The CDC calls antibiotic resistance the world’s most pressing public health threat

‘Don’t Mess With Part D!’ Congress Gets the Message 39
Centers for Innovation Crop Up in Health Plans 41

Biologics All Eyes on Biosimilars 44

www.managedcaremag.com
Indication
FYCOMPA (perampanel) is indicated as adjunctive therapy for the treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older.

Important Safety Information
WARNING: SERIOUS PSYCHIATRIC AND BEHAVIORAL REACTIONS
• Serious or life-threatening psychiatric and behavioral adverse reactions including aggression, hostility, irritability, anger, and homicidal ideation and threats have been reported in patients taking FYCOMPA
• These reactions occurred in patients with and without prior psychiatric history, prior aggressive behavior, or concomitant use of medications associated with hostility and aggression
• Advise patients and caregivers to contact a healthcare provider immediately if any of these reactions or changes in mood, behavior, or personality that are not typical for the patient are observed while taking FYCOMPA or after discontinuing FYCOMPA
• Closely monitor patients particularly during the titration period and at higher doses
• FYCOMPA should be reduced if these symptoms occur and should be discontinued immediately if symptoms are severe or are worsening

Please see next page and Brief Summary of full Prescribing Information for Boxed WARNING and additional Important Safety Information.

Learn more about FYCOMPA™ and access clinical reprints at www.fycompa.com
Serious Psychiatric and Behavioral Reactions

Hostility- and aggression-related adverse reactions occurred in 12% and 20% of clinical trial patients randomized to receive FYCOMPA at doses of 8 mg and 12 mg/day, respectively, compared to 6% of patients in the placebo group. These effects were dose-related and generally appeared within the first 6 weeks of treatment, although new events continued to be observed through more than 37 weeks. These effects in FYCOMPA-treated patients led to dose reduction, interruption, and discontinuation more frequently than placebo-treated patients. The combination of alcohol and FYCOMPA significantly worsened mood and increased anger. Patients taking FYCOMPA should avoid the use of alcohol. Patients, their caregivers, and families should be informed that FYCOMPA may increase the risk of psychiatric events. Patients should be monitored during treatment and for at least one month after the last dose of FYCOMPA, and especially when taking higher doses and during the initial few weeks of drug therapy (titration period) or at other times of dose increases.

Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including FYCOMPA, increase the risk of suicidal thoughts or behavior in patients. Anyone considering prescribing FYCOMPA or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Patients, their caregivers, and families should be informed of the risk and advised to monitor and immediately report the emergence or worsening of depression, suicidal thoughts or behavior, thoughts about self-harm, and/or any unusual changes in mood or behavior. Should suicidal thoughts or behavior emerge during treatment, consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Dizziness and Gait Disturbance

FYCOMPA caused dose-related increases in events related to dizziness and disturbance in gait or coordination. Dizziness and vertigo were reported in 35% and 47% of patients randomized to receive FYCOMPA at doses of 8 mg and 12 mg/day, respectively, compared to 10% and 16% of patients randomized to receive FYCOMPA at doses of 8 mg and 12 mg/day, respectively, compared to 2% of placebo-treated patients. These adverse reactions occurred mostly during the titration phase.

Somnolence and Fatigue

FYCOMPA caused dose-dependent increases in somnolence and fatigue-related events. Somnolence was reported in 16% and 18% of patients randomized to receive FYCOMPA at doses of 8 mg and 12 mg/day, respectively, compared to 7% of placebo patients. Fatigue-related events were reported in 12% and 15% of patients randomized to receive FYCOMPA at doses of 8 mg and 12 mg/day, respectively, compared to 5% of placebo patients. In the controlled Phase 3 epilepsy clinical trials, these adverse reactions occurred mostly during the titration phase. Patients should be advised against engaging in hazardous activities requiring mental alertness, such as operating motor vehicles or dangerous machinery, until the effect of FYCOMPA is known.

Falls

Falls were reported in 5% and 10% of patients randomized to receive FYCOMPA at doses of 8 mg and 12 mg/day, respectively, compared to 3% of placebo-treated patients.

Withdrawal of AEDs

A gradual withdrawal is generally recommended with antiepileptic drugs to minimize the potential of increased seizure frequency.

Most Common Adverse Reactions

In clinical trials, the most frequently reported dose-related adverse reactions in patients receiving FYCOMPA 8 mg or 12 mg vs placebo (≥4% and at least 1% higher than the placebo group) included dizziness (36% vs 9%), somnolence (16% vs 7%), fatigue (10% vs 5%), irritability (9% vs 3%), falls (7% vs 3%), nausea (7% vs 5%), ataxia (5% vs 0%), balance disorder (4% vs 1%), gait disturbance (4% vs 1%), vertigo (4% vs 1%), and weight gain (4% vs 1%).

Drug Interactions

FYCOMPA may decrease the efficacy of contraceptives containing levonorgestrel. Plasma levels of FYCOMPA were decreased when administered with carbamazepine, phenytoin, or oxcarbazepine. Concomitant use with strong CYP3A4 inducers such as St. John’s wort and rifampin should be avoided. Multiple dosing of FYCOMPA 12 mg/day enhanced the effects of alcohol on vigilance and alertness, and increased levels of anger, confusion, and depression. These effects may also be seen when FYCOMPA is used in combination with other CNS depressants.

Pregnancy Category C and Lactation

FYCOMPA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Physicians are advised to recommend that pregnant patients taking FYCOMPA enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. Caution should be exercised when FYCOMPA is administered to a nursing woman.

Hepatic and Renal Impairment

Use in patients with severe hepatic or severe renal impairment is not recommended. Dosage adjustments are recommended in patients with mild or moderate hepatic impairment. Use with caution in patients with moderate renal impairment.

Drug Abuse and Dependence

FYCOMPA is a Schedule III controlled drug substance and has the potential to be abused or lead to drug dependence.

Please see Brief Summary of full Prescribing Information on the next page for Boxed WARNING and additional Important Safety Information.
FYCOMPA (perampanel) tablets, for oral use, CIII

BRIEF SUMMARY-see package insert for full Prescribing Information

- FYCOMPA tablets should be administered at the initial dose of 2 mg once daily for 7 days, increase dosage by 2 mg per day increments after 7 days, and every 4 days until an optimal dosage is achieved or the maximum tolerated dose is reached. The recommended starting dosage of FYCOMPA is 2 mg once daily.
- In the presence of enzyme-inducing AEDs, the adverse reaction profile of FYCOMPA was observed to be similar in patients receiving FYCOMPA and placebo.

ADVERSE REACTIONS

- In controlled Phase 3 clinical trials, the most commonly reported adverse reactions leading to discontinuation were gastrointestinal disorders (≥4% of patients randomized to receive FYCOMPA at doses of 8 mg and 12 mg/day, respectively) and somnolence (≥4% of patients randomized to receive FYCOMPA at doses of 8 mg and 12 mg/day, respectively).
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Injury, Poisoning and Procedural Complications

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</tbody>
</table>

None.
an increase in visceral abnormalities (diverticulum of the intestine) at all doses tested. In a dose-ranging study at animal studies, perampanel induced developmental toxicity in pregnant rat and rabbit at clinically relevant doses. There are no adequate and well-controlled studies in pregnant women. In it adversely affects these activities.

Table 2. Adverse Reactions in Pooled Double-blind Trials in Patients with Partial-Onset Seizures

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Placebo</th>
<th>1/2 mg</th>
<th>5/10 mg</th>
<th>10 mg</th>
<th>20 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Coordination abnormal</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Balance disorder</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Ataxia</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Mood altered</td>
<td>&lt;1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Skin laceration</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Fall</td>
<td>3</td>
<td>2</td>
<td>5</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Falls</td>
<td>3</td>
<td>2</td>
<td>5</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5</td>
<td>8</td>
<td>8</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Neurologic Effects</td>
<td>Dizziness, Gait</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Confusional state</td>
<td>&lt;1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Limb injury</td>
<td>&lt;1</td>
<td>1</td>
<td>1</td>
<td>2</td>
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</tr>
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</tr>
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</table>

CONTRAINDICATIONS

Concomitant use with strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, rifampin, vecuronium, or dantrolene) should be avoided.

OVERDOSAGE

In general, the adverse reactions associated with overdoses were similar to the reactions at therapeutic doses with dizziness reported most frequently. There were no reported sequelae. In general, the adverse reactions associated with overdoses were similar to the reactions at therapeutic doses with dizziness reported most frequently. There were no reported sequelae. In general, the adverse reactions associated with overdoses were similar to the reactions at therapeutic doses with dizziness reported most frequently. There were no reported sequelae. In general, the adverse reactions associated with overdoses were similar to the reactions at therapeutic doses with dizziness reported most frequently. There were no reported sequelae. In general, the adverse reactions associated with overdoses were similar to the reactions at therapeutic doses with dizziness reported most frequently. There were no reported sequelae.
Insurance Plans Dropping the Ball In Regard to Antibiotic Resistance

By Frank Diamond

W
genever someone at a party talks about a desire to be born in another age, I’ll ask: “But what about antibiotics?” (OK. I don’t actually voice this because I want to be invited back. I do think it, though.) The first recipient of penicillin was a British constable, Albert Alexander, who, in 1941, had been infected by a rose’s thorn. He deteriorated rapidly before being treated with the cutting edge medication. He made a dramatic comeback, but then relapsed and died because the medical team had run out of the drug.

Penicillin didn’t become widely available until after World War II. Over the years came the other antibiotics. I am still here thanks to these medications, and there’s a good chance that’s the case with you.

Unfortunately, though, society now faces a variation of what Constable Alexander faced. We’ve reported on, and clinician executives at insurance plans and doctors have been dealing with, the growing problem of antibiotic-resistant bacteria for a long time.

We’re losing — losing so badly that contributing editor Joseph Burns can begin his excellent article about the problem (page 26) with this dramatic statement: “We have entered the post-antibiotics era.”

Constable Alexander didn’t have enough. We don’t have enough of antibiotics that work as intended. Antibiotic resistance is the world’s most pressing health care threat, according to the Centers for Disease Control and Prevention.

Here’s the brutal bottom line for health insurers: They aren’t doing enough, according to the National Committee for Quality Assurance. Plans’ efforts to ensure proper use of antibiotics have been stagnant, even in decline, over the last five years.

That needs to improve. This is not the sort of situation one can, as Constable Alexander might have put it, muddle through.
Swamped by Antibiotic-Resistant Bacteria

The CDC calls it the world’s most pressing public health threat. What can health plans do? First, get involved. Insurers don’t do a nearly good enough job in ensuring proper antibiotic use.

How Will ACOs Manage Pharmacy?

A lot depends on whether the management (along with the risk) of medical and pharmacy spending remain separate. Some experts see that as an unsustainable model.

Don’t Mess With Part D!

That’s the message Congress is getting from almost everybody, including insurers, manufacturers, payers, and beneficiaries who claim that proposed regulations would limit choice and access.

Meet the MCO Innovation Department

Independence Blue Cross and Aetna are just two insurers that have opened innovation departments dedicated to finding more efficient ways to work with providers. It’s about retaining a competitive edge.

FOCUS ON BIOLOGICS

Biosimilars Just Around the Corner

ACA implementation expected to hasten an FDA final rule.

Race on for Interferon-Free HCV Treatment

AbbVie and Gilead closer to seeking FDA approvals.

DEPARTMENTS

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Tomorrow’s Medicine..............................50
Old drug might help agitation.

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Specialists will be in high demand.
Until the mid-1990s, hospitals in England primarily got paid by block contracts, so history was the major determinant of the income a hospital could expect. This was somewhat akin to a capitated contract — without an underlying methodology.

Unsurprisingly, there was plenty of criticism of this, and when policymakers wanted to encourage a more market-orientated approach, it became important to develop a contracting currency that reflected case mix issues.

One option was to adopt and adapt DRGs. Instead, England opted to develop its own methodology, known as health care resource groups (HRGs). This created a mini-industry and HRGs are now on Version 4. They have been used as the payment mechanism for an increasing amount of acute hospital care since 2004, and there are now more than 2,500 different HRGs in use. For the most part, the reimbursement for each HRG is set nationally, with every hospital across the country paid the same amount, aside from an adjustment called a market forces factor meant to recognize the different costs of providing care across England.

Conceptually HRGs are similar to DRGs and essentially have the same virtues and flaws. Paying hospitals via HRGs is known as payment by results (PbR), but a more accurate title would be payment for recorded activity. This probably sounds familiar, but one key difference is that a National Health Service (NHS) hospital has no opportunity to charge different rates to different purchasers. There is one rate and no opportunity for cross subsidization.

Moreover, any emergency activity that exceeds that delivered by a hospital in 2009–2010 is paid at only 30% of the usual rate. The ostensible reason for this policy was to provide hospitals with a financial incentive to avoid admitting patients unnecessarily. Despite this, emergency admissions increased by a further 3% from fiscal year 2009–2010 to FY 2012–2013 (http://bit.ly/BritHospData). The money saved is supposed to be reinvested in admission-avoidance programs; however, evidence that reinvestment has happened is often lacking.

Tariffs, even when paid in full (payers are increasingly proactive in denying payment and imposing contract penalties) have been subject to a deflator since FY 2011–2012 to take account of efficiencies that the acute care sector is expected to deliver. In other words, the reimbursement levels for HRGs, after inflation is taken into account, are generally dropping. Yet despite the attention that is given to the pressure that PbR subjects the acute care sector to, a surprisingly large amount of care in hospitals — about 40% — relates to activity and income (e.g. teaching, research, charity, and private patients) that is not covered by PbR (http://bit.ly/PayByResults). With rates subject to a continuous squeeze, the financial viability of hospitals increasingly depends on the robustness and extent of these sources of income.

Further developments

There are in essence two strands of payment reform discernable in England. One relates to the further refinement of PbR through development of best-practice payment levels for care delivered to a higher standard, and additional money for hospitals via a scheme known as CQUIN (Commissioning for Quality and Innovation), which aims to encourage the adoption of national/local policy objectives such as ensuring medical coverage and access to diagnostic services on weekends that is similar to Monday–Friday access, and provision of venous thromboembolism (VTE) and dementia screening of patients.

Currently a hospital delivering on all its CQUIN targets can expect them to provide about 2.5% of its income.

The other strand looks to move away from PbR in favor of a variety of other contract
mechanisms, ranging from the development of bundled payments (as per the U.S.A.) to contracts based on clinical outcomes and even to capitation. U.S. readers will probably be unsurprised to hear that progress has been slow at best and that advocates of this approach face considerable resistance from providers to any changes that threaten their income, as well as formidable practical obstacles in terms of the data underpinning such contracts.

Resistance would probably be less if there were a more evident upside for providers in these new arrangements. Unfortunately these proposals are being made at a time of financial austerity for the NHS, and providers suspect that purchasers’ motives are less about improving outcomes than about saving money. The fate of such a potentially disruptive contracting change is made more uncertain by the desire of the government to maintain stability in the NHS — and avoid negative news headlines — in the run-up to the next election.

Another obstacle to both integrated care and innovation in the way services are contracted for has been the longstanding separation of primary care from acute care payment mechanisms. Primary care physicians (known as general practitioners in the U.K.) occupy a unique — and generally envied — space within the NHS. Most primary care is delivered by small numbers of GPs operating together as a self-employed business. They are not NHS employees. They are paid by a mixture of capitation and fees, with rates set by a national contract. Most of their income comes from one source — the NHS. In that respect, they are part of the NHS family, with most of their income essentially guaranteed, but legally (and as far as the taxman is concerned), they are independent small businesses. Given these circumstances, it is unsurprising that many primary care physicians look unfavorably on moving to new contract arrangements with uncertain income streams that potentially involve greater work and are subject to renewal every couple of years!

There is interest being expressed by a small number of acute care hospitals in moving into primary care service provision, employing primary care physicians and setting up the U.K. equivalent of integrated health care organizations.

Whatever the direction that payment mechanisms take, the core problem is likely to remain that for many organizations, payment is going to be less than income.

Currently 14 NHS Trusts (the name for the organizations that run hospitals), which constitute about 10% of the acute care sector in England, are officially in special measures. Special measures most likely has no counterpart in the U.S. health care system. It’s the name given for placing these hospitals under an intensive external supervisory system because there is significant concern about the quality of care being delivered, the financial situation — or both. If they don’t improve, there is a threat that the organizations that run them will be disbanded and other parties invited to run the hospitals.

Hospitals in the red

Many more trusts are running an in-year deficit, although determining how many is not easy as often the true financial position is disguised by a variety of government bailouts and “support” funding. I estimate that around 50% of acute care hospitals in England have an underlying deficit. As I have previously noted in Managed Care (http://tinyurl.com/Royce-July), the government shows periodic enthusiasm for getting the private sector involved in the running of NHS services, including hospitals. The latest example would be to take over such hospitals in special measures.

In considering the commercial opportunities and risks of running an acute care hospital in England, one might want to take into account that the average emergency department income per patient in one of the hospitals I recently worked in was about £115 ($184). In contrast the average bill for an A&E visit in the U.S.A. has been reported at $2,168 (http://bit.ly/Cost-ER). Neither number feels sensible, and in England, fines will be imposed if a hospital cannot meet national performance standards — including £200 ($320) every time it takes longer than 30 minutes to accept the clinical handover of a patient brought in by ambulance, rising to £1,000 ($1,600) should that handover take more than an hour. You also will not get paid should the patient be re-admitted within 30 days of discharge.
**POWER PATIENTS CAN HANDLE**

- **MMX® technology** is designed to target delivery of budesonide throughout the full length of the colon1,2
- **3 times** more patients taking UCERIS® achieved combined clinical and endoscopic remission compared with placebo3*
- The rates of overall expected glucocorticoid-related side effects were similar for UCERIS and placebo at 8 weeks—10.2% vs 10.5%, respectively1*
- Through the UCERIS savings program,† 90% of eligible patients with commercial insurance will pay only $25‡

**INICATION:**
UCERIS® (budesonide) extended release tablets are indicated for the induction of remission in patients with active, mild to moderate ulcerative colitis.

**IMPORTANT SAFETY INFORMATION:**
UCERIS® (budesonide) extended release tablets are contraindicated in patients with hypersensitivity to budesonide or any of the ingredients of UCERIS. When glucocorticosteroids are used chronically, systemic effects such as hypercorticism and adrenal suppression may occur. Since UCERIS extended release tablets are a glucocorticosteroid, general warnings concerning glucocorticosteroids should be followed. Care is needed in patients who are transferred from glucocorticosteroid treatment with higher systemic effects to glucocorticosteroids with lower systemic effects, such as UCERIS extended release tablets, since symptoms attributed to withdrawal of steroid therapy, including those of acute adrenal suppression or benign intracranial hypertension, may develop. Taper patients slowly from systemic corticosteroids if transferring to UCERIS extended release tablets.

Patients who are on drugs that suppress the immune system are more susceptible to infection than healthy individuals. Glucocorticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infection, untreated fungal, bacterial, systemic viral or parasitic infections, or ocular herpes simplex. More serious or even fatal course of chickenpox or measles can occur in susceptible patients.

Patients with moderate to severe liver disease should be monitored for increased signs and/or symptoms of hypercorticism.

Caution should be taken in patients with hypertension, diabetes mellitus, osteoporosis, peptic ulcer, glaucoma or cataracts, or with a family history of diabetes or glaucoma, or with any other condition where glucocorticosteroids may have unwanted effects.

Concomitant use of inhibitors of Cytochrome P450 3A4 (for example ketoconazole and erythromycin) should be avoided and patients should be closely monitored for increased signs and/or symptoms of hypercorticism. Avoid grapefruit juice, which is known to inhibit CYP3A4, when taking UCERIS.

In clinical studies, the most common adverse reactions (incidence ≥2%) were headache, nausea, decreased blood cortisol, upper abdominal pain, fatigue, flatulence, abdominal distension, acne, urinary tract infection, arthralgia, and constipation.

Please see complete Prescribing Information for UCERIS extended release tablets at www.UCERIS.com.

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UCERIS® (budesonide) extended release tablets are indicated for the induction of remission in patients with active, mild to moderate ulcerative colitis.

**CORE STUDY DESIGNS:**
Two randomized, double-blind, placebo-controlled studies were conducted in a total of 899 adult patients with active, mild to moderate UC (Ulcerative Colitis Disease Activity Index [UCDAI]: ≥4 and ≤10 at entry).

The primary endpoint was induction of combined clinical and endoscopic remission (defined as a UCDAI score of ≤1, with scores of 0 for both rectal bleeding and stool frequency, normal mucosa with no friability on endoscopy, and a ≥1-point reduction in the Endoscopic Index [EI] score) after 8 weeks of treatment.1

**INDICATION:**

**IMPORTANT SAFETY INFORMATION:**

| Supplied in bottles of 30 tablets | NDC 68012-309-30 | No AB-rated equivalent for UCERIS |
BRIEF SUMMARY
Placebo-controlled insert for Full Prescribing Information available at www.uceris.com
UCERIS (budesonide) extended release tablets, for oral use
Rx Only
INDICATIONS AND USAGE
UCERIS (budesonide) extended release tablets are indicated for the induction of remission in patients with active ulcerative colitis.

CONTRAINDICATIONS
UCERIS is contraindicated in patients with hypersensitivity to budesonide or any of the ingredients of UCERIS. UCERIS has been used for patients who have received corticosteroids or other medications that suppress the immune system, but the safety of UCERIS for such patients has not been established.

WARNINGS
Hypercorticism and Adrenal Suppression
Systemic glucocorticosteroid use may result in the following: hypercorticism and adrenal suppression or benign intracranial hypertension, may occur in patients with certain endocrine or paraneoplastic disorders, or in patients with a family history of diabetes or glaucoma, or with any other condition in which glucocorticoid use may result in an increased risk of these conditions.

Clinical Use of Budesonide: There is no evidence that budesonide use in a dosage of 9 mg daily for 9 months is associated with an increased risk of malignancy, including lymphoma, in the clinical trials of another drug and may not reflect the rates for other drugs in other clinical settings.

• Hypercorticism
• Adrenal Suppression

In the clinical trials of another drug and may not reflect the rates for other drugs in other clinical settings. It is unknown whether adverse reactions in patients receiving UCERIS are due to budesonide or another variable, such as severity of the underlying disease and/or prior glucocorticoid treatment to the risk is also not known. If exposed, therapy with varicella zoster immune globulin (VZIG) and/or intravenous corticosteroids should be considered. Glucocorticosteroids should be used with caution, if at all, in patients with a history of severe eosinophilic pneumonia.

From Systemic Glucocorticosteroid Therapy
Care in patients who are transferred from glucocorticosteroid treatment with high systemic effects should be reduced cautiously.

In an additional two-year study in male Sprague-Dawley rats, budesonide caused no tumors in the incidence of gliomas in male rats at an oral dose of 50 mcg/kg (approximately 0.05 times the maximum recommended human dose on a body surface area basis). However, it caused a decrease in body weight and a dose-related increase in the liver to body weight ratio. The drug is not a systemic drug and thus does not require a systemic drug study. Glucocorticosteroids with high systemic effects are not indicated for use in the treatment of inflammatory bowel disease.

Inhibitors of Gastric Acid Secretion
When glucocorticosteroids are used after treatment with gastric acid reducing agents, properties and uptake of the compound may be altered when UCERIS is used after treatment with gastric acid reducing agents (e.g., PPIs, H2 blockers and amantadine).

Geriatric Use
Clinical studies of UCERIS did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experiences have not identified differences in responses between the elderly and younger patients. In general, UCERIS should be used with caution in the elderly patient due to the potential for decreased renal, hepatic or cardiac function, and of concomitant diseases or other drug therapies. Hypoergic Impairment Patients with moderate to severe liver disease should be monitored for increased glucocorticosteroid related effects in patients with liver disease.

The risk of developing serious or systemic adverse reactions to budesonide in the clinical trials of another drug and may not reflect the rates for other drugs in other clinical settings.

OVERDOSAGE
Postsurgical anaphylactic shock may occur following oral glucocorticosteroid withdrawal, including those of acute adrenal insufficiency in patients with severe systemic illness.

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Adverse Reactions
Adverse reactions that have been reported include injection site reactions, headache, nausea, vomiting, anorexia, vertigo, dizziness, nervousness, nervousness, fever, chills, rash, pruritus, edema, pleural effusion, eosinophilia, leukopenia, and increased liver enzymes. Those reactions are reported voluntarily from a population of uncertain size. The available data do not allow the estimation of frequency or establish a causal relationship to drug exposure.

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Providers Need to Boost Efforts To Prevent Abuse of Narcotics

Pill hoarders, doctor shoppers, and just plain addicted patients are a growing problem for physicians — and thus for health plans, too

By Thomas Reinke

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reventing overdoses, addiction, and death from the illicit use of prescription painkillers has been an uphill battle for the U.S. Food and Drug Administration, the Drug Enforcement Administration, and many states that have implemented increasingly stringent control programs.

The FDA and DEA have been criticized for putting a chokehold on the legitimate use of these drugs. The two agencies recently stepped up their control efforts, with the FDA making hydrocodone a Schedule II drug — meaning that it requires written scripts with limited quantities. The DEA has been limiting quantities of controlled drugs distributed to pharmacies and to wholesalers, which in turn sell them to clinics and physician offices. Both actions are considered burdensome to elderly and low-income patients who must visit their doctor for each prescription. Experts say the effectiveness of these programs is questionable.

The Centers for Disease Control and Prevention points out that the use of potent painkillers has increased 300% since 1999, yet it is hard to imagine that the incidence of pain has increased threefold. Opioid-related deaths outnumber those from cocaine and heroin combined. In 2009, there were 475,000 visits to hospital emergency rooms associated with prescription painkillers, a number that doubled in just five years.

In 2010, 2 million people reported using prescription painkillers nonmedically for the first time, and more than 12 million said they used prescription painkillers for a high or without a prescription.

The federal blanket controls are not working — overuse and addiction are evolving in new ways and prevention efforts need to focus on a few key elements that are at the core of the problem.

“There is an incredible stockpile of prescription opioids in the medicine cabinets of American households,” says Mark Friedlander, MD, chief medical officer of Aetna’s behavioral health division, which is kicking off a new prevention education program targeting prescribers.

“In many cases, those prescriptions were written for dental or ambulatory surgical procedures,” says Friedlander. “Prescribers realize that prescription copayment is the same regardless of the quantity, so they order a month’s supply even when the pain should only last a week or so. Then patients often hold onto the leftover pills just in case they might be needed.”

Unused pills are a common path to narcotics abuse by teenagers and young adults,” says Mark Friedlander, MD, chief medical officer of Aetna’s behavioral health division.

Changing prescribing patterns and improving public awareness are obvious steps to address this problem.

“These unused pills are a common path to narcotics abuse by teenagers and young adults,” says Friedlander. According to the 2012 National Survey on Drug Use and Health, the 18-25-year-old age group had the highest rate of illicit drug dependence or abuse at 7.8%.

“These young adults haven’t developed a high rate of alcohol abuse, so illicit drug use generally comes from prescription narcotics,” he adds. “About 50% of all opioid-dependent individuals in this age group start with prescription narcotics.”

Driver of costs

“This age group has been a significant driver of our cost increases for chemical dependency treatment since the Affordable Care Act extended coverage to 18- to 26-year-olds who...
Robust quality control and a reliable supply are every bit as important as scientific innovation.

For more than 30 years, Amgen has poured commitment, passion, and a drive for perfection into every medicine we make.

So you can turn to Amgen for the biologic medicines that matter so much to your patients’ treatment...for generations to come.

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are on their parents’ plans,” says Friedlander. “In terms of dollars spent on behavioral health services, until recently about 90% of our facility costs were for traditional mental health services and about 10% was for chemical dependency; now the latter category has risen to more than 20% of our costs.”

While Aetna is seeing a dramatic increase in the demand for services by young adults, the CDC points out that the highest rate of prescription painkiller overdoses exists in middle-aged adults.

Aetna has recently stepped up its efforts — headed by Friedlander — to focus on prescriber and patient education about narcotics overuse. “There is an opportunity for primary prevention by educating prescribers about what to provide, and a similar opportunity to educate patients about the use and safekeeping of these drugs.”

Aetna’s new initiative is in its early stages. It will start with dentists, who are second only to primary care doctors in the volume of painkillers they prescribe. “It’s difficult for us to reach out to a patient and intervene at the early stages of a prescription,” says Friedlander. “We think there’s more opportunity for effectiveness in working with the prescribers and alerting them to the potential dangers of overprescribing narcotics.”

Dentists seem like a logical starting point because of the precise role painkillers play in dentistry. “We view a 30-day prescription written by a dentist as questionable because the pain from a dental procedure should commonly last only about a week,” says Friedlander.

Aetna has an additional overuse prevention program. “In our pharmacy division, we identify members who are receiving multiple narcotic prescriptions from multiple prescribers,” says Friedlander. “We found in many cases that doctors were not aware that their patients were receiving prescriptions from multiple sources. We reach out to the physicians to obtain their consent for one prescriber to become the only prescriber of narcotics.”

Doctor shoppers

Another group of patients, doctor shoppers seeking prescription narcotics, provides additional insight into focusing on prescribers in physician offices and clinics as a means to curtail narcotics overuse.

“Prescribers play a huge role in doctor shopping,” says Julie Worley, PhD, an assistant professor of nursing at Chicago’s Rush University and Rush Presbyterian Medical Center. “I don’t know if they grasp the reality that they are contributing to prescription drug abuse.”

Worley is also a psychiatric and family nurse practitioner formerly in private practice in psychiatry. She conducted a phenomenological study of 14 women who voluntarily identified themselves as doctor shoppers. The women, 19–50, came from a variety of educational and occupational backgrounds.

“Doctor shoppers are brazen in their efforts to get drugs,” she says. “I had one person tell me she would just call up dentists’ offices and ask if they prescribed oxycodone, and many practices were willing to answer that question over the phone. That is obvious doctor shopping, and those calls should be red flags to practices.”

Doctor shoppers are deceptive and manipulative, and prescribers are not very astute in detecting lying, says Worley. She points to a meta-analysis of 206 studies of the deception judgment skills of practitioners that concluded that the lie-truth discrimination rate was only 54% accurate, slightly better than flipping a coin.

Prescribers can take a number of steps to prevent doctor shopping and to identify patients who may be addicted or become addicted. Worley is a fan of state-run prescription drug monitoring programs, which are easy to access by practices using electronic health records. However, she admits, there is resistance to these programs by practitioners, and patients can defeat them by using different names.

Addiction to multiple drugs is common, she says, and medication histories can be a way to identify this problem. “Benzodiazepines played a big role in addiction,” Worley points out. “People think prescription drug abuse is primarily an opiate problem, but it also involves the benzodiazepines and the stimulants such as Adderall to a lesser degree.”

The CDC says that about half of prescription painkiller deaths involve at least one other drug — including, for example, benzodiazepines, cocaine, and heroin.

“I don’t think many psychiatrists are aware that people for whom they are prescribing benzos may also be abusing opiates,” she says.
ICU Stays Greatly Reduced By Use of Telemedicine

Telemedicine works in intensive care units (ICUs), no matter the size of the hospital or the region where it’s located, according to a huge study of the technology’s effectiveness. The study, published in the journal *Chest*, tracked about 120,000 patients from May 2003 to December 2006 in 56 ICUs, 32 hospitals, and 19 health systems.

“The large size of the study and its finding that improvements in performance were not limited to a single type of ICU, size of hospital or community served, hospital teaching status, or U.S. region suggests that these findings are broadly, rather than narrowly, applicable,” the study states.

Telemedicine allows critical care teams — which may be hundreds of miles away — to alert ICUs the minute a patient takes a turn for the worse.

The study found that patients monitored by telemedicine were:
- 26% more likely to survive the ICU
- Discharged from the ICU 20% faster
- 16% more likely to survive hospitalization and be discharged
- Discharged from the hospital 15% faster

“The association of the ICU telemedicine interventions with lower hospital mortality is notable because prior studies have not had adequate power to provide unequivocal evidence of this association,” says the study, “A Multicenter Study of ICU Telemedicine Reengineering of Adult Critical Care.”

For patients who stayed seven or fewer days, stays in the ICU were reduced by 0.5–1.1 days, thanks to telemedicine. The technology reduced by 1–2.5 days the stay for patients who were in the ICU 14 or fewer days. For patients who stayed 30 or fewer days, the reduction was 3.6–4.5 days.

A day here and a day there and pretty soon you’re talking about real money: Critical care costs the nation from $80 billion to $100 billion a year. Improved outcomes were primarily attributable to earlier intensivist management, coordinated timely usage of performance information, achievement of higher rates of adherence to best practices, shorter alarm response times, more frequent interdisciplinary rounds, and a more effective ICU committee,” the study states.

Cancer Screening Not Meeting Targets

An anticancer program to increase screening and counseling fell short of some of its objectives, according to a study in the government journal *Preventing Chronic Disease*. The Healthy People (HP) program, launched by the Department of Health and Human Services in 1979, tracks 10-year objectives for improving health based on guidelines from the U.S. Preventive Services Task Force.

Using the National Health Interview Survey (NHIS), which tracks cancer care, the HP program’s current objectives are for 2020.

So far, we’re behind schedule.

“From 2008 to 2010, rates of breast and cervical cancer screening declined slightly while colorectal cancer screening increased by 7 percentage points,” says the study “Challenges in Meeting Healthy People 2020 Objectives for Cancer-Related Preventive Services, National Health Interview Survey, 2008 and 2010.”

The target for 2020 for cervical cancer screening is 93%. In 2008, 84.4% of women who should have been screened based on guidelines were screened. In 2010, the number was 82.9%.

The 2020 target for breast cancer screening is 81.1%. In 2008, 73.7% of women who should have been screened were screened. In 2010, the number was 72.4%.

Cancer counseling by providers also did not hit targets.

The 2020 HP goal for cervical cancer counseling is 66.2%. In 2008, 60.2% of women who should have had counseling received it. In 2010, the number slipped to 53.9%.

The 2020 HP goal for breast cancer counseling is 76.8%. In 2008, the number was 69.8%. In 2010, the number dropped to 59.5%.

Colorectal cancer screening did better, but still fell short of the 70.5% 2020 goal. In 2008, 52.1% of those who should have been screened for colorectal cancer were screened. In 2010, the number climbed to 59.1%.

Researchers allow that “the gaps we observed for some HP measures may reflect the adverse state of the U.S. economy during 2008 through 2010. However, neither Pap test nor mammography use increased during the past decade, suggesting that factors influencing cancer screening trends predate the most recent economic downturn and that meeting HP 2020 targets for cervical and breast cancer screening may be challenging.”

The study also focused on subgroups, finding that Hispanics and people below 200% of the federal poverty level were furthest off target.

It suggests that “attaining HP cancer-related targets by 2020 may be challenging in the absence of new approaches to expand health insurance coverage, improve access to cancer screening and treatment services, better integrate clinical and commu-
Alzheimer’s Deaths More Than Estimated

Alzheimer’s disease (AD) may be the third largest cause of death, behind heart disease and cancer.

More than 500,000 die of AD each year, according to the study “Contribution of Alzheimer Disease to Mortality in the United States.” That’s much higher than the 84,000 estimate by the Centers for Disease Control and Prevention (CDC), which lists dementia as the sixth-largest cause.

“Overall, the data indicate that the proportion of older persons who die of AD is much higher than the number indicated by death certificates, which is less than 5% of all deaths in the elderly,” says the study, published March 12 in the journal Neurology.

Researchers, following about 2,600 people ages 65 and over for an average of eight years, believe that the under-reporting starts with how those death certificates are filled out. Dementia progresses over years, causing complications such as malnutrition that can lead to pneumonia.

“These more proximate causes are listed on the death certificate as immediate cause of death, while dementia is often omitted as an underlying cause,” the study states. “Attempting to identify a single cause of death may not capture the reality of the process of dying for most elderly people because multiple factors may contribute to death in the elderly, some proximate and some distal.”

It may be time for the medical profession to embrace the concept of mixed mortality.

“This more nuanced view of ‘cause of death’ is needed for an accurate understanding of the contribution of chronic diseases such as AD to death in rapidly aging populations.”

The data do not include deaths attributed to mild cognitive problems caused by AD “so we likely underestimated the true number of deaths attributable to AD; prior work has found that mild cognitive impairment is associated with mortality.”

However, “even if our estimates of hazard of death were off by a factor of two, this figure would be approximately 200,000, which is still substantially higher than the figure from the CDC.”

Insulin Misusers Flood Hospital EDs

It’s not exactly a matter of the cure being worse than the disease, but recent findings about diabetes and emergency department (ED) visits should at least give policymakers and clinicians pause.

The findings also ask: Just how should patients with diabetes who are 80 and over be managed?

Nearly 100,000 people wound up in the ED over five years because of mistakes made in diabetes treatment, most of it self-treatment, according to researchers at the Centers for Medicare and Medicaid Services.

It’s not perfect. But it’s a start.

Only a small number of births occur outside the hospital, but the number has been rising lately, according to the National Center for Health Statistics (http://tinyurl.com/CDC-birth-data). “If this increase continues, it has the potential to affect patterns of facility usage, clinician training, and resource allocation, as well as health care costs,” says the study.

Out-of-hospital births for non-Hispanic white women are two to four times as prevalent as for any other racial or ethnic group. Again, we’re talking about a relatively small number: 35,184 babies were born at home in 2012, which was 0.89% of all births that year.

The American Congress of Obstetricians and Gynecologists and the American Academy of Pediatrics say that giving birth in a hospital or birthing center is the safest option.

However, women at higher risk of having problem deliveries — such as teen mothers, and women 35 or over — tend to go to the hospital. This perhaps suggests that physicians and other providers do a good job of outlining the risks to those patients considering having their babies at home, says the study.

Risk profile for out-of-hospital births, 2004 and 2012

Of all out-of-hospital births, the percentage in each of five risk categories

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>2004</th>
<th>2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under age 20</td>
<td>4.3</td>
<td>3.5</td>
</tr>
<tr>
<td>35 and over</td>
<td>1.9</td>
<td>1.3</td>
</tr>
<tr>
<td>Preterm</td>
<td>6.7</td>
<td>5.4</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>3.2</td>
<td>3.0</td>
</tr>
<tr>
<td>Multiple birth</td>
<td>0.9</td>
<td>0.8</td>
</tr>
</tbody>
</table>

for Disease Control and Prevention. Those visits may have cost “well over” $600 million.

As the name suggests, the study in JAMA Internal Medicine, “National Estimates of Insulin-Related Hypoglycemia and Errors Leading to Emergency Department Visits and Hospitalizations,” looks at insulin-related hypoglycemia and errors (IHEs). The study took place from January 2007 through December 2011.

Patients ages 80 or older were more than twice as likely to head to the ED for IHEs as those 65 to 79, according to the study.

“Patients in the oldest group were also almost five times as likely to be hospitalized for IHEs as those 45 to 64 years,” the study states.

There were about 30,000 IHE-related hospitalizations in the five years.

Researchers point out that guidelines from such organizations as the American Geriatrics Society say that medications shouldn’t be used to achieve hemoglobin HbA1c control in most adults ages 65 or older.

The study states that “the high frequency and severity of ED visits for IHEs suggest careful consideration of hypoglycemic sequelae and a cautious approach when deciding whether to start or intensify insulin treatment among older adults, especially the very elderly.”

Of course, diabetes has everything to do with eating.

“Although meal planning is a well-recognized component of diabetes self-management education, the most commonly documented IHE precipitant in this study was meal-related misadventure, suggesting that further emphasis on meal planning in diabetes patient education efforts may be needed.”

The problem might very well be worse than the study suggests because “hypoglycemia, although a frequent cause of emergency medical service calls, is most often cared for outside the ED. Patients who have hypoglycemia unawareness and whose episodes do not result in EMS or ED care are not counted, nor are those who died en route or in the ED.”

**Push on for generic version of Copaxone**

In a few weeks, a generic version of the Copaxone multiple sclerosis treatment may become available and Teva Pharmaceutical is aggressively waging a battle to win over patients, physicians, and payers with a new version of its most important product. A new survey indicates the drugmaker may be succeeding.

Teva hopes to switch MS sufferers from its once-daily injectable, which carries a $60,500 price tag, to a new three-times-weekly version for just $1,000 less than the older Copaxone. A large-scale switch is crucial for Teva since the drug generates $4.3 billion in annual sales and half of its profits.

To make that happen, Teva is emailing people who registered for its patient support program, not just knocking on physician doors. The key selling point, however, is convenience, since Teva did not present any evidence to the FDA to prove its long-lasting Copaxone is better than its older version. Instead, studies only compared the new treatment to a placebo.

The lack of comparative clinical data has been seen as a hurdle, since a generic version is expected to cost less and, therefore, appeal to payers as well as physicians who are cost-conscious enough to consider patient finances. Nonetheless, a recent survey suggests that Teva may, in fact, be persuading physicians to switch.

About 25% of physicians queried expect to switch their current Copaxone patients to the three-times weekly version by June and about one-third of existing Copaxone patients should be switched by the end of this year. In two years, 40% are expected to be using the newest version of the medicine, a proportion that is in line with Teva estimates.

Why would physicians endorse a switch? Nearly half of those queried cited the convenience associated with the three-times weekly version as a key reason, according to the survey, which was conducted by Leerink Swann, a Wall Street brokerage. More specifically, about 30% of Copaxone high prescribers cited concerns over bioequivalence as a reason for not putting their patients on a generic.

Just the same, Leerink analysts forecast the market for generic Copaxone to reach a hefty $300 million to $400 million. And of course, there are already pricey alternatives in the form of pills, such as Gilenya and Tecfidera. For the moment, though, payers must decide whether to force patients off a three-times-weekly version of Copaxone in favor of a lower-cost generic. That might not be easy.

— Ed Silverman

**Briefly Noted**

**Infectious diseases are, unfortunately, making a comeback, and pharmaceutical manufacturers hope to address the problem. There are 394 drugs in the pipeline to fight these diseases, according to the Pharmaceutical Research and Manufacturers of America (http://tinyurl.com/infect-disease). In development are 226 drugs for viral infections, 124 for bacterial infections, 24 for fungal infections, and 15 for parasitic infections...**

Nearly 3 of 5 patients at risk of losing their eyesight as a result of diabetes do not recall being alerted by their physicians to the danger, according to a study in *JAMA Ophthalmology* (http://tinyurl.com/opth-study). The problem can be easily treated, say researchers, but doctors can’t treat what they don’t know exists, and the best early warning system is patient feedback. **Patients may obtain their test results directly from the labora-
The idea that engaged patients will have better outcomes is challenged in a study in the British Medical Journal for Quality and Safety (http://tinyurl.com/engaged-patients). One of the problems is defining just what patient engagement means. “Definitions of patient and family engagement were lacking, as well as evidence regarding the types of patients who might feel comfortable engaging with providers, and in what contexts,” the study says. Mental health patients are 4 to 16 times more likely to have HIV than the general population, according to a study in the American Journal of Public Health (http://tinyurl.com/Phil-Balt-study) that tracks about 1,000 patients who sought mental health treatment in Philadelphia and Baltimore. Researchers say the findings illustrate the need for routine HIV testing in mental health facilities. Yet more doubt thrown on the benefits of vitamin C and E supplements. In some cases they actually reduce the benefits of exercise, according to a study in the Journal of Physiology (http://tinyurl.com/vit-study). The study looked at 54 men and women who were already in pretty good shape. Most were runners or cyclists. Half got a placebo; the other half got the vitamins. After an intense 11-week training program, both groups showed improvements but the one taking placebo had more energy and better health. There’s an epidemic in thyroid cancer — but it’s an epidemic in diagnosis, not disease, according to a study in JAMA Otolaryngology—Head & Neck Surgery (http://tinyurl.com/thyroid-study). Incidence of the disease tripled since the 1970s, but mortality rates remain the same. A less aggressive form of the disease is being found and treated.

— Frank Diamond

Employers remain bullish on wellness in the health reform era

There might be a debate over the effectiveness of wellness programs (http://tinyurl.com/A-Lewis-wellness), but it doesn’t seem to resonate with employers. In an era where most employees are gratified to get a raise of 5% or more, companies increased the average amount they spend on wellness programs per employee by 15% in 2014 from 2013, according to a survey of about 150 companies of various sizes and a wide range of industries. That comes out to an average of $594 per worker. It’s not just the big employers that have signed on. Companies with 5,000 or fewer employees saw the largest increase; the average spent per employee on wellness climbed to $595, compared with $444 in 2013. In the health reform era, where so much seems in flux, many employers plan to keep with wellness through whatever might come; 93% plan to either expand or maintain their wellness programs. Meanwhile, 44% say that they’ll maintain or increase their wellness programs even if they move away from direct involvement in employer-sponsored health care.

### Mean employee incentive by year

<table>
<thead>
<tr>
<th>Year</th>
<th>Incentive</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>$430</td>
</tr>
<tr>
<td>2012</td>
<td>$460</td>
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<tr>
<td>2013</td>
<td>$521</td>
</tr>
<tr>
<td>2014</td>
<td>$594</td>
</tr>
</tbody>
</table>

### Mean 2014 employee incentive by company size

<table>
<thead>
<tr>
<th>Size</th>
<th>Incentive</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤5,000</td>
<td>$595</td>
</tr>
<tr>
<td>5,000–20,000</td>
<td>$493</td>
</tr>
<tr>
<td>20,000+</td>
<td>$717</td>
</tr>
</tbody>
</table>

### Long-term strategy of incentive programs (3 to 5 years)

- Remove 3%
- Expand further 57%
- Maintain the same 36%
- Reduced 5%
- Same 29%
- Increased 15%
- Don’t know 48%
- No longer invest 3%

Source: “Employer Investments in Improving Health,” the National Business Group on Health and Fidelity Investments, February 2014
INVOKANA™ (canagliflozin) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. INVOKANA™ is not recommended in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- History of a serious hypersensitivity reaction to INVOKANA™.
- Severe renal impairment (eGFR <30 mL/min/1.73 m²), end stage renal disease, or patients on dialysis.

Please see additional Important Safety Information and brief summary of full Prescribing Information on the following pages.

ENVISION NEW POSSIBILITIES

INVOKANA™ is the #1 branded therapy prescribed by endocrinologists when adding or switching non-insulin type 2 diabetes medications*

*Data on file. Based on NBRx data sourced from IMS NPA Market Dynamics Database, weekly data through 9/26/13.

INVOKANA™ canagliflozin tablets

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INVOKANA™ canagliflozin tablets

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Please see additional Important Safety Information and brief summary of full Prescribing Information on the following pages.
**INVOKANA™ 300 mg demonstrated greater reductions in A1C vs sitagliptin 100 mg at 52 weeks...**

**Adjusted Mean Change in A1C From Baseline (%): INVOKANA™ 300 mg vs Sitagliptin 100 mg, Each in Combination With Metformin + a Sulfonylurea**

<table>
<thead>
<tr>
<th>Dose</th>
<th>Mean Baseline A1C</th>
<th>Mean Change</th>
<th>Difference from Sitagliptin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitagliptin 100 mg + metformin and a sulfonylurea</td>
<td>8.3%</td>
<td>-0.46</td>
<td>0.27*</td>
</tr>
<tr>
<td>INVOKANA™ 300 mg + metformin and a sulfonylurea</td>
<td>8.3%</td>
<td>-0.69</td>
<td>-0.37*</td>
</tr>
</tbody>
</table>

**INVOKE ANA™ (canagliflozin) 300 mg:**

**Incidence of Hypoglycemia**

Insulin and insulin secretagogues are known to cause hypoglycemia when combined with insulin or an insulin secretagogue. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when combined with INVOKANA™.

**Insulin and insulin secretagogues**

Avoid using insulin or insulin secretagogues in combination with INVOKANA™. For patients already taking insulin or an insulin secretagogue, lower doses of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when combined with INVOKANA™.

**Diabetes Mellitus**:)

Diabetes mellitus is a metabolic disorder that interferes with the normal metabolism of glucose, resulting in hyperglycemia. Hyperglycemia can lead to a number of complications, including heart disease, kidney disease, and nerve damage. Patients with diabetes mellitus may benefit from treatment with INVOKANA™, as it has been shown to reduce A1C levels in diabetic patients.

**Important Information About Hypoglycemia**:)

Hypoglycemia can be caused by insulin or drugs that lower blood sugar. Patients with diabetes should be aware of the signs and symptoms of hypoglycemia, as well as the appropriate treatment.

**Hyperkalemia**:)

Hyperkalemia is a condition in which the potassium level in the blood is too high. Patients taking INVOKANA™ should be monitored for signs of hyperkalemia, as too high levels of potassium can be dangerous.

**Covered for >75% of commercially insured patients without prior authorization**:)

INVOKANA™ provides SGLT2 inhibition, reducing renal glucose reabsorption and increasing urinary glucose excretion.

**Adverse Reactions**:)

In 4 pooled placebo-controlled trials, the most common adverse reactions were female genital mycotic infections, urinary tract infection, and increased urination.

**References**:)


**Data on file (SGLT2 = sodium glucose co-transporter 2)**

**Learn more at INVOKANAhcp.com/journal**
### IMPORTANT SAFETY INFORMATION (cont’d)

**WARNINGS AND PRECAUTIONS**

- **Hypoglycemia:** INVOKANA™ can cause intravascular volume contraction. Symptomatic hypokalemia can occur after initiating INVOKANA™, particularly in patients with impaired renal function (eGFR 60 mL/min/1.73 m²), elderly patients, and patients on other drugs or medications that interfere with the renin-angiotensin-aldosterone system (eg, angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], or patients with low systolic blood pressure). Before initiating INVOKANA™, patients with one or more of these characteristics, volume status should be assessed and corrected; monitor for signs and symptoms after initiating therapy.

- **Impairment in Renal Function:** INVOKANA™ increases serum creatinine and decreases eGFR. Patients with hypertension may be more susceptible to these changes. Renal function abnormalities can occur after initiating INVOKANA™. More frequent renal function monitoring is recommended in patients with an eGFR below 60 mL/min/1.73 m².

- **Hyperkalemia:** INVOKANA™ can lead to hyperkalemia. Patients with moderate renal impairment who are taking medications that interfere with potassium excretion, such as potassium-sparing diuretics, or medications that interfere with the renin-angiotensin-aldosterone system are more likely to develop hyperkalemia. Monitor serum potassium levels periodically after initiating INVOKANA™ in patients with impaired renal function and in patients predisposed to hyperkalemia due to medications or other medical conditions.

### Contraindications

- **Specific Contraindications:** INVOKANA™ is contraindicated in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m²), severe hepatic impairment, and patients with type 1 diabetes mellitus.

### Drug Interactions

- **Drug Interactions:** INVOKANA™ can increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with INVOKANA™. Insulin and insulin secretagogues are known to cause hypoglycemia when combined with insulin or an insulin secretagogue.

### General Information

- **Hypersensitivity Reactions:** Hypersensitivity reactions (eg, generalized urticaria), some serious, were reported with INVOKANA™ treatment; these reactions generally occurred within hours to days after initiating INVOKANA™. If hypersensitivity reactions occur, discontinue use of INVOKANA™; treat per standard of care and monitor until signs and symptoms resolve.

- **Mycotic Infections:** Genital mycotic infections and uncircumcised males were more likely to develop genital mycotic infections. Monitor and treat per standard of care after initiating INVOKANA™.

### Adverse Reactions

- **In 4 pooled placebo-controlled trials, the most common (≥5%) adverse reactions were female genital mycotic infection, urinary tract infection, and increased urination.**

### References

3. SGLT2 = sodium glucose co-transporter-2.

### Learn more at

[INVOKANAhcp.com/journal](http://INVOKANAhcp.com/journal)
The use of INVOKANA® has not been studied in patients with severe hepatic impairment and it is therefore not recommended.

OVERDOSE
There were no reports of overdose during the clinical development program of INVOKANA® (canagliflozin).

In the event of an overdose, contact the Poison Control Center. It is also reasonable to employ the usual supportive measures, eg, remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment as dictated by the patient's clinical status. Canagliflozin was negligibly removed during a 4-hour hemodialysis session. Canagliflozin is not expected to be dialyzable by peritoneal dialysis.

ADVERSE REACTIONS
The most common (25%) adverse reactions were female genital mycotic infections, urinary tract infections, and increased urination.

Adverse reactions in 22% of patients were male genital mycotic infections, vulvovaginal pruritus, thirst, nausea, and constipation.

Please see brief summary of full Prescribing Information on the following pages.

INVOKANA™ (canagliflozin) tablets, for oral use

INDICATIONS AND USAGE
INVOKANA™ (canagliflozin) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (see Clinical Studies (14) in full Prescribing Information).

Important Safety Information

Hypoglycemia
- Patients taking INVOKANA™ are at risk of developing hypoglycemia, particularly with the use of insulin or insulin secretagogues, because of increased insulin sensitivity and decreased hepatic glucose production. The risk of hypoglycemia when combined with insulin or insulin secretagogues may be required to minimize the risk of hypoglycemia when used in combination with INVOKANA. Patients taking INVOKANA™ with insulin or insulin secretagogues may require a reduction in insulin or insulin secretagogue dose.

Central Myotic Infections
- INVOKANA increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections and/or patients unresponsive to standard of care therapy may require increased monitoring.

Hypersensitivity reactions (e.g., generalized rash, pruritus)
- Patients who develop a rash with INVOKANA should stop use and contact their healthcare provider.

Clinical Laboratory Measures
- Increases in Low-density Lipoprotein (LDL-c): Monitor LDL-C and treat per standard of care after initiating INVOKANA.

Hyperkalemia
- Canagliflozin is not expected to be dialyzable by peritoneal dialysis. Canagliflozin is not expected to be dialyzable by peritoneal dialysis.

Nursing Mothers
- Canagliflozin is not expected to be dialyzable by peritoneal dialysis.

- There is an increase in the area AUC and mean peak drug concentration (Cmax) of digoxin (20% and 36%, respectively) when co-administered with INVOKANA™ 300 mg.

- Digoxin: It is not known if INVOKANA™ is excreted in human milk. INVOKANA™ is secreted in the milk of lactating rats, reaching levels 1.4 times higher than that in maternal plasma. Data in juvenile rats directly from a 300-mg dose.

- Nursing Mothers: It is not known if INVOKANA™ is excreted in human milk. INVOKANA™ is secreted in the milk of lactating rats, reaching levels 1.4 times higher than that in maternal plasma. Data in juvenile rats directly from a 300-mg dose.

- Nursin...
**DRUG INTERACTIONS**

**Enzyme Inducers:** Rifampin: Co-administration of canagliflozin with rifampin, a nonselective inducer of several UGT enzymes, including UGT1A1, UGT2B7, decreased canagliflozin area under the curve (AUC) by 31%. This decrease in exposure to canagliflozin may decrease efficacy if an inducer of these UGTs (e.g., rifampin, phenytoin, phenobarbital, nitisimid) must be co-administered with INVOKANA™ (canagliflozin), consider increasing the dose to 300 mg once daily if patients are currently tolerating INVOKANA™ 100 mg once daily, have an eGFR greater than 60 mL/min/1.73 m², and require additional glycemic control. Consider other anti-hyperglycemic therapy in patients with an eGFR of 45 to less than 60 mL/min/1.73 m² receiving concurrent therapy with a UC inhibitor and requiring additional glycemic control.

**Digoxin:** There was an increase in the area AUC and mean peak drug concentration (C_{max}) (20% and 36%, respectively) when co-administered with INVOKANA™ 300 mg. Patients taking INVOKANA™ with concomitant digoxin should be monitored appropriately.

**IN USE IN SPECIFIC POPULATIONS**

**Pregnancy Category C:** There are no adequate and well-controlled studies of INVOKANA™ in pregnant women. Based on results from rat studies, canagliflozin may affect fetal development and maturation. In a juvenile rat study, increased kidney weights, renal pelvis and tubular dilatation were evident at 20.5 times clinical exposure from a 300 mg dose. These outcomes occurred with drug exposure during the second and third trimester of human development. During pregnancy, consider appropriate alternative therapies, especially during the second-and third trimester. INVOKANA™ should be used during pregnancy only if the benefit to the mother justifies the potential risk to the fetus.

**Nursing Mothers:** It is not known if INVOKANA™ is excreted in human milk. INVOKANA™ is secreted in the milk of lactating rats, reaching levels 1.4 times higher than in maternal plasma. Data in juvenile rat study directly exposed to INVOKANA™ showed risk to the developing kidney (renal pelvis and tubular dilatation) during maturation. Since human kidney maturation occurs in utero and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from INVOKANA™, a decision should be made whether to discontinue nursing or to discontinue INVOKANA™, taking into account the importance of the drug to the mother.

**Pediatric Use:** Safety and effectiveness of INVOKANA™ in pediatric patients under 18 years of age have not been established.

**Geriatric Use:** Two thousand thirty-four (2034) patients 65 years and older, and 345 patients 75 years and older were exposed to INVOKANA™ in new clinical studies of INVOKANA™. Patients 65 years and older had a higher incidence of adverse reactions related to reduced intravascular volume with INVOKANA™ (such as hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration), particularly with the 300-mg daily dose, compared to younger patients; more prominent increase in the incidence was seen in patients who were 75 years of age. Smaller reductions in SBP with INVOKANA™ relative to placebo were seen in older (65 years and older, -0.6% with INVOKANA™ 100 mg and -0.76% with INVOKANA™ 300 mg relative to placebo) compared to younger patients (0.72% with INVOKANA™ 100 mg and -0.81% with INVOKANA™ 300 mg relative to placebo).

**Renal Impairment:** The efficacy and safety of INVOKANA™ have not been established in patients with moderate renal impairment (eGFR 30 to < 60 mL/min/1.73 m²). These patients had less overall glycemic efficacy with a 300-mg daily dose, compared to younger patients; more prominent increase in the incidence was seen in patients who were 75 years of age. Smaller reductions in SBP with INVOKANA™ relative to placebo were seen in older (65 years and older, -0.6% with INVOKANA™ 100 mg and -0.76% with INVOKANA™ 300 mg relative to placebo) compared to younger patients (0.72% with INVOKANA™ 100 mg and -0.81% with INVOKANA™ 300 mg relative to placebo).

**Hepatic Impairment:** No dosage adjustment is necessary in patients with mild or moderate hepatic impairment. The use of INVOKANA™ has not been studied in patients with severe hepatic impairment and it is therefore not recommended.

**OVERDOSAGE**

There were no reports of overdose during the clinical development program of INVOKANA™ (canagliflozin). In the event of an overdose, contact the Poison Control Center. It is also reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment as dictated by the patient’s clinical status. Canagliflozin was negligibly removed during a 4-hour hemodialysis session. Canagliflozin is not expected to be dialyzable by peritoneal dialysis.

**ADVERSE REACTIONS**

**The most common (25%) adverse reactions were female genital mycotic infections, urinary tract infections, and increased urination.** Adverse reactions in ≥2% of patients were male genital mycotic infections, vulvovaginal pruritus, thirst, nausea, and constipation. Please see brief summary of full Prescribing Information on the following page.
In the pool of eight clinical trials with a longer mean duration of exposure to INVOKANA™, the following adverse reactions were reported: Thirst, Dry mouth, and Female genital mycotic infections. Baseline renal function was normal or mildly impaired in most patients. The mean duration of exposure to INVOKANA was 38 weeks, with a 1.8% increase in serious adverse events compared to placebo. Abdominal pain was more commonly reported in patients taking INVOKANA 100 mg (1.8%) than in those taking placebo (0.8%).

In the pool of four placebo-controlled trials where patients had normal or mildly impaired renal function, the incidence of volume depletion-related adverse reactions was calculated with the number of female subjects in each group as 1.5%, 2.2%, 2.3%, and 1.5%, respectively. InvoKana 100 mg (N=404).

The four placebo-controlled trials included one monotherapy trial and three combination trials with sulfonylurea, metformin, and/or pioglitazone. At the end of treatment, 4.6% with placebo, 3.4% with INVOKANA 100 mg, and 1.6% with INVOKANA 300 mg experienced a seizure. One patient with urticaria had an allergic reaction, and 2 patients discontinued INVOKANA. In a trial carried out in patients with moderate renal impairment with a mean baseline GFR (eGFR) of 30 mL/min/1.73 m2, the mean change in serum phosphate levels were 3.6% and 5.1% with INVOKANA 100 mg and INVOKANA 300 mg, respectively. In patients with moderate renal impairment at baseline, the changes in phosphate were moderate.

The use of loop diuretic was more common in the INVOKANA group (8.8%) than in the placebo group (3.2%). Table 4 shows the incidence of hypoglycemia in controlled clinical studies. In the placebo group, the overall incidence of hypoglycemia was 36.8%, while in the INVOKANA group, it was 49.3% with 1.8% and 2.5% severe hypoglycemia, respectively. The table also includes data for Placebo + sulfonylurea, Placebo + Metformin + sulfonylurea, and Placebo + Pioglitazone + sulfonylurea.
Thirst includes the following adverse reactions: Thirst, Dry mouth, and
infections (e.g., candidal balanitis, balanoposthitis) occurred in 0.6%, 4.2%,
and 4.8% of males treated with placebo, INVOKANA 100 mg, and INVOKANA
300 mg, respectively. Male genital mycotic infections occurred more
commonly in children than in adults. Table 1 presents a list of infections
on INVOKANA were more likely to experience recurrent male genital
mycotic infections. Treatment of male genital mycotic infections and
related adverse reactions (e.g., increased blood creatinine, decreased
phosphate levels increased by 1.2%, 5.0%, and 9.3% with placebo,
INVOKANA 100 mg, and INVOKANA 300 mg, respectively, compared to
placebo). In the pool of four placebo-controlled trials, the mean change in
serum phosphate levels were 3.6% and 5.1% with INVOKANA 100 mg and
INVOKANA 300 mg, respectively. In patients with mild renal
impairment, increases in phosphate were more common with a pooled
analysis of trials involving patients with moderate renal impairment (eGFR
30-45 mL/min/1.73 m2), moderate renal impairment (eGFR 46-59 mL/min/
1.73 m2), and patients with moderate renal impairment and baseline
systolic blood pressure (SBP) >130 mmHg. Changes in serum phosphate
levels were observed with INVOKANA. In the pool of four placebo-controlled
trials, mean serum phosphate levels increased by 3.7% with INVOKANA
100 mg, 5.4% with INVOKANA 300 mg, and 7.3% with Valsartan 320 mg.
In the pooled analysis of patients with moderate renal impairment, the
mean change in serum phosphate levels was -0.2% with placebo, 0.6% with
INVOKANA 100 mg, and 1.8% with INVOKANA 300 mg. However, in the
analysis of patients with severe renal impairment (eGFR <30 mL/min/
1.73 m2), the mean change in serum phosphate levels was 2.6% with
INVOKANA 100 mg and 3.5% with INVOKANA 300 mg. In patients with
mild renal impairment, changes in serum phosphate levels were
associated with an increased risk of hypoglycemic events in the intent-to-treat
population.

The mean change in serum creatinine and eGFR (percent changes) from baseline in hemoglobin were -0.18 g/dL and -0.22 mL/min/1.73 m2, respectively, in patients with mild renal impairment. The mean change in serum creatinine and eGFR (percent changes) from baseline in hemoglobin were -0.18 g/dL and -0.22 mL/min/1.73 m2, respectively, in patients with mild renal impairment.

### Table 5: Incidence of Hypoglycemia in Controlled Clinical Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Hypoglycemia Incidence</th>
</tr>
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### Table 5: Incidence of Hypoglycemia in Controlled Clinical Studies

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In the event of an overdose, contact the Poison Control Center. It is also reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment as dictated by the patient's clinical status. Canagliflozin was negligibly removed during a 4-hour hemodialysis session. Canagliflozin is not expected to be dialyzable by peritoneal dialysis.

Parent Counseling Information

See FDA-Approved Patient Labeling (Medication Guide).

Inform patients to read the Medication Guide before starting INVOKANA™ (canagliflozin) therapy and to reread it each time the prescription is renewed.

Inform patients of the potential risks and benefits of INVOKANA and of alternative modes of therapy. Also inform patients about the importance of adherence to dietary instructions, regular physical activity, periodic blood glucose monitoring and HbA1C testing, recognition and management of hypoglycemia and hyperglycemia, and assessment for diabetes complications. Advise patients to seek medical advice promptly during periods of stress such as fever, trauma, infection, or surgery, as medication requirements may change.

Inform patients to take INVOKANA only as prescribed. If a dose is missed, advise patients to take it as soon as it is remembered unless it is almost time for the next dose, in which case patients should skip the missed dose and take the medicine at the next regularly scheduled time. Advise patients not to take two doses of INVOKANA at the same time.

Inform patients that the most common adverse reactions associated with INVOKANA are genital mycotic infection, urinary tract infection, and increased urination.

Inform female patients of child-bearing age that the use of INVOKANA during pregnancy has not been studied in humans, and that INVOKANA should only be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Instruct patients to report pregnancies to their physicians as soon as possible.

Inform nursing mothers to discontinue INVOKANA or nursing, taking into account the importance of the drug to the mother.

Laboratory Tests: Due to its mechanism of action, patients taking INVOKANA may test positive for glucose in their urine.

Hypoglycemia: Inform patients that symptomatic hypoglycemia may occur with INVOKANA and advise them to contact their doctor if they experience such symptoms [see Warnings and Precautions]. Inform patients that dehydration may increase the risk for hypoglycemia, and to have adequate fluid intake.

Genital Mycotic Infections in Males (e.g., Balanitis or Balanoposthitis): Inform female patients that vaginal yeast infection may occur and provide them with information on the signs and symptoms of vaginal yeast infection. Advise them of treatment options and when to seek medical advice [see Warnings and Precautions].

Genital Mycotic Infections in Females (e.g., Vulvovaginitis): Inform female patients of the potential for vulvovaginitis (vaginal discharge and itch) to occur, and instruct them of treatment options and when to seek medical advice [see Warnings and Precautions].

Urinary Tract Infections: Inform patients of the potential for urinary tract infections[see Warnings and Precautions]. Provide them with information on the signs and symptoms of urinary tract infections. Advise them to seek medical advice if such symptoms occur.

Active ingredient made in Belgium. Finished product manufactured by: Janssen Ortho, LLC Titusville, NJ 08560
Janssen Pharmaceuticals, Inc. Gurabo, PR 00778
Janssen Pharmaceuticals, Inc. 10282400
Janssen Pharmaceuticals, Inc. Tokyo, Japan 158
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NOTICE TO HEALTH CARE PROVIDERS: INVOKANA™ (canagliflozin) tablets have not been studied in patients with severe hepatic impairment and is therefore not recommended [see Clinical Pharmacology (12.3) in full Prescribing Information].

Use of INVOKANA has not been studied in patients with severe hepatic impairment and is therefore not recommended [see Clinical Pharmacology (12.3) in full Prescribing Information].

The efficacy and safety of INVOKANA have not been established in patients with an eGFR of 45 to less than 60 mL/min/1.73 m2, and require additional glycemic control. Consider other antihyperglycemic therapy in patients with an eGFR of 45 to less than 60 mL/min/1.73 m2 receiving concurrent therapy with a UST inhibitor and require additional glycemic control [see Dosage and Administration (2.3) and Clinical Pharmacology (12.3) in full Prescribing Information].

Safety and effectiveness of INVOKANA in pediatric patients have not been established.

Pediatric Use:

The efficacy and safety of INVOKANA have not been established in patients under 18 years of age [see Nonclinical Toxicology (13.2) in full Prescribing Information, Dosage and Administration (2.2) in full Prescribing Information, and Clinical Pharmacology (12.3) in full Prescribing Information].

These outcomes occurred with drug exposure during periods of animal development that correspond to the late second and third trimester of human development. Due to postnatal growth and development (e.g., tubular dilatations) during maturation. Since human kidney maturation occurs in utero and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney. Because many drugs are not excreted in human milk and because of the potential for serious adverse reactions in nursing infants from INVOKANA, a decision should be made as to whether to discontinue or to discontinue nursing or to discontinue INVOKANA, taking into account the importance of the drug to the mother [see Nonclinical Toxicology (13.2) in full Prescribing Information].

Nursing Mothers:

It is not known if INVOKANA is excreted in human milk. INVOKANA is secreted in the milk of lactating rats reaching levels 1.4 times higher than that in maternal plasma. Data in juvenile rats directly exposed to INVOKANA showed risk to the developing kidney (renal pelvic and tubular dilatation) during maturation. Since human kidney maturation occurs in utero and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney. Because many drugs are not excreted in human milk and because of the potential for serious adverse reactions in nursing infants from INVOKANA, a decision should be made whether to discontinue or to discontinue nursing or to discontinue INVOKANA, taking into account the importance of the drug to the mother [see Nonclinical Toxicology (13.2) in full Prescribing Information].

Serious Adverse Reactions (e.g., nephropathy, renal failure, hyperkalemia) have been reported with INVOKANA. Patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m2) have unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment as dictated by the patient's clinical status. Canagliflozin was negligibly removed during a 4-hour hemodialysis session. Canagliflozin is not expected to be dialyzable by peritoneal dialysis.

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Blood pressure control still short of standards

Health plans accredited by the National Committee for Quality Assurance are twice as likely as nonaccredited plans to meet government standards for controlling blood pressure, according to the Morbidity and Mortality Weekly Report (http://tinyurl.com/blood-pressure-study), published by the Centers for Disease Control and Prevention. Controlled blood pressure is <140 mm Hg systolic and <90 mm Hg diastolic. About 67 million people in the United States have high blood pressure. An estimated 46,000 deaths could be avoided annually if 70% of patients with high blood pressure were treated, according to published guidelines.

In 2012, blood pressure was controlled in only 64% of members who were enrolled in HEDIS-reporting plans and who had diagnosed hypertension.*

While falling short of the 70% mark, it’s a slight improvement from 2010, and the change makes the MMWR authors think that the 70% goal might be achieved in the next few years. Modest improvements occurred in the 50th and 90th percentile plan-levels, the study says.

“The higher-performing plan categories are accredited commercial and Medicare Advantage HMOs, compared to the PPO population and Medicaid,” says Milesh M. Patel, MS, the lead author of the report.

Members with hypertension with controlled blood pressure by plan category, type, and year, according to HEDIS scores

* The population comprises plan members ages 18–85 who had one or more outpatient encounters in which a diagnosis of hypertension that was not pregnancy-related or complicated by end-stage renal disease was recorded during the first six months of the measurement period.

We have entered the post-antibiotics era. “There are patients for whom we have no antibiotic treatment options,” says Arjun Srinivasan, MD, associate director for the Healthcare Associated Infection Prevention Programs at the Centers for Disease Control and Prevention. “For those patients we see very high mortality rates. We know that roughly half of the patients who get the highly resistant bacterium carbapenem-resistant enterobacteriaceae in their bloodstream will die,” he adds. “So, it’s not hyperbole to say that some patients will die of these infections because we can’t treat them.”

For some patients with certain specific infections, there are no known therapies, he says, adding that five years ago, we could have treated patients with these infections. Today, antibiotic resistance has become one of the world’s most pressing public health threats, and treatment for patients with some infections is no longer possible.

In a report, “Antibiotic Resistance Threats in the United States, 2013,” the CDC said that at least 2 million people become infected each year with antibiotic-resistant bacteria, and at least 23,000 people die annually as a direct result of these infections, which increase hospitalizations and extend hospital stays, adding considerable and avoidable costs to the health care system.

Estimating the effects of antibiotic resistance on the U.S. economy is challenging, the CDC report said. The most recent estimate was done in 2009 and showed that excess direct health care costs could be as high as $20 billion and lost productivity costs could be as high as $35 billion. The CDC estimates come from “Hospital and Societal Costs of Antimicrobial-Resistant Infections in a Chicago Teaching Hospital: Implications for Antibiotic Stewardship,” a 2009 article by Roberts and colleagues published in Clinical Infectious Diseases.

Citing the same source, the Alliance for the Prudent Use of Antibiotics (www.APUA.org) at Tufts University said the cost in 2009 to treat one patient with an antibiotic-resistant infection was $18,588 to $29,069. The economic burden on the health care system from resistant infections was $20 billion annually.

One such infection in a hospital-
Many doctors "are unlikely to believe that denying an antibiotic to one patient will make a difference," says Janet Sullivan, MD, chief medical officer at Hudson Health Plan.

In its State of Health Care Quality 2013 report, the NCQA reported little or no progress on stemming the overuse of antibiotics, the main cause of antibiotic resistance. The NCQA’s Health-care Effectiveness Data and Information Set (HEDIS) measures the rate of avoidance of antibiotic treatment in adults with acute bronchitis. On this measure, plans’ HEDIS scores are strikingly and perpetually low.

In seven years, the rate has never exceeded 30% in HMOs or PPOs, the NCQA said. “Performance in 2012 was essentially flat, compared with the year before. Over five years, the only statistically significant changes have been performance declines.” Commercial HMOs’ average rate fell from 28.7% in 2006 to 24.6% in 2012. The commercial PPO rate fell from 29.3% to 21.4% in the same period (see “Avoidance of Antibiotic Treatment in Adults With Acute Bronchitis,” left).

Plans do better on the children’s version of this measure, Appropriate Treatment for Children With Upper Respiratory Infection, but performance there also has not improved, the NCQA added.

Physicians often feel that patients pressure them to prescribe antibiotics for viral infections, and yet the NCQA says physicians should not prescribe antibiotics except when indicated.

The New York State Health Department has a robust antibiotic monitoring system requiring health plans to report on efforts to avoid inappropriate antibiotic use in adults and children. The department published results in “2013 Health Plan Comparison in New York.”

Reporting on the performance of commercial health plans, the report shows the percentage of adults ages 18 to 64 who have acute bronchitis and who did not receive a prescription for antibiotics. A higher score indicates more appropriate treatment of patients with acute bronchitis.

The report compares scores for 11 commercial plans on avoidance of antibiotic therapy in adults with acute bronchitis to the statewide average of 23%. Of the 11 plans, 6 were significantly worse than the statewide average. Four were significantly better, and one was the same. Of 10 PPOs, 5 were significantly lower. Only two were significantly higher than the statewide average of 26%. In Medicaid, 6 of 17 plans were significantly below average. The performance of four was significantly better.

Doctors get ‘letters of shame’

In response to the efforts of the state Department of Health, Hudson Health Plan in Westchester County, New York, has been writing to physicians who do not follow guidelines for the proper use of antibiotics, says Janet Sullivan, MD, the chief medical officer. In this correspondence, which she calls “letters of shame,” the plan says it will pay physicians to counsel patients about the appropriate use of antibiotics because so many patients believe a prescription will help them get better regardless of whether their infection is bacterial or viral.

The plan sent similar letters to hospital emergency room directors when patients were given antibiotics after diagnoses of pharyngitis or tonsillitis but without a strep test.

At the same time, health plans do not want to restrict the appropriate use of antibiotics. “If we managed the use of antibiotics too closely, we could do more harm than good,” she says.

Sullivan believes sending letters after the fact may not have as strong an effect as a denial, but the alternative, requiring preapproval, would be counterproductive, she adds. "When patients really
Here’s how health plans can improve the use of antibiotics

By Scott A. Flanders, MD

Health plans have a significant role to play in managing antibiotic use. By that, I mean all health plans — those serving commercial populations and those serving Medicare and Medicaid members.

Beyond paying for care, health plans provide financial incentives to ensure that providers achieve certain goals, such as those associated with quality improvement, appropriate utilization, and cost containment. To date, health plans have not had much of a role in managing the use of antibiotics, but clearly we have reached the point where overuse has created a significant threat to patient safety. Therefore, it makes perfect sense that health plans would track antibiotic prescribing and provide financial incentives to ensure appropriate use.

Everyone involved in delivering and paying for care needs to be aware of the rates of infection for all organisms associated with antibiotic overuse. Hospitals need to track the incidence of infections potentially caused by antibiotics, such as *Clostridium difficile* — an organism that causes severe diarrhea and, in some cases, death. Having these data will allow plans to develop creative ways to provide financial incentives to reduce antibiotic overuse.

Many — but not all — hospitals have formal antibiotic stewardship programs. Every hospital should be asked to demonstrate that a stewardship team exists and that the team is reporting on resistance among organisms, tracking antibiotic use, and showing that the team is taking the appropriate steps to facilitate appropriate antibiotic use.

Scott A. Flanders, MD, is a professor of medicine at the University of Michigan and director of the hospital medicine program in the university’s Department of Medicine.

In the *Morbidity and Mortality Weekly Report* of March 7, researchers from the Centers for Disease Control and Prevention showed that hospitals often prescribe antibiotics incorrectly by failing to do the proper evaluation or follow-up. As my colleague, Sanjay Saint, MD, and I wrote in *JAMA Internal Medicine* on March 4, it is disheartening that after years of effort to educate physicians and hospital staff about the importance of appropriate use of antimicrobials, little progress has been made.

After reviewing data from its Emerging Infections Programs, CDC found opportunities to improve 37% of prescriptions for antibiotics by more timely use of diagnostic tests and better documentation of symptoms. These observations are similar to those of earlier studies showing that about 30% to 50% of antibiotic prescribing might be incorrect.

Fostering appropriate use of antibiotics is one step health plans can take, but there’s much more that can be done, starting with eliminating health care-associated infections in the first place. How many health plans require hospitals to establish infection-prevention strategies? We know that hand-hygiene programs are effective in stopping the spread of infections. But do health plans track how well hospitals enforce hand-hygiene rules?

We also know that the appropriate use of certain devices, such as catheters, can limit infections. Hospitals follow established procedures for minimizing infections from central-line associated bloodstream infections (CLABSI), for example, and the Centers for Medicare & Medicaid Services (CMS) tracks these numbers.

Here in Michigan, many hospitals have succeeded in reducing CLABSIs to near zero, in part by following checklists and implementing other best practices. It’s time for commercial health plans and CMS to do more to ensure that hospitals follow proven performance methods such as those adopted in Michigan and elsewhere.

Many hospitals are establishing efforts to reduce catheter-associated urinary tract infections (CAUTIs). By revising these efforts, hospitals could track the rate of physicians giving antibiotics to patients who are believed to have CAUTIs. Access to those data would allow health plans and hospital administrators to see prescription rates and prescribing patterns and identify physicians who need education on the use of antibiotics.

Physicians already recognize that a patient with a possible bacterial infection may or may not benefit from an antibiotic. As we noted in *JAMA IM*, physicians need to weigh the advantage of prescribing a potentially beneficial antibiotic against the potential harm to society.

At the point of care, this issue is not always easy to resolve. Doctors need antibiotics and they know that withholding them can cause great harm to patients. That’s why we need strategies not just to reduce the use of antibiotics but to ensure that we use the ones we have appropriately.
do need antibiotics, they need them right away,” she says.

Failing to understand that antibiotics are effective only against bacterial infections, some patients demand a prescription. One ER physician told Sullivan that visits with patients who demand antibiotics take three minutes if he prescribes an antimicrobial but 15 minutes if he refuses. Then, unhappy patients give physicians low satisfaction scores, potentially causing a decrease in payment or a missed chance for a bonus, Sullivan adds.

Compounding the problem, many physicians and patients view antibiotic resistance as a secondary concern. “If anything, patients view it as a future danger,” she says. “Even doctors who understand the risk of overuse are unlikely to believe denying an antibiotic to one patient will make a difference.”

**Pursuing the ‘ultimate’ ROI**

Physician scores are only part of the problem. Health plans could require hospitals and health systems to invest in more robust antimicrobial stewardship programs, which the CDC calls the ultimate return-on-investment strategy.

“Health plans can send a very clear message that there are certain processes that are associated with high quality medical care and that’s what they will pay for, such as preventing infections, more hand washing, and using antibiotics properly,” Srinivasan said.

“These are best practices, which health plans should pay for. Conversely, they should not pay for medical care processes that are not associated with delivering high-quality care.”

Health plans generally let hospitals manage their own antimicrobial stewardship programs, says Brian A. Potoski, PharmD, an associate professor in the Department of Pharmacy and Therapeutics at the University of Pittsburgh School of Pharmacy and the associate director of the Antibiotic Management Program at the University of Pittsburgh Medical Center.

“There’s a big push among health systems to develop stewardship programs and to get hospitals to talk to each other about these efforts, which are an important way to improve patients’ outcomes and control costs,” he says. “But the driver has been the hospitals, not managed care organizations.”

Antimicrobial stewardship programs are needed because physicians caring for hospitalized patients with infections often prescribe broad-spectrum antibiotics while waiting for laboratory tests to confirm the specific pathogen before a pharmacist can recommend an appropriate antimicrobial. Broad-spectrum antibiotics may be of little use when the pathogen is unknown.

Antibiotic stewardship programs help ensure that patients get the right antibiotics at the right time for the right duration, the CDC reports. By identifying appropriate therapies, these programs reduce lengths of stay and costs. For inpatients, stewardship programs in hospitals and health systems have consistently shown savings of $200,000 to $400,000 annually, the CDC says. A study done at the University of Maryland showed one antibiotic stewardship program saved $17 million over eight years.

**Cutting the time to treat**

At the University of Pittsburgh Medical Center, the microbiology laboratory has been testing a mass spectrometry analyzer that it plans to put online

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**Rapid detection of pathogens cut Methodist Hospital’s costs sharply**

In an article published in September in *Archives of Pathology*, researchers at Methodist Hospital in Houston, showed that using mass spectrometry combined with antimicrobial stewardship to identify Gram-negative bloodstream infections (BSIs) helped shorten length of hospital stays by 2.6 days.

In the article, “Integrating rapid pathogen identification and antimicrobial stewardship significantly decreases hospital costs,” the researchers reported that early diagnosis of Gram-negative BSIs, prompt identification of the infecting organism, and appropriate antibiotic therapy improved patient care outcomes and decreased health care costs.

The mean stay in a control group of 100 patients was 11.9 days versus 9.3 days in the intervention group of 101 patients. Mean hospital costs per patient were $45,709 in the control group and $26,162 in the intervention group, resulting in an average per-patient savings of $19,547 in the intervention group. The researchers estimated that if the intervention had been used for all patients with Gram-negative bloodstream infections, the savings would have been about $18 million annually, and if it were applied to all patients with bloodstream infections, the savings could reach $30 million a year.
soon. The technology requires only a few hours from the time a suspected bloodstream infection is drawn from a patient to when the pathogen is identified, Potoski says. Traditional testing can require at least 24 hours to grow an organism before it can be identified.

“This technology lets us identify the infection faster than the old biochemical way and therefore we can initiate antibiotics faster,” he says. “Because you are ahead of the game in identifying the infection, you are also ahead of the game in terms of choosing the proper antimicrobial. With this technology you can adjust your antibiotics to something more narrow-spectrum. Narrowing the spectrum likely prevents bacterial resistance to more broad-spectrum antibiotics and will help ensure patients receive the right antibiotic as early as possible, which will save lives and money too.”

Using mass spectrometry equipment may help cut costs by $80,000 per year, an amount that could mean a hospital would get a return on its investment within about three years, he adds.

Insurers with risk contracts or shared savings arrangements with hospitals and health systems may want to consider supporting the purchase of such equipment to improve patient care.

“It makes sense for an insurer partnering with a health system to invest in this technology. Then, the system can make the best impact on these diseases and shorten the length of stay, thus saving hospitalization costs,” Potoski adds. “Stewardship teams focus first on improving patient outcomes, and if you improve patient outcomes, the costs follow.”

Using mass spectrometry, an antimicrobial stewardship initiative for patients with Gram-negative bloodstream infections at the 1,000-bed Methodist Hospital in Houston has the potential to save an estimated $18 million over 12 months, according to a study published last year. One of the keys to the program was having a pharmacist on call to work closely with the staff in the microbiology lab to select the appropriate antibiotic. The hospital is now testing the same protocol on other bloodstream infections.

For MCOs, the importance of this study and others like it on the ROI potential of antibiotic stewardship programs is that the savings would accrue to any hospital that is part of an accountable care organization. By helping to contain infectious disease costs, the ACO would share in any savings under a risk contract.

**Using data to monitor disease resistance**

Another approach MCOs can use to limit antibiotic resistance is to track resistance in affiliated hospitals. Ramanan Laxminarayan, an economist and director of the Center for Disease Dynamics, Economics & Policy (CDDEP) in Washington, says most providers recognize the problem of antibiotic resistance but are indifferent about their own role in limiting it.

“There’s always a sense that it’s someone else’s problem because we don’t have enough data to show how much of a problem antibiotic resistance is in each facility,” says Laxminarayan, a research scholar and lecturer at Princeton University and an expert on the economic effects of drug resistance.

To simplify the tracking of antibiotics’ effectiveness and therapeutic options, CDDEP developed a drug resistance index (DRI).

The DRI is a simple index of the average effectiveness of antibiotics available to treat infections. It shows antibiotic resistance and consumption trends and can be applied at any geographical level, including individual hospitals. If enough facilities used the DRI, it could be employed to compare one facility against others.

“It’s a single number you can track and has been adopted in Vietnam, India, and South Africa. The U.S. military is using it in some of its hospitals, such as the VA hospitals in Baltimore and Pittsburgh. We need an easy way to talk about drug resistance, a way that’s simple to understand for administrators who may not be medical professionals. The DRI is just that: a simple tool that shows the overall levels of transient resistance,” he says.

The DRI, widely used, might help many healthcare providers shake off any apathy about antibiotic resistance. “Hospital administrators tend to think that many cases of methicillin-resistant *Staphylococcus aureus* (MRSA) just come in with certain patients and there’s nothing they can do about it. But in fact, it is possible to do better than your
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Discovery Health, one of the largest health insurers in South Africa, is developing a DRI as one component of its infection-control efforts with large public and private hospitals. Since 2009, Discovery Health has encouraged private hospitals to measure and report rates of four high-cost infections: central-line associated bloodstream infections (CLABSI), ventilator-associated pneumonia (VAP), catheter-associated urinary tract infections (CAUTI), and surgical site infections (SSI) as part of the nationwide Best Care ... Always! (BCA) campaign, says Gareth Kantor, MD, an anesthesiologist and senior clinical consultant to Discovery Health. The insurer also collects data on hospital use of measures of overuse and underuse of antibiotics, such as multiple concurrent antibiotics, surgical prophylaxis rates, and appropriate use of microbiology tests when selecting antibiotics.

The BCA campaign was inspired by the work of the Institute for Healthcare Improvement, in Cambridge, Mass., which has provided technical assistance for South Africa’s public hospitals. Another aspect of BCA involves developing and implementing antibiotic stewardship programs. “Currently, we have more than 200 public and private hospitals involved in this initiative,” Kantor says. “We have data from hospitals showing all infections declining in number. But the hospitals are not required to report. So we measure independently and feed our data back to providers, particularly on antibiotic utilization, both for stewardship purposes and as markers of health care-associated infections. We estimate that between 200 and 400 lives per year have been saved through the prevention of CLABSI alone.”

Diagnosis- and infection-rate data are often incomplete estimates because Discovery Health collects these numbers from claims.

“We don’t require hospitals to report their infection rate numbers partly because they have to learn to do so reliably and because we want to avoid any opportunity for gaming the system. Therefore, we are not confident in our measurements at the provider level, but we are sure that improvement is taking place overall,” Kantor says.

“Our most important objective is to promote improvement across all hospitals, and, of course, some hospitals are better than others. When we see that, we encourage the sharing of best practices with other hospitals,” he adds.

Tracking payment for antibiotics

The DRI would provide a high level measure of antibiotic resistance. To build the DRI, Discovery Health uses data on payments for quinolones and other antibiotics to treat urinary tract infections. These data are combined with numbers from the South African Society of Microbiology’s aggregated laboratory data from urine cultures growing Escherichia coli. The DRI shows that resistance to quinolones has been rising slowly in most areas.
"The problem is not so much with the methodology as that we don’t have all the data needed to measure a set of DRIs specific to common clinical syndromes, such as UTI or pneumonia and common pathogens. So far, we have simply looked at the use of antibiotics for one clinical syndrome," Kantor explains. "Now we want to ask the clinicians and microbiologists if these numbers look real. If these measures appear to be accurate, we would advocate their use, along with properly defined infection rates, to monitor the use of our antibiotic stewardship initiatives."

Using laboratory results for each pathogen and for each antibiotic being used in each hospital would produce a DRI for each hospital, Kantor says. "That could be our next step," he adds.

**Using incentives to foster improvements**

As Discovery Health shows, health plans can play an important role in preventing antibiotic resistance, says James Cottam, PhD, global product manager for antimicrobial stewardship and health care-associated infection at Alere. "There are many areas where health plans can make a difference in terms of limiting and preventing resistance, such as requiring consistent reporting of infections and associated data and emphasizing stewardship programs in health care facilities," he says.

"Another important area that health plans could concentrate on is increasing the awareness and use of rapid diagnostic testing among providers to better target and implement antibiotic choices as part of antimicrobial stewardship programs, both in primary and secondary care," he adds. Alere is working with the Alliance for the Prudent Use of Antibiotics (APUA) at Tufts University to provide educational materials to health care professionals and health plans on the effect that rapid diagnostics can have on informed decision making and the appropriate use of antimicrobials. This educational campaign is called Test Target Treat.

Cottam echoes the comments of the CDC’s Srinivasan when citing the role that payment mechanisms play in fostering improvements in the use of antibiotics. "Financial incentives can have a big impact, although care needs to be taken to ensure that the scope and execution are appropriate. Such programs can focus attention and resources on important areas and break down potential obstacles to implementation," he says.

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**New antibiotics in pipeline, but …**

A February report from the Pew Charitable Trusts finds 45 antibiotics in development — drugs that would treat some, but not all, of the resistant bacteria that cause systemic infection. The report says, "It is clear that there are too few drugs in development to meet current and anticipated patient needs." From the report:

- Of the 45 antibiotics in development, 15 were in phase 1 clinical trials, 18 in phase 2, nine in phase 3, and three have submitted new drug applications. Historically, about 60% of drugs that enter phase 3 will be approved.

- Four of the nine antibiotics in Phase 3 had the potential to address the single most pressing unmet need — infections caused by gram-negative pathogens. The cell structures of gram-negative bacteria and other factors render the pathogens particularly resistant to antibiotics and sometimes multiple drugs. The four drugs targeting gram-negative pathogens entered advanced development within the past five years and are being studied for the treatment of life-threatening bloodstream infections, intra-abdominal infections, complicated urinary tract infections, hospital-acquired bacterial pneumonia, and other infections.

- At least 17 of the antibiotics under development were designated as "qualified infectious disease products," meaning they were being studied for serious or life-threatening infections and receiving benefits provided under the Generating Antibiotic Incentives Now, or GAIN, Act of 2012. If approved, these drugs will get extra FDA exclusivity — or time free from generic competition — under GAIN.

- Only three antibiotics in early development attack bacteria in an entirely new way by sidestepping the resistance of some bacteria to available antibiotics. Other drugs in the pipeline attack the same targets in bacteria as available drugs but seek to thwart existing resistance by using new chemical compounds.

- Of the 30 or so companies developing antibiotics today, only four are in the top 50 pharmaceutical companies by sales. Almost 80% of the products currently in development are being studied by small companies rather than the large pharmaceutical firms that once dominated this field.

*The figures reported here do not include vaccines, biologics, new indications or formulations, or drugs to treat mycobacterial infections.*
Many factors are involved, not the least of which is the loss of patent protection for blockbusters like Lipitor and Plavix, but recently pharmacy management has been one of managed care’s success stories. Two reports last year, one from Express Scripts and the other from IMS Health, said spending on traditional medications (specialized pharmacy is a whole different story) didn’t just grow more slowly in 2012. *MIRABLE DICTU* — spending actually decreased! With that kind of tailwind, formularies and tiered pricing aren’t going to go away.

Meanwhile, these are early days for accountable care organizations (ACOs), and the uncertainty quotient is high for just about everything to do with them. The Centers for Medicare & Medicaid Services (CMS) is still test-driving its Medicare versions and, for now, the Medicare ACOs leave the Part D plans and the prescription drug plans that sell them intact. In the commercial market, insurers are moving cautiously with gradual rollouts and pilot projects.

**Will change be slight?**

If you look now for ACO-driven changes to pharmacy benefit management for payers, providers, or their customers, you will have a hard time finding them. Pharmacy benefits are a tangential concern for ACOs at this point because of their focus on medical spending, says Daniel Lyons, medical director of the ACO organized by AtlantiCare Regional Medical Center in Atlantic City, N.J. Greg Low, RPh, PhD, a pharmacist for the Massachusetts General Physicians Organization in Boston, says the formation of the Partners Healthcare ACO, which includes the physicians organization, has meant “just a broadening out of the scale” of the organization’s cost and quality efforts. “For us, it is not really a huge change,” he says.

**Similar theme**

His organization of more than 2,000 physicians has had commercial risk-sharing going back more than five years, says Low, so many of the systems and structures for dealing with pharmacy use are already in place.

Joseph Manganelli, PharmD, pharmacy director for Montefiore Medical Center’s ACO, sounds a similar theme. From his standpoint, participating in CMS’s Pioneer ACO program has meant using the same toolkit and staff developed under prior risk-sharing contracts. The one notable difference, he says, is that ACO beneficiaries are free to get care outside of the medical center’s network if they wish. Managing those patients means “getting a little more creative” — for example, using phone and fax for communication instead of relying on the network electronic health record as a source of patient information.

Maybe this is how it’s going to go with ACOs and pharmacy benefit management: status quo with a soupçon of change. But not everyone sees it that way, and a lot hinges on whether the management (and risk) of medical and pharmacy spending remains separate.

“That is an unsustainable model,” says Robert Da Silva, MS, a pharmacy director at Banner Health, a Phoenix-based chain of 24 hospitals that has been one of the most successful participants in Medicare’s Pioneer ACO programs. “You can’t keep the two risk buckets separate, because it creates perverse incentives. Sooner or later, with
the ACO contracts — at least the commercial ones — we are going to see those risk buckets combine into one.”

ACOs won’t be able to ignore pharmacy benefit management for very long, argues Edith Rosato, CEO of the Academy of Managed Care Pharmacy. “We are in a period of flux and change, but every ACO is going to have to start thinking about pharmacy benefits,” she says.

Effect on outcomes

If pharmacy benefit management does wind up more fully in the hands of ACOs, the motivations for it will differ from pharmacy management under the standard managed care arrangement, says Richard Stefanacci, DO, associate professor of health policy and public health at the University of the Sciences in Philadelphia: “The preferred agent is not going to be chosen because of the drug’s direct cost, but its effect on the outcomes that ACOs are held accountable for.”

Of course, ACOs still have some incentive to control drug costs if a shared savings contract extends to pharmacy spending. But if ACOs work as hoped, medication management will become a means to an end because, as Stefanacci and others point out, getting patients to take medications in the way that’s intended can mean avoiding big-ticket items like hospital admissions and emergency department visits that contribute heavily to medical spending.

Simple math

The math is simple: Just one unnecessary complication from diabetes or one readmission because of pulmonary edema from poorly controlled congestive heart failure is going to cost a lot more than any savings realized from medication management.

Of course, there’s nothing new about that math, but ACO contracts add two important new factors: First, they put provider organizations on the hook for it and, second, quality measures and shared savings amplify its effects, so substantial sums are at stake.

Pilot

Banner Health is conducting a pilot project with chronic obstructive pulmonary disease (COPD) medications to test whether the “pound-wise” rather than “penny-wise” mode of medication management that ACOs are supposed to engender does, in fact, work out that way. COPD medications are expensive brand-name drugs, so some patients take fewer doses than the prescription calls for to save money, says Da Silva.

The motivation was even greater when they feared falling into the now-partially closed “doughnut hole” of the Part D plans that meant paying full cost when spending on medications reached a certain amount. In some cases, the self-rationing leads to complications from COPD, even hospitalizations, so charging copayments for brands is probably counterproductive, says Da Silva.

“It’s like worrying about the water bill when you need the water to put out the fire that’s burning down your house,” he says.

In the pilot project, Banner will charge generic instead of brand copayments for COPD medications in the hope that people will use the medications faithfully. The pilot is for patients in the organization’s Medicare Advantage plan, not beneficiaries attributed to the Banner ACO, because for now the ACO beneficiaries still have their Part D plans.

Powers of persuasion

ACOs may eventually put a different spin on how pharmacy benefits are managed that will go beyond formularies and tiered pricing. A Cigna pilot project provides one example of how it might work. “Embedded nurse coordinators” are an important part of the Bloomfield, Conn., company’s ACO program, which now consists of “collaborative care agreements” with about 75 provider organizations.

The nurses are employed by Cigna but work at the providers.

Jon Maesner, PharmD, Cigna’s chief pharmacy officer, says, “It’s like worrying about the water bill when you need the water to put out the fire that’s burning down your house.”
If ACOs work as hoped, medication management will become a means to an end because, as many experts point out, getting patients to take medication in the way that’s intended can mean avoiding big-ticket items such as hospital admissions.

officer, says the company has been running a pilot project in five practices that involves having the embedded nurse coordinators identify patients who could switch to either a generic drug or a preferred brand-name drug, and then advising their doctors about it. Sounds pretty basic, but Maesner says patients are making those changes 5 to 10 times more often in this pilot project than they do otherwise.

Motivated to practice

He offers several possible explanations. First, the ACO financial incentives are, in fact, working the way they are supposed to, so physicians are motivated to practice in a way that takes cost into account. “You are beginning to see a natural alignment on affordability,” Maesner says.

Second, Cigna is providing doctors with cost-saving information that’s specific to individual patients, so doctors can tell patients how much they could be saving. Whether there might be some resistance from doctors or patients if Cigna were to scale this up has yet to be seen.

Third, the embedded nurse coordinators are right there in the provider organizations, “quarterbacking” the pharmacy benefit — they’re not working off-site by phone, fax, or e-mail.

Formularies

There are no “embeds” at the Massachusetts General Physicians Organization, but the softer powers of persuasion are also being used there to influence prescribing, according to Low, who is the lone pharmacist in a group of 30 employees devoted to measuring and managing clinical care. The organization doesn’t have any say over formularies, Low notes, and he doesn’t see a reason for changing that soon.

The insurer’s formularies are fairly predictable, and there haven’t been any glaring problems: “We don’t have weird cases where there is a really expensive drug that is in the first tier that winds up increasing our pharmacy spend just because an insurer gets a rebate.” So rather than lean on formularies, the organization has developed internal guidelines to influence prescribing. Avoiding complications and hospitalizations is the motivation.

Low says Partners has been careful not to take a heavy-handed approach to risk and rewards for individual physicians. “We don’t want any physician thinking, ‘I am going to be paid differently based on how I treat this patient,’” he says. If follow-up with a physician is necessary because his or her prescribing patterns are outside the norm, Low says it’s more effective because it’s coming from within the organization. Faxes or e-mails from insurers, on the other hand, tend to get ignored.

If there is a continual or major problem, “We reach out to the division chief to bring another person into the conversation,” says Low. “We’re likely to ask, ‘Would you help us understand what is going on with this physician and how we can help?”

Jockeying for position

One worry about ACOs is that they will accelerate the consolidation of health care into larger and larger organizations and, in the process, hasten the demise of competition on price, quality, or both — and possibly undo any progress on those fronts. If the incentives are strong enough and the fence around Part D gives way, pharmacy management and spending could become part of that consolidation.

Da Silva says Banner, partly as a result of its ACO, has plans for building about a dozen ambulatory pharmacies in its hospitals and clinics. With about $200 million in hospital pharmacy spending under its control and potentially about that much in ambulatory pharmacy spending, Banner would have ample clout to negotiate good prices with suppliers. “That’s almost half a billion dollars in throw-weight,” says Da Silva.

Medication management

But there’s lots of jockeying for position going on. It’s not going to be as simple as a few ACO-fueled health systems taking over. Pharmacy chains, large
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and small, are asserting themselves as extensions of the health care system — and are better situated than other parts of it to manage medications and improve adherence.

CVS has its Minute Clinics, and Walgreens has teamed up with physician groups in New Jersey, Florida, and Texas to form ACOs. Thrifty White Pharmacy, an employee-owned chain of pharmacies in the upper Midwest, is providing medication management services to a patient-centered medical home project launched by Blue Cross Blue Shield of North Dakota that could potentially provide care to 150,000 of the state’s residents. The National Association of Chain Drug Stores has given North Dakota State University a grant to evaluate the project.

**Building on success**

Justin Heiser, PharmD, a senior vice president for pharmacy operations at Thrifty, says the company is hoping to build on its success with getting pharmacists more involved in advising customers and with “medical synchronization,” which improves adherence by arranging refill schedules so people can pick up all their medications on the same day. “We want to cement our position in these new models of care, including ACOs,” says Heiser.

Pharmacy benefit management companies are also eyeing ACOs, looking for ways that they might fit in. David Calabrese, RPh, MHP, the chief pharmacy officer for Catamaran, the pharmacy benefit manager, says his company doesn’t currently have contracts with ACOs but is gearing up for doing business with them.

**ACO strategy**

Catamaran’s clinical leadership is mapping an ACO strategy, and the company has developed programs that should appeal to ACOs, such as one that quickly alerts providers if patients fall out of adherence after they have been discharged from the hospital. Catamaran’s existing business with the health plans that pay the bills shouldn’t be an impediment to working with ACOs that provide the care, says Calabrese.

In fact, quite the opposite: “It’s in both of their best interests for us to work both sides of the table” if the goal is reducing costs — sharing in the savings, while maintaining quality. “I don’t see any reason why someone would see that as a conflict,” says Calabrese.

**Contracts will vary**

The services that Catamaran provides will vary from contract to contract and will depend on the needs of the ACO. Calabrese touted his company’s data warehousing and analytics capabilities, which have been built out recently so they can handle medical claims and lab data if needed. If data collection is the kingdom, Calabrese makes it seem that Catamaran could hold the keys. “Much of the success of an ACO is going to depend on its ability to manage data, utilize data, and translate data into useful information that is going to help it achieve success,” he says.

Might Catamaran jump into the ACO game itself? Calabrese leaves the door wide open. “I don’t know if we are at the point today where we are looking to take on that risk,” he says. “Would we entertain a partnership with an ACO that is well established and has demonstrated value in managing quality and cost on the medical side? I think we certainly would. “Have we been approached to do that? We have not.”

Peter Wehrwein is a frequent contributor to Managed Care.

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Medicare’s Part D Fiasco Triggers Anger From All Sides

Opponents say that the new rules would reduce consumer choice and industry competition

By John Carroll
Contributing Editor

It’s unusual these days to find a bipartisan majority of legislators on the Senate Finance Committee able to agree on anything. Yet that’s what happened in February as opposition to a proposed change in the government’s regulations on Medicare Part D prescription drug plans swelled into a crescendo of angry reactions not only from legislators, but also from the legions of lobbyist organizations that follow every twist and turn in the heavily regulated world of health care.

Difficult to change

Faced with a coalition of critics, Centers for Medicare and Medicaid Administrator Marilyn Tavenner did an abrupt about-face in early March and dropped the proposals. The reversal provided a clear lesson in how difficult it will be to make any changes in Part D, even as support for at least one of the suggested provisions lingers on. It also showed how this powerful constituency plans to oppose any future alterations.

Medicare kicked off the fuss with three key initiatives on January 10. First, looking to provide a little added leverage that could win discounts for drug formularies used by Part D plans, the agency proposed to drop a provision that requires the drug plans to cover all approved therapies for a pair of drug categories: antidepressants and immunosuppressants.

Second, the agency wanted the preferred pharmacy networks that the drug plans turn to for discounts to include independent pharmacies willing to provide therapies at the same price.

The third proposal would limit the number of Part D plans a sponsor could field, claiming that seniors were confused by too many offerings.

The senators — a group that included Democrat Ron Wyden of Oregon and Republican Orrin Hatch of Utah — didn’t single out any particular problem they had with the proposed rules. They did make it clear that they felt that the administration was opening up Washington to protests from their constituents.

“Many of the proposed changes are untested and unstudied and could result in significant loss of beneficiary choice, access, and consumer protections,” the senators noted in a testy letter to Tavenner that clearly wasn’t ignored.

That position was mild compared to a gathering of more than 200 groups — including managed care players like the Blue Cross Blue Shield Association and WellPoint, drug giants like Merck and Pfizer, and patient organizations — that lined up in opposition. Like the senators, they didn’t oppose individual points. They wanted the whole thing tossed.

These rules would, they said in a joint communiqué to the administration, reduce consumer choice and industry competition, and expand the federal government’s role in Part D without affecting the quality or cost of Part D. The rules would ultimately saddle beneficiaries with higher costs, as well, they said.

Lawmakers and lobbyists all chimed in on one common theme: Why fiddle with Part D now after the drug provision turned out to be both widely affordable and hugely popular with beneficiaries?

“There’s a lot not to like about this rule from numerous different perspectives,” said Mark Merritt, CEO of the Pharmaceutical Care Management Association (PCMA), just days before CMS’s sudden retreat. PCMA represents the nation’s pharmacy benefit management companies. “It’s hard to unite everybody in town around one position on a health policy.”
With the exception of the independent pharmacies, which have been lobbying against the preferred pharmacy networks, he said, this was “universally opposed by patient groups, provider groups, payers, and so on. When you get that many people on the same page, usually it means the policy could have been vetted a little better than it was.

Trouble with contracts

“The overarching issue is that CMS tends to grant itself the authority to interfere in contracts in the way Part D is constituted,” added Merritt. “That opens the door to eliminating preferred pharmacy networks and other things.”

One of the other reasons why there was so much solidarity in the opposition to this regulatory initiative is that Medicare signaled its willingness to open the door again on Medicare’s nonintervention on drug prices, said Merritt. Medicare cannot negotiate drug prices, and legislators in both parties clearly want to leave the law alone.

The American Psychiatric Association (APA) also took exception to Medicare’s attempt to tamper with the protected drug status of antidepressants under Part D, with antipsychotics also at risk. Medicare got it wrong when it quoted the APA’s position — “the effectiveness of antidepressant medications is generally comparable between classes and within classes of medications” — as justification for the move, said the organization.

“APA guidelines that address the use of antidepressants and antipsychotics, including the guidelines on major depressive disorder, anxiety disorders, schizophrenia, and obsessive compulsive disorder, all recommend the opposite of CMS’s interpretation,” the APA replied to Medicare. “They recommend that choice of medication … be made on the basis of how a drug’s unique effects may interact with a patient’s individual situation. This includes such factors as gender, pregnancy status, age, ethnicity, co-occurring psychiatric conditions, and other co-occurring medical conditions. These unique drug effects include different mechanisms of action, pharmacological properties (e.g., drug-drug interactions), side effects, and safety concerns.”

Choices desired

In other words, all the drugs have to be covered to give physicians and patients the kind of choices they need to manage depression. Don’t look for the association to change its tune. Another issue that won’t go away relates to the preferred pharmacy rule. Within hours of Medicare’s withdrawal of the proposed rule change, the National Community Pharmacists Association (NCPA) fired back on what it sees as a sudden setback for a large number of its members.

“CMS has heard repeatedly from community pharmacists and patients regarding the inadequacies of ‘preferred pharmacy’ drug plans,” the group said in a statement. “They have been deceptively marketed and are confusing to patients.”

The NCPA has some supporters of its own in the move to get more independent pharmacists qualified to serve Part D patients, breaking into the preferred pharmacies that earned Medicare’s concerns.

For the National Rural Health Association’s Maggie Elehwany, vice president for government affairs, it’s about access.

“With the population scattered in rural areas with not a lot of big chain retailers, independent pharmacists are very tied in with the community,” says Elehwany. “Rural areas have a higher percentage of chronic diseases, like heart disease and obesity, and they rely on pharmacists to ask questions about the medication. If you’re not on the preferred list, seniors try to make arrangements to travel to a retail pharmacist. This will give them that choice. Many seniors just don’t drive anymore. It’s difficult to get transportation.”

No discount

For Merritt, though, if you want plan sponsors to negotiate discounts with preferred networks, you can’t open the program up to all comers.

“If everyone offers the same discount, then there’s no discount,” says Merritt, and that will simply eliminate the motive for going after discounts in the first place. “The rule goes against the administration’s entire policy of promoting providers that are more affordable or offer higher quality products.”

To cap it off, the PCMA cites a study by Milliman claiming that close to 7 million non–low-income beneficiaries would probably be hit by cost hikes if the rules on preferred pharmacies were changed.

For now, the political heat is putting this initiative on the back burner. But this is one rule change that may make a comeback and restart the Part D reform process.
When Independence Blue Cross (IBC) recently launched its Center for Health Care Innovation, it took on a task that many insurers seem eager to take up: research. It’s not what health plans historically pursue, but these days managed care is a lot more complicated than gatekeeping or measuring actuarial risk.

Commercial health care has historically been a business-to-business enterprise in which employers decided which benefit packages to offer workers, says Terry Booker, who runs IBC’s Center for Health Care Innovation. IBC launched the center in February.

With the Affordable Care Act, more individuals are buying insurance, making the system more dependent on business-to-consumer transactions. A patient-focused system requires transparency — for instance, doctor and hospital referrals based on quality metrics.

“Remember, patients are now dealing with things like high-deductible plans,” says Booker. “So they’re going to need to know how to spend their money.”

Booker refers to a system in which the government, payers, and providers work closely together. You can’t do it alone, says Booker. “You have to pull in the doctors, the hospitals, the medical-device makers. Everybody has to be pulled in on what you’re trying to work on.”

Of course, many insurers explore ways to do things more efficiently. For example, Aetna’s hub of experimentation is called Innovation Labs, a unit dedicated to making cost-effective clinical improvements in the five most expensive areas: cardiovascular, cancer, musculoskeletal, maternity, and gastrointestinal.

“We’ve had nine completed pilots as of the end of 2013,” says Michael Palmer, head of innovation at Aetna. One is a patient-centered medical home for oncology, which the insurer launched with the provider group Consultants in Medical Oncology and Hematology (CMOH). More than half of all new cancer patients are 65 or older and have comorbidities. CMOH oncologists function as primary care physicians who keep an eye on all the patient’s problems. Typically, patients end up in the ER when they have a complication with their medication. CMOH keeps an open schedule from 8 a.m. to 10 a.m.

“They have nurses taking calls for the practice in the off hours in the evening,” says Palmer. “The patients know that if they have a material issue, they can show up at 8 am the next day and get it dealt with rather than have to go to the ER overnight.”

Aetna’s Innovation Labs also recently completed a big data-analysis exercise on chronic kidney disease, creating predictive models that pinpoint which patients are likely to develop end-stage renal disease and require either dialysis or a transplant. For example, high levels of creatinine can be a predictor.

**Identifying candidates**

“All the medical, lab, pharmacy, and claims data that we have can help us identify those folks who would be a great candidate for a transplant,” says Palmer. “Having the kind of life you can have with a healthy kidney versus being on dialysis is a really big difference.” As we reported in November (http://tinyurl.com/Aetna-labs), Aetna houses the Inno-
plementation Labs program in Hartford, Conn. IBC’s Center for Health Care Innovation is in Philadelphia where, Booker says, “We have a number of health care institutions and systems. We feel that we can ultimately be the Silicon Valley of health, given the type of talent and type of capabilities that we have in our region.”

**Machine learning algorithms**

Like Aetna, IBC focuses on care delivery as a way of improving competitiveness. IBC launched several projects with the University of Pennsylvania, including one that uses GlowCap technology on pill bottles to improve medication adherence for heart attack survivors, and another study looking at how genomic testing can be used to improve clinical outcomes and lower cancer care costs.

IBC is also helping New York University use machine learning algorithms. Machine learning, says Booker, is the use of technology, statistical models, and data to understand what types of elements can be early indicators of certain conditions and behaviors. An example would be to predict what patients are most likely to get diabetes (http://tinyurl.com/IBC-Penn-Presser).

“Machine learning means that you’re taking data from a number of different sources to try to come up with predictive analytics that allow you to determine with a higher degree of certainty that somebody may be suffering from a particular disease or may be predisposed to get that disease,” says Booker. “It’s sort of genetic testing but without the genetic information.”

The information comes from various sources: health risk assessment forms, doctors’ records, claims. “Then we can reach out to them proactively to encourage them to see their doctor or to recommend a care management program before they have a crisis, like needing to go to the emergency room.”

The center is about 5,000 square feet and is available to staff members from nearby IBC headquarters for training and meetings, as well as to entrepreneurs. Independence Blue Cross cosponsors DreamIt Health Philadelphia, a business accelerator — or incubator — that encourages entrepreneurial startups.

DreamIt Health Philadelphia brought 10 health care startups to the Philadelphia area in 2013. Each received a stipend of up to $50,000 from IBC and Penn Medicine, and in-depth advice from experienced entrepreneurs and health care executives. DreamIt is a four-month program that IBC refers to as a boot camp.

“We’re going to do another DreamIt accelerator in 2014 that will select another 10 companies that will begin the boot camp class in July,” says Booker. Applications are due in May.

The companies selected last year were AirCare, Biomeme, Fitly, Grand Round Table, Lucidity Health, Medlio, Osmosis, Serati, Speso Health, and Stat. (Find out more about the companies at http://tinyurl.com/IBC-Presser.)

One of the things that makes this business accelerator unique, says Booker, is that IBC and Penn Medicine — insurer and provider — each provide data to help the fledgling companies. Health care’s most complex problems occur where payer and provider meet, says Booker. “The collaboration between Penn, IBC, and startups help make it possible to tackle these issues with real-world solutions.

“It really comes down to us being the epicenter,” he continues. “How can we take information and share it with others so that we can move away from the silos and start to work together on things to our mutual benefit?”

Doctors and hospitals get information from IBC’s partnerships, says Booker. “Penn may have information on 500,000 people. We may have information on 5 million people.”

Larger populations make for more effective predictive modeling. “Which type of person is going to get diabetes? Which type of person is likely to become obese? Things like that will allow physicians to be proactive in working with their patients to maintain or prevent those types of chronic illnesses and diseases.”

**Protocols**

A lot of effort at innovation involves cancer care. Aetna joined with several oncology practices in the New York/New Jersey area to encourage better
use of evidence-based care. Eviti, a cancer clinical
decision support vendor, supplied protocols that
are based on guidelines such as those provided
by the National Comprehensive Cancer Network.

“At baseline, before installing the Eviti system,
practices were following published guideline ther-
apies only 62% of the time,” says Palmer. When
the protocols were put in place “the percentage of
evidence-based cancer therapeutic plans increased
by an absolute 25%, up to 87%. We are hoping to
have an associated analysis of the effect on utiliza-
tion and costs later this year.”

As long as the doctors in the pilot selected one
of the evidence-based therapies presented by the
Eviti system, the protocols were automatically au-
thorized, thereby eliminating the need for the doctor
and his practice to go through sometimes lengthy
preauthorization procedures.

“The idea was to get patients moving along the
pathway as quickly as possible without the back-
and-forth from the insurance company about what
the treatment protocols would be,” says Palmer.

Research on cancer moves quickly.

“It’s one thing if you have doctors curing colds,”
says Palmer. “There’s not a lot of colds research out
there. But keeping up with the cancer research is
next to impossible. One reason why we have such
low adherence is that the science is changing so
quickly.”

The incentive models in place today are
grandfathered in, says Palmer, and a lot has changed
since grandfather’s day. “We’ve got to come up with
some really, really materially better solutions. That’s
really the reason for our significant investment in
this area. Without some significant investments in
R&D, it’s going to be very hard to upend the existing
health care system.”

Booker agrees: “All of us don’t want to waste a
whole lot of money going down the wrong path.”

Did you miss?

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Paul H. Keckley, PhD
Lucian Leape, MD
Lee N. Newcomer, MD, MHA
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Biosimilars Take Center Stage

Their cost advantage is incontrovertible, but will doctors and patients join reference product manufacturers in trying to restrict them?

By Katherine T. Adams

Biosimilars once again are taking center stage as the Food and Drug Administration prepares to issue additional guidance later this year.

Although the FDA has received 13 inquiries (as of the end of 2013) from companies considering entry into the biosimilars market, no formal applications have been submitted. This lack of activity is likely to end quickly now that implementation of the Affordable Care Act is under way and the need to rein in the high cost of health care and, especially, biopharmaceuticals is critical. The time for biosimilar manufacturers to get their foot in the door is now.

That was the message at the Biosimilars and Follow-On Biologics 2014 Americas Conference, held in Philadelphia in February. And a quick Google search will reveal that a number of similar conferences are scheduled in this country and abroad for the rest of 2014.

“I expect that a biosimilar will be on the U.S. market in two years,” says Michael A. Swit, special counsel at Duane Morris, in San Diego. Swit was one of several speakers at the two-day conference, which featured discussions about biosimilar entry into the U.S. pharmaceutical market and the critical issues that need to be addressed.

Fueling increased biosimilar interest is the recognition that 32 biologics with combined sales of $51 billion will lose patent protection by next year.

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A biosimilar, or something else?

To support consistent analyses across geographies, therapies, and manufacturers, IMS Health has established an industry-verified categorization of biologics. Although not every product fits neatly into these classifications, the schema applies in most instances.

**Classification of biologics**

<table>
<thead>
<tr>
<th>TYPE</th>
<th>Description</th>
<th>Target</th>
<th>Example</th>
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<tbody>
<tr>
<td>Originals</td>
<td>True innovator</td>
<td>New drug against new target</td>
<td>Eylea</td>
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<tr>
<td></td>
<td>Bio-betters</td>
<td>Same target but differentiated (e.g., better efficacy, safety, administration)</td>
<td>Pegasys</td>
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<td></td>
<td>Biosimilars</td>
<td>Clinical equivalence and comparability to originators</td>
<td>Inflectra</td>
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<tr>
<td></td>
<td>Nonoriginals/biosimilars</td>
<td>Drug aiming to copy innovator</td>
<td>Reditux</td>
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<tr>
<td></td>
<td></td>
<td>Focus on patient access, emerging markets</td>
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**DESCRIPTION**

- Disruptive technologies, big advances in efficacy
- Efficacy/safety improvements
- Affordable high quality
- Less stringent comparability

**TARGET**

- New drug against new target
- Same target but differentiated (e.g., better efficacy, safety, administration)
- Clinical equivalence and comparability to originators
- Drug aiming to copy innovator
- Focus on patient access, emerging markets

Source: Searching for Terra Firma in the Biosimilars and Non-Original Biologics Market: Insights for the Coming Decade of Change, IMS Health, 2013
IMS Health projects that the biosimilars market will reach up to $25 billion by 2020, 4% to 10% of the projected $250 billion biologics market. A 2011 Deloitte analysis projects that biosimilars will erode pharmaceutical industry revenues by $29 billion over the next 10 years.

Although biosimilars (also called follow-on biologics, copycat biologics, or nonoriginal biologics) will probably enter the U.S. market by the end of this decade, lack of physician or public acceptance could delay, if not derail, their use. Also, depending on the FDA’s actions, what is considered to be a biosimilar in Europe may be a different entity here in the United States.

The FDA issued three draft guidance documents in 2012 that describe how the biosimilar approval process will work. In its February 2012 guidance, “Scientific Considerations in Demonstrating Biosimilarity to a Reference Product,” the FDA acknowledged that a one-size-fits-all pathway is not possible and says it will consider the “totality of evidence” when assessing biosimilar applications. The agency’s stated intent is to encourage quick development of biosimilars so as to reduce consumer costs and to allow manufacturers to compete effectively in the worldwide biologics market.

The agency has not yet clarified what it will require for manufacturers to demonstrate interchangeability, nor has the agency addressed the issue of comparative studies. The Biologics Price Competition and Innovation Act of 2009 (BPCI) says that a biological product can be considered interchangeable with the reference product (the original biologic) if it is determined that the biological product can be expected to produce the same clinical result as the reference product in any given patient. Biosimilar manufacturers, however, are waiting on the FDA to specify what would constitute proof of interchangeability. Studies will need to be indication-specific, says Swit. “There is a strong argument that interchangeability must be proven in all indications to satisfy the ‘any given patient’ standard under the BPCI.”

Need for comparative studies

The clinical trials concern is a thorn that will have to be dealt with somehow. “Patients may be reluctant to participate in a clinical trial,” says Joseph P. Fuhr Jr., PhD, professor of economics at Widener University in Chester, Pa., and one of the presenters at the Philadelphia biosimilars conference. “A patient with breast cancer, for example, may not want to participate in a trial of Herceptin versus a biosimilar where there is a great uncertainty if the biosimilar will work.”

In addition, several companies may attempt to develop the same biosimilar, he adds, so “it may be difficult to get enough volunteers for a clinical trial.”

U.S. pharmaceutical companies also have called for clinical studies of biosimilars to include immunogenicity and safety and efficacy data. Physicians will want to know more about what they are prescribing and will want to see comparative studies and underlying data.

The first biosimilar was approved in the European Union in 2006, and the EU market now consists of 16 biosimilars in three classes — human growth factor, short-acting erythropoietin, and daily granulocyte colony-stimulating factor (G-CSF) — plus a monoclonal antibody approved in 2013. Lowering costs for the consumer has driven their approval, says Fuhr, but automatic substitution at the pharmacy has not occurred. “The European Medicines Agency advises against such substitution,” says Fuhr, “although France now allows for substitution in new patients not previously on a reference biologic.” The uptake of biosimilars in the EU has been slow, but no substantial safety issues have emerged thus far.

Canada and Japan, meanwhile, have approved a biosimilar of Omnitrope, a growth hormone.

Biologics — and the term is still confusing for many health care providers, payers, and patients

3 definitions of a biosimilar

U.S. Food and Drug Administration: A biological product that is highly similar to a U.S. licensed reference biological product notwithstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity and potency of the product.

World Health Organization: A biotherapeutic product that is similar in terms of quality, safety, and efficacy to an already licensed reference biotherapeutic product.

European Medicines Agency: A biological medicine that is developed to be similar to an existing biological medicine (the “reference medicine”). When approved, a biosimilar’s variability and any differences between it and its reference medicine will have been shown not to affect safety or effectiveness.
State legislation advances

Several states have already considered the issue of biologic substitution, though prematurely. Five states (North Dakota, Florida, Oregon, Virginia, and Utah) have adopted legislation; 10 have rejected legislation for the time being (Arizona, Arkansas, California, Colorado, Delaware, Illinois, Indiana, Maryland, Mississippi, and Texas). Legislation is pending in Massachusetts, Pennsylvania, and Washington, which has also said that 60% of cost savings must be passed on to the consumer.

— are large-molecule drugs manufactured in cells derived from living organisms,* in contrast to the small-molecule drugs that are synthesized in a laboratory. Generic versions of a synthesized drug are able to copy the original drug, although as time passes, slight differences do occur during the manufacturing process.

A biosimilar, however, is never identical to the “reference product,” which is the branded biologic. The BPCI describes biosimilars as having “no clinically meaningful differences” from the original product. But biologics and biosimilars are sensitive to, and altered by, changes in their manufacturing process. A biosimilar, by definition, is not a new biologic, Fuhr points out, but also not a replica of the original drug because of the nature of biologics. “They are, at best, highly similar.”

The FDA acknowledges this in its guidance. Because manufacturers own their own cell lines and use proprietary manufacturing techniques, the agency notes, each production method results in differences in the molecule.

Why develop a biosimilar?

Simply because it is easier and less costly to mimic than to innovate, says Fuhr: “Biosimilar companies believe they can make a good return on their investment.” The use of biologics is increasing, he points out, and given that biologics are costly, insurers and governments will pay more attention to the potential cost savings of biosimilars. “That could be the major force behind biosimilar uptake when finally there are guidelines and a path for approval in the U.S.,” says Fuhr. With a projected savings around 20%, which industry observers seem to agree on, the resulting savings could be huge given the relative high cost of a biologic. “For example a 20% difference in the price of a $100,000 biologic would result in a $20,000 savings. Savings could add up quickly.”

Big pharma is not sitting still

Branded companies have been following the strategy of developing superior second generations of their biologics, says Fuhr. However, this could result in considerable R&D costs as well as possible failure.

On the other hand, in February, Merck KGaA in Germany announced that it will step up its push into biosimilar manufacturing, and added it has all the capabilities to compete in the biosimilars market. Karl-Ludwig Kley, Merck KGaA’s CEO, said that he expected significant market growth by the second half of this decade. Merck KGaA has been working with Bionovis in Brazil and Dr. Reddy’s Laboratories in India on six biosimilars for cancer and arthritis.

Similar to Remicade

Celltrion, based in South Korea, has already developed a biosimilar version of infliximab (Remicade), which it calls Remsima. The company is seeking European approval and claims that the drug would be almost 30% cheaper than Johnson & Johnson’s TNF inhibitor. According to Standard & Poor’s reports, in 2011, global sales for infliximab were $7.2 billion.

Johnson & Johnson has said it may file a patent infringement lawsuit. Celltrion Chairman Seo Jung Jin has also said he plans to sell his $1.3 billion stake in the company and Roche, Teva, and AstraZeneca have been mentioned as potential buyers.

Patents, pricing, and prescription will be three primary barriers to approval and acceptance of biosimilars by the American public. But these barriers will not hold indefinitely. Despite the difficulties facing biosimilar makers, the market will develop — if only because the high cost of biologics is untenable in the long run.

* First-generation biologics have been derived from humans and animals, e.g., animal and human blood products or insulin from pigs. Second-generation biologics, however, are made by genetically engineering DNA in living organisms.

Katherine T. Adams is a Pennsylvania-based independent journalist. She may be reached at kadams@managedcaremag.com.
Gilead, Abbvie Ready Hep C Combinations for FDA

Last December’s approval of sofosbuvir (Sovaldi) ushered in the era of interferon-free treatment for hepatitis C (HCV). But sofosbuvir’s final labeling — recommending co-administration with pegylated interferon in patients with genotypes 1 and 4 — meant that the days of interferon and its harsh side effects were not quite over for a subset of people with HCV.

Now, two manufacturers are in a race to clear up some unfinished business. AbbVie made a splash at March’s Conference on Retroviruses and Opportunistic Infections, presenting results from six studies of a three-drug cocktail to treat patients with genotype 1 HCV. AbbVie’s regimen consists of the fixed-dose combination of ABT-450 and ritonavir coformulated with ABT-267, dosed once daily, and ABT-333, with or without ribavirin, dosed twice daily. In all six studies, involving more than 2,300 patients, the various combinations demonstrated cure rates of between 90% and 100% after 12 weeks. AbbVie will seek FDA approval of the combination product this spring.

The maker of sofosbuvir, however, is already a step ahead of AbbVie. On February 7, Gilead filed for FDA approval of a fixed-dose combination of sofosbuvir for people with genotype 1 HCV. The once-daily tablet combines sofosbuvir with ledipasvir, an NS5A inhibitor. No ribavirin, no interferon — and no speculation yet about what it will cost. When sofosbuvir hit the market, its average wholesale price was $84,000 for a 24-week supply.

Statin add-ons likely to renew a long-forgotten battle

It’s almost easy to forget that 15 years ago, many payers balked at the cost of statins — a fast-growing class that broke the psychological barrier of $1 a pill. Today, statin therapy is a standard of care and is considered cheap insurance against far more costly cardiovascular events.

Now, statin therapy promises to get a lot more expensive if part of a combination regimen with a monoclonal antibody. In January and March, Amgen announced results of two studies of evolocumab, a PCSK9 blocker that allows the liver to clear more LDL cholesterol from the body. These were the last of six phase 3 studies, some involving hard-to-treat patients. Evolocumab was coupled with various statins and strengths, depending on the study.

Numbers for the January study are being saved for a scientific conference later in the year, but they are believed to be similar to the eye-opening LDL-C reductions that approached 60% in phase 2 studies. The study revealed few instances of cognitive impairments, a side effect the FDA asked both Amgen and Sanofi — which is shepherding its own PCSK9 inhibitor, alirocumab, through clinical trials — to monitor. The problem appears to be self-correcting when patients stop taking the drug.

The March study was conducted in patients with homozygous familial hypercholesterolemia, a difficult-to-treat population whose rare condition acts as an LDL-C booster. Significant reductions were seen in almost half of these patients.

Amerex plans to file for regulatory approval for evolocumab later this year.

The outcomes may be life-saving for high-risk populations. The conversations to come about cost and access limitations, though, will be interesting.

Lung cancer: 2 up

A fast-emerging understanding of the genetic complexities that underlie lung cancer has made the condition a hotbed for drug development. In the first quarter of 2014 alone, four different investigational treatments for non–small-cell lung cancer made news. Two of those dispatches were positive for their manufacturers.

Ramucirumab, a VEGF blocker, showed a statistically significant increase in overall survival when paired with docetaxel. The results were a blessing for Eli Lilly following ramucirumab’s failure last year to meet its primary endpoint in a breast cancer trial. Nonetheless, the drug has already proven itself in a gastric cancer trial, and if it demonstrates further success in trials for liver and colorectal cancer this year, it could eventually become a huge seller.

LDK378 is still young in development, but that didn’t stop Novartis from filing for FDA approval. Novartis based its application on high response rates in a phase 1 study of 78 patients with homozygous familial hypercholesterolemia, a difficult-to-treat population whose rare condition acts as an LDL-C booster. Significant reductions were seen in almost half of these patients.

Amgen expects to file for regulatory approval for evolocumab later this year.

The outcomes may be life-saving for high-risk populations. The conversations to come about cost and access limitations, though, will be interesting.

Lung cancer: 2 down

On the downside, Genentech called off a late-stage trial of onartuzumab, one of its biggest pipeline assets, for lack of efficacy.
Nicknamed MetMab because it targets the MET pathway, onartuzumab was studied in combination with erlotinib (Tarceva) in patients with EGFR mutations. A 2011 phase 2 study had shown statistically significant improvements in overall survival and progression-free survival (PFS) in patients given onartuzumab with erlotinib, compared with erlotinib alone. Genentech is evaluating the implications of the phase 3 study across the onartuzumab clinical development program.

Pfizer took two on the chin in a pair of studies of dacomitinib, which inhibits HER1/EGFR, HER2, and HER4 kinase activity to prevent cell proliferation. In a head-to-head showdown against erlotinib in patients with advanced, previously treated disease, dacomitinib did not demonstrate an improvement in PFS. In a second trial in a similar population, dacomitinib did not improve overall survival versus placebo.

Pfizer will keep plugging along with dacomitinib, however. Another phase 3 trial — this one against gefitinib (Iressa) in patients with treatment-naive, EGFR-mutant disease — is to be completed next year.

Did you hear?
Researchers in the United Kingdom have successfully deployed gene-replacement therapy to repair retinal damage in patients who have a form of progressive vision loss. In a six-person trial, University of Oxford ophthalmologists injected a virus into patients’ eyes. The virus acts as a transporter for the CHM gene — the lack of which is a cause of retinal deterioration. Once the virus reaches light-sensing cells in the retina, it infects them, depositing the gene. The gene is then switched on to produce proteins that stop cell degeneration that leads to blindness. Researchers published their results in the Lancet.

President Obama’s fiscal year 2015 budget includes a provision to reduce biologic market exclusivity from 12 years to 7 years. Buried deep within the budget document, the reduction is touted as a way to save $4 billion in Medicaid spending. The budget architects don’t spell out how those savings will be achieved, however. Mysterious, indeed, considering that the FDA has not finalized a regulatory pathway and that no biosimilars have been approved in the United States since recombinant hyaluronidase reached the market in 2005.

— Michael D. Dalzell

All clinical trials described in this column are phase 3, randomized, controlled studies unless otherwise specified.
Provider-administered drugs move to specialty pharmacy benefit

Both payers and providers benefit

Payers are slowly moving specialty drugs from the medical benefit to the pharmacy benefit to reduce cost. The Pharmacy Benefit Management Institute’s recently released 2014 Specialty Drug Benefit Report calls it an example of a new management strategy to deal with the rapid growth of specialty expenditures.

This strategy attempts to redefine the coverage landscape described in the EMD Serono Specialty Digest, 9th Edition. According to the digest, almost all plans cover self-administered drugs exclusively under the pharmacy benefit, while nearly all cover office-administered drugs exclusively under the medical benefit.

How would a shift be possible? Providers commonly buy and stock drugs at their offices and administer them to patients as needed. Then they mark them up and bill the insurer. However, this model is unsustainable for most practices and payers alike in light of the cost of the product.

Instead, shifting coverage of the drug from the medical benefit to the pharmacy benefit allows providers to resort to white bagging and brown bagging. White bagging is where a specialty pharmacy ships the drug to the provider just before administration of the drug to a specific patient. Brown bagging is where a specialty pharmacy provides the drug to the patient, who then takes it to the appointment.

In both cases, the specialty pharmacy bills the payer for the drug, which effectively reduces cost for both the physician and payer.

Coverage under the pharmacy benefit can also provide payers with a greater ability to track and manage product utilization.

— Krishna Rutvij Patel, PharmD

**Sources:** EMD Serono Specialty Digest, 9th Edition; Pharmacy Benefit Management Institute 2014 Specialty Drug Benefit Report
Old Drug in New Package Promises to Calm the Agitated

Adasuve helps people with bipolar disease or schizophrenia recover from an intense state of agitation

Thomas Morrow, MD

Adasuve, an orally inhaled version of loxapine, may fill a void in the management of patients with schizophrenia or bipolar disorder.

Agitation is a ubiquitous human experience. Defined as an inner distress, it is associated with a number of feelings described as nervousness, restlessness, anguish, or panic or as a sensation of being out of control or overwhelmed. Most people have developed mechanisms to control these feelings and prevent them from degenerating to a dysfunctional state unless there is some catastrophic event, such as a death or a massive natural disaster.

But some people with bipolar disease or schizophrenia deteriorate into a dysfunctional state. These feelings result in a manifestation of hostility, difficulty controlling impulses, uncooperative behavior, and even violence. The time of escalation to agitation can be minutes to days, and it can happen randomly.

Current treatment can take hours to days to calm and stabilize the patient. During my ER service, it was not uncommon for a severely agitated patient to require three to four Marine-size orderlies to restrain him to administer an injection, typically of an antipsychotic. Often there was injury in these dramatic confrontations to aid a patient.

Inpatient psychiatric units and emergency rooms still routinely face this behavior. In fact, a survey of psychiatric emergency service facilities reported an average of eight patient-to-staff assaults per year; most resulted in injury to a staff sufficient to cause work-time loss. In another survey, done by the Emergency Nurses Association, more than 50% of nurses reported having been verbally or physically abused at work within the previous week.

For serious escalation of agitation, effective intervention is paramount. The Consensus Guidelines for Treatment of Behavioral Emergencies, published in 2001, identified a number of requirements for effective anti-agitation therapy. The ideal drug would have rapid onset, provide control of aggressive behavior, be reliable, and preserve the physician-patient relationship. Until recently, no drug met all of these criteria.

Current standard-of-care drug classes are antipsychotics in occasional combination with benzodiazepines. These drugs are available in pills and liquids, orally disintegrating tablets, and intramuscular formulations. Intramuscular forms are the most rapid, but even these have an onset of between 15 and 120 minutes for patients with schizophrenia and 30 to 90 minutes in patients with bipolar disorder. In addition, patients often resist, with the result that they need to be manually immobilized, risking a needle stick or other injury to the health care provider. The use of force to immobilize the patient can lead to mental trauma that compromises the patient-physician relationship.

New treatment for agitation

A unique technology has recently resulted in the reformulation of an old and trusted drug to allow for a rapid, readily available, and acceptable method of meeting the criteria of the consensus guidelines. Relying on the huge drug-absorptive surface area of the lungs that allows therapeutic peak serum levels in about two minutes, loxapine, introduced in 1975, is now approved for use in the proprietary Staccato delivery system developed by Alexza. Named Adasuve and marketed by Teva, this orally inhaled product consists of controlled, rapid heating of a thin film of loxapine to form a...
thermally generated, highly pure drug vapor. Inhaled, this vapor condenses into aerosol particles of a size that allows distribution deeply into the lung. It has gained approval “for the acute treatment of agitation associated with schizophrenia or bipolar disorder in adults.”

The device reminds one of an electronic cigarette, though functionally it is not similar. It consists of a tube-shaped article with a sealed inner assembly of stainless steel with a battery-operated heat-generating unit coated with loxapine.

A breath sensor activates the heat package, causing the drug to be vaporized and allowing it to be delivered in about 200 milliseconds after activation by the breath. After the drug leaves the device, a 99.6% pure drug aerosol rapidly cools to a safe temperature in the airflow and condenses to form the small particles that are distributed to the lung mucosa and then absorbed. There is no reliance on breath-hand coordination as with a metered-dose inhaler, nor on forceful inhalation, as with a dry powder inhaler. It also requires no priming, cleaning or maintenance, as it is a one-time-use device.

Adasuve was investigated in 11 studies including eight phase 1 studies, one phase 2 study and two phase 3 studies, providing sufficient safety and efficacy data to lead to FDA approval. The primary efficacy endpoint was the change in Positive and Negative Symptom Scale, Excited Component score as compared with placebo. This scale asks the investigator to rate, from 1 to 7, five symptoms associated with agitation: poor impulse control, tension, hostility, uncooperativeness, and excitement. The secondary endpoint was the Clinical Global Impression Scales, another measure of agitation and improvement over time. A given study participant received up to three doses and was observed for 24 hours, consistent with the intended short-term use of Adasuve.

**Measurable effect**

The Staccato aerosolized drug delivery technology provides intravenous-like kinetics. After administration, loxapine binds to and blocks several dopamine and serotonin receptors, providing rapid relief of agitation. On sedation scales, the effect can be measured in as little as two minutes. The effectiveness of Adasuve was evident in virtually all patients within 10 minutes, with the peak effect at about one half hour. In addition, efficacy was evident for all assessment times in the 24 hours after the first dose. Adasuve produced significant improvement of agitation in both scoring endpoints.

Roughly half of patients in all clinical studies required just a single dose of Adasuve.

Safety was studied in 524 patients who received the active drug, and it was compared with 263 people who received the placebo. Three patients using Adasuve required discontinuations, one experienced bronchospasm, and two experienced anxiety. No serious adverse events were thought to be due to the study drug. Most were mild and self-limited, with dysgeusia, an odd taste in the mouth, the most common, followed by throat irritation. Other adverse events were expected: sedation, somnolence, and fatigue. The drug carries a warning that it can cause bronchospasm and has the potential to lead to respiratory distress and respiratory arrest.

This has led to a Risk Evaluation and Management Strategy. The drug should be administered only in a health care facility prepared to handle airway emergencies.

Adasuve provides a welcome development for those health care professionals caring for patients with schizophrenia or bipolar disorder — and yet another example of how yesterday’s medicine can often be improved to provide Tomorrow’s Medicine for people in need.
2025: Many more elderly, many more specialists

There will be a lot more demand for vascular surgeons and cardiologists by 2025, according to a study in Health Affairs. At 31%, vascular surgery has the highest projected demand growth.

Demand will vary by state. So while there will be a 20–25% increase in demand for cardiology services nationally over the next decade, “the projected increase in demand ranges from 5% in West Virginia to 51% in Nevada,” the authors write.

Researchers constructed a model that takes into account a growing and aging population as well as better access to health care, thanks to the Affordable Care Act. The population is expected to grow 9.5% between 2013 and 2025, but the number of people 65 and older is expected to grow 45%.

Advances in technology will be one of the wild cards, say the authors, and “can lead to increased demand for services and providers (for example, new treatment options) as well as to reduce demand (such as cures for chronic conditions).”

They add that “the increased use of value-based insurance design and efforts to make patients and providers more cost-conscious might reduce demand for service.”

Projected growth in demand for FTE* physicians in selected specialties, 2013–2025

* Full-time equivalent

# Personalized Medicine and Payers

An educational session for payers focusing on cost efficiency, value, outcomes, and impacts on treatment of personalized medicine.

**AVBCC**

**May 8, 2014**

Loews Hollywood Hotel

Los Angeles, CA

## Agenda

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
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<tbody>
<tr>
<td>7:00am – 8:30am</td>
<td>Special Session: Value-Based Strategies for Patients with Multiple Myeloma&lt;br&gt;Supported by funding from Millennium: The Takeda Oncology Company</td>
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<tr>
<td>8:30am – 8:40am</td>
<td>Introductions and Opening Remarks&lt;br&gt;Michael A. Kolodziej, MD; Grant Lawless, RPh, MD, FACP</td>
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<td>8:40am – 9:20am</td>
<td>Session 1: Personalized Medicine and Value&lt;br&gt;Peter Bach, MD, MAPP, Memorial Sloan-Kettering Cancer Center&lt;br&gt;Michael A. Kolodziej, MD, National Medical Director, Oncology Solutions, Aetna</td>
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<td>9:20am – 10:00am</td>
<td>Session 2: Measuring the Value of Prognostic and Predictive Outcomes&lt;br&gt;Gary Palmer, MD, JD, MBA, MPH, Senior Vice President, Medical Affairs and Commercial Development, Foundation Medicine&lt;br&gt;Macey Johnson, Vice President of Managed Care and Reimbursement, BioTheranostics</td>
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<td>10:00am – 10:40am</td>
<td>Session 3: Utilizing Big Data to ID Phenotypes and Predictive Outcomes&lt;br&gt;Mark Kris, MD, Oncologist, Memorial Sloan-Kettering Cancer Center&lt;br&gt;Jennifer Malin, MD, PhD, Medical Director, Oncology, WellPoint&lt;br&gt;George W. Sledge, MD, FASCO, Chief of Oncology, Stanford University Department of Medicine</td>
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<td>10:40am – 11:20am</td>
<td>Session 4: Value Paradigm in Drug Development&lt;br&gt;Louis Jacques, MD, Director, Coverage and Analysis Group, Centers for Medicare &amp; Medicaid Services&lt;br&gt;Kevin Knopf, MD, MPH, California Pacific Medical Center&lt;br&gt;Christiane Langer, MD, Lead Medical Director for CRC, GU, and GBM, Genentech</td>
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<td>11:20am – 12:00pm</td>
<td>Panel Discussion - How will personalized medicine impact future treatment and use existing therapy?&lt;br&gt;Louis Jacques, MD, Director, Coverage and Analysis Group, Centers for Medicare &amp; Medicaid Services&lt;br&gt;Jennifer Malin, MD, PhD, Medical Director, Oncology, WellPoint</td>
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<td>12:00pm – 12:15pm</td>
<td>Break</td>
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<td>12:15pm – 1:15pm</td>
<td>Lunch/Product Theater</td>
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<td>1:15pm – 2:45pm</td>
<td>Meet the Experts Roundtables&lt;br&gt;Al Benson, MD, Professor of Medicine and Oncology, Northwestern University Medical School&lt;br&gt;Mark Kris, MD, Oncologist, Memorial Sloan-Kettering Cancer Center</td>
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<td>2:45pm – 3:00pm</td>
<td>Break</td>
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<td>3:00pm – 4:00pm</td>
<td>Poster Presentations</td>
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<td>4:00pm – 5:00pm</td>
<td>Poster and Session Discussant</td>
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<tr>
<td>5:00pm – 7:00pm</td>
<td>Cocktail Reception in the Exhibit Hall</td>
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Call for Papers

MANAGED CARE welcomes submission of many kinds of manuscripts. All papers receive editorial and professional review, but the degree varies. Authors of research and review articles will not go wrong if they follow the Uniform Requirements of Manuscripts Submitted to Biomedical Journals (http://www.icmje.org/urm_full.pdf), which are widely known.

We will be flexible on matters of form and methods of communication with the contributing authors, and on many other matters, but the journal does endorse the fundamental editorial standards expressed in the Uniform Requirements.

The editors are interested in reviewing manuscripts that report on original scientific research on a range of related topics that include processes, procedures, or programs; treatments; clinical outcomes; cost-effectiveness of programs and products; performance of various types of managed care organizations; disease management; pharmacy issues, especially regarding biotechnology; and policy implications. Academic submissions may also include, but are not limited to, drug class reviews, disease management reviews, pharmacoeconomic analyses, and outcomes research evaluations.

We also welcome commentaries, book reviews, letters to the editor, and so on. Many articles in MANAGED CARE take the form of business reporting. We welcome queries from professional business writers with experience in the subject they propose to write about, and also from people in medical, pharmaceutical, and health care business posts who can provide guidance and insight to our readers.

Submissions may be via e-mail; paper submission is no longer required. Please contact the editor, John Marcille, via phone (267-685-2784) or e-mail (jmarcille@medimedia.com) for more information and advice on the appropriateness of a topic or treatment of a topic.

All authors must disclose relationships that are or might be perceived to be conflicts of interest. Submitted articles may not be under review elsewhere — that is, no competing, simultaneous submissions. Articles may be withdrawn no later than four weeks before our printer’s deadline if a publication date has been assigned.

Submissions will be in any Microsoft Word format. Tables with more than two columns should be on spreadsheets, and all graphics should be in separate graphics files, not embedded in the Word document.

Further details about the peer review process, as well as conflict-of-interest forms, are at http://www.managedcaremag.com/callforpapers.