DECEMBER 2020

PERSPECTIVE ON THE Rx PIPELINE

Understanding changes in the medication market and their impact on cost and care.

Elixir continuously monitors the drug pipeline. As treatment options change, we evaluate and share our perspective on the clinical benefits, cost effectiveness and overall impact to payers and members. Our Perspective on the Rx Pipeline report provides ongoing actionable insights from our team of clinical experts and the steps we are taking to protect and improve plan performance.

TOP 6 PIPELINE DEVELOPMENTS TO WATCH IN 2021:

- Increasing Orphan Drug Market
- Continual Development of Gene Therapy
- Revolutionary Type 1 Diabetes Drug that Could Delay or Prevent Onset
- New Injectable Therapies for Atopic Dermatitis
- COVID-19 Vaccine Challenges and Long-Term Effects
- 2020 Pipeline Delays and Complete Response Letters

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CRAFTED Rx SOLUTIONS

Clinical Pipeline

Increasing Orphan Drug Market

Orphan drugs are used to treat rare diseases and conditions. According to the National Organization for Rare Disorders (NORD) there are more than 7,000 rare or ultra-rare diseases impacting more than 30 million Americans.[1] Programs such as the Food & Drug Administration's (FDA's) Orphan Drug Designation are designed to incentivize sponsors to develop drugs and biologics for uncommon diseases that otherwise may be overlooked for more profitable or broader population-impacting medications.[2] This program grants orphan status to drugs that treat rare or ultra-rare diseases or conditions and impact fewer than 200,000 people or more than 200,000 but the manufacturer is not expected to recover the cost of developing and marketing a drug treatment.[3] Manufacturers benefit from the orphan drug status with federal grants, a 50% tax credit and seven years of marketing exclusivity.[1]

Orphan drugs treat a range of indications, from spinal muscular atrophy to certain cancers to myeloma, and many more. Additionally, orphan drug status can be granted to existing medications used to treat common indications if the FDA approves a new indication considered "orphan." An example of such a situation is Simponi Aria®, which was originally approved for rheumatoid arthritis, but in 2020, received an approval for treatment of active polyarticular juvenile idiopathic arthritis (pJIA) in patients two years of age and older.

The program is working well and orphan drug designations have become fairly numerous. As of December 1, there were 73 FDA orphan drugs/indications approved for 2020. Unfortunately, many orphan drugs launch at very high prices. Worldwide sales of orphan drugs reached $100 billion in 2015 and are estimated to double by 2022.[4] It does not appear that orphan drug/biologic approvals will slow down in the near future and orphan products will continue to contribute to drug spend, with a possible notable increase in cost for the pediatric population.[5]

Utilization management, such as prior authorizations, step therapy and quantity limits may be appropriate for some products approved via the orphan indication pathway to ensure the right patient with the right condition gets their needed medication. Cost aside, orphan disease states often have limited treatment options and may not have another FDA-approved treatment option. Formulary coverage of many of these products may be necessary if an alternative drug or biologic does not exist, as most rare diseases are severe, lifelong and disabling.[1]

Clinical Pipeline

Continual Development of Gene Therapy

Genetic targets for drug therapy are ever increasing. Gene therapy involves ex vivo and in vivo modification of genes to replace or modify erroneous genes with healthy functioning exogenous genes in the patient.[6, 7] The ultimate goal of gene therapy is to prevent or cure a disease or disorder. Some gene therapies may not fully cure a patient, yet still provide clinical benefit. The FDA reviews all gene therapies for safety and efficacy.

Similar to gene therapy is cellular therapies. An example of an approved cellular therapy is chimeric antigen receptor (CAR) T-cell agents. CAR T-cell therapy requires removal of cells from the body. These cells are then modified and placed back into the patient to treat various forms of cancer.

Antisense oligonucleotide-based therapies, such as Spinraza, Exondys 51 and Tegsedi, or small interfering ribonucleic acid agents, such as Onpattro, have been approved to modify or silence genes, but do not fall under the FDA-defined umbrella of gene therapy.[8]

Gene editing, which takes part of the existing DNA and makes changes, is also making rapid advancements. Last year, Elixir's "Top 10 Developments to Watch in 2020" mentioned CRISP-R gene editing, however, currently there are no FDA-approved gene edited therapies.

Recently approved gene therapies include Zolgensma for spinal muscular atrophy and Luxturna for treatment of a rare inherited form of blindness (RPE65-mutation-associated retinal dystrophy). The near future drug pipeline consists of multiple gene therapy products that introduce genes or exogenous genes into the patient (see table below). Conditions targeted for gene therapy may include orphan indications, such as hemophilia or Duchenne muscular dystrophy, or more commonly occurring indications, such as heart failure or osteoarthritis.

Many gene therapy medications have complex administration requiring medical expertise in an inpatient setting, pushing the drug spend into the medical benefit. All forms of gene/cellular therapy products have the potential to revolutionize healthcare, but also can come with a hefty price tag. Gene therapy products require extensive clinical review and are often candidates for prior authorization to ensure clinically appropriate utilization and safety for the member.

Select Potential Upcoming Gene Therapy FDA Applications[9]

Name	Indication	Administration	Common/Rare Condition	Anticipated Approval/Stage	Insight
Lenti-D	Adrenoleukodystrophy	Intravenous	Rare	Phase III	Positive results from pivotal STARBEAM trial for a disease that leads to severe loss of neurological function and death in most untreated patients
Generx (Alferminogene Tadenovec)	Angina pectoris	Other	Common	Phase III	Stimulates and augments the heart's innate arteriogenesis to form new capillary vessels in select ischemic regions downstream from large coronary arteries

Name	Indication	Administration	Common/Rare Condition	Anticipated Approval/Stage	Insight
LentiGlobin (BB305)	Beta thalassemia Sickle cell disease (SCD)	Intravenous	Rare	Pending PDUFA/ Phase III	Received Break Through designation from FDA
Instiladrin (nadofaragene firadenovec)	Bladder cancer	Intravesical	Common	Phase III	For those who failed BCG therapy
PF-06939926	Duchenne muscular dystrophy	Intravenous	Rare	Phase III	Anticipated study completion is in 2025
RT-100	Heart failure	Other	Common	Phase III	Single-dose treatment of congestive heart failure to improve heart function
SB-525 (giroctocogene fitelparvovec)	Hemophilia A	Intravenous	Rare	Phase III	Anticipated study completion is in 2026
Roctavian (valoctocogene roxaparvovec)	Hemophilia A	Intravenous	Rare	Complete Response Letter	BioMarin received a Complete Response Letter from the FDA, requiring at least 2 additional years of data to support safety and efficacy
SPK-9001 (fidanacogene elaparvovec)	Hemophilia B	Intravenous	Rare	Phase III	Hemophilia B is the second most common type of hemophilia and can be inherited or acquired
AMT-061 (etranacogene dezaparvovec)	Hemophilia B	Intravenous	Rare	Phase III	
FLT180a	Hemophilia B	Injectable	Rare	Phase III	
GS010	Leber's hereditary optic neuropathy (LHON)	Ophthalmic	Rare	Phase III	A neurodegenerative retinal disease treatment that was granted Orphan Drug designation by the FDA
Invossa	Osteoarthritis of the knee	Injectable	Common	Phase III	A one-time intraarticular injection into the knee containing non-transformed and transduced chondrocytes designed to overexpress transforming growth factor β1 (cellular therapy)
OTL-101	Severe combined immunodeficiency (SCID)	Injectable	Rare	Phase III	Referred to sometimes as "bubble boy syndrome," received Break Through designation from FDA

Clinical Pipeline

Teplizumab *PRV-031*

Manufacturer: Provention Bio
Indication/Use: Delay or prevention of type I diabetes (T1D) in at-risk individuals
Dosage Form: Intravenous
Pipeline Stage: PDUFA 2H 2020

Approximately 34.2 million Americans, 10.5% of the United States' population, has diabetes.[10] Type 1 diabetes (T1D) accounts for 4.6% of this population.[11] In genetically susceptible persons, T1D progresses through two symptomatic stages prior to the development of clinical diabetes and the need for insulin. The first stage is the development of antibodies, with the second stage being dysglycemia.[12]

Teplizumab is a 14-day intravenous course designed to delay or potentially prevent the onset of T1D. This monoclonal antibody modifies immune cells in the body to prevent destruction of beta cells, the insulin producing cells in the body. There are no FDA-approved drugs for prevention of T1D. Standard of care is lifelong injections of insulin.

The TrialNet group studied individuals over eight years of age who were a high-risk nondiabetic relative of type 1 diabetics, along with having at least two autoantibodies and evidence of dysglycemia. In this phase II trial, the disease was diagnosed in 43% of the teplizumab group, with a median time to diagnosis of 48.4 months. Comparatively, the placebo group had a diagnosis in 72%, with a median time to diagnosis of 14.4 months.[13] Provention Bio stated in a June 2020 press release that additional findings showed patients treated with teplizumab maintained C-peptide levels, a marker of endogenous insulin production, while those in the placebo group had a marked decrease in this lab value.[14] This delay or prevention of disease onset could allow patients years without additional insulin injections.

Glossary of Terms **BLA** - Biologics License Application **NDA** - New Drug Application **PDUFA** - Prescription Drug User Fee Act

Clinical Pipeline

Tralokinumab

Manufacturer: MedImmune/AstraZeneca
Indication/Use: Adults with moderate to severe atopic dermatitis (AD)
Dosage Form: Intravenous
Pipeline Stage: PDUFA 2H 2020

Atopic dermatitis affects an estimated 13% of children and 7.2% of adults in the United States.[15] The standard of care for atopic dermatitis is topical therapy. However, if it is severe enough and patients have failed on topical therapy, injectable medication is now available with the additional indication granted to Dupixent® (dupilumanb), an IL-4/IL-13 antagonist, in May 2020. This was the first monoclonal antibody indicated for use in atopic dermatitis.[16-18]

Similar to Dupuxient, tralokinumab is an every other week subcutaneous injection. However, this medication has a novel target of IL-13 inhibition for atopic dermatitis. IL-13 inhibits inflammation pathways.[19] This inhibition leads to desensitization of the immune system, which will prevent/resolve disease flares.

In the phase III ECZTRA trials, tralokinumab had significantly better results in the primary outcomes of atopic dermatitis severity and reduction of eczema area, with a 75% reduction within 16 weeks. ECZTRA 3 compared tralokinumab and corticosteroids and found a 12.7% reduction in severity compared to the placebo group. Sixty-eight percent of the tralokinumab group saw a 75% reduction in eczema area versus only 36.7% of patients in the placebo group.[20, 21]

The American Academy of Dermatology guidelines for atopic dermatitis were last updated in 2014, prior to Dupixent's atopic dermatitis approval.[17] It is reasonable to think that tralokinumab and Dupixent would compete for place in therapy. Recent studies of Dupixent users has potentiated a link between inflammatory bowel disease and rheumatoid arthritis, hypothesized to be caused by inhibition of IL-4.[21, 22] Further data will be needed to confirm this newly emerging information and it will be interesting to see if tralokinumab bypasses these side effects with its more selective mechanism of action. Tralokinumab is also in Phase III trials for treatment in severe asthma exacerbation; however, tralokinumab did not reduce the number of annualized asthma exacerbation rates compared to standard of care.[23]

COVID-19 Vaccine Challenges and Long-Term Effects

As of December 1, 2020, there are 13 phase III trials in the vaccine pipeline for COVID-19. There are three front runners for Emergency Use Authorization (EUA). Two candidates have already submitted EUA applications:

Manufacturer	Vaccine Name	Dosing Regimen	Storage	Vaccine Efficacy	Date EUA Submitted
Moderna[25-27]	mRNA-1273	2 doses, 28 days apart	Short term: 2° to 8°C for up to 30 days Long term: 20°C for up to 6 months	94.1%	11/30/20
Pfizer/BioNTech[28, 29]	BNT162n2	2 doses, 21 days apart	-70 °C for up to 6 months Dry ice storage to maintain temperature	95%	11/20/20
Oxford/AstraZenca[30]	AZD1222	2 doses, 28 weeks apart	2° to 8°C for 6 months	70%	Has not been submitted

Please note, prior to publication, the Pfizer/BioNTech vaccine received EUA from the FDA. Distribution and administration has begun.

Cold Chain Storage and Manufacturing

With these vaccines nearing completion, the problem shifts from vaccine development to dissemination of these products to the general public. The Pfizer and Moderna vaccines are developed from mRNA, which is unstable unless adequate temperatures are maintained. During transport, there is a very real risk of the vaccines becoming damaged due to breaches in the cold chain storage. Potential problems could include leaking/malfunctioning coolers, delivery delays due to inclement weather and possible scarcity of dry ice. The cold chain storage problem is further exacerbated by pharmacies/hospitals/clinics not all having adequate refrigeration to maintain vaccine stability. This could potentially limit geographic availability of the vaccine.

Phase one of vaccine dissemination is anticipated to begin in December 2020, with available doses limited to those considered high risk, including those who are part of the critical workforce. The federal government is currently working with certain pharmacy chains for on-site administration of the vaccine in long-term care and assisted living facilities. Phase two will see a larger distribution of vaccines to the general public.[31]

COVID Patient Long Haulers

Approximately 10% of people who test positive for COVID-19 continue to have persistent symptoms after three weeks and have been named long haulers.[32] The more commonly reported symptoms include fatigue, dyspnea, joint pain and chest pain.[33] A smaller portion of people report continued symptoms of shortness of breath, neurocognitive difficulties, thromboembolic events and mental health conditions.[34]

Impact on Chronic Disease Management and Medication Adherence

At the start of the pandemic, primary care visits were delayed, rescheduled or switched to virtual care. A global survey found that the conditions most impacted by reduction in healthcare services during the pandemic were diabetes (36%), followed by chronic obstructive pulmonary disease (COPD) (9%), hypertension (8%), heart disease (7%), asthma (7%), cancer (6%) and depression (6%). While patients reported to be fair (48%) or good (26%) for disease management, most healthcare providers (67%) rated moderate or severe effects on their patients due to changes in healthcare services since the outbreak. Moreover, 80% reported the mental health of their patients worsened during COVID-19.[35]

One retrospective report looked at initiation of statins for cholesterol and metformin for diabetes. From February to May 2020, initiation of statins and metformin fell 52-60% and testing rates of LDL cholesterol and HbA1C fell 81-90% in February and March.[36] While these delays in chronic care are unlikely to cause immediate harm, there is a potential for future complications due to delay in treatment. Conversely, controller inhaler adherence increased in COPD and asthma patients from January to March by 14.5%.[37] Additionally, preventive care services, like colonoscopies, have become more complicated to schedule with some COVID testing requirements prior to procedures.

Chronic disease state management is key to reducing hospitalization for acute need (i.e., heart attack and stroke). In 2021, we may see more impact from delays and gaps in care and interruptions to drug adherence.

2020 Pipeline Delays and Complete Response Letters

With the global pandemic, clinical trials had to be halted and restarted to ensure the safety of participants and researchers, leading to some delays in FDA approvals. For some of these products the FDA has issued complete response letters (CRL), delaying review for approval. A CRL is a letter sent from the FDA to the drug manufacturer (applicant) with the rationale for why the product will not be approved and a possible recommendation for action the applicant may take to remediate the FDA's concern. Deficiencies in the application are highlighted and can range from efficacy and safety to manufacturing issues. It is then up to the manufacturer to determine how much information to share with the public in regards to the CRL.[38]

Pipeline Drugs	Date of Action	Indication	Administration	Insight
BIIB037[39] **(aducanumab)**	FDA subcommittee meeting on 11/6/20	Alzheimer's disease	Intravenous	FDA advisory committee provided recommendations for consideration. FDA will continue the review process with a decision on whether to approve the Biologics License Application (BLA) by 3/7/21.
Ocalvia[40] **(obeticholic acid)**	CRL issued 6/29/20	Non-alcoholic steatohepatitis (NASH)	Oral	CRL indicated that surrogate data provided did not outweigh the potential risk to support accelerated approval for liver fibrosis in NASH. Recommendation was given to submit additional post-interim efficacy and safety data from the ongoing REGENERATE study.
Roctavian[41] **(valoctogene roaxaparvovec)**	CRL issued 8/18/20	Hemophilia gene therapy	Intravenous	FDA requested at least two additional years of data to confirm safety and efficacy for substantial evidence of durable effect on annual bleed rate.
SPN-812[42] **(viloxazine)**	CRL issued 11/9/20	Attention deficit hyperactivity disorder (ADHD)	Oral	CRL given due to a potential facility issue, not for safety and efficacy of the product.
Viaskin Peanut[43]	CRL issued 8/4/20	Peanut allergy therapy	Topical patch	Concern for patch-site adhesion impacting possible efficacy and patch modification was needed requiring a new clinical study. No safety concerns in the CRL.

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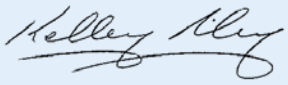
Our Clinical Steering Committee

The Elixir Clinical Steering Committee brings together leaders from across our national pharmacy care company to monitor the drug landscape, provide recommendations on how to address changes, and to ensure our clients and patients are prepared—in advance.

With any new development, we partner with our Pharmacy & Therapeutics (P&T) committee and consult with our best-in-class specialty pharmacy, to provide a balanced perspective on the clinical effectiveness of all available options, the cost impact to our plan sponsors and patients, and the impact on the overall patient experience.



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