Highlights of FDA Activities – 4/1/15 – 4/30/15

FDA Drug Safety Communications & Drug Information Updates:

Drug Information Update: FDA Issues Final Guidance on the Evaluation and Labeling of Abuse-Deterrent Opioids 4/2/15

To combat opioid misuse and abuse, the FDA is encouraging manufacturers to develop abuse-deterrent drugs that work correctly when taken as prescribed, but are formulated in such a way to deter misuse and abuse, including making it difficult to snort or inject the drug for a more intense high.

Drug Information Update: FDA Alerts Health Care Professionals and Patients Not to Use Products from the Prescription Center Pharmacy in Fayetteville, N.C. 4/2/15

Significant deficiencies were observed upon inspection of Prescription Center Pharmacy raising concerns about the company's ability to assure sterility, stability, and potency of their sterile and non-sterile human and veterinary drug products. Products from the Prescription Center should not administered to either human or animal patients. The pharmacy has been closed by order of the North Carolina Board of Pharmacy, and the Board has ordered a recall of all lots of sterile and non-sterile products compounded or repackaged and distributed by Prescription Center Pharmacy between Sept. 10, 2014 and March 10, 2015.

Drug Information Update: FDA Continues to Warn Consumers Not to Use Eu Yan Sang (Hong Kong) Ltd.'s "Bo Ying Compound" 4/10/15

The FDA is working with the Maryland Department of Health and Mental Hygiene and other states to continue to warn consumers and caregivers not to use Eu Yan Sang (Hong Kong) Ltd.'s "Bo Ying compound" because of possible lead poisoning risk associated with the product. This reminder comes after the Maryland's DHMH found elevated levels of lead in these products.

FDA Safety Notification: Problem with Quality of Mammograms at J. Bruce Jacobs M.D., Inc., Doing Business as Huntington Radiology in Huntington Park, CA 4/13/15

The FDA issued a mammography safety notification alerting patients who had mammograms at J. Bruce Jacobs M.D., Inc., doing business as Huntington Radiology, any time on or after September 8, 2014 about possible problems with the quality of their mammograms.

Drug Information Update – Amyotrophic Lateral Sclerosis (ALS) Statement 4/17/15

The FDA asked Genervon to release data from their recently completed trial of GM604 in the treatment of ALS to enable discussion of the trial results.

Drug Information Update – Counterfeit Botox Found in the U.S. 4/17/15

The FDA issued a notification that a counterfeit version of Botox has been found in the U.S. and may have been sold to doctor's offices and medical clinics nationwide. The product was sold by an unlicensed supplier; the manufacture, quality, storage, and handling of the counterfeit products cannot be confirmed to follow U.S. standards. The counterfeit product can be identified by the following differences from FDA-approved Botox: the vial is missing the lot number, the outer carton does not have any entries next to LOT, MFG, or EXP, and the outer carton and vial list the active ingredient as "Botulinum Toxin Type A" rather than "OnabotulinumtoxinA."

FDA MedWatch Alert – Flurbiprofen-Containing Topical Pain Medications – Illnesses and Deaths in Pets Exposed to Prescription Topical Pain Medication 4/17/15

The FDA alerted pet owners, veterinarians, health care providers and pharmacists about reports of cats who became ill or died after exposure to topical compounded medications containing flurbiprofen. The topical pain cream or lotion containing flurbiprofen and cyclobenzaprine (and varying other ingredients including baclofen, gabapentin, lidocaine, and prilocaine) was applied to the owner's neck or feet, and not to the animals directly.

FDA Safety Communication: Mammograms at Coastal Diagnostic Center (Pismo Beach, CA) – Quality Problems 4/30/15

The FDA issued a mammography safety notification alerting patients who had mammograms at Coastal Diagnostic Center any time on or after February 24, 2013 about possible problems with the quality of their mammograms.

Major Product Recalls Announced Through MedWatch:

Products from Prescription Center Pharmacy in Fayetteville, N.C.: Recall – Lack of Sterility Assurance 4/2/15

The North Caroline Board of Pharmacy has ordered a recall of all lots of sterile and non-sterile products compounded or repackaged and distributed by Prescription Center Pharmacy between Sept. 10, 2014 and March 10, 2015.

Intravenous (IV) Solutions (Select Lots) by Baxter: Recall – Potential Presence of Particulate Matter 4/10/15

Baxter International Inc. is voluntarily recalling select lots of IV solutions to the hospital/user level due to the potential presence of particulate matter. The lots being recalled were distributed to customers and distributors in the United States and Bermuda between January 14, 2015 and March 5, 2015. A completed list of recalled products can be found on the FDA MedWatch site.

VV13F Reinforced Dual Lumen ECMO Catheters by OriGen BioMedical: Recall – Potential for Separation of Tube from Hub 4/16/15

One lot (N18549, exp. 09/2018) of 51 VV13F catheters used in neonatal and pediatric ECMO centers has been recalled following reports of product failure.

Mucinex Fast-MAX liquid products: Recall – Incorrect Labeling 4/22/15

Certain lots of liquid Mucinex Fast-MAX Night Time Cold & Flu; Mucinex Fast-MAX Cold & Sinus; Mucinex Fast-MAX Severe Congestion & Cough and Mucinex Fast-MAX Cold, Flu & Sore Throat have been recalled because the drug facts label on the back of the bottle may not list the correct quantities of acetaminophen, dextromethorphan, guaifenesin, phenylephrine and/or diphenhydramine or adequately list the possible side effects. A complete list of the recalled products can be found on the FDA web site.

Bupivacaine HCl Injection by Hospira: Recall – Iron Oxide Particulate in Glass Vials 4/24/15

Hospira is recalling one lot of preservative-free bupivacaine HCl injection USP, 0.5%, 30 mL (NDC 0409-1162-02, lot 38-515-DK, exp 1FEB2016) due to the confirmed presence of visible embedded and free floating iron oxide particles in one vial. The recalled lot was distributed from July 2014 to September 2014.

Injectable Products by Mylan: Recall – Presence of Particulate Matter 4/24/15

Mylan is recalling select lots of gemcitabine for injection, carboplatin injection, methotrexate injection, and cytarabine injection due to the presence of visible foreign matter particulate in sampled vials. The recalled products were manufactured by Agila Onco Therapies Limited, and labeled with Mylan or Pfizer labels. A completed list of recalled products and lots can be found on the FDA MedWatch web site.

Dietary Supplement Recalls & Public Notifications

In April, the FDA issued notifications to the public regarding undeclared active ingredients in the following products. Patients are advised not to purchase or use these products.

Product	***Promoted Use***	***Hidden/Undeclared Drug Ingredient(s)***
Extreme Diamond 3000	Sexual enhancement	Desmethyl carbodenafil and dapoxetine
Black Panther	Sexual enhancement	Sildenafil
King of Romance	Sexual enhancement	Sildenafil

Product (continued)	***Promoted Use***	***Hidden/Undeclared Drug Ingredient(s)***
Viagra 007	Sexual enhancement	Sildenafil
Fatloss Slimming Beauty	Weight loss	Sildenafil
Superior	Weight loss	Sibutramine
Slim Forte Slimming Capsule	Weight loss	Sibutramine
Li Da Dai Dai Hua Slimming Capsule	Weight loss	Sibutramine

New Product Shortages Reported by the FDA: ***Date Initially Posted***

No new shortages were reported in April

Product Discontinuations/Withdrawals ***Date Posted***

No single source product discontinuations were reported in April

New Drug Approvals:	***Description***	***Date Approved***
Ivabradine / Corlanor / Amgen	See attached drug summary	4/15/15
Deoxycholic acid / Kybella / Kythera Biopharmaceuticals	See attached drug summary	4/29/15

New Indications:	***Description***	***Date Approved***
Onabotulinum toxin A / Botox / Actavis	Treatment of adults with upper limb spasticity	4/17/15
Valganciclovir / Valcyte / Genentech	Indication expanded to include heart transplant patients from 1 month to 4 months of age	4/23/15
Ramucirumab / Cyramza / Eli Lilly & Co.	For use in combination with FOLFIRI (irinotecan, folinic acid, and 5-fluorouracil) for the treatment of patients with metastatic colorectal cancer with disease progression on or after therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine	4/24/15
Fluticasone furoate + vilanterol inhaler / Breo Ellipta / GlaxoSmithKline	Treatment of asthma in adult patients	4/30/15

New Dosage Forms or Formulation:	***Description***	***Date Approved***
Methylphenidate / Aptensio XR / Rhodes	Extended-release capsule for the treatment of ADHD	4/17/15
Fibrin sealant [human] / Raplixa / The Medicines Company	Spray-dried fibrin sealant to control bleeding from small blood vessels during surgery. Can be applied directly from the vial or sprayed onto a bleeding site.	4/30/15

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Ivabradine / Corlanor / Amgen	
Generic Name / Brand Name / Company	Ivabradine tablets / Corlanor / Amgen
Date of approval	April 15, 2015
Drug Class (Mechanism of Action if novel agent)	Cardiovascular agent that reduces spontaneous pacemaker activity at the cardiac sinus node by blocking the hyperpolarization-activated cyclic nucleotide-gated (HCN) channel to selectively inhibit I_f current, thus reducing the heart rate. Ventricular repolarization and myocardial contractility are not affected.
Indication(s)	To reduce hospitalization risk for worsening heart failure in patients with stable, symptomatic chronic heart failure with left ventricular ejection fraction $\leq$ 35%, who are in sinus rhythm with resting heart rate $\geq$ 70 beats per minute and either are on maximally tolerated doses of beta-blockers or have a contraindication to beta-blocker use.
Comparative agent – Therapeutic interchange?	Ivabradine is the only approved I_f current inhibitor
Dosage forms/strengths. Common Dose/sig	Oral Tablet: 5 mg, 7.5 mg Dose: Initiate with 5 mg twice daily. After 2 weeks, adjust dose based on heart rate to achieve target rate of 50-60 bpm. Maximum dose is 7.5 mg twice daily.
DEA Schedule	Not scheduled
Date of market availability	Currently available
Similar Medications (Look-Alike Sound-Alike)	Corlopam, Cortane, Cordran, Cordarone, Clinoril
CLINICAL USE EVALUATION	
Common Adverse Effects	Adverse reactions occurring in ≥ 1% of patients are bradycardia, hypertension, atrial fibrillation and luminous phenomena (phosphenes, a visual change).
Severe Adverse Effects	Hypersensitivity reactions
Severe Drug-Drug Interactions	CYP3A4 inhibitors increase ivabradine plasma concentrations and CYP3A4 inducers decrease ivabradine plasma concentrations; contraindicated with strong CYP3A4 inhibitors. Negative chronotropes: Increased risk of bradycardia, monitor heart rate. Pacemakers: Not recommended for use with demand pacemakers set to rates ≥ 60 bpm.
Severe Drug-Food Interactions	Avoid grapefruit juice
Important Labs Values to assess prior to order entry or at point of clinical follow up. (Need Pop Up?)	No specific laboratory monitoring; heart rate and BP should be assessed prior to treatment and periodically during treatment.
Used in Pediatric Areas	Safety and efficacy in pediatric populations have not been established
Renal or Hepatic Dosing	No dosage adjustment is required with creatinine clearance 15-60 mL/min. No data exists below 15 mL/min. No dosage adjustments necessary in patients with mild or moderate hepatic impairment. However, ivabradine is contraindicated in patients with severe hepatic impairment (Child-Pugh C).
Critical Issues (i.e., contraindications, warnings, etc) that should be emphasized	Contraindications: • Acute decompensated heart failure • Blood pressure less than 90/50 mmHg • Sick sinus syndrome, sinoatrial block or 3rd degree AV block unless demand pacemaker present (not recommended with demand pacemakers set to rates $\geq$ 60 bpm); not recommended in 2nd degree AV block • Resting heart rate less than 60 bpm prior to treatment • Severe hepatic impairment (Child-Pugh C)

	• Pacemaker dependence • Strong CYP3A4 inhibitors Warnings: • Fetal toxicity: advise females to use effective contraceptions • Monitor for atrial fibrillation and bradycardia • Advise patients of possible visual side effects including temporary brightness in a patient's field of vision. This brightness usually occurs within the first 2 months of treatment and usually goes away during or after treatment. Advise patients to use caution when driving or operating machinery where sudden changes in light can happen, especially when driving at night.
Special administration technique or considerations	• Take ivabradine twice daily with meals.
Prepared by	Kenneth Hatzinikolis, PharmD Candidate Class of 2015

Deoxycholic acid / Kybella / Kythera Biopharmaceuticals	
Generic Name / Brand Name / Company	Deoxycholic acid / Kybella / Kythera Biopharmaceuticals
Date of approval	April 29, 2015
Drug Class (Mechanism of Action if novel agent)	Deoxycholic acid is a cytolytic agent which when injected destroys the cellular membrane inducing cell lysis.
Indication	To improve the appearance of moderate to severe convexity or fullness associated with submental fat in adult patients; it is not approved for the treatment of subcutaneous fat outside of the submental region and use in other areas cannot be recommended.
Comparative agent – Therapeutic interchange?	None
Dosage forms/strengths. Common Dose/sig	Injection: 2 mL vial at the concentration of 10 mg/mL. One package contains four vials; each vial is for a single use, should not be diluted and any unused portion of solution must be discarded. An area-adjusted dose of 2 mg per square centimeter should be injected into the subcutaneous fat tissue in the submental area; a single treatment consists of 0.2 mL subcutaneous injections spaced roughly 1 centimeter apart in all planned treatment areas. Up to 50 injections (10 mL) may be used in a single treatment and up to 6 treatments, spaced at least 1 month apart, can be utilized. The number of injections at a single appointment as well as the number of total treatments should be tailored to the patient's fat distribution as well as their goals of treatment.
DEA Schedule	Not scheduled
Date of market availability	June 2015
Similar Medications (Look-Alike Sound-Alike)	Deoxycholic acid for compounding, dicyclomine, doxazosin, doxycycline
CLINICAL USE EVALUATION	
Common Adverse Effects	The most common adverse reactions (occurring in > 20% of patients) were at the injection site (edema, swelling, hematoma, pain, numbness, erythema, and induration). Other reactions included paresthesia, formation of a nodule, itching, tightness of the skin, warmth at injection site and injury to the facial nerve, headache, oral cavity pain, hypertension, nausea and dysphagia.
Severe Adverse Effects	Injection site errors can lead to damage of the mandibular branch of the facial nerve which may cause an asymmetrical smile and paresis of the lip depressor muscles.

	Dysphagia due to the injection (pain, swelling and induration of injection site), but typically spontaneously resolved within 1 to 81 days (median 3 days).
Severe Drug-Drug Interactions	Use with caution in patients currently treated with antiplatelet or anticoagulant therapy due to increased bleeding and bruising risk.
Severe Drug-Food Interactions	None
Important Labs Values to assess prior to order entry or at point of clinical follow up. (Need Pop Up?)	None
Used in Pediatric Areas	Safety and efficacy has not been established in pediatric patients.
Renal or Hepatic Dosing	• Deoxycholic acid injection has not been studied in subjects with hepatic impairment, but because deoxycholic acid is not metabolized by the liver and is excreted intact in the feces via the cholesterol biliary tract, its effects are unlikely to be affected by hepatic impairment. • Deoxycholic acid injection has not been studied in patients with impaired renal function.
Critical Issues (i.e., contraindications, warnings, etc) that should be emphasized	• Proper administration technique is of the utmost importance due to the risk on nerve damage and dermal ulceration • Use with caution in patients with bleeding abnormalities
Special administration technique or considerations	• Draw up with a large bore needle into a 1 mL sterile syringe and remove all air bubbles. Then using a 30 gauge or smaller, half-inch needle 0.2 mL should be injected into the pre-platysmal fat. • Should be administered by a trained healthcare professional only, as needle placement is of the outmost importance; the medication should not be injected above the inferior border of the mandible or the 1 to 1.5 centimeter area below the inferior border. • Avoid injecting near the marginal mandibular nerve due to potential neuronal damage. • Injections into the dermis can lead to skin ulceration. • Do not inject into the platysma which is deeper than the dermis and subcutaneous fat The use of topical ice or cold packs as well as topical and/or local anesthesia may aid in the comfort of the patient post-injections.
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