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Strategies and Analysis for Managing High-Cost Specialty Products

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'Buy American' Executive Order Could Impact Specialty Drugs

President Donald Trump has issued another executive order focused on the pharmaceutical industry: a so-called "Buy American" order. While the approach presents some benefits, industry experts maintain that several challenges exist to its implementation, not the least of which is that it's coming in the middle of a pandemic. And multiple specialty therapies may be impacted by it.

The order, signed Aug. 6, comes only a couple of weeks after the president signed a handful of executive orders focused on drug pricing. One of them, a most-favored nation order, was criticized by industry experts as a last-ditch effort before the Nov. 3 election to show the country that the administration is doing something about drug prices *(RSP 8/20, p. 1)*. At the same time, critics argued that it's taking away from efforts to develop therapeutics and vaccines for the COVID-19 pandemic. The president held off on publicizing that order with the other three on July 24, saying that he was giving pharma one month to come up with alternatives. As of RSP press time on Sept. 9, that order had not been made public.

The more recent order is focused on protecting U.S. citizens, the economy, the country's "critical infrastructure" and military against "outbreaks of emerging infectious diseases and chemical, biological, radiological, and nuclear (CBRN) threats." The order is focused on decreasing U.S. dependence on foreign manufacturers for "Essential Medicines, Medical Countermeasures, and Critical Inputs deemed necessary for the United States" while boosting domestic production of them. It applies to government entities that purchase drugs.

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COVID Is Heating Up Payer Focus on Drug Pricing, Value

With the COVID-19 pandemic affecting a variety of health care stakeholders, the cost of these services is becoming even more important. Payers tightening their budgets are trying to make sure that they are truly paying for value. But that's easier said than done. All industry stakeholders, including pharma companies, should work to make changes in the health care system to bring value to the forefront of decision making, maintain industry experts.

Pointing out that people may never agree on the issue of whether prices for innovative drugs are too high, Kate Dion, value communications lead at 3D Communications, a company that provides strategic regulatory and value communications services to pharmaceutical, device and biologic companies, maintained that "what's really at stake, and COVID-19 is pushing this into sharp focus, is how urgently we need to get medicines to patients. And not just medicines for the pandemic. The challenge is formidable. All at the same time, we need to make medicines more accessible to patients, incentivize scientific innovation and keep investors happy."

Dion moderated a recent webinar sponsored by 3D Communications titled "COVID-19: Will it be a Catalyst that Moves us Forward in the Drug-Pricing

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Debate? Or The Barrier that Slows us Down?" She pointed out that the last decade has seen "some spectacular innovation in science. But what about innovation in the way we pay for medicines?"

When she asked the four speakers if they believed that COVID-19 would have an impact on the way medicines are priced, three said yes.

"There are many unknowns on how COVID-19 will impact health care in general, and I think pricing is just one piece of health care," said Indranil Bagchi, Ph.D., senior vice president and head of global value and access at Novartis Oncology. "But the longer the crisis lasts," it will only increase pressure on aspects of the health care system, including payer budgets. "It's a little hard to look at this and say nothing will change at all."

He noted that some trends were in place before the pandemic. "If you think of the Affordable Care Act and the goals of improving quality of life, ensuring satisfaction, reducing costs, that was all already happening. What we see is COVID-19 being an accelerator" of these.

"I think budgets will come under increasing pressure," said Edmund Pezalla, M.D., former Aetna senior executive and founder and CEO of Enlightenment Bioconsult, LLC. "The self-insured employers are under pressure to keep costs down generally, but now their revenues are decreasing, so they are keeping a lot of costs down, including health care costs. In this coming year, I think it will be difficult for many of them to sustain their current levels of contribution to health care."

According to Pezalla, measures they will take to reduce health care costs will include implementing "restrictive provider networks and leaner formularies, and this does put pressure on manufacturers to avoid pricing much above the existing therapies. COVID is bringing out components we haven't thought about before in terms of how much everything in the health care system is costing. So we're going to need to align drug pricing with other things, other values in the health care system. I think it's going to bring a lot of this into sharp relief."

Valentino Confalone, general manager at Gilead Sciences, Inc., Italy — the only panelist to say no to the question of whether COVID would have an impact — clarified that "of course there is going to be an impact, but what I see is more an acceleration of existing trends rather than a complete change in the way we look at value and pricing."

He has observed three emerging trends: "One is an evolution of value-based [pricing] that was already there, that's been there for a long time, but I see an evolution and a change in pace. Another one is for the first time, we're seeing drug spending, pharma spending seen as an investment for the long term rather than a current expenditure for the short term. And last but not least is an increasing momentum toward international pricing coordination by payers and regulators alike."

COVID Will Prompt 'Flurry of Investments'

Michael Schroter, Ph.D., founder of Swiss investment firm VIOPAS Partners AG, drew a parallel between COVID and another history-altering event: "I think COVID will be for health care what 9/11 was for the defense sector. There will be a flurry of investments to develop innovative treatments and build capacity to prevent the next crisis. But at the same time, the economic burden from COVID-19 will be forcing payers to spend more prudently. Innovation at rising costs will no longer work in this context. However, products from companies that offset existing costs will be

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in high demand. The pressure is really going to be on pharma and biotech to develop and deliver medicines with great clinical benefit that at the same time help reduce overall health care costs."

Asked if COVID will change the way payers and other stakeholders value innovative therapies, Pezalla replied, "I think the evaluation process will stay the same. We're still going to be looking for the same sorts of things in a medication: effectiveness, what's the benefit to the patient, are there cost offsets and other important things like that. But there's going to be an increased emphasis on comparative effectiveness — on choosing either the best product or reducing coverage of multiple products with similar efficacies."

Drugs' Value and Prices Need to Align

He asserted that stakeholders need "to work on a model that will align value and prices because we still don't have a way of valuing drugs that's universally accepted.…We have to determine is this medication, or any other treatment for that matter, a good value for money, and that's important, but the other thing is that it doesn't necessarily mean that we can afford it." Payer budgets are going to be tight, and "we don't really have a good framework or starting point" for payers to make decisions on the value of a therapy.

Schroter said he thought the pandemic would alter the way that payers and other stakeholders value innovative medicine. "One thing that COVID's shown us is the importance of the entire health care system to work together. All the subsectors, from pharma to hospitals to insurers, are dependent on each other. And what we need to overcome is the challenge that we are so siloed. We need to start looking at cost savings across the entire health care spectrum in order to make a real difference. Time has come to take a much more holistic approach to deliver health care.

"Just to put this into perspective," he continued, "about 85% of health care expenses are other than medicines, and we have to look at the total expenses rather than look at just one single cost element. That means payers need to look at costs differently and look at medicines rather as an investment than a cost."

Confalone agreed. "I think for the first time, it has emerged dramatically how much a health challenge can impact the whole of society. And spending on pharmaceuticals in terms of budget impact is definitely going to undervalue what is the real impact holistically of novel new and effective medicines on all of society."

COVID's 'Made Public Health Very Public'

"COVID has certainly made public health very public," observed Bagchi. "I mean, when can you turn on the TV and not hear a discussion about how everybody seems to be very conversant about when a vaccine is likely to hit the market or when treatments are going to be available? So I think people generally have a much broader understanding of what's at stake if large swaths of the population fall ill at the same time. We have seen our hospitals getting more burdened due to lack of extra capacity, which is something over the years as we're driving toward efficiency, you get an efficient health care system, but then the pandemic shows up, and the hospital system is just incapable of handling all that. So I would think — I would hope — there's a broader understanding from the public on the overall value of the health care system, including what role medicines play in it."

Pointing to the 15% that drugs make up in overall health care costs, he noted that "cost-wise, it's a small piece, but in terms of contribution, the piece is significant."

The biggest obstacle to change in the United States, said Pezalla, "is a lack of clear understanding. Determining the value of medical interventions, whether it's a drug or procedure, we just don't have a good handle on that. And we haven't been able, therefore, to reconcile that with our ability to pay."

Focus on All Health Care Services

He added that "this is not just about drugs. This is really about things across the spectrum of health care services [such as] diagnostics and hospital admissions. We can't just focus on drugs here. We've got to talk about the entire thing and how we value all of that and then how we reconcile that value with what we're willing and able to pay for it."

According to Bagchi, "we all know the U.S. has had over the years a relatively fragmented health care system. Often the medical budgets and the pharmacy budgets are separated, and when it comes to the budgeting process, often the focus is two to three years. So the system the way it was set up didn't lend itself to recognition of value within the system. So if I'm looking to put a medicine on the formulary, and my length of responsibility is two to three years, how am I going to understand the value of a medicine that might report out in five to 10 years? These days, we are talking about CAR-Ts and cell and gene therapies… with a one-time administration today, whose efficacy and effectiveness are supposed to last for a lifetime."

The fragmented and short-term-focused U.S. health care system "doesn't lend itself to recognizing

value," he maintained. "And then the other piece is data requirements." With single-treatment cell and gene therapies, "how do we capture the right data that helps us prove their efficacy and effectiveness over a long time? That's something that's a challenge that we need to work on. And then the last piece when it comes to the U.S. is the increasing amount of patient copay and coinsurance, which is a significant challenge. Especially as we move into specialty medicines, oncology medicines," coinsurance and copayments "can become significant for the patient. That's something that needs to be addressed."

Challenges Among Markets May Vary

Within emerging markets, the challenges may be different, said Bagchi. In many markets, it comes down to "improving infrastructure" within the existing health care system, "making sure we have the right personnel, making sure we have the right diagnostics," and ensuring affordability and availability.

In Europe, "sustainability is certainly a big, big challenge," said Confalone. Coordination among countries "can be very helpful," as seen recently with COVID, "when the European Union started to think about using joint procurement agreements to achieve one single agreement for all the member countries, and this could definitely be a way to speed up access" to COVID therapeutics once they are available.

Asked whether prices for medicines are sustainable for health care systems, Schroter said, "yes, they can be sustainable — even high-priced drugs can be sustainable for health care systems — but only if the prices of these medicines offset other costs in the system. And that's the challenge with the way we look at pricing today."

He contended that "we need to fully embrace value-based health care in a much broader way.…This approach needs to apply to the entire patient journey, not just when the person shows up at the doctor. This is especially true for chronic diseases and diseases that require long-term care." For example, he pointed to Alzheimer's disease, where caregivers carry a tremendous burden, often suffering from depression and sometimes losing their job. "Today, most payers would not consider the costs borne by caretakers since it does not hit their budget, but ultimately, we as a society still pay for these costs."

Schroter asserted that "we need to think more holistically as we do with COVID and think beyond individual siloed budgets and start thinking across these silos. Our common goal should be maximizing health and reducing costs.…And as we've seen with COVID, we all have to work together on it, or otherwise it won't work."

Contact the speakers via Dion at kdion@3dcommunications.us. ✧

Recently Approved Evrysdi May Have Big Impact on SMA Class

The spinal muscular atrophy (SMA) therapeutic category continues to expand with the Aug. 7 FDA approval of Evrysdi (risdiplam) from Roche Group member Genentech, Inc. Industry experts maintain that the drug has the potential to significantly impact the class for a variety of reasons, including its route of administration and price.

People with SMA cannot produce enough SMN protein, leading to the loss of motor neurons, which results in problems breathing, swallowing, speaking and walking. Before a therapy was available to treat SMA, the condition was the No. 1 genetic cause of infant death.

Most physicians recognize four types of SMA:

✦ ***SMA Type 1***: This is also known as Werdnig-Hoffmann disease and can impact infants *in utero* in the most severe form, known as Type 0, which some clinicians recognize as a fifth type. It usually is evident before a child is 6 months old. Most children with Type 1 will die before they are 2 years old if untreated.

✦ ***SMA Type 2***: Also known as Dubowitz disease, this form produces symptoms in children between six and 18 months of age. Most patients live into adolescence or young adulthood.

✦ ***SMA Type 3***: This also is known as Kugelberg-Welander disease. Symptoms present after 18 months of age. With treatment, most patients live a normal lifespan.

✦ ***SMA Type 4***: People with this form can develop symptoms as early as 18 years old and usually after they are 30 years old; their life expectancy is not affected.

First onto the U.S. market was Biogen's Spinraza (nusinersen), which was approved in December 2016 for the treatment of SMA in pediatric and adult patients *(RSP 1/17, p. 5)*. Spinraza, a survival motor neuron-2 (SMN2)-directed antisense oligonucleotide, is administered by or under the direction of health care professionals able to perform lumbar punctures; dosing is over one to three minutes as an intrathecal injection. The first three doses are administered at 14-day intervals, followed by a fourth dose 30 days after the third dose. After that, maintenance dosing is once ev-

ery four months. The first-year price of the therapy is $765,000 and then $382,500 for subsequent years.

Then in 2019, the FDA approved gene therapy Zolgensma (onasemnogene abeparvovec-xioi) from Novartis Pharmaceuticals Corp. subsidiary AveXis, Inc. for the treatment of people younger than 2 years old with SMA with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene *(RSP 6/19, p. 8)*. Dosing for the treatment is a one-time 60-minute intravenous infusion, and its price is $2.125 million.

The FDA approved Evrysdi for the treatment of SMA in people at least 2 months old. Roche developed the SMN2 splicing modifier in partnership with PTC Therapeutics, Inc. and the SMA Foundation. Dosing of the oral solution, which is administered by mouth or feeding tube, is based on age and body weight. A pharmacist must constitute the powder, but the drug can be administered by a patient or caregiver at home after a recommended consultation with a health care professional prior to the first dose. The price of the drug is tied to a person's weight and is capped at $340,000 per year once someone reaches 44 pounds. For a 15-pound patient, the price would be less than $100,000 per year.

"PTC/Genentech did a good job of strategically pricing Evrysdi," observes Winston Wong, Pharm.D., president of W-Squared Group.

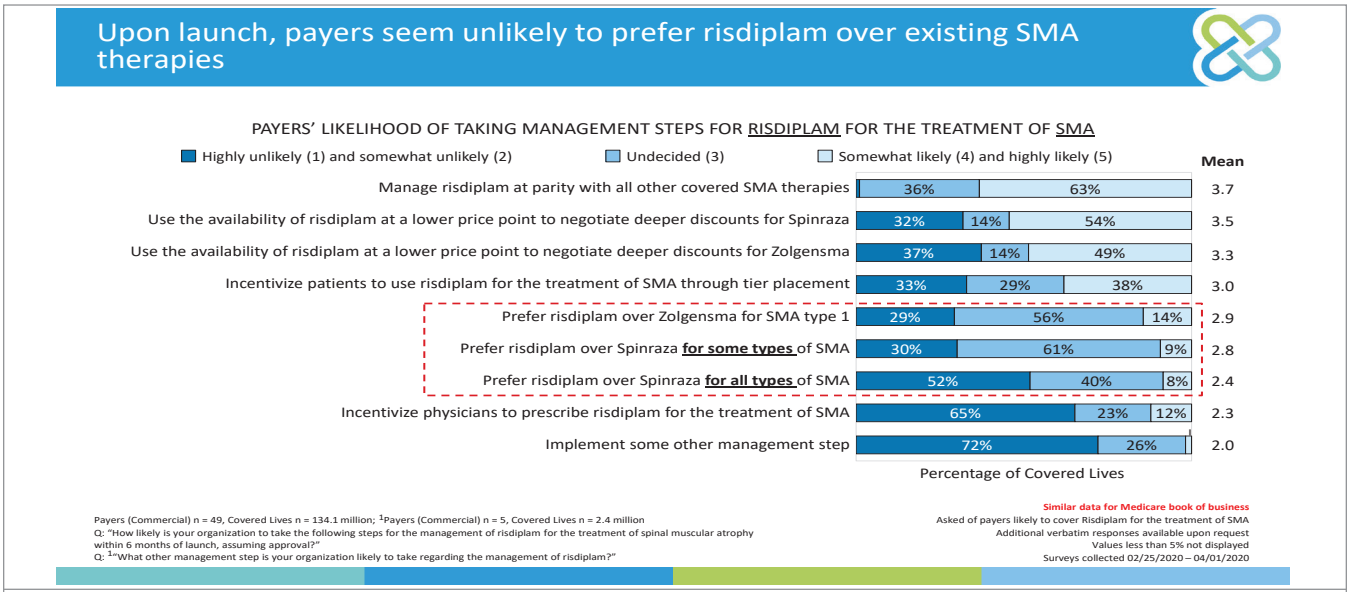
Elan Rubinstein, Pharm.D., principal at EB Rubinstein Associates, notes that Accredo Specialty Pharmacy, part of Express Scripts, a Cigna Corp. company, is involved with all three therapies. Accredo is the sole distributor for Evrysdi. For Zolgensma, AveXis offers two payment deals for payers: a five-year pay-over-time option that it is executing via Accredo and a five-year outcomes-based deal. Specialty distributor CuraScript SD, also an Express Scripts unit, will be the sole distributor of the drug. CuraScript and Accredo are the only providers of Spinraza, while Accredo manages patient enrollment, prescription intake, benefit verification, payer coverage and financial assistance needs; it also processes payments and coordinates shipments.

In addition to its price, Evrysdi's oral route of administration will help with uptake of the drug.

"As an oral administered at a patient's home, Evrysdi is covered through the pharmacy benefit," says Rubinstein. "In contrast, as infusibles, Spinraza and Zolgensma are likely to be covered under the medical benefit." Some coverage of Spinraza also falls under the pharmacy benefit.

"I absolutely do believe that the oral formulation will have real value to payers," says Jeff Myers, senior vice president of reimbursement, strategy and market access at Catalyst Healthcare Consulting Inc.

According to Wong, "the easy way to look at Evrysdi is that it is an oral form of Spinraza, impacting the SMN2 gene; is less expensive than Spinraza; and potentially more effective than Spinraza with its more systemic clinical effect as opposed to Spinraza being an intrathecal injection and limiting its



SOURCE: Zitter Insights, Managed Care Biologics and Injectables Index: Q1 2020.

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site of action to the CNS [i.e., central nervous system]. However, the true clinical benefit of the systemic effect has not been well-defined."

For these reasons, he tells AIS Health, he thinks Evrysdi mainly will compete with Spinraza. "The only negative vs. Spinraza is the adverse effect profile because Evrysdi appears to also impact other genes."

Payers, Patients May Prefer Evrysdi

Nicole Kjesbo, Pharm.D., principal clinical program specialist for Prime Therapeutics LLC, says her company also expects Evrysdi's main competitor will be Spinraza. "Evrysdi may provide an advantage in that it is orally administered every day vs. Spinraza, which is intrathecally administered every four months after loading doses," she says. "Prime anticipates Evrysdi will gain market share from Spinraza due to the more convenient dosing. In addition, Prime anticipates Evrysdi will capture new patients who have not elected to use Spinraza or who have stopped taking Spinraza." Due to Evrysdi's route of administration, combined with the lower wholesale acquisition cost (WAC), "Prime expects this drug to be preferred by both payers and patients alike," she tells AIS Health.

In response to AIS Health questions, Lynn Nishida, R.Ph., vice president of clinical product at WithMe Health, shared that company's recent white paper, which assessed the three drugs' safety profiles. Evrysdi "does not carry any black box warnings, contraindications or noted warnings or precautions." Among cases of infantile-onset SMA, upper respiratory tract infection, pneumonia, constipation and vomiting were the most common adverse events. For people with later-onset SMA, fever, diarrhea and rash were most common.

Spinraza's label contains "warnings for low platelet levels, coagulation abnormalities and renal toxicity, and similar common adverse reactions to Evrysdi," while Zolgensma's "carries warnings for cardiac laboratory abnormalities and low platelets with common adverse reactions of increase[d] liver enzymes and vomiting."

"The real question is for the type 1 and 2 SMA patients and the question of Zolgensma vs. Evrysdi," says Wong. "Zolgensma is replacing the more potent SMN1 type gene, whereas Evrysdi impacts the SMN2 gene, which produces a lower amount of functional SMN proteins. In my mind, the market will potentially be split between Zolgensma and Evrysdi for the Type 1 SMA patient over 2 months in age. Zolgensma still has the niche of the indication for less than 2 months." Longer-term follow-up of Zolgensma will help determine how durable it is and whether it or Evrysdi provides better outcomes for people between 2 and 24 months of age, he says. "There is no doubt past 2 years of age that Evrysdi is the first-line choice in my mind."

Study Shows Zolgensma and Spinraza Use

The WithMe Health white paper cites a study that found "results have shown 4 in 10 patients required additional Spinraza (nusinersen) therapy within 2 years of receiving Zolgensma." In addition, it points out that no studies have been conducted on "the safety and efficacy of combination therapy with Evrysdi" in people receiving or who have received Zolgensma or Spinraza.

According to Kjesbo, "Prime anticipates Zolgensma will remain the preferred treatment option in patients with SMA Type 1. Although we don't expect much competition between Zolgensma and Evrysdi, there is a chance that they will be used off-label in combination."

Adds Wong, "the only real unanswered question thus far given the three treatment options is if Zolgensma is administered in early Type 1 SMA (<2 months of age), can, should or would Evrysdi be a treatment option later? We do not have the answer to this question; nevertheless, it is an interesting one from a managed care perspective."

As far as potential payer management strategies of the class, "I suspect there will be full PA [i.e., prior authorization] on any product to start," Myers says, allowing payers to look at the clinical data and ensure that use of a treatment is appropriate.

WithMe Health recommends that Evrysdi utilization management include clinical documentation of the following:

- ***"A definitive diagnosis*** of Type 1, or non-ambulatory Type 2 or Type 3 SMA made by or in consultation with a neurologist with experience in SMA diagnosis, treatment, and management.
- ***"Confirmation of genetic testing*** showing documentation of both of the following: Confirmed genetic diagnosis of 5q-autosomal recessive SMA and at least 2 copies of the SMN2 gene.
- ***"Patient is at least 2 months of age***, and restrictions may vary by SMA type.
- ***"Documentation of baseline motor function tests*** (e.g. Hammersmith Infant Neurological Exam Part 2 [HINE-2], Hammersmith Functional Motor Scale Expanded [HFMSE], Upper Limb Module [ULM] Test [Non ambulatory], Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders [CHOP INTEND]).
- ***"Confirmation that the patient is not ventilator dependent.***

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✦ ***"Confirmation that the patient has not received Zolgensma*** (onasemnogene abeparvovec) therapy or will not receive concomitant Spinraza (nusinersen) therapy."

"If I were a payer, short of starting to have bad outcomes [with Evrysdi], moving toward that product makes sense," states Myers. He points out that commercial plans' management may be different than that of public payers such as Medicare, Medicaid and the exchanges, which have "pretty rapid turnover." For this reason, they likely "are going to do everything they can" not to allow the use of Zolgensma, which is "insanely expensive." These payers will want to try to keep SMA therapy coverage to the pharmacy benefit, he says, where they are "not facing the same level of medical expenses" incurred by Zolgensma and Spinraza.

Asked about reinsurance's potential impact on the drugs' use, Myers says that most companies do "lasering," where a person with a condition likely to exceed a deductible is given a higher deductible. Sometimes these companies will not cover over a certain amount or for certain conditions. For example, some firms are putting in riders saying they won't cover gene therapies for several years after approval or products with accelerated approval. In the case of patients new to a costly therapy, reinsurers may choose to raise their rates, reduce coverage for those individuals, impact how people access a drug or drop a plan entirely.

Many Payers Will Manage Drugs at Parity

Between Feb. 25 and April 1, Zitter Insights polled 49 commercial payers with 134.1 million covered lives over their anticipated management of Evrysdi within six months of its launch. Respondents with almost two-thirds of lives said they were somewhat likely and highly likely to manage Evrysdi at parity with the other SMA treatments (see chart, p. 5). Respondents with about half of the covered lives said a lower-priced Evrysdi would allow them to negotiate deeper discounts for both Spinraza and Zolgensma. Those respondents said they were looking for a 24% discount off Zolgensma's WAC and 18% off Spinraza's.

AIS Health and Zitter are both owned by MMIT.

Respondents with 90% of covered lives said they were likely to cover Evrysdi to label, those with 7% of lives said they would cover it more restrictively, and plans with 3% of lives said they would not cover the therapy within six months of launch. One plan said that if Evrysdi is less expensive than Spinraza, it would prefer Evrysdi.

Will Pandemic Boost Evrysdi Prescribing?

With many people staying home during the COVID-19 pandemic, will Evrysdi's route of administration be a benefit?

"Because Evrysdi is orally administered, the convenience over an intrathecal administration may come into play regardless of the pandemic but also especially during a pandemic," says Kjesbo.

The drug is "almost pandemic-agnostic," states Myers. "This is an incredibly serious disease [that] can't wait to be treated."

For more information on the Zitter data, contact Jill Brown Kettler at jbrown@aishealth.com. Contact Kjesbo via Jenine Anderson at jenine.anderson@primetherapeutics.com, Myers via Joe Reblando at joe@joereblando.com, Nishida at lynn@withmehealth.com, Rubinstein at elan.b.rubinstein@gmail.com and Wong at w2sqgroup@gmail.com. ✧

AllianceRx Walgreens Prime Unveils New Shipping Process

One common characteristic of specialty medications is that they require special handling. Quite often that means they need to remain refrigerated or frozen, which is critical while drugs are being transported to patients and providers. To help ensure these products' integrity — and, in turn, improve patient outcomes and reduce pharmaceutical waste — AllianceRx Walgreens Prime has begun using a new patented process when shipping specialty products.

When a drug needs to remain at a cool temperature and it isn't, that results in drug waste and reshipment. But that assumes that the person receiving the drug knows it's been compromised. If that's not the case, and the product has lost its potency, that puts people's health at risk if they are taking an ineffective drug. It also means that a payer is reimbursing for an inadequate drug.

> **"Maintaining the right temperatures is critical to ensuring the efficacy of specialty medications."**

According to the 90th Edition HDA Factbook: The Facts, Figures & Trends in Healthcare (2019-2020) from the Healthcare Distribution Alliance, all of that group's primary distributor member respondents with annual sales greater than $1 billion reported that they stocked cold-chain products in 2018. Forty percent monitored and recorded the temperature of these products in transit.

"In specialty pharmacy, cold-chain distribution refers to the process of shipping medicines that require refrigerated storage," explains Ed Musisko, senior director of data science and an-

alytics at AllianceRx Walgreens Prime. "Maintaining the right temperatures is critical to ensuring the efficacy of specialty medications, including costly biologics and injectables, which have special storage or temperature requirements." He tells AIS Health that specialty pharmacies historically have used two main shipping methods: universal packout, which can be used the entire year, as it can handle a broad range of temperatures but can be expensive due to its materials and shipping costs, and seasonal packout, which is less costly but able to be used in only certain

New FDA Specialty Approvals

✦ ***Aug. 5: The FDA gave accelerated approval to GlaxoSmithKline's Blenrep*** (belantamab mafodotin-blmf) for adults with relapsed or refractory multiple myeloma who have received at least four prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor and an immunotherapy agent. The agency granted the first-in-class anti-B-cell maturation antigen (anti-BCMA)-directed antibody priority review, as well as orphan drug and breakthrough therapy designations. The review was via the Real-Time Oncology Review. Recommended dosing is 2.5 mg/kg as an intravenous infusion over approximately 30 minutes once every three weeks. The price per 100 mg single-dose vial is $8,277; based on a patient weight of 175 pounds, the monthly treatment cost would be $23,900. Visit www.blenrep.com.

✦ ***Aug. 7: The FDA approved Guardant Health, Inc.'s Guardant360 CDx*** for tumor mutation profiling in people with any solid malignant neoplasm. The agency also approved the test as a companion diagnostic to identify people with non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) alterations who may benefit from treatment with AstraZeneca's Tagrisso (osimertinib). Visit https://guardant360.com.

✦ ***Aug. 7: The FDA approved Roche Group member Genentech, Inc.'s Evrysdi*** (risdiplam) for the treatment of spinal muscular atrophy (SMA) in people at least 2 months old. The agency gave the drug priority review, as well as fast track and orphan drug designations; the application was given a rare pediatric disease priority review voucher. Roche developed the survival of motor neuron 2 (SMN2) splicing modifier in partnership with PTC Therapeutics, Inc. and the SMA Foundation. Dosing of the oral solution, which is administered by mouth or feeding tube, is based on age and body weight. The price of the drug is tied to a person's weight and is capped at $340,000 per year once someone reaches 44 pounds. For a 15-pound patient, the price would be less than $100,000 per year. Visit www.evrysdi.com.

✦ ***Aug. 12: The FDA gave accelerated approval to NS Pharma, Inc.'s Viltepso*** (viltolarsen) for people with Duchenne muscular dystrophy who have a mutation amenable to exon 53 skipping. The agency gave the application priority review. Recommended dosing is 80 mg/kg once weekly as an intravenous infusion over 60 minutes. Its annual price is about $733,000 for a 66-pound person. Visit www.viltepso.com.

✦ ***Aug. 14: The FDA approved Genentech's Enspryng*** (satralizumab-mwge) for adults with anti-aquaporin-4 (AQP4) antibody positive neuromyelitis optica spectrum disorder. The agency gave the interleukin-6 inhibitor fast track, orphan drug and breakthrough therapy designations. The recommended loading dose of the subcutaneous injection is 120 mg at weeks zero, two and four, followed by 120 mg every four weeks. The first-year cost of the drug will be about $220,000; subsequent years will be about $190,00. Visit www.enspryng.com.

✦ ***Aug. 17: The FDA approved Mylan N.V.'s dimethyl fumarate*** to treat adults with relapsing forms of multiple sclerosis (MS), including clinically isolated syndrome, relapsing-remitting disease and active secondary progressive disease. It is the first available generic of Biogen's Tecfidera. The approval follows a June 18 court decision invalidating a Tecfidera patent that wasn't set to expire until 2028, a decision that Biogen is appealing *(RSP 8/20, p. 1)*. The capsules are available in 120 mg and 240 mg doses. The starting dose is 120 mg twice a day for seven days, followed by 240 mg twice a day. Visit https://bit.ly/3iX4cxn.

✦ ***Aug. 20: The FDA approved Amgen Inc.'s Kyprolis (carfilzomib) in combination with Janssen Biotech, Inc.'s Darzalex (daratumumab) and dexamethasone*** in two dos-

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seasons. Using a refrigerated truck to ship a product also can be an effective approach, but it "is cost-prohibitive."

Musisko, along with his colleagues Luke Holbrook, manager of logistics and engineering, and Dan Shandel, senior process analyst, developed and patented a cold-chain shipment packaging process that determines the expected shipping route of a drug, allowing for appropriate packaging of it. "The patent is an application to use in our fulfillment packing areas," states Holbrook. "It takes the expected transit lane of a shipment, assigns forecasted

New FDA Specialty Approvals *(continued)*

ing regimens — once weekly and twice weekly — for the treatment of people with relapsed or refractory multiple myeloma who have received one to three lines of therapy. Following a starting dose, once-weekly administration is 20/70 mg/m^2 via a 30-minute intravenous infusion, and twice-weekly administration is 20/56 mg/m^2. Website Drugs.com lists the price of a 10 mg vial of Kyprolis as $433.26. Visit www.kyprolis.com.

✦ ***Aug. 20: The FDA approved Novartis Pharmaceuticals Corp.'s Kesimpta*** (ofatumumab) for the treatment of adults with relapsing forms of MS, including clinically isolated syndrome, relapsing-remitting disease and active secondary progressive disease. The drug is available in a prefilled Sensoready Pen and in a prefilled syringe. Initial dosing of the targeted B-cell therapy is 20 mg via subcutaneous injection at weeks zero, one and two, and subsequent dosing is 20 mg monthly starting at week four. Its annual wholesale acquisition cost is $83,000. Visit www.kesimpta.com.

✦ ***Aug. 26: The FDA approved Foundation Medicine, Inc.'s FoundationOne Liquid CDx*** as a pan-tumor liquid biopsy for people with solid tumors. The comprehensive genomic profiling test analyzes more than 300 cancer-related genes and multiple genomic signatures, with results identifying alterations matched to FDA-approved therapies. The agency also approved the test as a companion diagnostic for Rubraca (rucaparib) in prostate cancer and for Iressa (gefitinib), Tagrisso (osimertinib) and Tarceva (erlotinib) in NSCLC. Visit https://bit.ly/3gINu3h.

✦ ***Aug. 28: The FDA approved Novo Nordisk, Inc.'s Sogroya*** (somapacitan-beco) for the replacement of growth hormone in adults with growth hormone deficiency. The FDA says it is the first human growth hormone to be dosed weekly instead of daily. Dosing starts at 1.5 mg once weekly via subcutaneous injection; dosing is to be increased 0.5 mg to 1.5 mg for a maximum dose of 8 mg until a desired response is achieved. The company says it is finalizing plans around the drug's availability. Visit www.novo-pi.com/sogroya.pdf.

✦ ***Sept. 1: The FDA approved Bristol-Myers Squibb Co. unit Celgene Corp.'s Onureg*** (azacitidine) for continued treatment of people with acute myeloid leukemia who achieved first complete remission or complete remission with incomplete blood count recovery following intensive induction chemotherapy and are not able to complete intensive curative therapy. The agency gave the application priority review and orphan drug designation. The recommended dose of the tablet is 300 mg once daily on days one through 14 of each 28-day cycle. Visit www.onuregpro.com.

✦ ***Sept. 1: The FDA approved Roche's cobas HIV-1/HIV-2 Qualitative Test*** for use on the cobas 6800/8800 Systems. The test can confirm HIV diagnosis and differentiate between HIV-1 and HIV-2, informing appropriate treatment options. Visit www.cobas68008800.com.

✦ ***Sept. 4: The FDA gave accelerated approval to Blueprint Medicines Corp. and Genentech's Gavreto*** (pralsetinib) for the treatment of adults with metastatic rearranged during transfection (RET) fusion-positive NSCLC as detected by an FDA-approved test (see brief below). The recommended dose of the capsule is 400 mg once daily, and its monthly list price is $19,250. Visit www.gavreto.com.

✦ ***Sept. 8: The FDA gave premarket approval to Thermo Fisher Scientific's Oncomine Dx Target Test*** as a companion diagnostic to identify people with RET fusion-positive metastatic NSCLC who are candidates for treatment with Gavreto (see brief above). The agency initially approved the test, which evaluates 23 genes associated with NSCLC, in June 2017 *(RSP 7/17, p. 8)*. The company says it will update the test to report RET fusions by the end of the year. Visit https://bit.ly/35cl5AC.

Contact sales@aishealth.com if you'd like to review our rates for group subscriptions.

temperatures of that shipment along the way, utilizes our internal packing material test data and puts everything into an algorithm to calculate the best packout solution we should use for that individual order. This application enables us to predict the experience of the shipment, then adjust packaging to prevent medicine from becoming ineffective, which can ultimately impact the patient's treatment plan."

Process Customizes Packaging

"AllianceRx Walgreens Prime is constantly looking at ways to evaluate its shipping processes as part of ongoing continuous quality improvement," says Musisko. "The package change is a process improvement initiative that customizes patient packaging depending on climate, transit time and medication. Almost all specialty drugs have a 2 degree to 8 degree Celsius requirement associated with the FDA product approval. Our goal was to eliminate the potential for medicine experiencing temperature excursions, which can impact the patient. The technology also prevents the need to reship orders, which can be wasteful and costly." The company says that while patient safety is the most important benefit, it also "anticipates a significant annual savings in reship costs."

The process has been tested using International Safe Transit Association 7E standards to make sure it follows manufacturers' storage guidelines.

Joe Renna, senior director of facilities management, logistics and engineering at AllianceRx Walgreens Prime, says that about 60% of the company's volume needs cold-chain shipping. "We primarily utilize overnight delivery, and our packaging is designed to maintain the 2 degree to 8 degree Celsius range for a minimum of 36 hours," he says. The company uses various packaging materials, including "expanded polystyrene, corrugated boxes, water-based gels, phase change materials and dry ice," he tells AIS Health. It also coordinates with patients on the shipping and delivery date before a drug ships.

"AllianceRx Walgreens Prime has its own testing lab with a simulation chamber in our Pittsburgh location," he notes. "Having this chamber allows us to evaluate packing materials and configurations in our continual improvement efforts. AllianceRx Walgreens Prime's testing lab performs about 200 +/- tests each year, whereas other pharmacies may need to go to an outside firm for testing."

According to Renna, "the process is a differentiator for our company and gives us a competitive advantage, which is why we sought to patent it. The patent means that no other specialty pharmacy has this capability."

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Order May Impact Specialty Drugs

continued from p. 1

The order charges multiple federal agencies to take a variety of actions, including limiting competition among essential medicines to those "produced in the United States." It also tasks the FDA with identifying a list of essential medicines within 90 days and speeding up the approval or clearance of those products. HHS can use the Defense Production Act to "prioritize" government contracts or orders for essential medicines over other agreements. The Environmental Protection Agency (EPA) will identify regulatory requirements that can be streamlined to speed up domestic production and boost the growth of advanced manufacturing facilities. Exceptions to the order to procure products domestically exist in a handful of situations.

Pharma pushback was swift.

"At a time when our nation's priority should be to beat COVID-19, President Trump today signed yet another executive order that creates even more barriers to ongoing biopharmaceutical manufacturing and innovation," said Stephen J. Ubl, president and CEO of the Pharmaceutical Research and Manufacturers of America.

Number of Chinese Facilities Doubled

An Oct. 30, 2019, testimony from Janet Woodcock, M.D., speaking as the director of the FDA's Center for Drug Evaluation and Research before the House Committee on Energy and Commerce's health subcommittee, revealed that 28% of facilities manufacturing active pharmaceutical ingredients (APIs) for the U.S. market as of August 2019 were located in the U.S. Of the remaining 72%, 13% of the sites were in China, which saw its registered facilities making APIs more than double between 2010 and 2019.

Underlying factors for this is "that most traditional drug production processes require a large factory site, often have environmental liabilities, and can utilize a low-cost labor force," she said, adding that the U.S. could use "advanced manufacturing technologies" that would enable the U.S. to become competitive on the global stage and "potentially ensure a stable supply of drugs critical to the health of U.S. patients."

Certainly some potential benefits of the approach exist, including (1) reduced vulnerability of the supply chain; "(2) increased security of the supply of 'essential medicines' to U.S. government purchasers, including the armed forces"; and (3) increased U.S.

drug manufacturing capacity, says Elan Rubinstein, Pharm.D., principal at EB Rubinstein Associates.

Implementing the order, however, will be easier said than done. And it won't happen overnight — or inexpensively.

According to Phil Ball, Ph.D., head of policy practice at Innopiphany LLC, "manufacturing pharmaceuticals and medical devices involves a complex, global supply chain, which has been established and refined over many decades. Enforcing a complete reshoring of this supply chain, if that is indeed the intent, will require a highly disruptive, expensive and lengthy process."

Few Products Meet Order's Requirement

"At this time, few finished pharmaceutical products meet the EO's 100% made in America requirement," points out Rubinstein. "Implementing definitions and regulations must be written, and international agreements renegotiated, involving the efforts of several federal departments — all within tight 30-, 60- and 90-day timelines set out in the EO. To accomplish the purpose of the EO, financial resources must be identified and applied, manufacturing capacity must be built or repurposed, methods must be developed, raw materials must be sourced, people must be trained, and international manufacturing processes and channels must be reconfigured."

For the FDA to put together a list of essential medicines "is not trivial," says Rubinstein, particularly over a three-month period. The agency has "no approved methodology, no dedicated personnel and no credible expert committee" for the process, he points out.

"Building the list from scratch would certainly be an involved process, but FDA has clearly been thinking about this for some time," says Ball. He points to the 2019 FDA report titled "Safeguarding Pharmaceutical Supply Chains in a Global Economy," which "discusses essential medicines in detail, referencing the 2019 WHO [i.e., World Health Organization] Essential Medicines List and describing how it matched 370 of the 461 drugs to those listed for the U.S. market. It is likely FDA already has developed its own list, at least partially."

However, Rubinstein says, while it "seems prudent and efficient" to start with the WHO list, the administration on July 6 said that the U.S. will withdraw from that organization, "so it may not be politically acceptable for the FDA commissioner to rely on the WHO list as a starting point."

WHO List Has Multiple Specialty Drugs

That list includes multiple antiretrovirals for the treatment and prevention of HIV, antihepatitis medications, chemopreventive therapies, immunomodulators, drugs to treat a variety of cancers, supportive care therapies, drugs for Parkinson's disease, antiemetics, bevacizumab as an anti-vascular endothelial growth factor and disease-modifying agents for rheumatoid disorders.

A release from GlobalData on June 9 mentioned 10 innovative blockbuster U.S. and EU products that are outsourced to contract manufacturing organizations in Spain whose supply could be impacted by the pandemic. On that list are HIV medications, including Gilead Sciences Inc.'s Truvada (emtricitabine/tenofovir), as well as AbbVie Inc.'s Humira (adalimumab). Both of those drugs are included in the WHO's list of essential medicines.

Other potential issues exist. The order, says Ball, "may also actually reduce the ability to respond to current or future crises, leading to shortages. For example, what if an emergency compromises the ability to manufacture the products domestically? A diverse and robust supply chain is needed in an emergency." In addition, he tells AIS Health, some concern exists that loosening or removing FDA and EPA regulatory requirements "may inadvertently result in lower quality product and impact public safety."

> **"It appears that the Trump administration has not considered potential conflicts among its EOs."**

When unveiling the order on Aug. 6 at a Whirlpool Corp. manufacturing plant in Clyde, Ohio, Trump said the order will "support advanced manufacturing processes that will keep our drug prices." Ball, however, maintains that the opposite will happen. "Manufacturing overseas is often less expensive and will remain so even with the implementation of advanced manufacturing technologies. The investment required to increase domestic production capabilities, either through facility expansion or new construction, along with higher labor costs, will inevitably drive up prices."

And multiple parts of the order are unclear. For example, Ball notes that with exemptions when an "application would be inconsistent with the public interest," the order does not define "public interest." In addition, "does the order really mean that absolutely all inputs and ingredients must be produced domestically?"

Another concern is whether this executive order is in conflict with the most-favored nation executive order. How the orders would align "is unclear," says Ball. "The administration

is attempting to drive production to the U.S. but is demanding prices equivalent to or lower than those paid in lower-income countries. It's difficult to reconcile how this makes economic sense."

Rubinstein agrees. "It appears that the Trump administration has not considered potential conflicts among its EOs."

The orders, said Ubl, "contradict and undermine each other." On the one hand, the administration wants to increase U.S. manufacturing, but through the most-favored nation order, it "is creating a huge disincentive to invest in U.S. biopharmaceutical research and manufacturing."

Ultimately, Ball says, "one cannot imagine that this order will be implemented without considerable opposition because disrupting such a global complex supply chain will take decades and cost billions. The timing is also unfortunate, as manufacturers are currently appropriately focused on addressing the global COVID-19 pandemic."

According to Ball, "the objective of the order is, in part, to prevent future shortages of essential medicines.

"Its impact may be the exact opposite."

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News Briefs

✦ ***Rep. Carolyn Maloney (D-N.Y.) said she plans to issue a subpoena to AbbVie Inc. for documents relating to Humira (adalimumab) and Imbruvica (ibrutinib)***. Maloney is the chairwoman of the Committee on Oversight and Reform and is seeking information on drug pricing as part of an investigation started by the committee's former chairman, Rep. Elijah Cummings (D-Md.), in January 2019 of 12 drug companies selling 19 of the costliest medications. Maloney, who unveiled her intentions via a Sept. 1 memo, said in that document that during the investigation, "AbbVie repeatedly failed to comply with the Committee's requests and provided inadequate responses regarding Humira and Imbruvica. AbbVie has produced only limited documents about its pricing practices and strategies to preserve market share and pricing power for both products." The Hill reports that an AbbVie spokesperson said the company has "provided thousands of documents and [has] had numerous conversations with the Committee staff. While we are surprised and disappointed the Committee chose to take this action, we will continue to work in good faith with them on this important subject." View the memo at https://bit.ly/2EZEytx.

✦ ***Mylan N.V. launched the first FDA-approved generic of Biogen's multiple sclerosis drug Tecfidera (dimethyl fumarate)*** on Aug. 19. The moved comes two months after the U.S. District Court for the Northern District of West Virginia ruled in favor of Mylan *(RSP 7/20, p. 12)*, invalidating a Tecfidera patent that wasn't set to expire until 2028 (No. 1:17-cv-00116-IMK-JPM). Mylan's drug at the time had an action date of Nov. 16, but the drugmaker worked with the FDA to move that up in the wake of the decision. Mylan did not respond to AIS Health requests for information on the drug's price, but Evercore ISI analyst Umer Raffat said it was approximately a 14% discount to Tecfidera. According to the National MS Society, Tecfidera's wholesale acquisition cost was $94,991 as of Nov. 13, 2019. A Jan. 3 Boston Business Journal article says Biogen raised the price 6% this year, putting its annual cost at $100,690. Visit https://bit.ly/2R6JS0H.

✦ ***Large employers continue to be concerned about high-cost drugs***, according to the Business Group on Health's 2021 Large Employers' Health Care Strategy and Plan Design Survey. Sixty-seven percent of respondents said the effect of million-dollar treatments was their No. 1 pharmacy benefits management concern. Almost half said they were excluding new products at launch, the top current tactic, while the top strategy being added for 2021 and under consideration for 2022/2023 was contracting for outcomes- or indication-based pricing. Download the report at https://bit.ly/328kgqz.

✦ ***PEOPLE ON THE MOVE***: The Association for Accessible Medicines (AAM) named ***Dan Leonard*** president and CEO. He most recently was president and CEO of the National Pharmaceutical Council. He succeeds ***Chester "Chip" Davis, Jr.***, who left in February and is now president and CEO of the Healthcare Distribution Alliance *(RSP 3/20, p. 12)*. ***Jeff Francer***, AAM's senior vice president and general counsel, served as interim CEO.

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