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BD, CR Bard Merger To Create Vascular Access Device Giant

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Becton Dickinson & Co. expects to jump-start its earnings growth by acquiring **CR Bard Inc.** for $24bn, the companies announced late on April 23.

Both company's boards have agreed to a definitive agreement for Bard to pay $222.93 in cash and 0.5077 shares of BD stock per Bard common share in cash and stock for a total value of $317 per Bard common share, about a 25% premium over Bard's closing price on the last trading day before the deal. The companies expect the deal to close in the fall of 2017, subject to regulatory approval.

It is one of the largest acquisitions in medtech history and third medtech acquisition worth over $20bn in the last three years, following Abbott's $25bn acquisition of St. Jude Medical in 2016 and Medtronic's $43bn blockbuster acquisition for Covidien in 2015. *(Also see "The Rumors Were True: Abbott Buys St. Jude For $25b To Create Third Cardiovascular Giant" - Medtech Insight, 28 Apr, 2016.)*

Currently, BD is number nine and Bard is number 24 on *Medtech Insight's table of biggest medtech companies by revenue*. The new company's annual revenues will reach around $16bn, potentially beating out Siemens Healthineers for the number four spot on the list, just behind GE Healthcare.

"This acquisition significantly accelerates and broadens our strategy," Becton Dickinson CEO Vincent Forlenza said during an April 24 conference call. "The combination of BD and Bard expands our breadth and depth in medication management and infection prevention, with product portfolios that are highly complementary. This transaction also enters BD into new, higher-growth, therapy-oriented device segments. And from a geographic perspective, we have additional opportunities to leverage our leading international footprint and capabilities to grow both BD and Bard faster around the world."

Bard CEO Tim Ring said his company is enthusiastic about the deal. "Over the past several years, we focused Bard's strategy and specific clinical improvements and therapy innovations in faster-growing segments. [But] as payment structures and demographics continue to change, there's an increased need to deliver better outcomes for our customers and their patients," he said. "At the same time, BD was building capabilities to improve efficiency and quality to meet some of the healthcare's foundational processes. This combination will accelerate the strategy of both of our companies to improve both the process of care and treatment of disease."

Under the terms of the acquisition agreement, Bard common shareholders will get $222.93 in cash and 0.5077 shares

CONTINUED ON PAGE 17

FROM THE EDITORS OF: **THE GRAY SHEET, CLINICA, START-UP** AND **MEDTECH INSIGHT NEWSLETTER**

POLICY & REGULATION
New EU regulation power-players, p. 7

COMMERCIAL
DePuy Synthes bones up on 3D-print tech, p.18

R&D
Wound-care firm under Start-Up Spotlight, p.21

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10


18


21

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inside:

Cover / BD, CR Bard Merger To Create Vascular Access Device Giant – BD, which plans to acquire CR Bard for $24bn, says Bard's product portfolio gives it a strong presence in fast-growing clinical areas and more reach outside the US, while Bard expects to reach more customers.

EDITORS' PICKS

5 **Despite Legal Dispute, Abbott Set To Buy Alere for $5.3bn –** Soon before it was set to take Alere to court in an attempt to break out of an acquisition deal, Abbott has reversed course and plans to buy the company for half a billion less than the original price tag.

6 **Cardinal Health, Medtronic Tie Up $6.1bn Lower-Margin Assets Deal –** Medtronic is selling certain lower-margin, lower-growth assets within its Patient Monitoring and Recovery division to Cardinal Health in a $6.1bn deal. While the deal may benefit Medtronic's debt situation, the same cannot be said for the buyer.

7 **New Bodies To Emerge Under Revised EU Governance Structure –** What is the governance structure under the forthcoming new EU Medical Device and IVD Regulations? Here, *Medtech Insight* attempts to answer that question and explain how the different organizations and groups relate.

POLICY & REGULATION

10 **New EU Regs Will Offer No Reprieve From Borderline Classification Chaos –** Challenges will persist for borderline and combination products under the new EU regulatory structure.

11 **MedTech Europe's John Brennan Moves On At Critical Time For Industry –** After nearly nine years, MedTech Europe's John Brennan is leaving the medical device and diagnostics trade association.

11 **What's In the Official Journal Of The EU? Fake News? –** A text has appeared in the Official Journal of the EU that is raising some questions.

12 **Japan's New "Fast-Break Scheme" To Reduce Clinical Trial Burden For Medtech –** Japan's "fast-break scheme" is coming soon and will be the country's fourth procedure for accelerating the approval of important medical devices.

Medtech insight

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12 Combo Product Rules Coming To Malaysia – New guidance explains how Malaysia's impending rules for registering combination products will work and how much sponsors will have to pay to have their applications assessed.

13 Feds Holding Workshop on Device Cybersecurity Gaps – Following several cases highlighting medical device cybersecurity vulnerabilities, US FDA is joining with Homeland Security and the National Science Foundation to hold a two-day workshop to discuss potential gaps and how to fix them.

14 US FDA Device Center Pushes "Total Product Life Cycle" Concept; Reorganization Coming – CDRH is shaking up how its pre- and post-market specialists interact under a new "Total Product Life Cycle" scheme.

15 Snapshot: Device Recalls Tick Up 1% In 2016 – A count of fiscal year 2016 recalls provided by the agency shows that there were 43 high-risk class I (4%), 1,090 class II (92%) and 50 class III (4%) recalls last year, up a mere percentage point from the prior year, even after a mid-calendar-year spike.

COMMERCIAL

18 DePuy Synthes Builds Out Trauma Offering – Underlining its focus on 3D-printing, DePuy Synthes has acquired the 3D-printed scaffold platform of Tissue Regeneration Systems, enabling the orthopedics leader to develop patient-specific trauma products in-house.

19 Nanjing BioPoint Shoots For 2018 Launch; Seeks $10m – A China-based IVD company, spun out of an Australian research institute, is seeking investors to support its plans for the 2018 launch its first two point-of-care tests for patients with infectious diseases including HIV and viral hepatitis.

R&D

20 STAT-DX Aims To Take On Syndromic Testing – The Barcelona start-up is gearing up to launch a multiplex PCR system in the growing field of syndromic testing.

21 Cellnovo Targets 2018 Launch Of Insulin Micropump With Artificial Pancreas Tech – Cellnovo has signed a commercial license agreement with digital-health firm TypeZero to integrate its artificial pancreas software technology into Cellnovo's digitally connected insulin patch pump.

START-UP SPOTLIGHT

22 Amniox Medical, Bringing The Benefits Of Amniotic Tissue To Ortho And Wound Care – Amniox Medical is developing biologics for wound-healing and orthopedic applicationsthat take advantage of the unique anti-inflammatory and anti-scarring properties of human amniotic membrane and umbilical cord matrix.

Despite Legal Dispute, Abbott Set To Buy Alere for $5.3bn

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After months of trying to get out of buying the diagnostics company **Alere Inc.**, **Abbott Laboratories Inc.** has decided to kiss and make up with the Massachusetts-based point-of-care diagnostics manufacturer. Abbott and Alere announced April 14 that they have agreed to an amendment to the original deal, and now expect it to close by the end of September.

Under the terms of an amended agreement, Abbott will pay $51 in cash per share for Alere, instead of $58 per share agreed-to in the original acquisition deal signed in January 2016, which reduces the total acquisition price from about $5.8bn to 5.3bn. *(Also see "Look Over Your Shoulder, Roche: Abbott's Coming Up Behind" - Medtech Insight, 1 Feb, 2016.)* The amendment extends the date after which either Alere or Abbott would have a right to terminate the merger agreement to September 30, 2017, rather than April 30 as previously agreed-to and the amendment reduces the termination fee that Alere would pay Abbott under specified circumstances from $177m to $161m.

"Any new and significant major adverse effects could still throw a spanner in the works, but it seems very likely the deal will close," Jefferies analyst Raj Denhoy writes in an April 17 note. "While Alere could have held out and taken the issue to court, it removes most of the uncertainty in the deal and for Abbott, the revised $51 price is now just $1 higher than the next bidder disclosed in the original proxy which provides some face saving and allows Abbott to move forward with a deal that has made strategic and financial sense from the outset."

Problems with the original merger agreement appeared just a few weeks after it was signed, when Alere delayed filing its 2015 sales and earnings with the US Securities and Exchange Commission and Alere revealed that the US government had opened criminal investigations into Alere's overseas business practices and its billing practices over the previous six years. In April, Abbott offered $50m to cancel the deal, which Alere rejected. In August, Alere sued Abbott in Delaware Chancery Court, saying that Abbott was trying to breach the merger agreement by delaying anti-trust and other regulatory filings necessary to complete the merger. In December, Abbott filed suit in the same court to terminate the deal, arguing that the criminal Alere was "no longer the company Abbott agreed to buy 10 months ago." *(Also see "Abbott Steps Up Effort To Abandon Alere Deal" - Medtech Insight, 7 Dec, 2016.)*

Completion of the amended agreement still requires the assent of a majority of both company's shareholders, the absence of any judgment or law enjoining or otherwise prohibiting the deal, and the approval of anti-trust regulatory authorities.

The amendment also states that the deal cannot go through if there is any "Material Adverse Effect" - as defined in the Amended Merger Agreement and that "The obligation of each of [Alere] and Abbott to consummate the Merger is also conditioned on the other party's representations and warranties being true and correct (subject to certain materiality exceptions) and the other party having performed in all material respects its obligations under the Amended Merger Agreement," Alere explains in a filing with the SEC.

The companies have also agreed that any "matter set forth" in public filings between January 1, 2014 and April 13, 2017 or "any matter of which Abbott or any of Abbott's representatives was made aware prior to April 13, 2017" can be considered a Material Adverse Effect Further for the purposes of the agreement.

Concurrent with the amendment to the merger agreement, Alere and Abbott have signed a separate settlement agreement which releases the legal claims arising out of or related to the merger, and resolves the parties' pending litigation in Delaware Chancery Court.

Denhoy points out that Alere still must bring its SEC filings up to date, specifically its 10-k annual reports. "Alere remains delinquent on its FY16 10-K due to the company uncovering revenue recognition timing errors dating back to 2013 in certain Asian countries," he explains. "We expect an update soon and think the company is likely to make changes to prior years in the 2016 10-K as opposed to refilling previous reports. Risks of a material change of prior financials seems remote given the various issues are essentially a wash across the periods under review. Filing of the FY16 10-K must occur prior to the issuance of the proxy and a shareholder vote on the amended merger agreement." This process, and the approval from government regulators, must be complete by Sept. 30 for the amended merger agreement to be consummated.

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Cardinal Health, Medtronic Tie Up $6.1bn Lower-Margin Assets Deal

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Medtronic has agreed to sell its patient care, deep vein thrombosis, and nutritional insufficiency business lines – deemed to be lower-growth, lower-margin assets – to Cardinal Health in an all-cash deal worth $6.1bn.

The significant liquidity which Medtronic will benefit from this deal will immediately boost Medtronic's top line and help bulk up its operating margins. The bottom line will be diluted modestly, with non-GAAP earnings in fiscal 2018 expected to shrink in the range of $0.12-$0.18 per share. Post-tax, the proceeds from the sale will be around $5.5bn, of which $1bn will go towards incremental share repurchases in its current fiscal year, and the balance used to reduce its debt. "This deployment of proceeds is consistent with Medtronic's near-term capital allocation strategy, improves the company's debt leverage ratio, and enables future investments in higher growth and higher margin opportunities," Medtronic stated.

The three businesses to be divested had been inherited from Covidien when Medtronic acquired the company in January 2015; they sit within the Patient Monitoring & Recovery (PMR) division of Medtronic's Minimally Invasive Therapies Group (MITG). Combined, the businesses generated approximately $2.4bn in revenue over the last four reported quarters but sales have declined at low single-digit rates.

Cardinal Health will gain a hefty inventory from this transaction, including offerings in dental/animal health, wound care, incontinence, electrodes, SharpSafety, thermometry, perinatal protection, blood collection, compression, and enteral feeding. The deal also includes 17 dedicated manufacturing facilities. Following the divestment, Medtronic's PMR division will encompass its Respiratory & Monitoring Solutions business, which includes its airway, ventilators, monitors, sensors, and health informatics product lines, as well as its Renal Care Solutions business.

While Medtronic had made it clear that the sale will benefit its debt situation, the same cannot be said for Cardinal Health, which will be funding the acquisition through a mix of new debt and existing cash. The news of the news sent shares in the Ohio-based medical supplies group tumbling down, with its stock price dropping 12% to close at $72.39 on April 18. However, the addition of these Medtronic assets might help boost Cardinal Health's longer term growth prospects. The latter is a recognized shopper of products of well-known brands but have become commoditized. In March 2015, it agreed to buy Johnson & Johnson's Cordis heart stent business; Cardinal Health's strategy is to extract growth potential from these well-established brands through efficient supply and distribution methods rather than through technology innovation. *(Also see " INTERVIEW: The bigger value picture behind Cardinal Health's Cordis buy" - Medtech Insight, 10 Apr, 2015.)*.

The $6.1bn transaction is expected to close in Medtronic's second quarter of fiscal 2018.

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New Bodies To Emerge Under Revised EU Governance Structure

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The new EU Medical Device and IVD Regulations, finally adopted on April 5, are going to require a whole host of new organizations responsible for governance and oversight of medical devices that had not previously existed under the medical device directives.

There is going to be a shake-up of responsibilities compared to how the system operates now. All stakeholders, without exception, are going to need to grasp as early as possible which organizations hold what responsibilities. They need to understand this as the new regulations are now being implemented and will likely take effect by early June.

The higher-risk the device, the heavier the involvement of the new organizations.

WHAT IS CHANGING AND WHAT IS STAYING THE SAME?

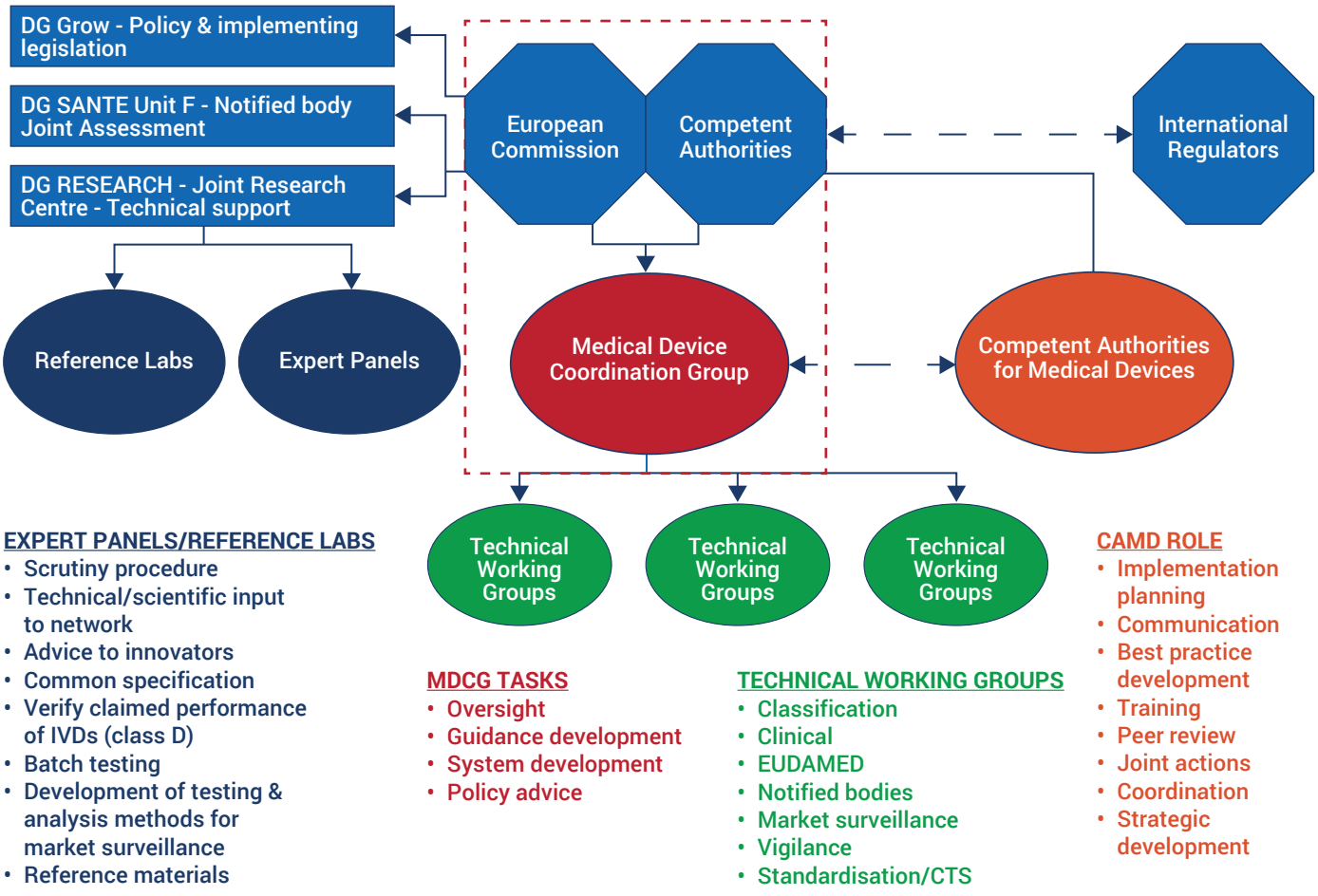
As a start, the European Commission and the competent authorities will remain the key organizations responsible for overseeing and implementing the new regulations. This is effectively the same as under the current directives.

The notified bodies – who do not feature in the governance chart below (see Figure 1) - will remain the third-party certification authorities that audit all products, with the exception of those deemed to be the lowest risk.

But there will be much more oversight of the notified bodies and their work, through the joint audits by designating

FIGURE 1

New EU Governance Structure



Source: This diagram was presented by the European Commission at its March 9 2017 meeting for stakeholders on the implementation of the MDR and IVDR. It is based on an original diagram put together by the Irish agency responsible for devices, the HPRA. It shows the inter-relation between the various bodies and their areas of responsibility.

bodies that have already been introduced through interim legislation and through the need for notified bodies to become certified again by designating authorities under the new regulations.

In the case of higher risk devices, there will also be the introduction of additional layers of scrutiny of notified body work by some of the new organizations being set up under the Medical Device Regulation – namely the Medical Devices Coordination Group (MDCG), expert panels and the references laboratories.

MDCG

The most pivotal new organization is the MDCG, which is to be set up within six months of the new regulations taking effect – ie by the end of the year and likely by the end of September. This is a task the Commission needs to accomplish quickly.

The group will comprise representatives of the Commission and the competent authorities. It will have a series of responsibilities which are focused on the successful implementation of the new rules.

Its other key responsibilities will include a role in the scrutiny of high-risk products.

In the case of medical devices and IVDs, it will have the opportunity to scrutinize the assessment by notified bodies of their review of certain high-risk devices. It will carry out this role along with the European Commission and with help from the expert panels.

The MDCG, made up of authorities only, will also effectively replace the current Medical Devices Experts Group (MDEG) which is made up of all stakeholders, including industry. This is a source of contention for industry but a matter on which the decision-makers would not back down.

The Commission has also made it clear, however, that there will be subgroups working within the MDCG which may also comprise industry and other stakeholders.

The MDCG will also make recommendations, based on the evidence with which it is presented, on which notified bodies should be designated.

EXISTING AND NEW WORKING GROUPS

The current working groups, which are made up of various stakeholders and are set up to focus on areas including clinical investigations, market surveillance, UDI etc, will – for the most part - continue to operate. But instead of working within the framework of the MDEG, they will work within the framework of the MDCG and also be important partners in delivering the aims and objectives of the Competent Authorities for Medical Devices Group (CAMD).

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The intention is that this consultation of the expert panels by notified bodies should then lead to a harmonized evaluation of high-risk medical devices by sharing expertise on clinical aspects which will then lead to the drafting of Common Specifications (detailed technical specifications) on categories of devices that have undergone the consultation process.

CAMD

CAMD will play a key role, amongst other things, in creating support around the implementation of the Regulations and enhancing the level of collaborative work among the competent authorities.

This organization already exists and is currently firming up its structure *[**Editor's note:** Medtech Insight is planning an update soon with chair of the executive committee, John Wilkinson (head of devices at UK's MHRA)].*

It is also creating joint actions in the area of market surveillance so that all authorities work together more closely and proactively to monitor their markets in future.

EXPERT PANELS AND REFERENCE LABORATORIES

The expert panels and the reference laboratories are two entirely new groups that will play a vital role when it comes to the highest-risk medical devices and IVDs – those that need additional review, or scrutiny. Expert panels and reference laboratories both play a role under the IVDR, and expert panels and expert laboratories under the MDR.

EXPERT PANELS UNDER THE MDR

The expert panels, as well as expert laboratories, will be created on a standing or temporary basis by the European Commission to provide scientific advice and clinical support to the Commission, MDCG, industry and notified bodies. The panels will also be clinically focused and made up of practicing clinicians with real world usability perspective. The Commission may require manufacturers and notified bodies to pay fees for their advice.

They can be appointed on a standing or ad hoc basis.

The Commission, following consultation with the MDCG, can appoint advisors to expert panels following publication in the Official Journal of the European Union and on the Commission website of a call for expressions of interest. Depending on the type of task and the need for specific expertise, advisors may be appointed to the expert panels for a maximum period of three years and their appointment may be renewed. The Commission may also, after consulting the MDCG, include advisors on a central list of available experts who are available to provide advice and support the work of the expert panel as needed.

The requirements concerning reference laboratories will only apply from six months prior to the full application of the IVD Regulation, according to the current IVDR text. Because a five-year transition period is anticipated for the IVD requirements, the reference laboratory provisions will not apply until, likely, the end of 2021.

But if reference laboratories are not appointed until that time, it will likely lead to a bottleneck as manufacturers all apply at the same time to use the services of the laboratories.

This is a growing concern that industry is seeking to have addressed.

The Commission only has to designate the EU reference laboratories for which a Member State or the Commission's Joint Research Centre have submitted an application for designation.

Under the new MDR, manufacturers of Class III devices may consult an expert panel concerning their clinical development strategy and proposal for clinical investigations (in which case they must document the panel's views).

Notified bodies will generally be obliged to request one of the relevant expert panels to scrutinize and provide an opinion on their clinical evaluation assessment report for Class III implantables and Class IIb active devices intended to administer and/or remove a medicinal product.

Where the expert panel being consulted by the notified body finds the level of clinical evidence is not sufficient or raises concerns, the notified body will have to take action.

It will need to advise the manufacturer to:

- restrict the intended purpose of the device to certain groups of patients, or certain medical indications; and/or
- impose a limit on the duration of validity of the certificate;
- undertake specific post-market clinical follow-up (PMCF) studies;
- adapt the instructions for use or the summary of safety and performance; or
- impose other restrictions in its conformity assessment report, as appropriate.

The MDCG and the Commission, in their turn may, based on reasonable concerns, request scientific advice from the expert panels in relation to the safety and performance of any Class III implantables or IIb active devices intended to administer and/or remove a medicinal product.

THE IVDR

Under the IVDR, notified bodies should consult an expert panel to scrutinize their performance evaluation reports of Class D devices for which no common specifications (CSs) exist. This will be the case where this is the first certification for that specific type of device and there is no similar device on the market having the same intended purpose and based on similar technology. As with medical devices, this consultation should be made with the aim of developing CSs on categories of IVDs that have undergone the consultation process.

Again, as with the MDR, the MDCG and the Commission may also, where there are reasoned concerns, request scientific advice from the expert panels.

There is no mention in the IVDR of expert laboratories as there is in the MDR, but there is a specific role for reference laboratories.

REFERENCE LABORATORIES

The reference laboratories only feature in the context of the IVD Regulation; they are to give an opinion on Class D IVDs (those intended to detect a transmissible agent in blood or cells to assess suitability for transfusion (and in some cases Class C, such as cancer diagnostics).

The notified body must request an EU reference laboratory to verify by laboratory testing the performance claimed by the manufacturer and the compliance of the device with the applicable CS, or with other solutions chosen by the manufacturer. Laboratory tests performed by an EU reference laboratory must, in particular, focus on analytical and diagnostic sensitivity using the best available reference materials.

Again, where notified bodies or member states request scientific or technical assistance or a scientific opinion from an EU reference laboratory, they may be required to pay fees.

For more about the reference laboratories, see Medtech Insight's piece from January this year.

BOTTLENECKS?

The Commission made it clear on Mar. 9 that the setting up on the governance structure is among its priorities. This will be critical in terms of the industry's ability to prepare for compliance.

Any delays will be not only frustrating but factors contributing to the bottlenecks that are anticipated as the whole industry – both the medical device and IVD sectors - squeezes themselves through the new system at roughly the same time in a relatively short time-frame.

The smooth creation of these structures will be vital to avoid chaos for the sector and for the uninterrupted supply of medical devices to patients.

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New EU Regs Will Offer No Reprieve From Borderline Classification Chaos

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Despite the clarifications surrounding the definition of a medical device under the forthcoming EU Medical Device Regulation and the elaborated procedure on borderline decisions that is to come, complex qualification questions are likely to persist when these new rules come into effect.

That is the view of Charlotte Ryckman and Dr Anna Wawrzyniak at the law firm Covington and Burling, presented in an April 7 blog following the adoption that day of the EU's Medical Device and IVD Regulations.

In the lawyers' view, there is not enough clarity in the new medtech regulations around the definitions of the physical or chemical mode of action of a borderline or combination product to help determine whether it is a device (physical action) or medicine (chemical mode of action).

The definitions are not spelt out in the Medical Device Regulation but rather in EU Commission guidance, the authors state. But whilst the new rules cover definitions of pharmacological, immunological and metabolic modes of action associated with medicines, they still leave many questions unanswered and do not always allow a clear-cut borderline determination.

They point out that the MDR seems to take account of this reality as it underscores the need to consult with the relevant EU agencies when deciding about the qualification of a product; but there are further challenges here as different organizations may apply different definitions of pharmacological, immunological and metabolic modes of action, as did the European Medicines Agency's scientific committee, CHMP, in the recent case of cranberry extract capsules for urinary tract infections. *(Also see " Fruitful Use Of EU Reg Loopholes Or Farce? How The Cranberry Is Dividing Opinions" - Medtech Insight, 23 Feb, 2016.)*.

This means that predicting definitive decisions over borderline products will remain tricky for all concerned.

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Borderline issues are of particular concern for members of AEGSP, the association of the European Self-Medication Industry.

In its statement on the adoption of the new Regulations, it calls for "greater transparency and stakeholder engagement at an early stage in the procedure foreseen for deciding on the regulatory status of products in borderline cases".

HOW MUCH WILL BORDERLINE DECISIONS BE TAKEN AT EU LEVEL?

The lawyers also question how effectively the new Regulations will ensure that borderline decision-making is made at EU level rather than the local member state level, as at present.

Under the current medical device directives, Ryckman and Wawrzyniak state that the Commission is entitled to decide whether a product falls within the definition of a medical devices, but only on "a duly substantiated request from a member state".

This structure means different products can be classified under different regimes (eg device/medicines/cosmetics) in different countries at the same time. This results in companies being forced to employ more resources to fulfil the regulatory requirements around Europe, as has been the case with tooth whiteners, organ-preservation fluids and *Gynocapslactobacilli*-containing vaginal capsules, *Medtech Insight* notes.

The Commission has used its borderline product decision-making entitlement only once – as in the previously mentioned case of the cranberry capsules. In that situation, the Commission had issued a draft implementing decision to the effect that these are not medical devices. But it has not yet issued a final decision.

NEW POWERS FOR COMMISSION

The new MDR, however, gives the Commission the power to decide about product qualification, not only at member state request, but also at its own initiative.

There is some optimism that this new ruling, in addition to the cranberry judgment, will be the catalyst for more developments of this kind to come.

But the authors say that it is hard to predict the extent to which the new regulatory regime will affect national decision-making.

To support a positive outcome, Ryckman and Wawrzyniak say it is important that the Commission consults the Medical Device Coordination Group (MDCG) and/or the relevant agencies (ie the European Medicines Agency, the European Chemical Agency and the European Food Safety Authority) to ensure an appropriate level of scientific expertise.

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MedTech Europe's John Brennan Moves On At Critical Time For Industry

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John Brennan is leaving his role as director of regulations and industry policy at the medical device and diagnostic industry trade association, MedTech Europe, to assume a new position as secretary general of the European Association for Bioindustries, EuropaBio, effective June 19. EuropaBio represents the EU agricultural, industrial, and health biotech sectors.

Brennan has been with MedTech Europe throughout the drafting of the new Medical Device and IVD Regulations, which have just been adopted and which will take effect by early June.

He has been instrumental in presenting the medtech industry's view on the new regulations to EU decision-makers throughout the eight years or so of discussion on this subject, and in that way has helped to shape the new regulatory framework. More recently, Brennan has been actively working on the steps that are to be taken to implement the regulations, as part of an action plan that is now being put together by the European Commission.

His departure will be a significant loss to MedTech Europe as its members prepare now to comply with the regulations, especially because so many of the necessary structures around the new rules are not yet in place and further support and guidance will be needed.

Brennan has already been overseeing working groups at MedTech Europe that are producing best-practice guides and the recent extension of his brief to cover IVDs as well as medical devices has brought the particularly challenging issues surrounding the implementation of the IVD Regulation into sharp focus. *(Also see "IVDs Should Get Equal Focus To Devices In EU Reg Implementation, Industry Says" - Medtech Insight, 15 Mar, 2017.)*

FUTURE SYNERGIES

There are many synergies between MedTech Europe and EuropaBio. EuropaBio lists advanced-therapy medicinal products and personalized medicine among its health-care biotech priorities.

Indeed, EuropaBio has been actively monitoring the drafting of the new EU medical device and IVD regulations, particularly from the point of view of its health-care biotech members who produce tissue-engineered products, as well as companies involved in companion diagnostics.

It will be interesting to see how the future relationship between Medtech Europe and EuropaBio evolves. Brennan's expertise in the medtech and IVD sector will be a great bonus for those EuropaBio members with products that overlap in this area.


John Brennan

STINT AT EUROPEAN COMMISSION'S DEVICES UNIT

Brennan has more than 25 years' experience with medtech regulators in addition to representing industry in the medtech sector. He worked for the European Commission unit responsible for cosmetics and medical device legislation in the four years running up to August 2008. That was the period when the revision of the current EU medical device directives was being drafted and adopted.

Prior to his role at the Commission, and after about six years working with various companies in the medtech sector, Brennan worked for nine years at the Irish National Standards Authority (NSAI), overseeing the authority's notified body activities, including efforts involved in the approval of high-risk medical devices.

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What's In the Official Journal Of The EU? Fake News?

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As the texts of the new EU Medical Device Regulation and IVD Regulations are expected in the next few weeks, all eyes are on the European Union's Official Journal (OJ) of the EU. And there has been some speculation over the nature and impact of a recent publication in the OJ regarding *in vitro* diagnostics.

The regulations must take effect on the 20th day after publication in the journal. On April 21, the position of the Council of the European Union on EU's IVD Regulation, as agreed to on March 7, was published in the Official Journal, but that is *not* the official final text that is awaited. The IVD and Medical Device Regulations were adopted without amendment on April 5 during the European Parliament's plenary. *(Also see "EU Finally Adopts New Regulations Despite Sabotage Attempt" - Medtech Insight, 5 Apr, 2017.)*

While the April 21-published version likely to be essentially the same as the final text, industry is advised to wait to ensure they are using the official publication of the finally adopted text. So the sector will still need to monitor the OJ daily.

Interestingly, the PDF of the version of the IVD Regulation published in the journal last week is densely packed into 154 pages, whereas the versions previously circulated have been spread over 477 pages.

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Japan's New 'Fast-Break Scheme' To Reduce Clinical Trial Burden For Medtech

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If all goes to plan, Japanese regulators will soon introduce a "fast-break scheme" for accelerating the approval of certain innovative medical devices by allowing manufacturers to submit marketing applications earlier based on less clinical data than usual.

Manufacturers using the fast-break scheme will be required to enhance their post-market surveillance and collect data on their product after they receive approval, and conduct extensive risk-management plans, Yumiko Aoyagi of Japan's Ministry of Health, Labour and Welfare told *Medtech Insight*. The new scheme, which might be introduced in July this year, could be said to be "rebalancing … pre- and post-market regulation," Aoyagi commented.

The new scheme will be used for innovative medical devices and products targeting critical illnesses for which there are no satisfactory treatments. The idea is that it will be used in cases where it is "difficult to conduct clinical trials because of [the] scarcity of patients or other reasonable reasons," explained Aoyagi, who is deputy director, Office of International Regulatory Affairs/Medical Device Evaluation Division, at the MHLW's Pharmaceutical Safety and Environmental Health Bureau.

Innovative medical devices sometimes target extremely few patients, meaning their development can be "stagnated" because of the difficulties involved with collecting cases for clinical trials, the MHLW said during a presentation last month at the International Medical Device Regulators Forum's Management Committee meeting in Canada. In view of this situation, and the MHLW's mission to introduce innovative devices to the public, a scheme is needed that would accelerate the approval of such products by minimizing the burden regarding clinical trials and enhancing post-market surveillance through extensive risk management under close cooperation with medical associations that ensures safe and effective device use.

The fast-break scheme is nearly at the final stage of development and the plan is to introduce it in a few months' time. Its concept has been reported to the section of the Pharmaceutical Affairs and Food Sanitation Council's advisory board that deals with general regulatory affairs for medical devices and pharmaceuticals, Aoyagi said. "We are planning to … ask [for an] opinion from another section of the PAFSC [which deals with medical device affairs such as approvals] to confirm the framework." In addition, "we still need to amend some parts of the Ministerial ordinance/notification under the Pharmaceuticals and Medical Devices Act slightly in order to introduce the scheme."

DIFFERENT FROM JAPAN'S OTHER FAST-TRACK SCHEMES

Once the fast-break scheme is introduced, it will be Japan's fourth procedure for enabling earlier access to medical devices for critical illnesses for which there are no satisfactory treatments. The other three procedures are: the Sakigake scheme for devices that are innovative and developed first in Japan; a scheme for orphan medical devices; and a scheme for devices for high medical needs that have already been introduced in foreign countries "or have some evidence such as clinical use or [for which there are] promising papers."

The other three procedures use "priority review" as the tool for accelerating approvals. Priority review is designed to reduce the time it takes for regulators to review a marketing application. The new scheme, on the other hand, will work by shortening the time to submit an application for approval.

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New Combination Product Registration Rules Coming To Malaysia

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New rules for registering combination products in Malaysia are coming into force in July 2018, according to new guidance clarifying the impending registration process, dossier requirements, timelines and fees that will be involved for makers of products that contain both a drug and medical device.

Combination products will be regulated either as a drug or a device and will need to satisfy the requirements of both the National Pharmaceutical Regulatory

Agency and the Medical Device Authority, the guidance document says.

The agency primarily responsible for the product will be determined by whether the primary mode of action of the product is achieved by its drug or device component.

Where the primary agency is the MDA (for medical device-drug combinations), sponsors will first need to obtain an endorsement from the NPRA, followed by certification by a device conformity assessment body (CAB), before they can apply for approval from the MDA. Device components that fall under Class A (low risk) do not need to be certified by a CAB.

The registration process is also split into three phases for products where the primary agency is the NPRA (for a drug-medical device combination). Here the device component will first need to be certified by a CAB and then endorsed by the MDA. After these two steps are complete, the combination product must then be submitted to the NPRA for review and approval. As before, Class A devices do not need to be certified by a CAB.

The guidance document provides several examples to help sponsors understand whether their combination product should be classified as a drug or device. For instance, certain drug-eluting beads would be classified as a medical device if the beads are sold separately from the drug. If, on the other hand, the beads and drug are packaged and sold together, then they will be classified as a drug.

Dossier requirements are dealt with in detail in two of the four appendices at the end of the guidance document. The guidance also outlines how long (in working days) the regulators might take to assess applications and what fees companies can expect to pay. Regarding fees for drug-medical device combination products, for example, the NPRA will charge between RM 2,200.00 ($500) and RM5,000.00 to process and analyze an application depending on whether the drug is a new product or a generic and how many active ingredients are involved, the document says.

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Feds Holding Workshop on Medical Device Cybersecurity Gaps

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Federal agencies want to fill perceived regulatory and scientific gaps in cybersecurity oversight for medical devices. To help, US FDA, along with the National Science Foundation and the Department of Homeland Security, are holding a meeting with stakeholders in mid-May, the agencies announced April 24.

The meeting, scheduled for May 18-19 at FDA's Silver Spring, Md., headquarters, comes as health-care systems are facing challenges in fighting ransomware attacks and the government has struggled to grapple with potential vulnerabilities that have been identified on devices that could be used to harm patients.

"The purpose of this public workshop is to catalyze collaboration among Health Care and Public Health (HPH) stakeholders to identify regulatory science challenges, discuss innovative strategies to address those challenges, and encourage proactive development of analytical tools, processes, and best practices by the stakeholder community to strengthen medical device cybersecurity," FDA said in announcing the meeting.

Device cybersecurity has been growing as concern amid several recent cases where vulnerabilities on devices have led to safety alerts from FDA, and even a company warning letter. In 2015, FDA issued its first cybersecurity safety communication for device, citing issues with **Hospira Inc.**'s *Symbiq* infusion pump. *(Also see "FDA Warns Of Hacking Threat From Hospira's Symbiq" - Medtech Insight, 3 Aug, 2015.)*

That incident followed other cases such as detected vulnerabilities with **Johnson & Johnson's** *OneTouch Ping* insulin pumps *(Also see "J&J, Hacker Work Together To Fix Insulin Pump Vulnerability" - Medtech Insight, 12 Oct, 2016.)* and with **Abbott Laboratories Inc./St. Jude Medical Inc.** cardiac devices that connect to the company's *Merline@Home* system. The latter issue was raised by FDA in a recent warning letter to Abbott/St. Jude. *(Also see "US FDA Warning Letter Scrutinizes Abbott Over Cybersecurity, Battery Lapses" - Medtech Insight, 13 Apr, 2017.)*

Analysts have also raised the alarm over cybersecurity attacks that use medical devices as a way in to infect hospital systems with ransomware that could be used to take control of patient records and other hospital documents, and, ultimately, to blackmail administrators. Congress has also pressed FDA to improve cybersecurity protections for devices. *(Also see "Lawmakers Question FDA On Medical Device Cybersecurity Concerns" - Medtech Insight, 3 Nov, 2016.)*

FD has also been collaborating with Homeland Security, which has been actively investigating potential threats and coming up with solutions. *(Also see "Homeland Security Official: Key To Cybersecurity Is People, Not Tech" - Medtech Insight, 28 Jan, 2016.)*

In addition to attending the workshop, interested parties can submit written comments on regulatory science applications to cybersecurity by June 23 to docket no. FDA-2017-N-1572 on regulations.gov.

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US FDA Device Center Pushes 'Total Product Life Cycle' Concept; 'Reorganization' Coming, Says Compliance Chief

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A shakeup is on the horizon for how pre- and post-market experts at US FDA's device center interact under a new "Total Product Life Cycle" initiative. The scheme aims to provide the agency with better visibility of products, device-makers and various device classes from cradle-to-grave to help guide its pre- and post-approval decision-making.

"One of the things we're doing inside the agency, inside CDRH specifically, is looking at how we work together. Not only are we trying to figure out how we can collaborate better across offices at the center, but we're literally talking about how do we blend pre-market and post-market specialists into the same team," said Robin Newman, director of the Office of Compliance within FDA's Center for Devices and Radiological Health.

With pre- and post-market teams working together, the agency can respond more quickly to critical safety issues because it will have immediate access to expanded array of data streams.

"This is ultimately going to result in a very significant reorganization in the future, but at this point in time we're still doing the modeling, trying to figure out what kind of organization does this most effectively," Newman said at FDAnews' 14th Annual Medical Device Quality Congress in Bethesda, Md.

"It's like the old saying: 'If only the company knew what the company knows.' Well, now it's, 'If only the agency knew what the agency knows,'" she said. The TPLC initiative "is a way to help ensure that we do know about these [critical] things."

There are nine overarching goals for the TPLC scheme. The first is to gain a "big-picture, holistic look across the lifecycle of a product so pre-market decisions can be informed by post-market experiences or post-approval experiences," Newman said.

TPLC Goals

- Promote a focus on "big-picture," holistic, patient-centered decision-making
- Promote increased responsibility and accountability for urgent safety issues
- Leverage knowledge from post-market and compliance programs to make better informed pre-market decisions, and vice versa
- Increase FDA knowledge about specific devices
- Increase staff access to and integration of Total Product Life Cycle information about the medical devices for which they are responsible
- Minimize delays in information-sharing
- Ensure process consistency
- Facilitate policy consistency
- Support timely review of all products

> "This is going to be, I think, a very powerful learning tool for all of us," CDRH compliance head Robin Newman says.

The agency is also looking to educate itself more on particular products. "This way, the post-market group, or the Office of Compliance's current teams, are being informed by the people who are really living in the science, and in OSB and ODE," Newman said. "This is going to be, I think, a very powerful learning tool for all of us."

OSB is FDA's Office of Surveillance and Biometrics, and ODE is the agency's Office of Device Evaluation.

FDA already has a publicly searchable TPLC database that includes pre- and post-market data about devices. It pulls information from various CDRH databases on PMAs, 510(k)s, adverse events and product recalls.

"But now, the real work starts. We have to design the re-org of the organization," Newman said. "Fortunately, we're not going to have to do it in isolation. We're going to get a little help from some specialists who understand this better than we do, but the bottom line is, we're not standing still. We're already in very rigorous discussion around some pilot programs that we can put together that encourage this information-sharing and this broad reach across the agency."

She admitted that the TPLC process is somewhat "scary" and "challenging." However, "I really believe … this will serve patients better than almost anything we can do, if we really are able to truly exploit the knowledge that we already currently have across the entire center."

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Snapshot: Device Recalls Tick Up Only 1% In 2016 Despite Midyear Surge

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Despite a midyear surge in medical device recalls initiated by manufacturers, the number of recall events remained relatively flat in 2016, increasing a mere percentage point from the prior year.

A count of fiscal year 2016 (Oct. 1, 2015, to Sept. 30, 2016) recalls provided by US FDA shows that there were 43 class I (4%), 1,090 class II (92%) and 50 class III (4%) corrections [a]nd removals last year, for a total of 1,183. That's up 1% from FY 2015, when 1,175 events were recorded. (See Figure 1.)

The 43 class I's counted by FDA in FY 2016 marks a decrease of 20% over FY 2015, when 54 of the high-risk recalls were reported. That's the lowest number of class I recalls since 2009, when there were 32. (See Figure 2.)

A class I designation is reserved for recalls where FDA believes patients face a reasonable probability of serious injury or death from use of the defective devices.

'ALARMING' MIDYEAR SPIKE

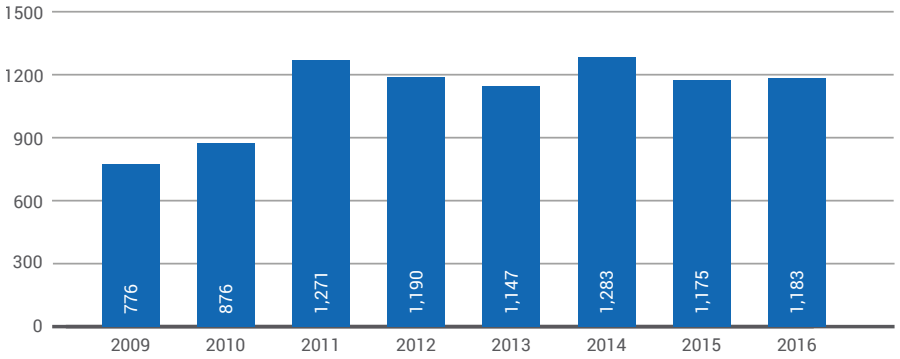
Meanwhile, consulting firm Stericycle conducted its own analysis of 2016 recall data by tallying the number of recall events published in FDA's Enforcement Report between Jan. 1, 2016, and Dec. 31, 2016. Stericycle counted 1,105 events using that method, a difference of 7% from the agency's fiscal-year total.

There can be a delay of weeks or months between a company's recall and its appearance in the Enforcement Report, leading to a slight difference between calendar- and fiscal-year counts. That means some of the recalls tabulated by Stericycle during the calendar year may have taken place prior to 2016, while some that happened during the year were not included in the consulting firm's tally because the agency hadn't yet published them in an Enforcement Report.

According to Stericycle's analysis, device manufacturers were on pace to initiate a more modest number of corrections and removals in 2016. That is, until the middle of the calendar year when a sud-

FIGURE 1

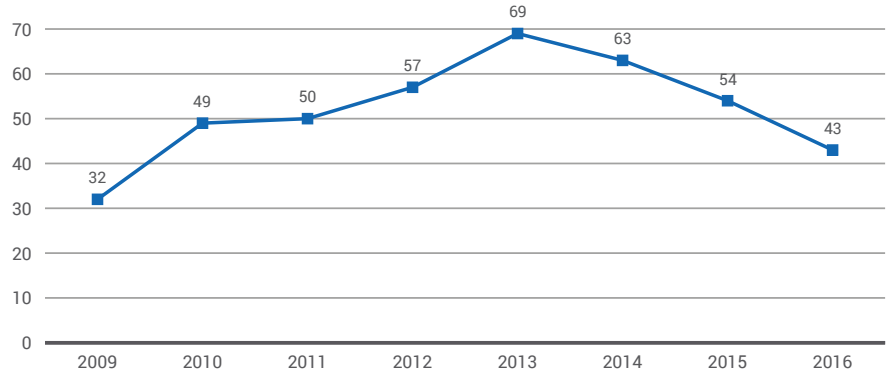
Medical Device Recall Events, FY 2009–2016



Source: US FDA

FIGURE 2

Class I Device Recall Events, FY 2009–2016



Source: US FDA

FDA Recall Classifications

- **Class I:** There is a reasonable probability that the use of, or exposure to, a violative product will cause serious adverse health consequences or death.
- **Class II:** Use of, or exposure to, a violative product may cause temporary or medically reversible adverse health consequences, or the probability of serious adverse health consequences is remote.
- **Class III:** Use of, or exposure to, a violative product is not likely to cause adverse health consequences.

den spike in recalls caused the total to rise substantially. The firm counted 453 recall events during the first six months of 2016, and 652 in the final six – a 44% increase.

"That was a little bit surprising for us. We did not expect to see such a significant jump," Michael Good, VP of commercial & client services for Stericycle, told *Medtech Insight*. "The 44% jump from the first half of the year to the second is something that was, I'd say, almost unprecedented. It was a little bit alarming."

Overall, "There was not one contributing factor that led us to say, 'Oh, my gosh. Q3 of 2016, we saw a huge spike in medical device recalls because of X.' I would love to be able to say that because that's a very easy answer, but it was diversified, the reasons why," Good said. "Parts issues and mislabeling, obviously, were big causes.

"Then, obviously, there were quality issues where there were failed specifications, and things like that, that took place," he continued. "Again, there was not one contributor to that significant jump in the number of recalls in the second half of 2016. We would like to put a bow on it and be able to say it was because of 'X,' but we can't."

While problems with software played the biggest role in recalls – found in 241 recall events in CY 2016 – mislabeling came in a close second, noted in 221 recalls. Quality issues rounded out the top three; it was the cause of 132 corrections and removals last year, Stericycle found. (See Figure 3.)

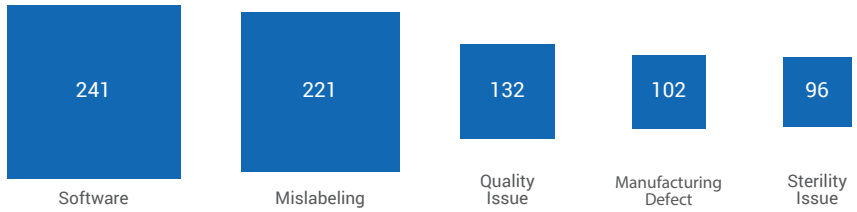
When it comes to quality issues, "within that category there is a number or variety of factors that are at play," Good said. "Those things include misalignment, unbalanced pH levels, improper transportation of the product – the list goes on and on once you delve into a subset of what's triggering a quality issue."

While the overall number of recall events has remained relatively flat since 2011, the number of recalled units has ballooned, Good pointed out.

"The average size of a recall from a units perspective went from about 48,000 units per recall in 2013, for example, to 207,000-plus units for a recall in 2016. So, from a units perspective, you're seeing a greater amount of volume on a per-unit basis. I think that's a staggering number from a units perspective," he said.

FIGURE 3

Top 5 Causes For Recalls, CY 2016



Source: Stericycle analysis of recalls data listed in FDA Enforcement Reports

Good won't speculate on how device recalls will shake out in 2017. "Forecasting recalls is right up there with throwing darts at a board," he said.

"I do think that while the rapid advancement of medical technology has improved, obviously, countless lives, the rush to innovate can lead to faulty devices and sometimes catastrophic results. Because of that, innovation is a double-edged sword. Firms will put out amazing products. But they'll take them to market quickly because there is a need, and they're trying to meet people at their greatest area of need with a particular product offering. And because of that, problems with products can crop up."

That's why it's important for device-makers to "pace" rather than "race," Good said.

"Racing means you could be first to market, but you risk product quality issues," he said. "A slower, more methodical pace might create a lag, if you will, from a competitive standpoint, but it also might slow down the risk of any type of recall. We see companies trying to balance that a lot."

BATTERIES – AN ISSUE FOR 2017?

Stericycle plans to keep an eye on medical devices with lithium ion batteries as recalls unfold in 2017.

"Obviously, lithium ion battery issues could become more commonplace in medical devices as their use continues to grow, and companies must consider how they're going to manage returns and processing if they receive a consumer complaint or must issue a recall," Good said.

Lithium ion batteries, which are powerful and lightweight energy sources, received public attention in the past year for the safety challenges they can present in the context of **Samsung Electronics Co. Ltd.**'s *Galaxy Note 7* smartphones. The phones had to be recalled due to a flaw in the battery cell that can cause fires.

"Defective batteries, unlike other types of recalls, require specialized transportation and permitting, and the destruction of them is handled completely differently," Good said. "There are a lot of nuances."

He says impacted firms should update and practice their recall procedures and readiness.

"There are medical device companies that are getting into products that have a lithium ion element to them that might not have existed in the past," he said. "There's a learning curve associated with that and how they should be recall-ready, if you will, or prepared for anything that should go on related to a lithium ion battery."

Number Of Units Recalled, 2016

- **Q1:**9,862,562
- **Q2:** 40,457,984
- **Q3:**115,954,287
- **Q4:** 63,102,245

Total: 229,337,078

That's an average of **207,581 device units recalled per event**, according to Stericycle.

CLICK

Stericycle's Michael Good wrote a guest column on US FDA's 'emerging signals' guidance. Check it out online at http://bit.ly/2mEOvhZ

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CONTINUED FROM PAGE 1

of BD stock per Bard share, or a total of value of $317.00 per Bard common share based on BD's closing price on April 21, 2017. When the deal closes, Bard shareholders will own approximately 15% of the combined company and hold $8bn of BD common stock. In an April 24 note, Wells Fargo analyst Larry Biegelsen agrees that the deal makes strategic sense "We view the BD offer as fair for Bard shareholders as it represents 27x the midpoint of Bard's updated 2017 earnings-per share guidance," he wrote in an April 24 note.

BD will fund the deal with about $1.7bn in available cash, about $10bn of new debt, $4.5bn in equity and equity linked securities issued to the market, and bridge financing. During the conference call, BD CFO Christopher Reidy mentioned that taking on so much debt will drop BD's rating with Moody's to "BBB," which is "below investment grade." "We will continue to operate as an investment-grade company by remaining committed to funding our growth strategies and investing in the business," he said. BD says it will continue working to deleverage its balance sheet over the next three years while also increasing annual dividends and reinvesting in the business to continue to drive long-term growth.

The companies expect the merger to be accretive to BD's earnings-per-share in the high-single digits by fiscal year 2019 and yield about $300m of estimated annual cost-synergies by fiscal year 2020. BD expects the transaction to improve its gross margins by about 3 percentage points in fiscal year 2018, pushing BD's earnings-per-share growth into the mid-teens, and generate strong cash flow.

Bard will become a new segment within BD primarily focused on "advancing disease management," BD explained. During the call, BD also announced that Tom Polen is now the President of BD, overseeing all of BD's operating segments, including the existing Medical and Life Sciences segments, as well as the new Interventional segment that will include Bard. Polen is currently executive vice president and president of the BD Medical Segment. He will continue to report to Forlenza, who is also BD's chairman. Ring, who is chairman of Bard, and one other Bard director will join BD's Board of Directors.

STRATEGIC FIT

The Bard deal is the biggest of a series of recent acquisitions BD has made to compete for customers who are increasingly demanding cost-effectiveness and value from medtech manufacturers, the most notable being the $12.2bn deal for **CareFusion Corp.** in 2015," Forlenza said. *(Also see "Infusion Pump-Makers Look to Improve Safety Through Interoperability" - Medtech Insight, 20 Feb, 2017.)*

"CareFusion complemented the strong foundation, and meaningfully accelerated our strategy to improve healthcare process and efficiency," he said. "[Adding Bard] further accelerates and broadens our strategy. As we serve our customers around the world, we continue to see changing healthcare needs, and the environment today is very different than it was just a few years ago. That's why this combination is so powerful."

Repeating a theme that has become prevalent throughout the industry in recent years, Forlenza explained "In today's environment, healthcare providers are becoming increasingly focused on improving outcomes and increasing efficiency. Payers are doing the same, and also, demanding value to justify reimbursement. Bard's differentiated technologies for better clinical outcomes, coupled with BD's capabilities in improving major healthcare processes, will make the combined organization an even stronger partner for healthcare providers to improve the lives of their patients all around the globe." *(Also see "Medical Devices Aren't Luxury Goods, So Why Does Medtech Try To Sell Them That Way?" - In Vivo, 17 Apr, 2017.)*

Specifically, the CEO said that Bard's complementary product portfolio will contribute to each of the "four pillars" of BD's current growth strategy: medication management, infection prevention, the treatment of chronic disease, and global expansion.

BD estimates that adding Bard will allow it to address 85% of the $20 billion medication management segment. The combined company will have products addressing the whole hospital drug-delivery process, including skin reparation, proper catheter insertion, and maintenance of the infusion site. "We believe this portfolio will deliver the most effective, safest, and cost-efficient outcomes across the care continuum from ICU to outpatient," Forlenza said.

> "Our solutions are ready to be ramped, leveraging BD's global infrastructure, and BD and Bard's global sales forces." – BD CEO Vincent Forlenza

Hospital-acquired infection costs the US healthcare system about $10bn a year, according to BD. BD's infection-prevention business addresses surgical site and catheter-related bloodstream infections, while Bard has products addressing urinary tract infections, which is the most common cause of hospital acquired infections, so BD and Bard together will be able to address 75% of the most significant and targetable hospital-acquired infections in the US, Forlenza said.

Bard's portfolio of peripheral vascular therapy, oncology and surgical products will bring Bard into new chronic-disease management sectors that complement BD's Diabetes Care business.

Commenting on the deal in an April 24 note, Jefferies analyst Raj Denhoy points out that the combined company will be "the undisputed leader" in vascular access solutions with BD's needles, syringes, intravenous catheters, and drug-infusion pumps complementing Bard's peripherally inserted catheters and ports. He also cites Bard's market-leading position in peripheral vascular disease, led by its *Lutonix* drug-coated angioplasty balloon, and strong presence in general surgery with its hernia repair technologies as important assets motivating the deal.

Forlenza also highlighted Bard's presence in the fast-growing areas of oncol-

ogy and surgery. "We see a unique opportunity in combining our oncology businesses in the high growth areas of biopsy and drainage. Together, the combination will add scale and strengthen our offering globally," he said. "The addition of Bard's strong solutions in hernia treatment and biosurgery, together with BD's solutions for surgical site infection prevention, will create a high growth and more clinically impactful BD surgery portfolio. As we think more broadly, these conditions are universal and impact the lives of patients around the world."

About 45% of BD's sales are outside the US, including 15% in emerging markets, while Bard is among the fastest-growing medtech companies in emerging markets, according to Forlenza. "The combination of these two companies will create a robust strategic partner for healthcare providers across the globe. With significant breadth and depth, we believe we are well-positioned to help customers and patients with their most critical healthcare issues," he said. "Our solutions are ready to be ramped, leveraging BD's global infrastructure, and BD and Bard's global sales forces."

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DePuy Synthes Builds Out Trauma Offering With TRS' 3D-Printed Tech

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DePuy Synthes has acquired a 3D-printing technology for making skeletal reconstruction and bone regeneration scaffolds, a move that underscores the orthopedics market leader's focus on adding more individualized, patient-specific solutions to its trauma portfolio.

The bone-scaffold technology comes from **Tissue Regeneration Systems Inc. (TRS)**, a privately held Michigan company with whom DePuy Synthes has been collaborating since 2014. The two companies had teamed up through **Johnson & Johnson Innovation** (JJI), the innovation-focused business arm of DePuy Synthes' parent company. *(Also see " Two medtech firms among 12 new J&J Innovation Centers' investments" - Medtech Insight, 20 Jun, 2014.)* The 3D-printing methods developed by TRS will enable DePuy Synthes to create patient-specific, bioresorbable scaffold implants. The porous micro-architecture of the implants is designed to facilitate bone integration, and engineered to allow the implant to bear significant load and support function. The geometry of the implants can be customized, using input from patient's CT scans, and, if necessary, adapted in the operating room to exactly replicate and replace missing bone anatomy, according to TRS' website.

TRS also has developed a proprietary mineral coating, called *Affinity*, intended to support bone healing in patients with orthopedic and craniomaxillofacial deformities and injuries. The acquisition does not include Affinity; instead, DePuy Synthes has licensed this technology from TRS.

Financial terms of DePuy Synthes' acquisition of the TRS technology have not been disclosed.

J&J has been increasingly vocal about its interest in 3D-printing, especially in the last couple of years, as the manufacturing technique becomes more commonplace in the medical field. JJI has more than 50 strategic collaborations with early-stage innovators like TRS, and academic institutions through the J&J Innovation Centers. Among these is a partnership between **Carbon 3D** and **Ethicon Endo-Surgery**; the two parties are using Carbon 3D's *Continuous Liquid Interface Production* (CLIP) technology, a form of 3D-printing in which the product grows from a pool of resin, rather than being printed line-by-line, to develop custom surgical devices. *(Also see "J&J Announces New Device Collaborations" - Medtech Insight, 7 Jan, 2016.)*.

More recently, and also in the area of orthopedics like with TRS, J&J announced that it was partnering with **Aspect Biosystems** to use the latter's Lab-on-a-Printer technology to develop meniscus implants. *Lab-on a Printer* differs from other 3D-printing technologies because it creates complex multi-cellular 3D tissues at "industrially relevant throughput," according to Aspect Biosystems. It has a microfluidic print-head capable of rapidly manipulating and sequencing multiple biomaterials, including living cells, extracellular matrix content, growth factors, bioactive compounds and other "bioinks." The results are three-dimensional heterogeneous, structurally accurate, functional tissues, bioprinted knee meniscus tissue suitable for surgical therapy. *(Also see "J&J Taps Aspect Biosystem's 3D Printing Tech For Meniscus Implant" - Medtech Insight, 18 Jan, 2017.)*

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Nanjing BioPoint Shoots For 2018 Double POC Launch; Seeks $10m

CAROLE GOLDSMITH

Chinese start-up **Nanjing BioPoint Diagnostic Technology Co Ltd** (Nanjing BioPoint) is looking to compete in the infectious disease testing market with plans to launch two point-of-care tests in China and other global markets in 2018. To advance these products through the clinical and regulatory hoops, as well as to expand its manufacturing capacity, the firm's holding company **BioPoint Hong Kong** is seeking to raise RMB68.8m ($10m).

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Nanjing BioPoint is located within the Jiangsu Life Science Technology and Innovation Park (JLSTI), close to Nanjing city in China, but the company was spun out from the Burnet Institute, a medical research institute in Melbourne, Australia. Speaking at the recent AusBiotech Investment Seminar in Singapore, Nanjing BioPoint's founder David Anderson told delegates that Burnet had already been working in China for several years in academic and public health collaborations, but wanted to move into more commercial activities. "Burnet is a 'not-for-profit' medical institute and we were keen to develop a 'not-for-loss' and ultimately profitable medical diagnostic company in China," he said.

Nanjing BioPoint was spun out of Burnet in 2013, with the mission to commercialize point-of-care diagnostic test products for China and global markets. These products would either come from the research labs of Burnet or developed in-house by Nanjing BioPoint.

The two point- of-care tests that are currently being developed at Nanjing BioPoint and will be the first to be launched by the company are a plasma separator for measuring HIV viral load and a test for the enzyme alanine aminotransferase (ALT), which is an indicator of liver function. Patients with viral hepatitis and other liver diseases, or those undergoing treatment for HIV or tuberculosis, require regular testing for ALT. Anderson said that the plasma separator is planned for launch in the first quarter of 2018 and the ALT test in the third quarter of 2018.

The Burnet Institute will continue to work with Nanjing BioPoint when both products are commercialized, to support effective clinical trials, advocacy and relevant policy development for use of the products, especially in emerging economies outside China. As well as its Melbourne headquarter, Burnet has major operations in Myanmar and Papua New Guinea plus collaborations worldwide with a range of global organisations among which include, WHO, Global Fund, World Bank, CHAI, MSF and UNICEF.

Anderson said that Burnet has a range of other diagnostics products in various stages of development and BioPoint will continue to build its collaborative R&D partnership with Burnet to provide effective commercialization on new diagnostics.

In terms of financial backing, the start-up received an initial RMB1m ($145,300) grant from Nanjing Municipal Government, "plus free rent on the company's facilities and free housing for the company head for three years in Nanjing," said Anderson, who is Burnet's deputy director and head of its diagnostic product development laboratory and R&D. The business also started receiving equity investments: Burnet put in RMB1m into parent company BioPoint HK the year Nanjing BioPoint was spun out, and a further RMB3m more recently. Other shareholders in BioPoint HK include Beijing GuoMin Yin He Group, which invested RMB12.5m in 2014, and a new unnamed investor.

Proceeds from these investments have enabled Nanjing BioPoint to open its R&D facility in 2015 and an adjoining GMP manufacturing facility in 2016. Currently the facility has five employees, including the Australian-Chinese managing director and three scientists, all Chinese nationals.

Capital raised in this current and ongoing financing round will be used for clinical validation and regulatory approval of the two lead products, meet initial manufacturing quota of up to three million units a year and then further expansion of manufacturing capacity in the next couple of years.

Anderson explained to *Medtech Insight* why Nanjing in the Jiangsu Province was chosen as a location for the Chinese company: "Nanjing is a second-tier city but with very good universities and the cost of living is lower than in Beijing. We identified a very good innovation park and government support linkages for the company there."

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STAT-DX Aims To Take On Rival BioFire In Syndromic Testing

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Barcelona start up STAT-DX (formerly known as STAT Diagnostica) is launching its *DiagCore* rapid, multiplex PCR platform and competing against the likes of established IVD players like French group bioMérieux in the fast-growing syndromic testing market.

STAT-DX's DiagCore platform detects and identifies up to 48 molecular targets simultaneously. The system automates sample homogenization, cell disruption and nucleic acid purification, utilizing single-use cartridges. It can provide results in one hour, with a total sample handling time of less than one minute.

DiagCore, is designed to offer lab-like performance in a range of clinical settings such as physicians' offices, emergency departments or intensive care units. "Essentially what DiagCore does is automate the preparation of the sample once its collected from the patient, so the only thing the end user needs to do is to get the sample into the DiagCore cassette, introduce the DiagCore cassette into the machine, click a few buttons and then everything is automated until about an hour later when the results are reported to the user and they can take clinical action," said STAT-DX CEO and co-founder Jordi Carrera, who believes the company is the only to offer real-time PCR so far. "The system is automating a complex technology into a very friendly and nice experience for end users."

STAT-Dx's first assay, the *DiagCORE Respiratory Panel* is intended for use with nasopharyngeal swab samples to test viral and bacterial pathogens from patients with acute respiratory symptoms. "The first product we are preparing to launch is a respiratory panel that has about 22 targets, it's a comprehensive syndromic test," said Carrera. "During the next month, we will start clinical trials in several European hospitals. The idea is to CE mark it in the second half of 2017 and then we will go into a limited release phase and then at the beginning of 2018 we will start fully fledged commercial operations."

STAT-DX also has other panels in its R&D pipeline, with the tests focused on clinical microbiology and infectious disease applications. The company will officially unveil DiagCore at the forthcoming European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), held in Vienna between April 22-25.

"There have been two names in this industry that have been pioneers," Carrera explained. "Cepheid [acquired by Danaher in 2016] were the pioneers of decentralizing highly automated solutions in molecular diagnostics. However, their systems have a low number of target areas, only detecting two or three microorganisms by cassette. Our true competitor in this field is BioFire because they were the first to automate assays in the multiplex format. They created the explosion of syndromic testing which is growing tremendously and we want to be part of that success."

BioFire Diagnostics Inc., which was acquired by French IVD firm **bioMérieux** in 2013 for $450m, currently markets the *FilmArray* multiplex PCR system. The device has four US FDA-cleared panels - the Respiratory Panel, the Blood Culture Identification Panel, the Gastrointestinal Panel, and the Meningitis/Encephalitis Panel.

STAT-DX believes the low manufacturing costs of its DiagCore device will make it "extremely competitive" compared to BioFire. Carrera said he hopes that these advantages will enable STAT-DX to "outcompete products from BioFire that have had a great impact in the markets."

Photo credit: STAT-DX

DiagCore detects and identifies up to 48 molecular targets simulataneously, providing results in one hour

STAT-DX currently has 50 employees and raised around €50m ($54m) in three fundraising rounds. It has won the backing of several heavyweight investors including Siemens Venture Capital, Gilde Healthcare, Kurma Partners, Ysios Capital, Idinvest Partners, Boehringer Ingelheim Venture Fund, Caixa Capital Risc and Axis.

Carrera said: "The brains and the ideas of this all come from Barcelona but, unlike other start-ups that try and build everything in-house, we've used a large team of partners throughout Europe and US to get the best technology and talent to work on the subject. In about six years, we've put together a very competitive product in a very dynamic environment to compete in this growing molecular diagnostics area."

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Cellnovo Targets 2018 Launch Of Insulin Micropump With Artificial Pancreas Tech

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Cellnovo believes it is one step closer to launching an artificial pancreas (AP) system after acquiring a commercial license from **TypeZero Technologies** to integrate the latter's artificial pancreas software into Cellnovo's all-in-one, mobile insulin pump platform.

TypeZero's AP software, known as *inControl AP*, will be integrated directly into Cellnovo's Bluetooth-enabled diabetes management system. The software is designed to continuously monitor blood glucose levels via a smartphone application and automatically delivers this information to the insulin pump so that the right dose of insulin is delivered to correct and regulate blood sugar levels. Cellnovo's system communicates with a continuous glucose meter (CGM) from **Dexcom Inc.** Blood glucose readings from the Dexcom sensorare sent via Bluetooth to the handset of the Cellnovo system and orders for insulin can also be sent from the handset to the pump via Bluetooth.

Under the terms of the non-exclusive agreement, Cellnovo can commercialize a Cellnovo-Type Zero product worldwide, with the launch of the integrated product expected in 2018. Financial terms of the deal were not disclosed.

The deal is an extension of the two companies' partnership which was first formed in 2016. They joined forces then to carry out a six-month study, the International Diabetes Closed Loop Trial, to test an artificial pancreas technology across the US and Europe. The joint system again used Dexcom's continuous glucose meter to monitor glucose levels, TypeZero's inControl AP and Cellnovo's patch pump.

"Artificial pancreas technology is the future of diabetes care and is going to be huge in Type 1 diabetes treatment," Cellnovo CEO Sophie Baratte told *Medtech Insight*. "Now, with insulin pumps people must go into the setting of the pump and decide with their physicians how much insulin they need to receive on an hourly basis. So, the pumps are easy to program but can only deliver insulin in advance under certain pre-set configurations."

Photo credit: Cellnovo

Cellnovo expects to launch the integrated product in 2018

"Artificial pancreas technology is completely different as the pump is receiving orders in real-time from software every other minute so the functioning of the pump delivers an amount of insulin that has just been calculated and is highly dependable upon parameters that the software has received and is now computing."

Cellnovo's all-in-one diabetes system comprises an insulin patch pump with an activity monitor and cellular-enabled wireless, mobile touchscreen handset that transmits data automatically. The CE marked system is currently marketed in France and the UK. In July 2015, the company joined the Euronext market in Paris, raising €31.56m. Previously, the company entered an agreement with Swiss giant Roche to combine technologies.

TypeZero's AP technology is currently licensed to Tandem Diabetes Care for development of a closed-loop AP system. Baratte explained the company sees the product as a "lifestyle device," that will provide diabetics with extra comfort that other pumps cannot currently afford users. "TypeZero has another partner but Tandem markets a tube pump which is currently only sold in the US. Cellnovo's differentiating factor in the pump market will not only be the artificial pancreas but also all the other benefits our pump can provide - such as being a wearable, micropump, a discreet pump compared to tube pumps which are much larger devices and more disruptive to everyday life."

As well as TypeZero, Cellnovo is participating in other AP development projects with Diabeloop, and Horizon 2020. Baratte said: "We believe we will sell in Europe first, as CE marking is generally quicker to obtain than [US] FDA approval and as we're based in Europe, it makes it easier for us to start there from an operational and strategic standpoint. Once Cellnovo gains experience selling the AP device in Europe we will expand commercially to the US."

"One of the features our patients love about our patch pump is that it's detachable so ensures freedom of movement and extra comfort. Another large benefit of our pumps and a key differentiator to others is that it's e-connected so it can deliver real-time data which is sent both to the clinicians and the patient's family so everyone can check on the person to see if they're okay. This gives parents reassurance that their children are okay, and for partners and families [knowing] they can check on loved ones without invading the privacy of the other person. It's also a useful tool for clinical teams to monitor patients and anticipate any problems. There's lots we can do in terms of that real-time data for seeking better patient outcomes so we're very excited about all the possibilities."

START-UP SPOTLIGHT:

Amniox Medical, Bringing The Benefits Of Amniotic Tissue To Ortho And Wound Care

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Venture-backed **Amniox Medical Inc.**, a division of **TissueTech Inc.**, is working with the National Institutes of Health to develop regenerative tissue products for musculoskeletal and wound care applications based on TissueTech's amniotic tissue matrix technology.

"Amniotic membrane technologies are the latest cutting edge of how to do these things," Amniox CEO Tom Dugan told *Medtech Insight*. "Clinicians are still in the very early stages [of] understanding what these amniotic membrane technologies can do for them."

Dugan told *Medtech Insight* that his company is focusing entirely on wound care and orthopedic products. Chronic wounds like diabetic foot ulcers and venous leg ulcers "are kind of recalcitrant and haven't been able to close using conventional means. [We] are able to regenerate tissue to close that wound to get granulation and epithelialization which will help to accelerate the closure of a difficult to close wound."

In this space, Amniox markets *Neox* wound allograft, indicated for covering dermal ulcers and defects, and *Clarix* regenerative matrix as a wrap or barrier that stimulates scarless healing of a surgical scar. Amniox also markets *Clarix FLO* and *Neox* FLO as particulate forms for Clarix and Neox, to provide higher volumes of the important matrix proteins. Clarix Flo is indicated to replace or supplement damaged or inadequate integumental tissue while Neox Flo is for wound covering of dermal ulcers or defects, according to the company.

Amniox is also developing products for orthopedic applications. For example, on Mar.30 at the 2017 American College of Foot and Ankle Surgeons conference in Las Vegas, Ryan Scott of the Core Institute in Phoenix and David Garras of the University of Illinois-Chicago presented results of an 18-week, 43-patient trial showing that injections of Clarix Flo can decrease pain and improve function in patients recovering from plantar fasciitis who had failed to find relief with more conservative therapies.

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Contact: Tom Dugan, CEO

Industry Segment: Orthopedics and wound care

Business: Amniotic tissue-based regenerative medicine

Founded: 2011

Founders: Scheffer C.G. Tseng, Amy Tseng

Employees: 243 (TissueTech, Amniox, Bio-Tissue)

Funding: $25mm total; Series A $10mm in 2013; Series B $15mm in 2015; Further supplemented by NIH grants since the founding of the company.

Investors: Ballast Point Ventures, River Cities Capital Funds

Board of Directors: Scheffer Tseng, Chairman, Co-founder and Chief Science Officer, Amy Tseng, President and CEO, J. Carter McNabb, Managing Director, River Cities Capital Fund, Matt Rice, Partner, Ballast Point Ventures, Billy Yeh, cardiologist.

In October 2016, at the North American Spine Society meeting in Philadelphia, Greg Anderson of the Rothman Institute in Philadelphia presented trial results from an 80-patient randomized trial showing that injection of Clarix in the disc space following surgical removal of a disc herniation improved the patients pain and functional scores compared to herniation removal alone.

The US FDA regulates Amniox' products as Human Cell, Tissue, and Cellular and Tissue-Based Products, produced in accordance with the Good Tissue Practices, so it does not need to go through a medical device approval process for each new indication, but Dugan said the company will continue to sponsor clinical trials to find new applications for its technology. "We have clinicians coming to us with new ideas and wanting to study it in new applications," Dugan said. "We've got a number of ongoing studies in those areas, both wound care and orthopedics.

"We have so many different opportunities that one of the challenges for the business is to stay focus and to be diluted by all of these new opportunities," he said.

As part of TissueTech, Amniox is supported by venture funding from Ballast Point Ventures and River Cities Capital Funds; the most recent round was $15m in growth-equity financing announced in June 2015. "As a company, we're fortunate to have a good financial footing for our business." The company is profitable already, but Dugan expects to add more financing this year and remain independent for the foreseeable future.

"We've assessed a couple of opportunities, but there's nothing that we've felt that we've needed a partner for yet," he said. "Down the road, I can envision that happening for certain clinical or market opportunities. We could look for a partner

to help us with distribution, comarketing or even out-licensing the product. But we don't need to really go public or exit. We take a long-term view of the business."

IMPROVING THE 'SOIL' BEFORE YOU 'PLANT'

TissueTech was founded in 2001 as the managing entity for **BioTissue**, which had been formed in 1997 to commercialize technology developed by ophthalmologist-scientist Scheffer C.G. Tseng with support from the US NIH, beginning in 1986. BioTissue markets products to treat wounds on the eye using regenerative therapies processed amniotic membrane – the inner layer of the placenta that surrounds fetus in the womb – and umbilical cord tissue donated voluntarily by mothers following Cesarean sections. Amniox, founded in 2011, is applying the same basic science insights to orthopedic and wound care applications.

Tseng, who serves as chairman of TissueTech and chief scientific officer for TissueTech and Amniox, told *Medtech Insight*: "Our technology can bring in a new therapeutic paradigm, because poor wound healing and would healing complications lead to infection and readmission," TissueTech's approach to regenerative medicine is different than the many approaches focused on transplanting stem cells, because it first creates a hospitable environment for new tissue to grow, he explained.

Tseng compares TissueTech's approach to growing plants by first improving the topsoil, rather than just optimizing the seeds.

"With any kind of regeneration, you need some progenitor cells like stem cells to do the work, [and this lead many researchers] to jump to the conclusion that when old tissue has failed and has lost the progenitor cells, it now requires the stem cells to come in and fix it," he explained. "And this is why people move quickly to deploy stem cells as a weapon. But this isn't going to be very successful because the recipient tissue isn't ready."

Researchers have known for decades that wounds created by in utero surgery show much more complete healing and regeneration than surgical wounds in adults, because the adult immune response is much more aggressive.

"We realized the birth tissue harnesses the process that we do not use very well in adult human healing," Tseng said. "It turns out that extracellular matrix has a lot of biological information [and] during the embryonic development, the cells are changing but the matrix is also changing all the time. We found out that there's a very primitive and primordial matrix used in the developmental stage that continues to be present in the tissue we are using and has a very important therapeutic function to guide regenerative healing."

TissueTech developed the *CryoTek* technology for deep-freezing the amniotic and umbilical tissue. Unlike other forms of tissue preservation that degrade the tissue by dehydrating it, CryoTek preserves the functional and structural characteristics of the tissue, according to the company. It devitalizes the living cells in the tissue, which prevents the graft recipient's immune system from rejecting it, while maintaining the important functional components of the tissue's extracellular matrix, including the heavy chain (HC)-hyaluronan (HA)/pentraxin 3 (PTX3) which create anti-inflammatory, antiscarring, and antiangiogenic properties in new tissue to promote wound healing.

Using the gardening metaphor again, Tseng explained "If you have the top soil, you'll want to prune and weed. There will be some things coming up that you don't want. [In tissue regeneration] the first is the chronic inflammation, and then the scarring. They go hand in hand. If they become the dominant force, the 'soil' is spoiled and nothing can grow."

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