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Intense Competition, Innovation Drive Healing Trends In Wound Care

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Major advances in the understanding of the basic science behind wound healing have led to an explosion in new wound-care technologies and improvements in existing products. This article delves into the competitive landscape for a variety of wound-care techniques – including advanced wound dressings, tissue-engineered skin replacements, active wound-repair modulators, advanced wound-closure technologies, surgical sealants and automated suturing devices. And it addresses the factors that are driving, or impeding, the widespread adoption of these products.

FOAM RULES ADVANCED WOUND DRESSINGS

Global sales of advanced wound dressings are expected to hit $4bn by 2020; foam wound dressings represent both the largest product segment and the most significant growth driver for the overall market.

According to a new report by *Meddevicetracker,* "Advanced Wound Care Products Market," worldwide sales of advanced wound dressings totaled roughly $2.6bn in 2015 and are expected to achieve a compound annual growth rate of 9%. This market encompasses a medley of different wound dressings, including alginates, film dressings, hydrocolloids, hydrogels, contact layers and antimicrobials – some absorbing wound exudate, others providing moisture to the wound, and some doing a combination of both. *(Also see "Acquisitions, New Technologies Reshaping Advanced Wound Care" - Medtech Insight, 30 Sep, 2014.)*

Foam wound dressings account for the lion's share of the market, at 38.6%, with sales of $997.3m in 2015. Sales are expected to rise to just over $2bn by 2020, representing a compound annual growth rate (CAGR) of 15.2%. (See Figure 1.)

MÖLNLYCKE BEATS S&N IN FOAM DRESSING

Foam wound dressings vary greatly from one manufacturer to another – with differences ranging from cell size of the dressing, adhesive and film backings, to thickness. This has left clinicians hesitant to switch, or even try, a new brand.

For years, the resistance among clinicians to try something new benefitted British medtech giant **Smith & Nephew PLC**, which had established a loyal following among clinicians with its broad line of *Allevyn* products. In 2015, however, Sweden-based **Mölnlycke Health Care** outpaced S&N with its *Safetac* technology, an adherent silicone adhesive that removes easily from the skin, used with the *Mepilex* foam product. Mölnlycke deployed a savvy product marketing campaign focusing on clinician education.

Subsequently, Mölnlycke's foam dressing sales jumped to about $360m in 2015,

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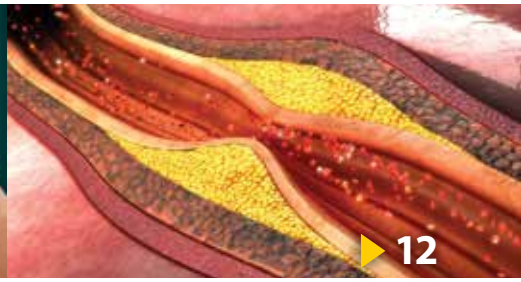

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CRT-Ds powered by Boston Scientific's *EnduraLife* could save England's National Health Service approximately £6 million in the first five years by reducing avoidable replacement procedures, the National Institute for Health and Care Excellence concludes in a new guidance.

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combination products. Regulatory requirements for these products for are among the most demanding and costly. Zwick discusses opportunities to utilize existing testing and maximize efficiencies on a global scale.

R&D

Unlocking Legalities: Antitrust Risk Rises In China

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A $17.2m fine imposed by the Chinese government against **Medtronic PLC** in December helps to highlight the risk of apparent price-fixing in emerging markets.

The National Development and Reform Commission (NDRC), a Chinese regulatory body, said the company had violated the country's anti-monopoly law since 2014 by:

- Setting the prices distributors could charge when reselling devices, including those that could be charged to hospitals;
- Fixing profit margins for e-commerce distributors; and
- Imposing minimum bidding prices via distribution agreements, and requiring distributors to seek permission before deviating from them.

The problematic behavior, which the Chinese government calls "resale price maintenance" (RPM), was identified in the company's diabetic, rehabilitation therapy and cardiovascular device business lines, NDRC said. The regulatory body also noted that the penalty was increased because Medtronic imposed an exclusive purchasing requirement, as well as territorial and customer restrictions. These moves increased the anti-competitive effects of the conduct at issue, the commission said.

Shortly after the Medtronic decision, Chinese courts hit **Smith & Nephew PLC**'s trading subsidiary in the country with a $108,000 fine for violating RPM while distributing scar tissue treatments.

ENFORCEMENT ON THE RISE

Since 2013, China has occasionally fined medical device manufacturers for price-fixing, but an attorney practicing in the country said the number of cases and the size of fines have increased more recently. "RPM remains one of the focus areas for antitrust enforcement, and NDRC's approach to RPM remains consistently strict," said Andy Huang, an attorney in Hogan Lovells, LLC's, Beijing office.

"For Western companies exploring the Chinese market, antitrust compliance is

critical – and increasingly so, in China," Huang said. "In particular, Western companies should have a good compliance system in place and regularly review their business practices, such as distribution agreements, IP license agreements, etc., to reduce antitrust compliance risks."

NDRC has been stricter than the courts in applying RPM standards, Huang explained in a Hogan Lovells newsletter. Through a series of cases, Chinese courts have established that a manufacturer could restrict resale prices its vendors could accept without violating RPM as long as the policy does not restrict market competition. However, the regulatory body has used a looser standard.

"In some of the past cases, NDRC seemed to consider the finding of RPM conduct to be sufficient to establish a violation of [anti-monopoly law], without the need to look at actual effects in the market," Huang said.

The Medtronic decision included more detailed reasoning, he noted, which could indicate that NDRC and the courts are coming to agree on a standard that would only punish RPM if the company involved "has a significant degree of market power and there is not sufficient competition in the marketplace." But he cautioned that it's too early to be sure.

He further speculated that NDRC's position against Medtronic's territorial and customer restrictions might also signal a shift in the law. Previously, there were no direct rulings against restrictions based on territory or specific customers.

"Even though NDRC did not find these additional restrictions to be illegal themselves, it found them to aggravate the competition problem and accepted Medtronic's commitments in that regard," he said. In addition, the commission recently published guidelines aimed at the automotive industry that target territorial and customer restrictions.

MEDTRONIC: COMMITMENT IN CHINA REMAINS STRONG

In addition to paying the fine, Medtronic promised to stop imposing the anti-competitive restrictions. The company accepts NDRC's decision and remains committed to complying with local laws, a company spokesman said. The firm has focused significantly on improving its Chinese market presence in recent years via a range of investments and purchases of local companies such as spinal manufacturer Kanghui Medical. *(Also see " China's M&A landscape may be too rich for acquisitive multinationals" - Medtech Insight, 4 Jun, 2015.)*

However, the country's device regulatory reforms that began in 2014, as well as a "buy China" policy, have posed some challenges for overseas manufacturers such as Medtronic. *(Also see "China's Medtech Regulatory Reforms Yet To Enter Steady Path" - Medtech Insight, 11 Aug, 2016.)*

"The government policy over the years – and they've gotten very good at enforcing this – they're pushing for maintaining imported products, but letting a lot of the growth come from local products," said Geoffrey Straub-Martha, executive VP & president of restorative therapies, during a March 7 earnings call.

For example, Chinese spine surgeons must offer patients at least one locally made option, which is often 30% to 40% less expensive than overseas products, he said. Still, he expects Medtronic's sales in China will outstrip US sales within the next decade.

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Device-Tax Repeal Opportunity Slips Away As GOP Pulls Health Bill From Consideration

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Industry lost a major opportunity to permanently repeal the device tax March 24 as US House Republicans pulled their health-care bill, the American Health Care Act, from consideration, rather than risk having the bill be voted down.

"Obamacare is the law of the land, and it will remain with us in the short-term," House Speaker Paul Ryan, D-Wisc., said in a televised statement in which he admitted defeat, adding, "We've got to do better." Ryan also acknowledged that as long as the ACA remains on the books, "the Obamacare taxes stay within the law," along with all the negative consequences those taxes impose on industry.

Ryan said that after failing to muster enough votes from House conservatives, he knew the AHCA would not pass, and advised President Trump to give up on the ACA repeal effort for now, so that Republican party leaders could devote themselves to other legislative initiatives. For example, House Ways and Means Chairman Kevin Brady, R-Texas, said Republicans are now "moving full speed ahead with tax reform" and that he is "still proud" of the AHCA, despite its failure to pass.

The legislation, which would have repealed the individual mandate, switched from income-based subsidies to age-based tax credits, phased out Medicaid expansion and repealed an array of ACA taxes, including the device tax. It proved very unpopular, with key medical groups, the American public and, it turned out, several dozen Republicans on Capitol Hill. But device industry lobbying groups had stood firm in support of the bill for the singular purpose of permanently repealing the 2.3% excise tax on most US device sales.

The tax was temporarily suspended by Congress in 2015, but it is set to restart in January. The industry argues that the tax was to blame for the loss of thousands of medtech jobs when it was in effect between 2013 and 2015. *(Also see "Thousands More Medtech Jobs At Risk If Tax Restarts, Think Tank Says" - Medtech Insight, 2 Mar, 2017.)*

While he was disappointed device tax repeal didn't move forward today, "a bipartisan bill to permanently repeal the device tax" continues to stay alive in the House and Senate, said MITA executive director Patrick Hope.

Device industry reaction to the setback was negative.

"We're disappointed the House was not able to move forward to fully repeal the medical device tax today," said Scott Whitaker, AdvaMed president and CEO. "Every day this tax remains on the books is a day longer of uncertainty in the innovation market, as well as further threatened job losses. Full device tax repeal continues to hold broad bipartisan support, and it is essential that no matter what next steps are taken, erasing this tax is part of the plan."

TAX REFORM OPPORTUNITY?

"We're going to have to think about other ways of accomplishing this … I'm sure there will be multiple opportunities," **Becton Dickinson & Co.** President and CEO Vince Forlenza, who just finished his two-year term as chairman of AdvaMed's board, told *Medtech Insight* in an interview just before the legislation was formally pulled.

Forlenza would not point specifically to other potential legislative vehicle options for device-tax repeal. But a fresh tax reform bill would provide one opportunity. In addition to Rep. Brady, President Trump and House Speaker Ryan signaled that tax reform would be on the near-term agenda. However, policy experts are questioning the prospect of the president and Congress being able to work together in the near-term to pass broad reforms after the health-care failure.

Patrick Hope, executive director of the Medical Imaging and Technology Alliance, pointed out that standalone device legislation has already captured, broad, bipartisan support.

"While we're disappointed the device tax repeal didn't move forward today, a bi-partisan bill to permanently repeal the tax currently has 248 co-sponsors in the House and 13 co-sponsors in the Senate,"

Hope said in a statement to *Medtech Insight*. "We look forward to working with our supporters in Congress on both sides of the aisle to move it forward."

Hope was referring to H.R. 184, the "Protect Medical Innovation Act of 2017," introduced by Rep. Erik Paulsen, R-Minn., Jan. 3 in the House; and companion legislation, S. 108, introduced by Sen. Orrin Hatch, R-Utah, on Jan. 12 in the Senate. *(Also see "As ACA 'Repeal-And-Replace' Plans Form, Some Senators Silent On Device Tax Repeal" - Medtech Insight, 9 Feb, 2017.)*

POLITICAL BLAME GAME

"Our [Republican] conference had disagreements, over how to proceed with Obamacare repeal and replacement," said Ryan in a press briefing after GOP leaders withdrew the bill from House consideration. While he added that all Republican House members agreed with repeal of the ACA, they could not agree on how to do it.

Ryan also blamed the more conservative members within the Republican fold, particularly members of the House Freedom Caucus, led by Rep. Mark Meadows, R-N.C. Caucus members could not agree to vote for the AHCA, even after more moderate Republican leaders agreed to remove a slate of federally mandated essential health care benefits from the bill that had displeased them.

Meanwhile, in public statements following the legislative failure, President Trump blamed the Democrats for not working with Republicans, and he suggested his plan for health care reform is to wait for the Affordable Care Act to "explode," providing an opportunity to work with the Democrats to fix it.

But House Democrats said that the AHCA failed on its own merits. "The bill went down, because the American people didn't like this bill," said House Minority Whip Steny Hoyer, D-Md., in a minority-led press briefing following the House debate and AHCA withdrawal. House Leader Nancy Pelosi agreed, noting, "The reason they lost was because the American people weighed in – all of our phone lines were deluged with calls."

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Combo Products Won't Get Special Review Pathway At US FDA Anytime Soon

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Shifting priorities at FDA means work on a specific review pathway for combination products has been superseded by implementation of the combo products provision in the 21st Century Cures Act, agency center directors said at a recent hearing in the Senate.

Testifying before the Senate Health, Education, Labor and Pensions (HELP) Committee on March 21, Device Center Director Jeffrey Shuren told Sen. Sheldon Whitehouse, D-R.I., that while FDA is "always open to other ideas to make the program work better," it is more concerned right now with putting the recently enacted Cures law into place. Janet Woodcock, director of FDA's drug evaluation center, concurred with Shuren.

The hearing was held to address reauthorization of FDA device and drug user-fee programs. *(Also see "Risks Of Missing Reauthorization Deadline Highlighted At User-Fee Hearing" - Medtech Insight, 21 Mar, 2017.)*

CURES PROVISIONS SHOULD RESOLVE COMBO PRODUCT DELAYS

The Cures act, signed into law in December, in the waning days of the Obama administration, included a combination products provision designed to streamline and hasten approval of these products. *(Also see "21st Century Cures: Device Provisions" - Medtech Insight, 1 Dec, 2016.)*

Requirements of the Cures provision include having the agency meet with combination product sponsors early on in the development process; clarifying the dispute resolution process when two product centers do not agree; and changing FDA's thinking about how "primary mode of action" is determined when designating a lead center to shepherd the product's application through to approval.

Shuren's comments at the Senate hearing came in response to a question from Whitehouse, who asked the witnesses whether they want Congress to establish a third pathway for combination products, distinct from the drug and device pathways.

"As long as there is no pressure for [Congress] to develop a third way right now, if [FDA] would rather work through [implementing the Cures legislation first], I think that is our understanding," Whitehouse said.

Committee Chairman Sen. Lamar Alexander, R-Tenn., agreed, noting that "being able to let you work through the best ways to do it before we jump to different pathway might be the more practical approach."

PRIMARY MODE OF ACTION

The Office of Combination Products assigns products to a specific lead review center based on the primary mode of action. Sponsors can inquire from FDA about how their product will be regulated through a formal, binding Request for Designation, or a more flexible, informal Pre-Request for Designation. *(Also see "Plan Carefully In Writing Combo Product Designation Requests, Experts Say" - Medtech Insight, 28 Dec, 2015.)*

The agency has historically had a bias toward assigning products to be regulated by the drug center, says Brian Boiani, an attorney with Epstein Becker and Green, most likely because device-regulated products have a less demanding regulatory pathway. *(Also see "Combination Product Designations At US FDA Need Faster Appeals, Petition Says" - Medtech Insight, 13 Mar, 2017.)* One of Boiani's clients filed a citizen petition with FDA March 3, stating that FDA's Office of Combination Products should set deadlines for appeals of designation decisions, in an effort to cut down on delays.

The 21st Century Cures Act combination device provision – which originated as a piece of separate legislation known as the Combination Product Regulatory Fairness Act, later added to Cures – also instructs that the agency be wary about designating a combo-product as a drug versus a device. *(Also see "Senate Bill Aimed At Streamlining Combo Product Regulation" - Medtech Insight, 20 Jul, 2015.)*

"In determining the primary mode of action of a combination product, the secretary shall not determine that the primary mode of action is that of a drug or biological product solely because the combination product has any chemical action within or on the human body," the Cures Act states.

A SHIFT FROM PRIOR THINKING

In June 2015, Shuren said that it may be time to consider a new pathway for combination products as a result of companies and FDA having frustrations with mismatches between drug and device regulations and with communication challenges between the product centers that lead to inefficiencies. *(Also see "Combo Product Reforms Are A Priority For Next User Fee Round, FDA Officials Say" - Medtech Insight, 24 Jun, 2015.)*

Former FDA Commissioner Robert Califf also expressed support for a third pathway for combination products during his confirmation hearing in November of 2015.

Califf said that the existing framework for combination products was not suitable, and that it is "a strong view at the FDA that we need another pathway that will give the FDA the flexibility to require the data that's needed to assure the public that the proposed treatment is safe and effective." *(Also see "Califf Supports Combo Products Pathway At Confirmation Hearing" - Medtech Insight, 17 Nov, 2015.)*

SHUREN TOUTS IMPROVEMENTS

FDA has faced multiple challenges in its review of combination products– including a lack of user fee goals and deadline coordination between review centers and inefficiencies with inter-center consultations. But Shuren told the senators that the agency has made recent improvements in the area.

He touted the creation of the cross-center Combination Product Policy Council, which has "been putting policies in place to help have much more coordinated activity."

"For example, the agency has already modified how we consult various centers," Shuren said. "We have time frames. … The early data on it is showing that it is helping."

The agency is also aiming to have its inter-center consult request (ICCR) process fully implemented by mid-2017, when it will apply to all combination product submissions. The pilot was initially launched in August 2016, and has the goal of facilitating "timely, appropriately tailored and well-informed submission review." *(Also see "Combo Product Safety: US FDA Rule On Post-Market Reporting Nears Finalization" - Medtech Insight, 5 Dec, 2016.)*

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Drug/Device Combinations: How To Harness Global Regulatory Efficiencies

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There is currently no such thing as the global harmonization of drug/device combination products, and in the view of Arkan Zwick, regulatory affairs director at Croma Pharma (Germany), there is not going to be harmonization for these products anytime soon.

With costs of meeting the regulations for these high-risk devices rising as requirements become more stringent throughout the world, what do companies need to know to be as quick, competitive and cost-effective as possible?

Medtech Insight tapped into Zwick's broad geographical expertise in this key and fast-growing market to find out how companies can make the best use of their resources. Read the transcript of the conversation below. Also see a table presented by Zwick in December at a Drug/Device Combination Products conference outlining the approach to high-risk device drug/device combination products (DDCPs) in different global markets.


Arkan Zwick

Given the different regulations that apply around the world to drug/device combinations, how difficult is it for companies to prepare for multi-market access with these products?

Zwick: For manufacturers unfamiliar with high-risk, class III products, DDCP projects are certainly demanding.

But for those device manufacturers experienced with class III devices, DDCPs do not add a significant level of complexity beyond the regular approval work based on the additional drug requirements.

Added to this, for those who are already EU or FDA compliant, these dossiers offer a good basis for registrations in the rest of the world. Indeed, those meeting EU and US requirements will also meet 90% of the regulatory requirements globally.

Also, in my view, it is important to screen regulatory requirements for the most important countries based on the company's market-penetration strategy at an early stage during the R&D phase of the DDCP.

This way, country-specific requirements are taken into account at an early stage in the design input of the product and confirmed during design verification and validation process.

Can you recommend a list of requirements that can be met to cover the basic principles of requirements globally, on which companies would then have to build to ensure that they meet the specific market's requirements?

Zwick: It is worth bearing in mind that DDCP requirements in Canada, Latin America, Asia Pacific are generally similar to the EU, while in China they are very different.

That said, if the manufacturer follows the Summary Technical Documentation (originally drafted by the Global Harmonization Task Force) for the medical device, and the globally recognized Common Technical Document (CTD) or the Certificate of Suitability European Pharmacopoeia (CEP) monographs for the drug part, then the company should be well prepared for every regulatory regime globally.

Ideally, during the development of a DDCP, you should select a supplier that is in compliance with the CTD/CEP requirements.

In most countries, it is sufficient to have the CEP and the raw materials information in the device file as the drug component will be seen as an integral part of the device application. However, there are countries that require the drug to be registered separately. If you have a CEP, they will accept this where mutual recognition is in place. If not, then the company will need to file the opening part of the CEP to get the drug substance approved.

The areas in which there are the main differences between countries are local clinical trial requirements and additional type-testing requirements (for example, in China) before clinical trials can be carried out.

In terms of meeting clinical requirements on a scale that goes beyond the EU, what would you recommend?

Zwick: Things are changing in Europe with the forthcoming adoption of the new Medical Devices Regulation, as well as the recently revised guidance document on clinical investigations, Meddev 2.7.1 rev 4. These close off the clinical equivalency route to class III devices and implants and so companies cannot avoid clinical trials with such products. On top of this, there are new scrutiny procedures that will impact DDCPs.

When it comes to beyond Europe, there may be ethical considerations, and some countries may not accept European data. They might require local population data.

So a company could go for clinical data in China and use this for registrations in other Asian countries or support safety and efficacy statements in the EU. But the regulatory bodies will be watching carefully to see if the local trial is really done to CGP and ISO 14155 requirements.

A couple of years ago, a clinical trial in China – which would not necessarily have been carried out according to ICH GCP [International Council for Harmonization Good Clinical Practices] requirements – would have led to market authorization. This is not the same approach as Europe and would not be accepted in the EU.

To use this data for other market approvals – even in other Asian countries like Japan – it is better to make sure that the trials are compliant with ISO 14155 and GCP. Otherwise there will be additional preparation and implementation time and costs to factor in.

Years ago, there were a lot of companies conducting trials in India or China – simply because the administrative burden was not so high. But the question arises of whether you can really use this clinical data for countries beyond.

But, as an additional observation, the requirements in these countries are also rising and our experience of GCP inspections in Asian countries show requirements are getting tougher.

So, in summary, having European data or US data that led to approvals in Europe or the US should be good in terms of clinical requirements for most other regulatory regimes. For example, US GCP data are particularly well accepted in Japan, Latin America and Asian countries, and EU data are widely accepted. But it is difficult the other way round – i.e., using Chinese or Indian data for approvals in the US or Europe.

Where does the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) fit in?

Zwick: Members of the ICH are the European Commission for the EU countries, the US FDA and the Japanese PMDA, as well as the Canadian and Swiss authorities. Together with these founding members there are regulatory members such as ANVISA Brazil, MFDS in Korea and additional observers and regional harmonization activities in Asia-Pacific, Middle East and Africa.

The ICH has the advantage of providing a common framework for the drug-related common technical document (so called CTD) that harmonizes the way quality, safety and ef-

ficacy information on drug substances is presented. Countries not part of the ICH might recognize CTD format; however, they might have their own structure to follow for the pharmaceutical component. This might add additional workload in the application process to restructure the needed information according to local regulatory requirements.

What other considerations are there? Are there any product or category-specific requirements that you are aware of in the markets you are familiar with for DDCPs?

Zwick: Yes, most of the regulatory regimes have product-specific guidelines that need to be taken into consideration for the safety and efficacy assessment of the products, including in the EU, US, Canada, LATAM countries, China or Japan. This is true for stand-alone medical devices as well as for DDCPs.

Identifying product specific requirements such as applicable harmonized standards for the EU, recognized/consensus standards for the US or Canada or testing-center standards in China is one of the first steps in the market authorization strategy. Together with the standards, there are often local guidelines to be met for the structure of the application documents and guidelines for the preparation of the safety and efficacy documentation.

When it comes to applying to various markets, where is the best place to start?

Zwick: During the start of the regulatory project, the first question we look at after classification is always whether there are specific product-related guidelines that need to be addressed.

We try to take these into consideration at the design input, and in the R&D stage, so that what we develop for the European market is also compliant with the main regulatory countries outside the EU.

As an EU based company, our strategy is to always start with the EU requirements, and then to deal with the lighter countries linked with the EU that accept CE marking next, for example Switzerland, Turkey, the Middle East, and Canada.

Australia is also linked but processes are lengthier so is not in the first wave in terms of accessibility time-wise. In terms of time, approvals take a similar time to those in Latin America and other Asia Pacific countries.

The last wave in our strategy are the heaviest regulated countries such as China, the US and Japan. These tend to be longer projects as they require a full range of separate preparations, clinical trials, type testing etc.

Can you be more specific about the time it takes to get products through the regulatory requirements in the different markets?

Zwick: In terms of timing to get products on the market, it takes about 12-18 months for the EU and those light access countries that accept CE marking, such as the Middle East and North Africa, and also including Canada and Russia.

When it comes to Latin America, and Asia Pacific, including Australia, it takes some 18-24 months.

But we would factor in over 36 months when approaching markets that require local testing and clinical trials, such as the US, Japan and Canada.

Are there any concrete plans for having a single approach globally to DDCP?

Zwick: No, not globally. There are the ICH requirements for harmonization cited above, and the Asian group of countries are trying to make common requirements, but there is nothing on the global stage covering both device and drug products.

In my view, the US will always be different from the EU, and the Latin American countries will always be separate from the Middle East. The Asian Pacific countries will always have their own regime, as will China and Russia. The only basis towards global harmonization are countries that accept the STED and the CTD/CEP format as discussed at the beginning of this interview.

Published online 03/22/17

Device-Type Combination Products: Country-By-Country Guide

	AUSTRALIA	BRAZIL	CANADA	INDIA	RUSSIA	CHINA	TAIWAN	KOREA
QMS/GMP requirements	Yes	Yes	Yes	No	No	No	Yes	Yes
Clinical trial literature data acceptance	Yes	Yes	Yes	Yes	Yes	No	No	No
Separate drug approval needed	Yes	No	Yes	No	No	No	Yes	Yes
Testing of finished product	No	(Yes)	No	No	Yes	Yes	No	No
Translations	No	Yes	No	No	Yes	Yes	No	No
Local MAH required	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
CE marking as a basis	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes

Source: Arkan Zwick, Knect 365 Drug/Device Combination Products meeting, December 2016, Berlin

ACC 2017:

Disappointing Absorb Results Blamed On Implant Approach

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This **Abbott Laboratories Inc.** got more disappointing news about its *Absorb GT1 BVS* bioabsorbable stent from the two-year results of the ABSORB III trial.

ABSORB III is a randomized, 2,008-patient trial comparing Absorb to Abbott's *Xience* cobalt-chromium drug-eluting stent for treatment of noncomplex coronary lesions. The one-year results showed Absorb was non-inferior to Xience for the composite endpoint of target-lesion failure (cardiac death, target vessel myocardial infarction, and ischemia-driven target vessel revascularization) – 7.8% vs. 6.1%. Absorb was also non-inferior to Xience at one-year for each of the component endpoints in the composite. These results helped Absorb earn FDA-approval in July 2016. *(Also see "Abbott's Absorb GT1 Is First FDA-Approved Absorbable Coronary Stent" - Medtech Insight, 7 Jul, 2016.)*

But in the two-year results, presented by Stephen Ellis from the Cleveland Clinic at the American College of Cardiology Scientific Session in Washington, DC on March 18, Xience is statistically superior to Absorb for the primary composite endpoint as well as target-vessel myocardial infarction.

At two-years, the target-lesion failure rates for Absorb and Xience in ABSORB III were 11.0% and 7.9%, respectively (p = 0.03). The target-vessel myocardial infarction rates were 7.3% and 4.9% (p = 0.04). The two-year results also showed some statistically non-significant trends in Xience's favor: the ischemia-driven target-vessel revascularization rates were 5.3% and 4.3% for Absorb and Xience, respectively, and the device thrombosis rates were 1.9% and 0.8%, respectively.

In the year between the end of year-one and year-two of follow-up, the changes in outcomes were not statistically similar between the Xience and Absorb groups, Abbott points out in a press release. During this period, target vessel failure rates were 3.7% for Absorb and 2.5% for Xience, cardiac death rates were 0.5% and 0.4%, target vessel myocardial infarction rates were 1.3% and 0.7%, ischemia-driven target vessel revascularization were 2.6% and 1.8%, and the device thrombosis rates were 0.3% and 0%.

Nevertheless, the US FDA sent physicians a "Dear Doctor" letter highlighting the 11% target-lesion failure rate, which the agency refers to as the major adverse cardiac event rate. The agency also points out the difference in thrombosis rates. "The FDA is working with Abbott Vascular, Inc. to conduct additional analyses to better understand the cause(s) of the higher cardiac event and device thrombosis rates in patients treated with BVS compared to the XIENCE stent," the letter explains.

This is not the first set-back for Absorb. The company and investigators hope that by slowly dissolving instead of leaving a permanent metal implant, Absorb will avoid some of the long-term risks associated with metal stents, but this has not been shown yet. In October 2016, three-year follow-up from the ABSORB II trial did not show that Absorb improved vasomotor reactivity or late-lumen loss compared to Xience. *(Also see "TCT 2016: Three-Year ABSORB II Data Fail To Show The Hoped-For Long-Term Benefit Of Bioresorbable Stent" - Medtech Insight, 31 Oct, 2016.)*

In a March 20 analyst note, Wells Fargo's Larry Biegelsen writes "Based on our conversations with clinicians, we expect the use of Absorb to significantly decline due to the FDA latter and ABSORB III data." Biegelsen expects Abbott will capture most of the lost Absorb sales because its Xience is so popular, so the impact on Abbott's bottom line will be minimal in the short-term, but "it's unclear at this point what Abbott's future DES strategy will be and how the company will eventually replace its Xience DES," he concludes.

RIGHT TECHNIQUE, RIGHT PATIENTS

During his presentation at ACC, Ellis pointed out that ABSORB III's pre-specified eligibility criteria included lesions with reference diameter from 2.5 mm to 3.75 mm by visual estimation. However, despite this rule, about 19% of the patients in the trial were treated for lesions with a reference vessel diameter under 2.25 mm as measured by quantitative coronary angiography and that post-hoc analysis of the results who that these smaller vessels are associated with an increased risk of target-vessel failure. Excluding these patients, the two-year target vessel failure rates were 9.4% for Absorb and 7.0% for Xience, a statistically non-significant difference.

The FDA-approved indication for Absorb only includes coronary lesions with a reference vessel diameter of 2.5 mm to 3.75 mm and the company has updated the instructions for use with specific guidance to avoid using it in narrower vessels.

Ellis also stressed that the implantation technique for Absorb has evolved in recent years and that there is a "growing body of evidence" from the ABSORB clinical trials and registries showing that optimal implantation techniques makes an important difference in patient outcomes. The FDA highlights this observation in its Dear Doctor letter: "An additional preliminary analysis of ABSORB III data suggests improved clinical performance and a lower rate of complications associated with BVS implantation when health care providers follow the recommended implantation methods."

The investigators have dubbed the optimal implant technique for Absorb "PSP," which includes pre-dilatation, appropriate vessel sizing, and high-pressure post-dilatation.

The investigator's analysis of the ABSORB III data confirms that PSP was often not followed in the cases of very-late stent thrombosis in patients treated with Absorb. It also shows that the target-vessel failure rate of patients treated with Absorb implanted with the PSP approach was 8.7%, versus 11.4% for Absorb patients treated without PSP, and 8.2% for all the patients treated with Xience. The rates of definite or probable stent-thrombosis were 1.1% in Absorb patients treated with PSP, 2.0% in Absorb patients treated without PSP, and 0.8% in patients treated with Xience.

Early results from ABSORB IV trial, which the company calls a "continuation" of ABSORB III, suggests PSP improves outcomes. Ellis showed that only 4% of the 2,546 patients in ABSORB IV have are being treated for a lesion with a reference vessel diameter under 2.25 mm and that post-dilatation of Absorb has been performed in 84% of cases, versus just 66% of cases in ABSORB III. So far the 30-day stent-thrombosis rate is 0.4% and the one-year rate is 0.5%, less than half the rates seen in ABSORB III.

"Longer-term data from the ABSORB III/IV program will determine whether better patient selection and technique improve short-term outcomes, and whether Absorb improves late outcomes compared to Xience," he concluded.

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ACC 2017:

Double-Whammy Trial Data Boost For Philips' iFR

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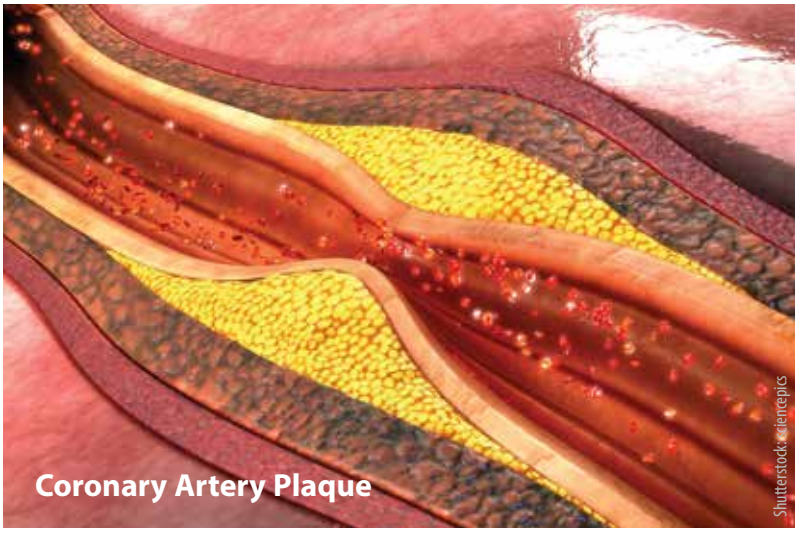
Philips Volcano's *iFR* (instantaneous wave-free ratio) is non-inferior to fractional flow reserve as a tool for guiding coronary revascularization, according to the results of two separate clinical trials totaling 4,529 patients.

iFR is Philips Volcano's proprietary technology for measuring the differential across a coronary lesion with a pressure-wire during the wave-free period of the heartbeat. It can assess lesion significance in about five heartbeats and, unlike fractional flow reserve (FFR) measurement, it does not require the induction of hyperemia with an intravenous or intracoronary vasodilator like adenosine. The US FDA cleared Volcano's 510(k) application for iFR in 2014, a few months before Philips bought Volcano for about $1bn. *(Also see "Philips splashes $1bn on Volcano" - Medtech Insight, 17 Dec, 2014.)*

Justin Davies of Imperial College London presented one-year of results from the DEFINE-FLAIR trial at as a late-breaking clinical trial at the American College of Cardiology Scientific Session in Washington, DC on March 18. During the same session, Matthias Götberg of Lund University in Sweden, presented one-year results from iFR SWEDEHEART trials.

Results of both trials, sponsored by Philips Volcano, were simultaneously published in the *New England Journal of Medicine*. Davies and colleagues point out that the results are similar to those reported by Götberg and colleagues, and vice-versa.

"The outcomes of these clinical studies underpin the value of iFR and its benefits for patient safety and effective diagnoses," Christopher Barys, Business Leader at Philips Volcano said in a release. "It is our hope that the results advance the adoption of iFR to help physicians improve patient care. This is one of the largest coronary physiologic datasets ever collected and truly demonstrates the value of iFR in the physiological assessment of coronary artery disease in patients."



In an accompanying editorial in *NEJM*, Deepak Bhatt of Brigham and Women's Hospital argues that iFR could help guide decisions about PCI "more rationally." He hopes that a noninvasive method to provide simultaneous anatomical and physiological assessment of coronary lesions will eventually supplant the need for invasive angiography, but "there will always be patients in the catheterization laboratory who have a coronary stenosis of intermediate severity on angiography. FFR has been the evidence-based standard for invasive evaluation of such lesions, but it now appears that iFR may be the new standard."

DEFINE-FLAIR FINDS SIMILAR OUTCOMES, FEWER ADVERSE EVENTS WITH IFR

DEFINE-FLAIR (Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularisation) randomized 2,492 patients with coronary artery disease to coronary revascularization guided by either iFR or FFR using a Philips Volcano coronary-pressure guidewire. The trial included investigators from 16 countries around the world, including the US.

In every patient, the treating physicians investigated all vessels with "questionable stenosis severity" with FFR or iFR, but in patients with an acute coronary syndrome, the nonculprit vessels were assessed after the culprit lesion had been revascularized. The prespecified treatment thresholds were an FFR of 0.80 and an iFR of 0.89 and when the FFR or iFR for a given stenosis was equal to or lower than the prespecified threshold, the stenosis was revascularized either with a drug-eluting stent coronary-artery bypass graft surgery. When the FFR or iFR was higher than the prespecified threshold, treatment of that vessel was deferred. If multivessel revascularization was necessary, the investigators could choose a staged treatment strategy, to be completed within 60 days.

The median procedure time was significantly shorter in the iFR group than in the FFR group – 40.5 minutes vs. 45.0 minutes.

At one year 78 of the 1,148 patients in the iFR group died, suffered a nonfatal myocardial infarction, or needed an unplanned revascularization procedure while 83 of 1,182 patients (7.0%) in the FFR group experienced one of those adverse events, so the trial met the non-inferiority threshold for the primary endpoint and the risks of each individual component of the primary endpoint, as well as the risk of death from cardiovascular or noncardiovascular causes, were statistically similar in both groups.

"These results suggest that the benefits of physiologically guided coronary revascularization with FFR can also be achieved with iFR," Davies et al. conclude. "It has previously been proposed that a hybrid iFR–FFR approach might be advantageous for the detection of functionally significant stenoses, with iFR used as the initial measure and FFR used only to evaluate stenoses that were of intermediate severity on iFR-guided assessment. However, the results of our trial suggest that iFR alone can effectively identify stenoses that require intervention."

The authors point out that if iFR is as effective as FFR, there is no good reason for administration of a hyperemic agent – the need for the hyperemic agent is one of the reasons the adoption of FFR has generally lagged in the last decade even as evidence supporting FFR-guided coronary revascularization has mounted.

In DEFINE-FLAIR 3.1% of patients in the iFR group reported symptoms during the procedure, such as chest pain or dypnea while 30.8% of the FFR group reported such symptoms, a significant difference. Also, there were eight serious adverse events, including broncospasm and ventricular arrhythmia, in the FFR group versus one event in the iFR group. The authors believe the difference in these events was a side-effect of the adenosine administered in the FFR group, which may have also allowed some of the FFR patients to correctly guess they had been randomized to the FFR group. "Such unblinding could have led to bias in the rates of unplanned revascularization, especially if patients discussed these symptoms with their physicians," the authors concede.

"Although adenosine is a generally safe drug that is used in millions of diagnostic procedures annually, its risks are well documented and it is not suitable for every patient; therefore, avoiding the use of adenosine is preferable," Davies et al. explain. "In addition, adenosine contributes substantially to the cost of physiological stenosis assessment, and its use is hampered in many countries because it is unavailable or not indicated for this purpose. Thus, the ability to perform physiological assessments of coronary-artery stenoses without the use of adenosine may increase the use of such assessments in clinical practice."

The authors point out that if iFR is as effective as FFR, there is no good reason for administration of a hyperemic agent. The need for the hyperemic agent is one of the reasons the adoption of FFR has generally lagged in the last decade even as evidence supporting FFR-guided coronary revascularization has mounted.

Interventionalist Ajay Kirtane from Columbia University, who was not involved in either of these iFR studies told *Medtech Insight* "These studies are very important, and demonstrate similar clinical outcomes to what had heretofore been the 'gold standard' - FFR. Especially because these were clinical studies, this suggests that iFR can be used to appropriately triage patients for revascularization.

"Especially for labs who don't do a lot of FFR, this is a very big deal. Adenosine definitely takes time and effort. The side effects can be dealt with, but from a throughput standpoint, I think this will represent a far greater time savings than the nearly five minutes it took in the studies," Kirtane said. "The fact that these trials focused upon intermediate lesions is a strength, because those are exactly the lesions for which physiologic guidance is most needed."

IFR SWEDEHEART CONFIRMS RESULTS IN SCANDINAVIA

The iFR SWEDEHEART trial enrolled 2,037 patients with either stable angina or an acute coronary syndrome at 13 hospitals in Sweden, one in Denmark, and one in Iceland. The trial relied upon the respective country's comprehensive national registries for patient data collection, randomization, and follow-up.

As in DEFINE-FLAIR, the patients were randomized to revascularization guided by either iFR or FFR and the endpoint was a composite of death, nonfatal myocardial infarction, or unplanned revascularization within a year of whichever procedure the patients underwent, CABG surgery or PCI with a drug-eluting stent.

In the iFR group, 68 of the 1,012 (6.7%) patients died, suffered an MI, or needed an unplanned revascularization within a year, compared to 61 of the 1,007 patients (6.1%) in the FFR group, demonstrating statistical noninferiority. The results were similar among major subgroups and the rates of myocardial infarction, target-lesion revascularization, restenosis, and stent thrombosis were about the same in both groups.

However, only 3% of patients in the iFR group reported chest discomfort during the procedure compared to 68.3% of the patients in the FFR group.

"On the basis of the findings observed in our study, iFR, which allows for lesion assessment without the use of adenosine, has the potential to increase the use of physiologically guided assessment among patients with coronary artery disease, the majority of whom still undergo angiographic assessment of lesion severity," the authors point out.

Götberg et al. found that more coronary lesions were assessed in the iFR group than in the FFR group. "It is possible that the adenosine-related chest discomfort that occurred when FFR measurements were obtained made the treating physicians less inclined to investigate additional lesions in patients with multivessel disease," they speculate. "This suggests that adherence to the protocol in the FFR group was suboptimal owing to the expected side effects of adenosine."

Although the iFR approach led to investigation of more lesions, the FFR strategy yielded significantly more lesions appearing to be "hemodynamically important," and therefore FFR was slightly more likely to lead to stenting the vessel. "Disagreement between the methods has usually been found to occur when the stenosis severity is in the intermediate range, close to the threshold, [but] This variation is unlikely to have an important effect on clinical outcomes, since observed rates of death and myocardial infarction are low in patient populations with FFR values close to the threshold of 0.80." They also point out that previous research has shown that, when iFR and FFR classify a lesion differently, iFR is usually more accurate and that FFR is more likely to overestimate lesion severity than iFR, most likely because the drug-induced hyperemia drops the blood-pressure in the vessel below the FFR threshold of 0.80 in some vessels even when coronary flow is actually normal.

Götberg et al. point out that including patients revascularized with CABG, as was permitted in both DEFINE-FLAIR and iFR-SWEDEHEART FFR may be a limitation of the studies because the clinical data on CABG guided by FFR is limited. Also, IFR-SWEDEHEART let the treating physicians and the patients know their randomized group assignment, which could potentially have influenced the decision to perform unplanned revascularization.

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ACC 2017:

Trial Shows FFR-Guidance Can Help Heart Attack Patients Avoid More Revascularizations

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Results from the Compare-Acute trial show that using fractional flow reserve measurements to guide complete revascularization of all the coronary arteries while treating a lesion causing an ST-segment elevation myocardial infarction (STEMI) can reduce patients' risk of needing another revascularization.

Primary investigator Pieter Smits, Maasstad Hospital in Rotterdam, presented the one-year Compare-Acute results at the American College of Cardiology meeting in Washington, DC, on March 18 and they were simultaneously published online by the *New England Journal of Medicine*.

"Although FFR-guided PCI is increasingly used in patients with stable angina, it has not been frequently used in patients with an acute coronary syndrome, mainly owing to concerns that disturbed microvascular function in the early stage of acute myocardial infarction might affect the reliability of the technique," the authors explain in *NEJM*. "However, the evidence supports the reliability of FFR assessment of non–infarct-related coronary arteries in this context. The use of an FFR-guided strategy for complete revascularization during STEMI has the potential to substantially decrease the number of unnecessary interventions during primary PCI and the number of subsequent revascularizations."

> New trials powered for "hard" end points like recurrent myocardial infarction or cardiovascular mortality are needed, says Lars Køber, University of Copenhagen

Percutaneous coronary intervention (PCI) with stents is well-established as the best approach to treating acute STEMI, but about half of these patients also have severe stenotic lesions in coronaries other than the one that caused the infarct, according to Smits.

FFR is the ratio of maximal blood flow in a diseased arteries compared to normal flow and is usually measured with a pressure-wire instrument inserted into the coronary with a catheter. It provides a more accurate assessment of the severity of a coronary lesion than regular angiography, which just shows the

shape and size of the vessel's lumen. Results of the FAME II trial, sponsored by**St. Jude Medical Inc.**, showed that FFR-guided PCI reduced the need for urgent revascularizations in patients with stable coronary disease and functionally significant stenosis. *(Also see "St. Jude's FAME II FFR Study Successful, But Impact Is Debated" - Medtech Insight, 3 Sep, 2012.)* And results from the DANAMI-3–PRIMULTI randomized trial of STEMI treatments showed that a staged, complete revascularization strategy guided by FFR resulted in fewer repeat revascularizations than treating only the infarct-related coronary artery.

TESTING ACUTE-SETTING FFR

So Smits and colleagues created the Compare-Acute trial to examine whether treating STEMI/multivessel-disease patients with FFR-guided complete revascularization in the acute setting – rather than a staged approach – would yield better outcomes than treating the infarct-related artery only. The trial was sponsored by the Maastad Cardiovascular Research Organization, as well as **Abbott Laboratories Inc.** and St. Jude.

The trial enrolled 885 patients who were treated with PCI for a STEMI and multivessel disease and randomized 295 of the patients to also undergo revascularization of non-infarct-related coronary arteries guided by fractional flow reserve. In the other 590 patients, only the coronary lesion that caused the infarction was treated. Both groups of patients underwent the FFR procedure, but the patients and the treating physician were only aware of the FFR results if the patients were in the group randomized to FFR-guided complete revascularization. The trial's primary end point was a composite of death from any cause, non-fatal myocardial infarction, revascularization, and cerebrovascular events at 12 months.

In the complete-revascularization group, 54.1% had one or more lesions in the non-infarct-related coronary arteries, with an FFR of 0.80 or less – indicating a physiologically significant blockage – and therefore underwent PCI to treat these lesions. Another five patients had PCI to treat non-infarct-related coronary artery lesions that were not based on FFR values. Of these 163 patients, 136 were treated with additional PCIs during the primary PCI while the remainder of these patients had staged, in-hospital PCI.

In the infarct-artery-only group, 47.8% had one or more lesions in the non-infarct-related coronary arteries with an FFR 0.80 or less; however, all but one of these patients were initially treated conservatively without additional PCIs during that procedure. However, 59 of these patients underwent staged elective revascularizations within 45 days after the initial PCI, and 44 of these patients had one or more non-infarct-related coronary artery lesions with an FFR of 0.80 or less.

The primary outcome occurred in 23 patients in the complete-revascularization group and in 121 patients in the infarct-artery-only group (eight events per 100 patients vs 21 events per 100 patients). Four patients in the FFR-guided-complete-revascularization group died while 10 patients the infarct-artery-only group died, and seven of the complete-revascularization group suffered a later myocardial infarction versus 28 in the group treated more conservatively. By far the biggest difference was in the need for another revascularization procedure –18 vs 103 patients (6.1% vs. 17.5%) in the complete-revascularization and infarct-only groups. There were two FFR-related serious adverse events in the group receiving infarct-related treatment only.

WHO SHOULD UNDERGO FFR?

FFR-guided complete revascularization "appears to be safe, but it may not be necessary in all patients," Lars Køber of the University of Copenhagen argues in an accompanying NEJM editorial. He points out that, as in DANAMI-3–PRIMULTI, only one-third of the repeat revascularizations were the result of acute coronary syndrome, so it is unclear whether all of the repeat revascularizations were strictly necessary and how these procedures may have influenced the trial's outcome.

The treatment allocation and angiographic results were known by the treating physicians, he points out, and "the observation that patients with FFR-negative nonculprit stenoses in the complete-revascularization group had fewer events than patients with FFR-negative nonculprit stenoses in the infarct-artery-only group suggests that knowledge that the patient had not undergone complete revascularization may have triggered earlier repeat revascularization in the infarct-artery-only group."

Because the cardiovascular benefits of FFR in Compare-Acute were driven almost entirely by the reduction in revascularizations, new trials powered for "hard" end points like recurrent myocardial infarction or cardiovascular mortality will be needed to determine the real clinical impact of an FFR-guided complete-revascularization strategy and to identify the subgroups of patients most likely to benefit from this strategy, Køber concludes.

He notes that a the COMPLETE trial, sponsored by the Population Health Research Institute, is currently enrolling 3,900 patients to determine whether complete revascularization at the time of primary PCI and optimal medical therapy or infarct-only PCI with optimal medical therapy is the better strategy for treating patients suffering an acute MI with multivessel disease.

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Acarix's Handheld CAD Device Proves Its Mettle As Frontline Test

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A handheld device, designed to use acoustic signals to identify obstructed blood vessels noninvasively, could be used as a frontline test for ruling out coronary artery disease in suspicious cases. Results from a multi-center trial, conducted by Scandinavian device maker **Acarix.** has shown that the company's *CADScor System* rules out CAD with a 97% negative predictive value.

The all-in-one CADScor system consists of a disposable adhesive patch and sensor with microphones and a touch display. It detects turbulent arterial flow and myocardial movement to provide a patient specific CAD-score in less than 10 minutes. It first received CE marking in August 2015.

Results from the trial were first presented at this year's annual American College of Cardiology meeting held in Washington, DC, on Mar. 17-19, and confirmed earlier preliminary trial data. The study involved 1,675 patients from two Danish hospitals with a low- to intermediate-likelihood of CAD and who were referred for coronary computed tomography angiography (CCTA). Most patients referred for CCTA do not have CAD and only approximately 20–30 % of patients are subsequently referred for further testing by invasive coronary angiography (ICA) or non-invasive perfusion evaluation due to suspected obstructive CAD.

A CAD-score was recorded in all 1,675 patients enrolled in the trial, with the CAD-score algorithm including both acoustic features and clinical risk factors (gender, age and hypertension). Low risk was indicated by a CAD-score value less or equal to 20. The algorithm CAD-score version 3 was developed using recordings from 711 patients from previous studies and a training cohort of 589 patients from the present study. The remaining 1086 patients were used as the validation cohort. The CAD-score was successfully analyzed in 1464 (87%) patients. Hemodynamic significant CAD was present in 134 (9.3%) patients. Data showed there were no differences in the performance of the CAD-score algorithm in the training versus validation cohorts.

Acarix believe the positive results from the trial could validate the possibility of CADScor's use as a frontline test to reduce patient waiting times, as well as improving triaging of patients who really need more expensive and invasive diagnostic modalities. In a statement, CEO Søren Rysholt Christiansen said: "Coronary artery disease affects more than 120 million people worldwide but the current diagnostic pathway, which can rapidly escalate to expensive imaging and coronary angiography, is inefficient. For example, a recent Danish study showed that more than 90% of patients presenting with chest pain symptoms to their general practitioner do not have CAD. If adopted, the CADScor System can provide rapid frontline assessment which could translate into a potential reduction in patient referrals by approximately 50%. – a win-win for patients, payers and physicians."

Shutterstock: Africa Studio

In November 2016, Acarix received a cash boost from new Chinese investors Puhua Jingxin Guzhou Health Management Partnership to accelerate the commercial launch of CADScor. *(Also see "Acarix's CADScor Attracts Chinese Investment" - Medtech Insight, 6 Nov, 2016.)*.

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CONTINUED FROM PAGE 1

representing 36.1% of the global foam dressings market. By comparison, S&N's foam dressing sales reached about $354m in 2015, accounting for a 35.5% share in the same market segment. (See Figure 2.)

In an effort to bolster its *Allevyn* line of products, S&N acquired the rights to Germany-based **Beiersdorf AG**'s *Cutinova* advanced wound-care product line for integration into its Allevyn product line. *(Also see "Smith & Nephew Buys Wound Care Line, Looks To Streamline Operations" - Medtech Insight, 3 Jul, 2000.)* This allowed S&N to develop an extensive product offering, including the *Allevyn Plus Cavity*, a cavity wound dressing with a unique 3-D shape, and the *Allevyn Tracheostomy*, which features a keyhole opening that allows the dressing to fit securely around a tracheostomy tube, or other drain or stoma.

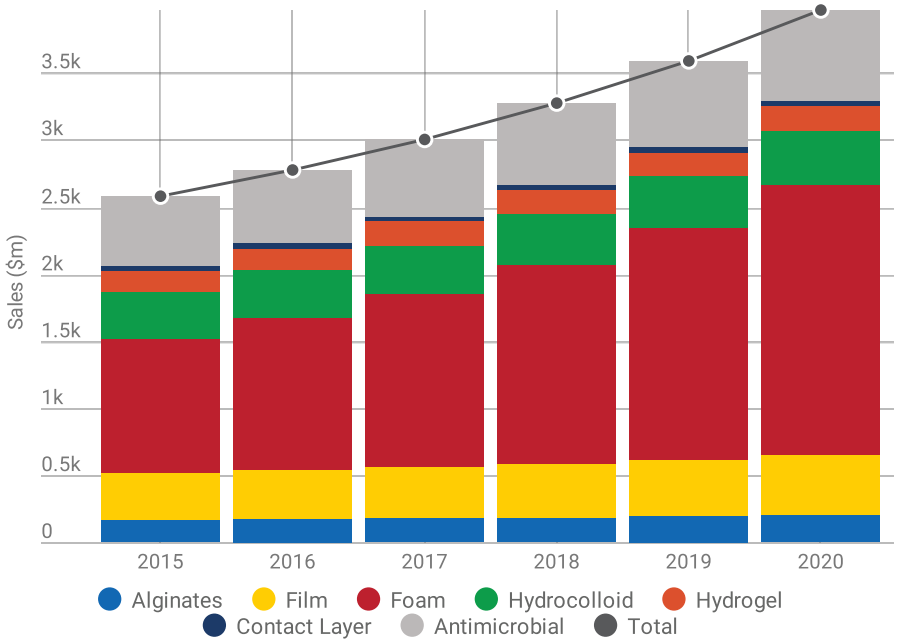
In addition, S&N offers *Allevyn Life*, a next-generation silicone foam dressing with a quadrilobe shape and multilayer design for cushioning, masking and dressing change indication. Allevyn Life showed positive results in two studies reported in the last two years. In a UK trial, the dressing allowed home-care nurse visits to be reduced from three to one per week; another trial in the US showed that intensive-care setting use of the product resulted in a 69% reduction in hospital-acquired pressure ulcers, according to *Meddevicetracker*.

Ranking third in the 2015 global foam dressings market was Forth Worth, Texas-based **Ferris Manufacturing Corp**. The company generated $137.6m in foam wound dressings revenue that year, capturing a 13.8% market share. Ferris competes in this market segment with its popular *PolyMem* dressing, which consists of a polyurethane foam membrane matrix that contains a cleanser, a moisturizer, and an absorbent starch copolymer, eliminating the need for a separate cleanser or debrider. PolyMem is a less costly alternative to other types of dressings, particularly in the non-acute care market, in which PolyMem has been shown to require fewer dressing changes in less time.

In 2015, another Texas company, San Antonio-based **Acelity LP Inc.** (formerly Kinetic Concepts), was the fourth-leading

FIGURE 1

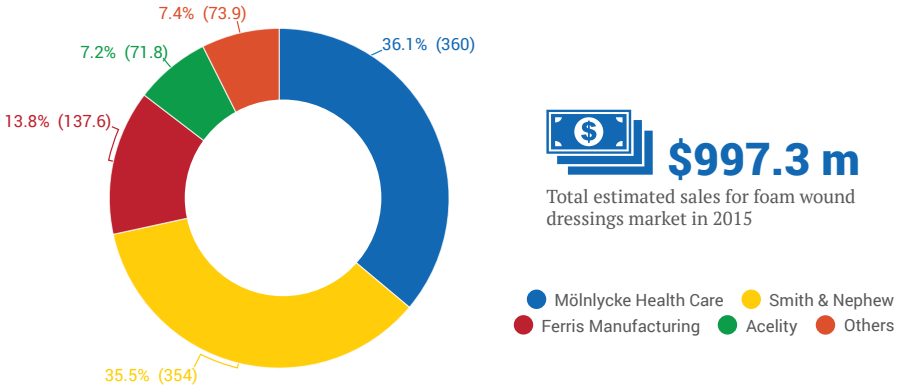
Advanced Wound Dressings Market Forecast, 2015-2020



Source: "Advanced Wound Care Products Market," Meddevicetracker

FIGURE 2

Foam Wound Dressings Market Share, By Supplier, 2015



Source: "Advanced Wound Care Products Market," Meddevicetracker

supplier of foam wound dressings with about $71.8m in sales and a 7.2% market share. The company competes primarily with its *Tielle* line of products, which has been known for its adhesive, conformability and handling properties.

Other competitors, including **3M Co.**, **Bio Med Sciences Inc.**, **Coloplast AS**, **ConvaTec Inc./ Nordic Capital** and Avista Capital Partners, **DeRoyal Industries Inc.**, **GentellCorp.**, **Medtronic PLC/ Medtronic Minimally Invasive Therapies**, and **Mylan**, among others, accounted for $73.9m in sales in 2015 and a 7.4% market share.

FOAM DRESSINGS INNOVATION TO DRIVE GROWTH

The foam dressings market has experienced significant growth and innovation in the last few years. What started as simple foam products have evolved into sophisticated, conformable dressings with film

A Whirlwind Tour Of The Advanced Wound-Care Market

- Product innovation and robust growth have intensified in the US advanced wound-care products market in recent years; however, similar growth patterns have yet to be realized in other geographic regions.
- The US accounts for more than half of the advanced wound-care products market as a whole, but accounts for more than 70% of negative-pressure wound therapy (NPWT), and more than 90% of tissue-engineered skin replacements/substitutes.
- The combined global market for advanced wound-care products totaled more than $7.6bn in 2015, and is expected to climb at a CAGR of 6.4% over the forecast period, reaching more than $10.4bn by 2020.
- Advanced wound dressings are experiencing particularly dynamic growth, driven by increased use of foam dressings. This market is expected to increase from $2.6bn in 2015 to nearly $4bn in 2020, a CAGR of 9%.
- In the biologics segment, amniotic tissue grafts are a fast-growing technology, with positive clinical outcomes and the rapid introduction of new technology driving market growth.

backings and adhesive layers. These more advanced products are especially useful in treating difficult wounds in home healthcare settings and alternate site locations.

More recently, manufacturers also introduced foam "island" dressings for the fixation of wound border areas and conformable dressings for specific body parts, such as the heel and sacrum.

Today's advanced foam dressings offer many benefits, including absorptive capabilities for heavily exuding wounds, lack of dressing debris and reduced dressing changes at a moderate cost. Manufacturers' successful marketing efforts to highlight the advantages of foam dressings over hydrocolloids and other dressing types – such as greater absorption and more appropriate use in patients with diabetes, who are particularly susceptible to the development of skin ulcers on the extremities due to neuropathy – have all helped win over practitioners.

Meddevicetracker expects that continued innovation, such as foam dressings with expanded capabilities, will not only drive growth in this market segment, but also take away market share from the hydrocolloid wound-dressings market.

These factors, coupled with positive clinical outcomes, will keep the foam-dressings market competitive, particularly in the current cost-conscious health-care spending environment. Pricing pressures are expected to mitigate greater growth, particularly outside the US.

TISSUE-ENGINEERED SKIN REPLACEMENT/ SUBSTITUTES MARKET

In 2015, the tissue-engineered skin replacements/substitutes market totaled about $725.8m, and *Meddevicetracker* forecasts that this market segment will rise to an estimated $991.9m by 2020, a CAGR of 6.4%.

US sales accounted for a whopping 93.5% of skin-replacement revenues, followed by European sales, accounting for 4.7%, and countries outside of the US and Europe accounting for a mere 1.8% of sales. According to *Meddevicetracker*, US sales of tissue-engineered products will climb from $678.4m in 2015 to $933.8m by 2020, a CAGR of 6.6%; in Europe, sales in this market reached $34.2m in 2015 and are expected to increase to $42.6m by 2020, a CAGR of 4.5%; in the emerging markets, sales of tissue-engineered products are expected to rise from $13.2m in 2015 to $15.5m, a CAGR of 3.2%.

Multiple factors contribute to the slow adoption of regeneration technologies outside the US. Among the biggest challenges for wider adoption, both in Europe and in the emerging markets, is the cultural aversion to using cadaveric tissue, as well as concerns surrounding disease transmission, and also limited reimbursement.

Figure 3 offers a more detailed market forecast (2015-2020) for tissue-engineered skin replacement/substitutes, which have a broad range of indications, from cosmetic and reconstructive surgery to future introductions of tissue-engineered skin replacement/substitute products for use in wound healing. Tissue-engineered skin replacements/substitutes consist of dermal- and amniotic-derived products, and do not include synthetic or tissue-engineered interactive dressings.

KEY PLAYERS IN SKIN REPLACEMENT/SUBSTITUTES

With its 22-year history, Acelity's *AlloDerm Regenerative Tissue Matrix* has created a loyal following among surgeons, and established itself as the market leader with a 35.1% share and $254.9m in sales in 2015, according to *Meddevicetracker*.

Behind AlloDerm's success is long-standing clinical use and a wide range of indications for its products, including in burn patients, and general surgical, periodontal, and plastic reconstructive procedures, as well as expanded indications in areas such as hernia repair.

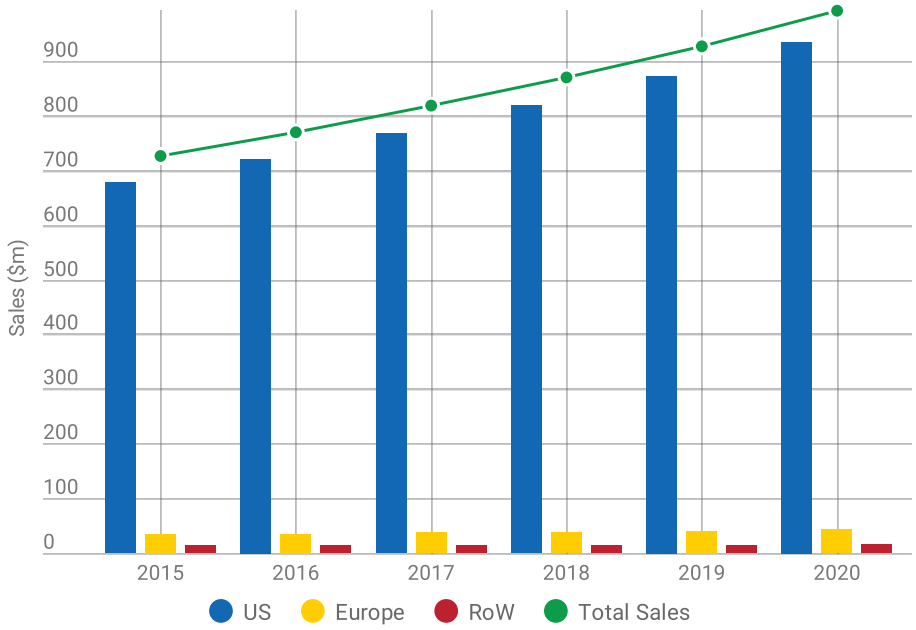
Acelity's management has made some shrewd marketing decisions to further expand indications for its acellular dermal technology. Among them was the creation of a marketing alliance for an orthopedic/wound management version of its technology, *GraftJacket*, with medical device company **Wright Medical Technology Inc.**

In 2015, these combined efforts led the two companies to achieve GraftJacket sales of about $65.2m and a 9% share of the global skin replacements/substitutes market, putting Acelity/Wright Medical Technology in fourth place in this market segment, according to *Meddevicetracker*.

Canton, Mass.-based regenerative medicine company **Organogenesis Inc.** ranked a distant second with a 21.4% market share and about $155.2m in revenue in

FIGURE 3

Tissue-Engineered Skin Replacements And Substitutes, Market Forecast, 2015-2020



Source: "Advanced Wound Care Products Market," Meddevicetracker

2015 in the skin replacement/substitutes market segment, which was bolstered by the acquisition of the rights to *Dermagraft* from **Shire PLC** the year before. *(Also see "Shire Sheds Dermagraft; Exits Regenerative Medicine" - Pink Sheet, 17 Jan, 2014.)*

Ranking third in this space in 2015 was the relative newcomer, **MiMedx Group Inc.**, which seized the market opportunity with smaller-sized and less expensive human amniotic tissue products, including *EpiFix*. In 2015, MiMedx had estimated revenues of $135.1m, which translated into an 18.6% share in the skin replacement/substitutes market. The company was able to gain significant market share (nearly 200%) in this segment over the last two years with its pass-through reimbursement status and by broadening its product line with various graft sizes.

SKIN REPLACEMENTS: HURDLES ABOUND

Skin replacement/substitute manufacturing has come a long way since the development of the earliest types of xenografts, followed by allografts and autografts. While today's autografts avoid problems of graft rejection and disease transmission, which are associated with xenografts and allografts, they too have limitations.

The road to market introduction for many skin replacement/substitute manufacturers continues to be fraught with clinical and financial disappointment.

Among the biggest hurdles for manufacturers are less than adequate clinical trial results for investigational products, difficulty in obtaining funding, and high development costs, along with a corresponding low-profit margin, once the product is introduced.

Some emerging biotechnology companies have had to make difficult decisions, including the need to curtail manufacturing and sales, to support clinical trials for indications in larger potential markets. Once on the market, manufacturers must sell skin replacement/substitute products at significantly higher prices than conventional therapies to recoup development costs.

To date, the high costs of these products remains the biggest obstacle for wider adoption.

Another significant obstacle to market growth and widespread use in the skin replacement/substitutes segment are potential complications and contraindications, especially in cases where the patient is known to have a wound infection or an allergy to a product component.

Complicated usage of some of these products also remains an issue. In many cases, health-care professionals need to be trained on how to use these products effectively, which can be a deterrent to wider adoption. Adding to these concerns are fear of infection transmission, the short shelf life of these products and special storage requirements.

Finally, the complicated reimbursement requirements and attempts by US FDA to regulate skin replacements/substitutes has also led to confusion among both clinicians and manufacturers in this market.

In the long term, *Meddevicetracker* expects that clinicians' selection of products based on cost will ease the regulatory burden somewhat. One example is the US Centers for Medicare & Medicaid Services' pass-through designation that offers full reimbursement for amniotic tissue products.

Some challenges have contributed to the bankruptcy filing of companies, including **Advanced Tissue Sciences Inc.** (which developed *Dermagraft (Also see "The Rebirth of Dermagraft" - Medtech Insight, 1 Feb, 2008.)*, as well as *Organogenesis*, which subsequently revived; *(Also see "Despite Advances, Regenerative Medicine Faces Funding Crisis" - Scrip, 1 Feb, 2010.)* For other firms, the financial burden forced them to stop development of products or pull products from the market -- examples include *Celaderm* and *TransCyte* made by **Advanced BioHealing**.

DRIVERS FOR SKIN-REPLACEMENT GROWTH

The good news is that a growing number of new companies are entering the skin replacement/substitutes market, which will offer medical practitioners and patients more product choices down the road, according to *Meddevicetracker*.

In addition, by 2020, *Meddevicetracker* expects to see more innovative tissue-engineered skin replacement/substitute products at lower prices on the marketplace, which will drive growth in this area.

That said, these less-expensive products will also slow overall market growth due to downward pricing.

Already, there has been considerable research done into combining growth factors with the technology of skin replacement matrices to accelerate healing and achieve more complete wound repair. Skin replacement products are also being evaluated as a delivery vehicle for different types of growth factors, for treating inconsistent pigmentation by adding melanocytes to skin grafts and for treating diabetes by delivering insulin with skin replacements.

To counter the high costs of skin replacements/substitutes, some companies are promoting their products for temporary and permanent tissue replacement, and for accelerating wound healing to improve patient outcomes, touting less associated pain, scarring and trauma.

When companies can show that their products enable fewer dressing changes and require fewer nursing visits, compared to conventional therapies, their products are seen as more cost-effective. Despite these positives, we find that health care providers often make purchasing decisions with a short-term view, based on per unit price, rather than long-term, based on cost-effectiveness.

This is especially true in the current economy, in which healthcare providers are constantly trying to find ways to cut expenses and tend to use higher-priced supplies only when medically necessary. With the slow economic recovery, these conditions are likely to extend over the forecast period covered by this analysis, *Meddevicetracker* reported.

However, the introduction of competing products and more companies entering this space will lead to more fragmentation and a consequent shift in market shares.

This market shift will be influenced by the entry of new performance-enhanced products, submittal of improved cost-effectiveness data and the approval of expanded indications for individual products. In terms of cost analysis, skin replacements/substitutes appear to have strong arguments in their favor, based on overall economy and improved outcomes.

Further, new technologies, such as the use of amniotic tissue grafts for wound healing, and new applications for skin replacements/substitutes, are expected to offset limitations and drive growth over the forecast period, according to *Meddevicetracker*.

ACTIVE WOUND-REPAIR MODULATORS

Regranex Gel 0.01%, made by S&N, currently is the only active wound-repair modulator on the market, and the first growth factor released for sale in this segment.

In 2015, worldwide sales of Regranex totaled roughly $99.8m and are expected to reach $111.8m by 2020, a CAGR of 2.3%, according to *Meddevicetracker*. These sales are for the US market only, as Regranex was pulled from the EU market in 2012 for commercial reasons. *(Also see "EU's CHMP advises against use of J&J's Regranex in patients with cancer" - Scrip, 25 Feb, 2010.)*

Regranex was developed by **Ethicon Inc.Johnson & Johnson**'s professional wound-care business and made headlines in 2008 when FDA added a warning label. According to the warning label, diabetics who reportedly used more than three tubes of the ulcer treatment had a higher risk of dying from cancer – *if* they developed cancer – than patients who didn't use Regranex extensively. The company divested the gel, and following a series of acquisitions, it is now marketed by S&N.

Studies have shown that Regranex – which is used for treating neuropathic foot ulcers that extend into the subcutaneous tissue or beyond, and that possess an adequate blood supply – has the ability to stimulate angiogenesis when combined with other advanced wound dressings.

REGRANEX CHALLENGES

Nevertheless, the warning label has hurt Regranex sales. The introduction of innovative products, such as tissue-engineered technologies and advanced wound dressings, have outpaced Regranex sales. Other potential limiters for Regranex future sales will be the introduction of gene therapy products. Researchers are already investigating gene therapy for the PDGF-BB growth factor, used in Regranex, as a substitute treatment, which will ultimately require a single dose instead of the multiple doses required for Regranex.

From the viewpoint of future manufacturers of wound-healing growth-factor products, the development of Regranex, however, shows that wound-care clinicians may be more open to trying truly innovative wound-care products.

Traditionally, wound-care clinicians have been slow to adopt new techniques. To get their attention, wound-care companies with innovative products responded by making substantial investments in education and training clinicians in using these new products.

However, for many companies that don't have deep pockets, making this type of investment remains a challenge, particularly in the current economy. It also represents a risk to companies that may have the resources and technologies, but lack depth of knowledge in this market.

Consequently, this market will continue to be driven by companies that are willing to invest in R&D for stem cells and gene therapy. Growth barriers in this area are ethical concerns, as well as limited application for technologies like growth factors.

ADVANCED WOUND-CLOSURE PRODUCTS

The advanced wound-closure product segment, comprised of surgical sealants and glues, energy-based closure-devices, automated suturing products, and negative-pressure wound therapy (NPWT), totaled about $4.2bn in 2015 and is expected to reach $5.4bn in 2020, a CAGR of 4.7%, according to *Meddevicetracker*.

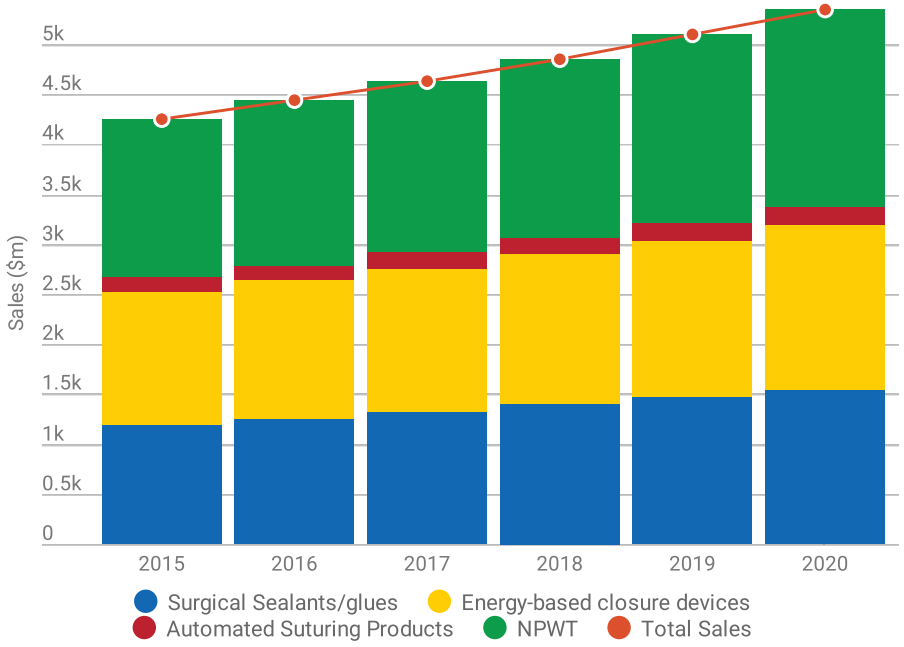
NPWT made up the largest component in this segment, accounting for a 37.1% market share and $1.6bn in revenues in 2015. Energy-based closure devices ranked second with a 31.3% market share and $1.3bn in sales in 2015. Surgical sealants and glues were in third place with a 28.2% market share and $1.2bn in sales in 2015, followed by automated suturing devices with a 3.3% market share and $142m in sales in 2015. (See Figure 4.)

ACELITY STILL LEADER IN NPWT

NPWT has gained popularity amid its ability to treat various acute, chronic and sub-

FIGURE 4

Market Forecast, Advanced Wound Closure Products, 2015-2020



Source: Advanced Wound Care Products Market, Meddevicetracker

acute wounds that have been refractive to conventional treatment. By applying negative pressure to the wound, clinicians have seen the stimulation of healthy, vascularized granulation tissue with the added advantages of reductions in local edema and a lower risk of infection.

Acelity has been the NPWT market leader in the US with a 76.6% share amid its highly successful *V.A.C. Therapy* line; and the company's *ABThera* open-abdomen negative-pressure system, introduced in 2009, is expected to propel its continued growth in the NPWT market for years to come. The firm's acquisitions of additional NPWT products, such as the *SNaP* system from **Spiracur Inc.** in December 2015, will further cement its dominance in the US market.

In the emerging markets, Acelity banks on the rising middle class and improved access to health care to increase adoption of advanced wound dressings. Meanwhile, in Europe, Acelity's sales will be driven by the rising push to provide health care in post-acute settings, along with the adoption of advanced technologies such as NPWT.

Smith & Nephew moved into the NPWT space with the acquisition of **BlueSky Medical** in 2007**.** *(Also see "Smith & Nephew breaks into new woundcare segment with BlueSky buy" - Medtech Insight, 18 May, 2007.)*Seven years on and with BlueSky's NPWT devices fully integrated into S&N's corporate strategy and formidable marketing force, Acelity will be facing increased competition. Although with a mere 10.1% market share in this space, S&N will need to strive for more diversity and clinical evidence for their products to draw significant market share from the top competitor.

According to S&N's 2015 annual report, revenue in this segment fell 3% from 2014-2015; however, the introduction of next-generation systems such as the *Renasys Touch*, as well as the relaunch of the Renasys line in the US, and continuing sales of the *PICO system,* are expected to bring growth over the forecast period covered by this analysis, according to *Meddevicetracker*.

While NPWT has been used successfully in treating wounds in various health-care settings –including in hospitals, skilled nursing facilities and in the home – it's facing competition from alternate therapies such as advanced wound dressings, growth factors and skin substitutes. The global economic downturn also had a repressive effect on NPWT's growth.

ENERGY-BASED WOUND CLOSURE

Energy-based wound closure represents an increasingly viable alternative to the traditionally used wound-closure methods, sutures and staples. Technological advances have led to energy-wound closure devices that are more precise and accurate for cutting and sealing in both open and laparoscopic procedures vs. traditional methods. Also, the fluid-tight closure eliminates the need for a second procedure to remove sutures or staples, which has shown to improve patient outcomes by shortening recovery time and hospital stays.

The historic US market leaders, **Ethicon Inc.** and **Covidien Ltd.**, have consistently introduced new products with expanding indications while making improvements to existing products. Both companies, however, are finding it increasingly difficult to compete against smaller companies that are finding niche positions in this market while pursuing their R&D for other indications. This is an alternative strategy to expand their product portfolio, creating additional product accessories or pursuing strategic alliances. These niche suppliers are also taking advantage of nonexclusive group purchasing contracts, now in place at many hospitals.

Ethicon still holds the biggest market share with 37.4%, but Covidien (now **Medtronic Minimally Invasive Therapies**) has been edged out by a newcomer, **Olympus Corp.**, which holds a 26.7% market share, repositioning Covidien into third place with a 18.3% market share (all market shares applied to the year 2015).

Despite potentially catastrophic events, such as litigation over proprietary technology, many companies have been able to form strategic alliances and sign agreements and financial settlements. Olympus ranks among the companies that have been able to form successful strategic acquisitions, all of which points to a positive, forward-looking trend in this market.

SURGICAL SEALS AND GLUES

Despite their higher initial cost and reluctant adoption by physicians, the many advantages offered by surgical sealants and glues are expected to give it the most

traction in the wound-closure market with a 5.4% growth rate by 2020, according to *Meddevicetracker*.

Benefits include improved wound closure with an associated improved cosmetic appearance, easy and fast application, rapid hemostasis, and reduced pain for the patient along with no need for anesthesia, reduced risk of infection, and lower overall costs associated with treatment by eliminating the need for a second procedure to remove sutures or staples.

Internal sealants and glues are gaining further recognition in specific applications, such as in sealing air and fluid leaks at the wound site. Their use is particularly helpful when closing tissues that contain air or fluids under pressure, such as blood vessels, the dural membrane surrounding the brain and spinal cord, the gastrointestinal tract, and the lobes of the lungs. Another trend that is expected to help stimulate growth in this market is the use of surgical sealants in novel applications such as with delivery vehicles for growth factors.

Over the past decade, smaller competitors in the surgical sealants and glues market have opted out due to their inability to compete with industry leaders such as **Baxter Healthcare Corp.** (which has a 51.3% market share) and Ethicon (with a 28.9% market share).

The rivalry between the larger suppliers has led them to step up their marketing efforts, and with the market entry of other formidable competitors such as **TissueSeal** and **Advanced Medical Solutions Group PLC**, there will be even more competition. To be successful in this space, companies must rapidly distinguish their products from their rivals through education and innovative development, such as novel delivery devices or new applications.

AUTOMATED SUTURING DEVICES

When several promising endoscopic suturing devices made their market debut in the early 2000s, industry experts were excited about the enormous applications of these devices. The expansion of minimally invasive surgeries initially contributed to the increased use of automated suturing devices, which do not require knot tying.

The unexpected reality, however, was that surgeons continued to favor using laparoscopic stapling devices, which are both speedy and simple to use. Consequently, earlier predictions of significant growth in this area weren't realized.

Despite this setback, *Meddevicetracker* expects that the automated suturing devices market will still see a modest increase of 4.9% by 2020 amid improvements in the technology and expanding applications for these devices, such as for gastric bypass or colonic closure.

In 2015, Medtronic Minimally Invasive Therapies led the global automated suturing devices market with revenues of $73.3m and a 51.6% share, driven by its successful entry into the bariatric/gastric surgical market with its *Endo Stitch* suturing device.

In second place, with a 24.7% market share, is Ethicon, which had $35.1m in 2015 revenues. The company was able to capitalize on the marketing of its automated suturing devices with its expertise in sutures and automatic staplers and a broad product line across these categories. For example, the company markets its *Suture Assistant* to the general surgery industry, touting the device provides advanced knot security with knots that are equivalent to those tied manually.

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