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# Medtech Insight

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## MTI 100:

# The Rise And Fall Of Medtech's Giants

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It might have taken some time but more than a year after Medtronic completed its historical $43bn merger with Covidien, the medtech giant has finally made it to the top of the leaderboard, a position long-occupied by Johnson & Johnson.

The 2016 edition of MTI 100 – *Medtech Insight*'s roll call of the top 100 companies ranked according to their medical device- and diagnostics-related sales for their most recent full fiscal year – show Medtronic easily beat J&J to the number one spot. Last year, Medtronic had only included one fiscal quarter's revenue from the acquired Covidien business and hence, fell short of overtaking its rival. But with a full fiscal year now in the bag, Medtronic's fiscal 2016 revenue of $28.82bn – an impressive 42% jump from the previous year's top-line – was over $3bn more than J&J's revenue generated by its now pared down medical device segment. J&J's medtech top-line sunk from $27.52bn in 2014 to $25.14bn in 2015, mainly due to gaps left by the sale of two significant businesses, Ortho-Clinical Diagnostics and Cordis.

And it's not just the top two spots that have seen a change. Apart from GE Healthcare and Siemens Healthineers (the new brand name for Siemens Healthcare as of May 2016), which have retained their respective number 3 and 4 positions from last year, there has been some shuffling about among the other top 10 companies in the MTI 100 league table:

Successful climbers among these top players were Cardinal Health and Danaher – both went up two positions – and Becton Dickinson, which made its debut in the top 10 by jumping four positions from number 13 to number 9 this year. Like Medtronic, BD benefited from a significant acquisition, the $12.2bn deal for medication management and patient care company CareFusion, which it closed in March 2015. Fiscal 2016, which ended Sept. 30 2016 for BD, included the first full-year contribution from the acquired assets, which inflated BD's medtech-related revenue from $7.76bn in fiscal 2015 to $9.96bn in fiscal 2016.

Among last year's top 10 players that slipped down the rankings – though only by one place – were Philips Healthcare, Roche Diagnostics and Stryker. Both Philips and Stryker did see growth in revenue and were largely shoved out of the way by the aforementioned climbers but Siemens Healthineers saw its revenue take a hit, partly due to negative currency effects but also due to the impact of an ongoing restructuring initiative that is seeing it streamline its operations and divesting non-core businesses.

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### COMPANY RANKINGS



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### POLICY & REGULATION



### COMPLIANCE CORNER

# UK Health-Tech Assessor Signs On With FDA Payer Task Force

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The UK's National Institute for Health and Care Excellence (NICE) has become the first non-US organization to work with FDA's ongoing Payer Communication Task Force (PCTF).

The task force is an effort US FDA launched this fall in which manufacturers of devices and diagnostics can get input from private payers during the device development process. It is intended as a complement to the ongoing FDA-CMS parallel review program. Other FDA partners include the BlueCross BlueShield Association, Duke University, ECRI Institute, Humana, Kaiser Permanente, and SelectHealth/InterMountain Health.

NICE evaluations of health-care technologies form the basis of National Health Service policies for including services in the UK single-payer health-care system.

NICE's involvement in this joint initiative will be fee-based for companies that wish to gain insight from the institute. As part of the program, NICE may review the evidence a company is gathering; provide advice in a pre-submission meeting with other advisory bodies and comment on the resulting company's minutes; or produce formal written advice as a follow-up to the pre-submission meeting.

Leeza Osipenko, who heads NICE's scientific advice division, told *Medtech Insight* that she hopes the institute's participation will encourage a type of communication that is rare in Europe between government payer organizations and manufacturers. In Europe, devices reach the market via the CE-mark process, which relies on third-party notified bodies to perform conformity assessments and other oversight tasks. Although manufacturers that approach NICE as part of the PCTF process will still need to get a CE mark separately, developers that think about payer needs while planning clinical trials to support regular approval are likely to win speedier reimbursement decisions, she said.

> NICE plans to charge companies that it engages with via the Payer Communication Task Force £5,000 for a phone consultation and £15,000 for a detailed report.

NICE has spoken to about 15 manufacturers independently about payer clinical trial requirements, but didn't have the benefit of FDA participation at that time. The PCTF process allows the institute to bring in a regulatory voice, she said.

Osipenko notes that the scientific requirements for reimbursement between the US and UK are broadly similar, so it's likely that feedback from NICE would also apply to manufacturers seeking coverage from US payers, and vice versa.

"Companies need to have dialogue with payers and regulators while they're developing products," she said. "You want to come while you're defining a clinical trial. …It's an extremely important engagement step, and companies aren't taking the opportunity to find out early whether they should progress with their plans." The advice can reduce the time it takes for devices to reach patients by eliminating delays at the payer level, Osipenko said.

She noted that she often sees small manufacturers facing coverage delays due to overly broad indications. For example, a company might believe a wound-care product will work on all kinds of wounds, but it's impractical to collect the amount of data a payer would need to get coverage for that. A payer might be able to guide the manufacturer to limit the proposed indication to diabetic ulcers, she suggested.

Osipenko hopes more European agencies will begin to work with FDA, but noted a practical barrier: Because most European countries have state-run health care, the coverage bodies aren't set up to accept user payments. NICE, which plans to charge companies that approach via PCTF £5,000 for a phone consultation and £15,000 for a detailed report, is a rare exception.

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# Combo-Product Sponsors Gain Some Favored Changes In Final Post-Market Reporting Rule

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US FDA's final rule on post-market reporting requirements for combination products is likely to be a welcome addition for industry.

The final rule, published Dec. 20, clarifies its scope, aims to minimize duplicative reporting, clarifies the definitions of certain terms and includes additional reporting requirements to address specific safety concerns related to medical devices and biological products.

"In reviewing the final rule, it is clear that FDA listened to stakeholders," said Brad Thompson, attorney with Epstein Becker & Green and general counsel to the industry Combination Products Coalition. "The agency made numerous changes in promulgating the final rule that reflected concerns commenters had expressed. The agency obviously invested quite a bit of effort into sorting through the issues and coming up with a simplified and clearer approach to PMSR [post-marketing safety reporting] for combo products."

The rule clarifies that it only applies to "combination product applicants" and "constituent part applicants." Some of the 16 commenters on the 2009 proposed rule raised questions as to whether the rule would apply to investigational combination products and to combination products that have not received marketing authorization.

Thompson, in particular, praised the rule's clarification of the different requirements that are applicable to the combination product applicant and those that are applicable to constituent-product applicants. For example, the final rule makes clear that the requirement to share information that involves a death or serious injury with other constituent-part applicants within five calendar days only applies to constituent-part applicants. It also clarifies that additional reporting requirements to address specific safety concerns related to medical devices and biological products – that are not in the proposed rule – only apply to combination-product applicants.

"This was a particularly gray area, and the changes the agency made are very helpful. In the original proposed rule, there were some ambiguities that might be interpreted as actually expanding the PMSR requirements for constituent product manufacturers and even component suppliers," Thompson said. "The final rule puts those issues to rest."

Thompson added that "constituent product manufacturers have a much better understanding of the who, what, when and how of reporting."

## ADDITIONAL REPORTING REQUIREMENTS

Section 4.102(c) of the rule mandates that combination product applicants must submit correction and removal reports and comply with related recordkeeping requirements for combination products that include a device constituent part.

FDA notes in many cases, correction and removal reporting requirements for combination products go into effect when manufacturers issue a recall related to an adverse event, which also triggers more general Medical Device Reporting (MDR) requirements. In such cases, the agency says an MDR that contains all the pertinent information will be sufficient reporting from the manufacturer, sparing them from reporting the issue twice to FDA.

"Under § 806.10(f), no separate correction or removal report is required to be submitted if a report of the correction or removal has been submitted under Part 803," states the agency. "However, in some instances, a correction or removal will not be associated with a reportable adverse event, or the action that a manufacturer takes in response will not trigger a five-day reporting requirement, but the action must still be reported as described in Part 806 to ensure, in part, appropriate coordination between the manufacturer and the agency. In such cases, the correction or removal report currently should be submitted to the appropriate agency field office."

Some corrections and removals may not trigger reporting requirements under either Parts 803 or 806, but may require recordkeeping under Part 806. FDA says combination products that include device constituent parts will be required to maintain records in such cases.

Section 4.102(c) also mandates combination product applicants for products that have a biological product constituent part must submit biological product deviation reports (BPDR).

According to the rule, "BPDRs address events associated with manufacturing that represent a deviation from current good manufacturing practice, applicable regulations, applicable standards or established specifications, or represent an unexpected or unforeseeable event that may affect the safety, purity, or potency of the product." Such a requirement or definition was not included in the proposed rule.

This only applies, however, when the combination product was approved under a new drug application, an abbreviated new drug application or a device application, where the constituent part was a biological product.

Combination product applicants for products that include a drug constituent part must submit a field alert report, which includes "information concerning any incident that causes the drug product or its labeling to be mistaken for another article," or "information concerning any bacteriological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of the drug product to meet the specification established for it in the application."

Marketing authorization in this case must have been under a Biologics License Application or a device application.

## EXTENDED DEADLINES

Under the proposed rule, combination product applicants would have been required to submit 15-day alert reports, under which applicants are required to report to FDA an adverse drug experience that is both serious and unexpected no later than 15 calendar days.

The final rule now allows a 30-day window for combination products that received marketing authorization under a device application. FDA believed the extended deadline would allow it to "continue to be able to respond in a timely manner to these reports if submitted within 30 days rather than 15 days for such combination products."

FDA added that the 30-day window would allow for better alignment of reporting for device-led combination products, as the timing would be consistent with the for the submission of Medical Device Reports.

"This alignment could be expected to improve the efficiency, clarity and completeness of reports for this class of combination products and to eliminate unnecessary complexity and potential for confusion," the final rule states.

Brad Thompson noted that "FDA also has been very practical in developing this final rule in that they have, on a couple of occasions, extended deadlines for the reporting information to take into account the added complexities of combination products and joint efforts of multiple stakeholders."

> "The agency may receive multiple reports regarding the same event ... but this approach ensures that the agency has the benefit of each constituent-part applicant's expertise and familiarity regarding its own constituent," the final rule states.

## AVOIDING DUPLICATE REPORTING

Many commenters on the proposed rule expressed the importance of avoiding unnecessarily duplicative reporting, including the Combination Products Coalition, **Pfizer Inc.**, **Genentech Inc.**, and the Pharmaceutical Research and Manufacturers of America.

The final rule authorizes applicants to submit only a single report for an event, even if multiple reporting duties apply to the same event.

FDA, however, shot down several other comments aimed at avoiding duplicative reporting. For example, several commenters – including **Abbott Laboratories Inc.** – called for the elimination of information-sharing requirements. The rule mandates that applicants that receive information about an adverse event submit that information to FDA or the reporter for the other constituent part within five days.

For example, the application holder for a drug constituent part of a combination product approved under an NDA would send information about the adverse event to FDA or the reporter for the device constituent part of the product within five days.

Abbott contends that the rule implies that applicants must share information with one another in addition to FDA, which will lead to "unnecessary duplication" and serve "no useful purpose." FDA disagreed.

"The trigger for a constituent part applicant to submit a report to the agency is not the mere act of receiving information but a determination that the event is reportable under the PMSR requirements applicable to that applicant," the rule states. "The agency may receive multiple reports regarding the same event … but this approach ensures that the agency has the benefit of each constituent-part applicant's expertise and familiarity regarding its own constituent part in assessing the information with respect to that constituent part."

## EXTENDING THE COMPLIANCE DATE

FDA ultimately decided to extend the rule's compliance date to 18 months following its Jan. 19, 2017, effective date.

The initial compliance date was 180 days following the effective date, but several commenters argued that would not provide ample time to comply. They noted that they would have to develop, validate, and implement new systems, alter procedures and commercial arrangements and train staff.

Thompson said he hopes FDA will issue specific guidance on the rule soon so sponsors can comply with the 18-month timeframe. Industry has been eagerly waiting for the rule to be finalized so FDA can start to work on a more hands-on guidance.

## FALLING SHORT ON HARMONIZATION

Thompson noted that the agency still needs to work on fixing its current "highly fractured system" that is in place, specifically citing the need for "a more unified approach" for adverse event reporting for combination products. He did say, however, that the rule "will help as an interim matter."

Thompson further touted the recently enacted 21st Century Cures Act, which he says "is trying to nudge FDA toward unifying regulatory requirements."

The legislation includes reforms to FDA's oversight of combination products, including establishing mandatory meetings between FDA and combo-product developers, clarifying the process for resolving disputes between FDA product centers, and instructing the agency to be wary about designating a combo-product as a drug versus a device.

It also requires the agency to create "inter-center institutes" to better coordinate its handling of major diseases. They are intended to streamline activities among the centers for devices, drugs and biologics evaluation.

In response to calls for harmonization, FDA noted it did consider alternative approaches for PMSR, and that it "determined that the approach described in this rule allows FDA to receive complete, timely post-marketing safety information regarding combination products."

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## BLOOD BROTHERS NO MORE:

# Hologic Unloads Blood-Screening Business To Partner Grifols

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**Hologic Inc.** is selling its interest in its blood-screening business to partner **Grifols SA** for $1.85bn to improve its top-line growth and free up more money for future acquisitions, the company announced Dec. 14.

"This transaction strengthens our efforts to build a sustainable growth company by accelerating our top- and bottom-line growth rates while significantly increasing our financial flexibility," Hologic CEO Steve MacMillan said during a conference call.

The Hologic/Grifols collaboration on blood-screening began in 1998 with the partnership of **Novartis AG** and **Gen-Probe Inc.** Gen-Probe developed the *Procleix* brand of blood-screening products, now marketed by Grifols, and Hologic acquired Gen-Probe for $3.7bn in 2012. Grifols bought Novartis' blood transfusion diagnostics unit in 2013 for $1.6bn.

The Procleix line includes molecular assays and instruments for blood banks that screen donated blood for viruses including HIV, hepatitis C and B, West Nile and, as of this summer, Zika. Hologic sponsored the research and development for blood-screening technology and manufactured the Procleix products, while Grifols commercialized them under its brand.

"Hologic is extremely proud of the contributions we have made to global blood safety and the market leadership position we have established in partnership with Grifols, but at the same time, the business is non-strategic for us, as we lack the ability to control our own commercial destiny," MacMillan said. "Moreover, since our partner manages sales and marketing, commercial synergies with our other product franchises and channels do not exist."

Once the sale closes – expected in early 2017 – Grifols will get the license to certain of Hologic intellectual property for blood-screening technology. Also, about 175 Hologic employees, mainly in operations and research and development, will transfer to Grifols and Grifols will take-over Hologic's blood screening manufacturing facility in Rancho Bernardo, California. Hologic will maintain the engineering expertise that created the *TIGRIS* and *Panther* automated blood-screening test systems, but says it "will partner with Grifols to ensure that blood screening customers continue to benefit from state-of-the-art instrumentation over the long term."

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### NON-STRATEGIC, LOW-GROWTH ASSET

MacMillan explained that the price Grifols is willing to pay for Hologic's share of the blood-screening business represents "excellent value … that exceeds what we could achieve in the current collaboration." The $1.85bn purchase price is a premium to Hologic's own internal valuation; and it is about eight-times Hologic's anticipated 2017 revenues from the business and approximately a factor of 12 higher than expected 2017 blood-screening earnings of $155 million.

For fiscal-year 2017, which began in September, Hologic projected its share of the blood-screening business would yield $240m of revenue, about 8% of its total revenues of $2.94bn to $2.98bn. The business was expected to contribute about $155m in earnings before interest, tax, depreciation and amortization, and $0.34 to earnings per share.

But the blood-screening business has been in decline in recent years as more stringent blood-management practices around the world have reduced the total volume of blood donations. Meanwhile, blood banks are in a stronger position to negotiate lower prices from screening test manufacturers as competition in the market, especially from **Roche**, has intensified.

"Divesting the blood screening business will remove a drag on our growth, which will enable us to increase both revenues and [earnings-per-share] more rapidly," MacMillan said. Hologic now expects its full-year *pro forma* revenues in fiscal 2017 to grow 30 to 40 basis points faster without the blood screening business than it would have with the business, and it expects the growth will accelerate in the future.

In a Dec. 14 note, Jefferies analyst Raj Denhoy points out that blood screening was a high-margin business for the company, but it "was the only business segment that was expected to be a long-term decliner [for Hologic.] Denjoy projected Hologic's revenues from blood screening would contract 2% annually between 2018 and 2020.

"The deal enables us to control our

own commercial destiny," MacMillan said. Hologic has moved from flat growth and shrinking earnings in fiscal 2014, to 5.4% revenue growth and 17.4% earnings-per-share growth for fiscal 2016, and "much of the turnaround magic that we have created over the last three years stems from our commercial teams and more specifically the close relationships our sales forces have cultivated with customers," he said.

"In businesses where we can manage customer relationships and drive demand, we have returned to growth such as in cytology and surgical, or accelerated growth such as in mammography and molecular diagnostics. But obviously our blood screening business is uniquely different, as commercialization is handled by our partner."

The deal will also increase Hologic's financial flexibility to grow through acquisitions, MacMillan said. "M&A – as a supplement to internal innovation, commercial execution and international expansion – will be an important part of our future growth strategy." Once this deal closes, Hologic's leverage ratio – net debt to earnings – will be around 2, "enabling us to exceed our long-standing leverage goal ahead of schedule… From a financial perspective, we will continue to seek out assets that are accretive to our organic revenue and earnings-per-share growth rates and that offer a compelling return on capital. In other words, we will continue to pursue a very deliberate and disciplined acquisition strategy, regardless of the amount of cash on our balance sheet."

### BOOST FOR GRIFOLS' MARGINS

On the other side of the deal, Grifols says that taking over Hologic's share of the blood-screening business will bring its earnings margin up to 40% compared to the 28.6% it reported at the end of the third quarter on Sept. 30. The Barcelona-based company plans to finance the acquisition a with $1.7bn term loan and existing cash on the balance sheet.

"This acquisition is part of the growth strategy foreseen for [our] Diagnostic Division," Grifols CEO and Chairman Victor Grífols explains in a release. "It is an obvious step that allows us to strengthen a leading position that we first achieved in 2014 in transfusion diagnostics with the acquisition of assets from Novartis, which, among other things, included the rights to market transfusion medicine assays and instruments using [nucleic acid testing] technology. The transaction enabled us to enhance our capabilities to be one of the only companies capable of offering comprehensive solutions to blood and plasma donation centers, from donation to transfusion. Now, with this new transaction, we have contributed our vertical integration process as we also have control over the production and R&D phases".

Grifols will structure the acquisition through its Grifols Diagnostic Solutions, a U.S. incorporated, wholly-owned subsidiary of Grifols, S.A.

Adding Hologic's part of the blood-screening business will not change the revenues for Grifols diagnostics division, which accounts for about 16% of the company's revenues, because all of the revenues for the whole business were being recorded through the division already.

The deal will raise Grifols' debt ratio from about 3.3 to 4.3, but the company says it is "committed to rapidly reducing its leverage level [and] plans to absorb this increase through a greater capability to generate cash flows. Historically, Grifols has demonstrated a track record of deleveraging ability post acquisitions." Grifols says it expects that streamlining and integrating the business will lead to operational efficiencies in production, research and development, and administration costs.

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# Allergan Gets Regen Med Assets, Acelity Gets Cash Boost Post-IPO Dump

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**Allergan PLC** will pay **Acelity LP Inc.** $2.9bn to buy the **LifeCell Corp.** portfolio of aesthetic and surgical products. The all-cash deal not only marks Allergan's first regenerative medicine transaction – and one that is accretive to the specialty pharma company's top- and bottom-line – but it will also provide Acelity with an alternative source of new capital now that the firm has finally quashed its long-held hopes for an IPO.

The LifeCell purchase gives Allergan a suite of commercial products for what chief commercial officer William Meury describes as the company's "most important customer": plastic surgeons.

"With the acquisition of LifeCell, we probably have the largest and most focused business for aesthetics and plastic surgery," Meury said in an interview with *Medtech Insight*'s sister publication *Scrip*.

LifeCell is the leader for acellular dermal matrices (ADMs) – biological meshes made from human allograft or porcine dermal tissue, which frequently are used in breast reconstruction and complex hernia surgeries – with an approximate 60% market share, Meury pointed out.

LifeCell products marketed in the US include *Alloderm*, a human allograft tissue matrix used for repair or replacement of damaged or inadequate soft tissue in challenging surgeries, including post-mastectomy breast reconstruction; *Strattice*, a porcine-based tissue matrix used in hernia surgeries, other complex abdominal wall repair procedures and surgeries to repair damaged or ruptured soft tissue; and *Revolve*, a single-use, fat-grafting de-

vice that plastic surgeons employ in aesthetic and reconstructive procedures to use patients' own fat to enhance volume.

However, the deal wasn't immediately greeted with universal optimism. Evercore ISI analyst Umer Raffat said in a Dec. 20 report that he heard three types of investor reactions to Allergan's LifeCell acquisition news that same morning: gratitude that the assets would be immediately accretive to the company's earning, satisfaction with LifeCell's aesthetic portfolio given Allergan's strong presence in that market, and concern that the company sold for $1.2bn less eight years ago.

Acelity (formerly Kinetic Concepts Inc.) acquired LifeCell for $1.7bn in 2008, and the regenerative medicine business had posted revenue of $191m the year before. Raffat pointed out that LifeCell is now expected to generate $450m in 2016 revenue, representing year-over-year growth in the mid-single digits.

According to Raffat, LifeCell's 2016 revenue is broken down as follows: $280m for Alloderm, which is growing in the low-single digits; Revolve, which accounts for about $10m in sales with high double-digit growth; and Strattice, which has stabilized at $180m in annual revenue.

## LIFE(CELL) AFTER ACELITY

Meury said Allergan is focused on integrating the LifeCell assets into the company's portfolio, but Allergan will assess how it can increase revenue from commercialized products as well as how the company can leverage LifeCell's research and development platform. Its R&D pipeline includes Artia – a porcine-based tissue matrix that is approved and marketed in some European markets – and potential applications of regenerative medicine for aesthetic uses to address aging and scarring on the face.

Meury noted than skin aging, scarring and overall skin quality is the biggest unmet need in aesthetic medicine – one that Allergan knows a lot about because its biggest-selling product is *Botox* (onabotulinumtoxinA), which is approved to reduce the appearance of wrinkles around the eyes and for therapeutic uses, such as migraine headaches, overactive bladder and severe underarm sweating.

Botox sales totaled $2.05bn during the first nine months of 2016, representing a 55.1% increase from $1.32bn during the same period in 2015. Allergan also reported $629.1m in sales of facial fillers and $261.7m in breast implant sales during the first three quarters of 2016, which grew year-over-year by 62.2% and 31.9%, respectively.

"The [LifeCell] deal had very good strategic logic," Meury said. "It was compelling financially and we believe it provides a platform to build out our aesthetics and plastic surgery platform."

He noted that the acquisition was negotiated at the end of a competitive process to buy the assets, which Acelity chose to sell so it could focus entirely on advanced wound-healing therapies and dressings. (See box.) The sale of LifeCell is expected to close during the first half of 2017.

Allergan is focused on the existing aesthetic and surgical repair uses of LifeCell's ADM products as they fit into the company's existing product offerings, but Meury acknowledged that there is some potential "to move into adjacent markets and acquire other technologies," such as surgical markets outside of breast reconstruction and hernia repair.

Both aesthetic and post-mastectomy breast reconstruction surgeries already are an important market for Allergan, given its breast implant business, and the company expects growth in that area to continue. Allergan noted in its announcement of the LifeCell acquisition that reconstructive breast surgeries are increasing, driven largely by breast cancer patients.

Nearly 250,000 women in the US are expected to receive invasive breast cancer diagnoses in 2016, and a third of those patients will undergo a mastectomy. Globally, 1.7bn women were diagnosed with breast cancer in 2012.

Given the purported surgeon preference for LifeCell's ADM products, including medical uses like post-mastectomy breast reconstruction and hernia repairs, the soon-to-be-acquired products add a new dimension to Allergan's aesthetic medicine portfolio – payer reimbursement. The company's existing Botox cosmetic, dermal filler and breast implant assets are largely cash-pay products.

"What was attractive to us was that LifeCell, unlike other ADM products in the market, has 100% coverage of their product Alloderm because it's a great product and has good demand," Meury said. "Seventy percent of plastic surgeons operate on the aesthetic and the reconstruction side of this space, so there are real strategic and commercial advantages to having this product-line depth. It's a powerful business for Allergan's most important customer, which is plastic surgeons."

## Acelity Fills Coffers And Sharpens Wound-Care Focus

Sales from LifeCell's products, which comprised Acelity's second and smaller regenerative medicine business unit, accounted for roughly one-fifth of Acelity's total revenue. Offloading LifeCell will enable Acelity to invest its resources on growing its much larger advanced wound therapy (AWT) business, which consists of the legacy negative wound-pressure therapy offering from Kinetic Concepts and advanced wound dressings from Systagenix – which Kinetic Concepts acquired in 2013.

The proceeds from the divestment should help strengthen Acelity's cash position and provide the liquidity it needs to further invest and grow. For more than a year, the company has been holding onto plans to raise some capital via an IPO and list its shares on the New York Stock Exchange. Its initial filing with the US SEC in August 2015 stated that it intended to raise up to $100m, and two months later, in October, this amount shot up to $1bn. However, in a Dec. 7 filing the company withdrew its IPO request, citing poor public market conditions as the reason.

As of June 30, 2016, Acelity had around $99m in cash and cash equivalents, down from $141m a year ago.

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CONTINUED FROM PAGE 1

Abbott dropped out of the Top 10 list this year, falling three places to number 11. The company saw its medtech-related revenue decrease from $10.18bn in 2014 to $9.71bn in 2015, as its outside-US diagnostics and medical device sales took a hit from unfavorable currency effects. Additionally, 2015 was a quiet year for the normally acquisitive Abbott, which meant it did not benefit from potential new sources of revenue. That said, Abbott returned to form in 2016, announcing not just one but two major deals – the first for IVD company Alere (ranked number 32 in the MTI 100) and the other for St Jude Medical (ranked number 32). While the St Jude deal looks to be going ahead, the Alere acquisition has now hit the rocks after a series of financial and regulatory problems chez Alere emerged and Abbott is working to extricate itself from the deal.

Another noteworthy change to this year's league table is the addition of a new name, LivaNova, the combined company resulting from the merger of Sorin and Cyberonics. Sorin had previous ranked number 58 and Cyberonics number 93 – LivaNova is ranked somewhere in the middle at number 70 in this year's MTI 100. The company has been facing some headwinds since the merger, having not impressed investors with its lackluster performance. It may well be that we see LivaNova slip down the ranks in next year's MTI 100 following its first full year as a merged entity.

Also, with the high level of consolidation that occurred during 2015, gaps left by bought up companies meant those that fell outside the top 100 got a foothold into this year's list. New additions to 2016's MTI 100 include: Quidel, Accuray, Consort Medical, Cardiovascular Systems, InvaCare, STratec Biomedical Systems, Endologix, Meridian Bioscience and Sectra.

## MTI 100: Top 10 medtech companies

| RANKING | PREVIOUS YEAR'S RANKING | COMPANY |
|---|---|---|
| 1 | 2 | Medtronic |
| 2 | 1 | Johnson & Johnson |
| 3 | 3 | GE Healthcare |
| 4 | 4 | Siemens Healthcare |
| 5 | 7 | Cardinal Health |
| 6 | 5 | Philips Healthcare |
| 7 | 6 | Roche Diagnostics |
| 8 | 10 | Danaher |
| 9 | 13 | Becton Dickinson |
| 10 | 9 | Stryker |

### WHAT'S AHEAD IN 2017

2016 has proved to be much quieter than 2015 in terms of deal-making, with fewer big-buck transactions and more bolt-on purchases. Taking into account that next year's MTI 100 will be looking at 2016 revenue, any changes to ranking will have to make sure that the transactions are completed in 2016 and the revenue from the acquired businesses are recorded by their buyers that year. Chances are the Abbott and Alere deal will be dropped and Alere will stay put in the next MTI 100. If the St Jude acquisition does close just before the end of 2016, St Jude will drop out of next year's list and Abbott could see itself moving up the rankings again with its bulked up 2016 revenue. But overall, the number of those bowing out should be fewer than the previous years. Another the familiar top 100 name to whom we will be waving goodbye to is ventricular assist device-maker HeartWare (current number 87), which was acquired by Medtronic for $1.1bn in August this year. Additionally, Danaher closed its acquisition of Cepheid in September (number 67) and we shall likely see the former climb even higher up the top 10 list.

Barring other factors that might significantly impact these top players' performance, 2017's list will likely see a more settled picture and less movement than it has in a year marked by substantial consolidation.

The full MTI 100 league table can be found on pp 12-13.

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# MTI 100: Medtech Insight's Top 100 Companies 2015/2014

| | | TOTAL MEDTECH SALES (US$ MILLION) | |
|---|---|---|---|
| RANK | COMPANY | FISCAL 2015 | FISCAL 2014 |
| 1 | Medtronic[1] | 28833.00 | 20261.00 |
| 2 | Johnson & Johnson[2] | 25137.00 | 27522.00 |
| 3 | GE Healthcare | 17639.00 | 18299.00 |
| 4 | Siemens Healthineers[3] | 15020.18 | 16625.01 |
| 5 | Cardinal Health[4] | 12430.00 | 11395.00 |
| 6 | Philips Healthcare | 12109.36 | 11811.08 |
| 7 | Roche Diagnostics[5] | 11255.57 | 11483.88 |
| 8 | Danaher[6] | 10949.90 | 9378.80 |
| 9 | Becton Dickinson[7] | 9955.00 | 7759.00 |
| 10 | Stryker | 9946.00 | 9675.00 |
| 11 | Abbott Laboratories[8] | 9710.00 | 10176.00 |
| 12 | Boston Scientific | 7477.00 | 7380.00 |
| 13 | Baxter International[9] | 7218.00 | 7674.00 |
| 14 | Omron | 6888.07 | 1263.77 |
| 15 | B Braun | 6802.42 | 6981.22 |
| 16 | Zimmer Biomet[10] | 5997.80 | 4673.30 |
| 17 | St Jude Medical[11] | 5541.00 | 5622.00 |
| 18 | 3M[12] | 5420.00 | 5572.00 |
| 19 | Olympus Medical[13] | 5031.56 | 7001.08 |
| 20 | Smith & Nephew | 4634.00 | 4617.00 |
| 21 | Smiths Medical[14] | 4507.56 | 4590.99 |
| 22 | Alcon Laboratories[15] | 3698.00 | 4073.00 |
| 23 | Fujifilm[16] | 3499.38 | 4944.52 |
| 24 | CR Bard | 3416.00 | 3323.60 |
| 25 | Fresenius Medical Care[17] | 3345.90 | 3581.60 |
| 26 | Thermo Fisher[18] | 3243.90 | 3343.60 |
| 27 | Varian Medical Systems | 3099.10 | 3049.80 |
| 28 | Terumo[19] | 3004.43 | 4114.37 |
| 29 | Hologic[20] | 2832.70 | 2705.00 |
| 30 | Dentsply[21] | 2674.30 | 2922.60 |
| 31 | Edwards Lifesciences | 2493.70 | 2322.90 |
| 32 | Alere[22] | 2463.30 | 2575.30 |
| 33 | Intuitive Surgical | 2384.40 | 2131.70 |
| 34 | Coloplast[23] | 2184.20 | 2146.69 |
| 35 | bioMerieux | 2180.62 | 2183.75 |
| 36 | Carestream Health | 2100.00 | 2360.00 |
| 37 | Getinge Group[24] | 1906.46 | 2082.89 |
| 38 | Teleflex Medical | 1890.70 | 1839.83 |
| 39 | Drager[25] | 1885.21 | 2038.46 |
| 40 | ResMed[26] | 1838.70 | 1678.91 |
| 41 | Miraca | 1749.63 | 2566.52 |
| 42 | Convatec | 1650.50 | 1735.50 |
| 43 | Horiba Ltd | 1412.13 | 1919.44 |
| 44 | Elekta[27] | 1330.54 | 1600.60 |
| 45 | Nihon Kohden | 1328.72 | 1921.05 |
| 46 | Bio-Rad[28] | 1310.40 | 1432.30 |
| 47 | Qiagen | 1281.20 | 1344.77 |
| 48 | AGFA Healthcare | 1219.59 | 1374.49 |
| 49 | Carl Zeiss Meditec | 1154.12 | 1169.09 |
| 50 | DJO | 1113.60 | 1229.17 |

[1] *Fiscal 2016 vs fiscal 2015*
[2] *Divested Cordis and Ortho-Clinical Diagnostics in 2015*
[3] *Fiscal 2016 vs fiscal 2015*
[4] *Medical segment only*
[5] *Diagnostic sales only*
[6] *Life Sciences & Diagnostics + Dental*
[7] *Fiscal 2016 vs fiscal 2015; acquired Carefusion Mar 2015; sales include BD Medical and Diagnostic Systems*
[8] *Diagnostics+Vascular+Other*
[9] *Total Renal + Fluid Systems + Surgical Care*
[10] *Acquired Biomet in 2015*
[11] *To be acquired by Abbott year-end 2016*
[12] *Healthcare only*
[13] *Medical business only*
[14] *Fiscal 2016 vs fiscal 2015*
[15] *Alcon's surgical sales only*
[16] *Based on healthcare being 17% of total sales; fiscal 2016 vs fiscal 2015*
[17] *Dialysis product sales only*
[18] *Specialty Diagnostics only*
[19] *Fiscal 2016 vs fiscal 2015; Cardiac Vascular + Blood management*
[20] *Fiscal 2016 vs fiscal 2015*
[21] *Merged with Sirona in Feb 2016*
[22] *Agreed to be acquired by Abbott in 2016; restated 2015 figures in Aug 2016*
[23] *Fiscal 2016 vs fiscal 2015*
[24] *Medical Systems only*
[25] *Medical division*
[26] *Fiscal 2016 vs fiscal 2015*
[27] *Fiscal 2016 vs fiscal 2015*
[28] *Clinical diagnostics only*

| | | TOTAL MEDTECH SALES (US$ MILLION) | |
|---|---|---|---|
| RANK | COMPANY | FISCAL 2015 | FISCAL 2014 |
| 51 | Fukuda Denshi[29] | 968.61 | 1357.69 |
| 52 | Integra LifeSciences | 882.73 | 796.72 |
| 53 | Cochlear | 850.65 | 958.50 |
| 54 | Align Technology | 845.50 | 761.65 |
| 55 | Straumann | 831.21 | 757.66 |
| 56 | NuVasive | 811.11 | 762.41 |
| 57 | Grifols | 767.27 | 797.21 |
| 58 | Konica Minolta | 742.84 | 984.39 |
| 59 | CONMED | 719.17 | 740.05 |
| 60 | Myriad Genetics | 695.50 | 748.20 |
| 61 | Greatbatch | 687.79 | 678.28 |
| 62 | Masimo Corp | 630.00 | 586.64 |
| 63 | Diasorin | 553.96 | 570.59 |
| 64 | Globus Medical | 544.75 | 474.37 |
| 65 | Guerbet | 542.32 | 525.88 |
| 66 | Merit Medical Systems | 542.15 | 509.69 |
| 67 | Cepheid[30] | 538.60 | 470.14 |
| 68 | Shimadzu | 533.89 | 745.39 |
| 69 | Analogic Corp[31] | 452.20 | 452.20 |
| 70 | LivaNova[32] | 415.71 | 291.56 |
| 71 | Wright Medical Group[33] | 415.46 | 298.03 |
| 72 | DexCom[34] | 400.70 | 259.20 |
| 73 | Orthofix International | 396.49 | 402.27 |
| 74 | Immucor | 389.30 | 388.06 |
| 75 | Hamamatsu Photonics[35] | 377.50 | 563.25 |

[29]*Fiscal 2016 vs fiscal 2015*
[30]*Acquired by Danaher Sept 2016*
[31]*Fiscal 2016 vs fiscal 2015; Medical imaging + Ultrasound*
[32]*Merged with Sorin; Livanova 10/15; sales fig corresponds to transitional year from Apr25-Dec 31 2015 and represents the merged entity*
[33]*Became Wright Medical Group NV on Oct 1 2015 on mergerof Wright Medical Group Inc. with Tornier NV*
[34]*Big sales + due to increased sales volumes*
[35]*Medical instrument sales only*
[36]*Fiscal 2016 vs fiscal 2015; Endoscopy + Dialysis*
[37]*CooperSurgical sales only*
[38]*Fiscal 2016 vs fiscal 2015; Bespak drug delivery revenue only*
[39]*Fiscal 2016 vs fiscal 2015*

| | | TOTAL MEDTECH SALES (US$ MILLION) | |
|---|---|---|---|
| RANK | COMPANY | FISCAL 2015 | FISCAL 2014 |
| 76 | Natus Medical | 375.90 | 355.83 |
| 77 | Cantel Medical[36] | 374.50 | 279.89 |
| 78 | AngioDynamics | 356.97 | 354.43 |
| 79 | Ypsomed | 350.68 | 327.04 |
| 80 | ICU Medical | 341.25 | 308.77 |
| 81 | Cynosure Inc | 339.46 | 292.37 |
| 82 | NxStage Medical | 336.12 | 301.50 |
| 83 | Abiomed | 329.52 | 229.95 |
| 84 | Cooper Companies Inc[37] | 309.30 | 325.10 |
| 85 | Endo Pharmaceuticals | 302.26 | 496.50 |
| 86 | RTI Surgical | 282.29 | 262.81 |
| 87 | Heartware | 276.84 | 278.42 |
| 88 | Spectranetics | 245.96 | 204.91 |
| 89 | Exactech | 241.84 | 248.37 |
| 90 | Luminex | 237.71 | 226.98 |
| 91 | Quidel | 196.13 | 184.16 |
| 92 | Accuray | 193.30 | 178.71 |
| 93 | Alphatec | 185.30 | 206.98 |
| 94 | Consort Medical[38] | 179.14 | 167.65 |
| 95 | Cardiovascular Systems[39] | 178.20 | 181.54 |
| 96 | Invacare Corp[40] | 167.50 | 191.00 |
| 97 | Stratec Biomedical Systems | 163.01 | 186.26 |
| 98 | Endologix | 153.61 | 147.59 |
| 99 | Meridian Bioscience[41] | 145.11 | 146.11 |
| 100 | Sectra[42] | 127.30 | 141.97 |

[40]*Respiratory therapy sales only*
[41]*Fiscal 2016 vs fiscal 2015; Diagnostics only*
[42]*Fiscal 2016 vs fiscal 2015*

*All medical device- and diagnostics-related revenues are for the full years 2015 and 2014, or for the most recent full fiscal year ending before Dec. 1 2016*

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https://medtech.pharmamedtechbi.com/datasets/company-rankings

# Abbott Highlights Predictive Potential Of Troponin Testing

**REED MILLER** reed.miller@informa.com

A new analysis of frozen plasma samples from the West of Scotland Coronary Prevention Study (WOSCOPS) suggest that troponin testing, which has long been used to diagnose heart attacks, could be used to identify people who have never had a heart attack but are at elevated risk for one in the future.

Results of the new analysis, by Ian Ford of the University of Glasgow and colleagues, were published in the *Journal of the American College of Cardiology* on Dec. 19. The study was sponsored by **Abbott Laboratories Inc.** and the British Heart Foundation (BHF).

"Serial high-sensitivity troponin concentrations may represent a new paradigm in the assessment of the efficacy and safety of novel cardiovascular and noncardiovascular therapies," Ford et al. conclude. "Troponin concentration predicts coronary events, is reduced by statin therapy, and change at one year is associated with future coronary risk independent of cholesterol lowering. Serial troponin measurements have major potential to assess cardiovascular risk and monitor the impact of therapeutic interventions."

"The hope from this new research is that we may be able to use this simple test earlier on to identify people at higher risk of suffering from a heart attack. Those found to be at higher risk could have their preventative treatments intensified," medical director at the BHF, Nilesh Samani, said. "Before the findings from this research can be clinically applied, the usefulness of measuring troponin findings need to be demonstrated in a wider group of patients. If this confirms its value, the test could easily be administered by [general practitioners] during standard check-ups, and could ultimately save lives."

## FROZEN PLASMA REVEALS PREDICTIVE VALUE OF TROPONIN

Ford et al. explain that cardiac troponin has been previously shown to be an independent predictor of cardiovascular mortality in individuals without symptoms or signs of cardiovascular disease, but the mechanisms for this association are uncertain, so this analysis was designed to determine whether troponin concentration could predict coronary events and respond to therapy in a primary prevention population.

WOSCOPS was a trial of statin drugs originally completed in 1995 that randomized men with raised low-density lipoprotein cholesterol but no history of myocardial infarction to either a daily regimen of pravastatin or placebo for five years. With frozen plasma samples taken from patients in WOSCOPS, Ford et al. used Abbott's *Architect*$_{STAT}$ high-sensitive troponin I assay to measure the troponin I concentration in the plasma at baseline and at one year in WOSCOPS' 3,318 participants. The primary endpoint was a composite of nonfatal myocardial infarction and death from coronary heart disease. All of the men in this analysis were middle-aged and hypercholesterolemic without prior myocardial infarction.

After adjustment for multiple variables, including baseline troponin concentration and LDL cholesterol, the change in troponin concentration after one year independently predicted nonfatal myocardial infarction or death from coronary heart disease five and fifteen years later in both the statin and control arms of the study.

The investigators then sorted the subjects into fifths based on the change in troponin concentration in the placebo group and found a clear gradient of risk across change in troponin. In the placebo group, relative to the middle fifth, those in the top fifth – with at least a 26% increase in troponin – had a higher risk of the coronary events over five years, and those in the bottom fifth – at least a 27% decrease in troponin concentration – had a lower risk. A similar trend appeared in the statin group, but pravastatin reduced troponin concentration by 13% and doubled the number of subjects whose troponin fell by more than 25%, which was also the group that had the lowest risk for future coronary events – 1.4% over five years.

The risk of the primary endpoint in subjects taking pravastatin was five times lower in those with the greatest reduction in troponin concentration compared to those with the greatest increase in troponin concentration, despite similar reductions in LDL cholesterol concentration. In both the statin and placebo groups, decreases in troponin concentrations were significantly associated with a reduction in coronary events.

"These findings suggest that high-sensitivity cardiac troponin has major potential to identify those at greatest risk and to assess their response to interventions for the prevention of coronary heart disease," Ford et al. conclude. The authors point out that unlike many previous studies of troponin as a predictor of coronary heart disease, this analysis only looked at primary prevention patients, rather than a population that included patients with established coronary heart disease. Also, because the original plasma samples were collected in the 1990s, the authors were able to collect robust clinical follow-up data on well-characterized participants over a 15-year period while using the latest-generation high-sensitivity cardiac troponin I assay, which detected troponin in 99.8% of the study population.

Abbott's Architect$_{STAT}$ high-sensitive troponin I test, which runs on Abbott's Architect lab system, is commercially available outside of the United States and is still in development in the US, the company says, but Abbott's *i-STAT* cardiac troponin-I test, which runs on the portable i-STAT system, is available worldwide.

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# Genomic Health Gets KO'd By Next-Gen Long-Term Breast Cancer Assays

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Results from the TransATAC trial show that **Myriad Genetics Inc.**'s *EndoPredict* and **NanoString Technologies Inc.**'s *Prosigna* second-generation tests are superior to **Genomic Health Inc.**'s *Oncotype Dx* first-generation test for predicting the long-term recurrence of breast cancer.

TransATAC "answers a critically important unmet need/question, which is how to we best manage patients with breast cancer after they've had their surgery – who needs chemo and who doesn't?" Myriad's chief medical officer, Johnathan Lancaster, told *Medtech Insight*. "We know that chemo does a lot of good things for a lot of patients, but if it's not necessary, it can also be harmful. And if it's not necessary, the risk-benefit ratio changes in a way that means that patients are getting more harm than good."

TransATAC is a substudy of the Arimidex, Tamoxifen, Alone or in Combination trial (ATAC) trial, which evaluated the efficacy and safety of anastrozole vs tamoxifen over five years in post-menopausal women with localized primary breast cancer. TransATAC evaluated formalin-fixed, paraffin-embedded tumor samples from a subset of women randomized to the monotherapy arms in the ATAC trial.

Results from 818 patients in TransATAC trial were presented at the 2016 San Antonio Breast Cancer Symposium by Ivana Sestak of the Queen Mary University of London. The patients in the trial were women who had undergone surgery for endocrine receptor-positive (ER+) or HER2-positive breast cancer, including 591 "node-negative" patients – cancer that has not spread to the lymph nodes – and 227 node-positive patients. TransATAC compared six tests used to predict a patient's long-term risk of cancer recurrence, and need for long-term chemo therapy or endocrine therapy. The primary endpoint was distant recurrence of breast cancer and the median follow-up period was 10 years after surgery.

Sestak's group also published results from the trial in the *Journal of Clinical Oncology* and the *Journal of the National Cancer Institute*.

The predictive approaches compared in TransATAC study included: standard clinical treatment score based on nodal status, cancer grade, tumor size, the patient's age, and their treatment history; an immunohistochemical markers score based on the status of the patient's endocrine receptor, the progesterone receptor, the Ki67 protein and the HER2 protein; the Oncotype Dx test, which produces a recurrence score based on 21 different genes; **bioTheranostics Inc.**'s *BCI* (breast cancer index), which combines a molecular grade index and test for the HoxB13/IL17BR estrogen signaling pathway; *Prosigna*, which is based on 46 genes, proliferation score, tumor size; and *EndoPredict*, which tests for eight genes related to cancer proliferation, differentiation, and estrogen, as well as nodal status and tumor size.

The three second-generation tests – BCI, Prosigna and EndoPredict – outperformed Oncotype Dx in the prediction of recurrence of breast cancer in both node-negative and node-positive patients across both the zero to ten years and five to ten-years post-surgery.

Sestak said that, for node-negative patients, all of the tests in the study proved to be good predictors for distant recurrence and were able to identify patients whose risk of recurrence within ten years is so low that they would not benefit from chemotherapy. Among the node-positive patients, however, only the EndoPredict and Prosigna tests could identify this low-risk group with acceptable accuracy, she explained.

Focusing just on the five- to 10-year risk of recurrence, among node-negative patients, BCI, Prosigna, and EndoPredict were all good predictors for late distant recurrence, above and beyond the clinical treatment score alone, and could identify patients whose risks of recurrence is so low that they would not benefit from extended endocrine therapy, Sestak concluded.

For node-positive patients, only Prosigna and EndoPredict could adequately identify the group with a low risk of distant recurrence within five to 10 years. And, with any of the tests, the incorporation of clinical variables proved important, Sestak explained.

"We need tests to help us because clinical parameters and clinical features alone … which we relied on for decades in looking after patients with malignancy, just are not good enough. They have way too high of a false-positive and false-negative," Lancaster said. "If we ignore the molecular biology and what the genes and molecules are doing, and just look at what it looks like under the microscope, we end up treating patients that potentially didn't need it and we don't give chemo to patients who potentially did need it, and they end up developing a recurrence."

## MYRIAD AND NANOSTRING CLAIM VICTORY

Myriad points out that, in a head-to-head comparison between EndoPredict and Oncotype Dx in this study, EndoPredict was a more powerful predictor than Oncotype Dx of recurrence risk across zero to 10 years. Based on the "likelihood ratio," a measure of predictive power, EndoPredict was twice as powerful as Oncotype in node-negative patients, and five-times as powerful in node-positive patients.

Also, in the five-to-ten-year window, EndoPredict was seven times as powerful as Oncotype Dx in node-negative patients and 13 times higher in node-positive patients, according to the likelihood ratio calculations. Oncotype DX failed to achieve statistical significance in predicting cancer recurrence in years five to 10 for either node-positive or node-negative patients. EndopPredict was also better than Oncotype Dx at identifying patients at low risk for recurrence over ten years.

However, NanoString boasts that TransATAC found that Prosigna provided the most accurate prognostic information of all four multigene expression profiles for post-menopausal women with node-negative, hormone receptor-positive, HER2-negative early stage breast cancer, and that Prosigna provided the most accurate differentiation between low- and high-risk patients.

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## ASIA REG ROUNDUP:

# Updates From China, Taiwan And Korea

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China has been active with medtech regulatory activity in the final two months of the year.

The China Food and Drug Administration has moved this year to launch a new priority-approval program for domestic class III devices, and imported class II and class III medical devices on Jan. 1, 2017. In addition, regional authorities in China are pushing to strengthen clinical-trial oversight for devices.

Those developments, along with medtech oversight updates from Taiwan and Korean, are the focus of *Medtech Insight*'s latest regulatory roundup from Asia.

### ACCELERATED ACCESS, TRIAL PROTECTIONS IN CHINA

Applications for devices will get priority attention under the soon-to-launched accelerated program if they meet one of several conditions, explains May Ng, a consultant with Singapore-based ARQon. The criteria include devices that treat rare diseases or malignant tumors, or products that that offer clinical benefits to children or elderly people with multiple diseases, or for which no alternative treatments exist.

The CFDA would accelerate the review and approval process for eligible devices by giving priority to technical reviews, medical device registration quality management system verification, and the administrative approval procedure. The entire process is design to speed up market access and usage of eligible devices.

Expedited approval procedures have been developed twice before in China – in 2009 (emergency approval procedures) and 2014 (innovative medical devices). The 2016 scheme is targeted at the examination and approval of medical device applications.

The news comes on top of the CFDA decision to expand the list of class II and class III medical devices, by 267 and 92, respectively, that do not need to undergo clinical trials nor perform equivalent device comparison for pre-market applications.

Among other recent Chinese initiatives is a drive to by the Shanghai Municipal Food and Drug Administration and Shanghai Municipal Commission of Health and Family Planning to secure better oversight of clinical trials, via a new system of special examinations, or inspections. Shanghai is a major center for clinical trials in China, including for multi-national companies, but there have been concerns about trial authenticity and compliance.

Jack Wong, secretary of the Asia Regulatory Professional Association (ARPA), says there are worries over "fake data" in China, which is why the Shanghai authorities decided to do the inspections. "They want to check if trial sites are real, and compliant, and generally want to check authenticity." It is likely that other Chinese provinces will follow Shanghai's lead.

### TRUMP EFFECT

Another important matter to watch for medtech impacts is the strong potential for the 12-nation Trans-Pacific Partnership (TPP) to fall through with the election of Donald Trump as the next US president. President-elect Trump's antipathy toward the TPP, which was due to begin in spring 2018, is well known. Trump has also stirred up feelings locally over his actions questioning the "One-China" framework and the status of Taiwan.

For China, the US's withdrawal from the TPP could be good news in terms of new trading possibilities. China might see itself as filling the vacuum left by the US. The other 11 TPP members are Vietnam, Malaysia, Singapore, Brunei, Canada, Mexico, Australia, New Zealand, Chile and Peru.

But a US withdrawal from the trade agreement could have negative impacts on the medtech sector in the region. The Taiwan FDA (TFDA), for instance, already has a system that is quite well aligned with US FDA's. TFDA had intended to exempt free sales certificate-holders from the national registration procedure if the applicant company came from a country that is part of the TPP. Taiwan has already passed related legislation in its own parliament.

### TAIWAN SYSTEM

Taiwan has been performing product registrations since 1973, Emily Wu, a section chief at the TFDA who is responsible for drafting medical device regulation, told the 2016 Informa Life Science emerging markets conference in Brussels earlier this year. And with 42,500 local dealers and more than 41,000 devices licensed in the country – 76% of which are imported –Taiwan cannot really be described as an "emerging" market. It is, in fact, saturated, she said.

The Taiwan device regulatory system has three risk classes (I, II and III) and groups its medical devices into 17 categories (three of which are for diagnostics). The system is continually being

supplemented with new regulations, guidelines and guidance documents. Most recently, the government has amended classification rules, issued new technical guidelines for industry on software and nano-devices, and released new administrative guidelines on instructions-for-use and a new version of good clinical practices (harmonized with ISO 14155), which was announced in late 2015 and came into force in 2016.

All manufacturers need good manufacturing practice compliance for quality systems. For class I products, manufacturers simply need to file an affidavit. Taiwan does not yet have an online registration system but plans to launch one in the future. For higher-risk products, technical documents need to be filed. But if products are EU- or FDA-approved, local testing can be waived. That waiver does not apply to class III (high-risk) products.

Taiwan also hopes to build a third-party accreditation system for medical devices, to help with work volumes, spare TFDA manpower and improve pre-market review efficiency. It is also seeking to strengthen post-market surveillance.

### KOREA AND UDI

Building a Unique Device Identification system is another aim of TFDA, and that effort has gathered steam in Taiwan in the past year.

Korea has similar aims on UDI, and has drafted a revision to its Medical Device Act to reflect that medical devices will in the future have standardized UDIs for device identification and tracking. The intention is for the Korean Ministry of Food and Drug Safety (MFDS) to set up a device integration data system to provide oversight over the lifetime of devices. This system will include data on the manufacturer, importer and seller.

"With UDI, every country in Asia is in learning mode – they are just starting up their activities. Korea is no different, and is on the learning curve," said Wong. He adds: "These elements are not country-specific – you need to link with the whole world on this."

### NEED FOR SPEED

While Asian regulatory reforms are moving at a brisk pace in parts of the continent, there is an apparent need for catchup, or simply a need for more speed, in some countries.

A good example of this, in Wong's view, is Vietnam. "There is a new law ahead, but no one is preparing for these regulations that are due in force in 2017," he said. He believes local companies are too embroiled with their own current projects. "But they've got to think long term. They must get their products, people, and money lined up and ready. The law is coming, but companies must not leave preparations to the last moment," he said.

Another example of the need for more speed is the draft medtech regulations law in Indian law. Proposed in summer, it appears to have experienced little progress since, sources tell *Medtech Insight*.

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## NEW EU REGS:
# Checking Facts On Dates and Progress

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Various EU experts have suggested at public meetings during the last three months that Europe's Medical Device and IVD Regulations are likely to be adopted and take effect by the end of May 2017. But some have expressed doubts that this will be possible and there is talk about adoption at a much later stage because of problems. So what is happening?

Sources close to EU level discussions on the regulations have confirmed to *Medtech Insight* that May is indeed tenable as a date for the regulations to enter into force. Adoption of the two regulations by the Council of the EU is planned for early March and, after that, the European Parliament will hold a plenary vote – planned for one of its April sessions to agree on the regulations as adopted by the Council.

As long as there is agreement, the regulations will be published shortly afterwards in the Official Journal of the European Union (OJEU) and enter into force on the 20th day after publication.

### MORE CLARIFICATION ON TRANSITIONAL ARRANGEMENTS

There has generally been a lot of confusion voiced at public meetings around interpretation of the currently available texts regarding the transition arrangements during the period between when the regulations take effect and when they are fully applied. This includes questions about the length of time that manufacturers can continue to be audited by notified bodies to the current EU medical device directives.

Those involved in further work on the text have acknowledged the feedback from member-state experts and interested parties has shown, indeed, that there was a need for further clarification and there is an aim to make the transitional arrangements easier to understand in the final documents.

### EUDAMED DATABASE

The same EU sources have indicated to *Medtech Insight* that nothing is changing in the regulatory texts concerning the timing of the setting up of new version of the Eudamed medical device database and the dates for reporting to this database.

But they confirmed that the application of certain obligations of the regulations presupposes a functional Eudamed, and therefore the application of these obligations "could hypothetically be delayed." The wording should become clearer on this when the final versions of the texts are made public, it seems.

### HUNDREDS OF ERRORS FOUND IN LEGAL-LINGUISTIC REVIEW?

The different language versions of the regulations have been undergoing a routine legal-linguistic review by the EU Commission.

There has been talk about delays being caused to the adoption dates because of huge numbers of corrections needed to the different language texts, which are translations from original English text, including some 500 corrections that need to be made to the German text. These fears of extra delay, however, are unfounded, according to sources close the EU developments.

They explained that equal implementation in all member states necessitates the use of legal concepts that have the same meaning in all official languages. It is very difficult and "not very meaningful" to compare the number of changes between language versions, since "most of them are trivial" and their number depends on the quality of the original text and the translations of the changes.

The aim of the legal-linguistic finalization is to check that terminology is used consistently throughout the text, "which - in a long text - results in many changes."

Among the changes anticipated as possible in the final versions of the regulations, according to sources, is some numbering of the articles within the documents.

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# US FDA Issues New Patient-Reported Outcome Tools For LASIK

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US FDA is circulating new Web-based patient questionnaires that it says can be used to more effectively assess patient expectations and outcomes from LASIK surgery and can also be used by device manufacturers to collect patient-reported outcomes for pre-market submissions.

The PROWL pre-op and post-op questionnaires were posted to FDA's website Dec. 14. They are based on outcomes from a seven-year effort performed in conjunction with the National Eye Institute and the Department of Defense. The LASIK Quality of Life Collaboration project was launched in 2009 to get a better understanding of the impact and prevalence of unwanted visual symptoms, such as starbursts, glare, ghosting, or halos, or severe dry eye, that result from LASIK.

Out of the effort, two studies were conducted – PROWL-1 and PROWL-2 – that found new visual symptoms occurred in 43%-46% of patients after LASIK. That is a higher rate than anticipated, but the research also found that less than 1% of patients in the study experienced "a lot of difficulty" or inability to do usual activities without corrective lenses, despite the symptoms.

A key take-home message from the research patients were more than twice as likely to report their visual symptoms when filling out a questionnaire, than to tell them to their health care provide, according to Malvina Eydelman, who directs the FDA review division that oversees ophthalmic devices.

"The newly-developed questions in the PROWL questionnaire can facilitate discussions between eye-care providers and patients considering LASIK surgery," Eydelman said in a Dec. 14 blog post.

She also pointed out that the questionnaire serves as a patient-report outcomes tool to inform studies of new devices.

"Manufacturers may wish to include such information in future LASIK product submissions along with other clinical and non-clinical evidence for FDA's benefit-risk determination," the agency official said.

Development of new patient-reported outcome measures is a major strategic priority for FDA's device center, an effort that is slated to get more support under the next medical user-fee program.

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# Zimmer Biomet Inspection Finds Extensive GMP Woes

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A 58-page, 14-observation FDA Form 483 issued after a recent US FDA inspection of **Zimmer Biomet Holdings Inc.**'s Warsaw, Ind., plant is likely to lead to a warning letter and ongoing remediation efforts, one analysis states.

The firm issued a statement Dec. 14 acknowledging receiving the FDA-483 form. Analysts at Wells Fargo Securities obtained the form from FDA via a Freedom of Information Act request.

The form sent to Zimmer is "one of the longest and most serious 483s our consultant has ever seen," Wells Fargo analysts said, citing the review by contracted by the investment bank. The consultant expects Zimmer Biomet to need at least a year to address all the problems identified, the team led by Wells Fargo senior analyst Larry Biegelsen stated Dec. 14.

FDA chose to give multiple examples for each observation, which caused the extreme length of the document. This may indicate a high level of concern on the part of the agency, the Wells Fargo analysts speculate.

The nature of the details in the FDA-483 includes some suggestions that the agency may feel the observations represent a risk to product safety, as opposed to being strictly technical violations. For example, the first observation suggests Zimmer Biomet may not have properly validated its sterilization procedures and notes that one product sample tested positive for microbial growth. In addition, multiple observations comment on potential problems with the plant's water supply. The inspectors found that while Zimmer Biomet had recorded 13 water samples that failed microbial or endotoxin testing between July 1 and Sept. 1, the company didn't follow up to see if the contamination could have influenced product safety.

The company's cleanroom air quality was also questioned, and the inspectors found dust on vents overlooking four work areas.

Overall, FDA said, the buildings were "not of a suitable design to perform necessary operations." For example, the layout of some areas required personnel to enter the work environment before donning a sterile gown, rather than putting it on first. In addition, ungowned staff can travel through some areas where gowns are required. The walkway goes within one foot of work surfaces, FDA said.

Complaint handling was another trouble spot, with FDA saying Zimmer Biomet was inconsistent in categorizing complaints. Several complaints about revisions tied to infections were not filed under the "infections" label, the 483 form states.

Inspectors also said Zimmer Biomet lacked procedures to control nonconforming product. Employees in the sports-medicine division often recorded product rejections on uncontrolled spreadsheets, rather than within the formal system. The FDA-483 also records a range of GMP issues, such as failure to properly record all design changes, a lack of process monitoring procedures, and a lack of acceptance activity procedures.

FDA inspected the plant between Sept. 12 and Nov. 22. The inspection wasn't continuous; instead, it was executed via a series of three-week sessions. The form doesn't explain the reasoning behind that scheduling.

In a written statement, Zimmer Biomet said it is in communication with FDA and is already working to execute a remediation plan. But the problems identified in the inspection haven't caused any known product safety issues, the firm says. The company believes the financial impact of the observations was reflected in its Oct. 31 quarterly report.

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## COMPLIANCE CORNER:

# 5 Tips For Successful FDA Inspections, From SOPs To Roleplaying

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From offering an FDA investigator a cup of coffee to discovering the best communicators to explain complex issues, four industry insiders share tips on how device manufacturers can better ensure smooth sailing during a facility inspection.

Comments from the experts, which came during a panel discussion at the 11th annual FDA Inspections Summit in Bethesda, Md., were edited by *Medtech Insight* for clarity.


## 1 HAVE ROBUST INSPECTION PROCEDURES

**Karl Vahey, VP of manufacturing quality, Medtronic:** "The inspection SOP [standard operating procedure] is like an action plan. It's used to describe your process of what to do when you get that knock on the door from an FDA investigator. You need to have a communications plan – who you need to inform inside the company – so make sure you've identified the right people. You also need to have your FDA readiness plan, whatever that may be, which should name documents that you know are going to be looked at by an investigator. Your SOP should also address how you're going to handle an inspection if it's unannounced.

"And have backups noted in your SOP. Very often when there's a knock on the door from FDA, not all of the required people are there; they're on vacation or whatever it may be. You need to be prepared for that. You need to have backups because it's a quality systems inspection, it's not a person inspection, so you need to have people in place regardless of whether your quality manager is out for the week, or whatever it may be.

"An inspection SOP is a very good document to have. I've often looked at our own inspection procedures when I come onto a [Medtronic] site. I want to see that everybody knows what goes on during an inspection. The employees should know who's going to be in the front room with the investigator and what the communication will be between the front and back rooms. I want to know that the employees know what the scribe is going to do, for example."

**Ricki Chase, compliance practice director at Lachman Consultant Services Inc., and a former director of FDA's Investigations Branch:** "If you don't have an inspection SOP in your organization, you should have one, and you should train on it and you should practice to it, and make sure that you could actually implement it. It's critical. There's nothing worse for you than having an investigator walk in the door and being completely unprepared."

**Bryan Coleman, senior director of pharmaceutical and device consulting services at EAS Consulting Group, and a former FDA consumer safety officer:** "But remember, if it's a procedure and it's in your portfolio, then it's sort of fair game for the agency to look at. I would never put anything in a procedure that I was not prepared to follow and I didn't feel was valid, and if you can stand behind that, then you should be proud to show it to the FDA.

"I've been laughed at by the agency when they've come to my facilities in the past to inspect because they see the SOP on how to manage the FDA inspection, and there's always a chuckle. The investigator will say, 'So, why don't you let me see the SOP so I know how you're supposed to take care of me?' So, I offer it. But they've never actually taken it and read it, but they do find it interesting that you have thought ahead and prepared enough to know that you are going to respond to their questions, and how you're going to follow up with their inquiries and give them information."

**Julie Larsen, principal and director of inspection readiness services at consulting firm BioTeknica:** "And I'll add to that: You wouldn't ever want to put anything in your inspection procedures that would be inappropriate for an investigator to see."

## 2 PROVIDE ADEQUATE INVESTIGATOR WORKSPACE

**Coleman:** "The perfect setup for an investigator's workspace is a room that's large enough to host one, two or three FDA investigators – or chemists, biologists or whomever happens to be there – so they can sit and have enough space on their

left and right to work. It should be the same on the other side of the table for the folks at your facility. You need to have enough room to work. You shouldn't be crammed in and on top of one another. It becomes very easy to cloud the room with lots of excess conversations when you're very close in proximity.

"During an inspection when I worked in industry, I always seated myself against the back wall where I could have folks come in through the door and hand me things without interrupting the FDA investigator while he or she was working."

**Chase:** "Don't put the workroom in the middle or back of your plant. It just doesn't make sense. What are you going to do, parade the investigators through your facility every morning? That's what's called a 'target-rich environment.' You might as well just throw open the doors and say, 'Hey, come see what we're doing!' That's not a good idea. So, you want to make sure you station investigators somewhere near the front of the facility where it's easy for them to get in and out.

"And temperature really is important. If a room cannot be temperature-regulated, then you don't want to use that room as the investigator's workroom. Nothing's going to make somebody crankier than if they're sitting there sweating to death, or if they're so cold that they must put on their mittens to be able to look at your documents.

"Also, providing water or coffee is good. That's just being a good host, right? You wouldn't invite somebody to your house and not offer them at least a glass of water or a bottle of water. It's always nice to have something to make the investigator comfortable.

"The bottom line is, the more time your investigator is spending dealing with operational issues and not really getting down to the tactics of the investigation is more time for them to find problems. And they will. If they're just sitting around waiting to get something, they're going to start thinking about, 'What else can I look at? Oh, that's interesting. What's that over there? Oh, that's interesting.' Or they'll start having conversations with your staff, which might not know how to fill the time, and your staff will start talking and begin saying all kinds of interesting things to the investigator."

> "Someone could be absolutely fantastic at their job but they might not be the right person that has the communication skillsets and the thought processes to speak to an FDA investigator," consultant Julie Larsen says.

## 3 MAKE SURE APPROPRIATE STAFF INTERACT WITH INVESTIGATORS – AND DITCH THE ATTORNEY

**Larsen:** "When it comes to personnel in the front room with the investigator, you need to have your senior people available because they're responsible. And there should be someone who knows in general how the operation works and can answer many of the basic questions very generally and provide basic information about what's going on without having to bring somebody else into the room.

"You also want someone working with the investigator every day, consistently, so they keep all of the pieces together for the investigator. And that person should also be that investigator's point person for any concerns and requests. There should also be a scribe in the front room who is taking notes. And there may or may not be someone in the room who's a runner to bring documents in and out. It depends on the situation. You may also need to bring in a technical subject matter expert or other people to answer more specific questions.

"But when it comes to having a corporate attorney present, I would not recommend that. That sets a certain tone, and it's not a positive one. I think in most cases it would put the investigator on the defensive. The investigators would wonder why you have an attorney present in the first place and it would certainly get their suspicions up as far as why that would even be necessary. And I also think that that results in the investigator probably being a little bit less open with you or willing to discuss things when there's an attorney sitting there. Certainly, have your attorneys available to you to consult if something happens that you're concerned about, but they should not be in the room, in my opinion."

## 4 SELECT SUBJECT MATTER EXPERTS CAREFULLY

**Larsen:** "A lot of device companies believe the person who knows the absolute most about a topic should be the SME

[subject matter expert] that interacts with the investigator. But that can be a pitfall because that person might know a lot about it and can speak about it in a very technical fashion, but describing things in a concise, clear manner may not be a skillset he or she has.

"So, as you're looking at who's going to represent a certain area, it's not always the manager. It's not always the person that knows the most. Rather, it might be the person who can best represent that area, and answer questions clearly, accurately and concisely. And if they need to be supplemented or if follow-up needs to occur, then that can happen.

"Sometimes people believe they're not good at their job if they're not the one that's selected to speak to the FDA, and that's really not true. There are different skillsets for different things, and someone could be absolutely fantastic at their job but they might not be the right person that has the communication skillsets and the thought processes to speak to an FDA investigator."

**Chase:** "It's vitally important to choose an SME who can speak to an investigator on a level that is comprehensible. Sometimes engineers or PhD scientists aren't the best people to do this. What the investigator needs is a layman's explanation. The investigator doesn't need a dissertation.

"If you have really smart people in your organization who are like that – which I know you do – and if they're not the kind of people who can adjust their communication appropriately to talk in layman's terms, then those are not the people you want talking to the investigator. Rather, you want somebody who knows what's going on but can communicate in such a way that the investigator can understand. It's very, very important."

## 5 USE ROLEPLAYING TO FIND BEST COMMUNICATORS

**Coleman:** "Roleplaying is invaluable at pointing out folks who need assistance preparing for when the FDA really shows up at your front door. Roleplaying helps to point out gaps in the mechanisms of how you're trying to manage an inspection. They tend to point out rather quickly some of the flaws in your own operating procedures around how you do something. Maybe you've done it right, but what you're finding during that mock inspection is, you're not telling the right story around the data you have. It causes a lot of heartache.

"I can't say enough for mock inspections. You don't have to hire a consultant to do that. If you have corporate auditors that come to look at your facility, you can take an annual corporate audit and treat it like a mock inspection. They don't even have to know they're playing the role of the FDA. Make sure your staff understands how you'd react and respond, and how to pull documents in a timely manner, giving a concise, consolidated answer to the auditors, so you are always practicing those skillsets, and not just because the FDA is there."

"The last thing you want to have happen is to come across or be perceived as being defensive, because that just doesn't go down well," Medtronic's Karl Vahey says.

"**Vahey:** "Roleplaying helps you find the right people to talk to investigators. In certain instances, you may find that a person just doesn't react well in front of an investigator, and you can see that in the roleplaying, and you're going to have to make a judgment call in terms of what you do. Might you bring someone else up-to-speed? Might you have the quality manager speak to whatever is being asked? It's all about making a staffer who's not typically used to being put in front of an investigator comfortable with doing so. So, relax them. And there's only one way of doing that: Practice makes perfect.

"It's like a dress rehearsal. You need to sit down with your staff and play the part of the investigator and play the part of different types of investigators. We've all seen different types of investigators, right? So, play different personalities because depending on who's in front of you, the last thing you want to have happen is to come across or be perceived as being defensive, because that just doesn't go down well. And that happens sometimes when people are nervous, they're not prepared and they haven't been trained appropriately."

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