Highlights of FDA Activities – 6/1/17 – 6/30/17

FDA Drug Safety Communications & Drug Information Updates:

Oxymorphone Hydrochloride/Opana ER: Benefits May Not Outweigh the Risks 6/8/17
The FDA requested that Endo Pharmaceuticals remove its opioid pain medication from the market due to the associated risk of injection abuse and outbreaks of HIV and hepatitis C.

Pfizer Drug Shortages: Drug Information Update 6/15/17 & 6/23/17
The FDA announced measures being taken to address shortages currently occurring with a number of injectable medications manufactured by Hospira/Pfizer, including finding alternative manufacturers, expediting reviews, considering regulatory flexibility, and extended expiration dates. Specifically, expiration dates of certain lots of emergency syringes have been extended based on stability data provided by Pfizer. Specific details on the extended use dates for atropine sulfate, dextrose injection 50%, and sodium bicarbonate emergency syringe products can be found on the FDA website.

Removal of Ratio Expressions of Strength from Drug Labeling 6/28/17
Single-entity injectable drug products (i.e., drug products that contain only one active ingredient) can no longer use ratios to indicate the strength of the drug. Strengths must be expressed as the amount per unit of volume. This revision affects Epinephrine Injection, Isoproterenol HCl Injection, and Neostigmine Methylsulfate Injection. An example of this change is: Epinephrine Injection, USP 1:1000 must now be labeled as 1 mg/mL.

New Draft Guidance: Product Identifier Requirements Under the Drug Supply Chain Security Act – Compliance Policy: Drug Information Update 6/30/17
The FDA issued a draft guidance describing their policy for enforcing requirements related to product identifiers and verification requirements, as well as requirements for repackagers, wholesale distributers, and dispensers to only engage in transactions involving products with product identifiers, and requirements for repackagers and wholesale distributers related to saleable returned product. Although the Drug Supply Chain Security Act required product identifiers be affixed or imprinted on each package or case, the FDA does not plan to take action against manufacturers who initially introduce product in a transaction without an identifier between 11/27/17 and 11/26/18. Manufacturers must still validate transaction history if the product is deemed suspect. In addition, all manufacturers and downstream trading partners are expected to use a product identifier in the verification process, if one is present. The FDA plans no action against dispensers engaging in a transaction with product introduced into the supply chain without an identifier between 11/27/17 and 11/26/18; however, dispensers should ensure products purchased from a repackager after 11/27/18 bear product identifiers. The FDA plans to issue additional guidance in the future to address "grandfathered" products in the supply chain at the time the DSCSA act is fully implemented.

Drug Competition Action Plan: Drug Information Update
The FDA announced a public meeting will be held July 18, 2017 to solicit input on reducing barriers to development and approval of generic drugs.

Major Product Recalls Announced Through MedWatch:

Eliquis (apixaban) by Bristol-Myers Squibb: Recall - One Lot of Eliquis 5 mg Tablets Found to Contain 2.5 mg Tablets 6/13/217
Bristol-Myers Squibb Company recalled one lot (#HN0063) of Eliquis 5 mg tablets to the consumer level following a customer complaint that a bottle labeled as Eliquis 5 mg was found to contain Eliquis 2.5 mg tablets. This lot was distributed nationwide in the U.S. to wholesalers and retail pharmacies in February 2017.

Topical Products by Phillips Company: Recall - All Lots of Tetrastem, Diabecline, Tetracycline-ABC, VenomX, Acneen, StaphWash, StringMed, NoPain, and LidoMed 6/14/17

These products are being recalled after an FDA inspection found significant manufacturing practices that calls into question the safety, identity, strength, quality, and purity of drug products made during the past three years.

Paliperidone Extended-Release Tablets 3 mg, Teva Pharmaceuticals: Recall - Dissolution Test Failure 6/15/17

Teva recalled to the retail-level one lot of Paliperidone ER Tablets, 3 mg, 90 count bottles, lot 1160682A, expiration 6/2018, NDC 0591-3693-19, that was distributed under the Actavis Pharma Inc. label due to dissolution test failure.

Nitroglycerin Injection in 5% Dextrose USP by Advanced Pharma: Recall - Sub-potency 6/15/17

Advanced Pharma recalled all unexpired lots of Nitroglycerin products that were produced between 3/3/17 and 5/31/17 to the hospital/user level. The recall is being issued based on laboratory test results indicating a lower than expected potency on certain lots of compounded Nitroglycerin Injection.

Sodium Bicarbonate Injection 8.4 Percent USP, Neut (Sodium Bicarbonate 4 Percent Additive Solution), Quelicin (Succinylcholine Chloride Injection USP), and Potassium Phosphates Injection by Hospira: Recall - Lack Of Sterility Assurance 6/16/17

Hospira recalled 42 lots of 8.4% Sodium Bicarbonate Injection, USP, 50 mL vials, 5 lots of Neut™ (Sodium Bicarbonate 4% additive solution) 5 mL vials, 5 lots of Quelicin™ (Succinylcholine Chloride Injection, USP) 200 mg/10 mL vials, and 7 lots of Potassium Phosphates Injection, USP, 45 mM vials to the hospital/retail level due to microbial growth detected during a routine simulation of the manufacturing process. A complete list of recalled lots can be found on the FDA website.

Clindamycin Injection USP ADD-Vantage Vials by Alvogen: Recall- Lack of Sterility Assurance 6/16/17

Alvogen recalled seven lots of clindamycin injection vials due to detection of microbial growth during simulation of the manufacturing process. A list of recalled lots, with expiration dates of 7/31/18 and 12/31/18 can be found on the FDA website.

Venture® Catheters by Teleflex Vascular Solutions, Inc.: Recall – Potential for Serious Adverse Health Consequences or Death 6/21/17

Teleflex Inc. recalled all unexpired lots of the Rapid Exchange (RX), Over-the-Wire (OTW), and Coronary Sinus (CS) versions of its Venture® Catheters. There is potential for excess material to be present within the inner lumen of the distal catheter tip, which may separate from the catheter during use and pose a potential risk of embolism. The recall notice on the FDA website lists affected lot numbers.

Potassium Phosphate and Succinylcholine Repacked and/or Compounded by Avella of Houston: Recall – Lack of Sterility Assurance 6/22/17

Advanced Pharma, Inc. d/b/a Avella of Houston recalled specific lots of Potassium Phosphate and Succinylcholine Chloride compounded from recalled lots of Hospira product. For specific lot numbers, refer to: https://www.avella.com/AP-Hospira-recall

Succinylcholine Chloride 20 mg/mL 5 mL Syringe by Fagron Sterile Services: Recall – Lack of Sterility Assurance 6/23/17

Fagron Sterile Services recalled three lots of Succinylcholine Chloride 20 mg/mL 5mL syringe to the hospital/clinical level. Affected lot #s C274-000000331, C274-000001274, C274-000001326 were repackaged from recalled lots of Hospira Succinylcholine Chloride.

Potassium Phosphate and Succinylcholine Chloride by PharMEDium Services: Recall – Lack of Sterility Assurance 6/27/17

PharMEDium recalled products compounded using recalled lots of Hospira Potassium Phosphate and Succinylcholine Chloride. Customers with affected product were notified by phone.

Dietary Supplement Recalls & Public Notifications

In June, 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)*
B3AST	Increases muscle mass/strength	Steroid and steroid-like substances[1]
D-Zine	Increases muscle mass/strength	Steroid and steroid-like substances[1]
Love Zen 3000	Sexual enhancement	Tadalafil[2]
M1 Alpha	Increases muscle mass/strength	Steroid and steroid-like substances[1]
Macho Man 3000	Sexual enhancement	Tadalafil[2]
Man of Steel	Sexual enhancement	Sildenafil[2]
Man of Steel 2	Sexual enhancement	Sildenafil[2]
Monster X 1350	Sexual enhancement	Tadalafil[2]
Own the Knight 1750	Sexual enhancement	Tadalafil[2], and dapoxetine[3]
Royal Master 1500	Sexual enhancement	Tadalafil[2]
Sten Z	Increases muscle mass/strength	Steroid and steroid-like substances[1]
Super Panther 7K	Sexual enhancement	Sildenafil[2] and tadalafil[2]
Super Powers	Increases muscle mass/strength	Steroid and steroid-like substances[1]
Titan	Increases muscle mass/strength	Steroid and steroid-like substances[1]
Titan Two	Increases muscle mass/strength	Steroid and steroid-like substances[1]
Triple Miracle Zen Plus1200mg	Sexual enhancement	Sildenafil[2] and tadalafil[2]
Triple Premium Zen Gold 1300mg	Sexual enhancement	Sildenafil[2], tadalafil[2], and dapoxetine[3]
Triple X 2000	Sexual enhancement	Tadalafil[2], and dapoxetine[3]
Ultra-Sten	Increases muscle mass/strength	Steroid and steroid-like substances[1]
XXX Zone Platinum	Sexual enhancement	Sildenafil[2], tadalafil[2], and dapoxetine[3]
XZone Gold	Sexual enhancement	Sildenafil[2] and tadalafil[2]

[1]Steroid and steroid-like substances are associated with risk of serious liver injury
[2]Sildenafil/tadalafil/vardenafil may interact with nitrates to lower blood pressure to dangerous levels
[3]Dapoxetine is not FDA approved

New Product Shortages Reported by the FDA:	*Date Initially Posted*
Cromolyn sodium inhalation solution	6/21/17

Product Discontinuations/Withdrawals	*Date Posted*
Epirubicin Hydrochloride Injection (Hospira): 200 mg/100 mL (2 mg/mL) Single Dose ONCO-TAIN Glass Fliptop Vial (NDC 61703-0359-59); 50 mg/25 mL (2 mg/mL) Single Dose ONCO-TAIN Glass Fliptop Vial (NDC 61703-0359-93); epirubicin injection remains available from other manufacturers	6/9/17
Mefloquine HCL Tablets (West-Ward Pharmaceuticals): 250mg (NDC 00054-0025-11). Mefloquine tablets remain available from other manufacturers	6/12/17

New Drug Approvals:	*Description*	*Date Approved*
Delafloxacin / Baxdela / Melinta Therapeutics Inc	See attached drug summary	6/19/17
C1 Esterase Inhibitor / Haegarda / CSL Behring LLC.	See attached drug summary	6/22/17
Betrixaban / Bevyxxa / Portola Pharmaceuticals	See attached drug summary	6/23/17

New Indications:	***Description***	***Date Approved***
AbobotulinumtoxinA / Dysport / Ipsen	Treatment of lower limb spasticity in adults	6/14/17
Daratumumab / Darzalex / Janssen	Treatment of multiple myeloma patients who have received at least two prior therapies including lenalidomide and a proteasome inhibitor	6/19/17
Panitumumab / Vectibix / Amgen	Treatment of patients with wild-type RAS metastatic colorectal cancer as first-line therapy with FOLFOX and as monotherapy following disease progression after a regimen including fluorouracil, oxaliplatin, and irinotecan	6/29/17
Dabrafenib / Tafinlar / Novartis	Use with trametinib for the treatment of patients with metastatic non-small cell lung cancer with BRAF V600E mutation	6/22/17
Trametinib / Mekinist / Novartis	Use with dabrafenib for the treatment of patients with metastatic non-small cell lung cancer with BRAF V600E mutation	6/22/17

New Dosage Forms or Formulation:	***Description***	***Date Approved***
Aminolevulinic acid HCl oral solution / Gleolan / NX Development	Optical imaging agent for use in patients with gliomas as an adjunct for visualization of malignant tissue during glioma surgery	6/7/17
Ritonavir oral powder / Norvir / AbbVie	Oral powder, 100 mg per packet; to be mixed with soft food such as apple sauce or vanilla pudding or a liquid such as water, chocolate milk or infant formula, and administered within 2 hours; only for use for dosing increments of 100 mg	6/7/17
Epinephrine injection / Symjepi / Adamis Pharmaceutical	Injection, 0.3 mg pre-filled syringe; emergency treatment of allergic reactions including anaphylaxis	6/16/17
Methylphenidate extended-release orally disintegrating tablet / Cotempla XR-ODT / Neos Therapeutics	8.6 mg, 17.3 mg, and 25.9 mg; Starting dose 17.3 mg, increase in 8.6 mg/day increments to maximum recommended dose of 51.8 mg; Indicated for treatment of ADHD in patients aged 6 to 17 years	6/20/17
Mixed salts of a single-entity amphetamine product extended-release capsules / Mydayis / Shire	Once daily capsule formulation containing three types of drug-releasing beads available in 12.5, 25, 37.5, and 50 mg strengths; indicated for treatment of ADHD in patients aged 13 years and older.	6/20/17
Rituximab and hyaluronidase human / Rituxan Hycela / Roche	New formulation for subcutaneous administration; indicated for treatment of follicular lymphoma, diffuse large B-cell lymphoma, and chronic lymphocytic leukemia	6/22/17
Triprorelin exteded-release / Triptodur / Arbor Pharmaceuticals	Extended-release IM injection for treatment of pediatric patients 2 years and older with central precocious puberty; administered once every 6 months	6/29/17

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Delafloxacin / Baxdela / Melinta Therapeutics Inc	
Generic Name / Brand Name / Company	Delafloxacin / Baxdela / Melinta Therapeutics Inc
Date of approval	6/19/2017
Drug Class (Mechanism of Action if novel agent)	Antibiotic, fluoroquinolone
Indication	Treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of the following: • **Gram-positive organisms**: *Staphylococcus aureus* (including methicillin-resistant [MRSA] and methicillin-susceptible [MSSA] isolates), *Staphylococcus haemolyticus*, *Staphylococcus lugdunensis*, *Streptococcus agalactiae*, *Streptococcus anginosus* group (including *Streptococcus anginosus*, *Streptococcus intermedius*, and *Streptococcus constellatus*), *Streptococcus pyogenes*, and *Enterococcus faecalis* • **Gram-negative organisms**: *Escherichia coli*, *Enterobacter cloacae*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*
Comparative agent – Therapeutic interchange?	Tigecycline, vancomycin, linezolid, daptomycin, clindamycin
Dosage forms/strengths. Common Dose/sig	**Injection**: 300 mg (lyophilized powder in a single dose vial for reconstitution with 5% dextrose of 0.9% sodium chloride) via intravenous infusion over 60 minutes every 12 hours x 5-14 days **Tablets**: 450 mg tablet by mouth every 12 hours x 5 -14 days
DEA Schedule	Not scheduled
Date of market availability	Unknown
Similar Medications (Look-Alike Sound-Alike)	None identified
Clinical Use Evaluation	
Common Adverse Effects	≥ 2%: nausea, diarrhea, headache, transaminase elevations, and vomiting
Severe Adverse Effects	Tendinitis, tendon rupture, peripheral neuropathy, central nervous system effects, exacerbation of myasthenia gravis, *Clostridium difficile*-associated diarrhea, and hypersensitivity
Severe Drug-Drug Interactions	**Tablets**: Aluminum or magnesium containing antacids, sucralfate, iron, multivitamins containing iron or zinc, and didanosine buffered tablets will interfere with the systemic absorption of oral delafloxacin and therefore it should be taken at least 2 hours before or 6 hours after these agents. **Injection**: delafloxacin should not be co-administered with any solution containing multivalent cations, e.g., magnesium/calcium through the same intravenous line.
Severe Drug-Food Interactions	No dietary restrictions
Important Labs Values to assess prior to order entry or at point of clinical follow up.	eGFR (estimated glomerular filtration rate)
Used in Pediatric Areas	Use in patients under 18 years of age is not recommended
Renal or Hepatic Dosing	**Renal**: No dosage adjustment is necessary in patients with mild (eGFR 60-89 mL/min/1.73 m^2) or moderate (eGFR 30-59mL/min/1.73m^2) renal impairment. In patients with severe renal impairment (eGFR 15-29 mL/min/1.73 m^2) the recommended dose is 200 mg intravenously every 12 hours or 450 mg orally every 12 hours. Delafloxacin is not recommended in patients with End Stage Renal Disease [ESRD] (eGFR of <15 mL/min/1.73 m^2) **Hepatic**: No dosage adjustment is necessary in patients with hepatic impairment
Critical Issues (i.e., contraindications, warnings, etc) that should be emphasized	**Contraindication**: known hypersensitivity to delafloxacin or other fluoroquinolones

	Warnings & Precautions: fluoroquinolones are associated with disabling and potentially irreversible serious adverse reactions that have occurred together, including tendinitis and tendon rupture, peripheral neuropathy, and CNS effects. • Discontinue delafloxacin immediately and avoid the use of fluoroquinolones in patients who experience any of these serious adverse reactions. Fluoroquinolones may exacerbate muscle weakness in patients with myasthenia gravis. • Avoid delafloxacin in patients with known history of myasthenia gravis. *Clostridium difficile*- associated diarrhea • Evaluate if diarrhea occurs
Special administration technique or considerations	**Tablets**: Administer delafloxacin at least 2 hours before or 6 hours after antacids containing magnesium, or aluminum, with sucralfate, with metal cations such as iron, or with multivitamin preparations containing zinc or iron, or with didanosine buffered tablets. Tablets can be taken with or without food **Injection**: Do not administer or co-infuse delafloxacin with solutions containing multivalent cations (calcium, magnesium) or with other medications. Lines should be flushed before and after each dose.
Prepared by	Jacqueline Ybarra, Pharm.D. Student, Class of 2018
Source	Baxdela (delafloxacin) tablet/injection [prescribing information]. Lincolnshire, IL: Melinta Therapeutics Inc; June 2017.

Betrixaban / Bevyxxa / Portola Pharmaceuticals, Inc.	
Generic Name / Brand Name / Company	Betrixaban / Bevyxxa / Portola Pharmaceuticals, Inc.
Date of approval	6/23/17
Drug Class (Mechanism of Action if novel agent)	Factor Xa inhibitor
Indication	Prophylaxis of venous thromboembolism (VTE) in adult patients hospitalized for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE.
Comparative agent – Therapeutic interchange?	Apixaban, dabigatran, edoxaban, fondaparinux, and rivaroxaban are other factor Xa inhibitors; however, none are FDA approved for VTE prophylaxis in the medically ill
Dosage forms/strengths. Common Dose/sig	Capsule: 40 mg and 80 mg. Initial single dose of 160 mg, followed by 80 mg once daily. Taken at the same time each day with food. Recommended treatment duration: 35 to 42 days.
DEA Schedule	Not scheduled
Date of market availability	Anticipated between August and November 2017
Similar Medications (Look-Alike Sound-Alike)	Apixaban, baricitinib, edoxaban
Clinical Use Evaluation	
Common Adverse Effects	Common (incidence >5%): bleeding
Severe Adverse Effects	Bleeding
Severe Drug-Drug Interactions	- P-gp inhibitors increase the blood level of betrixaban and the betrixaban dose should be reduced - Avoid concomitant use with other anticoagulants

Severe Drug-Food Interactions	No significant drug-food interactions. Should be taken with food; however, fatty food can decrease the peak concentration and area under the curve by 50%.
Important Labs Values to assess prior to order entry or at point of clinical follow up.	Renal and liver function tests
Used in Pediatric Areas	Safety and effectiveness in pediatric patients have not been established
Renal or Hepatic Dosing	**Renal Impairment:** Reduce the dose for patients with severe renal impairment (CrCl ≥ 15to < 30 mL/min) to 80 mg as an initial single dose followed by 40 mg once daily. No dosage adjustment necessary in mild to moderate renal impairment. **Hepatic Impairment:** Use is not recommended in patient with hepatic impairment because these patients may have intrinsic coagulation abnormalities.
Critical Issues (i.e., contraindications, warnings, etc) that should be emphasized	**Boxed Warning** - Increased risk for epidural or spinal hematomas in patients receiving betrixaban and neuraxial anesthesia or undergo spinal puncture. **Contraindications** - Active pathological bleeding - Severe hypersensitivity reaction to the drug **Warnings and Precautions** - Risk of Bleeding: can cause serious, potentially fatal bleeding - Severe Renal Impairment: increased risk of bleeding events; reduce dose - Concomitant P-gp Inhibitors: increased risk of bleeding events; reduce dose
Special administration technique or considerations	Daily oral doses should be given at the same time of day with food. The recommended treatment duration is 35 to 42 days.
Prepared by	Eric Kim, PharmD Candidate 2018, Washington State University
Source	Bevyxxa® (betrixaban). [Prescribing information]. South San Francisco, CA: Portola Pharmaceuticals, Inc.; 2017.

C1 Esterase Inhibitor [Human] / Haegarda / CSL Behring	
Generic Name / Brand Name / Company	C1 Esterase Inhibitor [Human] / Haegarda / CSL Behring
Date of approval	6/22/17
Drug Class (Mechanism of Action if novel agent)	Plasma-derived concentrate of C1 Esterase Inhibitor (Human)
Indication	Routine prophylaxis to prevent Hereditary Angioedema (HAE) attacks in adolescent and adult patients
Comparative agent – Therapeutic interchange?	C1 esterase inhibitor (Cinryze) intravenous
Dosage forms/strengths. Common Dose/sig	Available as a white lyophilized powder supplied in single-use vials For subcutaneous use after reconstitution only - Administer 60 units/kg body weight twice weekly (every 3 or 4 days)
DEA Schedule	Not scheduled
Date of market availability	Summer 2017
Similar Medications (Look-Alike Sound-Alike)	C1 esterase inhibitor
Clinical Use Evaluation	
Common Adverse Effects	>4%: injection site reaction, hypersensitivity, nasopharyngitis, and dizziness
Severe Adverse Effects	Severe hypersensitivity reactions
Severe Drug-Drug Interactions	No interaction studies have been conducted.
Severe Drug-Food Interactions	None known

Important Labs Values to assess prior to order entry or at point of clinical follow up.	None established
Used in Pediatric Areas	Safety and efficacy were evaluated in a subgroup of six patients 12 to <17 years of age in the randomized, double-blind, placebo-controlled, crossover, routine prophylaxis trial. Results of subgroup analysis by age were consistent with overall study results.
Renal or Hepatic Dosing	No dosage adjustments required
Critical Issues (i.e., contraindications, warnings, etc) that should be emphasized	**Warnings and Precautions** - Hypersensitivity: Signs and symptoms of hypersensitivity may include hives (local and generalized), tightness of the chest, difficulty breathing, wheezing, hypotension, and/or anaphylaxis during or after injection. - Thromboembolic Events: Thrombosis has occurred in treatment attempts with high doses. - Transmissible Infection Agents: product is made from human blood and may carry a risk of transmitting infection agents. This risk has been reduced by screening plasma donors for prior exposure to certain viruses. Processes have also been established to inactivate and/or remove certain viruses during manufacturing. However, the risk of transmission of infectious agents cannot be completely eliminated.
Special administration technique or considerations	- Prepare and administer using aseptic techniques - Use a silicone-free syringe for reconstitution and administration - Administer at room temperature within 8 hours after reconstitution
Prepared by	Eric Kim, PharmD Student, Class of 2018
Source	Haegarda® (C1 Esterase Inhibitor Subcutaneous [Human]). [Prescribing information]. Kankakee, IL: CSL Behring LLC; 2017.