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FIRM PULLED IN $100M SERIES A

Grail poised to raise $1B in series B, on path to shrugging off subsidiary status

By Omar Ford, Staff Writer

Early cancer screening start up Grail Inc. could raise more than $1 billion in a series B round, making it in one of the largest financings in med-tech history. Grail said the funding would be used to develop a blood-based test for cancer screening. In addition, part of the funding would be used to repurchase a portion of Illumina Inc.'s stake in Grail.

The San Diego-based company launched Grail almost a year ago. (See *Medical Device Daily*, Jan. 12, 2016.) Since that time, Grail has taken in $100 million in a series A round from the likes of Bill Gates, Bezos Expeditions and Sutter Hill Ventures. The liquid biopsy specialist has not revealed who the investors are for the series B round. Grail said it intends to close the round before the end of 1Q17.

See Grail, page 4

POGO TESTS IN ONE STEP

Intuity Medical bumps up to $55M to back streamlined blood glucose monitor in U.S.

By Stacy Lawrence, Staff Writer

Intuity Medical Inc. hopes to help rationalize blood glucose testing by diabetics with an all-in-one monitoring system that dispenses with the need for discrete supplies and multiple steps. Its Pogo Automatic Blood Glucose Monitoring System, which it claims is the

See Intuity, page 5

WARNING LETTERS

For launches, enforcement delays as critical as approval times

By Mari Serebrov, Regulatory Editor

When it comes to launching a new drug or medical device, time is money.

Thus, it's no surprise that the biopharma and med-tech industries center on FDA review and approval times when they negotiate user fee agreements with the agency. And when Congress looked to reduce the cost of new cures by

See FDA, page 6

FIRST OF ITS KIND ON MARKET

Optiscan's near continuous multianalyte monitoring device gains CE marking

By Melody Watson, Staff Writer

Optiscan Biomedical Corp. said the Optiscanner 6000, a bedside monitoring technology that can track both glucose and lactate levels, has received the CE mark, making it the first non-calibrated automated system on the market. The device was designed to overcome the limitations

See Optiscan, page 7

REGULATORY

FDA mum on non-*de novo* applications in device accessory final

By Mark McCarty, Regulatory Editor

The FDA's final guidance for classification of medical device accessories nods to provisions in the 21st Century Cures Act regarding the issue of risk classification, but despite comments from industry, the guidance did not spell out the use of regulatory pathways other than the *de novo* path for premarket applications.

See PMAs, page 8

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NEUROLOGY EXTRA

Production Editor Andrea Gonzalez on one of med-tech's key sectors

Read this week's Monday Special

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APPOINTMENTS AND ADVANCEMENTS

Axogen Inc., of Alachua, Fla., reported the appointment of Ivica Ducic as medical director of clinical and translational sciences. Ducic will be responsible for Axogen's global medical affairs programs as a non-officer member of the leadership team.

Entellus Medical Inc., of Plymouth, Minn., reported the promotion of Thomas Williamson to the position of vice president of sales; the resignation of Jim Surek as vice president of sales; and the promotion of Jonelle Burnham to the position of vice president and general counsel, all effective immediately.

Foundation Medicine Inc., of Cambridge, Mass., said as part of the succession of its executive leadership, its board has appointed Troy Cox as CEO to succeed Michael Pellini. Pellini, who has served as CEO of the company since 2011, has been appointed chairman of the company's board. Alexis Borisy, founding CEO and current chairman of the board for Foundation Medicine, will continue to serve on the board. Cox will also join the board. All of these changes will become effective by Feb. 6.

Invuity Inc., of San Francisco, reported the appointment of Andy Sale as senior vice president of global sales. Sale brings more than 17 years of experience in the medical-device industry.

DAILY M&A

Invitae Corp., a San Francisco-based genetic information company, said it has acquired San Mateo, Calif.-based **Altavoice** (formerly Patientcrossroads), a privately owned, patient-centered data company with a global platform for collecting, curating, coordinating and delivering safeguarded data from patients and clinicians. The two companies plan to integrate their efforts post acquisition in order to build a more robust network for combining genetic information and clinical data into a seamless network to accelerate research, clinical trials and disease management. Invitae purchased all of Altavoice's stock in exchange for $5 million in Invitae common stock issuable upon closing and up to an additional $10 million in Invitae common stock issuable based on certain future milestones.

FINANCINGS

Concord Medical Services Holdings Ltd., a specialty hospital management solution provider and operator of the largest network of radiotherapy and diagnostic imaging centers in China, reported that its subsidiary, Meizhong Jiahe Hospital Management Corp. Ltd (MHM), previously known as CMS Hospital Management Co. Ltd., has completed two rounds of the private offering of additional shares and received proceeds of approximately ¥141.67 million (US$20.46 million). MHM plans to use the proceeds of the private offering for its internal restructuring and working capital and general corporate purposes.

Richmond, Calif.-based **Ekso Bionics Holdings Inc.**, a robotic exoskeleton company, said it has entered into a term loan agreement with **Bridge Bank**, of San Jose, Calif. The agreement provides Ekso Bionics with up to $10 million of potential borrowing capacity. The initial term loan of $7 million funded on Dec. 30, 2016. Prior to Dec. 31, 2017, Ekso Bionics has the ability, at its discretion, to secure an additional $3 million term loan, provided certain conditions are met.

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BUSINESS OFFICE

Donald R. Johnston (Senior Director, Current Awareness), Penney Holland (Web Production Manager)

10 BIGGEST U.S. WINNERS FOR THE WEEK

By Percent		By Dollars	
Titan Medical	58.75	Athenahealth	10.69
Echo Therapeutics	23.52	Thermo Fisher Sci	6.17
Biolase	21.43	C.R. Bard	5.00
Transenterix	15.38	Henry Schein	4.47
iCAD	15.30	Teleflex	4.17
Fluidigm	10.58	Penumbra	4.10
Invuity	10.43	Edwards Lifesci	3.37
Mazor Robotics	10.31	Abiomed	2.74
Athenahealth	10.16	Agilent Technologies	2.43
Accuray	7.61	Abbott Laboratories	2.37

10 BIGGEST U.S. LOSERS FOR THE WEEK

By Percent		By Dollars	
Delcath Systems	-36.96	ICU Medical	-15.48
Pavmed Inc.	-13.04	Stryker	-2.06
ICU Medical	-10.50	Align Technology	-2.05
Sunshine Heart	-9.71	Inogen	-1.86
Seaspine	-9.37	Quidel	-1.03
Quidel	-4.81	Pavmed Inc.	-0.90
RTI Surgical	-4.62	Cardiovascular Syst	-0.77
Cardiovascular Syst	-3.18	Seaspine	-0.74
InspireMD	-2.80	Varian Medical	-0.57
Inogen	-2.77	Haemonetics	-0.57

MDD STOCK REPORT FOR PUBLIC MED-TECH COMPANIES

COMPANY	SYMBOL	CLOSE 12/30	CLOSE 1/6	%CHANGE WK	%CHANGE YTD	VOL (000)
Abbott Laboratories	ABT	38.41	40.78	6.17	6.17	58090
Abiomed	ABMD	112.68	115.42	2.43	2.43	1272
Accuray	ARAY	4.6	4.95	7.61	7.61	2902
Agilent Technologies	A	45.56	47.99	5.33	5.33	7948
Alere	ALR	38.97	39.61	1.64	1.64	2196
Align Technology	ALGN	96.13	94.08	-2.13	-2.13	3223
Allscripts Healthcare	MDRX	10.21	10.69	4.70	4.70	14068
Athenahealth	ATHN	105.17	115.86	10.16	10.16	2989
Baxter International	BAX	44.34	45.52	2.66	2.66	10375
BD	BDX	165.55	167.89	1.41	1.41	5060
Biolase	BIOL	1.4	1.7	21.43	21.43	320
Boston Scientific	BSX	21.63	22.15	2.40	2.40	26822
Bovie Medical	BVX	3.59	3.86	7.52	7.52	195
C.R. Bard	BCR	224.66	229.66	2.23	2.23	2395
Cantel Medical Corp	CMD	78.75	79.18	0.55	0.55	540
Cardiovascular Syst	CSII	24.21	23.44	-3.18	-3.18	781
Checkcap	CHEK	2.35	2.43	3.40	3.40	283
Conmed	CNMD	44.17	44.88	1.61	1.61	602
Cynosure	CYNO	45.6	45.15	-0.99	-0.99	3851
Delcath Systems	DCTH	0.92	0.58	-36.96	-36.96	8435
Dentsply Internat	XRAY	57.73	58.29	0.97	0.97	5041
Dextera Surgical	DXTR	0.96	0.94	-2.08	-2.08	110
Echo Therapeutics	ECTE	0.162	0.2001	23.52	23.52	89
Edwards Lifesci	EW	93.7	97.07	3.60	3.60	8729
Endologix	ELGX	5.72	5.705	-0.26	-0.26	12500
Fluidigm	FLDM	7.28	8.05	10.58	10.58	1020
Haemonetics	HAE	40.2	39.63	-1.42	-1.42	1207
Halyard	HYH	36.98	37.77	2.14	2.14	1107
Henry Schein	HSIC	151.71	156.18	2.95	2.95	1982
Hill-Rom Holdings	HRC	56.14	57.87	3.08	3.08	3237
Hologic	HOLX	40.12	39.88	-0.60	-0.60	9168
iCAD	ICAD	3.235	3.73	15.30	15.30	385
ICU Medical	ICUI	147.35	131.875	-10.50	-10.50	1177
Idexx Laboratories	IDXX	117.27	118.36	0.93	0.93	23426
Inogen	INGN	67.17	65.31	-2.77	-2.77	662
InspireMD	NSPR	2.5	2.43	-2.80	-2.80	161
Intersect ENT	XENT	12.1	11.85	-2.07	-2.07	625
Intuitive Surgical	ISRG	634.17	636.11	0.31	0.31	1382
Invuity	IVTY	5.75	6.35	10.43	10.43	554
Iridex	IRIX	14.06	13.74	-2.28	-2.28	126
Labcorp	LH	128.38	129.34	0.75	0.75	3529
Lianluo Smart Ltd	LLIT	1.5	1.5	0.00	0.00	11
Livanova	LIVN	44.97	45.82	1.89	1.89	1450
Luminex	LMNX	20.23	20.36	0.64	0.64	532
Masimo	MASI	67.4	67.83	0.64	0.64	1708
Mazor Robotics	MZOR	21.92	24.18	10.31	10.31	492
Medtronic	MDT	71.23	72.87	2.30	2.30	34119
Meridian Bioscience	VIVO	17.7	17.6	-0.56	-0.56	1126
Novocure	NVCR	7.85	8	1.91	1.91	921
Nuvasive	NUVA	67.36	67.14	-0.33	-0.33	2359
Nxstage Medical	NXTM	26.21	27.15	3.59	3.59	1658
Orthofix Internat	OFIX	36.18	35.67	-1.41	-1.41	779
Pavmed Inc.	PAVM	6.9	6	-13.04	-13.04	14
Penumbra	PEN	63.8	67.9	6.43	6.43	770
Quest Diagnostics	DGX	91.9	92.02	0.13	0.13	3806
Quidel	QDEL	21.42	20.39	-4.81	-4.81	896
RTI Surgical	RTIX	3.25	3.1	-4.62	-4.62	415
Seaspine	SPNE	7.9	7.16	-9.37	-9.37	78
Senseonics Holdings	SENS	2.67	2.84	6.37	6.37	924
Smith & Nephew	SNN	30.08	30.2	0.40	0.40	1759
Spectranetics	SPNC	24.5	24.25	-1.02	-1.02	1068
Stereotaxis	STXS	0.6499	0.68	4.63	4.63	189
Steris	STE	67.39	68.49	1.63	1.63	1772
Strata Skin Sciences	SSKN	0.44	0.47	6.82	6.82	45
Stryker	SYK	119.81	117.75	-1.72	-1.72	7573
Sunshine Heart	SSH	0.35	0.316	-9.71	-9.71	3091
Syneron Medical	ELOS	8.4	8.9	5.95	5.95	423
Tearlab	TEAR	0.5199	0.557	7.14	7.14	166
Teleflex	TFX	161.15	165.32	2.59	2.59	1616
The Cooper Cos	COO	174.93	177.21	1.30	1.30	1833
Thermo Fisher Sci	TMO	141.1	147.27	4.37	4.37	7829
Titan Medical	TITXF	0.24	0.381	58.75	58.75	7565
Transenterix	TRXC	1.3	1.5	15.38	15.38	3487
Varian Medical	VAR	89.78	89.21	-0.63	-0.63	3256
Vascular Solutions	VASC	56.1	55.75	-0.62	-0.62	1047
Wright Medical	WMGI	22.98	23.98	4.35	4.35	4594
Zeltiq Aesthetics	ZLTQ	43.52	43.17	-0.80	-0.80	2657
Zimmer Biomet	ZBH	103.2	104.96	1.71	1.71	6147

NOTES

Trading volumes for Nasdaq, Amex and NYSE are recorded as the total number of shares traded (in thousands) on a weekly basis (cumulative Monday through Friday); the weekly and YTD % changes are from IPO completion, where applicable.

Due to its acquisition by Abbott Laboratories on Jan. 4, 2017, St. Jude Medical has been removed from the report.

Average percent change week: +2.41%
Range: -36.96% to +58.75%; Number of companies: 78
(not market weighted)

Average percent change YTD: +2.41%
Range: -36.96% to +58.75%; Number of companies: 78
(not market weighted)

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Grail

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"Through high-intensity sequencing, population-scale clinical studies, and unparalleled computing power, we hope to transform the paradigm from late stage diagnosis and poor outcomes to early stage detection and more cancer cures," said Jeff Huber, Grail's CEO and a former Google executive. "The indication of interest for this capital raise is a testament to investors' shared belief in our commitment."

With the funding round, Illumina's stake in Grail will be less than 20 percent, and it will change its contract with the start up to a market based agreement. Grail will then be treated as a cost-based investment instead of a subsidiary. This move could make Grail one of Illumina's largest customers over time, both by providing royalties on future testing and through the gene sequencing company's appreciation in ownership.

Grail uses Illumina's gene sequencing technology to potentially spot any kind of cancer in the body before symptoms appear.

The gene sequencing company will no longer have representation on Grail's board said Doug Schenkel, an analyst with Cowen and Co. Illumina shares (NASDAQ:ILMN) were up 5.15 percent late last week.

Schenkel said this is a win-win for both companies as it gives Illumina the opportunity to return to its roots and Grail the chance to boldly go strike at the liquid biopsy market.

"Grail needed to get bigger," he said. "Grail now has the ability to focus on more than an asymptomatic pan-cancer test.

Grail is now free to pursue other areas such as tumor-specific indications and patient monitoring/therapy selection."

Previously, Grail had agreed to not participate in those areas because Illumina did not want to effectively directly compete with customers.

Already, Grail has started making bold moves on the liquid biopsy front – which would call for exorbitant funding. In December, Grail launched the Circulating Cell-free Genome Atlas (CCGA) study, a trial which will enroll at least 7,000 cancer patients and 3,000 healthy individuals, interrogating the biology of both tumor biopsy tissue samples and the circulating, tumor-derived nucleic acids in blood. (See *Medical Device Daily*, Dec. 6, 2016.) Circulating tumor nucleic acids in the blood are an emerging biomarker for earlier cancer detection.

Large-scale studies like CCGA will support the development of a pan-cancer screening test for asymptomatic individuals, which could, according to Grail, make a major dent in global cancer mortality. The company said these studies have to include samples from tens of thousands of people in order for researchers to identify the patterns required to detect many types of cancer. Confirming clinical validity and utility of these tests, however, will be an even bigger feat, which Grail said will require studies of hundreds of thousands of people.

Such a trial is also costly, which will likely consume a lion's share of the firm's investment dollars.

LIQUID BIOPSY LANDSCAPE

The true clinical impact of liquid biopsy technology remains to be seen, but the potential to represent a major shift in cancer treatment has attracted interest from a growing number of companies of all sizes. The promise of liquid biopsy technology is so strong, in fact, that 20 stakeholders, including biopharma companies, diagnostic players and academic institutions, are working to create a large database for cancer genomic profiling data as part of outgoing U.S. Vice President Joe Biden's Cancer Moonshot effort. This liquid biopsy database is expected to serve as the basis for the development of blood-based cancer tests, pooling data from assays that use circulating tumor cells, circulating tumor DNA and exosomes.

If Grail is successful with the CCGA study, then the company could be miles ahead of its competition in the liquid biopsy space, which includes Boreal Genomics Inc., Natera Inc., Personal Genome Diagnostics Inc., Pathway Genomics Corp. and Trovagene Inc.

While both blood-based and urine-based assays qualify as liquid biopsy tests, the majority of players in the space are focused on blood, leaving San Diego-based Trovagene Inc. one of few contenders on the urine-based side of the market. //

REGULATORY FRONT

The U.S. **FDA** has inked a draft guidance for 510(k) filings for bone anchors, which will overwrite the 1996 guidance for testing bone anchors. The guidance covers general suture and nitinol suture anchors as well as polymeric absorbable suture anchors, and includes sections on clinical and non-clinical performance testing. The scope of the guidance includes anchors used to attach soft tissue to bone, but excludes devices used to attach bone to bone, as well as devices intended for attachment of synthetic ligaments and tendons to bone. The agency is taking comment through March 6, 2017, under docket number FDA-2016-D-4436.

The U.S. **Center for Devices and Radiological Health** has upgraded to class II all surgical instruments associated with the implant of urogynecological mesh, applying the new regulatory term of "specialized surgical instrumentation for use with urogynecological mesh." The agency made note of a January 2016 advisory panel hearing that concluded that neither class I nor class III were appropriate for these surgical instruments, but the final order requires a demonstration that such instruments can be adequately sterilized between uses and that non-clinical testing be conducted to ensure devices perform as expected. Makers of these surgical instruments must obtain a 510(k) for existing devices by Jan. 8, 2018.

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Intuity

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first to enable testing in a single step, was cleared by the FDA last April.

Now, the Sunnyvale, Calif.-based start up aims to launch Pogo this year in the U.S. It has bumped up its most recent venture round to $55 million, from a prior close at $40 million in November. That brings the total raised by the company to about $175 million since it was founded in 2002.

With this additional capital, KCK Group joined lead investor PTV Healthcare Capital and affiliates of Luther King Capital Management as new investors alongside existing investors Accuitive Medical Ventures, Investor Growth Capital, U.S. Venture Partners, Venrock and Versant Ventures.

MAKING THE CASE FOR POGO

Intuity isn't divulging the Pogo pricing yet – but it does plan to be on par with existing testing products to appeal to payers and patients, who typically pay a co-pay for diabetes testing supplies.

"We'll be competitive, so patients can have access to the product," Intuity President and CEO Emory Anderson told *Medical Device Daily*. "Patients need to have a product that they can have access to and will fit in with their economic structure; we want to deliver this to as many patients as possible. We will price it consistent with other products on the market but deliver more value."

Anderson said Intuity has been working closely with payers for at least three years to educate them about the potential benefits of Pogo – which it sees as improving patient adherence to testing recommendations, thereby providing more accurate data upon which to determine the best insulin dosing.

Roughly half of the 29 million diabetics in the U.S. are not achieving adequate glycemic control in the management of their diabetes, according to the American Diabetes Association. At least some of that poor management is due to inconvenient blood glucose testing, with many patients not meeting the minimal testing recommendation from the ADA of thrice daily. They, therefore, don't have enough information to dose themselves appropriately – potentially putting themselves at greater risk for diabetic complications.

"All the other meters in the marketplace take approximately 15 steps, including putting the lancing needle in, putting the testing strip in and out, removing the needle when you're done. These devices look very simple, but the steps to get a result are quite cumbersome," said Intuity's Anderson.

"This is the number one obstacle to testing more frequently and at the right time. With Pogo, you turn the device on, put the finger on the device and get the result in four seconds," he continued. "We have research showing that nine out of 10 patients prefer Pogo versus the current products for ease of use, convenience and discretion."

EUROPE NEXT, AND AN IPO?

Anderson expects Pogo could become a replacement product, not just a convenient alternative, for busy diabetics who know they need to test frequently to help keep themselves healthy.

The data from the system is managed in Intuity's Patterns Diabetes Management System, a cloud-based platform to detect and manage patterns and trends in the data related to glucose control. That's set up to be shared by the patient with the physician as well as parents and other caregivers.

The Pogo system contains a cartridge with 10 tests. It requires only a tiny sample of blood, 0.25 microliters, to determine the glucose value. Once the 10 tests are completed, the cartridge is disposed of and replaced, with no need to handle the traditional test strips and lancets.

Intuity opted to obtain a regulatory go-ahead in the U.S. first, now this year it's aiming for a CE mark in Europe as well. The company is intent on marketing on its own thus far in the U.S. but may eventually look to strategic partners, particularly to address ex-U.S. markets.

An IPO may be in the cards for Intuity. Anderson said he will be keeping an eye on revenue growth for POGO and the opening of a solid IPO window. He noted that 2016 wasn't a particularly strong IPO market – and that potential next-gen diabetic monitor public market comps Dexcom Inc. and Insulet Corp. each went public before they had significant revenues.

"For Intuity, the focus right now is to bring the product to the patient and to generate revenue in a predictable growth ramp. That process will allow us to look at raising additional capital to grow the business," Anderson concluded. **//**

FINANCINGS

Neurometrix Inc., of Waltham, Mass., reported it has closed its previously announced private placement to a health care dedicated institutional investor of 7,000 shares of series E convertible preferred stock at a price of $1,000 per share and warrants to purchase an aggregate of approximately 10 million shares of common stock at an exercise price of $0.70 per share. Neurometrix has received gross proceeds from the first tranche of the offering of $4 million, and expects to receive gross proceeds from a second tranche, which is subject to shareholder approval and an effective resale registration statement, of $3 million. The proceeds of the offering will be used for commercialization of Quell, the company's over-the-counter wearable device for relief of chronic pain, in the U.S. Rodman & Renshaw, a unit of H.C. Wainwright & Co. LLC acted as the exclusive placement agent for the transaction.

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FDA

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streamlining R&D, it focused on clearing out obstacles in the agency's standard development and review practices.

What's been left out of the equation is how long it takes the FDA to address manufacturing problems noted in plant inspections. Its Center for Drug Evaluation and Research (CDER) and Center for Devices and Radiological Health (CDRH) won't approve new therapies if the facilities making them don't measure up, as lack of good manufacturing practice (GMP) compliance can affect the quality of a product.

Last year, GMP violations resulted in 14 complete response letters (CRL) for novel drugs, indefinitely delaying the launch of those products, said John Jenkins, the retiring director of CDER's Office of New Drugs. Many of those CRLs cited manufacturing issues as the primary deficiency. That's unusual, Jenkins said. CDER issued 47 CRLs for novel drugs from 2010 through 2015, but only four of those letters were due to GMP issues.

The CRLs should serve as a reminder to sponsors that all of their manufacturing facilities must comply with GMP regulations if they want to ensure approval of their applications, Jenkins said.

CAUGHT UNAWARES

A CRL citing GMP concerns can catch sponsors unawares, especially since CDER is taking longer and longer to send out warning letters after a company has responded to inspection findings. "That is a problem," David Rosen, a partner at Foley & Lardner LLP and a former FDA official, told *Medical Device Daily*. "This is a big issue."

In 2016, CDER sent 43 warning letters citing GMP violations. Even though the drug manufacturers responded to inspection concerns in a timely manner, 20 of the warning letters were sent at least a year after the inspection. One manufacturer in India received a warning letter 16 months after an inspection. The average time from inspection to CDER warning letter was seven months. (See GMP Warning Letters.)

CDRH seems to be doing a better job of notifying device companies of GMP violations. Of the 18 GMP warning letters it issued in 2016, one was sent out within eight months of the inspection, three within six months and the rest within four or five months. One of the 18 has been closed out already.

Getting timely feedback from the FDA on GMP compliance is crucial to sponsors, Rosen said, especially those developing new products. They need to know early on if their manufacturing plans for a new product are acceptable; otherwise, approval could be delayed and even a short delay can prove costly.

Recognizing that fact, Margaret Hamburg made the timely issuance of warning and closeout letters a priority soon after she came on board as FDA commissioner. She reduced the time companies had to respond to inspection observations to 15 days and said the agency would no longer indulge in a stream of back-and-forth correspondence before sending a warning letter.

That policy led to a shorter turnaround from inspection to warning letter – for a while. In 2011, after the policy was put in place, the average time between an inspection and warning letter for drug companies was 6.3 months. The time for device makers was two months shorter.

GMP WARNING LETTERS

	CDER	CDRH
2011		
Sent	**21**	**52**
Average wait	6.3 mos	4.3 mos
# taking 12 mos or longer	2	1
Placed on import alert/ DPE	2	11 threatened
# closed out	13	21
2016		
Sent	**43**	**18**
Average wait	7 mos	5 mos
# taking 12 mos or longer	20	0
Placed on import alert/ DPE	19	11
# closed out	0	1
Source: FDA Warning Letter Database		

SAFETY ISSUE

Slow FDA action on quality issues goes beyond approval delays; it also can impact the safety of drugs and devices already on the market. As a result of GMP issues, CDRH took steps to place products from 65 percent of the device makers receiving warning letters in 2016 on detention without physical examination (DPE).

Of the 43 drug manufacturers receiving a warning letter last year, 19 were placed on import alert. While CDER imposed the import alerts before sending the warning letters, it still took an average of 5.3 months to restrict the import of drugs that potentially had significant quality issues. In two instances, CDER waited nearly a year before imposing an import alert.

In another instance, CDER waited more than a year after inspecting Dongying Tiandong Pharmaceutical Co. Ltd.'s API plant in Shandong, China, to send it a warning letter spelling out the possibility that tainted heparin could have been used to manufacture API for the U.S. market. However, the company was not placed on import alert.

The letter was sent eight months after France's National Agency for Medicines and Health Products Safety (ANSM) cited similar problems and called on the EMA to revoke Dongying's

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FDA

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good manufacturing practice certificate. The ANSM recalled the company's products in March and urged other EU members to do the same.

When asked about the time it took to send Dongying the warning letter, a CDER spokesperson told *Medical Device Daily* that agency "experts must review all available information regarding serious violations and evidence uncovered during the FDA inspection and any responses by the company to determine the appropriate and necessary next steps. This review can take time."

But such delays can undermine confidence in the FDA's ability to ensure the quality of drugs and devices on the U.S. market. "If a company isn't doing something right, I want the FDA to do its job," Rosen said. There has to be a minimum standard of quality drug and device companies must maintain to continue to market products in the U.S., and the FDA has to be tough on compliance – in a timely way, he added. //

PRODUCT BRIEFS

Audubon, Pa.-based **Globus Medical Inc.**, a musculoskeletal implant manufacturer, reported that the Excelsius GPS, a system providing robotic trajectory guidance and navigation, is now CE marked. This platform technology supports both minimally invasive and open orthopedic and neurosurgical procedures, with applications ranging from the cervical spine to the sacroilium, long bones and cranium. Excelsius GPS integrates with Globus Medical implants and instruments and is compatible with pre-operative CT, intra-operative CT and fluoroscopic imaging modalities.

Myriad Genetics Inc., of Salt Lake City, reported that multiple **Blue Cross Blue Shield** (BCBS) affiliate plans have issued positive coverage determinations for Endopredict, including Independence Blue Cross, Blue Cross and Blue Shield of Kansas, Blue Cross and Blue Shield of Kansas City, Horizon Blue Cross Blue Shield of New Jersey and Bluecross Blueshield of South Carolina. These five BCBS plans provide coverage for an additional 12 million patients in the U.S. Endopredict is a second-generation, multigene test that is designed to predict disease recurrence in patients diagnosed with breast cancer.

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Optiscan

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found with current intermittent and manually operated monitoring devices.

Approximately 20 percent of intensive care unit (ICU) patients are thought to have pre-existing diabetes and up to 70 percent experience stress hyperglycemia, a temporary condition in which glucose levels are elevated. All of these patients require accurate glucose monitoring in order to maintain tight glycemic control. Lactate is a biomarker for a number of critical illnesses, such as sepsis, trauma and burns, and elevated levels are associated with adverse clinical outcomes. Recent literature suggests that interventions for these illnesses are considered to be effective if lactate levels are shown to decrease over a predetermined period of time.

Verifying changes in levels of either of these analytes is difficult with current devices whereas with the Optiscanner 6000 monitoring of both analytes is near continuous due to the automated serial measurements, providing physicians with the information they need to best manage patient glucose and lactate levels in the ICU. The Optiscanner 6000 also has an alarm function when levels reach a critical level.

In addition to providing near continuous monitoring, the system uses plasma for measurement of analytes, which is associated with superior accuracy, instead of whole blood, which is commonly used by various intermittent-measurement manually operated technologies. The Optiscanner 6000 may also increase available nursing time per patient, as current publications suggest that intermittent manually operated technologies may require up to two additional hours of nursing time.

SOLID GROWTH IN CGM DEVICE MARKET

The global market for continuous glucose monitoring systems is expected to generate revenue of $2.93 billion by 2021, yielding a compound annual growth rate of 31.3 percent during 2015-2021, according to a report by Allied Market Research. By 2020, the report said, the most lucrative customer segment market for continuous glucose monitoring will be the ICU due to implementation of mandatory tight glycemic control protocols that have been imposed by many healthcare regulatory authorities across both developed and developing regions.

SO FAR, NO COMPETITORS EXIST

Many companies have tried to emulate the Optiscanner 6000, according to Hayward, Calif.-based Optiscan's CEO Peter Rule, but all have failed. He told *Medical Device Daily* that "key technological differences between the Optiscanner 6000 and other attempts in continuous glucose monitoring systems in the ICU setting include the ability of the Optiscanner 6000 to work with any IV connection versus a dedicated catheter,

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Optiscan

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the lack of calibration ... and the capability of the Optiscanner 6000's fluidic system to withdraw a very small sample of blood (approximately 0.1 ml) and then centrifuge that to plasma."

Currently Optiscan is in dialogue with the U.S. FDA for the approval of glucose monitoring. They have submitted data demonstrating a best Mean Average Relative Difference (MARD) of 7.6 percent, the best MARD of any continuous glucose monitoring system worldwide. Commercialization of the system is also planned in Italy and Germany in the first quarter of this year.

Regarding future products in the pipeline, there are plans at the company to expand the platform with additional analyte tests. These will be announced following CE mark approvals later this year.

Rule said that "glucose has always been the core reason for the creation of the Optiscanner. We have always wanted to create a product that fit seamlessly into the ICU environment: without the need for calibration, with minimum blood consumption and with a compelling MARD. It has been proven in the outpatient environment that a near continuous system with a compelling MARD can improve patient outcomes, and the Optiscanner 5000 is poised to deliver on that promise for the ICU patient".

He went on to add that "we are grateful to the many ICU physicians who have given their time and shared their insights with us in the creation of the original Optiscanner 5000. During that process, we realized that the real time knowledge of lactate elevation would help a physician investigate a dangerous and life-threatening change in their patients. They impressed upon us how much they needed both the alarm that an elevation had occurred and also the knowledge of whether their intervention was effective by seeing a decrease in lactate levels over time. The Optiscanner 6000 assists ICU physicians with this important knowledge." //

PMAs

Continued from page 1

The draft guidance, which the FDA published in January 2015, provided definitions to terms that were previously undefined, a list that includes devices that support, augment and supplement the index device. The agency had previously defined the regulatory status of an accessory per that of the "parent" device (those which have undergone premarket review via the PMA or 510(k) pathways), or by issuance of a separate classification order for the accessory. The draft also acknowledged that an accessory could be allocated to a lower risk classification than the parent device.

Nonetheless, the draft said a new class I or class II accessory type should be reviewed via the *de novo* process and did not spell out any alternative paths for review. Any *de novo* application for the accessory would be reviewed within 120 days, but the draft also said that the risk profile of an accessory "can differ significantly" from that of the parent device.

The 21st Century Cures Act was amended so that the FDA should classify an accessory "based on the intended use" of that accessory without regard to the intended use of the parent device. In response, the final guidance said that the classification of accessory devices "should reflect the risks of the device when used as intended, and the level of regulatory controls necessary to provide a reasonable assurance of safety and effectiveness."

Nonetheless, the final guidance offers no insight into how the 510(k) process could be used to review an application for an accessory and reiterates text from the draft stipulating that even class I device accessories would be reviewed via the *de novo* process in the absence of a predicate. The guidance added that any application the agency declines to review necessarily renders that accessory a class III device.

Among those who commented to the docket for the draft was Sharon Segal of the Advanced Medical Technology Association, who said the agency should expand the scope of the draft to existing accessories that have assumed the classification of the parent device. Most accessories are typically slotted into the same device class as the parent device, and she said that the guidance offers no assurance that a low-risk accessory would not end up as a class II or III device after a *de novo* review.

Both the draft and final versions said that the *de novo* path is not appropriate for reclassification of an accessory that has already been classified by regulation or order. However, the final guidance offers little more on this subject other than to state that the guidance's focus is on the classification of a new accessory type via the *de novo* process. The agency also pointed to its adoption of the guidance by the International Medical Device Regulator's Forum for software as a medical device, adding that the accessory final guidance's provisions apply to software that would serve as an accessory.

The draft and final guidances offer examples of accessories, but the final omits an example seen in the draft of a battery used in an automated external defibrillator. The Medical Imaging & Technology Alliance had remarked in comments to the docket that a battery is better characterized as an essential component than as an accessory, a message the agency seems to have taken seriously, given the final guidance's passage stating that batteries are among those items that qualify as replacement parts and, hence, are excluded from the scope of the guidance.

The Orthopedic Surgical Manufacturers Association's (OSMA) response to the draft stated that the risks associated with surgical instruments used with orthopedic implants would always be lower than the risks associated with the implant itself. OSMA argued that surgical instruments should hence remain in class I, but the final retains a passage from the draft stating that a guidewire that augments a bone-cutting tool by improving precision would fall under the terms of the guidance. This passage did not indicate that the agency is amenable to a lower risk classification for the guidewire than for the bone-cutting tool. //

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OTHER NEWS TO NOTE

Seattle-based **Adaptive Biotechnologies Corp.**, a company focused on combining next-generation sequencing (NGS) and expert bioinformatics to profile T- and B-cell receptors of the adaptive immune system, reported it has entered into an agreement with **Amgen Inc.**, a biopharmaceutical company headquartered in Thousand Oaks, Calif., to further develop and commercialize Adaptive's NGS-based Clonoseq Assay to assess minimal residual disease (MRD) in patients with Acute Lymphoblastic Leukemia (ALL). The Clonoseq Assay detects and quantifies DNA sequences found in malignant cells, which can be tracked throughout treatment. The assay provides consistent, accurate measurement of disease burden, allowing physicians to visualize response to treatment over time to optimize patient management. Through the collaboration, the parties will work towards building the dataset for MRD as a validated measure of patient outcomes in ALL.

Sentreheart Inc., of Redwood City, Calif., said it has completed the stage I enrollment milestone in the aMAZE trial. The first stage of the trial is designed to assess safety and performance of the Lariat Suture Delivery System procedure in the first 100 consecutively enrolled subjects, assessed by independent adjudication and data monitoring committees. The first subject was enrolled in October 2015, and the trial is currently recruiting subjects in 34 U.S. centers. It is anticipated that by mid 2017, the aMAZE trial will expand to 50 centers across the U.S. and in limited international locations.

Synergeyes Inc., a Carlsbad, Calif.-based hybrid specialty contact lens company, announced a new partnership with **NKL Contact Lens**, a specialty contact lens manufacturer and wholly owned subsidiary of Japan-based **Menicon Co. Ltd**. The partnership paves the way for Synergeyes to offer a complete line of scleral, gas permeable (GP) and hybrid contact lens products in North America. The new line of Synergeyes GP and scleral contact lenses will be introduced in January at the Global Specialty Lens Symposium in Las Vegas.

Two Pore Guys Inc. (2PG), of Santa Cruz, Calif., reported it is collaborating with oncologists at the University of California at San Francisco to evaluate its hand-held, nanopore-based platform in the detection of cell-free, circulating tumor DNA (ctDNA) from patient liquid biopsies. The study will focus on detecting the KRAS G12D mutation among ctDNAs obtained from patient blood and urine samples. If successful, the device could be a new way to monitor patients for the recurrence of cancer from home on a daily basis. 2PG's platform is composed of a battery-operated reader device and disposable test strips containing reagents and solid-state nanopore chips that detect individual molecules, one by one. While 2PG made the reagents for its liquid biopsy assay, it does not intend to go to market with its own assays. 2PG's core IP defines how to make reagents that work with third-party diagnostic chemistries, thereby allowing industry partners to adapt existing assays and to enter new markets on 2PG's platform.

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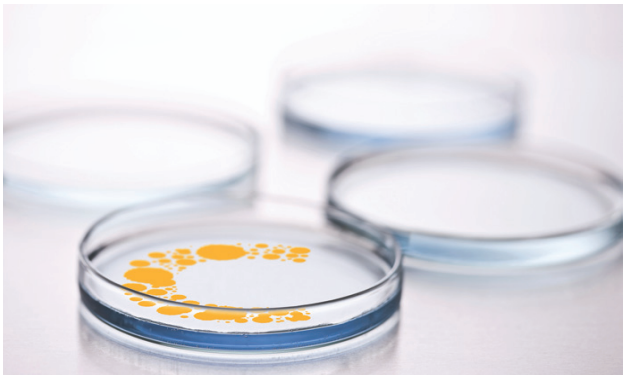

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NEUROLOGY EXTRA

Keeping you up to date on recent developments in neurology

By Andrea Gonzalez, Production Editor

Alzheimer's patients show improvement with Neuronix's NeuroAD Therapy System

Neuronix Ltd., of Yokneam, Israel, reported positive results from its pivotal double-blind, placebo-controlled, multicenter clinical study for the assessment of the safety and efficacy of the neuroAD Therapy System in the treatment of mild to moderate Alzheimer's disease. The neuroAD Therapy System is a patent-protected, non-invasive medical device that combines transcranial magnetic stimulation with cognitive training to target brain regions affected by Alzheimer's disease. This dual-stimulation is designed to improve cognitive performance of patients, following an intervention protocol. The results of the study were presented at the Clinical Trials in Alzheimer's Disease International Conference. The study enrolled 131 patients with mild-moderate Alzheimer's disease, either medicated (on stable dose) or non-medicated, at nine medical centers in the U.S. and one in Israel. Researchers evaluated the safety and efficacy of the neuroAD Therapy System in comparison to placebo, following six weeks of treatment and additional six weeks of follow-up, using the cognitive and behavioral standard scales for the evaluation of patients with Alzheimer's disease – ADAS-Cog and CGI-C, respectively. Positive efficacy results were reported for patients with milder disease as determined by the baseline ADAS-Cog. In that group of patients, which represented 85 percent of the enrolled population, a positive and statistically significant difference of -1.8 points in ADAS-Cog was noted between treatment group and placebo group. In the entire study cohort, including those with more severe disease at baseline based on the ADAS-Cog, results did not reach statistical significance. The CGI-C results in the overall population showed a trend toward improvement, with a difference between treatment and placebo groups of -0.4 points. When analyzing the group of milder patients, the difference between treatment and placebo groups reached -0.45. Furthermore, when measured on the CGI-C scale, only 16 percent of treated patients deteriorated, compared with 42 percent of patients in the placebo group. In addition, results showed a favorable safety profile. Patients also showed a high degree of adherence to the treatment, with few discontinuations and a high rate of treatment completion. The results, together with previous studies' similar outcomes, were used to support a U.S. FDA *de-novo* application filed by Neuronix in November 2016. The neuroAD Therapy System is approved for use in Europe.

Treating depression? There's an app for that

Researchers from the University of California at San Francisco (UCSF) and the University of Washington Health Sciences (UW) have found promising results for treating depression with a video game interface that targets underlying cognitive issues associated with depression rather than just managing the symptoms. The first study enrolled older adults diagnosed with late-life depression into a treatment trial where they were randomized to receive either a mobile, tablet-based treatment technology developed by Akili Interactive Labs called Project: EVO or an in-person therapy technique known as problem-solving therapy (PST). Project: EVO runs on phones and tablets and is designed to improve focus and attention at a basic neurological level. The results, published Jan. 3 in the *journal Depression and Anxiety*, showed that the group using Project: EVO demonstrated specific cognitive benefits compared to the behavioral therapy, and saw similar improvements in mood and self-reported function. According to one of the authors, most of the participants had never used a tablet, let alone played a video game, but compliance was more than 100 percent. The participants were required to play the game five times a week for 20 minutes, but many played it more. Participants in this arm of the study also attended weekly meetings with a clinician. The meetings served as a control for the fact that participants in the problem-solving therapy arm were seen in person on a weekly basis, and social contact of this nature can have a positive effect on mood. A second study, which was another joint effort by UW and UCSF, randomized more than 600 people across the U.S. assessed as moderately or mildly depressed to one of three interventions: Akili's Project: EVO; iPST, an app deployment of problem-solving therapy; or a placebo control (an app called Health Tips, which offered healthy suggestions). The study, published in the *Journal of Medical Internet Research*, found that people who were mildly depressed were able to see improvements in all three groups, including the placebo. However, those individuals who were more than mildly depressed showed a greater improvement of their symptoms following their use of Project EVO or iPST versus the placebo. The lead author stressed the apps should be used under clinical supervision because without a human interface, people were not as motivated to use it. In the second study, 58 percent of participants did not download the app. Akili's technologies are based on a proprietary neuroscience approach developed to target specific neurological systems through sensory and

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digital mechanics. Project: EVO is undergoing multiple clinical trials for use in cognitive disorders – including Alzheimer's disease, traumatic brain injury and pediatric attention deficit hyperactivity disorder, and the company is on path for potential FDA clearance for the game's use to treat pediatric ADHD.

Nrf2 protein may be key to treating Parkinson's

New details learned about a key cellular protein could lead to treatments for neurodegenerative diseases, such as Parkinson's, Huntington's, Alzheimer's and amyotrophic lateral sclerosis (ALS). In a new study, researchers at the Gladstone Institutes used the protein Nrf2 to restore levels of the disease-causing proteins to a normal, healthy range, thereby preventing cell death. The researchers tested Nrf2 in two models of Parkinson's disease: cells with mutations in the proteins LRRK2 and α-synuclein. By activating Nrf2, the researchers turned on several "house-cleaning" mechanisms in the cell to remove excess LRRK2 and α-synuclein. In the study, published in the *Proceedings of the National Academy of Sciences*, the scientists used both rat neurons and human neurons created from induced pluripotent stem cells. They then programmed the neurons to express Nrf2 and either mutant LRRK2 or α-synuclein. Using a one-of-a-kind robotic microscope developed by the Finkbeiner laboratory, the researchers tagged and tracked individual neurons over time to monitor their protein levels and overall health. They took thousands of images of the cells over the course of a week, measuring the development and demise of each one. The scientists discovered that Nrf2 worked in different ways to help remove either mutant LRRK2 or α-synuclein from the cells. For mutant LRRK2, Nrf2 drove the protein to gather into incidental clumps that can remain in the cell without damaging it. For α-synuclein, Nrf2 accelerated the breakdown and clearance of the protein, reducing its levels in the cell. The scientists say that Nrf2 itself may be difficult to target with a drug because it is involved in so many cellular processes, so they are now focusing on some of its downstream effects. They hope to identify other players in the protein regulation pathway that interact with Nrf2 to improve cell health and that may be easier to drug.

Possible higher risk of dementia for those who live near major roadways

New research from Public Health Ontario and the Institute for Clinical Evaluative Sciences has found that people who lived within 50 meters of high-traffic roads had a 7 percent higher likelihood of developing dementia compared to those who lived more than 300 meters away from busy roads. Published in *The Lancet*, the researchers examined records of more than 6.5 million Ontario residents aged 20-85 to investigate the correlation between living close to major roads and dementia, Parkinson's disease and multiple sclerosis. Scientists identified 243,611 cases of dementia, 31,577 cases of Parkinson's disease, and 9,247 cases of multiple sclerosis in Ontario between 2001 and 2012. In addition, they mapped individuals' proximity to major roadways using the postal code of their residence. The increase in the risk of developing dementia went down to 4 percent if people lived 50-100 meters from major traffic and to 2 percent if they lived within 101-200 meters. At over 200 meters, there was no elevated risk of dementia. However, the findings indicate that there was no correlation between major traffic proximity and Parkinson's disease or multiple sclerosis.

MDD PERSPECTIVES

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