Quarterly Trend Advisory

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Keep on Your Radar: Medical Device Cybersecurity – The New Reality

Ransomware, malware, distributed denial of service attacks, Mirai – bad actors in a scary sci-fi thriller targeting your personal computer (PC), tablet, or gaming device? Cyber attacks look for vulnerabilities in any system, not just your PC. Many sectors including credit cards, banking, government, retail, and social media are objects of cyber attacks. The healthcare ecosphere, particularly medical devices, are a prime target of cyber bugs. In fact, healthcare is the number 1 industry when it comes to breach of data and generally lacks specialized security controls. Moreover, personal health information is 50 times more valuable on the black market than a credit card.

Ransomware, which block access to a computer or network until money is paid, are on the rise with 88% of attacks occurring in healthcare. Earlier this year, a California hospital paid $17,000 to cyber intruders to regain control of its electronic health network. Just last year, Anthem's database of about 80 million people was also hacked.

Internet-connected medical devices, hospital networks, and other devices fall in the realm of Internet of Things (IoT). Like computers, these connected devices can be hacked, potentially affecting the safety and effectiveness of the device and compromising patient privacy and safety.

In October 2016, J&J reported the potential for hackers to exploit a security susceptibility in the Animas® One Touch Ping® insulin pump. This could force the pump to deliver unauthorized insulin injections, leading to a possible insulin overdose, which can be life threatening. In August 2016, there were denied allegations about a possible dangerous cyber bug with 1 manufacturer's cardiac devices. Last year, the FDA issued a few warnings about potential cyber bugs with Hospira's (now Pfizer) infusion pumps. Despite these reports, the FDA is not aware of any cases where hackers have exploited cyber vulnerabilities to harm a patient.

Inside this Issue

In January 2016, the FDA made medical device cybersecurity a priority by issuing draft guidance for manufacturers. It provides direction to monitor, identify, and address cybersecurity vulnerabilities throughout the medical device lifecycle. This is largely a voluntary framework to aid manufacturers in building a scaffolded approach to minimize and mitigate risk.

> ***"Personal health information is 50 times more valuable on the black market than a credit card."***

Cyber attacks on medical devices are expected to grow and become more sophisticated as hackers continue to hone their craft. Threatened connected devices range from security cameras to coffee makers and from the federal government to medical devices such as MRIs, infusion and insulin pumps, and the list goes on. There is a proliferation of wearables and medical devices with software and programmable logic. When factoring in the evolution of electronic medical records and telehealth, regulators, medical device manufacturers, and health networks need to get savvier in order to provide solid security against this new reality.

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Magellan Rx MANAGEMENT

Did You Know: Precision Medicine – Just How Precise?

The "5 Rights" of medication administration is an axiom historically taught to nursing students. The right patient, right drug, right time, right dose, and right route, have long have been promoted as a technique to reduce medication administration errors. Advances in molecular genomics takes this old axiom to a new level.

Precision medicine holds the promise of helping the prescriber determine the right drug for the right patient based on an individual patient's genetic makeup. In the field of oncology, precision medicine aims to identify DNA mutations or tumor markers in order to tailor treatments for individual patients. One challenge with precision medicine is determining exactly which patients will achieve benefit from a particular drug. Since it is not realistic to develop millions of drugs for every viable genetic mutation, clinical studies must be designed to identify all patients who may benefit from the drug while simultaneously determining which patients will not achieve benefits that outweigh risks.

One recent example of the complexity of this process involves 2 immunotherapy drugs for the first-line treatment of advanced lung cancer. During the design of these clinical trials, 1 manufacturer opted to administer their drug to patients who had 5% of their tumor cells expressing a certain protein, [programmed death-ligand 1 (PD-L1)], while another opted to test their drug only in patients where 50% or more of the tumor cells expressed PD-L1. The results of these studies determined that in patients with high (≥50%) PD-L1 expression, the immunotherapy drug was more effective than standard chemotherapy, but the other immunotherapy drug was not more effective in patients with only 5% PD-L1 expression. These results beg the question, what about patients whose tumor cells expressed more than 5% but less than 50% PD-L1? A robust answer would likely require additional large-scale clinical trials, which may not be feasible. Even in the era of "precision medicine," precision is not necessarily a synonym of certainty when it comes to the complexity of human disease.

Abuse-Deterrent Opioids – One Year Later

In a previous issue, we discussed the role of abuse-deterrent opioids. One year later, ongoing initiatives have been developed and implemented to confront opioid abuse, including the introduction of additional new abuse-deterrent opioid formulations. No opioid formulation can prevent people from abusing opioids by swallowing a large number of intact tablets or capsules, which is the most common method of abuse. However, multiple methods have been designed to prevent abuse with an adulterated opioid.

Types of abuse-deterrent properties include physical/chemical barriers to prevent breakdown of the product, agonist/antagonist combinations, added aversive substances, unique drug delivery systems (e.g., depot injections, implants), or new molecular entities or prodrugs with novel effects (e.g., altered receptor binding, enzymatic activation). Notably, while multiple medications have abuse-deterrent *properties*, only agents meeting the Food and Drug Administration's (FDA) requirements for evidence published in April 2015

Table 1. Opioids Recognized as Abuse-Deterrent Formulations

Drug	Methods of Abuse-Deterrence					Specific Technology
	Antagonist	Aversion	Delivery System	Physical/Chemical Barriers	Prodrug	
Embeda® (morphine/ naltrexone, extended-release)	X	X				Sequestered naltrexone
Hysingla® ER (hydrocodone extended-release)				X		Resistec™
OxyContin® (oxycodone extended-release)				X		Intac®
Xtampza® ER (oxycodone extended-release)				X		DeteRx®

The FDA has recognized other formulations as abuse-deterrent, but they are not currently available. These include Targiniq™ ER (oxycodone/naloxone, extended-release), MorphaBond™ (morphine extended-release), and Troxyca® ER (oxycodone/naltrexone, extended-release).

are approved as abuse-deterrent *formulations* (see Table 1). The types of studies the FDA requires are laboratory-based *in vitro* manipulation and extraction studies, pharmacokinetic studies, and *in vivo* clinical abuse potential studies, which commonly measure drug-liking by subjects without pain. As a result, the labeling of these products includes information regarding these abuse-deterrence studies, reflecting the FDA's approval of these products as abuse-deterrent formulations. Since November 2015, 2 new agents were approved, but only 1 has launched: Xtampza ER (oxycodone extended-release).

Telehealth: The Wave of the Future? – Part 2, Telepharmacy

In our last edition, we looked at the current role of telemedicine in the delivery of healthcare. Telepharmacy, a component of telehealth, is built on a similar principle. The National Association of Boards of Pharmacy has developed a definition for the practice of telepharmacy; practically speaking, it is the provision of pharmacy services via telecommunication. Telepharmacy, though not new, has expanded as technology has grown.

The use of telepharmacy varies throughout the United States (U.S.), particularly based on the need for rural pharmacy services or convenience. The North Dakota (ND) Telepharmacy Project was established to combat pharmacy closures in rural areas. Technicians operate local remote pharmacies, while pharmacists are available via video conferencing to assist the technician, verify the medication, and counsel the patient in real time. There are 25 central pharmacy sites and 56 remote telepharmacy sites currently, providing pharmacy services to over 80,000 rural ND citizens who would not otherwise have local pharmacy services.

In select states, such as California and Illinois, telepharmacy may be provided through a pharmacy kiosk, functioning as a medication ATM. A pharmacist or technician are available via phone but the patient may need to actively inquire with questions rather than the pharmacy providing routine counseling. Most of these programs are in the pilot stage. Throughout the U.S., telepharmacy is also used to provide Medication Therapy Management (MTM) services, expand inpatient clinical pharmacy services, and assist with transitions in care.

The ND Telepharmacy Project has provided significant safety data over the years. A cross-sectional study conducted in 2003 evaluated quality-related events (QREs) consisting of either a near miss or an error at 24 pharmacies (14 remote, 10 central). While overall QREs were similar, the type of event and cause differed by location. For instance, remote sites had a higher rate of near misses (more likely to be caught by the pharmacist on final check). They were also more likely to have incorrect directions during the entry process compared to other types of errors. Other studies of telemedicine have demonstrated generally comparable safety within the reported national average.

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Challenges of telepharmacy include electronic security and state regulations. Software specifically marketed for telepharmacy purposes must ensure adequate databases as well as privacy compliance. Since the need for telepharmacy programs differs by state and continues to unfold, uniform regulation is difficult. In 2001, the same year ND established their program, Washington (WA) began using remote dispensing and interactive video conferencing for counseling to provide federal 340B Program medications; however, there are fewer specific regulations regarding telepharmacy in WA than in ND. Individual state licensing and fee requirements for telepharmacy also vary.

The role of telepharmacy is still evolving. Technology offers methods to provide remote areas with greater access to pharmacy services. Likewise, telepharmacy can provide clinical pharmacy services to broader groups of healthcare providers and patients in urban areas. Regulations and infrastructure are still being developed, but telepharmacy may improve safety, access, and clinical support for an expanded group of clinicians and patients.

Pipeline Report: 4th Quarter 2016 / 1st Quarter 2017

Drug/Manufacturer	Clinical Use	Anticipated Date	Projected Market Impact
Select Branded Pipeline Agents: Potential New Emerging Expenses for Health Plans			
lutetium Lu 177 dotatate (Lutathera®) Advanced Accelerator Applications	Neuroendocrine tumors (NET)	December 28, 2016	Injectable somatostatin analog using peptide receptor radionuclide therapy; demonstrated improved Progression Free Survival (PFS) versus octreotide acetate; Orphan Drug/ Priority Review/Fast Track status
ocrelizumab (Ocrevus®) Roche/Genentech	Primary progressive multiple sclerosis (PPMS); relapsing-remitting multiple sclerosis (RRMS)	December 28, 2016	CD20-directed cytolytic antibody; intravenous; first agent for PPMS; positive results in ORATORIO trial versus placebo in PPMS and OPERA studies versus Rebif in RRMS; Priority Review/Fast Track status
nusinersen (Spinraza™) Ionis/Biogen	Infantile onset spinal muscular atrophy (SMA); later-onset SMA	4Q 2016	Increases the production of fully functional survival motor neuron protein by modulating closely related gene (antisense oligonucleotide); intrathecal injection; first approved agent for SMA and only drug to treat the underlying genetic disorder in patients with SMA; ENDEAR and CHERISH trials demonstrated improvement in reaching motor milestones and motor improvement; Orphan Drug/Priority Review/Fast Track status
telotristat etiprate Lexicon/Ipsen	Carcinoid syndrome	February 28, 2017	Tryptophan hydroxylase inhibitor; likely to be first oral therapy for symptoms mediated by hormones secreted from carcinoid tumors; TELASTAR and TELECAST trials demonstrated decreased bowel movements versus placebo; Orphan Drug/Fast Track status
Select New Generics/Patent Expirations			
ezetimibe tablets generic for Merck's Zetia®	Dyslipidemia	December 12, 2016	Settlement agreement with Glenmark/Par; 180-day exclusivity; Zetia had $2.29 billion in sales in 2015
oseltamivir capsules generic for Roche's Tamiflu®	Influenza	4Q 2016	Settlement with Natco to launch in 4Q2016; settlement with Lupin to launch shortly prior to or on February 23, 2017; sales of $415 million in 2015
oseltamivir suspension generic for Roche's Tamiflu®	Influenza	1Q 2017	Settlement with Lupin to launch prior to or on February 23, 2017; sales of $190 million in 2015
Select Biosimilars			
Lapelga™-biosimilar to Amgen's Neulasta® Apotex/Apobiologix	Neutropenia associated with chemotherapy; neutropenia associated with radiation	2H 2016	Subcutaneous colony stimulating factor approved for neutropenia associated with chemotherapy or radiation; product launch likely to be delayed due to regulatory hurdles; Neulasta had $4.04 billion in sales in 2015