



MRx CLINICAL ALERT

YOUR MONTHLY SOURCE FOR DRUG INFORMATION HIGHLIGHTS

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FDA REPORT ON DRUG SHORTAGES

In recent decades, healthcare in the United States (US) has been negatively impacted by an increasing number of drug shortages. In 2018, the US Food and Drug Administration (FDA) assembled an interagency Drug Shortages Task Force to identify drug shortage root causes and recommend possible solutions. The panel analyzed 163 drugs that went into shortage between 2013 and 2017. Identified shortages most often impacted low-price and financially unprofitable drugs, notably sterile injectable products.

The panel identified 3 root causes: lack of incentive to produce less profitable drugs, modest value for mature quality manufacturing systems that monitor and improve supply chain issues, and logistical and regulatory obstacles to market recovery after a supply disruption. Interestingly, during a shortage, prices typically did not rise and there was not ample increase in production to achieve pre-shortage levels. Further, many manufacturers stopped production of a medication before a shortage due to declining profits.

The panel offered 3 key solutions. First, there should be a shared understanding of the impact of drug shortages on patient care and the contracting practices that contribute to the shortages. Next, a rating system should be developed to incentivize drug manufacturers to invest in quality management maturity for their facilities. This rating system goes

beyond the Current Good Manufacturing Practices (CGMPs), which set a minimum standard for drugs in the marketplace. Lastly, the panel encourages sustainable private sector contracts (e.g., with payers, purchasers, and group purchasing organizations) to ensure a reliable supply of medically important drugs.

The report also describes several legislative proposals for the President's fiscal year 2020 budget. The FDA will publish initiatives focused on preventing supply disruptions that lead to shortages, including lengthening drug expiration dates and harmonized international manufacturing guidelines.

ICER REPORTS ON CVD

The Institute for Clinical and Economic Review (ICER) published an evidence report on the comparative clinical effectiveness and value of the oral anticoagulant rivaroxaban (Xarelto®) and the oral omega-3 fatty acid icosapent ethyl (Vascepa®) as additive therapy for cardiovascular disease (CVD).

The COMPASS clinical trial reported a significantly reduced composite risk of cardiovascular (CV) death, stroke, or myocardial infarction (MI) in patients with stable CVD treated with rivaroxaban + aspirin (ASA) compared to ASA alone (4.1% versus 5.4%, respectively). Based on these results, ICER determined with high certainty that rivaroxaban + ASA provides a small-to-substantial net health benefit when treating patients with coronary artery disease (CAD) and/or peripheral artery disease (PAD). A network meta-analysis,

however, showed no significant difference in CVD risk with rivaroxaban + ASA versus dual antiplatelet therapy (DAPT) (e.g., ASA + clopidogrel or ticagrelor), which led ICER to conclude that there is insufficient evidence to recommend rivaroxaban + ASA over DAPT in patients with CAD or PAD. Rivaroxaban's annual wholesale acquisition cost (WAC) of \$5,457 falls within ICER's value-based price benchmark of \$5,200-\$7,600 per year.

The REDUCE-IT trial revealed a 25% risk reduction for the composite CV outcome in patients with established CVD or diabetes mellitus (DM) and additional risk factors who received icosapent ethyl compared to optimal medical management alone (e.g., placebo). As a result, ICER concluded with high certainty that icosapent ethyl provides a small-to-substantial net health benefit in adults with established CVD or at high CV risk who are on statin therapy. Icosapent ethyl's annual WAC of \$3,699 is significantly lower than ICER's value-based price benchmark of \$6,300-\$9,200 per year.

Key recommendations from ICER include the following: (1) payers should not consider DAPT as an appropriate first step prior to receiving coverage for rivaroxaban, since they are not considered interchangeable; (2) clinical and specialty societies should develop a decision algorithm to determine the most appropriate additive therapy for CVD for a given patient; and (3) regulators and researchers should agree on a common, single definition for key outcomes (e.g., major bleeding).

■ UPDATED GUIDANCE FOR CAP

The American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA) updated their guidelines for the diagnosis and management of community-acquired pneumonia (CAP). The guidelines focus on the treatment of CAP in immunocompetent adults. Antibiotic selection for empiric treatment is based on efficacy against the major pathogens that cause CAP, typically, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Staphylococcus aureus*, *Legionella* species, *Chlamydia pneumoniae*, and *Moraxella catarrhalis*. The ATS/IDSA recommend against routine Gram stain and culture of respiratory secretions and blood cultures in the outpatient setting. These tests, however, are recommended in patients with severe CAP, as well as in the hospital setting in patients empirically treated for methicillin-resistant *S. aureus* (MRSA) or *Pseudomonas aeruginosa*. During flu season, patients with CAP should be tested for influenza using a rapid influenza molecular assay. The Pneumonia Severity Index (PSI) score should determine the need for hospitalization.

In the outpatient setting, for otherwise healthy adults without risk factors for antibiotic resistant pathogens, the ATS/IDSA recommend treatment with amoxicillin (strong recommendation), doxycycline, or a macrolide (conditional recommendations for both). For outpatients with comorbidities, they recommend monotherapy with a respiratory fluoroquinolone (strong recommendation) or combination therapy with amoxicillin/clavulanate or a cephalosporin *plus* a macrolide or doxycycline (conditional recommendations). Continue antibiotic therapy until the patient is clinically stable and for a minimum of 5 days. In patients who test positive for influenza, influenza antiviral therapy is recommended regardless of the duration of illness before diagnosis. Treatment in the inpatient setting is also detailed in the guidelines.



BEHAVIORAL HEALTH CORNER

HHS GUIDANCE ON OPIOID TAPER

The US Department of Health and Human Services (HHS) published a new guideline for appropriate tapering or discontinuation of long-term opioid therapy. Unless a life-threatening issue exists, the HHS recommends against rapid tapering or sudden discontinuation in patients on prolonged opioids due to the risk for patient harm, including opioid withdrawal, pain exacerbation, psychological distress, illicit opioid use, and suicide. A reduction in opioid dosage may be considered for any of the following reasons: improvement in pain; patient request to reduce the dose or stop opioid therapy; no apparent benefit with higher doses; evidence of misuse or overdose; diminished quality of life; signs of confusion or sedation; concurrent medications increasing the risk for adverse outcomes; or uncertain benefit/harm ratio of opioid treatment. Changes to the opioid regimen should be individualized, based on a shared decision between the patient and clinician that considers the patient's pain and opioid-related problems. Prior to opioid taper, clinicians should: (1) refer patients with serious mental illness, high suicide risk, or suicidal ideation to a behavioral health provider; (2) assess for opioid use disorder if the patient exhibits signs of opioid misuse and offer medication-assisted treatment if appropriate; and (3) advise patients of the risk for overdose if they abruptly return to their higher opioid dose. Opioid tapers should be individualized. A dose reduction by 5% to 20% every 4 weeks is common, but longer time periods may be necessary. In addition, transition to buprenorphine for patients on high doses and unable to taper may be considered.

DRUG INFORMATION (DI) HIGHLIGHTS

- In a November 2019 statement, the FDA advised that nitrosamine impurity levels found in ranitidine products were similar to the levels in grilled or smoked meats. To assure product safety, the FDA will request manufacturers to voluntarily recall any product with levels over the FDA's acceptable daily limit of 96 ng or 0.32 ppm. This also applies to the histamine-2 (H2) blocker nizatidine. To date, other H2 blockers and proton pump inhibitors (PPI) have not tested positive for nitrosamine impurities. Voluntary recalls continue with recalls by Aurobindo (38 lots of ranitidine 150 mg tablets and capsules, 300 mg capsules, and 15 mg/mL oral syrup), Amneal (12 lots of ranitidine 150 mg and 300 mg tablets and ranitidine 15 mg/mL syrup), American Health Packaging (8 lots of ranitidine syrup 150 mg/10 mL unit dose cups of repackaged product affected by the Lannett recall), and Golden State Medical Supply (all lots of 150 mg and 300 mg capsules manufactured by Novitium).
- As an update to their 2017 safety communication, the FDA is reminding the public and healthcare professionals (HCP) that biotin (vitamin B7), found in dietary supplements, can interfere with laboratory test results. Of particular concern are falsely low values for troponin, a biomarker used to diagnose MI. To date, not all lab test developers have successfully addressed biotin interference, which may result in a missed MI diagnosis leading to serious clinical effects.
- The American College of Physicians (ACP) released guidelines regarding screening for colorectal cancer in asymptomatic, average-risk adults. In this population, screening is recommended for individuals between the ages of 50 and 75 years. Suggested screening includes fecal immunochemical testing or high-sensitivity, guaiac-based fecal occult blood testing every 2 years, colonoscopy every 10 years, or flexible sigmoidoscopy every 10 years plus fecal immunochemical testing every 2 years. Screening should be discontinued in patients ages > 75 years or with a life expectancy of ≤ 10 years.
- The FDA released 6 new or revised guidelines as a continuation of their 2017 Digital Health Innovation Action Plan addressing key digital health provisions of the 21st Century Cures Act. Overall, the guidelines clarify the FDA's risk-based approach to digital health products and identify software and devices that they no longer consider as medical devices under the amended definition of a device. As part of this plan, the FDA will increase staff with expertise in digital health and have piloted a software precertification (Pre-Cert) program designed to provide more streamlined regulatory oversight of software-based medical devices.
- Pfizer discontinued all strengths of the opioid agonist/opioid antagonist Embeda® (morphine sulfate/naltrexone) capsules used to treat pain. The last sale date planned was November 15, 2019, and the anticipated unavailability timeframe is early 2020.

PIPELINE NEWS: UPCOMING PRESCRIPTION DRUG/BIOSIMILAR USER FEE ACT (PDUFA/BsUFA) DATES

- **December 2019:** methotrexate; SC folate analogue metabolic inhibitor; rheumatoid arthritis (RA), psoriasis (PSO); Cumberland.
- **December 2019:** olaparib (Lynparza®); oral poly (ADP-ribose) polymerase (PARP) inhibitor; pancreatic cancer (1st-line, metastatic, BRCA+); AstraZeneca.
- **December 2019:** RVT-802; postnatal thymus tissue transplant; pediatric congenital athymia; Enzyvant.
- **December 2019:** ubrogepant; oral calcitonin gene-related peptide (CGRP) inhibitor; migraine treatment; Allergan.
- **Dec 2019–Jan 2020:** dulaglutide (Trulicity®); SC glucagon-like peptide 1 (GLP-1) inhibitor; type 2 DM-related CV outcomes; Eli Lilly.
- **December 2, 2019:** atezolizumab (Tecentriq®); intravenous (IV) programmed death-ligand 1 (PD-L1) inhibitor; non-squamous non-small cell lung cancer (NSCLC) (1st-line, with nab-paclitaxel); Genentech.
- **December 14, 2019:** infliximab, biosimilar to Remicade®; IV tumor necrosis factor (TNF)-α inhibitor; RA, ankylosing spondylitis (AS), PSO, psoriatic arthritis (PsA), Crohn's disease (CD), ulcerative colitis (UC); Amgen.
- **December 24, 2019:** vernakalant; IV antiarrhythmic; atrial fibrillation; Correvio.
- **December 27, 2019:** cabotegravir; oral human immunodeficiency virus (HIV) integrase inhibitor; HIV-1 infection treatment; GlaxoSmithKline.
- **December 27, 2019:** cabotegravir/rilpivirine; intramuscular (IM) integrase inhibitor/non-nucleoside reverse transcriptase inhibitor; HIV-1 infection treatment; GlaxoSmithKline.
- **December 27, 2019:** icosapent ethyl (Vascepa); oral omega-3 fatty acid; CV risk reduction; Amarin.
- **December 27, 2019:** lemborexant; oral orexin receptor antagonist; insomnia; Eisai.
- **December 27, 2019:** lumateperone; oral serotonin and dopamine receptor agonists/serotonin reuptake antagonist; schizophrenia; Intracellular Therapies.

RECENT FDA APPROVALS

DRUG NAME MANUFACTURER	DESCRIPTION
New Drugs	
phenylephrine (Biorphen™) Eton	<ul style="list-style-type: none"> • 505(b)(2) NDA approval 10/21/2019 • Indicated for the treatment of clinically-important hypotension resulting primarily from anesthesia-induced vasodilation in the setting of anesthesia • Alpha-1 adrenergic receptor agonist • Injection: 0.5 mg/5 mL ready-to-use single-use ampule • Recommended dosage is 40 mcg to 100 mcg IV bolus every 1 to 2 minutes as needed; do not exceed 200 mcg; do not dilute
diroximel fumarate (Vumerity™) Alkermes	<ul style="list-style-type: none"> • 505(b)(2) NDA approval 10/29/2019 • Indicated for the treatment of relapsing forms of multiple sclerosis (MS) • Nuclear factor-like 2 (Nrf2) activator and nicotinic acid receptor agonist; monomethyl fumarate prodrug • Tablets, delayed-release (DR): 231 mg • Recommended initial dosage is 231 mg orally twice daily for 7 days; maintenance dosage is 462 mg orally twice daily; swallow tablet whole; avoid taking with high-fat, high-calorie meals or snacks
omeprazole magnesium/ amoxicillin/ rifabutin (Talia®) Redhill	<ul style="list-style-type: none"> • 505(b)(2) NDA approval 11/01/2019; Priority Review, QIDP • Indicated for treatment of <i>Helicobacter pylori</i> in adults • Combination of a PPI, a penicillin-class antibacterial, and a rifamycin antibacterial • Fixed-dose capsule, DR: omeprazole 10 mg, amoxicillin 250 mg, and rifabutin 12.5 mg • Recommended dosage is 4 capsules orally every 8 hours with food for 14 days; swallow capsules whole
pegfilgrastim-bmez (Ziextenzo™) Sandoz	<ul style="list-style-type: none"> • BLA approval 11/04/2019; biosimilar to Amgen's Neulasta® • Indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anticancer drugs • Leukocyte growth factor • Injection: 6 mg/0.6 mL solution in a single-dose prefilled syringe for manual use • Recommended dosage is 6 mg SC once per chemotherapy cycle; weight-based dosing should be used for pediatric patients < 45 kg
luspatercept-aamt (Reblozyl®) Celgene	<ul style="list-style-type: none"> • BLA approval 11/08/2019; Orphan Drug, Priority Review • Indicated for the treatment of adults with beta thalassemia who require regular red blood cell (RBC) transfusions • Erythroid maturation agent • Injection: 25 mg and 75 mg lyophilized powder for reconstitution in single-dose vials (SDV) • Recommended starting dosage is 1 mg/kg every 3 weeks administered SC by an HCP; assess hemoglobin (Hb) prior to each administration and delay or adjust dose for Hb ≤ 11 g/dL; do not exceed 1.25 mg/kg per dose
cefiderocol (Fetroja®) Shionogi	<ul style="list-style-type: none"> • NDA approval 11/14/2019; Priority Review, QIDP • Indicated for adults with limited or no alternative treatment options, to treat complicated urinary tract infections (cUTI), including pyelonephritis caused by susceptible Gram-negative microorganisms • Cephalosporin antibacterial • Injection: 1 gram lyophilized powder for reconstitution in SDV • Recommended dosage is 2 grams every 8 hours by IV infusion over 3 hours • Product availability is expected in Q1, 2020

ANDA = Abbreviated New Drug Application; BLA = Biologics License Application; NDA = New Drug Application; Q = Quarter; sBLA = Supplemental Biologics License Application; QIDP = Qualified Infectious Disease Product; sNDA = Supplemental New Drug Application; 505(b)(2) = FDA approval pathway that allows for submission of data from studies not conducted by or for the applicant

RECENT FDA APPROVALS *continued*

DRUG NAME MANUFACTURER	DESCRIPTION
New Drugs <i>continued</i>	
zanubrutinib (Brukinsa™) Beigene	<ul style="list-style-type: none"> • NDA approval 11/14/2019; Accelerated Approval, Breakthrough Therapy, Orphan Drug, Priority review • Indicated for the treatment of adults with Mantle cell lymphoma (MCL) after at least 1 prior therapy; continued approval may depend on confirmatory trials • Bruton tyrosine kinase (BTK) inhibitor • Capsule: 80 mg • Recommended dosage is 160 mg orally twice daily or 320 mg once daily taken without regard to food; swallow capsule whole • Product availability is expected the week of 12/18/2019
adalimumab-afzb (Abrilada™) Pfizer	<ul style="list-style-type: none"> • BLA approval 11/15/2019; biosimilar to Abbvie's Humira® • Indicated for the treatment of adults with RA, AS, PSO, PsA, CD, or UC and juvenile idiopathic arthritis (JIA) in patients ages ≥ 4 years • Injection: 40 mg/0.8 mL, 20 mg/0.4 mL, and 10 mg/0.2 mL single-dose prefilled syringes; 40 mg/0.8 mL SDV (institutional use only) • Recommended maintenance dosage is 40 mg SC every other week, except for JIA with dosage of 10 mg to 20 mg every other week • Product availability is expected in 2023
crizanlizumab-tmca (Adakveo®) Novartis	<ul style="list-style-type: none"> • BLA approval 11/15/2019; Breakthrough Therapy, Orphan Drug, Priority Review • Indicated to reduce the frequency of vaso-occlusive crises in patients ages ≥ 16 years with sickle cell disease • Selectin blocker • Injection: 100 mg/10 mL solution in SDV • Recommended dosage is 5 mg/kg by IV infusion over 30 minutes at weeks 0 and 2 and every 4 weeks thereafter; administered by an HCP
Expanded Indications	
ravulizumab-cwvz (Ultomiris®) Alexion	<ul style="list-style-type: none"> • sBLA approval 10/18/2019; Orphan Drug, Priority Review • New indication for the treatment of adults and pediatric patients ages > 1 month with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (TMA) • Recommended dosage is a weight-based IV regimen as described in the prescribing information; maintenance dose is administered every 4 or 8 weeks, depending on body weight
treprostinil (Orenitram®) United Therapeutics	<ul style="list-style-type: none"> • sNDA approval 10/18/2019 • Expanded indication for the treatment of pulmonary arterial hypertension (WHO Group 1) to include delay disease progression in addition to improvement in exercise capacity • Recommended initial dosage is 0.125 mg orally 3 times daily or 0.25 mg orally twice daily; titrate up every 3 to 4 days to highest tolerated dose
levetiracetam (Keppra®/Keppra XR®) UCB	<ul style="list-style-type: none"> • sNDA approval 10/23/2019 • New indication as monotherapy for the treatment of partial-onset seizures (POS) in patients ages ≥ 1 month for immediate-release (IR) formulations and patients ≥ 12 years for extended-release (ER) formulation; previously only approved for adjunctive therapy for POS • Recommended dosage for monotherapy is the same as for adjunctive therapy for POS and is weight-based for the IR formulations and 1,000 mg orally once daily for the ER formulation; titrate as needed

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RECENT FDA APPROVALS *continued*

DRUG NAME MANUFACTURER	DESCRIPTION
Expanded Indications <i>continued</i>	
delafloxacin (Baxdela®) Melinta	<ul style="list-style-type: none"> • sNDA approval 10/24/2019; Priority Review, QIDP • New indication for the treatment of community-acquired bacterial pneumonia (CABP) caused by designated susceptible bacteria • Recommended dosage is 300 mg infused IV over 60 minutes every 12 hours or 450 mg orally every 12 hours for 5 to 10 days
levonorgestrel-releasing intrauterine device (IUD) (Liletta®) Allergan	<ul style="list-style-type: none"> • sNDA approval 10/25/2019 • Expanded indication for the prevention of pregnancy for up to 6 years; previously approved for use up to 5 years • Recommended dosage is insertion of 1 IUD by a trained HCP; may remain in place for up to 6 years
influenza vaccine (Fluzone® High-Dose Quadrivalent) Sanofi	<ul style="list-style-type: none"> • sBLA approval 11/04/2019 • Indicated as active immunization for the prevention of influenza disease caused by influenza A subtype viruses and type B viruses in individuals ages ≥ 65 years • Recommended dosage is a single 0.5 mL IM injection administered during influenza season
calcipotriene foam (Sorilux®) Mayne	<ul style="list-style-type: none"> • sNDA approval 11/05/2019 • Expanded indication for the topical treatment of PSO of the scalp and body to include patients 4 to 11 years of age • Apply a thin layer to affected areas twice daily
ledipasvir/ sofosbuvir (Harvoni®) sofosbuvir/ velpatasvir (Epclusa®) sofosbuvir/ velpatasvir/ voxilaprevir (Vosevi®) Gilead	<ul style="list-style-type: none"> • sNDA approval 11/15/2019 • Expanded indication for the treatment of chronic hepatitis C virus (HCV) infection to include patients with severe renal impairment or end-stage renal disease (ESRD) • No dosage adjustment is required in this patient population

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