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Photo credit: American Diabetes Association

From Pipe Dream To Reality: Artificial Pancreas Set To Debut

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If its product stays on track, **Medtronic PLC** is positioned to make history in 2017 with the first artificial pancreas (AP) device to obtain US FDA approval. But while the company will likely have a monopoly of the market for at least a year or more, numerous competitors are set to follow. These new devices will drastically change and improve the way type 1 diabetes (T1D) is treated and launch a new level of competition in a market Medtronic has dominated for years.

It is no surprise that Medtronic is set to be the first company to launch an AP, a closed-

loop system that links an insulin pump to a continuous glucose monitor (CGM) that can automatically determine when and how much insulin a user might need. Medtronic pioneered the insulin pump market with its *MiniMed* series, introduced in 1999, and one of the primary goals has always been to create a device that functioned with as much autonomy as safely possible. Those who have followed the company have seen improvements in technology over the years, as well as in market share.

Medtronic is the undisputed leader in insulin pumps with about 70% of the US

market, followed by **Johnson & Johnson's Animas Corp.** with about 15% and **Insulet Corp.** with 10%. (see Figure 1, p18)

Medtronic also manufactures the *Enlite* CGM sensor, a key piece of technology that has helped push the march toward an AP forward; it is notable that Medtronic is the only company that produces both a pump and CGM, the two key components of an AP. However, competition in the CGM arena is much more intense than in the pump market. One former start-up that is now a major player in the CGM field is **Dexcom Inc.**, with its *G5* sensor, and the company has working relationships that integrate the technology with pumps produced by Medtronic's competitors.

As to which has the bigger share of the CGM market, that is sometimes a matter of opinion, with neither Dexcom nor Medtronic providing specific figures. However, Dexcom points to data from diabetes market research firm dQ&A, which has listed Dexcom with as high as 70% of the US market, whereas the T1D Exchange, which maintains the T1D Exchange Clinic Registry, has shown Dexcom's device is used by more than 60% of patients in the registry. However, the figures from dQ&A and the T1D Exchange do not represent the entire CGM market, and many people within the industry believe the companies are very close in market share.

Regardless of which has the largest market numbers for CGMs, Medtronic is clearly leading the race toward an AP

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event types



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catalyst types



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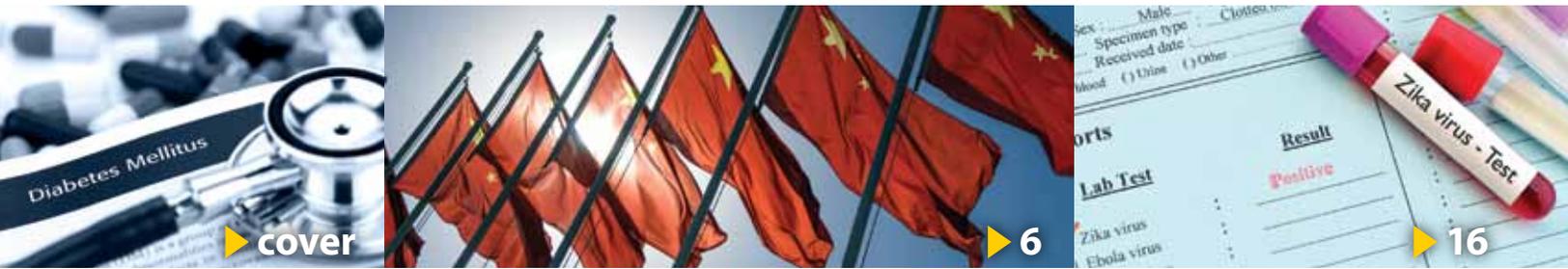
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Q&A: What's next for UK regs?

<http://bit.ly/2aYYHuV>

How should the UK medtech regulatory landscape look once the country separates from the EU? Phil Brown of the Association of British Healthcare Industries weighs in on alternatives.

Infectious disease Dx to go OTC?

<http://bit.ly/29zivFF>

Look for coverage of FDA's advisory panel meeting weighing the prospect of tests for flu, strep and other infections to be sold over-the-counter.

M&A summer slowdown

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2016 looks to be heading for a drop in overall M&A deals as July spells yet another slow month.

BSX Lotus recalls

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Boston Scientific is recalling unused Lotus TAVR valves after three patient deaths.

Device Week

<http://bit.ly/2bmLXUa>

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To Debut – Medtronic is leading the race to get an artificial pancreas to market, and by this time next year the company could be the first manufacturer to reach the finish line. The achievement would be historic, but with a group of established and young companies running about two to three years behind, Medtronic will have to continue to improve on its offerings to maintain its impressive dominance.

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Helps Drive Manufacturers Toward Gold-Star Device Quality – A best practices document for quality metrics developed by the Medical Device Innovation Consortium urges firms to adopt a "right-the-first-time" approach early on in device development and drive a continual improvement loop across their organizations to reduce risks to product quality, save money and shield brand reputation.

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Medtech insight

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with International Electrotechnical Commission standards, and avoid filing 510(k) notifications and Electronic Product Radiation Control reports with FDA, according to a new draft guidance from the US agency.

- 12 Feds Closer To Dx Distinguishing Zika From Dengue As HHS Tries To Plug Funding Gap** – The US Department of Health and Human Services gave up on getting new funding from Congress in 2016 to fight Zika virus, and instead juggled its budget this week to throw \$81m at the Zika vaccine effort. And while there has been headway on a test to differentiate Zika from Dengue, HHS Secretary Burwell told House Minority Leader Nancy Pelosi in an Aug. 11 letter that NIH currently lacks funds to support diagnostics and other Zika priorities.
- 22 US FDA Gives More Time For Public Response To NGS Microbial Identification Guidance** – To give stakeholders more time to respond, FDA has extended its comment period on a draft guidance that addresses next-generation sequencing tests that are used to detect microbes and antimicrobial resistance.

R&D

- 13 More Data Is Not Always Better In Device Trials, Experts Says** – The public-private Medical Device Innovation Consortium reported new findings on device trial designs, including on the vast array of data points that are typically captured in the studies. Companies should take care to ensure they are only collecting necessary data points, experts say.
- 14 MRI Labeling For Boston Scientific's Emblem MRI S-ICD Approved By US FDA** – Boston Scientific cardiac rhythm management has been struggling to compete with MRI-compatible devices from rival Medtronic.

COMPANIES

- 15 Zimmer Biomet Rolls Out Comprehensive Episode-Of-Care Program** – The orthopedics giant is integrating a suite of products and services to help hospitals transition to value-based health-care payment models. The initial focus will be joint-replacement procedures, but Zimmer Biomet anticipates expanding the concept to spine surgery and other sectors.
- 16 Hologic Wins \$4.1m To Advance Zika Blood Screen** – The US Biomedical Advanced Research and Development Authority (BARDA) recently granted \$4.1m to Hologic to advance development of a blood screen to detect Zika in the blood supply. Also, lawmakers are asking more questions about readiness in the US for detecting emerging infectious diseases and bioterrorism-related toxins.
- 17 FDA Panel Supports Baebies' Seeker Newborn Screen Test** – The US agency's Clinical Chemistry and Clinical Toxicology Devices panel showed support Aug. 10 for a de novo submission by Baebies Inc. on its *Seeker* system for newborn screening for lysosomal storage disorders. Panelists said the need for the newborn screen outweighed the uncertainties in setting cutoff points and false-positive/false-negative rates.

FDA Approves Edwards' Rapid-Deployment Minimally Invasive Surgical Valve

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Edwards Lifesciences Corp.'s *Intuity Elite* rapid-deployment aortic valve replacement is now commercially available in the US. FDA approved the device based on clinical data showing it may reduce cross-clamp time and cardiopulmonary bypass time compared to traditional aortic valve replacement surgery.

The agency approved the *Intuity Elite* bioprosthesis on August 12 for a broad indication: The replacement of diseased, damaged, or malfunctioning native or prosthetic aortic valves. Edwards announced US commercial availability Aug. 15.

The system is built on Edwards' established *Perimount* surgical tissue valve platform. But it incorporates technology used in the company's successful *Sapien* transcatheter aortic valve system. It is designed to reduce the invasiveness and time required for complex aortic valve replacement surgery.

Edwards' development of *Intuity Elite* shows that the company still sees at least a short-term future for surgical valve replacement even as it is working to expand the indication for transcatheter valves to include a greater number of patients who historically would undergo traditional surgery. Edwards' *Sapien 3* transcatheter aortic valve is currently FDA-approved to treat inoperable or high-risk surgical patients, but the company hopes to earn supplemental approval to expand the indication to moderate risk patients and may eventually push that even further to include low-risk patients.

Intuity Elite is not the first surgical valve system specifically designed as a less-invasive alternative to conventional surgery. Earlier this year, **LivaNova PLC** gained FDA approval for its *Perceval* "sutureless" surgical heart valve replacement system.

FDA approved *Intuity Elite* based on results from the 839-patient, single-arm TRANSFORM trial. One year outcomes from TRANSFORM were presented by Walter Chitwood of East Carolina University on May 16 at the American Association for Thoracic Surgery's annual meeting in Baltimore. The data demonstrated that the *Intuity Elite* system is safe, effective, and consistently produces clinically acceptable rates of paravalvular leak and device-related new permanent pacemaker implants. The data also showed "exceptional survival" rates at one year, with significant improvement in heart failure functional class and in most patients, according to Chitwood.

The average cross-clamp time during the procedures performed in the TRANSFORM study was 63.1 minutes when *Intuity Elite* was implanted with a mini-upper-sternotomy and 49.3 minutes with a full-sternotomy. This compares favorably to the averages of 82.9 and 76.3 minutes for traditional valve surgery with the mini-sternotomy and full-sternotomy, respectively, as recorded in the Society of Thoracic Surgeons' database. Like-



Source: Edwards Lifesciences Corp.

Intuity Elite rapid-deployment aortic valve

Data from the TRANSFORM trial of *Intuity Elite* showed "exceptional survival rates" at one year - Walter Chitwood, East Carolina University.

wise, total cardiopulmonary bypass time was shorter with the *Intuity Elite* than the historic average for conventional surgery in the STS database. The average bypass time was 84.6 minutes with a mini-sternotomy technique and 69.2 minutes with a full-sternotomy technique. The average bypass times for aortic valve replacement surgeries in the STS database are 111.4 minutes with the mini-sternotomy technique and 104.2 minutes with the full-sternotomy technique.

Intuity Elite has been available in Europe since 2014. In April, Edwards applied for a US 2017 Medicare new-technology add-on payment for *Intuity Elite*, but CMS turned down the application because the FDA had not approved the device in time. Edwards can now reapply for the add-on reimbursement for 2018. ▶

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China's Medtech Regulatory Reforms Yet To Enter Steady Path

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More than two years after China FDA introduced sweeping regulatory reforms governing medical devices – affecting clinical trials, product approvals, post-market surveillance and other areas – companies are concerned that the implementation of the new requirements has yet to enter a steady, predictable path.

It is no wonder then that most of the 19 company CEOs who participated in a survey conducted by consultancy firm McKinsey & Co. earlier this year concluded that regulation tops the list of critical issues facing medtech senior managers in China.

Based on the findings of the survey, McKinsey – along with law firm Ropes & Gray – organized a roundtable in April to discuss the issues at hand, which was attended by regulatory affairs personnel of 16 companies, including major players such as Medtronic, J&J, Abbott Vascular, Siemens, Baxter, Becton Dickinson, Boston Scientific, Stryker and others.

A report on the roundtable, released on Aug.3, makes it clear that interpreting and following the CFDA's "highly complex" clinical trial authorization and clinical trial exemption policies have presented the most challenges. The roundtable delegates also discussed: the costs and benefits of navigating submissions through the CFDA's fast-track application process; the differences between China's GMP requirements and ISO standards; and the "unpredictability" of post-market enforcement. The roundtable report was jointly authored by McKinsey and Ropes & Gray.

In fact, such is the level of anxiety within the industry due to the number of reforms initiated by CFDA of late that the report begins by stating that "regulatory changes will invariably be among the first things mentioned" when senior managers of medtech companies in China are asked about what keeps them awake at night.

The CFDA began introducing the regulatory changes through its "Regulations



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on the Supervision and Administration of Medical Devices," better known to the industry as the State Council Order No. 650, which came into effect in June 2014.

Most of the changes – including exempting the need for local trials for devices that can be shown to be as safe and effective as a predicate device; fast-tracking the approval of innovative devices; and allowing automatic renewal of licenses if there are no changes to the approved product – are aimed at reducing regulatory burden on companies. However, their practical interpretation and implementation means that these changes have not reaped full benefit and, in some cases, have caused much anxiety for companies, the report indicates.

The report highlights some of the regulatory challenges being faced by companies, such as:

>1 CLINICAL TRIALS: In August 2014, the CFDA released a catalogue of class III medical devices subject to clinical trial authorizations (CTAs). While the statuto-

ry timeline for obtaining a CTA is 60 to a hundred working days, real-world experience suggests that it's a much lengthier process. McKinsey's survey showed that the average processing time for clinical trial applications (including queuing time) ranges from one- to two-and-a-half years, depending on the complexity of the clinical trial, with a median time of 21 months.

Delays can add up because before submitting a CTA application, the sponsor must obtain the approval of ethics committees from all study sites, which can be a lengthy process. In addition, for imported devices, the sponsor must also have a marketing authorization issued by the relevant foreign competent authority and include it in the CTA submission.

In 2015, the CFDA introduced the possibility to waive the requirement for clinical trials if the sponsor can show the device to be as safe and effective as a predicate device. However, most roundtable attendees said that, in practice, obtaining such waivers was challenging because

companies can rarely get access to the competitor's predicate device data.

The report points out that the exemptions are mostly granted for local versions of an established, approved imported device, or for incrementally upgraded versions of an approved device of the same applicant. Despite the challenges, however, most companies would prefer to use the exemption route as their first option.

22 AUTOMATIC RENEWALS OF PRODUCT LICENSES: Several roundtable participants expressed concern over a lack of clear guidance from the CFDA on what product changes would require a re-application or the amendment of a license. While some believed that an amendment is required if any change is made to the listed items on the product license, others said an amendment is required only when the changes affect the safety and effectiveness of the device in question. There was also confusion over whether companies can proceed with an amendment submission in parallel with an application for license renewal.

23 FAST-TRACKING INNOVATIVE DEVICES: While 70% of the respondents in the survey said they were considering the fast-track route for future registrations, the report points out that the benefits of the fast-track process "remain hard to grasp." During the roundtable, it was pointed out it can be difficult to obtain detailed guidance from CFDA reviewers on the registration or study requirements of a designated device.

As of April this year, the CFDA had approved 55 fast-track applications, of which only four were from MNCs.

MORE CHANGES ON THE WAY?

A widespread concern among companies is that the future regulatory landscape will remain a "moving target." As per the survey, 55% of the respondents expect continuous regulatory changes in the next three-to-five years. Some 85% believe that the new device regulations will continue to be interpreted and implemented differently by individual provinces/cities. ▶

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Brazil Gives Medtech More Time to Deal With Technical Dossier Rule

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Brazilian health-care product regulator Anvisa is giving manufacturers of low-risk medical devices and IVDs that are already registered in Brazil more time to comply with a new requirement to prepare and maintain technical dossiers for their products.

Anvisa has granted companies making low-risk devices an extra two years, and IVD firms an additional three years, to meet the requirement. The new mandate could result in some companies having to carry out additional tests and studies, according to attorneys at Brazilian law firm Trench, Rossi e Watanabe – in cooperation with Baker & McKenzie International.

The extended deadlines were introduced by Resolution RDC No. 95/2016, published in the *Diário Oficial da União* on July 28, 2016. The requirement for companies to prepare technical dossiers for low-risk devices (classes I and II) and IVDs is designed to make it easier for Anvisa to search for and access information on these products, Henrique K. Frizzo, a partner at Trench, Rossi e Watanabe, told *Medtech Insight*.

The requirement means companies will have to prepare additional documentation and, in some cases, conduct additional studies and tests, Frizzo said, adding that the new rule would introduce additional costs for companies.

Certain companies will be less affected than others, though, since Brazilian regulations accept foreign documents and some companies will already have in their possession the required infor-

mation, the lawyer added.

The requirement to prepare technical dossiers for low-risk devices and IVDs was established last year by RDC 40/2015 (on medical devices) and RDC 36/2015 (on IVDs). The maintenance of such high levels of documentation was previously not a requirement for such products.

However, it has since become clear that the original deadline to comply with requirements was too short, and some companies would need additional time to prepare their dossiers. This is one of the reasons for the extension, said Frizzo. The new deadlines for compliance are July 28, 2018, for medical devices and July 28, 2019, for IVDs.

Frizzo added that the technical dossier requirement had not been introduced for class III and IV devices because those products were already subject to more thorough scrutiny during Anvisa's registration procedure.

RDC 40/2015 and RDC 36/2015, published on Aug. 27, 2015, are designed to help both the regulator and medtech manufacturers in terms of simplified processes and quicker path to market.

RDC 40/2015 specified that all class I and class II (cadastro) medical devices would be subject to pre-market notification, and dispenses with their normal five-year renewal if the file has not been amended. RDC 36/2015 established the same provisions for IVDs, and set requirements for their labeling and instructions for use. ▶

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Metrics ‘Best Practices’ Laid Bare In New Guide That Helps Drive Manufacturers Toward Gold-Star Device Quality

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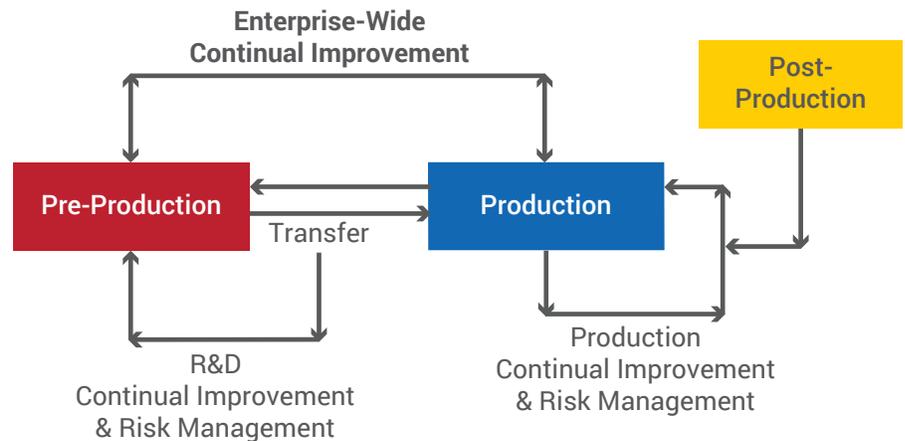
Manufacturers should adopt a “right-the-first-time” approach early on in device development and drive a continual improvement loop across their organizations to reduce risks to product quality, save money and shield brand reputation. That’s according to a new manual that helps firms define and apply measurements to strive for ever-enhanced device quality.

Released Aug. 1, the best practices document for quality metrics was developed by the Medical Device Innovation Consortium (MDIC) in conjunction with US FDA and Xavier University. The guidance aims to help firms understand how to use outputs from three specific metrics to inform decisions and prompt particular actions, as well as to aid manufacturers in understanding how to calculate each metric.

“The intent of the FDA/Xavier work was to arm industry with practical metrics to implement commensurate with the needs of the business and complexity of the products, such that the right-first-time mentality could be shifted as close to the initial days of development as possible,” the manual states.

Quality metrics are measures used to assess the overall quality of medical device manufacturing. Metrics are an important issue for FDA; the agency’s device center included development of metrics in its 2016-2017 strategic priorities list issued in January.

“The goal of a robust metrics program is to help drive continual improvement by enabling an organization to focus on operational areas requiring improvement,” the guide notes. MDIC’s system of metrics is intended to inform company decisions and trigger action when necessary. Three metrics developed by MDIC address device pre-production, production and post-production actions. The metrics also address industry consideration of how to implement enterprise-wide continual improvement.



Source: Best Practices for Metrics Identified Across the Total Product Lifecycle

The three metrics “need to be assessed along with other metrics and sources of information to provide a more holistic view of the overall risk to product quality,” the document states. The purpose of a continual improvement process is to use MDIC’s metrics – and other quality measurements – to “enrich knowledge” across an organization.

The guide also illustrates a continual improvement loop that “links the production and post-production phases of the product lifecycle back to the develop-

ment phase. This feedback loop enables systemic improvements to be made to the rigor of product development.” (See figure above.)

Examples of how to implement an organization-wide continual improvement process is included in the document, which points out that it’s important for manufacturers to “drive the enterprise-wide review to the lowest points in the organizational structure as possible.” It notes that companies should assess data

across all products and consistently use that data to make an array of decisions.

For example, “In the case of senior management review, employees should assess and evaluate the data prior to providing it to senior management in order to be able to explain the data context and propose an appropriate course of action for senior management approval,” the best practices manual states.

“These recommendations would be further accompanied by an understanding of risk impact to product quality, patient safety, organizational finances and brand equity,” it notes. “The data should be provided to senior management with an analysis of the underlying root causes and any contributing causes; a description of what action has already been taken at various stages throughout the TPLC [total product lifecycle]; and a proposal of what other action could be taken to mitigate any additional cost of poor quality.”

An enterprise-wide improvement approach calls for a comparative analysis of devices using tools such as heat maps, dashboards and scorecards. “The process represents the highest level of analysis to allow senior leaders to keep their fingers on the pulse of the performance of their total product portfolio,” the document states.

MDIC’S QUALITY METRICS EXPLAINED REDUX

A July *Medtech Insight* article explained the process for calculating each of MDIC’s three metrics. The synopsis of how each of the metrics will work is recapped below.

The **pre-production metric** tracks the number of changes that occurred during the transfer stage that were triggered by product and/or process inadequacies. This metric helps to signal the frequency and volume of changes that could possibly have been avoided by a more robust research and development (R&D) system.

By tracking the metric, the firm has information that can inform the decisions of senior leaders related to potential improvements to the R&D process. For example, upon review, it might be recognized that the rigor of the voice of the customer could be improved, that there could be a more thorough evaluation of

Quality Metric 1: Pre-Production

* **Total Number of Changes**
(product & process across projects)

-**{divided by}**-

* **Total Number of Changes**
(product & process for each project)

and/or

* **Total Number of Projects**

literature, or even that improved human-factors studies are needed.

For this metric, it’s up to the manufacturer to define “project.” For example, does the firm want “project” to indicate the total finished product, or does it want “project” to be the last step in its pre-production process?

“If you then take what you know about each individual project, you can look across your total number of projects,” Marla Phillips, director of Xavier Health at Xavier University in Cincinnati and co-chair of MDIC’s quality metrics working group, explained at a June MDIC forum. “How many changes are you having, again, based on product and process, across the total number of projects coming up?”

“Then you can see, ‘OK, from the R&D group that’s feeding products to me, how many times are we getting projects from them that require a lot of changing? So it gives you an idea of the R&D group’s effectiveness – not just product,” she said.

“That’s important because if you see a systemic trend, then you can go back and look at how you are gathering development data. Firms can ask, ‘How can we make it more rigorous so we don’t have these changes?’ But again, this has to be commensurate with the needs,” Phillips added.

“If you’re seeing that you have three changes, or two changes and they’re minor, don’t drive a huge, company-wide initiative to drive that down and pull resources from things that are actually needed. But you’ll know. You’ll know when it’s too much for

your company, and when it’s causing problems and costing a lot of money.”

And at a separate June meeting of the Association of Food and Drug Officials, Phillips reiterated that one of the pre-production metric’s goals “is to help senior management see what’s going on, and unless you measure that or have a way to get that bubbled up, it’s difficult. You just know people are complaining and that there’s a lot of churn, but you just can’t put your finger on it. The pre-production metric will help.”

Quality Metric 2: Production

* **Number of Units Manufactured**
Right the First Time Within or
Across Lots

-**{divided by}**-

* **Number of Units Started**

The **production metric** is the “right-the-first-time” measurement that many manufacturers already track. MDIC recommends triaging the root causes such that resources – employees, capital, etc. – can be focused on areas that will result in true improvement, and therefore, a reduction in risk to product quality.

Additionally, MDIC suggests that firms use root cause trend analysis in such a way that any nonconformances related to product and/or process inadequacies are relayed back to R&D through senior management. Again, this type of review will enable the organization to assess the effectiveness of its systems and processes.

“The strengths of this metric are tracking right-the-first-time based on product and process inadequacies,” Phillips said. “We can track and trend within and across lots on a rolling basis to identify the highest area of risk. You can apply predetermined action limits. And again, we said we want to inform decisions and trigger action, so is the number good? I don’t know. Maybe a low number for one product is actually good. It might even be

world-class. So, you have to decide based on your product profile risk what your action limits and trigger limits are.

“The metric is not skewed by volume. However, the volume in this particular case gives you some insightful information, so it is good to know the number of units started because it’s very different to say you have 50 right-first-time out of 500, versus 50 right-first-time out of 55. So, you do want to know that ratio,” she said.

The production metric “can be used to monitor the startup success across products, and then the timeframe needed to reach a mature state,” Phillips said. “What’s the right-first-time in the first year that you’re manufacturing this product, and then what does it look like in year two or year three? And then you can see that maybe it’s something that’s indicative of your company.

“It might take you two years to say, ‘OK, we’ve got the hang of it. We’ve got our workforce ready to go,’ or you might have a very mature workforce and it’s within a product line that you’re familiar with. It’s an extension or just something a little bit tweaked on a product you already have. So, it can give you an idea of how your company is operating.”

Quality Metric 3: Post-Production

* MULTI-STEP OPTIONS:

- 1) Calculate each post-production indicator separately with defined equations provided.
- 2) Aggregate the post-production indicators using weighting factors that are based on product and process risk profiles.
- 3) Comparative analysis can be conducted through mechanisms such as dashboards, scorecards or heat-map tools.

The **post-production metric** has three levels of implementation based on the business needs of the organization and product-risk complexity. The first level involves tracking post-market indicators that should be tracked by organizations anyway, but solidifies these metrics as best practices and provides the metric equations for industry references. The indicators to track are: service records;

installation failures; complaints; Medical Device Reports; recalls by number of units involved; and number of recalls.

The second level involves an equation through which to aggregate post-market indicators, resulting in a total post-market score for each product during the time period specified. This can provide a dashboard number that gives a higher-level indication of product quality performance on the market.

Finally, the third level includes a comparative analysis of products through the use of heat maps, dashboards and/or scorecards. This is the highest level of analysis recommended by MDIC to allow senior leaders to keep their fingers on the pulse of the performance of their overall product portfolio.

“The strength of this metric is that it allows for flexibility for companies to decide what the right fit is for them,” Phillips said. “It provides a mechanism to foster the discussion against triggering action informing those decisions. You might not see just by viewing complaints on its own as a trend and recalls on its own as a trend, so it does give you a different view.

“This will probably be the most difficult metric for manufacturers to tackle.” ▶

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Electrosurgical Device 510(k) Guides Issued By FDA

FDA finalized two guidance documents Aug. 12 to assist companies in submitting 510(k)s for electrosurgical devices. The first guidance broadly addresses pre-market submission expectations for general surgery electrosurgical devices and the second document more specifically targets bipolar electrosurgical vessel sealers.

The guidance documents, which were each issued in draft form in 2014, are focused on devices with general indications for cutting, coagulating or sealing tissue. Devices for which companies seek more specific indications, for instance, to treat a particular disease, will, in many cases, be subject to additional requirements, FDA states.

Clinical testing is typically not needed for general-indication electrosurgical devices, according to FDA. But the guidance documents spell out non-clinical performance data that should be collected. That includes basic mechanical testing of instruments, accessories and electrodes. The agency will also want data on parameters such as the area of anticipated “thermal damage” on tissue from the device, based on testing of *ex vivo* animal tissue. FDA

is also likely to expect monitoring of the temperature and tissue-contact quality for electrosurgical cutting or coagulation devices.

For vessel-sealing devices in particular, the agency says it will look for assessments of “burst pressure” to evaluate the seal strength of vessels sealed with the investigational device compared to a predicate device. For bipolar vessel sealers that can be “reasonably expected to modify the tissue effect of the system,” FDA says it will expect animal studies where the device performance is assessed three weeks after a procedure is performed in at least five animals, with multiple vessels sealed per animal.

Recently approved devices covered by the general electrosurgical guidance include **AngioDynamics Inc.’s NanoKnife** system – cleared last year for surgical ablation of soft tissue – and **Bovie Medical Corp.’s Bovie** disposable bipolar ablaters, cleared last month.

An example of a vessel-sealer device addressed by the target guidance is **Ethicon Endo-Surgery Inc.’s Enseal G2** cordless curved-jaw tissue sealer, cleared in 2013. ▶

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FDA Looks To Reduce Regulatory Duplication With Draft X-Ray Guidance

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Some manufacturers and importers of X-ray imaging devices may avoid 510(k) reporting requirements if their product conforms to certain International Electrotechnical Commission (IEC) standards, according to a new US FDA draft guidance. The agency says it is trying to address complaints from manufacturers about duplicate reporting of X-ray products that need to meet its 510(k) premarket notification requirements and Electronic Product Radiation Control (EPRC) reporting.

“Conformance with recognized consensus standards may in some situations support a substantial equivalence determination,” states the guidance. “Moreover, declaration(s) of conformity to recognized consensus standard(s) could be sufficient to eliminate the need for manufacturers to submit in their 510(k) (and for FDA to review) the actual test data for those aspects of the device addressed by the standards.”

Currently, makers of diagnostic X-ray beam lighting devices, spot-film devices and radiographic film changers are technically required to file 510(k) notifications, although FDA has been using its oversight discretion for the past five years to give companies a pass on that requirement.

“If this draft guidance goes into effect, you would simply submit a declaration of conformity to one of these standards in your 510(k),” said Robert Sauer, a CDRH policy analyst. “And then we would use that information to say you’ve met the reporting requirement and that you have met the performance standard.”

Device-makers who are not required to file 510(k) applications would simply file an abbreviated report declaring conformity to IEC standards.

“While the legal authorities relating to medical devices and electronic products focus primarily on safety/effectiveness and radiation safety, respectively, there is some overlap in the requirements established by these authorities,” the agency says in the guidance. “FDA is issuing this draft guidance to clarify the relevant, applicable standards and to help to ensure a streamlined regulatory review of submissions for these devices.”

HARMONIZING INTERNATIONAL STANDARDS

FDA says it wants to harmonize performance standards outlined in EPRC regulations with IEC standards to ensure its regulatory review is streamlined and companies don’t have to submit the same information in their 510(k) notifications and their EPRC reports. The agency says it believes that if industry conforms to certain IEC standards they could provide the same level, if not better, of safety assurance from electronic radiation than companies do with compliance to some EPRC standards, because IEC standards are more comprehensive.

In the guidance, FDA notes that it has previously addressed some concerns expressed by companies about submitting du-



“This really encourages manufacturers to conform to IEC standards, and we think this will result in equivalent or improved safety of these devices, and on the manufacturer side we think this will reduce regulatory workloads,” FDA’s Robert Sauer says.

licate information when products are considered both medical devices and electronic products. While it has tried to address the issue of duplication for ultrasound devices, laser products and computer tomography scanners with respect to computed tomography dose index, this is the agency’s first attempt at addressing X-ray imaging devices.

In the document, FDA lists out class I and class II X-ray devices that would be covered by the guidance. It also provides tables of EPRC regulations that are covered by IEC standards and those that are not covered.

“This really encourages manufacturers to conform to IEC standards, and we think this will result in equivalent or improved safety of these devices, and on the manufacturer side we think this will reduce regulatory workloads,” said Sauer.

If finalized, he says he hopes the guidance will encourage convergence of global regulatory requirements, and says it may make it easier for companies to bring X-ray imaging devices to market.

Sauer also notes that when IEC standards are developed, FDA is part of the discussion, so the standards are well-vetted by the agency.

GUIDANCE ALIGNS CLOSER TO EU SCHEME

Megan Hayes, director for regulatory and standards strategy at the Medical Imaging & Technology Alliance, notes the European Union has long relied on IEC standards as a key component of its regulatory scheme. While FDA and industry groups such as MITA have been tackling the problem with standards duplication for some time, she says the draft guidance will finally bring US regulators closer to their European counterparts on the issue.

“The FDA performance standards, which are included in regulation, take significant time and effort to revise and are therefore often out-of-date,” she said. “The relevant IEC standards referenced in the guidance document are developed in an open, consensus-based fashion. This process provides more flexibility and the ability to keep up with technology.”

Hayes says one of the key takeaways of the guidance is that FDA is acknowledging that voluntary consensus standards can be useful tools in streamlining the regulatory process.

“The FDA seems committed to partnering with industry and other stakeholders to consider conformance to voluntary stan-

dards as a pathway for regulatory compliance,” she added. “MITA anticipates the guidance will allow industry with the ability to rely on consensus standards that reflect the state-of-the-art in lieu of often outdated regulatory requirements.”

Overall, Hayes says MITA likes that FDA is considering an alternate pathway for regulatory compliance, and notes the organization develops and publishes standards of its own in collaboration with device companies. ▶

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Feds Closer To Dx Distinguishing Zika From Dengue As HHS Tries To Plug Funding Gap

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The US Department of Health and Human Services has had to dig deep into its own budget, diverting dollars from cancer and diabetes research, to funnel \$81m more to NIH and the Biomedical Advanced Research and Development Authority (BARDA) to carry out work on a Zika virus vaccine, NIH’s Anthony Fauci confirmed at an Aug. 11 briefing led by several government, state and local officials in Washington, DC. However, the funding supplement does not include additional needed dollars to support diagnostics development.

The secretary had been hoping for additional funding from Congress to fight the virus, but the House and Senate reached a stalemate in late July over emergency appropriations, and adjourned for the August recess without contributing any extra dollars to the Zika battle.

HHS Secretary Sylvia Burwell said she is giving \$34m to the National Institutes

of Health and \$47m to the Biomedical Advanced Research and Development Authority to rapidly develop a Zika virus vaccine, but that “NIH currently lacks sufficient funds to support diagnostics” in an Aug. 11 letter to House Minority Leader Nancy Pelosi, D-Calif.

BARDA has estimated it will need \$342m more in FY 2017 – which starts Oct. 1 – to continue research on a vaccine, as well as for diagnostic development and pathogen reduction work, the letter states.

Additional work is needed on a more precise Zika diagnostic, because the ones approved by FDA through emergency use authorizations this year are not specific enough to rule out Dengue or Chikungunya viruses, said BARDA’s Influenza Division Acting Director Rick Bright at the Aug. 11 briefing. He noted that the FDA “has been working very hard to evaluate all the data” on the molecular-based diagnostics that have been approved through EUAs.

“The challenges we are facing still is the development of a test that has the specificity, sensitivity – the accuracy – of the serological-based assays,” Bright explained. “With Zika, the challenge we face is the cross-reactive nature of the antibodies of Zika virus to other flaviviruses, such as Dengue, or yellow fever.

“When people are infected with the Zika virus, and we try to use our Zika virus diagnostics, the antibodies to the Dengue are going to cross-react and it gives us false, inaccurate information,” he added.

The BARDA official noted that at least “a dozen” diagnostics are now under development with more precision, but that the agency needs additional funding – as well as sufficient samples from people recently infected with Zika virus – to bring them across the finish line. ▶

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More Data Is Not Always Better In Device Trials, Experts Say

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More than 40% of data points collected during device clinical trials are not used to support regulatory approval, according to an analysis by the Medical Device Innovation Consortium. While approval is not the only purpose for conducting trials, sponsors should take care to ensure they are not collecting more data than necessary in a study, experts commenting on the findings say.

MDIC, a public-private partnership, revealed the analysis Aug. 10. The study found that device trials collect an average of 998 data points per patient. Of that data, 33.2% supports core endpoints; 56.6% is used for regulatory purposes; and 28.9% is used to support other purposes, such as journal publication.

MDIC presented the findings in conjunction with a presentation on the Clinical Trials Transformation Initiative's ongoing "Quality by Design" project. CTTI is a public-private partnership co-founded by FDA in 2007. Its Quality by Design effort encourages manufacturers to use critical thinking to improve device trial design, and therefore trial results. Specific challenges under discussion include the difficulty of recruiting a patient population that both regulators and payers will accept, and cutting out time and money wasted collecting unneeded data points. The group is reviewing factors including feasibility; protocol design; third-party engagement; study reporting; study conduct; patient safety; and feasibility.

CTTI issued a Quality by Design principles document last year, which project lead Ann Meeker-O'Connell described during an Aug. 10 webinar as "a set of checks to make sure things that are critical aren't overlooked" during trial planning. Next, the group held several workshops bringing together a range of stakeholders. CTTI found that workshop attendees tended to agree with Quality by Design's goals, but worry about the extra time the approach could take and

"Device trials tend to add lots of steps beyond the standard of care," says regulatory expert Susan Alpert. "The question is, how do we make sure we're only doing what needs to be done?"

the difficulty of switching to a new trial-design strategy. To allay those concerns, the group now offers an online toolkit compiling documents, templates and guidelines to help organizations integrate Quality by Design tactics into trial design.

But challenges remain. MDIC has been looking at how to best make clinical trials efficient for facilities and patients, and to ensure data collected during trials is pertinent.

"Device trials tend to add lots of steps beyond the standard of care," said Susan Alpert, a consultant, former Medtronic executive, and former FDA official. She noted that 54.5% of trials call for more patient visits than the standard of care. "The question is, how do we make sure we're only doing what needs to be done?"

She said MDIC has found that a more complex trial is not necessarily better than a simple one. Instead, the most important element is careful trial planning. Alpert further recommended that sponsors consider splitting the collection of data needed for regulators or payers between two or more trials to keep any one trial from becoming too burdensome.

MDIC also advocates for taking a close look at potential clinical sites to make sure they've been successful and efficient in participating in similar trials in the past. "It's not just about whether they have patients," Alpert said. "You also have to look at all the other issues, like whether they have the right kind of medical expertise, whether they have specific kinds of imaging you need, and whether they have expert teams so other procedures will be available."

And the expertise needed in trial sites goes beyond the technical details of device use to include data control issues, such as data masking and patient privacy concerns, she added. She further recommended that the sponsor plan to have someone at each site to make sure the device being tested is used properly, including any integration into electronic medical records.

Trial sponsors also need to keep in mind that the long follow-up on device trials mean that patients might not see the same doctor or go to the same location throughout the trial, so flexibility can help with patient retention, Alpert said. In addition, the trial design should include outreach and education for patients and family caregivers, because so many devices are now used outside a formal health-care setting.

Finally, Alpert noted that it's important for a wide array of representatives to provide input on trial design and study conduct. Company management need to be made aware of any particular trial management issues known to researchers, or the trial might not be given the time and resources it deserves, she said.

MDIC and CTTI will next discuss the Quality by Design project at MDIC's Sept. 21 annual meeting in Washington, DC, where contributors and members of the public will be able to offer feedback on the project. The consortium was founded in December 2012 and includes representatives from the device industry and federal agencies, including FDA and CMS. 

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MRI Labeling For Boston Scientific's *Emblem MRI S-ICD* Approved By US FDA

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US FDA's approval of **Boston Scientific Corp.**'s *Emblem MRI S-ICD* subcutaneous implantable defibrillator, announced Aug. 9, is the latest in a string of approvals of *ImageReady* magnetic resonance imaging-compatible devices that should help the company become more competitive in the cardiac rhythm management market.

Emblem MRI S-ICD, which earned a CE mark in April, is an MR-compatible version of the *Emblem S-ICD*. The original Emblem, which FDA approved in March 2015, is smaller than the original S-ICD and works with Boston Scientific's remote management system.

Emblem S-ICD and Emblem MRI S-ICD are the only subcutaneous ICDs available in the US. The S-ICD is implanted outside the patient's ribcage with no transvenous leads, eliminating the risk of lead fracture and possibly reducing the long-term risk of device infection. Medtronic is developing the *EV-ICD*, which also provides anti-tachycardia pacing and short-term pacing for bradycardia, but *EV-ICD* is not yet commercially available.

On top of the MR-conditional labeling, Emblem MRI S-ICD includes two other new features: *SMART Pass* software and *Atrial Fibrillation (AF) Monitor*. *SMART Pass*, which can also be uploaded into previously implanted Emblem S-ICDs, increases the accuracy of the device's *In-sight* algorithm to reduce inappropriate shocks, without preventing the device from shocking the patient out of an arrhythmia when necessary, according to the company. The *AF Monitor* feature identifies and alerts physicians about atrial fibrillation episodes.

Emblem MRI S-ICD is one of a series of MR-compatible devices, or upgrades to existing devices, that Boston Scientific has released in 2016. In April, the company earned FDA approval for the *Accolade* and *Essentio* MRI-compatible pacemakers and the *Ingevity* MRI pacing leads, all marketed under the *ImageReady* brand.

Boston Scientific is also sponsoring the 500-patient *ENABLE* MRI open-label trial of the *ImageReady* MR conditional defibrillation system.

Boston Scientific's *Emblem MRI S-ICD*



Photo credit: Boston Scientific Corp.

MR-compatibility has proven to be a critical differentiator for cardiac rhythm management devices. **Medtronic PLC** has an edge in MR-compatible devices – in the US market, at least – with its *SureScan* line of MR-compatible devices. Trying to compete with Medtronic without a full line of MR-compatible devices has been a major challenge for Boston Scientific and **St. Jude Medical Inc.** ▶

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Zimmer Biomet Rolls Out Comprehensive Episode-Of-Care Program

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Zimmer Biomet Holdings Inc. is rolling out the *Signature Solutions* program, a package of software and consulting services to help hospitals take advantage of the orthopedic surgery industry's ongoing transition from fee-for-service to value-based payment models.

"This is really critical at this time, because more payers are looking at episode-of-care management ... and other bundled payment programs," Zimmer Biomet's Joe Tamaro told *Medtech Insight*. Tamaro is the General Manager of Accelero Health Partners, a subsidiary of Zimmer Biomet that operates the firm's consulting division. "Hospitals are, in a lot of cases, responsible for that, so now they have to manage outside the walls of the episode. These technologies allow them to do that."

Signature Solutions is an extension of Zimmer Biomet's existing consulting services, which have worked with more than 450 hospitals and health-care facilities since the early 1990s. The program will integrate the consulting business with a "strategically curated suite of technologies and services" to help hospitals coordinate all aspects of care for musculoskeletal patients, according to the company.

The program will be initially rolled out to select academic facilities in the US, followed by a broader release in 2017, Tamaro said.

A catalyst for Zimmer Biomet's decision to create Signature Solutions was the company's recognition that "we've been a good provider of medical devices, but we really want to get to the next level or partnership with hospitals. That's what hospitals are asking from us," Tamaro said. Sustainable Solutions will help hospitals not only make process improvements that improve care and save money, but sustain those improvements over time. "We want these technologies to have stickiness in the hospital," Tamaro said.

EPISODE-OF-CARE MANAGEMENT

The demand for more comprehensive products and services is driven by the ongoing shift toward episode-of-care and quality-driven payment models over traditional fee-for-service models that are transforming how hospitals care for orthopedic surgery patients, Tamaro said.

For example, the US Centers for Medicare & Medicaid Services' (CMS) new bundled payment program, the Comprehensive Care for Joint Replacement Model (CCJR), makes hospitals financially responsible for the overall quality of care and costs associated with total hip and knee replacement surgeries. CMS also recently announced plans to extend existing bundled payment models for hip replacement to other hip surgeries. More broadly, the 2015 Medicare Access and CHIP Reduction

Act (MACRA) requires CMS to develop alternatives to traditional fee-for-service payment models that better incentivize quality of care over quantity of care.

"We're the orthopedic experts, and we should be able to provide technologies and this background in the consulting component," he said. "These are, in a lot of cases, elective surgeries, so the expectations for patients should be higher for these. They're having it done to improve their quality of life. It's that level of consistency we want to help hospitals to provide to their patients."

"There are other players in our industry doing certain parts of this, but we've been looking at this for a long time period and have experience in the field, so our goal is to put together the complete package, not just elements of it," Tamaro said. "We think that for us as a company, it's a big differentiator."

IMPROVING COMMUNICATION AND COORDINATION

Hospitals that participate in the program will pay Zimmer Biomet some fees upfront for technology installation and consulting, and then pay on a per-case basis, he said.

The technologies hospitals will buy as part of Signature Solutions include software for patient engagement and communications between the patients and nurse navigators, both before surgery to help patients prepare, and after the procedure to track outcomes. The communications solutions will also allow hospitals to monitor at-home post-procedure recovery care and rehabilitation. The package also includes technology that helps to improve the efficiency of the operating room, Tamaro said.

Signature Solutions also includes a data-mining and analysis platform that collects critical patient-reported outcomes that are factored into the reimbursement calculation for each procedure. "All of those together, the goal is to deliver more value to the hospital, the value being how they deliver better care at a lower cost," he explained.

The company expects to eventually expand the Signature Solutions program beyond joint surgery to other areas where it sells devices and has expertise. For example, Signature Solutions, or a program like it, will eventually support Zimmer Biomet's growing spine surgery business, in which the company has been aggressively investing lately. Tamaro said that the patient engagement and monitoring functions of Signature Solution could help hospitals treat non-surgical back pain as well as surgery patients. "This is a perfect solution to keep ahead of that part of it," he said. "We've already started some work in that area." ▶

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Hologic Wins \$4.1m To Advance Zika Blood Screen

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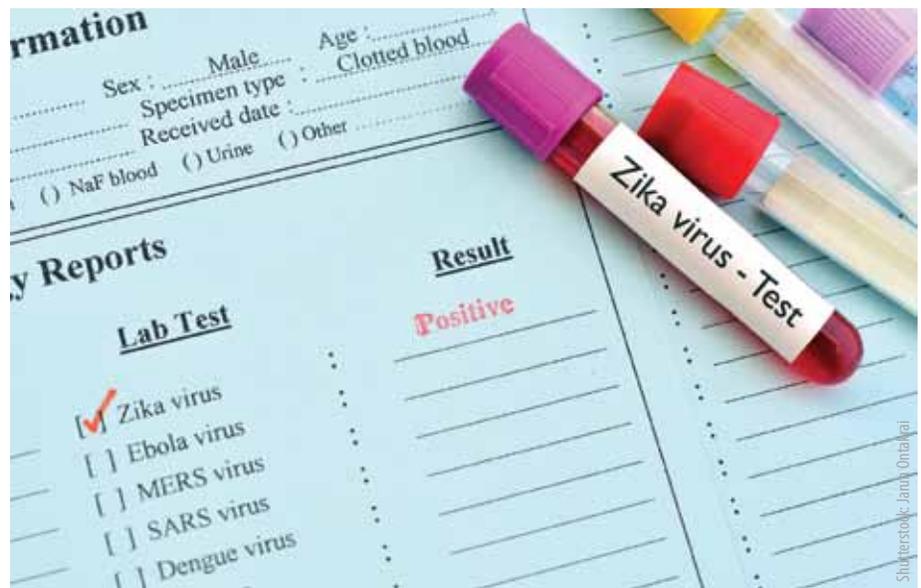
Hologic Inc. recently signed an agreement worth \$4.1m with HHS's Biomedical Advanced Research and Development Authority (BARDA) to advance development of a blood screening test, the *Procleix* Zika virus assay, designed to detect the presence of Zika in donated blood plasma. The blood screen won investigational new drug status on June 17 by US FDA.

The government funding agreement comes as individuals have contracted the virus in recent weeks within the contiguous US. Also, a congressional oversight panel has been pressing federal agencies on the nation's laboratory capacity, and whether there is enough to identify both toxins that could be released by bioterrorists, as well as sufficient capacity to pinpoint emerging health threats including new strains of viruses and other infections.

Accurate blood screening tools are important in identifying infected blood donations, and help ensure patients' safety as viruses spread in a state or a locality, said Richard Hatchett, BARDA's acting director. The *Procleix* blood screen can detect Zika-virus RNA up to seven days post-infection in plasma from individuals who live in, or have visited, areas of active Zika transmission, according to a June 20 company announcement. "Most people infected with Zika do not develop clinical symptoms and might donate blood, not knowing that they are infected," BARDA stated.

BARDA's contract with Hologic could be extended for up to a total of 18 months and \$6.2m once additional funding has been identified for this activity, the agency said Aug. 9. The additional funding would support a clinical study evaluating the sensitivity and specificity of the *Procleix* test in its actual use, which is needed before it can be approved by FDA for commercial marketing.

HHS Secretary Sylvia Burwell told congressional leaders in a recent letter that as of Aug. 11, "there have been more than 7,300 cases of Zika virus infection, 972 pregnant women with any laboratory evi-



dence of Zika virus infection, and 15 babies born with Zika-related birth defects in the United States." HHS was able to repurpose \$81m last week from its 2016 budget to carry out work on a Zika virus vaccine, but BARDA has estimated it will need \$342m more for diagnostics development, a BARDA official said Aug. 11.

HOUSE MEMBERS ASK CDC ABOUT NATION'S LABORATORY READINESS

Several members of Congress are worried about the US testing capacity to deal with both newly emerging viral infections and the potential for chemical warfare within US borders by terrorists. For example, House Energy and Commerce Committee leaders Aug. 11 sent a letter to the Centers of Disease Control and Prevention asking about the capacity of CDC's Laboratory Response Network (LRN) – a national network of local, state and federal public health laboratories – to provide enough services to both detect toxic agents released by bioterrorist groups and emerging infectious diseases.

Among the LRN's responsibilities are to ensure the nation has appropriate coverage and rapid detection technology and assays to quickly test suspicious materi-

als and detect potential events so they might initiate immediate clinical intervention, surveillance, and other public health measures such as quarantines.

Questions asked of CDC by committee members include:

- Does the CDC LRN have the capability to detect emerging infectious diseases (e.g., Zika, MERS, Ebola, novel Influenza, Chikungunya)? If so, how many CDC LRN labs across the nation have such capabilities at the same time?
- Do all the CDC LRN labs have equivalent capability? If not, please provide the number of labs with their specific capability.
- What are the types of assays (PCR, ELISA, Culture, etc.) developed by CDC LRN and deployed?
- Please explain the roles and responsibilities between the Department of Homeland Security Science and Technology Directorate, and HHS CDC relating to the Public Health Actionable Assay Program.

The committee leaders asked CDC Director Thomas Frieden to respond by Aug. 25. ▶

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FDA Panel Supports Baebies' Seeker Newborn Screen Test

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Despite observing problems with the way cutoff points and false-positive and negative-rates were established in a pivotal study of **Baebies Inc.**'s *Seeker System*, a US FDA advisory panel decided that the medical need for the unique screening system outweighed its weaknesses.

Members of the Clinical Chemistry and Clinical Toxicology Devices panel discussed at length the precision of Baebies' screen in finding an exact cutoff point for determining if infants had lysosomal storage disorders.

But ultimately, "We have no problems with using FDA's analysis for setting the cutoff points," said panel chair Karol Watson, M.D., a cardiology specialist at the David Geffen School of Medicine at the University of California, Los Angeles.

All the panelists agreed with John Davis, chief of the Division of Newborn Medicine at Tufts Medical Center, who said he supported use of the screen, and many were impressed by Baebies' pilot and pivotal studies backing it. "Also, using this screen to get the kids affected by the enzyme disorders into treatment earlier is so important," Davis remarked.

The panelists were asked to discuss how to assess the variety of false-positive rates recommended by the sponsor.

"I think that [rather than setting definitive false-positive rates] we will have to rely on a putative analysis of what the false-positive might be, by the sponsor and FDA," said Brent Blumenstein, a biostatistician and clinical trials expert with Trail Architecture Consulting.

"You don't see the need for extra work or studies by the sponsor, such as active surveillance ... to get at the false-positive rate?" asked Courtney Lias, division director of FDA's device chemistry and toxicology division.

"Actually, if this is approved, I feel a guidance coming on, for screening tests and on how to set the false-positive rates for them," Blumenstein remarked.

But one other panelist, Charleta Guillory of Baylor College of Medicine, said labs that have to interpret results will need more "standardization" if FDA approves the test. She also recommended that physicians "monitor outcomes of patients" who undergo screening as they age to better validate the screen.

NEWBORN SCREEN'S INDICATIONS

The firm's *Seeker System* and *Seeker Reagent Kit* was developed to detect reduced levels of multiple lysosomal enzymes in infants based on dried blood samples. There is currently no screening test that has been cleared in the US to screen babies with lysosomal storage disorders, and Baebies' offering might fill an important medical gap. But in FDA's review of the test, it found higher false-positive rates than the company did for α -L-mucopolysaccharidosis Type I (IDUA) and the α -D-glucosidase (GAA) lysosomal deficiency portions of the screen.

The *Seeker System* is intended to screen for quantitative measurement of activity of multiple lysosomal enzymes from new-

Enzymes and related deficiency disorders

ENZYME	DISORDER
α -L-iduronidase (IDUA)	Mucopolysaccharidosis Type I (MPS I)
α -D-glucosidase (GAA)	Pompe
β -glucocerebrosidase (GBA)	Gaucher
α -D-galactosidase A (GLA)	Fabry

born dried blood samples, as reduced activity of enzymes may indicate a lysosomal storage disorder, the company and FDA explained. Reduced activity for any of the four enzymes (*see table below*) must be confirmed by another confirmatory diagnostic method, the company said.

The panel discussed how Baebies and FDA calculated the false-positive rate for the screen, as well as how best to set the cutoff points for reduced lysosomal activity and for determining which infants should be considered at risk for IDUA and GAA and other lysosomal deficiencies that Baebies' screen can detect.

The panel also had recommendations for the agency on how to protect test samples from excessive heat and humidity, which had been found to affect results. Some suggested the use of frozen medical gel packs to keep samples cool. Other panelists advised limiting the days that test samples are in transit, and making certain that couriers moving the test samples around keep them in a certified cooler.

"Standardized shipping recommendations for enzymes should be followed," panel chair Watson said. ▶

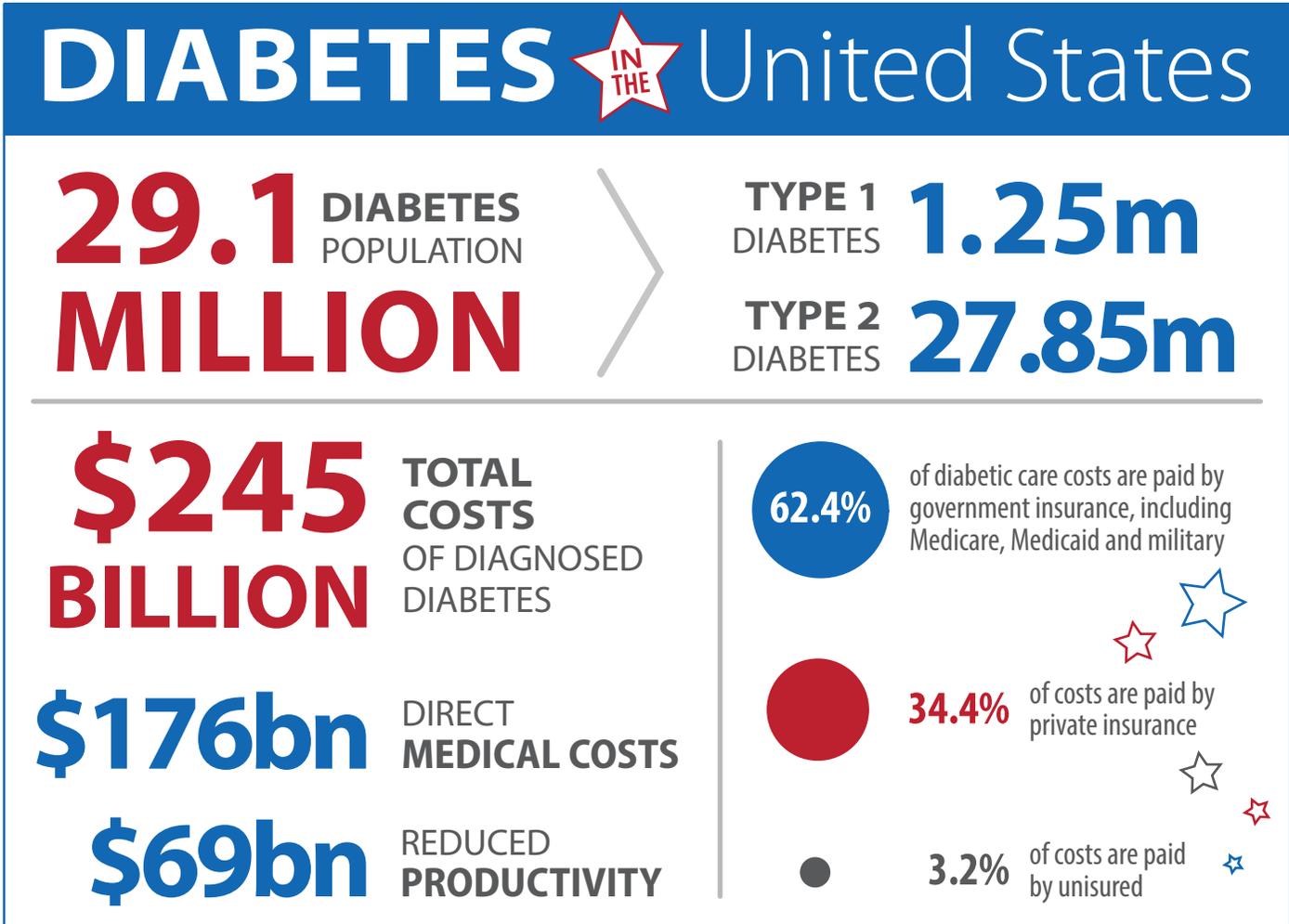
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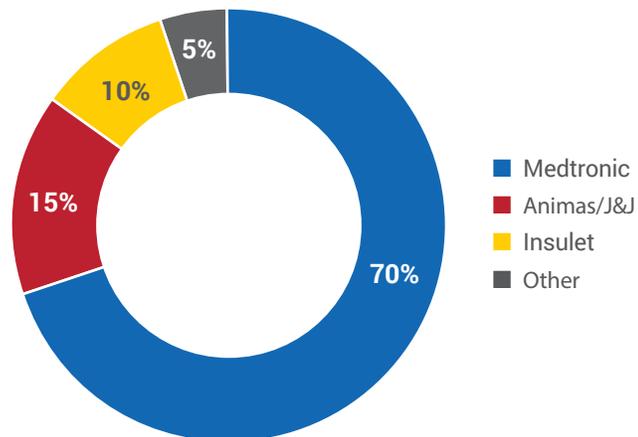
system, and the company's Diabetes business unit – the smallest of the group's four business units – is clearly having a good year in a number of respects. The most recent financial figures show Diabetes generated \$496m in worldwide revenue in its fourth quarter and \$1.86bn for the fiscal year, both ended April 29, 2016. The growth represents a 6% increase over the previous year, and is part of the \$7.57bn in fourth-quarter 2016 and \$28.83bn for fiscal year 2016 in revenue for the entire company. (See Table 1.)

Medtronic's 2016 fiscal year ended April 29, 2016.

On the product development side the company has boldly – and accurately – stated it is at least two to three years ahead of the competition. Officials from the company made that statement recently at 76th Scientific Sessions in New Orleans, put on by

FIGURE 1

US external insulin pump % market share by manufacturer, 2016



Source: Diabetic Investor

TABLE 1

Medtronic worldwide revenue (diabetes vs. group) for fiscal 4Q and year-end 2016/2015

	4Q16	4Q15	REPORTED GROWTH	CONSTANT CURRENCY GROWTH*	FY15	FY16	REPORTED GROWTH	COMPARABLE CONSTANT CURRENCY GROWTH**
Diabetes	\$496m	\$467m	6%	10%	\$1.86bn	\$1.76bn	6%	12%
Group	\$7.57bn	\$7.30bn	4%	6%	\$28.83bn	\$20.26bn	42%	7%

*Constant currency growth measures the change in revenue between current and prior year periods using average exchange rates in effect during the applicable prior year period.

**Medtronic uses comparable, constant currency growth rates as a way to evaluate the underlying performance of Medtronic's sales.

the American Diabetes Association (ADA), where Medtronic presented data from its pivotal trial of the product that is set to usher in the first approved, automated hybrid closed-loop system. That product is the *MiniMed 670G*, integrated with the improved *Enlite 3* CMG sensor, which reads a user's glucose levels and automatically adjusts insulin delivery from the pump according to those readings.

The three-month clinical trial found patients using the system achieved significant improvements in key areas that measure patient health. Specific highlights – important not only in gaining physician adoption, but also for US FDA approval – included a reduction in A1c levels from 7.4% to 6.9% as well as a 44% reduction in the time a patient spent with low blood glucose and a 40% drop in the time spent with dangerous hypoglycemia. Additionally, there was an 11% decline in the time a patient spent with high glucose levels.

The diabetic community has reacted positively to the results, and as planned, Medtronic filed with the FDA for approval of its AP system at the end of June, which means the company is on a path that is expected to lead to a launch as soon as April 2017.

The 670G is an improvement on the company's 640G – available in the UK, but not yet in the US – and is capable of predicting low glucose levels and of suspending insulin delivery within 30 minutes of hypoglycemia. Insulin delivery resumes automatically after glucose levels begin to reach safe levels or through manual intervention. The algorithm for the 670G

is now able to address the prevention of high glucose levels, but the improved algorithm is only one of the things that make the new system more complete.

Physicians and researchers at the ADA meeting noted that the *Enlite 3* sensor is more accurate than previous versions and has a mean absolute relative difference (MARD) of 11%, which compares with 14% from previous versions of the product. Of all the numbers and stats used to evaluate CGM and AP technology, the MARD is proving to be one of the most important, because it measures the accuracy of the product by determining the difference between a CGM reading and actual blood glucose levels.

The lower the MARD, the better, and despite the company's leading position in the market and the advances that have been made, the perceived vulnerable spot in Medtronic's offerings has been a MARD rate that researchers and clinicians have seen as too high. It is believed a MARD of below 10% is ideal for a CGM and an AP device, and as competition moves forward, expect rival companies to continue using the stat as a key indicator to try and demonstrate superiority.

Dexcom's CGMs have been measured at about 9% MARD, and the Dexcom sensor is being used in several AP products in development by rival pump manufacturers. However, like many aspects of a very competitive field, stats are not always viewed the same way, and Medtronic executives say they do not believe a MARD rate below 10% is actually necessary, because the company's algorithm is capable of correct-

ing for discrepancies. That view, of course, is not likely to be shared by everyone, and, as mentioned, the topic will continue to be debated going forward. Meanwhile, Medtronic's pipeline shows a future sensor is expected to be more accurate.

The company's next generation of sensors will usher in a new brand with the *Harmony 1*, currently in development and expected to be ready for market by 2019. The new sensor will have several advantages over the *Enlite 3* starting with a MARD of 10% and an indication for 10 days of use and a single finger stick per day for calibration. That compares with seven days of wear for *Enlite 3* and two calibrations a day. *Harmony 2* would follow in 2020, and although the MARD and days of wear would not change, the product itself would be 30% smaller and have the ability to measure additional biometrics besides glucose levels.

As mentioned, the competitors in the pump market are working with Dexcom to bring additional AP systems to market, and these players include familiar companies such as **Tandem Diabetes Care Inc.**, **Animas** and **Insulet**, as well as younger operations such as **Beta Bionics Inc.** and **Bigfoot Biomedical Inc.** (See Table 2.)

Of all the AP competitors, Tandem may be the closest to market, though the company is still a step or two behind Medtronic. Tandem is currently working to bring to market a predictive, low-glucose suspend product that features an algorithm and a Dexcom 4 sensor, which, similar to Medtronic's 640G, would suspend insulin delivery when glucose levels reach a certain point. A closed-loop system is farther

TABLE 2

Companies with artificial pancreas technology and estimated market launches

COMPANY	PRODUCT	ESTIMATED MARKET LAUNCH
Beta Bionics	iLet device with Dexcom CGM	Late 2018 or early 2019
Bigfoot Biomedical	Bigfoot Biomedical Type 1 Diabetes Management System	End of 2018
Insulet	OmniPod pump with Dexcom CGM	2018/2019
Medtronic	MiniMed 670G with Enlite 3 CGM	2017
Tandem/TypeZero	t:slim pump with Dexcom CGM	2018

Source: Medtech Insight

away, but Tandem recently took a major step forward when it signed a licensing agreement with **TypeZero Technologies LLC**, a software start-up that sprang out of the **University of Virginia (UVA)**. The company was formed to help commercialize some of the groundbreaking diabetes research from UVA, and the firm describes itself as an operation that applies mathematical analysis and modern engineering practices to the problem of diabetes.

The agreement with Tandem will allow the pump company to integrate TypeZero's AP technology, including a series of algorithms, into a next-generation t:slim Insulin Pump. TypeZero's CEO, Chad Rogers, told *Medtech Insight* that the company's technology has already been involved in 28 clinical studies, starting with the initial research performed at UVA. The AP system has been operating under the name *inControl Diabetes Management Platform*, but that likely will change as it is integrated into Tandem's technology.

Rogers says inControl is an AP system that automatically controls insulin delivery with a combination of an insulin pump, a Dexcom CGM device, an algorithm and a smartphone. For now, the TypeZero technology will be part of an app that runs on a phone, but going forward, more and more functionality could be moved directly to the pump with a goal of creating a "light" system that uses as few hard devices as

possible. Rogers says, "We recognize how much stuff needs to be carried around by diabetics, and we want to minimize that as much as possible."

Currently, the technology is involved in a UVA study called Project Nightlight, examining a Closed-Loop Control (CLC) Medical Platform System, designed to help control in a home setting blood sugar in people with T1 diabetes mellitus. Meanwhile, another study, the International Diabetes Closed Loop Trial (iDCL), funded by the **US Department of Health and Human Services' National Institutes of Health (NIH)**, began in July and is testing the safety and efficacy of TypeZero's AP system versus a standard insulin pump and CGM system. The randomized study will ultimately involve 240 patients, with 80 of those in a control group, and is scheduled to run two and one-half years.

The actual time an individual patient will be taking part in the iDCL study is six months, and groups of patients will be staggered over the course of the trial, which means the first sets of data, which could be used for FDA submission approval, should be ready by the beginning of 2017. Rogers says the plan is to file with the FDA by mid-2017, and Tandem, which has more experience with regulatory issues, will likely lead the process. If everything goes well, a product could be launched to market by early 2018.

Rogers says he understands the product will be behind Medtronic's in terms of time on the market, but he also says the AP system his company is creating is much more powerful than a basal rate modulator and has a powerful algorithm that should not be overlooked, as well as a Dexcom CGM sensor, which has proven to be the most accurate sensor on the market. Ultimately, he notes the market, heavily influenced by diabetic patients, will determine which AP systems succeed or fail, but it is clear there will be a number of choices.

Meanwhile, TypeZero is also working with emerging insulin pump maker **Cellnovo Group** to use the inControl AP system with a Cellnovo pump and a Dexcom CGM.

Another one of those choices will come from Insulet, also two to three years away from market with a hybrid closed-loop artificial pancreas system. The company is currently running a feasibility study using an algorithm-enabled prototype of its trademark, tubeless OmniPod pump and a Dexcom sensor. The product also contains an algorithm licensed from Mode ACG (**Automated Glucose Control LLC**) in an agreement announced in February.

The importance of the algorithm sometimes gets lost in the device discussions about pump and CGM technology. However, the algorithm is essentially the brains of the system and is responsible for determining ongoing insulin delivery needs.

The industry has made great progress from the early systems and algorithms that first focused on insulin suspension and now have evolved to the study of advanced control algorithms that not only take into account blood glucose levels, but also account for food intake and exercise. Insulet's deal with Mode ACG gives the pump company access to an algorithm originally created at the **University of California, Santa Barbara**, and Insulet's scientists are continuing to improve the algorithm's functionality. In addition to the feasibility study currently underway, an on-body clinical trial is expected to begin before the end of the year.

Ultimately, Insulet's hybrid system will use a smartphone and an app to display data. Insulet says, more importantly, the system will be the only completely on-

body system, meaning the algorithm will be housed in the OmniPod pump, which attaches directly to a patient, as does the CGM sensor. The algorithms for competitors' systems are also housed in the pump, but those pumps use tubing that goes from the pump, usually worn on a patient's waistband or belt, to the infusion set on the patient's body.

To some, Insulet's distinction of "completely on-body" may just be a matter of marketing; however, the company has developed into an important player in the diabetes space due to the development of its ease-of-use pod pump, which has removed some of the hassle of wearing a tubed pump. The accomplishment is important, because bringing patients into the emerging AP market will likely come with some of the same obstacles that have so far kept pump adoption at notoriously low levels.

For all the advances in insulin pumps over the years, manufacturers have only been able to penetrate about a third of the T1D market, with around 30% of T1 patients actually using a pump. Insulet's executive vice president and president of diabetes products, Shacey Petrovic, told *Medtech Insight* there are about 3.2 million people in the US who need insulin on a daily basis. Of that number, however, she notes the vast majority rely on multiple daily injections (MDIs) as opposed to pump therapy.

Clearly, industry needs to work on bringing new patients into the market, and that is something Insulet has shown it can do. Petrovic says she is not as interested in pump market-share numbers as she is with the fact that 70% to 80% of patients adopting the OmniPod patch pump are coming from the MDI segment rather than existing pump usage, and that bodes well for the company's plans to attract users for its upcoming AP device.

She says every patient who is eligible for therapy with the OmniPod is going to be interested in the AP product, but she also knows a lot of work needs to be done by industry to make sure patients have access to that technology, and that payors and insurers cover the system for all of those patients.

Beyond the regulatory issues and even beyond the tremendous technological advances – regarding AP systems, a key factor

in the success of these devices achieving a better adoption rate than pumps rests largely with their ease of use. Petrovic says the user experience has to be exceptional, and in this digital age, users expect devices to be intuitive and easy to set up and maintain. Insulet believes it is positioned well to bring those qualities to AP systems.

The company's rise in the market has been tied to its OmniPod patch pump, introduced in 2005, which offered an alternative to traditional-tubed insulin pumps,

A key factor in the success of these artificial pancreas systems achieving a better adoption rate than pumps rests largely with their ease of use.

which many potential users – rightly or wrongly – view as bulky devices that restrict users, and, as some diabetic bloggers have stated, the pumps made them feel like they were "wired to their disease."

In some ways it was a psychological barrier, but with the low adoption rate of pumps, this issue needs to be taken seriously with AP systems, and Insulet is confident it can duplicate the success it has had with OmniPod.

Meanwhile, a younger company on a similar time line as Insulet is Beta Bionics, developing the *iLet Bionic Pancreas*, scheduled to begin a pivotal study in 2017 with the hope of launching in late 2018. The device, which uses a Dexcom sensor, has gone through several incarnations since its original design by Ed Damiano, PhD, an associate professor of biomedical engineering at **Boston University** (BU). Damiano, who is Beta Bionics' president and CEO, developed the system at BU with the idea of having a dual chamber pump for insulin and glucagon, something most other companies have not pursued heavily.

As it turned out, the dual chamber aspect of the system worked well; however, an adequate form of glucagon has not been found yet, and the pharmaceutical industry is working to develop an acceptable product. In the meantime, Beta Bionics is moving forward on a system

that will deliver only insulin, but the pivotal trial will involve an insulin automated system as well as a dual insulin and glucagon system. The idea is to receive FDA approval for a device that would have the two chambers, but only the insulin chamber would be operational. Later, when the appropriate glucagon is available, the company would file for the additional functionality.

Beta Bionics has also been making news for its business setup as a public benefit

corporation, a relatively new design in the business world that allows companies to raise money from investors without the same pressure to produce profits the way traditional for-profit companies do. The process has been made possible by the JOBS Act of 2012, which allows private companies to sell shares directly to the public through crowdfunding rather than exclusively through professional investors.

In July, Beta Bionics became the first start-up to raise \$1m using this method, and interest in the company is believed to have been aided in part by a \$5m investment by **Eli Lilly & Co.** earlier in the year. The investment came with a seat on Beta Bionics' board for Lilly's global brand development leader, Deirdre Ibsen.

Another start-up that could have a product on the market in a few years is Bigfoot Biomedical, which began an interventional study for its AP system this summer and hopes to file with the FDA by the end of the year with a goal of launching to market by early 2018. Like the other non-Medtronic systems mentioned, Bigfoot's uses a Dexcom sensor.

The other player in the market that gets attention is Animas; however, that attention is related more to the company connection with its parent, Johnson & Johnson, rather than being farther along with an AP product than its competitors. For now, Animas' current *Vibe* pump uses a Dexcom

CGM sensor, and the plan is to bring an improved version of that pump to market, possibly by the end of 2017. The new product would use an upgraded algorithm that could predict high and low glucose events and increase or decrease insulin delivery automatically to reduce the chances of hypoglycemia and hyperglycemia.

Fittingly, the company calls the new algorithm HHM, for Hypoglycemia-Hyperglycemia Minimizer, and a pivotal trial is taking place this year with a plan

to launch in 2017; however, an AP system is farther away. Still, Animas is part of the mix that will make the next three years historical for diabetes treatment as the number of AP systems available on the market grows. Medtronic is likely to remain a few steps ahead of the competition and will be working to improve its offerings while rivals focus on getting their products to market, but, just as it is in the pump market, there seems to be room for multiple players in the AP field.

The next step may be to take the AP technology and find the best ways to use it for the T2D population, something investors would like to see happen as T2D represents the largest number of patients afflicted with diabetes. Most all the companies working on AP systems believe closed-loop technology can eventually be utilized in treating T2 diabetics, whose number continues to increase. ▶

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US FDA Gives More Time For Public Response To NGS Microbial Identification Guidance

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Stakeholders will have more time to mull FDA's May draft guidance on next-generation sequencing (NGS) tests to detect microbes, antimicrobial resistance and virulence markers. The agency originally set Aug. 11 as the end of the public comment period, but in response to requests for more time, formal feedback will now be accepted by FDA through Sept. 12.

The guidance attempts to explain how infectious-disease NGS test developers can meet analytical and performance thresholds to pass regulatory muster. The agency emphasizes that in contrast to human-sequencing diagnostics, the tests discussed in the draft guidance require very rapid results that could be critical to not just the patient but to public health in general.

"This draft guidance provides detailed information on the types of data FDA recommends be submitted in support of a class II pre-market submission," the agency said in the draft. "This document does not apply to devices that are intended to screen donors of blood and blood components, or donors of human cells, tissues, and cellular and tissue-based products (HCT/Ps) for communicable diseases."

However, the agency also states that certain diagnostic indications such as hepatitis B, hepatitis C and HIV could upgrade the test to a class III device. In such situations, FDA says sponsors should contact the agency for further guidance. It also says that, in general, sponsors should discuss clinical and validation studies with FDA prior to starting them to learn about additional recommendations, because it is a "fast-moving field."

While the draft guidance is still open for comment, there have been at least 10 comments submitted by stakeholders. Only two have so far been publicly posted by the agency. In one set of comments, Charles Chiu and Steve Miller, associate professors of laboratory medicine at the University of California-San Francisco, raised concerns about the scope of the guidance.

"The scope of this draft guidance includes infectious disease NGS Dx devices that employ targeted or agnostic (metagenomic)

sequencing approaches," they write. "However, the fundamental differences between these two approaches – which are significant – are not well defined."

They argue that many of the recommendations in the draft, including panel-based approach, and recommended number of positive specimens per claimed organism or marker aren't practical when trying to sequence metagenomics. Instead, the academics recommend the agency create separate sections for each approach and provide more guidance depending on the number of organisms that a test targets.

Besides touching on the two very broad topics of how sponsors should describe NGS tests in pre-market submissions and provide information to validate their product, the agency also outlines a pathway that sponsors can use to modify their device with new microbial targets. The pathway could be used for public-health purposes or in an emergency situation, the agency notes.

"Since many studies have been conducted to establish the performance of the previously cleared or approved device, and we presume that the assay's performance has not changed, only a subset of the evaluations may need to be repeated for the new submission," said FDA. "In your submission, you should also provide a detailed procedure for adding new species to your device. These procedures include: acceptance criteria, risk analysis and validation testing."

FDA has been prolific recently in drafting guidances affecting NGS technology. In July, the agency issued two draft guidance documents: one on the topic of using standards to support regulatory approval of germline NGS tests, and the second on leveraging databases to support regulatory approval. The drafts have so far been positively received by industry and the agency says there are more to come.

Stakeholders can comment on the NGS guidance on regulations.gov under docket No. FDA-2016-D-0971 until Sept. 12. ▶

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