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THE AI TOUCH:

Artificial Intelligence Could Boost Quality Systems, Cut FDA Inspections – But Is Industry Ready?

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Pioneering device-makers that use advanced artificial intelligence systems to analyze their vast streams of data to pinpoint predictive outcomes for quality systems and marketed products could one day see fewer US FDA facility inspections, an agency official says.

Art Czabaniuk, program division director/district director for the Division of Pharmaceutical Quality Operations III within FDA's Office of Regulatory Affairs, foresees "great benefit from AI in the regulatory environment" – especially for ORA, which handles all of the agency's inspectional activities in the field.

"This is how I see artificial intelligence unfolding: AI will reduce investigational time and increase FDA's speed in taking action on a problematic firm, and promote preventative action and speed with regard to corrective action," he said. AI will also "elevate quality because firms will understand the quality of their products and their manufacturing systems to a greater degree if they monitor all of their many data points."

Czabaniuk's conclusion? "AI is everything we're looking for."

Most device companies have already dipped a toe into more rudimentary forms of artificial intelligence, using AI systems to help spot trends in, say, the number and types of complaints they receive.

But industry is looking to push artificial intelligence even further, exploring ways to use AI to review, sort and process extremely large quantities of quality and manufacturing data to find problems that would simply take too long for human eyes to see – if they could even spot them at all – and "training" AI systems to self-correct and create more positive outcomes. In other words, machine learning.

The topic has become so hot that Cincinnati's Xavier University launched an Artificial Intelligence Initiative earlier this year to better determine how AI can be used in the quality and regulatory space in the device and pharma industries. The initiative's core team is made up of officials from Xavier and FDA, IBM Watson Health, and experts from device and drug firms. *(Also see "Artificial Intelligence Center To Offer Quality, Regulatory Solutions" - Medtech Insight, 13 Apr, 2017.)*

At the first-ever AI Summit at Xavier in August, Czabaniuk explained how artificial

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More on AI

http://bit.ly/2z8CzxC
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Read about AdvaMed's efforts to engage the government on the future regulation of artificial intelligence, and the new Artificial Intelligence Initiative at Xavier University.

Balloon tech inflates fat-loss market

http://bit.ly/2z0S8Fw

The global market for minimally invasive weight-loss devices is expected to grow to $290m by 2021, and a key driver of that growth is the increasing adoption of intragastric balloon technologies.

When a 510(k)?

http://bit.ly/2yhBMLv

A 20-year-old document laying out US FDA's recommendations for determining when a 510(k) is needed to support a device modification has finally been updated after years of debate and controversy.

More from TCT

http://bit.ly/2z48ywN
http://bit.ly/2z45bZt

Find out the interventional cardiology highlights from this year's Transcatheter Cardiovascular Therapeutics meeting in Denver.

Compliance 360° podcast

http://bit.ly/2z8x95J

Listen to the second of a two-part conversation on managing relationships with contract manufacturing organizations in the latest episode of Compliance 360°, a podcast on medtech compliance and enforcement issues.

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market is expected to exceed $20bn by 2020. To fully capitalize on this opportunity, Israel-based Sisram Medical, one of the leading suppliers of energy-based devices to China, is looking to grow its portfolio through acquisitions and in-house R&D.

COMPANIES

START-UP SPOTLIGHT

POLICY & REGULATION

TCT 2017: Fewer Stents Are Better Than More For Initial AMI-With-Shock Treatment

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Fewer stents are better than more for the initial treatment of patients with multivessel coronary disease suffering an acute myocardial infarction (AMI) complicated by cardiogenic shock, according to new randomized trial results. Existing professional guidelines are likely to change due to the findings, which were presented Oct. 30 at the Transcatheter Cardiovascular Therapeutics (TCT) scientific symposium in Denver and simultaneously published in *The New England Journal of Medicine*.

Results from the randomized, 706-patient CULPRIT-SHOCK trial showed that initially approaching these difficult-to-treat patients with culprit-lesion-only percutaneous coronary intervention (PCI) – stenting just the vessel causing the AMI reduces, rather than treating multiple vessels in the same procedure – reduces the composite risk of 30-day mortality and/or severe renal failure.

The results were reported by Holger Thiele of the University Hospital Leipzig on Oct. 30 at the TCT conference. "The major message from our trial is keep it simple. Do the PCI on the infarct-related artery and then look how the patient is doing later on and then you can do a staged revascularization," Thiele concluded.

The trial randomized patients with multivessel disease and cardiogenic shock to either culprit-lesion-only PCI with the option of staged revascularization procedures later, or immediate multivessel PCI. About half of enrolled patients had been resuscitated prior to randomization, with 62% presenting with ST-elevated myocardial infarction (STEMI). About 28% of the stenting procedures included mechanical circulatory support with intra-aortic balloon pump, extracorporeal membrane oxygenation, or circulatory assist devices, including **Abiomed Inc.**'s *Impella 2.5* and *Impella CP* percutaneous pumps, and **Cardiac Assist Technologies Inc.**'s *TandemHeart*.

The primary endpoint was a composite of death or severe renal failure leading to renal-replacement therapy within 30 days after randomization. Safety endpoints included bleeding and stroke.

At the one-month follow-up, the rate of the primary composite endpoint was significantly lower in patients assigned to culprit-lesion-only PCI compared to immediate multivessel PCI (45.9% vs. 55.4%; p=0.01). There was also significant difference between the risk of all-cause mortality (43.3% vs. 51.5%; p=0.03) between the culprit-only and multivessel groups. There was a trend toward a difference in the rates of renal replacement therapy, but this did not reach statistical significance (11.6% vs. 16.4%, p=0.07).

There were no significant differences in the rates of bleeding or stroke experienced by patients in the two study groups. There were also no significant differences in the time to hemodynamic stabilization, length of intensive care unit stays, or requirement for and duration of catecholamine therapy.

Thiele further pointed out that the patients treated with Impella circulatory support showed a trend toward worse outcomes, even though the Impella improves circulation in these patients. "[The worse outcomes are] not because of Impella, but because of selection bias - the investigators felt, 'ok, this is a patient who is extremely sick and they have a very high mortality risk.' And that's the reason why they implanted the Impella. We have to do further analysis of this."

Currently, some professional guidelines favor more complete revascularization of all vessels in these patients, Thiele explained. 2017 guidelines from the European Society of Cardiology on treating patients with AMI identifies multivessel PCI in this population as a IIa-C recommendation, indicating that the weight of the existing evidence and expert consensus is in favor of the treatment based on small trials or registries. Also, 2016 guidelines from the American College of Cardiology and other societies state "PCI of a noninfarct artery may be considered in selected patients with STEMI and multivessel disease who are hemodynamically stable, either at the time of primary PCI or as a planned staged procedure." This recommendation is rated IIb, meaning it is a "weak" recommendation based on moderate-quality data.

Thiele said evidence of a mortality benefit with the simpler culprit-lesion-only

approach versus the multivessel approach will lead to changes in the professional guidelines. "We know from registry data that in clinical practice – both in the US and Europe – multivessel PCI is currently only used in about 20% of the patients," he said. "We've stopped doing multivessel PCI in patients with cardiogenic shock [at our center]. We are now only doing culprit-lesion-only PCI and then we assess the patient later on to see if the patient really needs additional staged revascularization. These data are so convincing with a mortality reduction. That's why we stopped doing multivessel PCI in these patients."

"This is a landmark study and it will absolutely change our practice," Cindy Grines of Hofstra Northwell School of Medicine in East Garden City, New York, explained. "The registry [data] always suggested that there was higher mortality [with multivessel PCI] and that the benefits of multivessel PCI in the acute setting were only a reduction in recurrent ischemia. So, with this landmark trial, I think we're going to take a step back and really try to limit the patients we treat with multivessel acute PCI. That's not to say they won't benefit from a staged procedure, and we may have some subgroup analysis that shows who may benefit from that. But for right now we should take a step back and just treat the culprit."

Other cardiologists at TCT agreed that the trial results will change how physicians approach these patients in many cases. "This will change practice. This is a very important study," Jonathan Hill of Kings College Hospital in London said during a press conference at the meeting.

Hill agreed with Thiele that many interventionalists already suspected that culprit-only PCI was the better option for these patients. "It's already been implemented from a practical perspective. Most of the decision-making about multivessel revascularization is made on a pragmatic basis."

David Cohen of Saint Luke's Mid America Heart Institute in Kansas City, who has conducted many cost-effectiveness studies of cardiovascular procedures and technology said he is confident that performing more culprit-lesion-only PCIs instead of multivessel PCIs will save the health care system money.

"This is an easy health-economic question," he said. "I haven't seen any health economics or length of stay information or anything like that, but this looks like a clear place where 'less is more' - Less resource utilization during the initial procedures and better outcomes including mortality and renal replacement therapy – both of which are very expensive. It's hard to believe that an economic analysis would not show this is cost-savings as well."

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Hurricane Recovery Costs Vary For Medtech Firms, Q3 Reports Show

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Medical device manufacturers with facilities on Puerto Rico are reporting widely varying estimates of recovery costs during the current round of quarterly earnings calls. Several companies say they expect no meaningful financial impact, while others offer impact estimates ranging from $7m to $70m.

Baxter International Inc. was one of the companies worst hit by Hurricane Maria, with CEO José Almeida anticipating fourth-quarter losses of around $70 million, despite attempts to offset diminished production in Puerto Rico by increasing imports from elsewhere. Inventory for some products won't return to normal levels before the first quarter of 2018, he said during an Oct. 25 earnings call reporting third-quarter results.

The company has three facilities in Puerto Rico, each of which is now producing at least 70% to 80% of their normal output. One of them should be back on the power grid within the week, Almeida said. But full recovery will take some time, he noted.

"But I want to make sure that people understand that the infrastructure in Puerto Rico is devastated," he said. "We are operating under an emergency situation with generators, and we have water in our plants and everything else. So, the plants are fully operational, but we need to make sure the federal government continues to provide the support for the recovery of the island."

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Integra LifeSciences is also facing significant hurricane costs. During an Oct. 26 Q3 earnings call, CEO Peter Arduini estimated a total disruption in the third and fourth quarters of about $15m.

While Integra reported only "minor structural damage" at a facility, in Añasco, Puerto Rico, that supports about one-fifth of Integra's bil-

lion-dollar annual revenue, the company was unable to fill many orders for private-label products made in Añasco, CFO Glen Coleman said. He added that the company had lost $7m in revenue due to the storms: $2m in private-label wound care supplies that couldn't be shipped from Puerto Rico, and $5m from Florida orthopedic procedures that Hurricane Irma delayed past the end of the quarter.

"We've completed all repairs and have re-established manufacturing capabilities utilizing our backup generators, but we are running at less than full capacity," Arduini said. The company expects further losses of about $8m in the fourth quarter. It has now shifted some private-label production to New Jersey.

DELAYED PROCEDURES LOWER PROFITS

In addition to storm damage to facilities, companies are also grappling with lowered sales caused by storm-delayed medical procedures. For example, **Edwards Lifesciences Corp.** CEO Mike Musallem said during an Oct. 24 earnings call that "a number" of operations scheduled to take place in Houston and Florida during Hurricanes Harvey and Irma, respectively, were postponed. The company believes most of the patients have since been treated, he said, but the delays cost Edwards several million dollars in third-quarter sales.

Boston Scientific Corp. CFO Daniel Brennan said Oct. 26 that, while the company doesn't expect a major financial hit from storm damage in Puerto Rico, the situation remains challenging. Key priorities for the company include aiding employees; stopping the use of generators; and "validating the resiliency assurances we have from our raw materials and component suppliers," he said.

Several other companies also reported minimal financial impact, including **Stryker Corp., Cooper Cos. Inc.**, **Abbott Laboratories Inc.**, and **Merit Medical Systems Inc.**

Abbott saw facilities imperiled by disasters including the 8.2-magnitude earthquake in Mexico on Sept. 7 and California fires early this month, on top of the hurricanes. But the hurricane itself caused not much more than "a little bit of roof damage and a little water leakage here and there," CEO Miles White said in an Oct. 18 earnings call. The largest single issue has been access to power within Puerto Rico, which he said company staff had quickly addressed to get facilities back up and running. In the end, the company could absorb its storm costs within already-set quarterly estimates.

Merit Medical CEO Fred Lampropoulos said in an Oct. 25 earnings call that the company's Houston facility sustained only minor damage in Hurricane Harvey, and lost less than four production days. The greater cost from the storm came in the form of damage to employee's homes, he said.

"I think the biggest cost was that of the psychological cost," Lampropoulos said, echoing comments from other manufacturers. "And of course, anytime you have employees that are disrupted it's always bothersome to all of us."

Companies including Cooper, Edwards and Stryker have announced funds to assist displaced employees on the island.

Meanwhile, US FDA says it is closely monitoring supplies of about 50 critical medical devices made in Puerto Rico. *(Also see "FDA Tracks Critical Device Supply During Puerto Rico Hurricane Recovery" - Medtech Insight, 20 Oct, 2017.)* Commissioner Scott Gottlieb says the agency is mindful of the substantial economic impacts of getting device, and drug, manufacturing facilities back and running to full capacity on the island. *(Also see "US FDA's Gottlieb Warns Congress Of Shortages, Potential Job Losses In Puerto Rico" - Medtech Insight, 25 Oct, 2017.)*

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India-US Tensions Grow In Device Pricing Cap Controversy

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Tensions over India' regulatory actions this year capping prices of first stents and then knee implants has spilled over to trade-war territory after the US medical device lobby group AdvaMed sought the intervention of the US Trade Representative.

AdvaMed recently petitioned the USTR to suspend or withdraw benefits to India under the Generalized System of Preferences (GSP) in view of its failure to provide "equitable and reasonable" access to its market for medical devices. The GSP program essentially permits duty-free entry into the US for specific products from beneficiary countries.

The price caps were instituted for stents toward the beginning of the year and were followed by caps for knee implants handed down over the summer. *(Also see "India Strikes Pricing Blow To Knees After Stent Cuts" - Medtech Insight, 18 Aug, 2017.)* The actions have also captured the attention of US lawmakers. *(Also see "US Trade Rep May Take Enforcement Actions Against India Over Device Price Controls" - Medtech Insight, 21 Jun, 2017.)*

AdvaMed's action, though, has triggered an avalanche of protest

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in India, with health-advocacy groups opposing what they termed as the US trade association's "barefaced" attempt to intimidate the Indian government and retaliate against its decision to fix the retail prices of cardiovascular stents and knee implants in the public's interest.

All India Drug Action Network (AIDAN), an NGO, has underscored that access to health products is "non-negotiable and that India must not give in to the bullying tactics of the US-based medical devices industry."

AIDAN referred to data from India's drug prices regulator, the National Pharmaceutical Pricing Authority (NPPA), which claimed that stents were being sold by hospitals at unreasonable mark-ups compared to the price at which they were procured – 436% for bare metal stents and 654% in the case of drug-eluting stents, on average.

"This was an outcome of unethical business practices, established and institutionalized by the leading foreign stent manufacturers, which rely upon commissions to hospitals and kickbacks to members of the medical fraternity to boost sales and gain market share," AIDAN charged in an Oct. 25 statement. "Helpless patients were therefore being charged artificially inflated prices that bore no relation to the manufacturing or import costs."

Political voices also joined the protest, with Dharamvira Gandhi, a member of Parliament, underscoring that India should not buckle to pressure from industry or the US and it should "uphold the sovereign right to protect people's health". Gandhi's Oct. 25 note to India's Commerce and Industry Minister Suresh Prabhu, pressed for the Competition Commission of India to probe the issue of device manufacturers allegedly "acting in cohort" with hospitals to keep prices high.

Gandhi added that should the US withdraw GSP, in part or full, India must retaliate by raising tariffs, not just on medical devices where domestic manufacturing capabilities exist, but also on some luxury goods, such as Harley Davidson bikes.

INDUSTRY'S ARGUMENT

Foreign device manufactures, however, maintain that India's pricing mechanism for medical devices "should not strangulate" the flow of innovative and critical care devices in the country. Both pharmaceutical and medical devices firms have long maintained that pricing of products cannot be viewed in isolation. Affordable health care, they assert, is not only about the price of a medicine or a device, but also the associated costs of care – diagnostics, hospital charges, doctor fees, sometimes unnecessary tests and other costs that pile up for patients.

This is reflected in AdvaMed's Oct. 17 statement, which notes that India's singular focus on controlling ceiling prices of high-quality medical devices, without any attempt to address the larger picture and correct inefficiencies in the health-care system, will not achieve its intended benefits. "Recent reports indicate that the lowering of prices on medical devices – which are only one component of overall procedure costs – are not being passed along to patients. Price controls may also block innovations and limit patient access to the best available care."

Industry's arguments appear to hold true on the ground, at least in some specific instances. In one such case, *Medtech Insight* learned that overall costs for a knee implant procedure before and after the price cuts were almost on par, as prices of other costs in the hospital increased, making up for the price reduction in the device.

One industry veteran told *Medtech Insight* that the entire device price cap issue could perhaps have been "handled differently," targeting high trade margins instead. Discussions around capping distributor and retailer margins for devices are already believed to be underway.

The Medical Technology Association of India (MTaI), whose founding member companies include **Johnson & Johnson**, **Bausch & Lomb, Smith & Nephew**, and **Boston Scientific Corp.**, among others, indicated earlier this month that it endorsed the Department of Pharmaceutical's trade margin rationalization committee report to ensure that industry viability and continued supply of critical care medical devices is balanced with patient access, though specifics are not immediately clear.

But, in the interim, price cuts have irked industry's big names. Indian device price cuts were mentioned in J&J's recent Q3 earnings call. The company's management referred to it as a "much more extreme example of what we've seen in other marketplaces, which are a lot more moderated."

Another industry watcher with a foreign firm told *Medtech Insight* that the NPPA decision to turn down foreign firms' requests to pull their products from India was perhaps the last straw. This was further complicated by ongoing "conflicting signals" and a situation of general mistrust. "We don't know what next now," the industry expert said.

There is also concern among some in industry about the prospect for India's price-cap approach to be modelled by other countries in the region that are grappling to rein in health-care costs.

"For example, the Asian Harmonization Working Party (AHWP) meeting scheduled later this year, though essentially about harmonizing medical device regulations in the Asian and other regions, can potentially be a useful platform to exchange ideas, even unofficially, and pricing issues are generally of interest to everyone," an industry expert said. *Medtech Insight* has no official word on the final agenda of the AHWP meeting, slated for early December in New Delhi, and whether there is any real scope for price-related discussions at all.

ENFORCEMENT ACTIONS

Significantly, in June, US Trade Representative (USTR) Robert Lighthizer indicated to Senate Finance Committee Chairman Orrin Hatch, R-Utah, that if India's ongoing practices to impose price controls on US device imports continue, he would consider "enforcement actions." *(Also see "Lawmakers Prod Trump To Talk Trade Barriers, Stent Price Caps With India's Modi" - Medtech Insight, 26 Jun, 2017.)*

A letter from Lighthizer to India's minister of commerce and industry, Suresh Prabhu, in September followed up on concerns relating to the price control policy for stents that were raised during Indian PM Narendra Modi's visit to the US in June.

Among the string of points highlighted, the USTR notes that the pricing policy has created "serious problems" for US companies selling these products in India. The letter dated Sept. 18, in particular, notes that the NPPA order on stents does not sufficiently differentiate drug eluting stents based on the level of technology, affecting the most innovative and advanced stents, most of which are imported into India.

In February this year, the NPPA capped the prices of stents in India into two broad buckets – bare metal stent prices were capped at INR7,260, while prices of drug-eluting stents, including me-

tallic stents and bioresorbable vascular scaffold/biodegradable stents were capped at INR29,600.

"The ceiling price under the NPPA order is also below the cost of production for the most innovative stents," Lighthizer said. Besides, tensions have intensified since the NPPA isn't immediately allowing US firms to withdraw their products from India.

Interestingly, on Oct. 24, the USTR announced a "new effort" to ensure beneficiary countries are meeting the eligibility criteria of the GSP trade preference program, though not necessarily directed at any particular country. The new efforts, the USTR said, aim to ensure all countries receiving trade benefits are meeting eligibility criteria

"By creating a more proactive process to assess beneficiary countries' eligibility, the US can ensure that countries that are not playing by the rules do not receive US trade preferences. This sets the correct balance for a system that helps incentivize economic reform in developing countries and achieve a level playing field for American businesses," Lighthizer said in the statement.

MIDDLE GROUND?

Meanwhile, it appears there have been some ongoing efforts to reach a middle ground, if not an understanding, to avoid further pain on both sides.

Lighthizer's letter also adds that the US government is committed to working with India to identify "a policy solution" that will address the Indian government's priorities related to patient costs, but will also promote trade, innovation and access to the most advanced technologies.

The previously quoted medtech industry veteran underscored to *Medtech Insight* that India cannot really afford an escalation of issues.

"A middle path - containing trade margins and no further major price action – should possibly be considered for now to avoid things spiraling out of control," the veteran added.

The device caps issue was expected to feature at the US-India trade policy forum in Washington on Oct. 26, though specifics on the overall meeting are not immediately clear. Minister Prabhu tweeted that he had engaged in positive discussions with Lighthizer in the US. "Despite differences over minor issues, alignment on capturing the huge potential of bilateral trade," the minister's tweet read, though there's no clarity if any of these references pertain to medical devices. Some reports in the Indian media said that Prabhu emphasized that India desires to address the concerns of providing affordable health-care to its citizens and "at the same time work towards striking a balance between affordable health-care needs and introduction of high-end technology".

While the jury may still be out on how the Indian device price caps row will eventually play out, industry experts caution that a complete pull back by India doesn't not seem very likely, given the move has been publicly recognized by no less than Prime Minister Modi. On May 26, India's Department of Pharmaceuticals tweeted that savings that have resulted from the price cap on coronary stents are estimated at INR44.50bn.

And then there is the timing – with India heading into general elections in 2019, any pull back will be great domestic political fodder to highlight US influence on Indian policy. Striking a balance between business and vote-bank interests is unlikely to be an easy task.

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China's High Demand For Aesthetic Solutions Brings Attractive Opportunities

FANGQING WANG

Medical lasers manufacturer Sisram Medical caused a recent buzz in the global aesthetic industry when it became the first Israeli company to list on the Hong Kong Stock Exchange, raising $112m in its IPO. The firm, which was formerly known as Alma Lasers before it was renamed Sisram when acquired by Chinese pharmaceutical company Fosun Pharma in 2013, decided to float in that market not only because it had a Chinese owner but because of its belief in China's great potential to power Sisram's future growth, said company chairman Yi Liu.

"We are very confident about the Chinese market opportunity, which has seen a fast-growing number of Chinese [consumers] actively seeking beauty through aesthetics solutions," Liu told *Medtech Insight*. But instead of open surgeries, he continued, Chinese customers in general prefer either minimally- or non-invasive procedures (M/NIP).

"It's clear that high-quality M/NIPs are in great demand in China," Liu said.

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Globally, the volume of nonsurgical aesthetic procedures increased 10% year-on-year in 2016, compared with 8% for surgical procedures, according to the International Society of Aesthetic Plastic Surgery.

In a bid to address this demand, Sisram plans to invest about $15.6m in R&D of minimally- and non-invasive aesthetic technologies, Liu said.

Additionally, the company will be looking at global acquisitions to bring suitable solutions into the portfolio. The ideal acquisition targets could be either service providers, like beauty salon chains, or technology developers, like companies with unique, novel M/NIP products. Sisram is also looking at firms that can facilitate geographic expansion and give it access to new markets, including Japan, India and East European countries.

In its IPO prospectus, Sisram claimed it is the largest supplier in China of energy-based devices, including lasers, intense pulsed light and radiofrequency (RF) devices, enjoying 16.2% - the largest share – of the market, with the body contouring RF device Accent Ultra V among its best-selling products.

"Driven by the market growth, we will work with Fosun Pharma and our long-term Chinese distributors to continue our expansion in the country," Liu said.

In 2015, China was the world's third largest medical aesthetic market, behind the US and Brazil, according to ISAPS. However, China significantly lags behind in terms of aesthetic service penetration rate. Only 1.7 people out of 1,000 in China received medical beauty services in 2015, compared with 12.6 out of 1,000 in the US, and 11.6 out of 1,000 in Brazil.

Nonetheless, the Chinese market for medical aesthetic devices is estimated to reach $20.6bn by 2020, if the annual compound growth rate can stay at 22.7%, according to the consulting company Deloitte.

Wu Yuling, an analyst at Guangzhou-based research company Zhongwei Intelligence, said it's not only China's female population, but also male, who are in pursuit of beauty.

"Affluent Chinese women are the major clients in the market, but recently, we've seen also a growing number of male customers," Wu said, adding skin resurfacing and hair implants are among the items favored by Chinese men.

CYNOSURE AND THE COMPETITION

With China presenting so much opportunity for aesthetics technologies, it is little wonder that competition among multinational device makers, which started decades ago, has now elevated to an intense level.

According to Zhongwei Intelligence, foreign brands like Sisram and CynoSure dominate China's current aesthetics device sector. Whilethere are several big Chinese manufacturers, such as Wuhan-based Miracle Laser and Shenzhen-based GSD, "this is a field requiring heavy investments in R&D, which is not what most Chinese companies are currently capable of," Wu said.

For CynoSure, which was acquired by Hologic in March this year, China has been "instrumental" to the company's overall APAC strategy and senior vice president Joseph LaBruzzo said he sees the country playing a "significant ongoing role."

Since entering China in 1999, CynoSure has well positioned its laser skin solutions including MedLite C6 and Picosure, in the Chinese market, and these products are overwhelmingly popular among Chinese women seeking smooth, flawless skin.

"Our growth with Picosure has assured us that our product has been accepted as a great advancement in picosecond technology," LaBruzzo continued.

Acknowledging an increasingly crowded market, LaBruzzo said a nationwide network of direct offices in China ensures the company to provide support in a fast manner, which is a key advantage for doing businesses in a market as vast and fragmented as China.

COUNTERFEIT CHALLENGES

But these days, CynoSure, like many other multinationals in China across different industries, is facing one big challenge – counterfeiting.

Picosure has been subject to this unabatingly rife problem. Since the Chinese celebrity Fan Bingbing last year gave a high-profile endorsement of the device, there have been numerous Picosure counterfeit devices permeating the market.

These imitation products have reportedly cause users' skin to burn and complaints have been spreading across social media, which has led to the Chinese police taking measures. In Sept, the police in Guangzhou, Guandong province, caught a group who manufactured and sold fake Picosure devices at the price of only CNY40,000 (US$6024) each to clients in and outside China, most of whom are small beauty salons and beauty schools.

A quick search on internet showed various Chinese-made fake Picosure devices priced between CNY50,000 and CNY200,000, whereas the authentic one costs over a million.

"Counterfeiting is indeed an issue in China. We actively defend our position through legal, regulatory and sales channels to assure that our years of investment in China is protected," CynoSure's LaBruzzo said.

Currently, Picosure and Picoway, which is from the Israeli company Syneron Candela, are the only two imported picosecond laser tech devices approved by China's Food and Drug Administration to sell in China. By law, China requires all licensed beauty clinics to purchase the medical devices registered with the CFDA, but, in reality, non-registered devices are sold across the country to unlicensed beauty clinics dotted in small cities and rural areas.

"Some counterfeit devices were sold a lot more than authentic products, and it severely disrupted the market and posed great risks to customers," Zhongwei Intelligence's Wu said.

In the past decade, about 20,000 complaints related to failed cosmetics surgeries were reported on average each year due to bad practices and low quality products, according to Beijing-based China Consumers Association.

The authorities knew the danger and took action. In May, the central government issued a notice to crack down unlicensed beauty clinics nationwide, aiming to destroy the whole supply chain of illegal aesthetic devices and medicines. For example, nail salons are now banned to perform any kind of N/MIPs, including injections of hyaluronic acid, another victim of counterfeits.

"Licensed beauty salons will no doubt improve compliance in the market. However, I think it will be a long journey to regulate the aesthetic market," Wu said.

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Novartis Confirms Rumors With $3.9bn Deal For AAA's Nuclear Med Biz

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Novartis AG has finally put to rest rumors about its intention to acquire France-based nuclear medicine specialist **Advanced Accelerator Applications SA** (AAA) when it confirmed Oct 30 that the two parties have agreed to an all-cash $3.9bn M&A deal.

The rumors had gathered intensity in the last month or so, but when *Medtech Insight* had asked AAA's CEO Stefano Buono if there was any basis to the speculation, he had been coy, saying that the firm has had "general interest from pharma."

AAA was spun off from Europe's physics research center CERN 15 years ago and listed on NASDAQ in 2015. Novartis' pharma division established a molecular diagnostics unit eight years ago. The transaction's size is in line with Novartis oft-stated M&A parameters.

But analysts say AAA's real attraction for the diversified Swiss drug-maker is the French group's pipeline.

Its lead candidate, Lutathera, is a cancer therapeutic for treating neuroendocrine tumors, an area which Novartis already has expertise in. Lutathera combines the somatostatin analog peptide *Octreotate* with the radioisotope lutetium-177 for treatment of gastroenteropancreatic neuroendocrine tumors (GEP-NETs) in adults, which often originate in the pancreas.

Lutathera (177Lu DOTA-octreotate) was approved at the end of September in Europe for treatment of unresectable or metastatic somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors. It is also under review for a similar indication in the US, with a user fee date of January 26, 2018, following a complete response letter and resubmission. *(Also see "Keeping Track: Review Underway For Linhaliq, New Uses Of Lenvima, Cimzia; New Cycle Starts For Lutathera" - Medtech Insight, 30 Jul, 2017.)*

The product was granted orphan status in the EU in June 2014. More than 1,700 neuroendocrine tumor patients across 10 European countries have already received the treatment under compassionate use and named patient programs. In the US, Lutathera has already been granted orphan status and is available under an expanded access program.

LUTATHERA: POTENTIAL 'GAME CHANGER'

Lutathera is a potential therapeutic "game changer," according to Jefferies analysts Peter Welford and Lucy Codrington. The pair said in a reaction note that "impressive Phase III NETTER-1 data, clinician feedback, and a proprietary US physician survey all underpin our confidence in Lutathera."

They said the therapy, based on a well-known concept of somatostatin analogues for neuroendocrine tumors, has already treated more than 3,000 patients, and addresses an unmet medical need. Jefferies is therefore forecasting $650m peak sales treating mid-gut gastroenteropancreatic neuroendocrine tumors. "Adoption to treat other types of neuroendocrine tumors could offer significant potential upside, with … $285m incremental peak sales," the duo added.

The efficacy and safety of Lutathera were established in the Phase III NETTER-1 trial whose primary endpoint was progression free survival with secondary endpoints including objective response rates, overall survival, safety and tolerability. The Phase III NETTER-1 study found that Lutathera significantly prolonged progression-free survival (PFS) when added to the standard therapy, Novartis' long-acting *Sandostatin LAR* (octreotide) 60 mg in patients with advanced mid-gut neuroendocrine tumors. *(Also see "Advanced Accelerator Preps Lutetium-Tipped Warhead For NETs Filing" - Medtech Insight, 29 Sep, 2015.)*

In explaining its reasons for wanting AAA, Novartis in a statement said it was also attracted by the broad set of skills AAA could bring in developing, manufacturing and commercializing radiopharmaceuticals, including the companion diagnostics for Lutathera, such as NETSPOT and SomaKit TOC.

Datamonitor Healthcare analyst Ali Al-Bazergan said, "The AAA acquisition fits in line with Novartis's bolt-on M&A strategy with a de-risked late stage asset in Lutathera for neuroendocrine tumors."

"Price-wise, Advanced Accelerator Applications had sales of $118m in 2016 so the $3.9bn looks on the expensive side, but provides Novartis with a strong platform to explore the company's expertise and RadioLigand Therapy technology."

Informa's *Biomedtracker* currently estimates Lutathera's likelihood of approval at 76% following AAA's receipt of the FDA complete response letter and subsequent resubmission.

Informa's *PharmaVitae* views the acquisition as a modest addition to Novartis' oncology portfolio and will primarily act as lifecycle management to its $1.6bn long-acting Sandostatin LAR (octreotide) *Sandostatin*, with Lutathera is expecting to command a higher price due to improved efficacy.

TRANSACTION DETAILS AND LOGIC

Under their planned transaction, Novartis proposes to make a cash tender offer of $82 per ADS, for a total value of $3.9bn. This represents a 47% premium to the 30-day volume weighted average price prior to the unaffected share price on Sep 27, before rumors of the planned deal started to spread in markets. AAA's board is recommending the offer. Jefferies International is acting as exclusive financial advisor to AAA.

Bruno Strigini, who heads Novartis' oncology division said in a statement that "Novartis has a strong legacy in the development and commercialization of medicines for neuroendocrine tumors … with Lutathera, we can build on this legacy by expanding the global reach of this novel, differentiated treatment approach and work to maximize Advanced Accelerator Applications broader RadioLigand Therapy pipeline and an exciting technology platform."

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ANALYST:

Amazon Possibly Priming Itself As Medical Device Retailer

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For months market analysts have been discussing **Amazon.com Inc.**'s potential foray as a mail-order pharmacy, but after recent reports detailed the company's regulatory efforts at least one analyst says the real deal may be that the it is showing signs of trying to conquer the medical device supply sector.

Last week, the *St. Louis Post-Dispatch* reported that, over the past year, the online retail giant has gained approval to be a wholesale drug distributor in 12 states, including Nevada, Arizona, North Dakota, Louisiana, Alabama, New Jersey, Michigan, Connecticut, Idaho, New Hampshire, Oregon and Tennessee. The news sent stock prices for retail pharmacies, such as **CVS Health Corp.** and Walgreens, plummeting and even mail-order drug service **Express Scripts Holding Co.** experienced an initial drop in share price that has since rebounded.

However, at least one analyst says Amazon's efforts seem to signal the company may instead be interested in putting a stake in the online medical device retail business rather than targeting online drug-retail, a point first highlighted by *CNBC*.

"News of Amazon's receipt of wholesale pharmacy licenses drove a sell-off yesterday in pharma supply chain stocks," said Brian Tanquilut, an analyst with Jefferies, in a research note. "While that news strengthened investors' fears about Amazon's entry into drug retailing, our due diligence suggests that the licenses Amazon obtained are likely associated with their sale and distribution of medical equipment rather than prescription drugs."

Tanquilut and his team say the state wholesaler licenses acquired by Amazon seem to indicate that the firm is interested in existing business-to-business medical device sales and distribution rather than the mail-order drug industry. They argue that the wholesale distribution licenses acquired between October 2016 and January 2017 coincide with the launch of Amazon's professional medical device B2B website, which was made publicly available between November and December 2016 to support sales of medical and dental equipment to professional practices.

The analysts also argue the out-of-state wholesaler license acquired by Amazon in Nevada does not cover controlled substances, which indicates the company is looking at a narrower market reach.

"While we acknowledge that there are prescription drugs that don't fall under the definition of 'controlled substances', the active decision to choose not to distribute those types of drugs leads us to believe that Amazon will not be using these licenses to distribute any prescription drugs despite the lack of clarity around the types of products the company would be allowed to distribute via other state license filings," said Tanquilut. "Investor fears that these licenses serve as a gateway to Rx retail/B2C sales & distribution are unlikely to abate over the near term."

The analysts also state that Amazon faces a substantial hurdle to entering the mail-order pharmacy business due to lack of payer and pharmacy benefit management (PBM) relationships. They say that PBM market share is highly concentrated and it is doubtful those already in the market are interested in signing any deal with Amazon for fear of competition.

Shutterstock: Jonathan Weiss

On the other hand, Tanquilut and his team note, Express Scripts has said it would be open to a partnership with Amazon. But "we still doubt that management's willingness to create a large mail-order competitor, considering that they are currently the largest mail pharmacy operator in the market and derive a significant percentage of overall company profitability from their mail operations; we believe Express Script's willingness to work with Amazon pertains mostly to cash-pay patients."

Without acquiring a large PBM, the analysts say, it will be tough for Amazon to capture enough market share and leverage to justify getting into the pharmacy business.

IMPACT ON DEVICE DISTRIBUTORS REMAINS TO BE SEEN

Meanwhile, they add, it's difficult to assess the impact on medical device distributors such as **Cardinal Health Inc.**, **McKesson Corp.**, and **AmerisourceBergen Corp.** if Amazon enters that market.

"While we believe that the distributors have strong and deep relationships with both large health systems and smaller physician practice groups, Amazon's entry into medical device/supply distribution certainly poses risks that we believe are difficult to quantify at this point, given uncertainty about Amazon's planned breadth of product offering and the willingness of physicians and hospitals to purchase products from multiple suppliers/systems," they state. "Additionally, tapping into the large health system market will likely prove more difficult, so meaningful disruptions in the near future to the distributors' medical distribution businesses seem unlikely."

Amazon has listed a number of products that retailers can sell through its website, including medical devices that are autho-

rized by US FDA as over-the-counter products such as eyeglass frames, tanning devices and otoscopes. Other FDA-approved or -cleared products, such as asthma inhalers, cardiac monitors, surgical kits, electrosurgical cutting and coagulation devices, circumcision devices, and certain cancer tests (e.g., prostate specific antigen assays), that require a prescription and are sold only to professionals are available only through Amazon's Professional Health Care Program.

The company also says it will not allow products that have not been given the green-light from FDA or have been altered to be sold on their site, including psoriasis lamps, certain hearing aids and certain diagnostic tests such as those use to diagnose sexually transmitted disease (STD) and testosterone.

Amazon isn't the only major tech company eyeing opportunities in the medical device arena. But while Amazon considers advancement in the device distribution space, companies like Apple and Google-parent spin-off **Verily Life Sciences LLC**, are eyeing the device sector as an opportunity for innovative product development. *(Also see "'Excellence' In Health-Software Design: US FDA Taps Nine Firms To Figure Out What That Means" - Medtech Insight, 26 Sep, 2017.)*

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START-UP SPOTLIGHT:

MeMed, Making Infectious Disease Dx Clearer With Immune Responsive Signatures

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Recognized as a worldwide public health concern, antimicrobial resistance (AMR) has become one of the key priorities of the World Health Organization, which launched a global multi-pronged action plan in 2015 to tackle this threat. But the numbers which governments must battle against are significant. According to the WHO, the EU sees around 25,000 AMR-related deaths per year while the US has over 23,000.

In less developed countries, these figures start to rocket; for example, in Thailand, AMR kills over 38,000 people each year and results in 3.2 million hospital days (compared with 2.5 million AMR-related hospital days in the EU).

The misuse and overuse of antibiotics underpin the continuing threat of AMR, largely because it is very difficult to tell apart a bacterial infection from a viral infection. "If you have a child who is sick and has a fever, and you take them to hospital, the doctor has to decide whether to treat them with antibiotics or not. And the problem is they don't know because the symptoms between bacterial and viral infections are often clinically indistinguishable," said Eran Eden, CEO and co-founder of **MeMed**, an Israeli company that has received over $20m in grants from the European Commission and US Department of Defense in the last year and a half to support its technology designed to solve this very problem.

MeMed's ImmunoXpert is an ELISA test based on the company's platform that uses the human immune system as the disease sensor. The immune system, according to the Tirat Carmel-based firm, responds differently to viruses and bacteria and it activates distinctive physiological pathways to fight these pathogens. MeMed's technology uses the pathogen's "immune responsive signature" as the biomarker, instead of trying to isolate and identify the actual pathogen causing the infection.

"In the process of developing these immune responsive signature, we screened through many biomarkers and we identified signatures which are optimal for distinguishing bacterial versus viral infections and have significant amount IP around those particular signatures, as well as around many other alternative signatures related to immune responsive infections," Eden told *Medtech Insight*.

Current diagnostic techniques that use the direct pathogen-identification ap-

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Contact: Eran Eden, CEO

Industry Segment: IVD

Business: Rapid tests based on immune system biomarkers to distinguish bacterial infections from viral

Founded: 2009

Founders: Eran Eden, Kfir Oved

Employees: over 35

Financing to Date: Around $50m; $30m from equity investors, $20m from grants

Investors: Blue-chip VCs and private investors from Silicon Valley, Israel and Asia, including Social Capital and Horizons Ventures (private investment of Sir Li Ka-Shing)

Board of Directors: Hanina Brandes (Naschitz-Brandes); Patrick Terry; Shmuel Eden (formerly Intel); Anne Lo (Horizons Ventures); Eran Eden; Kfir Oved

Scientific Advisory Board: Itamar Shalit (Tel Aviv University); Paul Feigin (Technion); Israel Potasman (Bnai-Zion Medical Center); Louis Bont (University Medical Center Utrecht); Keld Sorensen (Siemens Healthcare Diagnostics); Yoram Reiter (formerly Technion); Zohar Yakhini (Agilent Laboratories/ Technion); Modi Segal; Eli Opper; Ellen Bamberger

proach for distinguishing bacterial and viral infections – namely culture, rapid antigen tests and nucleic acid-based tests – do work to an extent but there are several limitations, explained Eden. These challenges include: not being able to detect pathogens in cases where the infection site is not readily accessible or is unknown; taking too long a time to turn around results (ranging between hours or days); not distinguishing whether the detected bacteria is the disease-causing agent or a colonizer and thus may give false alarms; and not being able to adapt to the evolutionary change of pathogens which then leads to missed detection.

MeMed's alternative approach of detecting host proteins induced by the immune system in response to the bacterial infection gives it certain immediate advantages over current methods. Not only can the test diagnose cases where the infection site is not readily accessible or is unknown, it is also insensitive to the presence of colonizers.

Over the last seven years, ImmunoXpert has been validated in a trilogy of clinical trials – Curiosity, Opportunity, and Pathfinder – which enrolled over 2,300 patients in total. The results of the international multi-center, external double-blinded Pathfinder study were the latest to come out, when they were published in September in the online version of Pediatrics, the official journal of the American Academy of Pediatrics.

The study enrolled 597 pediatric patients with suspected acute infection including fever without identifiable source, upper and lower respiratory tract infections, urine tract infections and non-infectious controls. It demonstrated that ImmunoXpert could accurately distinguish between bacterial and viral patients with 94% sensitivity and 90% specificity, and a negative predictive value of 98%. The test outperformed routine laboratory parameters used to manage patients with infections, including white blood count, C-reactive protein and procalcitonin.

One of the study's lead investigators, Isaac Srugo, chief of the pediatric department and director of microbiology laboratory at Bnai-Zion Medical Center in Israel, commented that the test demonstrated its potential especially in harder-to-diagnose cases, "as it assigned a clear diagnosis to the majority of cases where there was no agreement on the underlying cause of infection among three independent senior physicians examining the patient medical records," he said. "This is a critical capability as it allows clinicians to use the test confidently even when they are unsure what is causing the infection."

FROM CENTRAL LAB TO POC

ImmunoXpert was CE marked in 2014 and the company rolled it out that year to a few select centers to get more data and feedback on the core technology. Kfir Oved, MeMed's chief technical officer and other co-founder, said the company has had "very warm and enthusiastic feedback" from the 10,000-plus patients who have been diagnosed using ImmunoXpert as part of routine care. However, there have been a couple of elements of ImmunoXpert that have had "serious push-back" from users, he told *Medtech Insight*. The first issue was with the two-hour result turnaround time, as the test needed to be performed by a technician in a central lab. "Two hours is a lot of time when it comes to an acute infectious disease workflow. Acute infectious disease is very similar to acute coronary syndrome, where you need to make a decision right here, right now and if you give a result after more than 30-45 minutes, your test will have less impact on the physician's decision making and on the patient management," said Oved.

The second pushback came from the overall burden that was required from the central lab to run the test. Neither of these two issues came as much of surprise to MeMed, said Oved, which is why the firm has been building a point of care platform, ImmunoPOC, over the last few years while validating its core technology.

Currently in development, the final ImmunoPOC product will be a small benchtop analyzer with a disposable cartridge. The analyzer could sit in the physician's office or in an emergency department and the patient's blood sample will placed in the test cartridge, which is then loaded into the analyzer. The system will be designed to be user-friendly, without the need of a highly trained health care professional to operate it. With a push of a button, the results will be at hand in 15 minutes. "The whole idea is to have central lab chemistry in this POC platform so we do not compromise on the performance of the test," said Oved. "By having the results in 15 minutes, it can have an impact on the physician's decision making on the next steps to treat the patient."

The ability to identify bacterial-infected patients very early also has the added value of being able to give them antibiotics in time and prevent their condition from deteriorating even further. This is especially important for critically or severely ill patients, where if the problem is confirmed quickly as a bacterial infection, a wide spectrum antibiotic treatment could be prescribed first, followed by another microbiological investigation to further narrow down and isolate the pathogens, said Oved.

MeMed's core technology will not identify the substrain of the pathogen, Eden concedes, but distinguishing bacterial from viral infections is "a very critical point in overcoming the issue of antibiotic use."

"Does it solve everything? No, it doesn't," he said. "But it turns out that for the majority of patients, particularly the masses who turn up at the physician's offices and emergency departments, knowing the substrain of the pathogen – while nice to have – is not the real question at hand [for the clinician]. The real question at hand is whether they should treat the patient with antibiotics today, because they have a bacterial infection, or whether they should send the patient home with chicken soup."

MeMed is aiming to complete development of ImmunoXpert and sharing it with its immediate partners toward the end of this year. The firm is shooting for a soft launch in the second half of next year; initially in Europe, followed by the US, then China and the rest of the world. It will not be taking ImmunoXpert to the US, but introducing the POC system instead to this market.

Eden said that MeMed's commercialization strategy will be based on a hybrid

model, with the company going direct in certain territories, while enlisting partners in others. The CEO indicated that the firm would not have too much trouble finding these partners, not only to help commercialize the test for distinguishing bacterial and viral infections, but also for other indications/platforms.

"The high level clinical evidence and the platform that we've created have not been left unnoticed by governments [which is what triggered the grants from the US DoD] and strategic partners. And we are working with different stakeholders in the ecosystem to make sure that this core technology is going to be launched not on our platform but also on other platforms," he told *Medtech Insight*. "This is too big a thing for one entity to take on by itself; we're partnering with governments, clinical centers and key opinion leaders and commercial partners to see how we can take this core technology – that we've been working on for the last eight years and substantially derisked – and enable it to reach as many patients, as fast as possible."

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ASIA REG ROUNDUP:

Vietnam's Medtech Filers Under More Deadline Pressures

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Vietnam's Decree on Management of Medical Devices (No. 36/2016/ND-CP) stipulates that companies with class B, C & D devices must complete Registration Notification Dossier submissions by Dec. 31, 2017. In addition, the current import licenses for class B, C & D will be invalid from the same date, as high-risk devices in the country changes over to a fully regulated system in a series of phases. *(Also see "Asia Reg Roundup: Vietnam On Track Launching New System, Plus Updates From Bangladesh, Hong Kong" - Medtech Insight, 1 Jun, 2017.)*

More and more people in industry believe that it's not possible to meet the deadline, and this, in turn, is putting pressure on the Vietnam government, according to local regulatory experts Jack Wong and May Ng. In fact, the regulators are struggling over whether to allow companies more time. The feeling among local stakeholders is that the regulator may be ready to extend the deadline, but that it would be difficult, politically, to change the regulation. Industry is stuck in the middle of this dynamic, Wong observes.

Ng, of ARQon (Asia Regulatory & Quality Consultancy), believes that companies will simply have to make haste and get all the necessary information collected and dispatched so they can receive their new license approvals and continue importing and selling in Vietnam. The local ministry of health sympathizes with industry's plight, understanding the needs of all stakeholders. It is working with local associations in a bid to help industry meet the requirements for the deadline.

Wong, of ARPA (Asia Regulatory Professional Association), says lessons should be learned from other regional systems. Regulators should set longer, more realistic enforcement dates, he believes. But it's a balancing act: telling industry too soon of any extension would slow matters again. In Malaysia, deadline extensions for regulatory system compliance were announced only at the last minute. *(Also see "Malaysia's New Medtech Regulatory System Imminent - And No More Extension This Time" - Medtech Insight, 21 Jun, 2016.)*

The situation is not helped by the Vietnam regulator's growing workload. A lot of companies are trying to submit documentation for thousands of medtech products. On the other hand, Vietnam is not seen as a main market by some manufacturers, who are already aware of the strict rules that took effect for class A products in July. And some manufacturers are simultaneously seeking product classifications from recognized third-party agencies in Vietnam, while also going through the new regulatory procedures, adding to the confusion.

So industry has no option but to comply – or try to – even though it is not totally ready to meet the deadline. Will the government extend it? That's the big question – legally, they cannot, but many hope that, technically, they will find a way, Wong comments.

REGIONAL ROUND-UP

Elsewhere, the Malaysian Medical Device Authority (MDA) has released a medical device guidance document on change notifications for registered medical devices. MDA/GD/0020 Second Edition (October 2017) sets out points for consideration by registration holders when a registered medical device is in the process of change or modification.

The MDA has also issued a circular (Oct. 2) recognizing the Institute for Medical Research (IMR) as being qualified to provide reports/data on clinical evidence or performance evaluation for the purposes of conformity assessment by conformity assessment bodies (CABs).

Ng adds that the MDA is additionally making efforts to ensure that by the end of this year, all products regulated under the Medical Devices Act 2012 (Act 737) have proper documentation. The authority says it will fully enforce the medical device registration requirements as prescribed under section 5 of Act 737 on importing, exporting or placing medical devices on the market beginning Jan. 1, 2018 (notice in Malay).

Manufacturers' experiences of using Singapore's priority-review channel for certain categories of medical devices, in place

for two months since its Aug. 22 launch, have been scant so far. Wong and Ng are yet to hear any industry feedback. *(Also see "Singapore's Priority-Review Scheme Goes Live" - Medtech Insight, 22 Aug, 2017.)* [**Editors' note:** Medtech Insight *will report Singapore updates in future columns*.]

Meanwhile, Bangladesh's move to put a temporary hold on registrations for new medical device imports has been extended by another six months – until December 2017. *(Also see "Asia Reg Roundup: Vietnam On Track Launching New System, Plus Updates From Bangladesh, Hong Kong" - Medtech Insight, 1 Jun, 2017.)* This does not mean that local companies may not submit documents to the regulatory authorities for registration; it is merely an import relaxation measure. Dealers can build up stocks for the coming months and can later apply to register these products.

Hong Kong continues to prepare for mandatory medical device regulation in two years' time, to replace the system of voluntary registration that has applied for the past 6-7 years. But Wong sees the progress as slow. "From my angle, it's time to make it mandatory," he says, but he believes it will be some 2-3 years before new regulations will be passed. The intention is to charge fees to run the system on a cost recovery basis. But the fee levels being talked of remain confidential for now. *(Also see "Asia Reg Roundup: Vietnam On Track Launching New System, Plus Updates From Bangladesh, Hong Kong" - Medtech Insight, 1 Jun, 2017.)*

The intention in Hong Kong is for cosmetic/aesthetic devices to be regulated first, however. Earlier this year, Ng reported that the Hong Kong Department of Health's (DoH) legislative council has presented a proposal for the regulation of such devices that are used in the beauty/cosmetic industry. Stakeholders have provided their input and, in fact, have voiced considerable objection to the plans. The proposal is for all medical devices used in beauty/aesthetics, except low-risk products, to be regulated.

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NOTIFIED BODY CODES: EU Commission Needs To Act Fast

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Plans are afoot for the European Commission to issue a single "implementing regulation" on codes that would be used by notified bodies to specify their scope of designation under the EU's Medical Device and IVD Regulations by November 26, 2017.

This will be the first implementing act under the new regulations and will combine the MDR and IVDR codes for "reasons of user-friendliness," sources suggest

Experience shows that conformity assessment bodies applying for designation in the IVDR also apply for designation under the MDR, the Commission explains in a recital to the implementing regulation. That's why it is planning to merge the two sets of codes in one document.

November 26 is the earliest date that notified bodies can apply for designation under the MDR and IVDR, so the pressure is already on for notified bodies to comply with these requirements, even though they are not yet finalized. But it is unlikely that any announcements of designations will be made for 12-18 months, according to expert estimates. *(Also see "Three-Year EU MDR Transition Period? More Like 12-18 Months" - Medtech Insight, 12 Oct, 2017.)*

Separate draft codes have been available for the MDR and IVDR on the website of the Notified Bodies Operations Group since August.

But the date of consultation on the implementing regulation that reflects those draft codes only just completed on October 26. Comments will need to be reviewed, and where considered appropriate, implemented within the month, if the document is to be ready in time for the Nov. 26 designation start date.

This puts notified bodies who are first to apply for designation in a difficult situation, as they have only drafts to work with that may change – particularly in the case of the IVD codes. *(Also see "Could First EU Implementing Acts Threaten Timely Designation Of Notified Bodies?" - Medtech Insight, 23 Oct, 2017.)*

The EU Notified Body Association, TEAM-NB, is hoping that 16-18 of its 23 members will be ready to submit for designation by late November. *(Also see "Notified Bodies Apply For EU MDR/IVDR Designations Despite Document Shortfall" - Medtech Insight, 14 Sep, 2017.)* It is not known how many EU notified bodies that are not members of this association will also be among the first wave.

The draft text states that conformity assessment bodies will use the list of codes and corresponding types of devices set out in its "Annexes I and II" when specifying the types of devices they wish to include in their application.

The Commission also states that the lists of codes and corresponding types of devices "should take into account various device types which can be characterized by design and purpose, manufacturing processes and technologies used, such as sterilization and the use of nanomaterials".

"The lists of codes", it continues, "should provide for a multi-dimensional typology of devices, which ensures that conformity assessment bodies designated as notified bodies are fully competent for the devices they are required to assess".

Commenting on the text, Ronald Boumans, senior global regulatory consultant at Emergo, raises the question of whether experts in each of the fields designated by a code will need to be available during an audit. Some fields of expertise are rare, like the Zika virus, he noted. An expert in this subject may not have a full-time job reviewing these types of devices and so availability may be limited, he warned.

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CONTINUED FROM PAGE 1

intelligence could make a difference in how FDA investigators approach inspections, and how audit outcomes could prove to be more favorable for manufacturers.

"On the medical device side, we've had cases where we've seen several MDRs [Medical Device Reports] – serious ones – and we followed up immediately, inspected the firms, and determined there was a failure with their supplier. So, it was a faulty component – the supplier changed the specifications without notifying the manufacturers," he said.

"So, from an investigator's point of view, the first questions they are going to ask are, 'How and why are *we* catching this? Isn't there some sort of a control or system in place where this could be caught before we get here?'" Czabaniuk said. "Unfortunately, models to predict those kinds of failures are not always in place at companies, and it can be complicated, especially for large firms that probably have millions of inputs."

But device-makers could mitigate problems by using AI to more easily detect such troubles before an investigator even arrives at their facility.

"From my view – from the regulatory point of view – AI is a solution," he said. In the near term, "AI in its entirety and its scope may not be achievable, but an incremental approach might be worthwhile – just focusing AI on those risk-based potential events that could occur in a manufacturing environment.

"I think all manufacturers know what those risk-based events are," Czabaniuk added. "For example, if you make implantable devices, an event is probably going to be infections. So, how can a firm weed out infections that occur from an unsterilized product or a sterilization failure, from those that occurred in the practice of medicine? Firms could focus AI in those areas that would reduce the risk in the fastest possible manner.

"And that's what our investigators would like to see: an AI model in place in the regulated environment that would take the place of some of their investigational activities and determine the root cause of some of the problems they see in the field."

Czabaniuk theorizes that as more manufacturers use AI to catch current problems and predict future ones, the less time agency investigators will spend inspecting.

When it comes to artificial intelligence, "I think there's some value added for everybody," he said. "From the regulatory point of view, AI could in fact reduce inspections, and I know how important that is to everybody – not only to the regulated industry, but to FDA. We don't have the resources to inspect the global inventory we have. So, if we could reduce that inspection time, then I think that would give us the capacity to inspect a greater part of our inventory. Anything we could do to save time in the field would be critical from my perspective in the Office of Regulatory Affairs."

Further, AI could result in faster market action by device-makers when a nonconforming product results in a recall event.

"Historically, we've inspected firms once every few years, and we sometimes find a device failure that happened nine months previously, or even a year before we arrived at the firm," Czabaniuk said. "It would be great if firms could find that problem within a shorter timeframe by using AI and taking an appropriate action."

FDA: AI CAN AID 'CASE FOR QUALITY'

Francisco Vicenty – a program manager in FDA's device center compliance office, and a leader for the joint FDA/Medical Device Innovation Consortium (MDIC) Case for Quality – says artificial intelligence offers a host of opportunities when it comes to how – and how often – FDA might inspect.

"Can you imagine what something like [AI] could do to change [FDA's] oversight paradigm?" Vicenty said at MedCon 2017 in May. "If you use AI systems that are looking at all of the interconnectedness that's going on within your facility, that's really where your quality will show."

A Case for Quality initiative that's been underway since last year is focused on developing quality metrics for firms – measures that can be used to assess the overall quality of device manufacturing. FDA will use the metrics as another tool to help it determine which firms have gold-star quality systems. That, in turn, helps guide the agency's selection of facilities to inspect. *(Also see "At The Intersection Of Quality And Metrics: What's Ahead In FDA's Effort To More Objectively Measure Quality" - Medtech Insight, 13 Jul, 2016.)*

> "How often does a regulator like FDA really need to show up at a facility to inspect if we've already done the high-level work of assuring that its AI systems are established well, and have pulse-checks we can do based on the data?" FDA's Francisco Vicenty says.

Vicenty says it's nearly impossible to have a one-size-fits-all approach to quality metrics. "That's a struggle we've had with the Case for Quality – determining what is the right metric when it's really dependent on the company. But AI would be something that would take [the guesswork] out of it" and give a much clearer signal of a quality system's health – and whether the agency should inspect.

To use AI is to go beyond using simple metrics, which can take a firm only so far. Metrics can help guide a manufacturer to become proactive after a failure has already occurred, but artificial intelligence can be predictive, which is much more valuable.

Another Case for Quality initiative – this one focusing on a maturity model assessment of quality systems – could also be strengthened by artificial intelligence, Vicenty said separately at the recent AI Summit.

Under FDA's upcoming Voluntary Medical Device Manufacturing and Product Quality Program, the quality systems and

manufacturing processes of participants will be evaluated by third-party appraiser against the Capability Maturity Model Integration (CMMI) appraisal framework. Results of a manufacturer's CMMI assessment will be shared with FDA; the agency will then use the information to help shape its regulatory, compliance and enforcement decisions. *(Also see "Quality On The Brain: FDA Maturity Pilot Aims To Shift Industry's Compliance Mentality To A 'Quality Mindset'" - Medtech Insight, 29 Sep, 2017.)*

"The approach and the perspective in a company to start thinking in AI terms, enabling AI systems, starting to put them in place – that shows from a maturity appraisal approach that the firm is considering and asking the right questions, and it's delivering on continuous improvement," Vicenty said.

"It's not about what's happening right now – 'I met the compliance check, I met the regulation. Great. FDA, verify it, and please leave for two years.' Instead, with AI, firms have taken the onus on themselves to find ways to look for improvements."

And additional information that AI could provide to FDA about a specific firm would "help change what we at FDA consider to be the demonstration of assurance," he said. "Getting that extra data, and FDA being able to incorporate that into its decision-making – down the road we're talking about enabling a whole different paradigm in terms of checking in" by way of an agency inspection.

After all, "how often does a regulator like FDA really need to show up at a facility to inspect if we've already done the high-level work of assuring that its AI systems are established well, and have pulse-checks we can do based on the data?" Vicenty wondered.

AI: IT'S FOR QUALITY AND REGULATORY

Marla Philips, director of Xavier Health at Xavier University, says the mission of the school's Artificial Intelligence Initiative is clear: to use AI to augment quality and regulatory systems to better predict QA/RA decisions and outcomes.

A major theme of the initiative is to determine "how we can use artificial intelligence to give us more information as quality and regulatory professionals to make better decisions about our products before they get out on the market and we find out, 'Oh, gosh. We didn't realize that problem was related to what we've been experiencing for the past five years. Somehow we missed that thread,' Philips said at MedCon.

She offered an example of how quality and regulatory professionals could use AI to their advantage.

> "With AI you can very quickly gain the power to see the 'small things' and say, 'Hey, maybe there's something there that we should look into,'" IBM Watson Health's John Daley says.

"Imagine the vast amount of structured numerical data that comes in for any single product you have, starting with the components coming in the door. They can be in a spec range, sometimes so wide that you could drive a truck through it," she said. "Components could come in on this end, or that end, or somewhere in the middle, or anywhere in-between. The component then passes inspection and it goes into your product, and your product goes out the door.

"And that's just one variable," Philips continued. "Just think of all the variables that go into your product: the room temperature, the humidity, the operating speed, the operators themselves. There are so many variables that go into getting your product out the door. Now, imagine if you could train your system, through AI, to look at all of those variables and to see what lines up with success – or what led to the edge of failure. Then, you could say, for example, 'My gosh. Every time Marla is involved with that product, we're on the edge of failure.'"

AI can pick up on those types of troubles because it looks across all product variables, and detects what works and what doesn't.

"AI can pick up trends in a variable that you might not even be connecting with your release decisions, or ever bring into an investigation when you have a product failure," Philips said.

John Daley, VP of quality and regulatory affairs for IBM Watson Health, noted that artificial intelligence excels at pattern recognition, which can give device-makers a leg-up when trying to find product or manufacturing nonconformances.

Daley is a veteran of device giants Boston Scientific and Johnson & Johnson, where he held various senior quality positions.

"If your firm could partner with others to get data, that would be helpful," he said at MedCon. "Let's say you make artificial hips and partner with providers such as Kaiser, Blue Cross and Blue Shield. You get access to their data for your devices and you start to see, 'Hey, for this new hip, we're noticing that people are on narcotics longer,' or something else that might be such a low signal that you'd never see it without AI.

"If it's a low signal, there's a good chance that no one would complain," Daley said. "They might not think, 'Hey, everybody else is on narcotics for nine days but my patients are on them for 11 days.' But with AI you can very quickly gain the power to see the 'small things' and say, 'Hey, maybe there's something there that we should look into.'"

Separately, at the AI Summit, Philips pointed out that siloed data is an issue for many QA/RA experts – a problem that could be solved by using artificial intelligence systems.

It can be troublesome "if you're not pulling all of your quality data together because it's in different siloes or different systems – or even different divisions – of your company," she said.

"If you have a centralized organization, and there's information that some of your sites have that your other sites aren't seeing – is that getting linked to what's happening in R&D? Does it ever cycle back enterprise-wide to inform the way the next product is being developed?" Philips asked.

AI can break down walls that surround data by pulling from many different streams of information.

"There's a lot of opportunity for AI to do things that we don't have the bandwidth to do today, but are so important in giving you the competitive edge, the efficiency, the speed to market – all of that is something that's there but can't be taken advantage of because most firms aren't set up for AI systems," Philips said.

J&J SUBSIDIARY JANSSEN DIGS INTO AI

Artificial intelligence systems can also analyze textual information – written language – and put it into context to detect trends. While numerical data is known as structured data because it's highly organized, textual data is unstructured – and can be a bit unruly.

AI can analyze unstructured data from internal audit reports, giving quality and regulatory experts a better view of quality and manufacturing systems.

Let's say a device manufacturer conducts a quality audit of its facilities once a year. "Usually when you're auditing, you can probably look at about 2% of your documents. That means you're reviewing only 2% of your documents yearly and determining if you're in control or not, which can be dangerous," Xavier's Philips said.

But by using natural language processing, or NLP, "AI can look at more than just that small number of documents and be better positioned to give a clearer representation of how your quality system is operating," Philips said.

Natural language processing allows AI systems to extract and evaluate human language data, which can be tricky.

At **Johnson & Johnson** pharma subsidiary Janssen, a team of 37 data scientists are working to bring advanced AI systems and approaches to its quality, regulatory, supply chain and clinical trial spaces. That includes work with NLP, extracting textual data from various reports, including FDA-483 inspection observation forms and documentation related to corrective and preventive actions (CAPAs).

"We can use natural language processing to take those unstructured sources and use them as data, and put them into a structured format where we can use them in machine learning models and in other types of big data analytics to derive some insights," Ryan Schoenfeld, Janssen's director of data sciences, said during an April Xavier University webinar on artificial intelligence.

Schoenfeld said the firm uses AI to tackle more traditional problems, revisit old issues, and even question assumptions the company has made in the past that were based on using older types of analytical techniques.

At Janssen, "what we can do is leverage machine learning, artificial intelligence and big data analytics approaches to automate workflows, and look for new business opportunities, as well," Ryan Schoenfeld says.

"The ability to leverage capabilities such as high-performance computing really expands the realm of what's possible and what's economical from a computational perspective, versus just a few years ago," he said. For Janssen, "AI is going to have an impact on a number of areas. Certainly, and probably most importantly, it's going to impact our decision-making. We can make more data-driven decisions and reduce bias in our decision-making by allowing the data to drive things."

Schoenfeld stressed that "artificial intelligence is not machines thinking for us. Rather, AI is going to be leveraging the technology to help us make better decisions, and it's going to also help us automate workloads. There are a lot of manual processes that go on [at firms] today across all areas, in clinical development, manufacturing and the supply chain. What we can do is leverage machine learning, artificial intelligence and big data analytics approaches to automate workflows, and look for new business opportunities, as well."

Robert Studt, Janssen's senior director for data quality metrics & reporting, said the firm's quality and compliance group is fiddling with NLP to identify trends, better determine the root causes of product problems and be more efficient in handling nonconformances.

"We want to leverage the knowledge that we have sitting in many years of audit reports, CAPAs, and corrective and preventative action plans, where a lot of the data that is in those reports is a lot of pretext," Studt said during the AI webinar. "What we're developing are algorithms – mechanisms – to take all of that historical knowledge that is encompassed in pretext, and all of our audit reports and root cause analyses, and analyze it."

Janssen also plans to roll out this year a software portal that can be used for inputting and analyzing textual data.

"If we receive an inspection report and it has a description of the observation or what's gone wrong, the user can paste that observational text into the portal and use natural language process algorithms to look for similar situations that have occurred in the past, hopefully reducing the time we spend developing a plan" to fix an issue, Studt explained.

"Within a company like J&J, we have multiple large therapeutic areas. So, imagine you're sitting in the oncology group and receive an observation from FDA. Well, someone in the cardiovascular group may have received a very similar inspection observation two years ago, and may have developed an approach – a response – that was either effective or not," he said.

"That would be very useful for you to know as the current-day oncology person who is developing a plan to respond to the agency."

Janssen's quality and compliance group is working with colleagues in the firm's supplier control group to figure out how it can leverage a similar approach to nonconformances in its supply chain.

"You can use advanced analytics and predictive analytics for things like reducing stock write-offs and for optimizing pro-

cesses in different ways. Or, better ways to catch label mismatches. There's a long list of potential applications for advanced analytics in the supply chain," Schoenfeld said.

Janssen also wants to add external information to its collection of data. "For example, FDA warning letters that may have been issued to other companies in certain areas – we can bring those into our knowledge base and supplement the data that we've gathered internally over the years," Studt said.

And while Janssen is a drug-maker, Studt foresees the firm's parent company using AI systems in its other commodity areas, including medical devices.

"J&J is a big manufacturer. Ryan and I sit in the pharma segment, but we also have consumer and device segments with a large footprint," he said. "We have, internal to the company, possibilities to expand this AI work there with data from other segments, and to expand the impact of some of our AI tools."

VALIDATING AI OUTPUTS

One hurdle that device-makers will have to jump is determining the best way to validate results generated from AI systems.

"The traditional validation of where you do something and then say, 'OK, I have full confidence in what I've got' is absolutely different in the world of artificial intelligence," Bakul Patel, associate director for digital health in FDA's Center for Devices and Radiological Health, said at MedCon.

When it comes to machine learning, "you can't train the system to recognize cats and then try to see if it can detect dogs," Patel said. "I think that's an example of the fundamental things that you must figure out as you use AI – and that's where validation needs to start from. You need to know what your features are that you're trying to identify."

CLICK

To read about teams formed by Xavier University's Artificial Intelligence Initiative to decide how to best use AI to scan for signals of device and drug troubles, and validate the results, click here: http://bit.ly/2yR99C1.

Might AI Replace Humans?

"The way we see artificial intelligence is, it's really a path forward to use more and more and more unbiased approaches based on data to make decisions. So, it's not a threat to the human decision-maker. We still need the human decision-maker," Janssen's Ryan Schoenfeld said.

"Maybe someday we'll be more in a state where we can assign more decisions to machines, but I can tell you as someone who sees the forefront of the current field today, we're not there. And I don't see us getting there anytime soon," he said.

"Humans are making the decisions, and these AI tools just help us make better ones, really. So, I don't think, from an AI perspective, that it's a threat," Schoenfeld said. "Now, some workflow automation can reduce the number of hours that people now need to spend on certain tasks. But those folks can focus on other areas where they didn't have time before to do things to push the frontier in other ways.

"So, that's the opportunity."

The integrity and quality of data is also important when verifying AI outputs.

"If you have too much noisy information in your AI system, you will get indefinite answers. Then, when you test the system, you will still get those indefinite answers," Patel said.

IBM Watson Health's Daley agreed that using quality data is of the utmost importance to ensure adequate AI validation activities.

"I would say the quality of data is key, and then it's all about classic validation – knowing your predetermined outputs," he said. "Know very precisely what target you want to meet, and I would strongly suggest that it should be equal to or better than human performance in whatever you're starting out with. That's how it should be."

As manufacturers work toward AI validation, Daley also urged firms to know their products' risk profiles, and to understand "where and when humans may still be in on the decision-making."

Xavier's Philips echoed Daley's remarks, noting that AI outcomes should reflect, at a minimum, the same conclusions that humans would arrive at.

"But the important thing is that the system then continues to learn, and you have to make sure you're verifying that you agree with what it's learning before you just say, 'We'll take that information and make our decision based on it,'" Philips cautioned.

"Remember: AI can be used to help inform your quality and regulatory decisions with more information than you've ever had before, but validation is a key step," she said.

For now, drug-maker Janssen is not implementing machine learning approaches in specific quality, regulatory or other areas that must be highly validated.

"The earliest places where we're implementing AI in our workflows are in areas that are support functions for the most validated and most regulated areas. That's where we're getting our feet wet," Janssen's Schoenfeld said.

And, although validating artificial intelligence outcomes may be different from traditional manual process validation activities, the same principles apply, he said.

"If you're going to put an advanced analytics tool into a workflow that's going to have an impact on decisions that have a direct impact on regulatory or regulated activities, such as releasing products to patients and clinical trial management, you must validate," Schoenfeld said.

"But the big question is, how do we validate down the road? As machine learning algorithms become more and more accurate in making various decisions, how will we validate those?"

CLICK

To read about what AdvaMed is doing to engage on how artificial intelligence can be regulated in a way that doesn't stymie innovation, click here: http://bit.ly/2yQkh1T

INDUSTRY, REGULATORS MUST SING OFF SAME AI SONG SHEET

Much of the answer, Schoenfeld says, lies in industry's willingness to work hand-in-glove with regulatory agencies on AI issues.

"We'll have to carefully work with regulators like the FDA to make sure everyone is aligned with the validation process," he said. "If we have to adapt it or modernize it in some ways, working with regulators ensures that everyone is on the same page."

No matter how industry chooses to move forward with advanced artificial intelligence systems, Philips says it indeed must happen in conjunction with regulators.

"The understanding of what's going on has to be done together. It's not best to have FDA going off and understanding something about AI, with industry having no idea what it's talking about, and vice versa," she said. "It has to be done in-step together."

David Lowndes, head of small molecule operations at biopharmaceutical company **Shire PLC**, sees eye-to-eye with Philips and Schoenfeld.

"We have a long journey to travel, and it's a journey that we need to travel in close conjunction with our regulatory agencies. There's a lot of learning to be done," Lowndes, who leads the supply chain for the firm's Specialty Pharmaceuticals Division, said at the AI Summit.

"We need to bring AI experts, manufacturing and production experts, and the agencies together, to travel this journey together so we're on the same page, aligning on how to leverage AI and how to regulate in the new environment where we're using AI," he said.

USE PURSE STRINGS TO GAIN ATTENTION OF TOP LEADERS

As artificial intelligence marches forward in industry, it's likely that top management will need to be convinced that using AI in quality and regulatory applications is worthwhile.

That can typically be done by explaining to senior leaders that AI systems can save their companies money, Shire's Lowndes said.

"Recently I was at an API [active pharmaceutical ingredient] plant for one of our contract manufacturers, and we toured the facility," he said. "We walked into a control room, and there must have been 15 or 16 screens in the room, each of which had huge amounts of data on it.

"I asked: 'How much data do you have?' And they said: 'For each lot, we have 20,000 data points,'" he recounted. "I then asked: 'How much of that data are you using to control the process, and to learn about the process, and to improve it?' And they said: 'We take about six to eight data streams and we use that to control the process.'"

That's when it dawned on Lowndes that an AI system could help the facility take fuller advantage of its big data.

"Presumably the original investment – the ability of this plant to get all of this data – had a reason or logic behind it. So, it is a lost opportunity that they aren't using all of the data they are capturing," he said. "That's a loss of value to the business – a loss of competitive edge, a loss of performance – and that's something that senior leadership needs to understand."

> "There's an argument to be made that it's taken AI a long time to catch on because we've not been able to show how AI can save companies money," Shire's David Lowndes says.

Although Lowndes recommended an AI solution to top officials at that particular plant, he received pushback.

"The response I got from senior leaders was, 'Well, yes, AI would help, but AI's really expensive, isn't it?'" he said. "Well, expense is all relative to the potential savings and benefits you can get, and I would argue that if you're not using much of the data you're collecting, that means you've already spent a lot of money, and you're wasting a lot of money by not using [the data], and you're missing an opportunity to turn that into value for the company."

Lowndes is concerned that if the drug and device industries do not use artificial intelligence in a way that demonstrates a meaningful return on investment, then their efforts will fail.

"AI has been around for decades already and it hasn't really gotten to anything close to what its potential is," he said. "So, I think we've got to be looking for opportunities where there's a great return on investment. Because if we don't generate solutions that drive value, then potentially AI becomes a clever niche technology.

"There's an argument to be made that it's taken AI a long time to catch on because we've not been able to show how AI can save companies money."

Despite the potential savings, firms should nevertheless exercise caution when handling artificial intelligence.

"The loss of oversight and learning for us as human beings is an area where we need to be extremely careful," Lowndes warned. "If we let artificial intelligence take us from the data collection to the decision and the implementation of that, and we're sitting there saying, 'What just happened?' – that's when we start to lose the knowledge of our processes."

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Opioid Use Disorder App Marks A Path For 510(k) 'Breakthrough' Devices

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A heavily studied mobile medical app intended to support treatment of opioid use disorder (OUD) is among the first 510(k)-route products to gain entry into US FDA's Breakthrough Devices Program, providing some insight into the types of products that might be considered breakthroughs even though they are seeking a "substantial equivalence" claim to something already on the market.

Pear Therapeutics announced Expedited Access Pathway designation earlier this month for its *reSET-O Prescription Digital Therapeutic* for OUD. FDA has recently started to refer to the 2015-launch EAP program as the Breakthrough Devices Program to align with a provision of the 21st Century Cures Act that updates the program. The agency issued a draft guidance Oct. 24 on the updated program, which offers an expedited development route for devices that may address an unmet need for life-threatening or irreversibly debilitating diseases or conditions. *(Also see "'Breakthrough' Blueprint: US FDA Draft Guideline Outlines Revised Expedited Development Program" - Medtech Insight, 24 Oct, 2017.)*

"First and foremost, by going through the pathway, it helps fundamentally recognize the life-threatening and public-health epidemic of opioid use disorder, which many people are of course talking about," Pear Therapeutics' Yuri Maricich says.

For the first year-and-a-half of the program's existence, FDA only allowed devices seeking PMA or *de novo* approval to qualify for the benefits of the EAP/Breakthrough program, including closer collaboration with agency staff on flexible trial designs, acceptance of more pre-market uncertainty, priority-review designation and streamlined manufacturing oversight. The agency was wary of including 510(k) s both due to resource concerns and questions about whether the pathway would benefit devices on the clearance path. *(Also see "US FDA Ready To Accept 510(k) Devices To Expedited Access/Breakthrough Pathway" - Medtech Insight, 8 May, 2017.)* But Congress added 510(k)s to the program via the Cures Act, which was enacted December 2016.

Since then, "a few potential 510(k)s" have gained the breakthrough designation, according to an agency spokeswoman. Pear appears to be the first company to publicly disclose acceptance into the program for a device that is explicitly seeking pre-market clearance. (Only about one-third of firms with designated devices have publicly announced it and those are tracked on *Medtech Insight*'s US Expedited Access Tracker).

ALIGNS WITH FEDERAL OPIOID-ABUSE PRIORITY

The system's clinical target aligns with one of the top public-health priorities of FDA. Scott Gottlieb has made a major push with initiatives and public messaging to support development of medicines and technology to counter the opioid abuse epidemic - the breakthrough designation of reSET-O likely fits into those efforts. It also aligns with President Trump's formal designation of the opioid crisis as a "public health emergency" on Oct. 26.

Via a mobile app that is linked to a clinician dashboard, the reSET-O system delivers cognitive behavioral therapy to patients to aid treatment of OUD, with the goal of increasing abstinence from opioids and retention in therapy programs. It is specifically intended to be used in combination with opioid replacement therapies including buprenorphine.

Pear gained a *de novo* classification for its similar *reSET* prescription digital therapeutic last month for substance use disorder, not including OUD. *(Also see "First Anti-Addiction App Approved In The US" - Medtech Insight, 14 Sep, 2017.)* Compared to reSET, reSET-O includes seven additional therapy modules targeted to OUD individuals, and also a "buprenorphine function" to align with the combination therapy. Pear plans to claim the reSET system as a predicate for its reSET-O 510(k) submission.

In addition to addressing the high-profile opioid crisis, chances of getting the breakthrough designation may have been helped by the fact that reSET-O is a digital-health product. Streamlining the regulatory pathway for software, mobile apps and other digital health tools is another top-line priority for FDA's leadership, and, in fact, Pear is one of nine companies recently selected to participate in a pilot program seeking to identify shortcuts that can be gained for such products by certifying software development practices. *(Also see "'Excellence' In Health-Software Design: US FDA Taps Nine Firms To Figure Out What That Means" - Medtech Insight, 26 Sep, 2017.)*

Also relevant is that reSET-O's 510(k) will rely on clinical data. A significant emphasis of the Breakthrough Program is on streamlining a data-development plan and relying on flexible study designs. The program may be less relevant to 510(k)s that will not rely on clinical trials.

PRODUCT POSITIONED AS "POTENTIALLY LIFE-SAVING"

On the other hand, Pear already had its pivotal clinical data in hand before it gained the latest designation. The company has collected randomized clinical trial data from a total of 465 patients comparing reSET-O and pharmacotherapy against pharmacotherapy alone. That includes a 170-patient pivotal study that the firm says shows that the software system increases opioid abstinence and improves treatment retention.

With that data portfolio in hand, the firm is unlikely to leverage several elements of the Breakthrough Program. Yuri Maricich, VP of Clinical Development for Pear, says the firm will still benefit from priority review, which might help speed access. But, perhaps, more important than that, he suggests, the designation can help position the product as a significant offering in the health-care community.

"First and foremost, by going through the pathway, it helps fundamentally recognize the life-threatening and public-health epidemic of opioid use disorder, which many people are of course talk-

ing about, including the FDA and Dr. Scott Gottlieb," Maricich said in an interview. "Two, by going through the pathway, it identified reSET-O as a potentially life-saving and breakthrough technology.

The company won't disclose a specific timeline for product submission. "Our goal is to try to work with the FDA and move through as quickly as possible," Maricich said.

Pear has yet to commercially launch the reSET system for non-opioid substance use disorder, but plans to do so next year. That system, according to the company's CEO Corey McCann, represents the "first time that any piece of software has ever been cleared by the agency to treat any disease."

reSET-O, meanwhile, is the first software tool designed to be used hand-in-hand as a co-treatment with pharmacotherapy. That, Maricich says, is likely the model for the future for Pear, which is developing its system for a range of mental health disorders including schizophrenia, post-traumatic stress disorder and anxiety disorder.

"The majority of diseases that Pear intends to develop therapeutics for, because pharmacotherapy is already indicated as the standard of care, these digital therapeutics would be used in combination with that pharmacotherapy," he said.

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Patients Have Rights To Their Own Device-Generated Data, FDA Clarifies

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Manufacturers and physicians need to share the patient-specific information that is recorded with vital signs devices like blood pressure monitors, implantable devices or diagnostics upon the patient's request, FDA clarified in a final guidance on the topic released Oct. 27.

"Providing patients with accurate and complete information about their diagnosis and treatment, including the data collected from medical devices like blood pressure or heart rhythm monitors, allows patients to be better informed about their health and more active participants in their health care," said FDA Commissioner Scott Gottlieb in a statement.

"We want to eliminate any policy obstacles that might prevent manufacturers from sharing with patients their own personal health information."

FDA first issued a draft of the guidance in June 2016 in response to grassroots efforts by patients to gain more access to their own data from some implanted devices including cardioverter defibrillators (ICDs), which previously had only been made available to physicians. Some manufacturers were worried that patients would have a hard time interpreting the results, but patient-data advocates such as Hugh Campos told the agency that patients want and need access to that information. *(Also see "Patients Have Right To Device Data, FDA Says, But Precautions Urged" - Medtech Insight, 13 Jun, 2016.)*

Similar comments were made by patients and patient advocates at the inaugural Patient Engagement Advisory Committee (PEAC) meeting on Oct. 11-12, which focused on getting more patients involved in clinical trials. Patients at PEAC said they wanted more updates on their own personal trial results to stay engaged, and wanted access to data recorded on them during check-ins, to better make their own health decisions. *(Also see "Patients Want Industry To Minimize Burdens, Augment Comforts Of Device Trial Participation" - Medtech Insight, 13 Oct, 2017.)*

The guidance, titled "Manufacturers Sharing Patient-Specific Information from Medical Devices with Patients Upon Request," defines patient-specific information as any data that has been recorded, stored, processed, retrieved, or derived from a legally-marketed medical device. This could be device usage/output statistics, health-care provider inputs, incidence of alarms, or records of device failures.

It includes the interpretations of data normally reported by the device to the patient, or to the patient's health-care provider, but not to intermediary diagnostic steps, such as results of individual component tests for specific analytes that comprise, or are used in, an FDA-cleared assay, the agency added.

In a legal interpretation in the guidance, FDA also noted that manufacturers who want to share some patient-specific information upon request but are hesitant to do so for fear of triggering additional pre-market requirements having to do with labeling, may feel free to share the information.

"FDA generally would not consider patient-specific information to be 'labeling' as defined under Section 201(m) of the Food, Drug and Cosmetic Act," the agency wrote. Further, the agency said it is aware that when manufacturers share patient-specific information with patients, manufacturers also may provide them with supplemental information such as descriptions of intended use, or risk information.

NOT ALWAYS FEASIBLE

In some instances, devices may be designed to record or transmit information in a format not easily provided to a patient, FDA pointed out. In other cases, devices record and retain information in a closed system not easily accessible by the manufacturer. Under both situations, "it may not be feasible for manufacturers to share patient-specific information with patients, as doing so would require … device redesign," FDA noted.

The agency also pointed to the important role health-care providers play in providing interpretation of patient-specific data, and recommended to manufacturers that they remind and advise patient to contact their providers, should they have any questions on the information they receive.

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