PHARMACY SURVEY

Report reveals top industry challenges and opportunities

› Cost curbing strategies
› Biosimilar outlook
› Value pricing predictions
› Noteworthy FDA approvals

PLUS

DRUG PIPELINE REPORT

AND

RIGHT-TO-TRY IMPLICATIONS
YES CART T IS HERE

YESCARTA®, THE FIRST CAR T THERAPY FOR CERTAIN TYPES OF RELAPSED OR REFRACTORY LARGE B-CELL LYMPHOMA

The following data reflect results from the ZUMA-1 pivotal trial*1

// PROVEN EFFICACY

51%

Patients achieved a best response of complete remission (CR) (52/101)

// CYTOKINE RELEASE SYNDROME

13% 94%

Grade ≥3 incidence  Overall incidence

// RAPID & RELIABLE MANUFACTURING

17 DAYS

Median turnaround time†

// NEUROLOGIC TOXICITIES

31% 87%

Grade ≥3 incidence  Overall incidence

VISIT YESCARTAHCP.COM/CENTERS TO FIND A LIST OF AUTHORIZED TREATMENT CENTERS

*ZUMA-1 was an open-label, single-arm study in 101 adult patients who received YESCARTA® therapy. Patients received lymphodepleting chemotherapy prior to a single infusion of YESCARTA® at a target dose of 2 x 10^6 viable CAR T cells/kg body weight (maximum of 2 x 10^8 viable CAR T cells). Patients had refractory disease to their most recent therapy, or had relapsed within 1 year after autologous hematopoietic stem cell transplantation.

†The median time from leukapheresis to product delivery.

INDICATION

YESCARTA® is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

Limitation of Use: YESCARTA® is not indicated for the treatment of patients with primary central nervous system lymphoma.

IMPORTANT SAFETY INFORMATION

BOXED WARNING: CYTOKINE RELEASE SYNDROME AND NEUROLOGIC TOXICITIES

• Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving YESCARTA®. Do not administer YESCARTA® to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids.

• Neurologic toxicities, including fatal or life-threatening reactions, occurred in patients receiving YESCARTA®, including concurrently with CRS or after CRS resolution. Monitor for neurologic toxicities after treatment with YESCARTA®. Provide supportive care and/or corticosteroids as needed.

• YESCARTA® is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the YESCARTA® REMS.

Important Safety Information continued on adjacent page.

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IMPORTANT SAFETY INFORMATION (continued)

CYTOKINE RELEASE SYNDROME (CRS): CRS occurred in 94% of patients, including 13% with ≥ Grade 3. Among patients who died after receiving YESCARTA®, 4 had ongoing CRS at death. The median time to onset was 2 days (range: 1-12 days) and median duration was 7 days (range: 2-58 days). Key manifestations include fever (78%), hypotension (41%), tachycardia (28%), hypoxia (22%), and chills (20%). Serious events that may be associated with CRS include cardiac arrhythmias (including atrial fibrillation and ventricular tachycardia), cardiac arrest, cardiac failure, renal insufficiency, capillary leak syndrome, hypotension, hypoxia, and hemophagocytic lymphohistiocytosis/macrophage activation syndrome. Ensure that 2 doses of tocilizumab are available prior to infusion of YESCARTA®. Monitor patients at least daily for 7 days at the certified healthcare facility following infusion for signs and symptoms of CRS. Monitor patients for signs or symptoms of CRS for 4 weeks after infusion. Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time. At the first sign of CRS, institute treatment with supportive care, tocilizumab or tocilizumab and corticosteroids as indicated.

NEUROLOGIC TOXICITIES: Neurologic toxicities occurred in 87% of patients. Ninety-eight percent of all neurologic toxicities occurred within the first 8 weeks, with a median time to onset of 4 days (range: 1-43 days) and a median duration of 17 days. Grade 3 or higher occurred in 31% of patients. The most common neurologic toxicities included encephalopathy (57%), headache (44%), tremor (31%), dizziness (21%), aphasia (18%), delirium (17%), insomnia (9%) and anxiety (9%). Prolonged encephalopathy lasting up to 173 days was noted. Serious events including leukoencephalopathy and seizures occurred with YESCARTA®. Fatal and serious cases of cerebral edema have occurred in patients treated with YESCARTA®. Monitor patients at least daily for 7 days at the certified healthcare facility following infusion for signs and symptoms of neurologic toxicities. Monitor patients for signs or symptoms of neurologic toxicities for 4 weeks after infusion and treat promptly.

YESCARTA® REMS: Because of the risk of CRS and neurologic toxicities, YESCARTA® is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the YESCARTA® REMS. The required components of the YESCARTA® REMS are: Healthcare facilities that dispense and administer YESCARTA® must be enrolled and comply with the REMS requirements. Certified healthcare facilities must have on-site, immediate access to tocilizumab, and ensure that a minimum of 2 doses of tocilizumab are available for each patient for infusion within 2 hours after YESCARTA® infusion, if needed for treatment of CRS. Certified healthcare facilities must ensure that healthcare providers who prescribe, dispense or administer YESCARTA® are trained about the management of CRS and neurologic toxicities. Further information is available at www.YESCARTAREMS.com or 1-844-454-KITE (5483).

HYPERSENSITIVITY REACTIONS: Allergic reactions may occur. Serious hypersensitivity reactions including anaphylaxis may be due to dimethyl sulfoxide (DMSO) or residual gentamicin in YESCARTA®.

SERIOUS INFECTIONS: Severe or life-threatening infections occurred. Infections (all grades) occurred in 38% of patients, and in 23% with ≥ Grade 3. Grade 3 or higher infections with an unspecified pathogen occurred in 16% of patients, bacterial infections in 9%, and viral infections in 4%. YESCARTA® should not be administered to patients with clinically significant active systemic infections. Monitor patients for signs and symptoms of infection before and after YESCARTA® infusion and treat appropriately. Administer prophylactic anti-microbials according to local guidelines. Febrile neutropenia was observed in 36% of patients and may be concurrent with CRS. In the event of febrile neutropenia, evaluate for infection and manage with broad spectrum antibiotics, fluids and other supportive care as medically indicated. Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with drugs directed against B cells. Perform screening for HBV, HCV, and HIV in accordance with clinical guidelines before collection of cells for manufacturing.

PROLONGED CYTOPENIAS: Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and YESCARTA® infusion. Grade 3 or higher cytopenias not resolved by Day 30 following YESCARTA® infusion occurred in 28% of patients and included thrombocytopenia (18%), neutropenia (15%), and anemia (3%). Monitor blood counts after YESCARTA® infusion.

HYPOGAMMAGLOBULINEMIA: B-cell aplasia and hypogammaglobulinemia can occur. Hypogammaglobulinemia occurred in 15% of patients. Monitor immunoglobulin levels after treatment and manage using infection precautions, antibody prophylaxis and immunoglobulin replacement. The safety of immunization with live viral vaccines during or following YESCARTA® treatment has not been studied. Vaccination with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy during YESCARTA® treatment, and until immune recovery following treatment.

SECONDARY MALIGNANCIES: Patients may develop secondary malignancies. Monitor life-long for secondary malignancies. In the event that a secondary malignancy occurs, contact Kite at 1-844-454-KITE (5483) to obtain instructions on patient samples to collect for testing.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES: Due to the potential for neurologic events, including altered mental status or seizures, patients are at risk for altered or decreased consciousness or coordination in the 8 weeks following YESCARTA® infusion. Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, during this initial period.

ADVERSE REACTIONS: The most common adverse reactions (incidence ≥ 20%) include CRS, fever, hypotension, encephalopathy, tachycardia, fatigue, headache, decreased appetite, chills, diarrhea, febrile neutropenia, infections-pathogen unspecified, nausea, hypoxia, tremor, cough, vomiting, dizziness, constipation, and cardiac arrhythmias.

Please see Brief Summary of Prescribing Information, including BOXED WARNING, on the following pages.
WARNING: CYTOKINE RELEASE SYNDROME and NEUROLOGIC TOXICITIES

- Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving YESCARTA. Do not administer YESCARTA to patients with active infection or inflammatory disorders.
- Treat severe or life-threatening CRS with tocilizumab or dexamethasone and corticosteroids [see Dosage and Administration (2.2, 2.3), Warnings and Precautions (6.1)].
- Neurologic toxicities, including fatal or life-threatening reactions, occurred in patients receiving YESCARTA, including concurrently with CRS or after CRS resolution. Monitor for neurologic toxicities after treatment with YESCARTA. Provide supportive care and/or corticosteroids, as needed [see Dosage and Administration (2.2, 2.3), Warnings and Precautions (5.2)].
- YESCARTA is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the YESCARTA REMS [see Warnings and Precautions (5.3)].

1 INDICATIONS AND USAGE

YESCARTA is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL), not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

Limitation of Use: YESCARTA is not indicated for the treatment of patients with primary central nervous system lymphoma.

2 DOSAGE AND ADMINISTRATION

2.2 Administration: YESCARTA is for autologous use only. The patient’s identity must match the patient identifiers on the YESCARTA cassette and infusion bag. Do not infuse YESCARTA if the information on the patient-specific label does not match the intended patient [see Dosage and Administration (2.2, 3)].

Preparing Patient for YESCARTA Infusion: Confirm availability of YESCARTA prior to starting the lymphodepleting regimen. Pre-treatment: Administer a lymphodepleting chemotherapy regimen of cyclophosphamide 500 mg/m² intravenously and fludarabine 30 mg/m² intravenously on the fifth, fourth, and third day before infusion of YESCARTA. Premedication: Administer acetaminophen 650 mg PO and diphenhydramine 12.5 mg intravenously or PO approximately 1 hour before YESCARTA infusion. Avoid prophylactic use of systemic corticosteroids, as it may interfere with the activity of YESCARTA.

Preparation of YESCARTA for Infusion: Coordinate the timing of YESCARTA thaw and infusion. Confirm the infusion time in advance, and adjust the start time of YESCARTA thaw such that it will be available for infusion when the patient is ready. Confirm patient identity. Prior to YESCARTA preparation, match the patient’s identity with the patient identifiers on the YESCARTA cassette. Do not remove the YESCARTA product bag from the cassette if the information on the patient-specific label does not match the intended patient. Once patient identification is confirmed, remove the YESCARTA product bag from the cassette and check that the patient information on the cassette label matches the bag label. Inspect the product bag for any breaches of container integrity such as breaks or cracks before thawing. If the bag is compromised, follow the local guidelines (or call Kite at 1-844-454-KITE). Place the infusion bag inside a second sterile bag per local guidelines. Thaw YESCARTA at approximately 37°C using either a water bath or dry thaw method until there is no visible ice in the infusion bag. Gently mix the contents of the bag to disperse clumps of cellular material. If visible cell clumps remain, continue to gently mix the contents of the bag. Small clumps of cellular material should disperse with gentle manual mixing. Do not wash, spin down, and/or re-suspend YESCARTA in new media prior to infusion. Once thawed, YESCARTA may be stored at room temperature (20°C to 25°C) for up to 3 hours.

Administration: For autologous use only. Ensure that tocilizumab and emergency equipment are available prior to infusion and during the recovery period. Do NOT use a leukodepleting filter. Central venous access is recommended for the infusion of YESCARTA. Confirm the patient’s identity matches the patient identifiers on the YESCARTA product bag. Prime the tubing with normal saline prior to infusion. Infuse the entire contents of the YESCARTA bag within 30 minutes by either gravity or a peristaltic pump. YESCARTA is stable at room temperature for up to 3 hours after thaw. Gently agitate the product bag during YESCARTA infusion to prevent cell clumping. After the entire content of the product bag is infused, rinse the tubing with normal saline at the same infusion rate to ensure all product is delivered. YESCARTA contains human blood cells that are genetically modified with replication incompetent retroviral vector. Follow universal precautions and local biosafety guidelines for handling and disposal to avoid potential transmission of infectious diseases.

Monitoring: Administer YESCARTA at a certified healthcare facility. Monitor patients at least daily for 7 days at the certified healthcare facility following infusion for signs and symptoms of CRS and neurologic toxicities. Instruct patients to remain within proximity of the certified healthcare facility for at least 4 weeks following infusion.

2.3 Management of Severe Adverse Reactions

Cytokine Release Syndrome (CRS): Identify CRS based on clinical presentation [see Warnings and Precautions (6.1)]. Evaluate for and treat other causes of fever, hypoxia, and hypotension. If CRS is suspected, manage according to the recommendations in Table 1. Patients who experience Grade 2 or higher CRS (e.g., hypotension, not responsive to fluids, or hypoxia requiring supplemental oxygenation) should be monitored with continuous cardiac telemetry and pulse oximetry. For patients experiencing severe CRS, consider performing an echocardiogram to assess cardiac function. For severe or life-threatening CRS, consider intensive care supportive therapy.

Table 1. CRS Grading and Management Guidance

<table>
<thead>
<tr>
<th>CRS Grade (a)</th>
<th>Tocilizumab</th>
<th>Corticosteroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Administer tocilizumab (b) 8 mg/kg intravenously over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed if not responsive to intravenous fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.</td>
<td>Manage per Grade 3 if no improvement within 24 hours after starting tocilizumab.</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Administer methylprednisolone 1 mg/kg intravenously twice daily or equivalent dexamethasone (e.g., 10 mg intravenously every 6 hours). Continue corticosteroids use until the event is Grade 1 or less, then taper over 3 days.</td>
<td>Manage per Grade 3 if no improvement within 24 hours after starting tocilizumab.</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Administer methylprednisolone 1000 mg intravenously per day for 3 days; if improves, then manage as above.</td>
<td>Manage per Grade 3 if no improvement within 24 hours after starting tocilizumab.</td>
</tr>
</tbody>
</table>

(a) Lee et al 2014. (b) Refer to Table 2 for management of neurologic toxicity. (c) Refer to tocilizumab Prescribing Information for details

Neurologic Toxicity: Monitor patients for signs and symptoms of neurologic toxicities (Table 2). Rule out other causes of neurologic symptoms. Patients who experience Grade 2 or higher neurologic toxicities should be monitored with continuous cardiac telemetry and pulse oximetry. Provide intensive care supportive therapy for severe or life-threatening neurologic toxicities. Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis for any Grade 2 or higher neurologic toxicities.
4 CONTRAINDICATIONS: None.

5 WARNINGS AND PRECAUTIONS

5.1 Cytokine Release Syndrome (CRS): CRS, including fatal or life-threatening reactions, occurred following treatment with YESCARTA. In Study 1, CRS occurred in 94% (101/108) of patients receiving YESCARTA, including Grade 3 (Lee grading system) CRS in 13% (14/108) of patients. Among patients who received YESCARTA for at least 7 days, the median time to onset was 2 days (range: 1 to 12 days) and the median duration of CRS was 7 days (range: 2 to 58 days). Key manifestations of CRS include fever (78%), hypotension (41%), tachycardia (25%), hypoxia (22%), and chills (20%). Serious events that may be associated with CRS include cardiac arrhythmias (including atrial fibrillation and ventricular tachycardia), cardiac arrest, cardiac failure, renal insufficiency, capillary leak syndrome, hypotension, hypoxia, and hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) [see Adverse Reactions (6)]. Ensure that 2 doses of tocilizumab are available prior to infusion of YESCARTA. Monitor patients at least daily for 7 days at the certified healthcare facility following infusion for signs and symptoms of CRS. Monitor patients for signs or symptoms of CRS for 4 weeks after infusion. Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time [see Patient Counseling Information (17)]. At the first sign of CRS, institute treatment with supportive care, tocilizumab or tocilizumab and corticosteroids as indicated [see Dosage and Administration (2.3)].

5.2 Neurologic Toxicities: Neurologic toxicities, that were fatal or life-threatening, occurred following treatment with YESCARTA. Neurologic toxicities occurred in 87% of patients. Ninety-eight percent of all neurologic toxicities occurred within the first 8 weeks of YESCARTA infusion, with a median time to onset of 4 days (range: 1 to 43 days). The median duration of neurologic toxicities was 17 days. Grade 3 or higher neurologic toxicities occurred in 31% of patients. The most common neurologic toxicities included encephalopathy (57%), headache (44%), tremor (31%), dizziness (21%), aphasia (18%), delirium (17%), insomnia (8%) and anxiety (8%). Prolonged encephalopathy lasting up to 173 days was noted. Serious events including leukoencephalopathy and seizures occurred with YESCARTA. Fatal and serious cases of cerebral edema have occurred in patients treated with YESCARTA. Monitor patients at least daily for 7 days at the certified healthcare facility following infusion for signs and symptoms of neurologic toxicities. Monitor patients for signs or symptoms of neurologic toxicities for 4 weeks after infusion and treat promptly [see Management of Cytokine Release Syndrome (CRS); Neurologic Toxicities (5.3)].

5.3 YESCARTA REMS: Because of the risk of CRS and neurologic toxicities, YESCARTA is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the YESCARTA REMS [see Boxed Warning and Warnings and Precautions (5.1 and 5.2)]. The required components of the YESCARTA REMS are:

- Healthcare facilities that dispense and administer YESCARTA must be enrolled and comply with the REMS requirements. Certified healthcare facilities must have on-site, immediate access to tocilizumab, and ensure a minimum of two doses of tocilizumab are available for each patient for infusion within 2 hours after YESCARTA infusion, if needed for treatment of CRS.
- Certified healthcare facilities must ensure that healthcare providers who prescribe, dispense or administer YESCARTA are trained about the management of CRS and neurologic toxicities.

Further information is available at www.YescartaREMS.com or 1-844-454-KITE (5483).

5.4 Hypersensitivity Reactions: Allergic reactions may occur with the infusion of YESCARTA. Severe hypersensitivity reactions including anaphylaxis, may be due to dimethyl sulfoxide (DMSO) or residual gentamicin in YESCARTA.

5.5 Serious Infections: Severe or life-threatening infections occurred in patients after YESCARTA infusion. In Study 1, infections (all grades) occurred in 38% of patients. Grade 3 or higher infections occurred in 23% of patients. Grade 3 or higher infections with an unspecified pathogen occurred in 16% of patients, bacterial infections in 9%, and viral infections in 4%. YESCARTA should not be administered to patients with clinically significant active systemic infections. Monitor patients for signs and symptoms of infection and treat appropriately. Administration of prophylactic anti-microbials according to local guidelines. Febrile neutropenia was observed in 36% of patients after YESCARTA infusion and may be concurrent with CRS. In the event of febrile neutropenia, evaluate for infection and manage with broad spectrum antibiotics, fluids and other supportive care as medically indicated. Viral Reactivation: Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with drugs directed against B cells. Perform screening for HBV, HDV, and HIV in accordance with local guidelines before collection of cells for manufacturing.

5.6 Prolonged Cytopenias: Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and YESCARTA infusion. In Study 1, Grade 3 or higher cytopenias not resolved by Day 30 following YESCARTA infusion occurred in 28% of patients and included thrombocytopenia (18%), neutropenia (15%), and anemia (3%). Monitor blood counts after YESCARTA infusion.

5.7 Hypogammaglobulinemia: B-cell aplasia and hypogammaglobulinemia can occur in patients receiving treatment with YESCARTA. In Study 1, hypogammaglobulinemia occurred in 15% of patients. Monitor immunoglobulin levels after treatment with YESCARTA and manage using infection precautions, antibiotic prophylaxis and immunoglobulin replacement. The safety of immunization with live viral vaccines during or following YESCARTA treatment is not well studied. Vaccination with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during YESCARTA treatment, and until immune recovery following treatment with YESCARTA.

5.8 Secondary Malignancies: Patients treated with YESCARTA may develop secondary malignancies. Monitor life-long for secondary malignancies. In the event that a secondary malignancy occurs, contact Kite at 1-844-454-KITE (5483) to obtain instructions on patient samples to collect for testing.

5.9 Effects on Ability to Drive and Use Machines: Due to the potential for neurologic events, including altered mental status or seizures, patients receiving YESCARTA are at risk for altered or decreased consciousness or coordination in the weeks following YESCARTA infusion. Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, during this initial period.

6 ADVERSE REACTIONS: The following adverse reactions are described in Warnings and Precautions: Cytokine Release Syndrome, Neurologic Toxicities, Hypersensitivity Reactions, Serious Infections, Prolonged Cytopenias, Hypogammaglobulinemia.

6.1 Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety data described in this section reflect exposure to YESCARTA in the clinical trial (Study 1) in which 108 patients with relapsed/refractory B-cell NHL received CAR-positive T cells based on a recommended dose of 1 x 10^6 lentiviral vector-expressing CD19 CAR T cells per kg body weight (14). Patients had a history of CNS disorders (such as seizures or cerebrovascular ischemia) or autoimmune disease requiring systemic immunosuppression were ineligible. The median duration of follow up was 8.7 months. The median age of the study population was 58 years (range: 23 to 76 years); 68% were men. The baseline CD8+ T-cell performance status was
Summary of Adverse Reactions Observed in at Least 10% of the Patients Treated with YESCARTA in Study 1

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Any Grade (%)</th>
<th>Grades 3 or Higher (%)</th>
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</thead>
<tbody>
<tr>
<td>Cardiac disorders</td>
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<td></td>
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<tr>
<td>Tachycardia</td>
<td>57</td>
<td>2</td>
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<tr>
<td>Arrhythmia</td>
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<td>7</td>
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<tr>
<td>Gastrointestinal disorders</td>
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<tr>
<td>Diarrhea</td>
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<tr>
<td>Nausea</td>
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<tr>
<td>Vomiting</td>
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<tr>
<td>Constipation</td>
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<tr>
<td>Abdominal pain</td>
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<tr>
<td>Dry mouth</td>
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<td>0</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
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</tr>
<tr>
<td>Fever</td>
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<tr>
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<td>Decreased appetite</td>
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<tr>
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</tbody>
</table>

The following events were also counted in the incidence of CRS, tachycardia, arrhythmia, fever, chills, hypoxia, renal insufficiency, and hypertension. For a complete list of events that contributed to the incidence of certain adverse reactions, please see footnote Table 3 in Section 6.1 of the Full prescribing information.

Other clinically important adverse reactions that occurred in less than 10% of patients treated with YESCARTA include the following: blood and lymphatic system disorders: coagulopathy (2%); cardiac disorders: cardiac failure (6%) and cardiac arrest (4%); immune system disorders: hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) (1%); hypertension (1%); infections and infestations disorders: fungal infections (5%); nervous system disorders: ataxia (6%), seizure (4%), dyscalculia (2%), and myoclonus (2%); respiratory, thoracic and mediastinal disorders: pulmonary edema (9%); skin and subcutaneous tissue disorders: rash (9%); vascular disorders: capillary leak syndrome (3%).

Grade 3 or 4 Laboratory Abnormalities Occurring in ≥ 10% of Patients in Study 1 Following Treatment with YESCARTA based on CTCAE (N=108)

- Lymphopenia 100%, Leukopenia 96%, Neutropenia 93%, Anemia 66%
- Thrombocytopenia 58%, Hypophosphatemia 50%, Hypoalbuminemia 10%, Uric acid increased 13%, Direct Bilirubin increased 13%, Hypokalemia 10%, Alanine Aminotransferase increased 10%.

6.2 Immunogenicity: YESCARTA has the potential to induce anti-product antibodies. The immunogenicity of YESCARTA has been evaluated using an enzyme-linked immunosorbent assay (ELISA) for the detection of binding antibodies against FMC63, the originating antibody of the anti-CD19 CAR. Three patients tested positive for pre-dose anti-FMC63 antibodies at baseline and Month 1, 3, or 6 in Study 1. There is no evidence that the kinetics of initial expansion and persistence of YESCARTA, or the safety or effectiveness of YESCARTA, was altered in these patients.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy: Risk Summary: There are no available data with YESCARTA use in pregnant women. No animal reproductive and developmental toxicity studies have been conducted with YESCARTA to assess whether it can cause fetal harm when administered to a pregnant woman. It is not known if YESCARTA has the potential to be transferred to the fetus. Based on the mechanism of action, if the transduced cells cross the placenta, they may cause fetal toxicity, including B-cell lymphocytopenia. Therefore, YESCARTA is not recommended for women who are pregnant, and pregnancy after YESCARTA infusion should be discussed with the treating physician. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% - 4% and 15% - 20%, respectively.

8.2 Lactation: Risk Summary: There is no information regarding the presence of YESCARTA in human milk, the effect on the breastfed infant, and the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for YESCARTA and any potential adverse effects on the breastfed infant from YESCARTA or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential: Pregnancy Testing: Pregnancy status of females with reproductive potential should be verified. Sexually-active females of reproductive potential should have a pregnancy test prior to starting treatment with YESCARTA. Contraception: See the prescribing information for fludarabine and cyclophosphamide for information on the need for effective contraception in patients who receive the lymphodepleting chemotherapy. There are insufficient exposure data to provide a recommendation concerning duration of contraception following treatment with YESCARTA. Infertility: There are no data on the effect of YESCARTA on fertility.

8.4 Pediatric Use: The safety and efficacy of YESCARTA have not been established in pediatric patients.

8.5 Geriatric Use: Clinical trials of YESCARTA did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently or have different safety outcomes as compared to younger patients.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide). Ensure that patients understand the risk of manufacturing failure (1% in clinical trial). In case of a manufacturing failure, a second manufacturing of YESCARTA may be attempted. In addition, while the patient awaits the product, additional chemotherapy (not the lymphodepletion) may be necessary and may increase the risk of adverse events during the pre-infusion period. Advise patients to seek immediate attention for any of the following: Cytokine Release Syndrome, Neurologic Toxicities, Serious Infections, Prolonged Cytopenia [see Warnings and Precautions (5.1, 5.2, 5.3, 5.5) and Adverse Reactions (6) for more information and signs and symptoms]. Advise patients for the need to: Refrain from driving or operating heavy or potentially dangerous machinery after YESCARTA infusion until at least 8 weeks after infusion [see Warnings and Precautions (5.2)], Have periodic monitoring of blood counts. Contact Kite at 1-844-454-KITE (5483) if they are diagnosed with a secondary malignancy [see Warnings and Precautions (5.8)].

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Some of the most amazing things are happening in the delivery of medical care these days. Surgical techniques, new devices, drugs, and diagnostics can treat and cure many medical conditions. Now, the only challenge is who pays for these advances and how. More than ever, managed care pharmacy is at the center of healthcare and needs to help design, develop, and implement new solutions to address this challenge.

This special issue of Managed Healthcare Executive discusses the changing nature of managed care pharmacy and the role it needs to take in curbing healthcare costs. Here are some of my thoughts.

**What needs to happen**

With the growth of specialty pharmaceuticals, the roles of the physician, pharmacist, and patient need to be redefined and the total cost of care must be evaluated to see what really adds value in medical care. We need to develop new models of care to address the new world of healthcare.

The administrative costs of medical and pharmacy benefits must decrease and there must be more price transparency as patients begin to act as consumers.

Currently, purchasers measure the effectiveness of PBMs by whether they reduce the unit cost of prescription drugs. Utilization management is also used to make sure the right drugs are used by the right patients. Systems and processes for this work are driving physicians and pharmacists crazy.

We need to merge pharmacy claims data with medical claims data and patient reported outcomes to measure drug performance and have value-based contracting. Managed care pharmacy needs to reinvent itself to make value-based contracting happen on the healthcare financing side.

**What’s already happening**

Most industry leaders agree that value-based contracting is a top priority. When asked, “What is the biggest opportunity to reduce specialty pharmaceutical costs?” The most popular response among healthcare executives who took our Managed Care Pharmacy Survey 2018 was value-based contracting (see page 14). Further, 60% of respondents said value-based contracting with manufacturers is the best coverage strategy for new, innovative therapeutics and biologics.

It’s also good to see that new technology to deliver healthcare, such as telemedicine, is growing. The kitchen countertop in the patient’s home is where the action will happen. New technology from Google, Amazon, and others will drive this change.

As younger patients view time and space differently from seniors, the roles of physicians and pharmacists will change and the movement of information will be digital. Pharmacist house calls will be used to provide patient supportive care and lead to more collaboration between physician, pharmacist, and patient.

The use of companion diagnostics to drive personalized medicine will become the standard of care for certain diseases.

Lastly the use of data, analytics, and reporting will drive decision making in the delivery and financing of healthcare to ensure the best use of resources.

Exciting times are ahead, and managed care pharmacy is well positioned to drive the necessary changes.

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INSIDE Three questions for David Calabrese PAGE 19
Managed Healthcare Executive

Volume 28 Issue 6
JUNE 2018

COVER STORY
Pharmacy Survey
Top industry challenges and opportunities  PAGE 14

ESSENTIALS
8 RIGHT-TO-TRY PROS AND CONS  by Mari Edlin
12 AMCP MANAGED CARE & SPECIALTY PHARMACY ANNUAL MEETING  by Aine Cryts
19 THREE QUESTIONS FOR ... DAVID CALABRESE, RPH, MHP  by Tracey Walker
20 FOSTER INNOVATION  by Aine Cryts
22 PHARMACY REGS TO WATCH  by Karen Appold
24 AUTOIMMUNE DISEASES  by Rachael Zimlich, RN
29 PHARMA PIPELINE REPORT  by John Schieszer, MA
32 PBMS UNDER FIRE  by Karen Appold

COMMENTARY
5 HEALTHCARE’S NEW QUARTERBACK  by Perry Cohen

DEPARTMENTS
6 ADVISORY BOARD
33 THE BOTTOM LINE

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Some patients with life-threatening diseases will now be able to receive experimental treatments without receiving approval for their use from the FDA first. That’s because President Trump, on May 30, signed the Right-to-Try Act into law. The signing came shortly after the House passed the legislation May 22. The Senate passed the legislation in August 2017.

Under the legislation, patients can access experimental treatments if they are unable to participate in any clinical trial involving an investigational drug and if they have exhausted all other approved treatment options. The bill requires that any unapproved drug must have an active application and not be subject to clinical hold. In addition, the government may not use a clinical outcome associated with use under the legislation to delay or adversely affect a product’s review or approval, unless it is critical to determining its safety or the sponsor requests use of the outcome.

Proponents and critics, who we spoke to prior to the president’s actions, have a lot to say about the potential effects.

What proponents say
Starlee Coleman, senior policy advisor, Goldwater Institute, says the FDA is the ultimate arbiter of which drugs should be made available. Still, she believes that the FDA approval requirement under the Expanded Access Program (which is already in place) is too time consuming. It requires doctor/patient application to the FDA for a single patient investigational new drug treatment and approval from an independent review board, especially for terminal patients.

“We don’t think Americans should have to apply to the government to save their lives,” she says. “The government shouldn’t be able to say ‘no’ if a manufacturer and doctor approve. Right to Try provides access to potentially life-saving treatment for patients without other options who cannot get into a trial.”

Coleman says drugs available through Right to Try have passed phase 1 trials and continue to be tested, making them safe enough for terminal patients while offering possible benefits. “Right to Try could be particularly beneficial if a trial ends with positive results, but a drug has not yet been approved,” she says.

She also emphasizes that Right to Try is voluntary for patients, doctors, and manufacturers.

What opponents say
The most virulent opponents of federal Right-to-Try legislation say that is not significantly different from Expanded Use but is simply part of an effort to reduce the regulatory scope of the FDA and the federal government in general, says Harold Bishop, senior legal analyst, Health Law Group, Wolters Kluwer, a global information company.

Other criticisms, according to Bishop include:

- Lack of FDA involvement could reduce safety because information regarding a product’s use, based
Right to Try could drive patients away from clinical trials if they could obtain investigational drugs without participation, thus, narrowing trial population and data accrued though trials.

Arthur Caplan, director, Division of Medical Ethics, New York University’s Langone Medical Center, says proponents of Right to Try believe the drug approval process is too slow and if a patient is dying, there is no time for patients to enter a clinical trial because they might not qualify if they are too sick.

He isn’t convinced, however, that the FDA is preventing patient access to experimental drugs, as proponents assert. “It’s drug manufacturers who decide who gets a drug, but instead of doing anything to help persuade companies to make their products available to patients, which is the key for access, they (proponents) set their sights on the FDA and accuse it of keeping patients from promising experimental medicines,” Caplan wrote in a recent *Forbes* article.

Amy K. Dow, member of law firm Epstein Becker Green, agrees. “Proponents of Right-to-Try legislation seem to overlook the fact that the FDA is not, in general, a significant barrier to access to products. Rather, it approves the vast majority of expanded access requests it receives.”

She says the legislation is unlikely to significantly impact the number of patients obtaining access to these products, adding that limitations on supplies of investigational products and burdens imposed on manufacturers in responding to drug requests are not addressed by the legislation.

**Manufacturer’s role**

Under Expanded Access and Right to Try, manufacturers may choose whether to make an investigational drug available.

Brookings, a public policy organization based in Washington, D.C., suggests that drug manufacturers are hesitant to provide preapproval access because of a limited supply—only enough available for a clinical trial—and if a patient suffers adverse effects after taking a drug, that might deter other patients from participation in clinical trials or from purchasing the product after FDA approval.

The Pharmaceutical Researchers and Manufacturers of America, a trade group representing pharma companies, has not taken a formal position on Right-to-Try at press time. Still it has created criteria for determining when to grant access to an experimental treatment outside of a clinical trial, including if a patient has a serious or life-threatening illness and is ineligible for, or otherwise unable to participate in, a clinical trial.

Mari Edlin, a frequent contributor to Managed Healthcare Executive, is based in Sonoma, California.

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**Right-To-Try Timeline**

1987 The FDA puts an expanded access program into place enabling patients, under specific circumstances, to access drugs or biologics that are still in development for treatment purposes.

2009 The FDA amends rules to ensure broad and equitable access to investigational drugs for treatment.

2013 The Goldwater Institute, a public policy research and litigation organization that leads the national effort to pass the legislation in Congress, drafts a report upon which states’ Right-to-Try laws are based.

2014 Colorado passes first state-based Right-to-Try legislation.

2017 The Senate passes the Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right-to-Try Act of 2017, which enables eligible patients with life-threatening diseases or conditions to receive experimental treatments without requiring the approval of the FDA first.

2018 House passes the Senate legislation.
SPECIALTY SUCCESS: STRENGTHENING CARE across the continuum with a health system specialty pharmacy

An interview with Angela Ward, Vice President, Pharmacy Services for Memorial Hermann Health System

What are the leaders of health system pharmacies doing today to help lower costs and improve the quality of care? For Angela Ward, one answer has been to develop a specialty pharmacy dedicated to serving patients and specialty physicians across the healthcare continuum.

Angela Ward is the Vice President, Pharmacy Services for Memorial Hermann Health System — the largest not-for-profit health system in Southeast Texas, with 15 hospitals and numerous specialty programs and services. For nearly five years, she has led pharmacy, quality, infection control and risk management efforts across the organization and has been responsible for pharmacy management from purchasing to inventory.

Collaborating with AmerisourceBergen® — including the Pharmacy Healthcare Solutions (PHS) team — Ms. Ward recently developed the health system’s own specialty pharmacy.

We asked what motivated her to lead the initiative and how it has enhanced revenue, cost savings and the quality of patient care. She also discusses her vision for continuing to expand the role of health system pharmacy organizations to further impact these goals.

As the pharmacy executive for a major health system, what are your top priorities today?

One of my most important goals is to support the Memorial Hermann Accountable Care Organization, which we created to provide quality patient care across the healthcare continuum from end to end.

Because the pharmacy is a critical component of the healthcare continuum, we are expanding our footprint to support quality care to a broader patient population. Creating our own specialty pharmacy has been a foundation of this effort — improving speed-to-therapy and compliance by helping to ensure patients receive the right medications and consultation in a timelier way than relying on a third party, such as a mail order pharmacy.

In addition to supporting quality outcomes, having our own specialty pharmacy has also strengthened our relationships with specialty-prescribing physicians. For example, we help physicians improve compliance and work directly with payers to resolve issues, freeing up office staff time for other responsibilities.

What was the first step in creating your specialty pharmacy?

Educating our senior leadership on the value of specialty pharmacy was job #1. We explained what specialty pharmacy is and its vital role in a healthcare continuum — promoting patient compliance, supporting quality outcomes and controlling costs.

At the same time, we made the financial case for having our own specialty pharmacy. In the absence of a specialty pharmacy, that revenue would go to a third party who would not know our patients as well or have the opportunity for continual personal contact.

Once you had executive support, what did you do?

Our next step was to identify the right consulting team to help us explore the opportunity. Based on my experience, we wanted a consultant who had multiple success stories, not just one. Further, the right consultant would have experience starting from ground zero to standing up a full-fledged specialty pharmacy. And the consultant must have more than one expert on staff; there is so much movement of talent in the pharmacy industry that we did not want to risk losing the only expert once the project had begun.

We ultimately chose the AmerisourceBergen PHS team because of their depth of experience and bench strength. Then together, we began exploring the specialty opportunity more deeply for Memorial Hermann.
How did you explore the opportunity?
We started by creating a business plan. First, we wanted to get a sense of the market potential, including the number of specialty physicians throughout the health system, how many specialty prescriptions are written and how easy they are to fill.

With this information, we knew what our space requirements for the new pharmacy would be. So we began developing construction and information technology plans and costs — as well as a staffing plan. During this stage, we developed four cost and revenue modeling scenarios:

1. Base case
2. Best case without 340B business
3. Best case with 340B
4. Worst case

What is the decentralized model and why did you choose it?
In a decentralized model, our pharmacists do not stand behind a counter and wait for patients to come to them. Instead, they are embedded directly in specialty physician offices, where the patients are. Our pharmacists work directly with and advise patients and physicians right on-site, where they will have the greatest impact on improving care. Prescribed medications are then delivered either by FedEx® or local courier.

In addition, our on-site pharmacists are able to work one-on-one with specialty physicians — hearing their pain points firsthand. As a result, we can help minimize their time and effort to ensure patients receive the right medications.

Here is a perfect example of the value: when a patient’s hepatitis C medication was stolen, our pharmacists worked directly with the insurance company to obtain patient assistance funds. The patient received a refill at no charge — without the involvement of the physician office staff. We handled it all.

In addition, our decentralized model strongly supports Memorial Hermann’s patient care strategy of delivering a quality experience across the continuum. We did not want to create another “big box pharmacy”; instead, we are building stronger and more personal relationships with both patients and specialty providers.

And we are strengthening ties with payers as well — working directly with them to better serve our mutual customers, the patients.

What lessons have you learned through this process?
This process reinforced the importance of partnership, such as working with managed care colleagues to protect reimbursements and improve access and patient care. An example is our partnership with AmerisourceBergen’s US Bioservices subsidiary, to lower barriers to access. Before our own specialty pharmacy was open, US Bioservices dispensed all of our specialty medications. Today, we continue to rely on this key relationship to help obtain limited-distribution drugs, meet 340B requirements and navigate the complexities of payer contracts.

Now that you’ve established your specialty pharmacy, what’s next?
We are pursuing several additional strategies to support our health system’s quality and cost containment goals:

• Offering specialty drugs to large, self-insured companies: Again, our pharmacy intervention improves care while reducing costs.

• Leadership training for emerging directors of pharmacy: Directors of Pharmacy are key to helping us manage population health, and there is a shortage of them.

• Managing the uninsured patient population: The Houston area has one of the nation’s largest; how do we better meet their needs across the healthcare continuum?

• Maximizing our 340B opportunity: Most Memorial Hermann hospitals are 340B eligible. We should optimize this savings opportunity while best serving our patient population.

What advice would you give other pharmacy executives who may be thinking about developing a specialty pharmacy?
As health systems face mounting pressure to improve patient outcomes and satisfaction at a lower cost, we are confident that pharmacy organizations like ours will play an even greater role in achieving success. By leveraging the specialty pharmacy and other strategies outlined here, we all can make a difference. And at Memorial Hermann, we are just getting started.

To start a conversation regarding specialty care, email solutions@amerisourcebergen.com
The cost to treat cancer in the United States could reach $156 billion in 2020, according to the National Cancer Institute. And innovative medications have a significant impact on the cost of care.

To illustrate the growth of new therapies, Jacob Chaffee, PharmD, clinical pharmacist for emerging therapies at Blue Cross Blue Shield of Michigan, noted during his presentation at the recent AMCP Managed Care & Specialty Pharmacy Annual Meeting, that more than 45 novel cancer therapies have been approved by the FDA since 2013, and more than 600 molecules are in the late-stage pipeline.

Chaffee defined some of the terms used in novel cancer treatment, including:

- **CAR-T therapy**, where a patient's immune cells are reengined and returned to their body. The cells, in turn, expand and serve as “living drugs” to recognize and target tumor cells. These cells can remain within the patient's body for months after the infusion, which can lead to long-term remission.

- **CRISPR**, which is also referred to as CRISPR/Cas9, targets specific stretches of DNA for editing using programmable systems. In this process, genes in living cells can be modified or corrected in the treatment of genetic causes of disease or to improve current therapies to treat cancer, muscular dystrophy, and HIV and other infectious diseases.

According to the International Society for Stem Cell Research, using CRISPR/Cas9 together with CAR-T therapy may improve the engineering of T cells where they carry multiple therapeutic features for either increasing specificity or suppressing side effects, or both. Further, the risk of inserting the CAR gene in inappropriate locations can be reduced through the use of CRISPR/Cas9.

**Payers’ primary concerns with CAR-T therapy**

Chaffee noted that payers are particularly concerned with the following when it comes to CAR-T therapy:

- Efficacy and outcomes
- Safety profile
- Cost
- Billing

He then broke down the total cost of care associated with CAR-T, which can range from $523,000 to $795,000 per case. The breakdown of those costs includes:

- Drug cost, which can range from $373,000 to $475,000;
- Administration and monitoring, which can range from $50,000 to $120,000; and
- Adverse events, which can range from $100,000 to $200,000.

More than 45 novel cancer therapies have been approved by the FDA since 2013. More than 600 molecules are in the late-stage pipeline.
Payers are stepping up efforts to manage the cost and utilization of orphan drug treatments.

That’s according to Steven Jung, PharmD, BCPS, drug information pharmacist at San Diego’s MedImpact Healthcare Systems, who discussed the topic at the conference.

**What is an orphan drug?**
The FDA's orphan drug designation program provides orphan status to drugs and biologicals that treat rare diseases and disorders that fit the following criteria:

- Affect fewer than 200,000 people in the United States
- Affect more 200,000 people but aren’t expected to recoup the costs of developing and marketing the treatments

Organizations that sponsor the development of orphan drugs can take part in incentive programs, such as tax credits for clinical trial costs, relief from prescription drug user fees, and marketing exclusivity eligibility upon FDA approval.

Jung pointed out the growth in orphan drug approvals by the FDA has increased from fewer than 30 in 2013 to 70 in 2017.

Because of a backlog in reviewing orphan drug applications, the federal agency launched the “90 in 90 Plan,” which means it will respond to all requests within 90 days, while maintaining consistent, scientifically rigorous review of such applications.

In addition, Jung said the FDA issued draft guidance to the pharmaceutical industry in December 2017 that it would no longer grant orphan drug status to pediatric subpopulations if the following conditions weren’t met:

- The disease in the pediatric population is a valid orphan subset and the drug meets all other criteria for orphan designation.
- The disease in the pediatric subgroup is a different disease from the disease in the adult population.

**What payers are doing**
Payer sensitivity to the cost of orphan drugs continues to rise, according to Jung. That’s because these treatments can cost hundreds of thousands of dollars each year per patient. In addition, new treatments and indications are being approved by the FDA, and there are few, or in some cases, no available treatment alternatives.

In response, payers have undertaken benefit design changes to manage both utilization and the cost associated with these treatments, he said. These changes include:

- Formulary restriction and specialty tiers
- Shifting from copayments to co-insurance
- Prior authorization

Presenting the results of his analysis of reimbursement data, Jung also noted that payers put more coverage restrictions—the most utilized method was prior authorization—on orphan drugs than they do for non-orphan drugs.

Prior authorization criteria typically include the following:

- Documentation of clinical diagnosis
- Appropriate age
- Prescriber specialty
- Baseline data, such as genetic screening and laboratory values
- Renewal criteria, such as documentation of response
- Quantity limit, such as appropriate dosing

**Orphan drug examples**

Jung’s colleague, Christina Bui, PharmD, a drug information pharmacist, discussed the use of Spinraza (nusinersen), an orphan drug for spinal muscular atrophy, a rare, autosomal recessive neuromuscular disorder where patients experience degeneration of motor neurons of the spinal cord; this results in severe and progressive atrophy of skeletal muscles and generalized weakness. Further, patients experience poor weight gain with growth failure, restrictive lung disease, scoliosis, joint contractures, and sleep difficulties.

There are two clinical trials underway for Spinraza where patients have achieved positive results, she said. The cost for the first year on Spinraza is $900,000, which includes six doses, and $450,000 in subsequent years for three doses.

Bui also highlighted the use of Brineura (cerliponase alfa) as an orphan drug to treat ceroid lipofuscinosis type 2 (CLN2), an ultra-rare condition that results in rapid deterioration in cognitive and motor functions, and Radicava (edaravone) to treat amyotrophic lateral sclerosis (ALS), which affects 16,000 people in the United States.
Managed Healthcare Executive conducted its annual pharmacy survey during the first quarter of 2018. The survey received more than 100 responses from executives at medical practices, hospitals, large healthcare systems, benefit management organizations, health plans, long-term care organizations, group purchasing organizations, consulting firms, and more.

Q: What is the most effective way to reduce pharmaceutical costs (specialty and non-specialty)?

- 51% increased collaboration to identify the most effective and cost-effective treatments
- 17% more aggressive and expanded utilization management strategies (e.g., prior auth, step therapy, and limited initial refills)
- 15% adoption of more stringent, evidence-based clinical pathways
- 4% more narrow and/or exclusionary formularies
- 13% other

*Other responses included: More use of generics, government subsidies for specific more expensive drugs, more government interference, pharmacy case management for specialty drugs

“When it comes to working toward a more collaborative system, it’s all about the alignment of incentives. We need to demonstrate efficacy and then give the physicians a reason to care about prescribing the most cost-effective treatment.”

—Managed Healthcare Executive editorial advisor Doug Chaet, chief managed care officer, Sentara Healthcare, and chairman, American Association of Integrated Healthcare Delivery Systems
**Q:** What is the biggest opportunity to reduce specialty pharmaceutical costs?

- 39% Performance-based (outcomes-based) pricing
- 23% More aggressive and expansive utilization management strategies
- 11% Exclusive specialty pharmacy contracting
- 10% Increased government regulation
- 5% Formulary exclusions
- 12% Other*

*Other responses included: Increase formulary addition of biosimilars, more competition on the product and supply chain side

**Q:** What is the best coverage strategy for new, innovative therapeutics and biologics?

- 60% Value-based contracting with manufacturers
- 23% Use manufacturer net pricing (wholesale acquisition cost plus discounts)
- 5% Adjust the premium costs across the broader pool of members/employees
- 12% Other*

*Other responses included: Full pricing and cost transparency based on manufacturer market price or Medicaid floor, prevent manufacturers from using orphan drugs “loophole,” closer monitoring of patient response to medication

**Q:** Will biosimilars reduce specialty drug costs?

<table>
<thead>
<tr>
<th>Year</th>
<th>Yes, starting in 2018</th>
<th>Yes, starting in 2019</th>
<th>Yes, starting in 2020</th>
<th>Yes, post-2020</th>
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</thead>
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<tr>
<td>2017</td>
<td>25%</td>
<td>13%</td>
<td>14%</td>
<td>12%</td>
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<tr>
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<td>16%</td>
<td>14%</td>
<td>20%</td>
<td>15%</td>
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“In the long term, pharmaceutical companies need to tie their drug pricing to outcomes.

Since Health Plans have medical and pharmacy claims data, they can calculate ‘total cost of care’ for patients with certain diseases that are treated by specialty pharmaceuticals and can therefore measure the benefit of value of these medications on total healthcare spend. This means they have the ability to do outcomes based contracting and make pharmaceutical companies price their drugs accordingly.”

—Editorial advisor Perry Cohen, PharmD, CEO of The Pharmacy Group and the TPG family of companies

“As noted in the survey responses, the promise of biosimilars is always one or two years away. Thus far, specialty drugs in the same class (e.g., TNF Inhibitors) have, if anything, increased total spend. Saying that, at some point biosimilars should have the same impact as generics and reduce total drug spend.”

—Editorial advisor David Schmidt, president of the TPG International Health Academy and a healthcare consultant
**Q**: What will be the biggest driver of specialty drug costs in 2018?

- **New specialty drugs**: 16% (2018) vs. 29% (2017)
- **Growing demand due to aging population/increased prevalence of chronic disease**: 28% (2018) vs. 36% (2017)
- **Manufacturer pricing for new products**: 12% (2018) vs. 20% (2017)
- **Broadened labeled indications and off-label use of existing products**: 9% (2018) vs. 16% (2017)
- **Inflation rates for specialty drugs already on market**: 8% (2018) vs. 11% (2017)
- **Other**: 5% (2018) vs. 5% (2017)

**Q**: How will performance-based pricing evolve over the next 3-5 years?

- **Performance-based pricing will be used somewhat more than reference-based pricing**: 41% (2018)
- **Neither of these two models will dominate**: 22% (2018)
- **Reference-based pricing will be used somewhat more than performance-based pricing**: 20% (2018)
- **Reference-based pricing will dominate**: 9% (2018)
- **Performance-based pricing will dominate**: 7% (2018)

“While the readers’ response here is not surprising, recent trends suggest that it also may not be on target. The response is not unexpected given that the predominant proportion of pipeline activity and new FDA approvals in recent years has been ultra-high-cost orphan drug therapies. Secondly, we are now witnessing a further transition in the management of high-prevalence conditions from traditional drug categories to much higher cost specialty biologics in areas like hyperlipidemia, respiratory conditions, migraine and Alzheimer’s disease. Regardless however, early signals indicate that the most significant factor likely to drive specialty trend in 2018 will remain the same as it has for the last several years … manufacturer inflation rates.”

—Editorial advisor David Calabrese, RPh, MHP, senior vice president and chief pharmacy officer at OptumRx

“Performance-based pricing has a great appeal, however, to succeed in helping bend the cost curve and improve quality, behavioral and cultural change from all players—patients, providers, payers, pharma, and other suppliers must occur. Healthcare is notoriously slow to adopt new approaches and performance-based pricing requires all parties to accept risk and uncertainty.”

—Schmidt
**Q:** What is the best long-term approach to addressing the high cost of rare disease treatment?

- **46%** A more integrated approach by benefit managers around total cost of care across the healthcare continuum
- **21%** Deploying more expansive strategies to assess risk vs benefit with long-term use
- **15%** Government guidelines and/or regulations
- **14%** Use of benefit incentives to drive consumer engagement and higher-value care
- **5%** Other

**Q:** Should pharmacists be compensated under Medicare Part B for prescribing medications and helping assess patient conditions?

- **76%** Yes
- **24%** No

**Q:** Who should play the biggest role in combating the opioid epidemic?

- **66%** Providers
- **17%** Government
- **10%** Payers and PBMs
- **7%** Pharmacists

"I believe that pharmacists should be part of the solution to Medicare Part B costs and prescribing issues, but thus far I don’t believe there has been sufficient research to ‘prove’ the value. Without the proof, the other actors in the system will remain resistant to allowing any of ‘their’ money to be allocated to the pharmacists."

—Schmidt

"I would agree with the readership that providers are the most critical entity in driving change here, as they ultimately serve in the most influential role to affect all aspects of proper opioid risk management. This includes, but is not limited to, properly educating patients; minimizing initial opioid exposure; managing proper continuation or discontinuation of opioid use; promoting alternative therapies; recognizing and proactively managing opioid dependency; and ensuring proper treatment."

—Calabrese

"Combatting the growing opioid epidemic in a lasting and meaningful way will take the efforts of all healthcare stakeholders. Insurers, such as Independence Blue Cross, are key players, not only as repositories of vital health data, but as active partners, working with communities, doctors, hospitals, patients, and their families to improve well-being."

—Editorial advisor Daniel J. Hilferty, MPA, president and CEO, Independence Health Group
Q: How will global markets affect the U.S. pharmaceutical marketplace?

- 38%: They won’t
- 37%: Increasing regulation will lower costs outside of the U.S. and lead to increased costs here
- 19%: Increasing competition will stabilize the market somewhat for the short-term
- 7%: Increasing demand as European markets recover will help drive down costs in the U.S.

Q: Which new pharmaceutical approved over the past 12 months are you most excited about?

- 40%: CAR T-cell therapies (Kymriah and Yescarta)
- 34%: Ocrevus (first approved primary progressive MS drug)
- 18%: Luxturna (gene therapy that delivers a functional RPE65 gene to the patient through a viral vector)
- 8%: Dupixent (first specialty drug for moderate-severe atopic dermatitis)
- 5%: Other

Q: What pharmaceutical in the pipeline—specialty, new, generic, or other—are you most excited about over the next 24 months?

- 40%: Sotagliflozin (oral SGLT inhibitor for T1DM; may be first oral therapy for T1DM)
- 31%: Tezacaftor/ivacaftor (cystic fibrosis drug)
- 21%: CGRP antagonists (erenumab, galcanezumab, fremanezumab - specialty drugs used for migraine prophylaxis)
- 7%: Other
Helping our partners solve their toughest specialty health challenges so they can deliver exceptional care.

We’re better together.
Three questions for . . .

David Calabrese, RPh, MHP

OptumRx’s senior vice president and chief pharmacy officer  by Tracey Walker

The International Rare Diseases Research Consortium hopes to develop 200 new drugs for rare diseases by 2020, and it seems as if things are better than on track. The FDA granted 77 orphan drug approvals last year and granted 476 orphan drug designation requests, according to law firm Hyman, Phelps & McNamara.

David Calabrese, RPh, MHP, Managed Healthcare Executive (MHE) editorial advisor and OptumRx’s senior vice president and chief pharmacy officer, discusses ways to stabilize economics, access, and appropriate use of new drugs.

Q. MHE: What can be done to balance economic efficiency with proper access and use?

Calabrese: First, the evaluation of the clinical evidence and projected financial impact must be conducted in as robust and proactive a manner as possible. Ideally, pharmacy and therapeutics committees should be conducting these assessments prior to FDA approval. Secondly, utilization management programs must be designed in as comprehensive and academically rigorous a fashion as possible to limit usage to the most appropriate patients. Third, once patients initiate therapy, close monitoring and care management support is essential to ensure maximal adherence, achievement of therapeutic goals, and that benefits obtained outweigh any unforeseen safety/tolerability issues. Finally, population-based analytics will be critical to assess both short- and long-term real-world outcomes for those receiving these therapies.

Q. MHE: Which new drugs in the near-term pipeline will most impact pharmacy cost trends over the next three to five years?

Calabrese: Newer options for the treatment and prevention of migraines and cluster headaches (CGRP antagonists) are long-awaited additions to helping manage migraine frequency and severity. Uptake could be rapid and substantial.

Several drugs are also in late-stage development for treatment of nonalcoholic steatohepatitis. This class is of key significance as there are no FDA-approved treatment options and an estimated 16 million U.S. adults with this condition.

Q. MHE: How can pharmacy benefit management best change to become more holistic in focus and function?

Calabrese: This will require major industry transformation encompassing, but not be limited to:

- Enhanced data integration (medical, pharmacy, lab, EHR, behavioral health, and social determinants of health);
- Advanced analytic support including real-world evidence assessment, predictive analytics, and machine learning;
- Progressive, consumer-focused digital resources and engagement vehicles;
- Point-of-service provider engagement tools fully-integrated into daily workflow;
- Newer formulary and utilization management models that de-emphasize rebates and promote greatest value;
- Reformed business models that deliver optimal transparency in all clinical, operational, and financial offerings; and
- Greater alignment with target clinical and financial goals between PBMs and clients.

There are numerous drugs, primarily biologic, that are in development for the treatment of Alzheimer’s disease. These include drugs in novel classes like the BACE inhibitors and RAGE antagonists. With the aging of the population, increased prevalence of disease, and limited array of effective treatment options, these drugs also hold the potential for significant market penetration should clinical data prove positive.

Tracey Walker is content manager for Managed Healthcare Executive.
Foster Innovation
Cultivate smart ideas, beat your competitors

by AINE CRYTS

Every year in the United States, approximately 700 women die due to pregnancy or childbirth-related causes, according to the CDC—and that’s despite the fact that 17 cents of every dollar is spent on healthcare, according to 2012 numbers from the Organization for Economic Co-operation and Development.

This and other pressing healthcare challenges—such as the need to encourage appropriate adoption of new treatments including immunotherapy—mean the industry is ripe for creative thinking and innovation, says Managed Healthcare Executive Editorial Advisor Don Hall, principal of DeltaSigma LLC, a consulting practice specializing in strategic problem solving for managed care organizations.

“We have to start finding innovators in our business,” Hall says. “We have to start creating innovative cultures, because the opposite is really what we have in our industry. [Healthcare] cultures tend to be very conservative—and focused on reducing risk.”

Here are four recommendations from Hall and other experts regarding how you can spark creative programs and solutions at your organization.

1 Create a “sponsorship spine.” Julie Coffman, a partner at consulting firm Bain & Company, recommends forming a leadership cadre that partners with your health system’s innovative researchers and physicians. This leadership cadre should help make the ideas brought forth by these physicians and researchers come to fruition.

WHAT STIFLES INNOVATION? Managed Healthcare Executive board members weigh in

“Leaders who stop listening to learn and stop entertaining new thoughts stifle creativity, innovation, and ultimately passion in their teams.”

Kevin Ronneberg, MD, VP and associate medical director, Health Initiatives, HealthPartners

“Far too many leaders surround themselves with echo chambers that neither allow nor foster productive criticism and divergent ideas. This ‘my way or the highway’ thinking fosters organizations that are often characterized by low morale, non-adaptation to critical market trends, and at worst, serious compliance issues.”

Don Hall, principal, DeltaSigma LLC

“Good leaders create atmospheres where people are encouraged to take risks and promote ideas that sometimes will fail. on the other hand, dysfunctional leadership creates a punitive environment where people are not encouraged to speak their minds. I found having many viewpoints helps me think through all my options. I want our staff to feel free to promote ideas even if they might be shot down or eventually fail. Some of them will succeed and will be of great benefit to our member plans.”

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Coffman provides the example of a young physician-researcher with a breakthrough therapy that he’s working hard to get the facility to embrace. Enabling the physician-researcher’s success starts with connecting him to individuals who can help move the project up the chain, she says. Make sure your organization has a system in place to encourage this type of partnership.

“The key to effective change management, in lots of ways, is developing the early victories, being able to talk about them, and celebrating them with the right people who carry a lot of sway in the organization,” she says.

2 Consult frontline employees who work one-on-one with customers. Far too many employees are never asked for insight on improving the customer experience—and that means their valuable ideas never arrive in the executive suite, says Hall. Explore how your organization can more effectively solicit feedback and ideas and make them a reality.

3 Focus on empowerment, not accountability. At many organizations, prioritizing accountability has become a key management philosophy, says Joe Tye, CEO and head coach at Values Coach training and consulting firm. He says that tends to discourage employees from taking creative approaches to solving problems. While holding employees accountable is important, you should also make sure employees feel empowered to suggest changes and share ideas, without the fear that they will face repercussions if those ideas don’t pan out as expected.

Tye previously served as chief operating officer at The Toledo Hospital in Ohio and Baystate Medical Center in Worcester, Massachusetts.

4 Use insight from customers to drive enlightened decision making. “No one is calling an insurance company to compliment them,” says Hall. “Nobody is calling to say, ‘I love this product.’ They’re telling you about a problem they’re having.”

Whether customers are looking for more online access to providers or quicker access to lab results and treatment recommendations, those problems need to be brought to the executive suite and addressed, Hall says.

Aine Cryts is a writer based in Boston.

Top 6 leadership deficiencies

We asked our board members to identify the biggest leadership problems they see in healthcare.

- Being resistant to change.
- Assuming you know what you don’t know.
- Not valuing and cultivating partnerships with other leaders in the industry and outside it.
- Being closed-minded.
- Fearing risk.
- Creating an intimidating atmosphere.

Innovation success story

Sometimes, seemingly small ideas presented by staff members can result in big changes.

Case in point: A patient journal developed by nurses in the ICU at Newton-Wellesley Hospital, which is part of Boston’s Partners HealthCare.

Ostensibly a wire-bound notebook, the patient journal was developed by nurses in response to requests from patients and family members to be more informed about what occurred while patients were intubated or sedated in the ICU, says Rodilyn Glushchenko, RN, MSN, nurse director of the ICU.

Patients’ families and nurses use the journal to document the patient’s stay. For example, a nurse might share that the patient received a visit from a family member. Family members read nurses’ comments in the journal, and they also use it to write about their time with the patient or to pose questions to nurses, who respond within the journal, Glushchenko says.

The journal development underscores the importance of leadership supporting staff members’ ideas. Carving out time for nurses to participate in meetings to develop the patient journal was key to the success, says Glushchenko.

Also important was connecting Glushchenko’s team to an in-house nurse who specializes in clinical innovation, and providing access to on-staff project managers so her team could learn project management skills.

Glushchenko notes that, while she provided her team with access to resources and encouraged their success, she also gradually stepped away from their team meetings to encourage nurses to take ownership of the project.

Always looking for opportunities to further innovate, Glushchenko says the patient journal could be a good fit for the hospital’s oncology department because patients could use it to write about their experience with cancer treatment. Other medical specialties, including geriatrics and pediatrics, could use a similar approach.
Policy Outlook

LEGISLATIVE / POLICY DEVELOPMENTS, TRENDS AND IMPACTS

Pharmacy Regs to Watch

How they could impact you  by KAREN APPOLD

Preparing for pharmacy policy changes can help your managed care organization stay ahead of the competition. Here, pharmacy experts highlight three areas to watch closely.

1 340B

Through this federal program, which started in 1992, pharmaceutical companies participating in Medicaid agree to provide outpatient drugs to covered entities at significantly reduced prices. Hospitals and clinics that participate in the program must apply for eligibility and meet specific requirements, says John M. Lonie, RPh, EdD, associate professor of social and administrative sciences at Long Island University – College of Pharmacy in Brooklyn, NY. “The program enables covered entities to stretch federal resources and provide more comprehensive services.”

Over the past few years, the 340B program has grown because of policy changes that increased opportunities for purchasing drugs at discounted rates and because eligible entities became more aware of the program, says Emily Cook, MSPH, JD, partner, McDermott Will & Emery, an international law firm.

The program’s growth, however, has led to scrutiny from Congress, drug manufacturers, and other stakeholders. “Among the expressed concerns are that the program is not governed by clear rules, making it difficult to hold participating providers and drug manufacturers accountable for compliance with program requirements,” Cook says. For example, drugs purchased by providers through the 340B program cannot also be eligible for Medicaid discounts, and drug manufacturers must accurately calculate 340B prices. In addition, a lack of reporting requirements makes it difficult to review and analyze purchases and use of drugs purchased at the discounted rates, she says.

Chris Hudson, managing director, Dacarba LLC, a professional services firm, points to questions regarding the eligibility rules and whether they are restrictive enough, and concerns about the lack of transparency around how savings are used.

Cook expects a lot of legislative activity in the 340B space this year. Though no new legislation has been passed at press time, five bills have been introduced since mid-2017 and additional bills are coming, she says. To date, the bills have primarily focused on additional oversight and data reporting requirements. Future bills could address which patients can receive discounted drugs, the arrangements for dispensing drugs, and the prices that hospitals can charge for these drugs, she says.

2 Pharmacist provider status

Pharmacists and the patient care services they provide are not included in certain sections of the Social Security Act, which determines eligibility for programs such as Medicare Part B. The omission limits Medicare beneficiary access to pharmacist services in the outpatient setting.

“If pharmacists were designated as providers under Medicare Part B, private health plans could no longer use this as a reason to exclude pharmacists as providers,” says Fernando Gonzalez, RPh, MS, assistant professor of pharmaceutical sciences at Long Island University – College of Pharmacy. “Pharmacists are now on the verge of obtaining provider status as a result of many states pushing for this status. The federal government will have the ultimate decision. Once the federal government grants provider status, states will follow suit.”

Pharmacist status would give them the ability to bill for services such as medication management, and receive payment from Medicare, Medicaid, and other private payers, Gonzalez says.

Provider status is closely linked to scope of practice. In some states, pharmacists could be given the same authority to provide services to Medicare patients as

Five bills related to 340B have been introduced since mid-2017 and additional bills are coming, says Emily Cook, a partner at McDermott Will & Emery law firm.
nurse practitioners and physician assistants. These services might include continuing therapy, which involves monitoring drug levels, side effects, adverse reactions, and compliance; and ordering diagnostic tests to evaluate patient disease parameters, such as blood levels of narrow therapeutic index drugs. “Pharmacists’ ability to bill for nontraditional pharmacy services such as ordering diagnostic tests for checking cholesterol or ordering tests to check blood levels of drugs like Warfarin could positively impact healthcare executives’ bottom line, maximizing therapeutic outcomes that will reduce hospitalizations and changes in courses of therapy,” Gonzalez says.

**Orphan drug designations**
The Orphan Drug Act of 1983 provides benefits and incentives to drug companies that address the more than 7,000 rare diseases that exist. To be granted orphan designation, the disease or condition that a drug treats must affect fewer than 200,000 people. If it affects more, the company must prove that it cannot reasonably recoup the costs associated with the drug’s research and development.

Drugs receiving orphan designation are rewarded with seven years of market exclusivity as well as sizable tax credits and other benefits, says Edward Buthusiem, managing director, Berkeley Research Group, a strategic advisory and consulting firm. “Many drugs receiving orphan designation are older versions of drugs which, in several cases, have been on the market for many years and are often without patent protection,” Buthusiem says. “In other words, these drugs are repurposed for use to treat an orphan disease.”

Since the number of orphan drugs tends to be small, reflecting the limited number of targeted patients, they tend to cost more than drugs to treat nonorphan drugs, Buthusiem says. The costs of producing and selling these drugs tends to be higher since they are distributed through specialty wholesale channels. However, the price of such drugs also extends to the nonorphan indications of these drugs.

This lack of price differentiation between orphan and nonorphan indications has drawn the ire of Congress, which is seeking to limit the incentives granted to orphan drugs.

The Closing Loopholes for Orphan Drugs Act is one pending bill to watch. Currently, orphan drugs are excluded from the 340B program to avoid invalidating company incentives to develop such products. In other words, drug makers are not required under the 340B program to discount orphan drugs. If passed, the pending legislation would limit the 340B drug pricing program’s orphan drug exclusion to apply only when a drug is used for the rare condition or disease it was developed to treat.

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FERNANDO GONZALEZ, LONG ISLAND UNIVERSITY – COLLEGE OF PHARMACY

76% of healthcare executives believe pharmacists should be compensated under Medicare Part B for prescribing medications and helping assess patient conditions.

Source: Managed Care Pharmacy Survey 2018
There are roughly 100 autoimmune diseases, plus about 40 more that are immune-based. The total annual direct healthcare cost for these debilitating conditions is nearly double that of cancer treatments, according to the American Autoimmune-Related Diseases Association. For this reason, the stakes in autoimmune disease research are high. Read on to discover some of the newest innovations affecting common autoimmune diseases.

**LUPUS**

“Lupus has been a particular challenge because it is a very complex disease in terms of the immunopathogenesis and the fact that it impacts so many different organs and can present differently from one person to another,” says Mary Crow, MD, co-chair of the Lupus Research Alliance Scientific Advisory Board and physician-in-chief of the Hospital for Special Surgery, an orthopedics and rheumatology hospital in New York City.

Much of the focus in lupus research is on interferons, which are signaling proteins made and released by cells in response to the presence of pathogens. Interferons have been found to be overproduced in many lupus patients.

“This observation has led to interferon itself being identified as a therapeutic target,” Crow says. Anifrolumab, in phase 3 clinical trials, is one medication showing promise in this area, she says, noting it’s likely that at least one new medication could be approved for use in the next year.

More than 30 clinical trials are ongoing in various phases of lupus drug development.”

**“More than 30 clinical trials are ongoing in various phases of lupus drug development.”**

**Rosalind Ramsey-Goldman, MD, Northwestern University**

Lupus is a chronic autoimmune disorder that can result in pain and inflammation in skin, joints, and organs. With more than 16,000 new cases diagnosed each year and no cure, lupus is a prime area for research. There is no one therapy that works for everyone, and the disease can turn fatal when damage occurs in vital organs like the kidneys, according to the Lupus Foundation of America.
of Medicine and medical director of the clinical research unit at Northwestern University in Chicago. In the last six months, several phase 2 trials showed positive results and are likely to move on to the next phase, she adds.

Ustekinumab, which blocks the IL12/23 pathway linked to the pathogenesis of lupus, and previously approved for psoriasis, psoriatic arthritis, and Crohn's disease, has been evaluated in lupus in a phase 2 trial, Ramsey-Goldman says. One study showed efficacy in the treatment of active lupus and plans are in place for more studies.

Another study is evaluating sirolimus, which is already approved by the FDA for immunosuppression and to prevent rejection after organ transplantation. Ramsey-Goldman says this medication may be useful in lupus to restrict T cell activity.

Two phase 2 clinical trials in 2016 that are now in phase 3 could result in FDA approval for anifrolumab and voclosporin, a calcineurin inhibitor and immunosuppressant that blocks T cells.

Researchers are also working to identify biomarkers that can help clinicians improve diagnosis and better identify those at risk for developing the disease, Goldman says. Biomarkers may also help clinicians predict flares, as well as how patients will respond to different treatments.

Celiac disease affects an estimated 10% of the world’s population, according to the Celiac Disease Foundation. These individuals have an immune response when gluten is ingested, resulting in damage to the small intestine that prevents appropriate nutrient absorption. The Celiac Disease Foundation estimates that 2.5 million Americans are still undiagnosed.

More than 20 different immunotherapy targets are also being investigated, one in particular for refractory celiac disease—a particularly bad form of the disease that does not respond to a gluten-free diet.

PETER H.R. GREENE, MD, COLUMBIA UNIVERSITY

Celcius, which is entering phase 3 trials, is helpful in reducing symptoms of celiac disease. Budesonide and prednisone, along with other steroids, have been used to reduce symptoms in celiac patients. Researchers are also working on a vaccine that involves the injection of peptides that may protect patients from some gluten contamination, Greene notes, adding that study is moving to phase 2 trials.

More than 20 different immunotherapy targets are also being investigated, one in particular for refractory celiac disease—a particularly bad form of the disease that does not respond to a gluten-free diet. “There is a lot of interest, and some of the bigger pharma companies are getting involved,” Greene says.

MULTIPLE SCLEROSIS
Kathy Costello, adult nurse practitioner and

More than 2.3 million people around the world have multiple sclerosis, which occurs when the immune system attacks a coating on the nerves in the brain and spinal cord that transmit signals. The progression of the disease and its symptoms can be unpredictable, but may include blurred vision, loss of balance, slurred speech, tremors, paralysis, and more. Women are diagnosed more frequently, and symptoms usually begin between the ages of 20 and 50, according to the National Multiple Sclerosis Society.
associate vice president of clinical care for the National Multiple Sclerosis Society, says several genes have been identified as posing a risk for multiple sclerosis development, but there’s not enough definitive data yet to prevent the disease onset through gene therapy.

There are many new developments in treatment on the horizon, though, including an oral medication that was approved for relapsing forms of multiple sclerosis. Fingolimod, approved for adult MS patients since 2010, received a breakthrough therapy designation from the FDA for children and adolescents ages 10 years and older with relapsing MS.

Other medications are in development that restrict the activation and circulation of immune cells, therefore reducing the inflammatory process in multiple sclerosis.

Another medication to watch is ibudilast, used in Japan and Korea for a variety of issues like post-stroke and bronchial asthma since the 1980s. Researchers are looking into the medication’s potential benefit for problems including multiple sclerosis, amyotrophic lateral sclerosis, substance abuse, and neuropathic pain, Costello says. In recent phase 2 clinical studies, patients experienced a significant reduction in the progression of whole brain atrophy. The research may move to phase 3 trials soon and ibudilast has been designated as a fast-track product in terms of its development as a possible treatment for progressive MS, says Costello.

Additional treatments in the research pipeline have a similar focus, by reducing activation of the immune system, reducing the activation of immune cells, or blocking the entry of those cells into the central nervous system.

“They’re each coming at the immune system problems from various directions. This is good news for people with multiple sclerosis who may need to switch to a different medication due to a suboptimal response or side effects. Having medications with differing mechanisms of action will allow greater chance to impact the disease process,” says Costello.

There is also interest in how gut microbiota and exercise can impact multiple sclerosis, particularly regarding what exercises are best for stimulating different parts of the brain and improving mobility.

Stem cells transplants may also be an option. “Interim results from a study of hematopoietic stem cell transplant showed the procedure was well-tolerated and there may be benefit to rebooting the immune system,” Costello says. “You are essentially suppressing the immune system and then reintroducing the patient’s own stem cells, and in multiple sclerosis the hope is they will regenerate in a less harmful way.”

KATHY COSTELLO, NATIONAL MULTIPLE SCLEROSIS SOCIETY

A GROWING PROBLEM

More than 23.5 million Americans are affected by autoimmune diseases, according to the Office of Women’s Health at HHS.

Autoimmune diseases occur when a person’s immune system becomes unable to tell the difference between normal and unhealthy cells, causing the immune system to attack the body’s healthy organs and tissues.

Spending on autoimmune drugs continues to increase and utilization is rising, says April Kunze, senior director, clinical formulary development and trend management strategy at Prime Therapeutics. Autoimmune drugs are the number one drug spend category at Prime, comprising approximately 14% of the overall drug spend in the pharmacy benefit.

“Autoimmune disease is not a specific condition but rather an umbrella term that encompasses multiple individual diseases including lupus, celiac disease, multiple sclerosis, rheumatoid arthritis, and type 1 diabetes, among many others,” says Farrah Wong, PharmD, RPh, senior director, pipeline and drug surveillance at OptumRx. “Autoimmune diseases are among the most prevalent in the United States, affecting millions of Americans and, for reasons unknown, are becoming more and more prevalent.”

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Additional treatments in the research pipeline have a similar focus, by reducing activation of the immune system, reducing the activation of immune cells, or blocking the entry of those cells into the central nervous system.

“They’re each coming at the immune system problems from various directions. This is good news for people with multiple sclerosis who may need to switch to a different medication due to a suboptimal response or side effects. Having medications with differing mechanisms of action will allow greater chance to impact the disease process,” says Costello.

There is also interest in how gut microbiota and exercise can impact multiple sclerosis, particularly regarding what exercises are best for stimulating different parts of the brain and improving mobility.

Stem cells transplants may also be an option. “Interim results from a study of hematopoietic stem cell transplant showed the procedure was well-tolerated and there may be benefit to rebooting the immune system,” Costello says. “You are essentially suppressing the immune system and then reintroducing the patient’s own stem cells, and in multiple sclerosis the hope is they will regenerate in a less harmful way.”

TYPE 1 DIABETES

Jessica L. Dunne, PhD, research director at the Juvenile Diabetes Research Foundation, says development of treatments for type 1 di-
Type 1 diabetes is less common than type 2, but unlike type 2, there are no lifestyle changes that prevent development. In Type 1 diabetes, the immune system attacks the beta cells of the pancreas. Sometimes, individuals might not feel the effects of this damage for a long time, but damage from the disease can lead to kidney failure, neuropathy, and other complications.

Increased interest in adjunct therapies like this for type 1 diabetes will improve access for patients, Dunne says. “It will make them easier to prescribe and improve insurance coverage,” she says. “It’s a huge step. I hope this opens the door for more adjunct therapies.”

There are also studies investigating the role of cytokine inhibitors and antigen-specific therapies, a viral vaccine that may prevent the development of type 1 diabetes, and how the gut microbiome affects disease development and progress, she says.

“There has been some evidence showing the microbiome is changed in diabetes, but the big question now is, what do we do about it?” Dunne says.

RHEUMATOID ARTHRITIS

Christopher Morris, MD, a Tennessee board-certified rheumatologist who serves on the government affairs committee for the American College of Rheumatology and on the board of directors for the Southern Medical Association, says biologics, such as adalimumab (the top-selling medication in the world) have shown tremendous progress in treating RA. Still, the cost of these new treatments can be prohibitive, Morris says, and the problem is compounded in rheumatology because there are so few FDA-approved medications and treatments are often used off-label. Patients have trouble getting medications.

Rheumatoid arthritis is on the rise, with the number of cases about 70% higher than previously thought, according to the CDC. The debilitating disease is caused when the immune system attacks a patient’s joints, causing painful swelling and inflammation.

Autoimmune vs. Cancer

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<tr>
<th></th>
<th>Autoimmune diseases</th>
<th>Cancer</th>
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<tr>
<td>Annual direct healthcare costs</td>
<td>$100 billion</td>
<td>$57 billion</td>
</tr>
<tr>
<td>Prevalence</td>
<td>23.5 million Americans</td>
<td>9 million</td>
</tr>
<tr>
<td>Research funding*</td>
<td>$591 million</td>
<td>$6.1 billion</td>
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Source: American Autoimmune-Related Diseases Association
approved for coverage by insurance companies, and can rarely afford them on their own, he says.

“This is something we are frustrated with in medicine. My first consideration when I write a patient a medication is, are they able to afford it?” Morris says. “We want a medicine that works and we want a medicine they can afford.”

Biosimilars could be a more cost-effective alternative to biologics, he says, but there is hesitation over fears that cost savings could come at the expense of efficacy.

He says Janus kinase (JAK) inhibitors are likely the next big thing in treating RA, and future treatments are becoming increasingly selective to improve efficacy while reducing negative effects.

There has also been some research into vagal nerve stimulation—which usually involves either manual or electrical stimulation of the vagal nerve, Morris says, highlighting the idea that there is a neurologic component to some autoimmune diseases. “Maybe by modifying how the body is reacting neurologically, it can have an effect on rheumatoid arthritis.”

**SKIN DISEASES**

New medications being investigated for psoriasis and psoriatic arthritis include JAK inhibitors. Upadacitinib, for example, is being studied for use in psoriasis, psoriatic arthritis, atopic dermatitis, and other autoimmune diseases like Crohn’s, says Morris. The once-a-day medication is now in phase 3 trials, he says. “It’s an interesting medicine. We want to see what pro-inflammatory markers are there and direct against that.”

Several autoimmune diseases affect the skin, with psoriasis and atopic dermatitis among the more well-known. In psoriasis, there is an added complication on joint damage in some cases. **About 11% of individuals diagnosed with psoriasis also have diagnoses of psoriatic arthritis, and another 30% will eventually develop it**, according to the National Psoriasis Foundation.

The issue with the psoriasis family of diseases and other autoimmune conditions, he says, is finding balance between toning down the immune system response to pathogens that trigger the conditions, without damaging the immune system too much. “Every one of these medicines is playing with your immune system.”

Rheumatologists need to look at a patient’s individual symptoms and condition to determine the best medications for them. For example, ustekinumab works well for psoriasis, but is not the first choice for patients with joint problems. Adalimumab, on the other hand, is approved for both, says Morris. “The more different approaches we have, the better.”

**Biosimilar obstacles**

Biosimilars for autoimmune diseases are prevalent, but ongoing challenges impede their use.

“The FDA continues to approve biosimilar products, but unfortunately, due to patent litigation, they are unable to launch,” says April Kunze, senior director, clinical formulary development and trend management strategy at Prime Therapeutics.

“Another issue deterring biosimilar uptake is that although biosimilars are highly similar to their reference products, none of the approved products are interchangeable, [so] the doctor has to specifically prescribe for the biosimilar product.”

Biosimilar developments to watch include:

- Erelzi (etanercept-szzs) from Novartis, a biosimilar of Amgen’s Enbrel (etanercept). This is approved but cannot launch yet due to patent litigation.
- Amgen’s Amjevita (adalimumab-atto) and Boehringer Ingelheim’s Cyltezo (adalimumab-abdm). These are FDA approved biosimilars for AbbVie’s Humira (adalimumab). These also have not yet launched.

“As more biosimilars become available, there may be a decrease in price among the product thereby decreasing the pressure on the healthcare system and patients by providing a more cost-effective alternative to brand name products,” says Kunze.

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Rachael Zimlich, RN, is a writer in Columbia Station, Ohio.
Unique trends are occurring in the pharmaceutical pipeline that would have been unheard of just five years ago. One agent coming on the market may cost up to $1 million for a one-time infusion, and a new agent derived from cannabis may be the first of many such products for a host of illnesses.

Perry Cohen, Managed Healthcare Executive editorial advisor, and CEO of the Pharmacy Group consulting firm, says some remarkable agents will be coming on the market that will significantly help individuals who previously had no treatment options.

Here, industry experts share more information about noteworthy new drugs in the pipeline.

**Aimovig**
(ereumab – Amgen/Novartis)

**What it is:** A calcitonin gene-related peptide (CGRP) receptor antagonist monoclonal antibody for prevention of migraine in patients with four or more migraine days per month. It is given by subcutaneous injection monthly, according to Peterson.

**Potential impact:** Research published in November 2017 in the New England Journal of Medicine reported positive results from the six-month phase 3 STRIVE study evaluating the drug versus a placebo for the prevention of episodic migraine. It found that the drug delivered clinically meaningful and statistically significant differences from placebo for all primary and secondary endpoints in a study that included 955 patients. Patients taking this agent experienced a significant reduction in mean monthly migraine days and were significantly more likely to achieve a 50% or greater reduction in monthly migraine days than those taking placebo.

**Status:** The FDA approved Aimovig for the preventive treatment of migraine in adults on May 17.

**Cost estimate:** Approximately $9,000 per year, according to Tharaldson.

“The new CGRP inhibitor class of medications will provide a treatment option for patients with chronic or episodic migraines,” says Christopher Peterson, PharmD, director, clinical evaluation and policy, Express Scripts. “Many of these patients are resistant or intolerant to currently available therapies. As a debilitating condition, decreasing the number of migraine days in patients with chronic or episodic migraines is an important advancement for these patients.”

**Larotrectinib**
(LOXO-101, Loxo Oncology)

**What it is:** Larotrectinib is a potent, oral and selective investigational new drug for the treatment of patients with cancers that harbor abnormalities involving the tropomyosin receptor kinases (TRKs), according to Loxo Oncology.

**Potential impact:** A drug targeting a gene fusion that occurs in lung, colon, and other cancers, larotrectinib was shown to be effective in 75% of patients of all ages in clinical trials, and an even higher percentage of pediatric patients, according to study investigators at UT Southwestern’s Simmons Cancer Center.

**Status:** The FDA has accepted the company’s New Drug Application (NDA) and granted priority review for larotrectinib for the treatment of adult and pediatric patients with locally advanced or metastatic solid tumors harboring an NTRK gene fusion. The FDA has set a target action date of November 26, 2018, under the Prescription Drug User Fee Act (PDUFA).

**Cost estimate:** Unknown

Most cancer drugs are targeted to specific organs or locations in the body. Larotrectinib is the first cancer drug to receive FDA breakthrough therapy designation for patients with a specific fusion of two genes in the cancer cell, no matter what cancer type, according to Laetsch. While the TRK fusions occur in only a small percentage of common adult cancers, they occur frequently in some rare pediatric cancers, such as infantile fibrosarcoma, cellular congenital mesoblastic nephroma, and papillary thyroid cancer, says Laetsch.

“I do think this is a gamechanger,” Laetsch says. “Larotrectinib has received breakthrough designation for the treatment of patients with a TRK fusion positive solid tumor, regardless of the type of tumor in which that fusion occurs. I see this as the next big step in the development of precision medicine and molecularly targeted therapy.”
**Epidiolex**  
*(GW Pharmaceuticals)*

**What it is:** Purified cannabidiol (CBD) without any psychoactive properties for adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) and Dravet syndrome (DS), rare forms of epilepsy. It is an oral liquid therapy (once daily). GW Pharmaceuticals says about 18,000 patients in the U.S. have LGS and 8,000 have Dravet syndrome. Lennox-Gastaut syndrome typically occurs between the ages of 3 to 5 years. Dravet syndrome affects infants. Both conditions can cause severe intellectual and developmental disabilities and early death.  
**Potential impact:** In clinical trials, cannabidiol was effective in lowering seizure rates in these patients.  
**Status:** Orphan drug with approval expected by June 27, 2018, according to Aimee Tharaldson, PharmD, senior clinical pharmacist advisor, Express Scripts.  
**Cost estimate:** More than $100,000 per year, according to Tharaldson.  

Cannabidiol is a pharmaceutical formulation of purified cannabidiol. GW Pharmaceuticals reported in phase 3 studies that cannabidiol added to other antiepileptic therapies significantly reduced the frequency of seizures in patients with LGS and Dravet syndrome. If approved, this agent would be the first pharmaceutical formulation of purified, plant-based CBD, according to GW Pharmaceuticals. This product is a cannabinoid lacking the high associated with marijuana and it would be the first in a new category of anti-epileptic drugs, according to GW Pharmaceuticals. Tharaldson says cannabidiol looks like a promising drug that could be a gamechanger for these patients. "There is a need for new treatment options for these patients. In three pivotal clinical studies, Epidiolex demonstrated strong efficacy in reducing seizure frequency in patients with LGS and DS," Tharaldson says.

**AVXS-101**  
*(Novartis)*

**What it is:** AveXis, Inc., says it is using an adeno-associated virus vector (AAV9) containing the SMN1 transgene for the treatment of spinal muscular atrophy (SMA) infusion (one-time). The company says about 7,200 infants have SMA Type 1, which represents infants from birth to six months of age. Babies with SMA Type 1 have difficulty breathing and swallowing. They cannot sit, crawl, or walk and only 8% of babies with SMA Type 1 survive to 20 months of age.  
**Potential impact:** All patients in the therapeutic dose cohort in the phase 1 trial were alive and event-free at 24-month follow-up. Patients observed in long-term follow-up from the phase 1 trial continued to gain strength and achieve new milestones, including two additional patients who could stand with assistance.  
**Status:** Orphan drug. Biologics License Application (BLA) filing possible in mid-2018 with approval in late-2018 or early-2019, according to Christopher Peterson, PharmD, director, clinical evaluation and policy, Express Scripts.  
**Cost estimate:** $750,000 to $1 million for the one-time infusion, according to Peterson.

AVXS-101 could be the first one-time gene replacement therapy for SMA, a disease which results in early death or lifelong disability with considerable healthcare costs. It is expected to be available in the U.S. in 2019.  
Sukumar Nagendran is chief medical officer and senior vice president of AveXis, which is developing this product. He expects to submit a request for a pre-BLA meeting with the FDA by the end of June to discuss the regulatory path for AVXS-101. "We will be able to provide more guidance after the meeting minutes are received, typically approximately a month after the meeting," says Nagendran.

**Solriamfetol**  
*(Jazz)*

**What it is:** Jazz says it is testing this dopamine andnorepinephrine uptake inhibitor (DNRI) for the treatment of excessive sleepiness in adult patients with narcolepsy or obstructive sleep apnea (OSA). It is a daily oral medication.  
**Status:** This product is under FDA review with a PDUFA date of December 20, 2018, according to Peterson.  
**Potential Impact:** The solriamfetol phase 3 clinical program includes one study evaluating excessive sleepiness in adult patients with narcolepsy (TONES 2), two studies evaluating excessive sleepiness in adult patients with OSA (TONES 3 and TONES 4), and an open-label, long-term safety and maintenance of efficacy study (TONES 5) in the treatment of excessive sleepiness in patients with narcolepsy or OSA. The company says solriamfetol significantly improves wakefulness in patients with obstructive sleep apnea who suffer from excessive sleepiness.  
**Cost estimate:** $10,000 per year of therapy, according to Peterson.

Jed Black, MD, senior vice president of sleep medicine at Jazz Pharmaceuticals and an adjunct professor, Stanford University Medical Center, Stanford Center for Sleep Sciences and Medicine, says Jazz expects to launch solriamfetol in the U.S. in the first quarter of 2019. "We believe solriamfetol will provide a meaningful option for patients living with excessive sleepiness due to narcolepsy or OSA once approved," says Black.
Sotagliflozin (Lexicon)

**What it is:** A dual SGLT1 and SGLT2 inhibitor for use in combination with insulin therapy to improve glycemic control in adults with type 1 diabetes mellitus, according to Peterson. He says the dual inhibitor of SGLT-1 and SGLT-2 can influence how the intestines and kidneys process blood sugar. It is also under investigation for treating type 2 diabetes. It is a once-daily oral therapy, according to Peterson.

**Status:** This product is under FDA review with a PDUFA date of March 16, 2019, according to Peterson.

**Potential impact:** Sotagliflozin has a unique mode of action that, if approved, could potentially improve glycemic management beyond insulin alone, according to Lexicon. It says phase 3 data with 1,402 patients with type 1 diabetes showed a benefit with sotagliflozin combined with insulin. An NDA was filed with the FDA on March 26, according to Peterson.

**Cost estimate:** Approximately $5,000 a year, according to Peterson.

“I would categorize this therapy as an ‘incremental improvement’ as there are many currently available therapy options for treating diabetes, including the SGLT-2 inhibitors that have a somewhat similar mechanism of action,” says Peterson. However, diabetes is a large therapy class (the number two therapy class, according to Express Scripts’ 2017 “Drug Trend Report”) affecting about 30 million Americans. “As a result, the introduction of effective therapies within the class have the potential to achieve blockbuster status.”

Fremanezumab (Teva)

**What it is:** Anti-CGRP monoclonal antibody for the prevention of chronic and high frequency episodic migraines. It is a subcutaneous therapy (monthly/quarterly), according to Tharaldson.

**Status:** On December 18, 2017, Teva announced the FDA accepted for review a BLA for fremanezumab. Additionally, the FDA has granted fast track designation for fremanezumab for the prevention of cluster headache, according to Teva. At press time, it is under FDA review with a PDUFA date of June 15, 2018, according to Tharaldson. The product may be delayed due to a recent FDA warning issued to a Celltrion plant, the main active pharmaceutical ingredient supplier for this drug, according to Tharaldson.

**Potential impact:** The BLA includes data from the HALO clinical trial program, which enrolled more than 2,000 patients with episodic migraine and chronic migraine. Using both quarterly and monthly dose regimens, fremanezumab demonstrated statistically significant results across all trial endpoints, according to Teva.

**Cost estimate:** Approximately $9,000 a year, according to Tharaldson.

Joshua Cohen, MD, global therapeutic area lead for migraine and headache at Teva, says his team is also studying fremanezumab for the prevention of chronic and episodic cluster headache as part of the phase III ENFORCE clinical research program. “Additionally, Teva has recently initiated a fremanezumab phase 2 clinical program for the treatment of post-traumatic headache disorder,” says Cohen.

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— CHRISTOPHER PETERSON, PHARMD, EXPRESS SCRIPTS
Suing physicians and pharmacists over the opioid crisis is nothing new, but up until recently, PBMs have flown under the radar. Earlier this year, however, a south Texas county included the three largest PBMs—CVS, Express Scripts, and OptumRx—as well as some smaller ones operating in Texas, in a nationwide lawsuit. The lawsuit alleges that PBMs drove the opioid epidemic as a result of increasing profits from the drugs.

PBMs set the rules that determine drug availability and how much patients pay out of pocket to get them. So why haven’t they been targeted until now? “While PBMs play a critical role in drug pricing and availability, they are not expected to question physicians’ therapeutic choices,” says Harry Nelson, managing partner, Nelson Hardiman, LLP, a healthcare law firm. “They don’t have the same professional obligations that pharmacists do to avoid suboptimal dispensing choices. As unlicensed entities, they don’t hold individual licenses as physicians and pharmacists do, so they are not held to the same standard. Their roles and responsibilities are less well-defined, so there is less basis to hold them responsible.”

Nonetheless, PBMs actually have a lot of power, says Christopher J. Metzler, PhD, JD, CEO, Gordium Healthcare, a multidisciplinary behavioral healthcare organization. They are the middlemen who operate between the doctor, patient, and pharmacy, he says. They provide insurance contracts with pharmacies and can deny a claim’s payment.

Lawyers could “find a treasure trove of evidence” to present to a jury.
—CHRISTOPHER J. METZLER, GORDIUM HEALTHCARE

SIMILAR LAWSUITS LIKELY
Nelson says since it doesn’t cost much to name a PBM as an additional party in litigation, he expects this will happen more often. “While it takes some creativity to do something new (like looking at PBMs) as a responsible party, my hunch is that other lawyers are likely to learn from this and will be interested in a potential additional source of settlement funds,” he says.

Metzler also expects more lawsuits. “Lawyers who present a well-written and brutal set of discovery questions, review the prescription paper trail, and talk to pharmacies and patients, will find a treasure trove of evidence to present to a jury,” he says.

ON WHAT GROUNDS?
Nelson says PBMs may not hold licenses that impose obligations, but their contractual commitments as intermediaries between health plans and pharmacies provide a potential argument that they also owe responsibility to patients, who are arguably third-party beneficiaries of those contracts. In other words, health plans are contracting with PBMs for the benefit of patients, so PBMs have the responsibility to protect patients from harm. There may also be an argument that PBMs are in a better position than individual pharmacies because of their data access to red flag problematic prescribing practices, he says.

Lawrence Ingram, a partner in the law firm Freeborn & Peters’ Litigation Practice Group, says allegations could be that a PBM somehow allowed more opioids to be permitted in communities than could be supported by legitimate medical needs.

LIKELY OUTCOMES
As a novel legal theory, lawyers will have to explain to the courts what PBMs are and how they operate. “Unless lawyers are able to do so and prove causation, this will be a very difficult road to travel,” Metzler says. “As in most novel legal theories, this is a test, the outcome of which is uncertain. It is up to lawyers to educate, persuade, and prove causation.”

Karen Appold is a medical writer in Lehigh Valley, Pennsylvania.
Customer Experience is Top Priority for Health Leaders

49% of provider executives say customer experience will be a top strategic priority over the next five years.

81% of payer executives say their company is investing in technology to improve member experience.

Source: “Customer experience in the New Health Economy: The data cure.” PwC.

Quotable

“Healthcare employers should have a financial wellness structure in place that not only has empathy for their workers, but also gives their employees the resources they need to move beyond living paycheck-to-paycheck.”

— Edukate CEO Chris Whitlow, in reaction to a survey by Career Builder that found that 78% of full-time workers live paycheck to paycheck.

PHYSICIANS: PATIENT DATA ACCESS COULD BE BETTER

Only 50% of physicians are very or extremely satisfied with their access to patient information.

83% believe access to medication adherence information is a high priority, yet only 17% can easily retrieve that information electronically.

Source: “Physician Perspectives on Access to Patient Data,” Surescripts.

What Americans Most Want in Healthcare

1. CONVENIENCE
2. QUALITY
3. SUPPORT
4. PERSONALIZATION
5. COMMUNICATION

Source: “Customer experience in the New Health Economy: The data cure.” PwC.

TOP 10 IN-DEMAND MEDICAL SPECIALTIES

#10. Cardiology
#9. Neurosurgery
#8. Endocrinology
#7. Occupational medicine
#6. Gastroenterology
#5. Obstetrics & Gynecology
#4. Hematology
#3. Oncology
#2 Urology
#1. Geriatrics