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Manufacturers Scramble To Meet UDI Deadline – Too Many Are Unprepared

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Far too many device firms are woefully unprepared for, and undereducated about, US FDA's Unique Device Identification program, industry experts say. This comes as many makers of class II products rush to comply with the next phase of the agency's UDI rule, which begins in a scant few weeks.

A recent USDM Life Services/Loftware survey of 120 device industry professionals illustrates the level of unpreparedness. A whopping 102 respondents – or 85% – said they aren't ready for the looming September UDI deadline, while 43 people (36%) said their biggest challenge is understanding and applying the agency's regulation.

For those firms having trouble, "FDA has developed and shared many resources, and has provided multiple opportunities for training and webinars"; however, "we believe some companies are not taking full advantage of those resources," according to Linda Sigg, FDA's associate director for informatics and head of the agency's UDI program.

In its UDI rule, FDA directs class II devicemakers to be compliant with the law by Sept. 24, 2016. Manufacturers of high-risk class III products and makers of lifesaving and life-sustaining class II devices already fall under the umbrella of the regulation; those firms were required to comply with UDI in September 2014 and September 2015, respectively. Manufacturers of low-risk class I and non-classified products have until September 2018 to add UDI to labels.

Firms have until three years after each deadline to sell non-UDI-marked product supply.

The agency has been exercising enforcement discretion when looking at Unique Device Identification activities during facility inspections, and declining – for now – to cite manufacturers with UDI troubles.

Makers of class II devices that kicked the can down the road and are scrambling to meet next month's UDI deadline might be out of luck when it comes to getting help from the agency at this late date. That's because FDA is "experiencing 'brisk business' with many companies seeking help," Sigg wrote in an Aug. 12 email to *Medtech Insight*.

"CDRH has received hundreds of questions from labelers over the past few weeks, many of which can be easily answered by referring to materials on our website. Those who have submitted questions and are awaiting a response from FDA" can seek out the resources available there, she wrote.

A labeler is essentially the entity that affixes a label to a product before it is sent to

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US FDA Panel Sees Benefits To OTC Pathogen Tests, But Urges Caution

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Allowing patients to test for certain pathogens at home could lead to swifter treatment, but carries with it a host of practical concerns, US FDA's Microbiology Devices Panel concluded at an Aug. 16 meeting.

The panel met to review the possibility of allowing over-the-counter (OTC) sales of tests for influenza, sexually transmitted infections, such as gonorrhea and chlamydia, and Group A streptococcus (strep throat). In addition to assessing the safety and effectiveness of such tests, they were also tasked with discussing risk-mitigation strategies, clinical trial design, and strategies to ensure that patients who perform home tests ultimately access appropriate medical care.

Overall, the panel said the potential benefits of the OTC tests outweighed the risks, though the advisors had more questions about the effectiveness of respiratory illness tests compared to STI tests. Flu and strep throat tests would likely require a throat swab that may be hard for patients to self-administer, panelists said.

FOCUS ON INSTRUCTIONS

In terms of risk-mitigation strategies, panelists recommended developers find ways to make sample collection less invasive. In addition, they stressed the importance of including robust educational materials in test packaging, and that OTC tests generated a simple readout that could easily be interpreted by users.

Maureen Beanan, a program officer at the National Institutes of Health's Office of Biodefense Research Resources and Translational Research, said the package inserts "need to indicate these tests aren't perfect." She further recommended that the packaging include written directions as well as a diagram showing how to use the test, and that manufacturers consider posting a video online demonstrating proper use. Other panelists concurred that the instructions on the packaging should be written at a relatively low reading level and in multiple languages.

In addition, Barbara Van Der Pol, a professor of medicine at the University of Alabama at Birmingham, said STI test packaging might need to be separated by gender to ensure patients used the right sample type. She further recommended the tests include a card for patients to bring to physicians with space for patients to write in the date and result. That would cut the risk of patients forgetting what specific test they took, she said.

Panelists also recommended that the outside of the packaging make it clear how long after exposure to an infection it will take for the test to become effective. "We need to educate people about biology," said panel chair Angela Caliendo, chief of internal medicine at Rhode Island Hospital. "You won't test positive the day after high-risk behavior."

The panel also raised the concern that home testing could diminish the amount of data collected to support public health efforts. For instance, physicians now report STI cases to the county. Van Der Pol recommended tests include an online reporting tool that could pass positive test results along to the county anonymously.

Some panelists advocated for a 24-hour hotline for patients to discuss test results, while others fretted about the potential costs of such an arrangement. One compromise, suggested by Charlotte Gaydos, professor of medicine, Johns Hopkins University, would be a common "warm line" funded by more than one manufacturer and staffed only during business hours.

FOCUS ON RESEARCH

As for clinical trials, panelists stressed the need to recruit patients from underserved and racial minority communities by engaging schools, churches, Planned Parenthood and STI clinics, community groups and social media. It's also key that sponsors draw in younger people, said patient advocate Natalie Compagni Portis.

"The challenges of designing good trials might be overwhelming," said FDA medical officer Steven Glitterman. "I hope this is a call for manufacturers to bring in experts while they're developing these tests."

Some research on how OTC tests might perform in the marketplace has already been conducted. Gail Bolan, director of the division of STD prevention at the Centers for Disease Control and Prevention, discussed the results of a CDC pilot program in which women could order an STI testing kit online and then return the swabs for analysis. About 3,100 women requested the kit between 2011 and 2015, she said. However, only 42%-65% of the swabs were returned. Women said the test samples were easy to collect and preferred the kit to seeing a physician; how-

ever, CDC wasn't able to collect much information on whether patients who tested positive received treatment.

CDC recommends STI diagnostics follow the World Health Organization's ASSURED criteria that tests should be affordable, sensitive, specific, user-friendly, rapid and robust, equipment-free and deliverable to end users. In addition, clinicians say point-of-care tests should be better than 90% sensitive, take no more than 20 minutes, and cost no more than $20.

However, some panelists worried about possible effects of making STI tests available over-the-counter. For example, Margaret Hammerschlag, director of pediatric infectious diseases, SUNY Downstate Medical Center, urged caution, stating there were "legal implications" to testing minors for STIs. A positive result could lead to child abuse or statutory rape charges even if it's later shown to be a false-positive, she said.

Nonetheless, panelists expressed particular enthusiasm that OTC tests could make diagnosis more readily available to marginalized patients, such as racial and sexual minorities and the working poor who might not be able to find the time to see a physician.

"We have an opportunity to empower people to think about their own sexual and respiratory health, and that's something we can't gloss over," Gaydos said. "But at the same time, it has to be carefully monitored."

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Device Firms Advised To Prepare For Hurdles Under China's RoHS2

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China's revised regulation on restricting the use of hazardous substances in electrical and electronic products (RoHS2) that came into effect on July 1 is posing a challenge for some product manufacturers, including medical device-makers, which need to update their product labels in accordance with the new requirements.

Specifically, some manufacturers can find it difficult to get hold of the information they need to comply with the labeling requirement.

Under RoHS2, if an affected product contains a hazardous substance beyond its prescribed limit, then the product's user manual has to be updated with this information, explained Steven Wen of consulting firm Brandwood Biomedical.

The information has to be presented in a specified tabular format and should identify which hazardous substances are beyond the limit in each part of the product, said Wen, the firm's director of China operations.

However, based on Wen's experience with RoHS2 so far, he said the main challenge that affected manufacturers face relates to collecting accurate information from upstream suppliers on the content of hazardous substance in each product part.

Many upstream suppliers either do not know this information or refuse to provide it, Wen told *Medtech Insight*. And in cases where this information does come through, it is difficult to verify its accuracy, he added.

Wen also pointed out that compared with China's RoHS1, which only applied to "electronic information products," RoHS2 has an expanded scope as it affects electrical and electronic products.

For device manufacturers that were already complying with the requirements of RoHS1, Wen does not believe the transition to RoHS2 will be too difficult, beyond the difficulty of obtaining accurate information on the content of hazardous substances in their products.

Companies complying with RoHS1 would not have to make too many changes to their existing processes and would only need to update their product's user manual in the prescribed format, he explained.

However, compliance with RoHS2 is expected to become tougher in the future when the government actually begins restricting the use of hazardous substances beyond their prescribed limit.

Wen explained that at present RoHS2 only requires affected manufacturers to display information about whether or not their product contains hazardous substances beyond the prescribed limit. In the future, the government intends to issue a "mandatory compliance list," and manufacturers of all products on this list will have to take steps – such as changing existing product parts – to ensure that the content of the hazardous substances is within the prescribed limit. The list is expected to be revised regularly, with more products being added to it from time-to-time.

Just when exactly this list would be published is anybody's guess. Wen said that, at the moment, there is "no clue [on] how soon it will be published." However, he pointed out that once the government is ready to publish the mandatory compliance list, it is expected to invite product manufacturers to join the discussion.

For device companies that might be affected by the mandatory compliance list, Wen believes that they can start preparing now by collecting all information on the content of hazardous substances in their respective products. He also noted that once the mandatory list is published, there will be a transition period to allow manufacturers to change parts of the enlisted products.

Wen clarified that for other products under RoHS2 that are not added to the list, there will be no restriction on the use of hazardous substances as long as this information is displayed accurately on the product label and the user manual.

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Getinge Ousts CEO Mid-Restructure

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The board of Swedish health company **Getinge AB** has ejected Alex Myers from his role as president and CEO, citing strategic differences as the reason for the move. Myers had been at the helm for only 17 months.

Company chairman Carl Bennet stated that the board and Myers hold "different views on the future direction of the Getinge Group, and the board has therefore concluded that a replacement … is necessary."

Myers joined Getinge in March last year to succeed the company's chief executive for the previous 18 years, Johan Malmquist. Under Myers' leadership, Getinge has undergone a major restructuring to increase cohesiveness between its three distinct product brands: Getinge, Maquet and ArjoHuntleigh. The company was reorganized to three new business units – Surgical Workflows, Acute Care Therapies, and Patient & Post-Acute Care – which has been operating since the start of 2016. Myers This reorganization was part of a larger three- to four-year transformation program, underpinned by five strategic initiatives called the "Big 5," to drive the bottom line and achieve an EBITA improvement of SEK2.5-3bn by 2019.

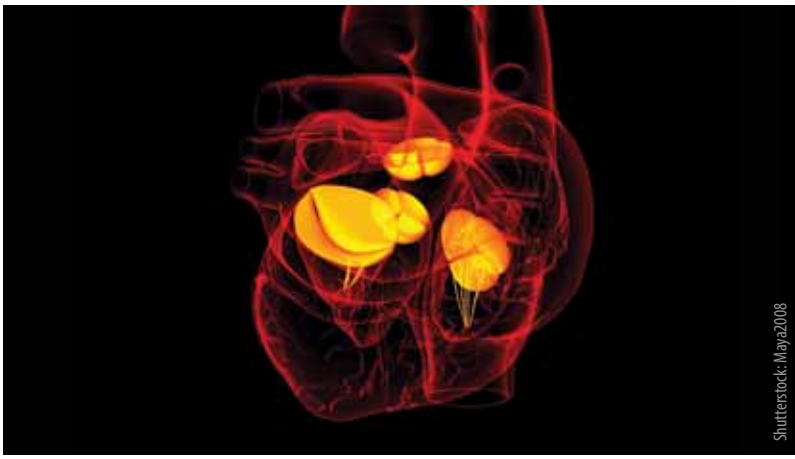
And it looked like Myers' efforts were bearing fruit and the company was able to curb the consecutive quarterly losses seen prior to Myers' appointment. Excluding negative currency effects, Getinge reported a 3% increase in orders for the second quarter of 2016, while EBITA rose over 10% to SEK788m, and pre-tax profits jumped 28% to SEK311m.

Chris Cooper, an analyst at Jefferies International, speculated that the disagreement between Myers and the board wasn't so much about the restructuring plan itself but its execution. In an Aug. 22 research note, Cooper also suggested that there may have been discontent over the speed at which the company's longstanding regulatory problems – specifically the company's consent decree with US FDA concerning the quality management systems within its Medical Systems business – were being resolved. "In the midst of a major restructuring program, it is unclear what the precise strategic differences may be, and could be many. We had heard in February that Mr. Myers' relationship with the Board was good but, despite reporting a sequentially better 2Q last month … progress on regulatory matters has been slow," noted Cooper.

Getinge indicated that it has begun its search for a permanent replacement for Myers. Holding the fort on an interim basis is Joacim Lindoff, currently president of the Surgical Workflows business unit. Linden has been with Getinge since 1999, and prior to his current role heading up Surgical Workflows he was executive VP of Infection Control.

Published online 08/22/16

US FDA Approves First Intermediate-Risk Indication For TAVR



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Edwards Lifesciences Corp. has beaten its rivals to yet another milestone in the development of transcatheter aortic valve replacement (TAVR) systems with the first US FDA-approved indication for intermediate-risk patients.

The agency announced Aug. 18 that it approved an expanded indication for Edwards' *Sapien XT* and *Sapien 3* TAVR systems to include patients with aortic valve stenosis who are at intermediate risk for death or complications associated with open-heart surgery. Sapien XT and Sapien 3 were previously only approved for inoperable or high-risk patients.

The intermediate-risk indication, the first approved by the FDA, covers about one-third of patients referred for open-heart surgery to replace an aortic valve. It includes patients with between a 3% and 15% risk of dying within 30 days after surgery, based on the judgment of the multispecialty Heart Team treating the patient.

Edwards earned the expanded indication based primarily on results from the 57-center PARTNER II trial and the Sapien 3 observational study. Results of both trials were presented at the American College of Cardiology annual scientific sessions in Chicago in April and published in *The Lancet*.

The PARTNER II study randomized 2,032 intermediate-risk patients with severe aortic stenosis to either TAVR with Sapien XT or surgical replacement, and showed TAVR with Sapien XT creates larger aortic-valve areas than surgery and is associated with lower rates of kidney injury, severe bleeding and new-onset atrial fibrillation. Patients treated with open surgery had fewer major vascular complications and less paravalvular aortic regurgitation than the Sapien XT patients, but the percentage of patients needing a repeat hospitalization within two years of a procedure were similar for both groups. TAVR patients had a significantly shorter

median stay in the intensive care unit than the surgery patients, and a shorter median index hospitalization.

The Sapien 3 observational study compared the one-year rates of all-cause mortality and incidence of strokes, re-intervention, and aortic valve regurgitation from 1,078 intermediate-risk patients treated with Sapien 3 at 51 North American sites to the one-year outcomes of the 944 intermediate-risk patients treated with open-valve surgery in PARTNER II. The one-year all-cause mortality rates were 7.4% in the Sapien 3 group and 13% in the PARTNER II intermediate-risk surgery group. The rates of stroke were 4.6% for the Sapien 3 group and 8.2% for the surgery group, and the rates for the composite of all-cause death and disabling stroke were 8.4% in the Sapien 3 group and 16.6% in the surgery group.

In an Aug. 18 note, Wells Fargo analyst Larry Biegelsen writes that the US Centers for Medicare and Medicaid Services' national coverage policy makes Medicare reimbursement available for TAVR in intermediate-risk patients automatically based on FDA's latest approval.

Edwards' only rival in the US TAVR market, **Medtronic PLC**, is also seeking FDA-approval for the intermediate-risk indication for tis *CoreValve Evolut R* TAVR system, based on results from the SURTAVI trial. But, Biegelsen writes, "Importantly, Edwards stands to disproportionately benefit from this approval because its only competitor in the US, Medtronic's CoreValve, won't have an intermediate risk indication for about a year and Medicare won't pay for CoreValve implants in intermediate-risk patients until it has that indication. We believe it will be difficult for any center in the US to not stock Edward's Sapien 3 now given that it (and Sapien XT) will be the only devices with an intermediate indication."

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Arch Therapeutics Closes In On Year-End CE Mark For Novel Blood Control Agent

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Arch Therapeutics Inc. says it is still on track to earn a CE mark for its *AC5* topical hemostatic agent by the end of 2016 – a few months later than originally planned – as preliminary data from the first clinical trial of shows it is safe and effective in the treatment of wounds created by the excision of skin lesions.

The 46-patient, single-center, randomized trial – begun in March at University College Hospital in Galway, Ireland – compared the AC5 synthetic self-assembling peptide to a standard water-resistant wound dressing in the treatment of skin wounds created by the surgical removal of dermatological lesions. Each patient in the trial had at least two excision wounds, so they served as their own controls, with one of their wounds treated by AC5 and another treated with the standard wound-dressing. The trial's endpoints include treatment-related adverse effects and time to hemostasis.

"It was the first time that AC5 was demonstrated in humans, so that's a big deal for [the product and the company]," Arch Therapeutics president and CEO Terrence Norchi told *Medtech Insight*.

The early trial results for AC5 are "as good as can be hoped for on a first clinical trial," Arch Therapeutics' Terrence Norchi says.

Photo credit: Arch Therapeutics, Inc.

Arch Therapeutics CEO Terrence Norchi

He said the trial was completed at the end of May, but that it takes many weeks to collect all of the topline data from the trial. The full report from the trial, including important subset data on patients in the trial who were taking antiplatelet drugs during the treatment for bleeding excision wounds, will not be available for a few more weeks.

However, the company is encouraged by the data it has collected so far. "This product, in this trial, is shown to be exceptionally safe. It is at least as safe as control, with very few adverse events in either group," Norchi said. Also, AC5 showed a statistically significant and clinically relevant improvement in time-to-hemostasis, just over 40% faster than the control arm, he said. "We think this is very powerful news for a first trial with this product."

The results are "as good as can be hoped

for on a first clinical trial for a product like this that's going to be submitted for the approval process," he said.

The company hopes to announce more of the results when it completes the subanalyses, but cannot reveal too many details before the data is published. "Our clinical advisor committee, which is a pretty esteemed group of people, is very excited," he said "But in order to maintain the integrity of the PI and the team who plan to publish it, we have to be circumspect with regard to revealing too much."

Next Steps

Massachusetts-based Arch Therapeutics plans to use the data from this first trial to earn a CE mark and launch AC5 in Europe while simultaneously developing a plan for a US clinical trial.

When it began the first trial in March, Arch Therapeutics predicted it would file for a CE mark by the end of summer. It is now unlikely to meet that target, but Norchi assured this is part of the normal regulatory process and does not reflect any unexpected issues with the trial. "Fundamentally, nothing has changed other than we now have some pretty good validating data from our first trial for our first product," he said.

"A lot of people do expect that once you get data, you push a button, the application is filed and then you're in. That is actually not what happens," he said. "[Filing for a CE mark] requires a coordination of a number of activities such as quality, manufacturing, compliance of key suppliers, *et cetera*. So we're working very hard on all of that coordination," so the new conservative target for the CE-mark filing is the end of 2016.

Norchi said the discussions with US FDA on plans for a US trial have been "very thoughtful and very supportive," but could not speculate on the design of the US trial since that will be influenced by the final results of the first trial.

Arch Therapeutics is not planning to commercialize AC5 in Europe by itself, but is instead looking for a commercial partner, he said – "And this is the time to take those discussions for the next level."

The company is confident it can market AC5 as "easier to use, more efficacious, and less likely to cause adverse events" than other hemostatic agents available for excision wounds, according to Norchi. He said AC5 is easier to use because it does not have to be stored in a freezer, and the consistency of the material is a bit thicker than water, and not sticky or stiff like some other hemostatic agents that can get stuck to the treating physicians' other instruments, or make it harder to see the wound they are trying to treat.

"It is simple, effective, versatile and safe – We think that's a big selling point," he said. "A lot of products on the market don't work reliably; others might be complicated to use. Others can make someone prone to untoward side-effects, but we haven't seen anything, to date, on the side-effects front."

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MagDent Ltd.

Israeli start-up MagDent Ltd. has developed a miniaturized electromagnetic healing cap designed to stimulate and improve bone formation at the site of dental implants.

The first step in replacing missing teeth with a dental implant is an incision into the jawline where the crown is to be eventually placed. This is followed by creation of a small entry hole, then insertion of a screw inside the jawbone to allow the bone around the screw to grow and hold the screw tight, a process that takes several months. During this initial procedure, a small healing cap, which looks like a spark plug, is also threaded inside the original screw, with the top of the cap residing above the gum line. The purpose of a traditional healing cap is to let the gum heal in a circular shape to minimize further surgery.

But a new healing cap from Israel-based **MagDent Ltd.** stimulates and improves bone formation as well, thanks to miniature electronics within the cap that create an electromagnetic field around the implant screw. The miniaturized electromagnetic device called MED is shaped the same as a normal healing cap and threads inside the first screw the same way, either manually or with a wrench. According to company chief operating officer Elad Yakobson, the bone grows three times faster with MED than with a standard healing cap, for a total healing period of one to two months rather than the standard three to six months. Then, in a follow-up procedure, the healing cap is exchanged with a third screw to anchor a new crown affixed over the first screw.

For the past roughly hundred years, the orthopedic field has been using electromagnetic fields, now in desktop size, to treat mostly nonunion fractures by stimulating bone growth and enhancing bone quality. "The electromagnetic field operates on the membrane of the cell by manufacturing osteoblasts, bone-creating cells that stimulate bone growth," Yakobson says. "Basically, we took the bigger machine from orthopedics and miniaturized it to fit dental implants. It is the same technology and the same type of treatment performed the same way, but with smaller equipment."

MED particularly benefits relatively older patients or people who are diabetic or smoke, all of which are risk factors that affect bone quality. "Many of these patients are not even candidates, or poor candidates, for a dental implant," Yakobson notes. "MED improves the quality of the bone substantially by allowing the bone to become denser."

MED is suitable for nearly every patient who undergoes a dental implant procedure to replace teeth. Worldwide, this represents between 6 million and 8 million procedures yearly, for an annual market opportunity of roughly $560m for the product, which received CE mark in 2012 and is expected to receive 510(k) clearance in mid-2017.

MagDent co-founder Shlomo Barak, a maxillofacial and oral surgeon in Tel Aviv, was inspired to help start the company due to a 1988 encounter with a middle-aged female patient who had undergone cancer radiation, resulting in loss of bone

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Contact: Elad Yakobson, COO

Industry Segment: Dental devices

Business: Miniature electronics create electromagnetic field to stimulate and improve bone formation surrounding the implant

Founded: May 2010

Founders: Shlomo Barak, DMD, CEO; Moshe Neuman, DMD

Employees: 2

Financing To Date: $1.94m

Investors: Shlomo Barak; MOFET Institute, Tel Aviv; Igor Remennik; Gil Unger; DM Benatav Ltd.

Board Of Directors: Moshe Neuman; Shlomo Barak; Igor Remennik; Gil Unger

mass and a fractured jawbone. Typically in these patients, the jaw is held together with a metal plate and four screws. But in this case, the screws would not hold in place. Over a six-month period, the patient functioned with a fractured jaw and consulted with many experts before coming to Barak, who told her that he had heard about treating orthopedic fractures with an electromagnetic field system. The patient agreed, and therapy was administered a few hours each weekday by placing on the jaw a patch that was connected by wires to the larger machine. "After a month, the pain stopped, and in three months, the fracture was completely healed," Yakobson says.

The other co-founder of MagDent, Moshe Neuman, is a periodonist at Barak's clinic and holds a master's degree in bone biology. To miniaturize a desktop orthopedic system, the two founders contracted with electronic engineers who devised a tiny microelectronic device that can operate on a battery with low-energy capacity. The entire healing cap is made of titanium, with a 5 mm diameter and a 6 mm height.

Yakobson is trained as an industrial engineer and spent most of his early years as an officer in the Israeli Army. Since then, he has accumulated more than 15 years of managerial experience in Israel, including as a department manager for United Parcel Services (UPS) from 2009 to 2011, followed by a stint as a business consultant for a fire-safety systems manufacturer. In 2014, Yakobson joined MagDent. The company has one issued and one pending patent, and will share royalties with the MOFET Institute in Tel Aviv, which financed the development of MED.

The device is delivered to the dentist in lots of 10, each individually packaged. Inside the package are a nonsterile plastic outer tube and a sterile plastic inner tube that contains the MED itself. The inner tube is placed inside a complementary electronic product from MagDent, Activator, which costs between $150 and $200 and activates the MED in a mere two seconds. The MED is then taken out of the sterile plastic inner tube and placed on a sterile tray. Next, the dentist simply picks up the MED and threads it to the inside of the original screw through human visualization. The whole procedure, including activation, takes only about one minute.

The top portion of the cap contains the electronics, battery and coil, in descending order. "We use the same treatment protocol as a standard titanium healing cap," Yakobson states. "The only difference is that our cap is hollow inside and houses the microelectronics." The single-use cap is inserted for up to one month in the lower jaw and for two months in the upper jaw. The patient is not monitored during the healing period, but at the conclusion returns to the dentist to have the cap removed by screwing counterclockwise, again by hand or wrench, depending on the tightness. An abutment or connecting screw is then threaded inside the original screw before the crown is attached to the abutment.

Nearly every company that makes dental implants also offers healing caps, foremost **Nobel Biocare Services AG**, **Zimmer Biomet Holdings Inc.** and Israel-based **MIS Implants Technologies Inc.**, but none has any therapeutic effect, according to Yakobson.

With a price tag of around $70 for a dentist, MED should begin selling in June, primarily in Europe, through either a network of distributors or dental implant firms.

MagDent has raised $1.94m to date in three rounds of financing: an R&D grant of nearly $700,000 from the MOFET Institute that closed in 2011; a Series A of $500,000 from three private investors that concluded at the end of 2014; and a Series B of $800,000 from a different solo private investor that closed in March. A Series C round in the amount of $2m should conclude early-to-mid 2017, targeting perhaps private investors, VC firms and/or a strategic partner in the dental or orthopedic space.

"Our market is extremely competitive," Yakobson says. "Everyone is trying to develop an implant that will shorten the healing period, just like our product does. Furthermore, the biggest entity in the dental implant market is prevention of peri-implantitis, an infection forming around the implant, which our technology can treat." MagDent is also in active discussions with potential strategic partners, but would like to remain independent. Meanwhile, the company is pursuing orthopedic screws containing an electromagnetic field to fixate titanium plates in fractures that would decrease healing time. "Orthopedics is a much larger field than dentistry," Yakobson observes.

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Zimmer Biomet Adds CD Diagnostics To List Of 2016 Acquisitions

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A week after launching a new comprehensive consulting and technology program to help hospitals manage orthopedic surgery episodes-of-care, **Zimmer Biomet Holdings Inc.** is adding *in vitro* diagnostics to the program with an acquisition of **CD Diagnostics**.

On Aug. 15, Zimmer Biomet announced plans to acquire the Claymont, Del.-based company, which specializes in diagnostics based on biomarkers in the synovial fluid of the joints. Terms of the deal were not disclosed.

Zimmer Biomet says adding CD Diagnostics buttresses its new Signature Solutions program, intended to help hospitals weather the transition from fee-for-service to value-based payment models for orthopedic surgery, especially large-joint surgery. Zimmer Biomet leads the large-joint orthopedics device segment with roughly a third of the global market share.

CD Diagnostics and Zimmer, which merged with Biomet in 2015, have been working together since 2012 to develop the *Synovasure* alpha-defensin test for periprosthetic joint infection (PJI), the only validated test of its kind, according to the companies. Prior to Synovasure, diagnosis of PJI required a combination of tests, including scans and bacterial culture, that are more costly and time-consuming, and are not very specific or sensitive.

Synovasure, which has a CE mark but is not yet approved in the US, can achieve 97% sensitivity and 96% specificity by measuring synovial fluid alpha defensin, an antimicrobial peptide released by neutrophils in response to pathogens, according to Zimmer Biomet.

In addition to the Synovasure PJI test, CD Diagnostics and its Baltimore-based subsidiary lab **Citrano Medical Laboratories** offer several other diagnostics services related to diseases of the joints, including synovial fluid white blood cell count, synovial fluid human neutrophil elastates testing, and synovial fluid crystal analysis.

"Our acquisition of CD Diagnostics cements our leadership and competitive advantage in musculoskeletal diagnostics, strengthens our Signature Solutions offering, and advances our mission to provide comprehensive musculoskeletal health care," said Dan Williamson, group president of Zimmer Biomet Joint Reconstruction. "As value-based health care replaces fee-for-service models, there will be a growing need for diagnostics that can either prevent or minimize costly complications, or personalize the course of treatment to speed up recovery time and optimize the patient experience and, ultimately, the patient's outcome." He said Zimmer Biomet's resources will allow CD Diagnostics to accelerate the development of diagnostics and standard testing protocols that can help guide orthopedic surgeons' decisions.

Zimmer Biomet has announced five other acquisitions in 2016, including at $1bn deal for **LDR Holding Corp.** and a $130m acquisition of **Medtech SA**, which makes the *ROSA Spine* robot system for spine surgery.

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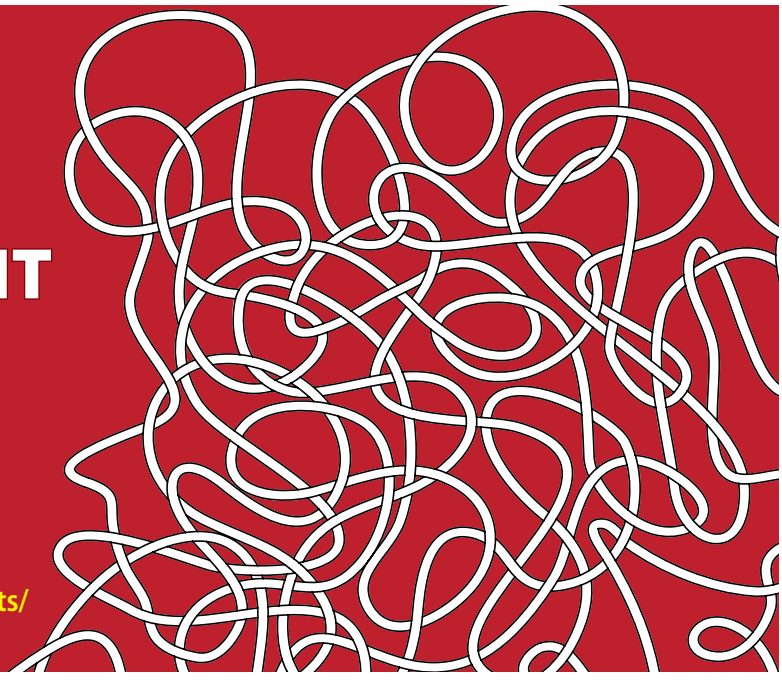

Advanced ICU Care Launches Cardiac Telemetry Service

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Advanced ICU Care, a provider of telehealth services to help hospitals monitor high-acuity patients, is rolling out a new real-time cardiac patient-monitoring service that works with any manufacturer's monitoring devices.

The new cardiac-monitoring service is a natural outgrowth of the St. Louis-based company's tele-ICU services, the largest of its kind in the US, serving 60 hospitals from eight service centers. In that program, intensivists monitor intensive care unit patient data around the clock, including vital signs, medications, lab tests and clinical status. The service also provides data-management tools, and remote or face-to-face consultation.

"We've been very focused on growing our footprint in the tele-ICU space and we continue to be very focused on that as our primary interest," Advanced ICU Care CEO Lou Silverman told *Medtech Insight*. "But we've also been trying to give careful thought to areas that are related to what we do. That is, providing care to patients that are hospital-based and looking for places where we can add value in underserved areas where technology and clinical care are fused together, and where value can be added by smart remote-monitoring that helps a number of stakeholders in the health-care delivery system. And telemetry is one of the areas that we elected to pursue."

Silverman explained that, generally, hospitals' systems for monitoring telemetry from cardiac patients are fragmented, and, therefore, often inefficient and not as effective as they could be. "Some of the monitoring is done by telemetry techs, while some is done by nurses at a nursing station, and we felt like there was an opportunity to provide an expert service that makes telemetry not an afterthought," he said. "We specialize in it – we can field the alerts, we can process the alerts, and help the nurses deal with 'alert-fatigue.'

"Telemetry is already being provided today at most hospitals. We are simply providing a more flexible, more technology-forward service for them so if they chose to outsource this, we have a very appealing model for that," Silverman added.

FLEXIBLE AND SCALABLE

An important feature of Advanced ICU Care's program, according to the company, is that hospitals pay for it on a per-patient basis so the hospitals will not have to pay for employees or services they are not using when the patient volume is low, or scramble to scale-up when patient volume increases. "We can deal with economies of scale in terms of monitoring numbers of patients," Silverman said.

"You have to start with a [full-time employee] if you're going to do telemetry monitoring with a telemetry tech and, candidly, sometimes it's hard for hospitals to make that cost justified," he explained. "Clearly for smaller hospitals we know that they struggle with the staffing of this function and the economics of the function." But Advanced ICU Care can also serve larger hospitals or hospital systems too, or create a program where Advanced ICU Care handles cardiac telemonitoring for some of a hospital system's centers while the system builds an in-house program for its larger centers, Silverman explained.

Gian Cavallini, Advanced ICU Care's VP of strategy and development, added that hospitals "can extend what they have today in a way that gives them flexibility. They may have difficulty scaling-up as necessary, so we can give them an alternative solution that doesn't require full investment and a dedicated number of FTEs [full-time employees], and lets them accommodate their needs on a flexible basis."

Advanced ICU Care's system is also "technology agnostic," so it is compatible with just about any cardiac telemetry device that needs to be monitored regardless of the manufacturer, according to the company.

"We've become very adept at taking this cacophony of input and bring it into something logical and manipulable and readable," he said. "There are a handful of telemetry vendors compared to the many more EMR vendors, but the notion is the same: We can and will work with any hospital that has any system. We don't want to be out on the marketplace saying, 'We only want to talk to you if you telemetry system is from manufacturer XYZ.' That's an important part of our capability and we think it's an important part of what we do to provide service to a range of clients."

Silverman said that, beyond the patients and hospitals the company is already serving, there is a lot of room in the market for companies like Advanced ICU Care to help hospitals monitor high-acuity patients. The company is currently focused on patients that require 24/7, facility-based care, but Advanced ICU Care may look for partners to address patient groups that need episodic monitoring, like patients recovering from a stroke or other neurology patients.

He said to expect more announcements from the company on new ventures in the next six to eight months.

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Q&A: What's Next For UK Regs? ABHI's Phil Brown Discusses Post-Brexit Industry Strategizing

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Phil Brown

Much uncertainty abounds about how the UK will regulate medical technology once it has left the EU. No one knows quite when that departure will happen following the public's Brexit vote in June, but the medtech industry is looking to get ahead of the debate by exploring the most likely regulatory alternatives.

The big question is, will the UK continue with plans to implement the EU's pending Medical Device and IVD Regulations, albeit with less influence over EU decision-making? Or will the country take a sharp turn and follow US FDA-style regulations?

These questions and other creative ways forward are the focus of the regulatory policy staff within the Association of British Healthcare Industries' Brexit Steering Committee, Phil Brown explained to *Medtech Insight*.

Brown was recently appointed to take over as director of technical and regulatory functions at the association. He is leading the ABHI regulatory policy work area with a mission to help create a unified industry position on how the UK regulatory future should look. His work is part of a broader Brexit initiative at ABHI: other experts are heading groups focused on wider medtech aspects impacted by Brexit, including: trade; manufacturing; R&D; people; and fiscal and IP.

Brown said in an interview that he believes, ideally, any future regulatory agreement would be based on mutual recognition of the EU's Medical Device Regulation, or at the very least, the EU's "New Legislative Framework," to ensure continued access to the European Market.

But these are early days and nothing is cast in stone, he acknowledged. There are a series of complex, interrelated questions that need to be considered from the point of view of each possible outcome and its impact. *Medtech Insight*'s interview with Brown, captured below, shows just how wide-ranging and complex those considerations are.

Medtech Insight: Could you imagine a future where the UK decides not to follow the Medical Device Regulations and whether it possible that the UK may go it alone and have its own medtech regulations?

Phil Brown: Speaking on a personal level as a regulatory professional of nearly 30 years, I cannot imagine a future where the UK is not aligned with the MDR. The global move toward regulatory convergence rather than divergence would suggest that globally regulation is aligning with an EU-style "New Legislative Framework" structure, anyway, rather than anything else.

However, the referendum result has allowed for a debate on the subject, and the consideration of several options does offer some interesting possibilities.

What is your view in the short and the longer term about following the MDR?

The message we are giving members is that in the short term we should concentrate on the implementation of the MDR. After all, until such time that Article 50 is invoked triggering the start of the UK formally leaving the EU and even for two years post that, we will still be part of the EU and bound by the UK transpositions of European law.

Longer term, the answer may be very different, but at present impossible to predict. It is always dangerous to make assumptions in such uncertain circumstances as you may end up making mistakes.

As an organization, however, ABHI has conducted a series of assessments which we will be sharing with our interested stakeholders in the coming weeks and months, on the understanding that these are indeed "living documents" and liable to change as a result of Government strategy.

To what extent will the chosen regulatory route satisfy critics out there of the EU medtech regulatory system as it currently operates, including those who say it is not strict enough?

Without going into these assessments in any great detail – as they are complex – the general feeling is that the best option, offering the least risk for the industry, is the adoption of the MDR. With the significant raising of the bar with respect to safety and performance, particularly, we hope this will go a long way to answer the criticisms in certain areas of the media.

But the satisfaction of regulatory criticism lies not necessarily with the chosen regulatory pathways, per se, but more with the education efforts made by industry and organizations such as ABHI. It is only by appropriate explanation of how medical devices are controlled that criticism can be addressed.

So what will be the first steps you will take in leading the regulatory policy work area for the ABHI Brexit Steering Committee? How

will you move forward in getting a position together in this area? Who will be involved? And how transparent will the process be?

A subsection of ABHI's Technical Policy Group is obtaining data and intelligence on the Brexit impact. This information is then going to be married with the output of another sub-set, the "Implementation Working Group," focusing on the implementation of the Medical Devices Regulation. Both groups will work independently so that any impacts can be assessed objectively.

The Technical Policy Group [TPG] members are essentially the senior regulatory and technical personnel from the ABHI's membership. The TPG is one of the most widely and well attended policy groups within the ABHI, regularly attracting over 40 persons to the quarterly meetings.

The Implementation and Brexit Groups will be making recommendations to the TPG, which is where the collective positions will be generated. The whole process is as transparent as we can make it – although having said that, and as part of the process, the members will abide with requirements related to commercial sensitivity, *et cetera*.

What are the main concerns of the UK medtech industry? What does it need to safeguard, in your view?

The main concern for the medtech industry at the moment is the uncertainty. Each of our members will have their own unique strategy for dealing with Brexit, as they range from SMEs to large medical device companies and from UK manufacturers to Authorized Representatives.

The true dilemma posed by Brexit, however, is whether opportunities are true opportunities or whether the "doom-and-gloom" predictions are more accurate – and then what to do as a result. At the moment, with the referendum still less than two months in the past, speculation and uncertainty are at the top of most people's agendas, making any form of regulatory strategic thinking almost impossible.

What needs to be safeguarded, though, is the British sense of pragmatism and realism. As things really do start to "come out in the wash," ABHI has to make sure that its members are fully informed and aware of all the potential outcomes so as to enable them to reach their most appropriate decision regarding strategy. In the short-term, however, questions are not wholly related to regulatory, as the fall in the value of the pound has meant many more business-related questions. ABHI is therefore busy on all fronts to make sure that business is informed, of which regulatory is just one part.

How does UK industry feel given its regulator may no longer be part of the formal process of law-making in the EU?

Over the years, the MHRA has become one of Europe's most influential competent authorities, and has often – in our eyes anyway – been a voice of reason in some tough negotiations – such as those for re-use of single use devices [SUDs], for example.

Although not set in stone, the possibility that the MHRA will be outside any formal EU regulatory process is not an eventuality we relish. Of course, this assumes that the UK will adopt the Medical Device Regulation in the future, which is not a foregone conclusion.

If the UK regulator is distanced from the formal law-making process, it will be important for the MHRA to engineer a role in which it can still be seen as an expert or as a resource for the EU. ABHI would certainly support this effort.

Having said this, and knowing that it may be premature to discount the possibility of a more indigenous regulatory platform in the future, a national regulatory system may allow UK manufacturers greater access and lobbying potential on regulation that affects the UK Industry. In such a case, it could be the rest of Europe that needs to then evaluate the pros and cons of the UK as an opportunity for investment and innovation.

"The general feeling is that the best option, offering the least risk for the industry, is the adoption of the MDR."

What, at the moment, do you think the options under discussion will be in terms of the future regulation of medical devices in a post-Brexit UK?

As part of our due-diligence, ABHI has already and principally considered two extreme situations and a number of secondary possibilities in between.

From an extreme viewpoint, we consider that the wholesale adoption of the Medical Device Regulation [MDR] as has been recently finalized would present the least confusion for industry and would maintain public confidence in the regulatory system. After all, the MDR has been largely welcomed by industry already and will represent a raising of the bar when it comes to safety and performance requirements.

On the flipside, a registration scheme based on the mutual recognition of regulatory structures in other territories, such as the EU or US FDA, may provide for the greatest flexibility and adaptability, and may actually encourage innovation and speed to market.

Each of these possibilities has drawbacks of course, none more so than in the case where the UK would adopt the MDR without being a member of the EU, as the UK would potentially have little influence over subsequent changes in the EU to regulation or publication of the implementing and delegated acts that have still to follow.

In the case of a registration-type scheme based on MRAs [mutual-recognition agreements], confidence in such a system – which involves mutually recognizing an existing approval by

ABHI is principally exploring four alternatives, according to Brown:

- Wholesale adoption of the EU MDR by the UK.
- A registration scheme based mutual-recognition agreements with other territories.
- An indigenous UK regulatory system based on the EU's New Legislative Framework.
- A UK regulatory system that is more aligned with US FDA.

"A national regulatory system may allow UK manufacturers greater access and lobbying potential on regulation that affects the UK Industry."

another government's body other than the UK MHRA – may be low when considering whether a registration scheme is appropriate for what is regarded as a sophisticated medical device manufacturing nation.

The learning curve imposed, the uneven playing field this would present to industry, as well as the difficulties with respect to European affiliates and notified bodies, would make this a greater challenge with little in the way of observed benefits.

Of course, there are a myriad of alternatives in between these two extremes. As an organization, we have considered just two of these alternatives – where an indigenous system based on the EU's New Legislative Framework would be comparable to the EU/global market, and perhaps a second possibility, where adoption of a system more aligned with the US FDA could flourish.

Assessments of these four potential systems have been made, determining their relative strengths, weaknesses, opportunities and threats. Again, as previously mentioned, each of these assessments have been determined after making huge assumptions as to outcomes and possible MHRA strategies. So our thinking is still arguably premature.

Will the regulatory model depend on a broader, overall economic/trade agreement for medtech products?

Yes, without a doubt, as the regulatory system requirements are an adjunct of the overall business process.

The regulatory path is only one consideration when trying to determine what is best for the UK medical device industry. Clearly, any future EU regulatory models will be influenced by the trade pathways taken.

Whatever trade path is taken, it will be important for the UK industry, competent authority and notified bodies to be part of the decision-making process.

ABHI represents UK companies, but also subsidiaries of European companies and UK companies that have operations in other EU countries too. How do you think this will influence the position of ABHI?

The Technical Policy Group within the ABHI, which will be over-seeing any discussions on Brexit and/or implementation of the MDR, is made up of all members, including UK affiliates of EU companies and authorised representatives. This transparency will ensure that the outputs of ABHI are sympathetic to all needs and are therefore adequately addressed in any lobbying activities.

In some ways, of course – and completely tongue-in-cheek – the UK centricity of Brexit and the concerns of industry outside of the UK may be an opportunity for ABHI to initiate a recruitment drive.

What is the likely future of notified bodies and authorized representatives in the post-Brexit era? And what news have you heard about how are they being affected now in terms of client numbers?

I'll answer the second question first. All notified bodies, whether in the UK or elsewhere, are suffering from capacity issues. The introduction of the MDR will only exacerbate this effect, as the role of the notified body is expected to significantly increase. ABHI, along with Eucomed and other medical device trade associations, are closely monitoring this situation – although affecting any remedial activity would be beyond our scope.

As for the first question related to client numbers, ABHI has no intelligence on the future fate of UK notified bodies, although it is genuinely hoped that they will be able to continue supporting UK industry in the New Legislative Framework context. Of course, if government strategy dictates that the UK will follow alternative regulatory regimes, the outcomes for notified bodies are likely to be different.

The same can be said for authorized representatives – ABHI has no intelligence as to how they will be affected post-Brexit. It is a well-known fact, however, that the UK probably has more resident authorized representatives that any other EU member state, so, therefore, it is hoped that some agreement can be reached whereby their status is preserved.

What will be the overall financial impact of the various regulatory options post-Brexit on medtech companies and the medtech support industry?

A financial impact of Brexit from a regulatory perspective has yet to be done. However, it was clear pre-referendum that the adoption of the MDR would certainly increase the financial

burden of regulatory compliance – whether this was as a result of the increased clinical requirements, notified body audit requirements, classification changes, new labelling, or any number of other factors implicit in the regulation.

The financial aspects will only become apparent as the dust begins to settle and governmental policy evolves.

It should also be noted that ABHI understands that the plans for "fees" mooted by the MHRA are being re-modelled. The outcomes of these discussions will depend on what regulatory pathway is eventually chosen, but if this is not along the lines of the MDR adoption, then modification of previous discussions would clearly be in order.

As for support industries, the supply and demand principle and the required expertise can only mean one thing – an increase in workload. ABHI has been in communication with both lawyers and consultants as a result of the referendum to try and understand different scenarios and potential outcomes. Although it is impossible to say, and having once been a consultant myself, you could envisage that this is a good time to be in the support industries.

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Put Clinical Utility Into Context For Molecular Tests, Pathologists Say

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The Association of Molecular Pathologists (AMP) is promoting the use of a modified evidence model for molecular diagnostics combining analytic validity, clinical validity and utility with ethical-, legal- and social-implication models that stress a patient-centered approach, the group says in an Aug. 17 report. The document was released online ahead of its publication in the September 2016 issue of the Journal of Molecular Diagnostics.

AMP notes that future advancements in precision medicine "are threatened by drastic shifts in evidence demands and the adoption of very narrow clinical utility definitions that do not address all the important applications of molecular diagnostic testing."

The groups points out in its report that Medicare administrative contractors have linked evaluations of both analytical validity and clinical validity with Medicare's "reasonable and necessary" requirement and have demanded evidence of both, in addition to evaluations of clinical utility. The payers are most concerns about expensive genomic sequencing procedures involving next-generation sequencing and even whole exome sequencing.

"Ultimately, we need to capture evidence for the clinical utility of molecular pathology procedures outside of a traditional randomized, controlled trial setting, recognizing that any individual test result is an intermediate outcome that relies upon proper clinical interpretation and utilization in context for that specific patient," said Elaine Lyon, 2014 AMP Chair and a pathologist with the University of Utah School of Medicine.

> "We need to capture evidence for the clinical utility of molecular pathology procedures outside of a traditional randomized clinical trial setting," AMP's Elaine Lyon says.

CLINICAL UTILITY DEFINED FOR MOLECULAR DIAGNOSTICS

AMP also said it recommends that the definition of clinical utility (CU) for molecular diagnostics be based on the Centers for Disease Control and Prevention's ACCE model, which says that clinical utility is "the ability of a test result to provide information to the patient, physician and payer related to the care of the patient and his or her family members to diagnose, monitor, prognosticate, or predict disease progression, and to inform treatment and reproductive decisions."

While expensive genomic sequencing procedures "may be cost-effective compared with testing several known relevant genes, a potential indirect cost of large oncology gene panels is the increased likelihood of finding a mutation for which there is an expensive therapy, possibly off-label or in a clinical trial," AMP states.

It adds that the challenges of evaluating clinical utility of molecular diagnostics include:

- A low prevalence for specific disorders;
- A lack of available targeted therapies;
- The difficulty in quantifying the impact of testing on psychological well-being and long-term care; and
- The difficulty obtaining pertinent family information.

But despite the challenges, "patient-centered clinical molecular diagnostics, including interpretation conducted by appropriately trained and certified molecular pathologists or clinical medical geneticists, can provide compelling CU," AMP concludes.

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market. A majority of labelers will be manufacturers themselves. But a labeler might also be a specification developer, a single-use device reprocessor, a convenience kit assembler, a repackager or a relabeler, FDA states in its 2013 UDI rule.

Despite its backlog in answering industry questions, the agency is still taking them. "FDA continues to be committed to getting the Unique Device Identification system implemented correctly, and to helping companies comply with system requirements," Sigg wrote. "Labelers having trouble with GUDID data submissions or with completing other UDI requirements should contact us so we can try to help them resolve their issues."

> "There are definitely small companies that have said, 'The FDA's going to move the date that we'll have to comply.' And so they were waiting for the date to be moved. And now that it's not moving, they're saying, 'Oh, my God, I've got to do something,'" GS1's Greg Bylo says.

GUDID is FDA's public Global Unique Device Identification Database, where UDI data is stored.

Manufacturers that don't receive a timely answer from FDA can always approach their UDI-issuing agency for guidance, Sigg suggested. There are three such FDA-approved agencies that sell identifiers to device firms: GS1, HIBCC, and ICCBBA.

ICCBBA – the International Council for Commonality in Blood Banking Automation – is an international standards organization that provides identifiers for human blood, tissue, organs and other products of human origin, while HIBCC – the Health Industry Business Communications Council – is an industry-sponsored and -supported nonprofit organization whose standards have been used worldwide for barcode labeling.

Like FDA, HIBCC is answering questions as fast as it can. "We literally spend all day providing tech support to our labelers," said Bob Hankin, CEO and president of the organization. "In some cases it's a five-minute call. In some cases it's a one-hour call. It's usually the newer labelers, of course, that need the help because they've never done it before. And in parallel with that we're answering a lot of e-mail questions in writing.

"Some of these companies didn't understand what was going to be involved and now they have only a few weeks left, and they're trying to get it all done," Hankin said in an Aug. 4 interview.

Meanwhile, GS1 is a global organization that designs and implements standards to improve the efficiency and visibility of supply-and-demand chains globally and across various industries.

The GS1 system is the most widely used supply-chain standards system in the world, so it comes as no surprise that GS1 codes are by-and-far the most popular in industry, with roughly 90% of device firms buying identifiers from the group since 2013, said Greg Bylo, GS1's VP of health care.

GS1 is also taking calls from a variety of panicked firms, most of them smaller. "There are thousands of small manufacturing companies out there that make medical devices. It's not uncommon for us to get a phone call from a company that makes only four products. And we've been getting a tremendous influx of phone calls over the last two months, mostly from small companies," Bylo told *Medtech Insight* on Aug. 10. He noted that GS1 offers webinars, workshops and training courses on UDI implementation.

"What we're seeing right now is that a lot of small companies are just figuring out that the UDI requirement exists and that the deadline is this coming Sept. 24, and that they have to comply," Bylo said.

"Some of those small firms don't understand that UDI exists. Some of them don't understand how it pertains to them," he said. "And there are definitely small companies that have said, 'The FDA's going to move the date that we'll have to comply.' And so they were waiting for the date to be moved. And now that it's not moving, they're saying, 'Oh, my God, I've got to do something.'"

Bylo pointed out that too many small firms don't understand industry's good manufacturing practices (GMPs) – a problem when a manufacturer is attempting to create a UDI.

"If you're following the GMPs, implementing UDI is not that big of a deal. It's very, very much in line with GMPs," Bylo said. "It's really just proper labeling. It's uniquely identifying a product to a specific set of requirements, and it's pairing the production information with that product so you know when it's expiring, what its lot and batch are, if it has a serial number, and what its production date is – all of which are good manufacturing practices.

"All large corporations are going to follow GMPs. All mid-size companies typically are going to follow GMPs," he added. "So when you get down to the smaller ones, it really depends on the staff they have in those organizations and where they stand relative to GMP compliance."

Bylo says large manufacturers, by comparison, are on top of their UDI game because they don't want to be forced by FDA to stop shipping product if they fail to comply.

"Those very large device giants such as Medtronic, Covidien, BD and J&J – the billion-dollar corporations and up – are doing well and they're on-track," he said. "And most likely all of them are done with UDI and are just waiting for the compliance dates to … get everything labeled. They're not having a problem with that. They have the regulatory staff. They have the money. They have the project planning skills and capabilities to get all of this done very effectively.

"Internal compliance is the single thing that will drive an organization to move."

But UDI guru Jay Crowley sees things a bit differently. "If you're a really small firm, then UDI is probably pretty easy. That's because you've one product or two products, and it's fairly straightforward," he told *Medtech Insight* on Aug. 2.

Crowley was FDA's former senior advisor for patient safety and point person for developing the agency's UDI program. He is currently VP of UDI Services and Solutions with consulting firm USDM Life Services.

When it comes to UDI, it's typically the large firms that fall down. That's because of the large volume of devices they make, Crowley said. "You're talking about so many products across so many divisions, and organizational inertia. It's a mindset of, 'This part of the organization does it this way, and that part of the organization does it that way.'"

A firm will then have to decide "if it's going to try to reconcile that, or whether it's going to leave those systems and processes alone to be different," he said. "Large firms can have trouble getting their arms around UDI."

As for medium-sized companies, it's important to "have the right people on the project who understand their products well, who understand why things are done the way they are done, and just getting their heads wrapped around it so they can drive toward making whatever label changes are needed, and getting the data organized for GUDID," Crowley said.

Despite the various troubles encountered by firms – the USDM Life Services/Loftware survey that revealed only 15% of firms are ready for FDA's September UDI deadline – Crowley remains optimistic.

"There are a lot of people who are going to be bouncing up against the deadline. They've been working on it. They're making label changes. They're collecting the data. They're in the final stretch," he said. "So it's not that they're not doing it, but they are saying, 'We've got to get this done. We're moving along.'

"Early September will be busy for some folks as they dot the I's and cross the T's, and get it all done. But most folks are moving along. It's just it's not a slam-dunk."

UDI CHALLENGES AGING LABELING SYSTEMS, PROCESSES

A problem that both large and small manufacturers appear to share is that too many try to shoehorn aging labeling processes to fit modern UDI requirements, while others simply have too many labeling systems to reconcile.

The recent industry survey found that 54 respondents (45%) said pulling data from labeling systems was their biggest challenge. Further, 84 people (70%) reported that they maintain between two and four barcode labeling software solutions.

Firms will "try to make do with whatever old systems and processes they have. As they've gotten into UDI and into label redesign, I think it's become obvious to them that that's hard to maintain," Crowley said. "It's probably not a sustainable model for manufacturers that have a number of labels. Trying to manage all of this can be a challenge using whatever systems or processes they have in place, which oftentimes have been cobbled together over time" through company acquisitions.

"As these companies have tried to implement UDI across the board, that's when they start realizing, 'Wait. We've got all these different systems and all these different ways of doing things, and all these different ways that labels are managed.' Trying to remediate all of that can be quite a challenge," he said, suggesting that "maybe this is a good time to integrate some of your activities and systems and processes."

"Those very large device giants such as Medtronic, Covidien, BD and J&J – the billion-dollar corporations and up – are doing well and they're on-track," GS1's Bylo says. But UDI guru Jay Crowley sees things a bit differently.

But in the meantime, "what we've been seeing is companies saying, 'OK. We're UDI-compliant. We got it done. Whew. Now we need to kind of go back and figure out how to do this in a more systematic and sustainable way over time, because we can't keep this up,'" Crowley said. "They can't do this one-off kind of activity on a constant basis."

HL7 SPL: Not For Everyone

"When deciding between GUDID submission options (web interface vs. HL7 SPL), some companies may plan to use the HL7 SPL submission option without fully understanding the upfront investment of time and effort this requires," FDA's Linda Sigg says.

HL7 is Health Level Seven, an international organization that develops standards for health care. Its submission option is typically used for large-batch transfers.

SPL is Structured Product Labeling (SPL), an HL7 standard for the exchange of product information using XML files.

Investing in HL7 SPL "can pay off for companies that have a large number of records, but we see companies intending to use HL7 SPL for just a small number of records numbering in the tens or hundreds. The benefits of this system may not be worth the upfront investment for this small number of records," Sigg said.

"We encourage labelers of class II devices subject to the Sept. 24, 2016, UDI compliance date who have not yet completed their HL7 SPL testing to look at the web interface submission option. As last year's UDI compliance date approached, we saw a number of device labelers switch to using the web interface because it requires less upfront time for testing."

And FDA sees the same troubles. "Labelers may house necessary information in multiple internal systems and locations, making system coordination a key aspect of preparing data for submission to GUDID," FDA's Sigg wrote in her email to *Medtech Insight*. "Some companies have told us that this aspect of UDI implementation can be more challenging and time-consuming than they originally anticipated."

Keeping employees up-to-speed on labeling processes is also important, Crowley said. For example, a firm's processes "might have been developed 10, 15 or 20 years ago. All of those people are gone, so now you've got somebody who's been there for two years, or two months, or whatever. They'll say, 'I don't know why we do what we do. We just do it.' So they have trouble untangling that from a UDI perspective. That's where I'm really seeing a challenge."

UDI EXCEPTION REQUESTS BOTTLENECKED

Meanwhile, manufacturers seeking an exception or alternative to UDI are stuck in a holding pattern while FDA decides not only whether to grant those firms' wishes, but also how it will ultimately make that decision available to the public. Posting a list of devices that have been exempted – or examples of firms that take a different approach to UDI – would be helpful guidance to makers of similar products.

For example, "if a contact lens manufacturer wrote to FDA and said, 'There's a better way to do UDI for my product. We're going to do it this way,' and FDA said, 'That's a good idea. Go ahead and do it that way,' then the agency would publish that on the website. Then, other contact lens manufacturers could look at that and say, 'That's a good idea. We're going to do that, too,' and not have to reinvent the wheel in another request," USDM's Crowley said in a separate Aug. 3 interview.

"Conversely, if FDA said, 'No, that's a stupid idea. That's never going to work. Don't do that,' and publishes that on their website, then other manufacturers of either contact lenses or similar products could look at that and say, 'OK. Maybe we could do this,' or 'We're not going to do that,' or what have you. So it would be a public vetting of the whole conversation," he said.

"That was the thought going into this: that posting results online would be a nice way to evolve UDI without manufacturers submitting an entirely new request if it wasn't needed. But that just hasn't happened," Crowley added. "I don't know if the problem is how we constructed this approach in the UDI regulation, or if FDA is having trouble in figuring out how to implement it, but it has been a big issue for people."

That's because some firms won't know by the Sept. 24 class II UDI deadline whether their device is exempted, or whether they can use an alternative type of label. If that happens, Crowley recommends that manufacturers ask for an extension from the agency.

The cutoff date for asking for an extension for class II products was Aug. 24, yet Crowley says it wouldn't hurt to submit an application for extension anyway.

In an Aug. 18 email to *Medtech Insight*, FDA's Sigg said the agency indeed wanted extension requests by Aug. 24 to allow for adequate review time, noting that there's no guarantee that requests sent to FDA after that date will be addressed by the Sept. 24 class II compliance deadline.

Adds Crowley: "If you haven't heard whether your exemption or alternative request has been approved, and you're not sure what to do, and the resolution of the request could be fairly significant in terms of how you apply UDI, then I think you should go ahead and request additional time to allow that process to continue and hopefully get the answer you're looking for.

"And you may then need more time on top of that," he continued. "If you're hoping you can do things one way and it turns out you have to do it another, then it may take you some more time to get the new way implemented."

Despite the extension/alternative scheme being outlined in the UDI rule, "I guess it turns out that maybe it's not a legal authority that FDA has, to publish the information," he said. "I'm not sure of the subtlety there, but I know FDA is working on it. It just hasn't been figured out yet."

Sigg offered little new information. She would only acknowledge that "a number" of exemptions and alternatives have been granted by FDA, and that it plans to eventually make that information available to the public.

DRAFT UDI GUIDANCE LAYS DOWN PROCESS

FDA released a new draft guidance on July 25 that gives manufacturers advice on how to put together a UDI.

USDM's Crowley says there isn't anything new, per se, in the document titled "Unique Device Identification System: Form and Content of the Unique Device Identifier," but it lays down exactly how firms should assemble a unique identifier.

5 FDA Tips

1. Follow the step-by-step instructions for submitting data to FDA's Global Unique Device Identification Database (GUDID).
2. Verify your data before it is published in GUDID.
3. Think about how you ensure accurate data at every stage in your internal GUDID data submission process.
4. At the end of the data submission process to GUDID, download your data and look at it from different angles to assess data quality.
5. Communicate with your customers and business partners about UDI implementation. Labelers can benefit from thinking about how UDI implementation can help their business processes, and importantly, how UDI will work best for health-care systems and device users, such as health-care providers and patients.

Source: Linda Sigg, FDA

UDI Guidances & Drafts

- **Unique Device Identification System:** Form and Content of the Unique Device Identifier (UDI) (draft)
- **Unique Device Identification:** Convenience Kits (draft)
- **Global Unique Device Identification Database (GUDID):** Data Submission Compliance Date of September 24, 2015
- **Unique Device Identification:** Direct Marking of Devices (draft)
- **Unique Device Identifier System:** Frequently Asked Questions, Vol. 1
- **Unique Device Identification System:** Small Entity Compliance Guide
- **Global Unique Device Identification Database (GUDID)**

The draft document reads "more like a FAQ," Crowley said. "It's FDA basically saying, 'We're getting a lot of questions about what this basic UDI information means.'"

Crowley noted, "It seems to answer some very basic questions about the UDI and its construct, and the printing of barcodes, and other things for folks who are trying to wrap their heads around it."

The agency released a separate FAQ guidance document in 2014.

FDA's latest draft guidance is also its way of saying, "OK, rest of the world. Now that you're paying attention to UDI, let's explain what it is and what it looks like, and what it means and how it's created," Crowley said.

HIBCC's Hankin agreed with Crowley that "there's nothing new" in the draft guidance. In fact, for firms that want to learn how best to put a UDI system in place, Hankin recommends firms use a different FDA guidance.

Released in 2014, "Unique Device Identification System: Small Entity Compliance Guide" "covers the most topics and it's a more complete guide," he said. "The recent FAQ-type draft guidance actually covers a lot of the same information, but the small entity compliance guide is really the most robust of all the guidances."

FDA "is on a learning curve. It's seeing what questions are coming into its help desk, so based on what they're seeing, they're releasing new guidance documents to try to summarize and clarify existing information, and make it easier for people to find it," Hankin said.

Sigg admitted that the draft guidance does intend to answer "hundreds" of questions frequently asked by labelers. "Also, standards development organizations that the FDA works with on issues related to adoption of UDI in health IT and reimbursement systems indicated that additional clarity and specificity regarding the form and structure of the UDI would help improve the incorporation of UDI in these systems," she wrote.

IDENTIFIERS EXPLAINED

The new draft guidance explains that there are two distinct parts of a UDI: "device identifiers" and "production identifiers." A DI distinguishes the version or model of a device and its manufacturer, while a PI lists the product lot number, serial number, expiration date and/or date of manufacture.

However, "while some of the FDA-accredited issuing agencies may allow for non-UDI elements – such as quantity – in the UDI carrier, we do not recognize any such additional non-UDI elements as being part of the UDI," the agency's document states.

The proposed guidance points out that a UDI must appear on a label in plain text as well as in a format that can be read by a barcode scanner or other type of Automatic Identification and Data Capture (AIDC) device. The agency does not prescribe a particular technology for the AIDC portion of the UDI.

"UDIs, particularly when provided through AIDC technology, will allow rapid and accurate data acquisition, recording and retrieval," the FDA draft document states.

The UDI system allows firms to use any type of barcode, RFID [radiofrequency identification] tag, near-field communication, or any other AIDC technology, including those that currently exist or will be developed in the future. According to the draft, manufacturers "may choose to use more than one type of AIDC technology form to assist users who may be employing different methods of UDI capture technology."

Further, barcodes – if they are used – should be tested for print quality. "We do see barcodes that wouldn't pass the minimum grade, for various reasons. Either people have made them too small or too big, or they've got old printers," USDM's Crowley said. "The whole idea behind the print quality is an assurance that it will be scannable."

Moreover, plain-text UDI information must include the product's DI, PIs and "data delimiters," and be limited to characters specified under ISO/IEC 646, FDA's draft guidance states.

International standard ISO/IEC 646 "specifies a set of 128 control and graphic characters, such as letters, digits and symbols with their coded representation," according to the International Organization for Standardization.

The plain-text portion of the UDI can be listed as a single line or multiple lines, and should be affixed below or near the AIDC barcode or other AIDC form.

"The availability of the easily readable plain-text form allows patients, health-care professionals, FDA, and other users of the UDI system to still read and enter the UDI into patient records, reports to FDA and data systems without any technological assistance," the draft notes.

The document also points out that the area on product packaging reserved for the UDI – called a "UDI carrier" by FDA – should precede all non-UDI elements. In addition, plain-text information should specify the device identifier first, followed by production identifiers, the agency writes.

WHAT ARE DATA DELIMITERS?

Aside from device identifiers and production identifiers, there is a third UDI component – "data delimiters" – which is a defined

FIGURE A

Data delimiters are highlighted on this UDI label example.

character or set of characters that identifies specific data elements within an encoded data string.

"The draft guidance provides recommendations that go into greater technical detail than the requirements in the [UDI] regulation and that reflect FDA's initial experience with the Unique Device Identification system," FDA's Sigg wrote.

"We have also learned as part of UDI adoption pilots and early adoption activities that providing more clarity around the format of UDI, including definitions of concepts like data delimiters – which are used by each of the FDA-accredited issuing agencies, is important to those who capture UDI at the point of care."

So what do delimiters look like? At the bottom of the Medtronic label (Figure A) is a UDI built according to the GS1 standard. There is a parenthetical (01) highlighted in yellow and 14 digits that follow, underlined in blue. The (01) is a GTIN (Global Trade Item Number) delimiter that tells the reader that the numbers that follow it are the Unique Device Identifier. "If you were to look up those 14 digits [in GUDID], then you would find that it's this particular product," Crowley said.

He continued: "There also are parenthetical (17) and parenthetical (10) delimiters that tell you that there is an expiration date [underlined in red] and lot number [underlined in green] embedded in there. And if you look at the top right, there is a plain-text lot number and an expiration date [circled in orange], which is why there is an expiration date and a lot number included in the GTIN UDI."

GS1's Bylo added: "You can't see the delimiters in the barcode itself, but when you look at the human-readable information, if you know what the (01) is, and what the (11), the (17) and the (21) signifies, then you have all the information you need."

The delimiter (21) denotes a product's serial number; it is not included in the Exhibit A label example.

"There are two parts of a barcode. There is the barcode itself and there is the human-readable information. The human-readable information is there because if the barcode is marred and you can't scan it, then you have to know what each section of the UDI signifies by using the delimiters," Bylo said.

Further, "when you scan the barcode, that system you just scanned it with grabs the information. Now, it needs to process that information. And if it needs to move it into an electronic health record, or if it needs to move it into a warehousing system or a purchase order, then it needs to pull that information, capture it, and put it into the right field," he said.

"So understanding those delimiters is extremely important to be able to – from an IT perspective – parse it out and place it into the proper systems," Bylo noted. "Because that's really the benefit of barcoding: it facilitates and automates the process, and reduces the errors that you would have in manual keying. One percent of every manual entry is going to be incorrect. And if you're doing thousands of entries every day, and you have a 1 percent error rate, that's not very good."

BY 2020 ...

USDM's Crowley is confident that by 2020, "industry will have most of it well figured out. I think it will become like retail, where we don't remember a time before UPC codes and scanning. But even in retail it doesn't work all the time. You go into Home Depot to buy nuts and bolts. It doesn't work. But there are the work-arounds that are in place.

"By 2020, we'll all be 80 percent of the way there," he continued. "There are a few things that don't fit real smooth into the model, or it might take some time to figure out how to get them to fit into the model. There are big systems that have long lives that evolve, such as X-ray machines and MRI systems. There are orthopedic implants. Trying to figure out how that's all going to work is difficult because there are kits of them and trays of them and sets of them.

"I think that's the conversation by 2020: 'OK, how do we improve this? We have this new product. How are we going to do this?' I think the basic nuts-and-bolts of it will be figured out. People will expect to see it. We'll start using it, but we'll continue to work on the stuff that's not easy, and then we'll continue to evolve that part of it."

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