values, but in a somewhat more systematic way than simply in the usual subjective manner that perhaps doctors and other clinicians might have to incorporate these values into their decisions [in the past]."

Lo pointed out that the FDA recently approved **Sarepta Therapeutics Inc.**'s Duchenne muscular dystrophy treatment *Exondys 51* – a decision supported by patient advocates, but opposed by some of its own scientists. "One could argue that the data do not

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support very strong evidence that the drug works," Lo said. "But the fact is that it's a desperate patient population and children and their patients showed up to the FDA and said 'We really need this drug.' So that's a case in point where a p-value of 0.05 isn't really relevant. They're taking into account that patient preferences matter. What we're trying to do is take that same consideration and engage patients directly and incorporate the information in a more systematic, repeatable, transparent, consistent way."

In order to get a small p-value, the effect of the therapy being studied has to either be very large, or the number of patients in the trial has to be large, or both. This is often an impractical requirement for therapies for rare conditions or conditions that make it difficult for the patients to participate in trials. And the p-value alone cannot show if the improvement caused by the therapy actually improves the patients' quality of life. Some outcomes in clinical trials may be statistically significant but clinically insignificant.

"Five-percent is not the whole story. One size does not fit all for therapies that are treating diseases where [the patients] don't have any other therapies in existence and the consequences are pretty dire. You might want to take a 10% chance or a 15% chance [of a false positive]. The question is how to do that in a systematic way instead of throwing your hands up and saying 'anything goes,'" he said. "We're trying to incorporate patient preferences to figure out what that level is, but still balance the desire to make sure that we don't approve therapies that don't really work."

Brett Hauber, an economist specializing in health preference assessment with RTI Health Solutions, explained to *Medtech Insight:* "We will use one of a number of potential patient-preference methods to quantify how much those things matter and, potentially, the tradeoffs the patients are wiling to make, among all of these different endpoints, benefits vs benefits, and benefits vs risks, … how much uncertainty are they willing to accept in the evidence behind it."

Lo explained said that the model he and Hauber are developing for this project is based on Bayesian efficiency analysis, a well-established statistical approach for balancing risks and benefits of different choices when information is incomplete. "You can either approve an ineffective [therapy] or decline or reject an effective [therapy] and the Bayesian decision analysis says 'Let's try to come up with the best decision that will minimize the average decision that will minimize the average mistake that you're going to make in these two ways.'"

He suggested that, depending on the disease and the other options available, patients "may want to minimize that more than the other kind of error." It might make sense for some patients to risk using an ineffective therapy in the hopes that they can find an effective therapy soon, rather than waiting for more data to be collected to provide more certainty. "So you have to actually spend some time modeling exactly what it is that patients really prefer," Lo said.

WATCH

To see a video interview with MDIC CEO Bill Murray go to: http://bit.ly/2dWpEUp

BRINGING A NEW APPROACH TO FUTURE TRIALS

Stephanie Christopher, MDIC's Program Manager for Patient Centered Benefit-Risk Assessment added: "We envision this as an additional regulatory-science tool, that as others design clinical trials and bring them to the FDA in pre-submission process that they would have these tools available to them. And we have a number of stakeholders from the FDA who are very hands-on in the research of this, so this is helping to inform their understanding of this design works as well."

The results of this collaboration will be available free online. This project will yield an analysis of the outcomes that matter to Parkinson's patients, as well as the patient preference survey developed for this hypothetical study, that will be available to anyone researching Parkinson's, Bardot said. MDIC will also create an open-source software tool so that other researchers can apply the new statistical methodology to future clinical trials.

Lo added, "The FDA, in a way, already takes into account known [patient] factors, so our approach is not, in any way, intended to criticize FDA but provide them with an additional tool that will allow them to do their work in a more systematic fashion."

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GE Healthcare Pilots New Patient-Focused Mammo Tech

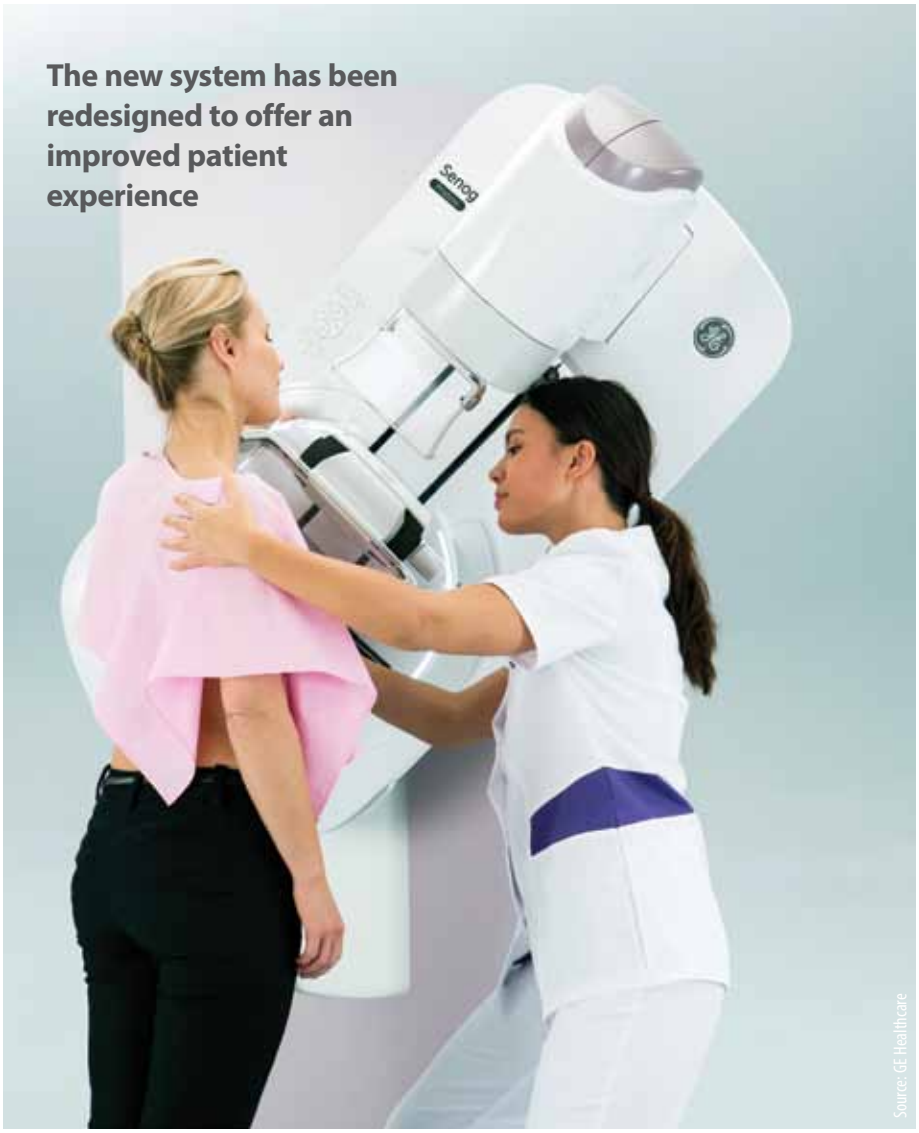
CATHERINE LONGWORTH catherine.longworth@informa.com

GE Healthcare has developed a new digital mammography system, the *Senographe Pristina,* which has been designed to increase patient comfort and feature enhanced, integrated 2D mammography and digital breast tomosynthesis (or 3D mammography) technology for better imaging quality. The company expects to CE mark the system in the coming weeks.

The next-generation technology landed at Paris-based cancer institute Gustave Roussy in August 2016, where in under three months the system has already been used to image more than 300 patients. The Senographe Pristina incorporates the core imaging technology of the other systems from GE's established Senograph digital mammography platform, but enhanced with a new anti-scatter grid for higher image quality and its allows a lower dose in denser breasts. The system is also expected to be compatible with contrast-enhanced spectral mammography to minimize some artifacts inherent to this technology.

The Senographe Pristina's 3D tomosynthesis technology uses two proprietary algorithms – one with a calcification artefact correction to deliver better off-plane images, and another that can render calcifications as if each were in its optimal plane, making the images easy to read, said the company.

GE Healthcare designed and developed the new system in partnership with Gustave Roussy; and production of Pristina is at GE Healthcare's European site in Buc, France. One of the key features of the Senographe Pristina is the redesign of the gantry – with a different shaped bucky – and the usability of the system. Despite recent positive steps in mammography technology, one of the common reasons still reported for poor participation in screening programs is a fear of pain. According to a UK study published in the medical journal *The Breast*, 25%-46% of women cited pain as a reason why they had not repeated breast screening.



The new system has been redesigned to offer an improved patient experience

Source: GE Healthcare

Claire Goodliffe, global marketing manager for women's health at GE Healthcare, said: "Senographe Pristina was designed in a way so that it would help reduce anxiety. There's a lot of thought that's gone into the design – from the materials, the lighting, the color, the curves - so that it doesn't hurt women when they go for the examination."

The company conducted focus groups with patients and technologists from Gustave Roussy to determine areas for improvement and found that anxious patients were more prone to moving and contracting muscles. This created a challenge for technologists to position them precisely, resulting in clinical image deficiencies and the need for a rescan.

"During mammography, the breasts are positioned on a bucky, a flat plate on which the breasts rest and are then compressed for scanning. The flatness of the bucky is a major discomfort factor, so we have created a carbon fiber bucky that is gentle and rounded to help reduce anxiety and discomfort for patients. Instead of patients tensing pectoral muscles while grabbing the conventional handgrips, they can lean comfortably on the armrests, relaxing their muscles to simplify compression and improve image quality," said François Enfant,

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Old vs New

Senographe Pristina is the latest addition to GE Healthcare's mammography line

head of European design at GE Healthcare.

Senographe Pristina also incorporates an external remote control so patients have the option to participate in the mammogram and auto-compress. To begin with, the minimum compression needed for an image is taken by the technician and then patients are invited to add more compression using the remote controlled device.

Corinne Balleyguier, specialist radiologist at Gustave Roussy, admitted she was skeptical at first about the benefits of letting the patient self-compress during the procedure but has been surprised at the positive patient response. «We have received very good patient feedback about this device and many patients are using it to self-compress during their mammograms, providing better quality mammograms.»

The preliminary feedback confirms GE Healthcare›s belief that being able to take control eliminates a psychological barrier for patients, the company says. «What you don›t know, you fear, while if you›re in control you tend to accept more pain» said Enfant. «Pain is a problem but the fear of pain is more powerful so even if the patient is not willing to use the tool to self-compress, the fact that you have a tool to stop the compressions makes a huge difference.»

GATHERING MORE EVIDENCE

A set of multi-center observational studies are currently being designed to monitor and gather more evidence of the new system's impact in clinical practice. It has also been installed at five investigational sites across France and Denmark with plans to expand to other sites in Belgium and Italy.

Gustave Roussy also intends to launch three clinical studies to evaluate the optimum clinical protocol for combining 3D tomosynthesis mammography with 2D. 3D tomosynthesis is currently approved by US FDA, but it is not yet considered a standard of care for breast screening in Europe. Research by GE Healthcare so far found a slightly longer acquisition time when the 2D imaging is performed first, followed by 3D imaging. The company told *Medtech Insight* that, as there was "no clinical reason" for pushing 2D imaging first, apart from usage volume, it plans to implement a "3D acquisition first" approach for its automated combo imaging mode in the future.

According to a report by Global Industry Analysts, the global market for mammography equipment is projected to reach $628.6m by 2020, driven by a growing female geriatric population worldwide, and a continued conversion from analog to digital mammography equipment. "Today, mammography is giving the best diagnostic imaging results bar MRI. Although MRI is the gold standard because there is no radiation, MRI is extremely expensive and access is limited. There's more access to mammography, it's cheaper and a very quick exam," said Goodliff.

Currently, Europe represents the largest market for breast diagnosis, but GE healthcare acknowledges it is not alone in trying to corner this space, and names Siemens, Toshiba, and Philips as its key rivals.

Despite this, GE Healthcare seems confident that they have an advantage due to their patient-centric approach with the Senographe Pristina.

Enfant said: "The real challenge in technology is how can we optimize and humanize as there is a need beyond technology to improve patient experience and this product is a great example of what we can do."

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