DRUG FORMULARY REVIEW™
Utilization, Criteria and Outcomes

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NOVEMBER 2004
VOL. 20, NO. 11 (pages 81-88)

Rofecoxib withdrawal from market shakes the pharmaceutical industry

Patients should reconsider basic NSAIDs as alternatives, pharmacist says

The recent withdrawal of the popular arthritis drug rofecoxib (Vioxx) from the market has left patients scrambling for alternatives and providers looking at long-term consequences.

"I was not dramatically surprised [about the withdrawal], but it has shaken the industry," says **Gordon J. Vanscoy**, PharmD, CACP, MBA, assistant dean for managed care and associate professor of pharmaceutical sciences at the University of Pittsburgh School of Pharmacy. He also is chairman and chief executive officer of University Pharmacotherapy Associates in Monroeville, PA. "There has been concern about the COX-2 inhibitors, even since the original FDA submission."

The facts behind the withdrawal

Merck & Co. announced the voluntary withdrawal of its drug Sept. 30 after viewing three-year data from a prospective, randomized, placebo-controlled clinical trial — APPROVe (Adenomatous Polyp Prevention on VIOXX).

Merck is stopping the trial, which was designed to evaluate the efficacy of rofecoxib 25 mg in preventing recurrence of colorectal polyps in patients with a history of colorectal adenomas. In this study, there were nearly twice as many cardiovascular events, such as heart attack and stroke, beginning after 18 months of treatment in the patients taking rofecoxib compared to those taking placebo. The trial's enrollment began in 2000 and included 2,600 patients.

"Although we believe it would have been possible to continue to market VIOXX with labeling that would incorporate these new data, given the availability of alternative therapies and the questions raised by the data, we concluded that a voluntary withdrawal is the responsible course to take," says **Raymond V. Gilmartin**, chairman, president, and chief executive officer of Merck, in a statement.

Merck already had changed the drug's labeling following the results of the safety study VIGOR (Vioxx Gastrointestinal Outcomes Research). The

trial had found an increased risk of serious cardiovascular events, including heart attacks and strokes, in patients taking rofecoxib compared to patients taking naproxen. After reviewing the results of the VIGOR study and other available data from controlled clinical trials, the FDA had consulted with its Arthritis Advisory Committee in February 2001 and implemented labeling changes in April 2002. Those changes included information about the increase in risk of cardiovascular events, including heart attack and stroke.

After the announcement, the bad news continued for Merck. In early October, *The Wall Street Journal* reported that a study led by a FDA safety official projects that the widespread use of rofecoxib may have led to more than 27,000 heart attacks and sudden cardiac deaths before the drug's withdrawal.

Drug Formulary Review (ISSN#1548-2790), including **Drug Criteria & Outcomes**™, is published monthly by Thomson American Health Consultants, 3525 Piedmont Road, Building Six, Suite 400, Atlanta, GA 30305. Telephone: (404) 262-7436. Periodical postage paid at Atlanta, GA 30304. POSTMASTER: Send address changes to **Drug Formulary Review**, P.O. Box 740059, Atlanta, GA 30374.

Subscriber Information

Customer Service: (800) 688-2421 or fax (800) 284-3291, (customerservice@ahcpub.com) **Hours of operation:** 8:30 a.m.-6 p.m. Monday-Thursday; 8:30 a.m.-4:30 p.m. Friday.

Subscription rates: One year (12 issues), $499. Outside U.S., add $30 per year, total prepaid in U.S. funds. Discounts are available for multiple subscriptions. For pricing information, call Steve Vance at (404) 262-5511. Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue date. **Back issues**, when available, are $80 each. (GST registration number R128870672.)

Thomson American Health Consultants is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This program, #381-000-04-015-H01, will be available **July 8, 2004, to July 7, 2007.**

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The number compares how many similar incidents would have occurred had the same patients been taking celecoxib (Celebrex) from the time of rofecoxib's approval in 1999 through 2003. The figures are projections based on findings from an analysis of a database of patients of the HMO Kaiser Permanente.

Reaction is varied

One Atlanta rheumatologist saw the withdrawal as inevitable. "As [Merck] said in its press release, there is probably a place for Vioxx in a certain [patient population]," says **Hayes Wilson**, MD, a rheumatologist at Piedmont Hospital in Atlanta and a medical adviser for the Arthritis Foundation.

"The problem in the global overall picture is that they marketed it as a safer drug and they, and everyone else, lost confidence that it was a safer drug. I think it is kind of a shame because Vioxx sure helped a bunch of my patients."

The risk, at least in the trials, was not one in which Merck could just restrict its labeling, Vanscoy says. "The findings that they had were broad enough where there weren't any predictors of specific individuals who were going to experience some of these adverse effects. You couldn't [say], 'We're going to take these 1.2 million people who are using the product, and we are going to isolate it to the 300,000 where we think it's going to be safest.' I don't think they could do that.

"When we end up with broad and long-term use of these agents — sometimes that is the only way we discover these adverse events," he continues.

A cardiologist from The Cleveland Clinic called the rofecoxib withdrawal an "enormous public health issue." "Even a fraction of a percent excess in the rate of serious cardiovascular events would translate into thousands of affected people," says **Eric J. Topol**, MD, chairman and professor of the department of cardiology at The Cleveland Clinic. His comments were made in an editorial in the Oct. 21 issue of the *New England Journal of Medicine* (which also was published Oct. 6 on the web site).

Officials have not heeded previous warning signs about rofecoxib, Topol says. "The senior executives at Merck and the leadership at the FDA share responsibility for not having taken appropriate action and not recognizing that they are accountable for the public health." He goes on to call for a full congressional review of the case.

What to do next?

The immediate question now is how to treat patients who have been taking rofecoxib. The

decision obviously should be based on the individual, Wilson says. "If they have risk factors for gastrointestinal bleeding and they are not sulfonamide allergic, I think the (COX-2) cousins Celebrex or Bextra are good choices."

Patients who are put on other COX-2 inhibitors should work with their pharmacists and physicians to ensure that they are being monitored appropriately for analogous side effects that were seen with rofecoxib, Vanscoy says. **(For more information about concerns about the COX-2 inhibitor class, see article, below.)**

Patients who need to be on a nonsteroidal should have patience in terms of their clinical response for the other products, he says. "The other products do provide reasonable alternatives. However, sometimes you get into the mentality that, 'What I was on was working so well, and nothing else will work.'"

Patients also should consider alternatives that may not have been given an appropriate chance, he adds, such as some of the basic nonsteroidal anti-inflammatory drugs that are known to have a broad margin of safety. ■

The focus now shifts to COX-2 inhibitor class

Some providers demanding investigations now

Now that Merck & Co. has withdrawn rofecoxib (Vioxx) from the market because of increased risk of heart attack and stroke, the attention is shifting to the other drugs of this class.

Rofecoxib, celecoxib (Celebrex), and valdecoxib (Bextra) are a subclass of nonsteroidal anti-inflammatory drugs (NSAIDs) that selectively block the enzyme COX-2 (cyclooxygenase-2). When Merck announced the rofecoxib withdrawal, it said that its study results were not necessarily applicable to others in the COX-2 inhibitor class. **(For more about the rofecoxib removal, see cover story.)**

A rheumatologist who says rofecoxib has benefited many of his patients is not too concerned about the cardiovascular risk of the other two drugs — at this point. "I think we should go by the data that we have," says **Hayes Wilson**, MD, a rheumatologist at Piedmont Hospital in Atlanta and a medical adviser for the Arthritis Foundation. "Vioxx was pulled because they got new prospective data that said that it was trending in the wrong direction for heart disease. But the data for Celebrex and Bextra are that it is safe. Any medication that is strong enough to help you is strong enough to potentially give you a side effect. Any time you take a medication, it is a calculated risk."

The other COX-2 inhibitors, though, are a concern for **Gordon J. Vanscoy**, PharmD, CACP, MBA, assistant dean for managed care and associate professor of pharmaceutical sciences at the University of Pittsburgh School of Pharmacy. He also is chairman and chief executive officer of University Pharmacotherapy Associates in Monroeville, PA. "I definitely think there needs to be more studies."

It is not known if the problem is a class effect, he says. Are the side effects inevitable after the broad use of the COX-2 products, or are they truly specific to the chemical structure of rofecoxib?

Vanscoy foresees more clinical monitoring of patients on celecoxib and valdecoxib to see if the patients experience any of the same serious cardiovascular side effects as those taking rofecoxib. "I think there is an obligation on behalf of the other manufacturers to ensure that we don't have an analogous situation."

The call to arms

Other physicians are alarmed about the rofecoxib withdrawal. The *New England Journal of Medicine* published two editorials from such physicians; the editorials were published on its web site on Oct. 6 and will appear in the Oct. 21 printed issue.

One of the editorials calls for further investigations of the COX-2 class. The APPROVe (Adenomatous Polyp Prevention on VIOXX) trial, the results of which led Merck to pull rofecoxib from the market, has shifted the burden of proof, says **Garret A. FitzGerald**, MD, professor and chair of the department of pharmacology at the University of Pennsylvania School of Medicine in Philadelphia. "[It] now rests with those who claim that this is a problem for rofecoxib alone and does not extend to other coxibs.

"We now have clear evidence of an increase in cardiovascular risk that revealed itself in a manner consistent with a mechanistic explanation that extends to all the coxibs. It seems to be time for the FDA urgently to adjust its guidance to patients and doctors to reflect this new reality."

It is essential to determine whether the cardiovascular risk is or is not a class effect, FitzGerald says. "We must remember that the absence of evidence is not the evidence of absence."

The withdrawal is a warning to the class,

although [the risks] may not hold across the class, Vanscoy says. "You are better off being safe than sorry." ■

HIV management guidelines emphasize primary care

Drug therapy adherence strategies key component

New HIV guidelines address long-term management in the context of a person's overall life and health — and emphasize the importance of strategies to improve adherence to drug regimens.

The HIV Medicine Association and the Infectious Diseases Society of America, both in Alexandria, VA, developed the guidelines. The guidelines are more about comprehensive general medicine — the primary care of patients, says **Judith A. Aberg**, MD, an HIV/ADIS care specialist at New York University and lead author of the new guidelines.

"They are not specific therapy recommendations. It's more about the general care that a patient needs."

The guidelines cover information such as prevention and early diagnosis of chronic conditions that some patients with HIV may have high risk of contracting, including diabetes and heart disease. The guidelines also address HIV transmission, diagnosis, risk screening, and management. There are special sections on caring for women and children with HIV as well.

Strategies to improve drug regimen adherence

Other guidelines may recommend specific therapies but then just brush on drug regimen adherence, Aberg says. "They don't really spend any detailed amount on it."

Adherence, however, is a critical piece to the HIV guidelines. "That is why we emphasize it, she says. "The primary care provider should educate patients about whether they need to be on therapy. And if they should be, [providers should emphasize] how important it is for them to have appropriate follow-up and monitoring and for them to take their medicines."

Adherence is so important to HIV treatment because the long-term effectiveness of HAART (highly active antiretroviral therapy) is dependent on achieving a maximum and durable suppression of viral replication, the guideline authors say. In some clinical practices, however, as few as 40% to 50% of patients achieve this goal. "The primary reason for failure to achieve maximum suppression of virus load, particularly among patients taking initial regimens, is suboptimal adherence to medications."

HAART regimen characteristics can affect patients' adherence to their regimen, the authors explain. This includes the complexity of the regimen, side effects, and the "fit" with the patient's lifestyle and daily routine. Given this, they recommend the following regimen-focused adherence strategies:

- **Prescribe simpler HAART regimens.** Focus on constructing regimens that involve fewer pills and fewer doses and that minimize food-dosing restrictions.
- **Individualize HAART regimens.** Work with each patient to choose a regimen that is tailored to his or her lifestyle and schedule. Avoid adopting a "one-regimen-fits-all" philosophy. Get the patient involved in choosing and individualizing the regimen.
- **Choose regimens with fewer side effects.** Whenever possible, avoid prescribing medications known to frequently cause very unpleasant side effects.
- **Proactively manage side effects.** Let patients know what side effects may be experienced and how each side effect will be managed if it occurs.

No matter how simple or complex the regimen is, make sure patients understand exactly how to take their medications, the authors say. "Confusion is an important cause of suboptimal adherence. Providing a dosing schedule with photographs of the medications and helping patients to correctly fill a medication organizer with their new medications are two strategies that will help decrease confusion."

Health care providers can assess patients' understanding of the regimen by having them repeat back the regimen, the authors say. Providers also should be open to patients' requests to change their HAART regimen because of side effects.

Measuring adherence to HAART in clinical practice is important, too. "Clinicians should avoid making assumptions about patients' adherence, because these assumptions are usually incorrect," the authors say. "Ideally, the adherence measurement strategy should be easily incorporated into clinical care, be inexpensive, and be helpful in assessing both baseline adherence and the effectiveness of adherence interventions."

Adherence to HAART can be measured by a

variety of methods, they continue. The most commonly used methods in clinical trials are patients reporting their own adherence and electronic medication monitoring devices, such as medication event monitoring systems. Other possible ways to assess adherence include pill counts and checking pharmacy refill records. "No single method has been established as the reference standard for measuring adherence; all have advantages and disadvantages. Once a method has been chosen, it should be used consistently to monitor each patient's adherence at each visit," the authors say.

The adherence component of these guidelines is particularly important to pharmacists, Aberg says. "One of the great movements in the past few years has been the pharmacist taking part in patient education."

When patients refill their medications, pharmacists can talk with them about the drugs, discuss side effects, and reinforce that it is critical that they take their medicines every day because of the risk of the medications failing, Aberg says. "Then [the patients] can develop resistance and could potentially lose options. If the pharmacist can [emphasize] the need for adherence, it's very important to the patients' overall care."

The guidelines were published in the September issue of *Clinical Infectious Diseases* and are available free on-line at www.journals.uchicago.edu/CID/journal/contents/v39n5.html. ■

Should AIDS therapy start at higher cell counts?

New research suggests that AIDS therapy should be initiated at higher CD4 levels than current guidelines recommend.

In the study, published in the Sept. 15 issue of *The Journal of Infectious Diseases*, researchers wanted to reevaluate the optimal time to initiate highly active antiretroviral therapy (HAART). Current guidelines recommend initiating therapy when CD4 counts are between 200/µL and 350/µL.

The researchers followed 583 HIV-seropositive and 920 HIV-seronegative injection drug users from 1997 to 2000. HIV-seropositive participants were categorized according to receipt of HAART (either initiated or switched to HAART) and initial CD4 cell count. Survival analysis that included delayed-entry and Cox proportional-hazards models was used to evaluate the effect of HAART, with adjustments for factors associated with access to HAART.

Mortality among HIV-infected injection drug users with CD4 cell counts greater than 350/µL who received HAART was similar to that of HIV-seronegative injection drug users. In addition, both groups had lower mortality than HIV-infected subjects with CD4 cell counts greater than 350/µL who did not receive HAART and those with CD4 counts between 200/ìL and 350/µL who did receive such therapy.

"Survival of HIV-seropositive participants receiving HAART approximated that of HIV-seronegative participants only when therapy was given at CD4 cell counts [are greater than] 350 cells/µL," the researchers say. "These data, restricted to seronegative injection drug users, suggest initiating or switching to HAART at higher CD4 cell levels than are currently recommended."

In an accompanying editorial, **Mauro Schechter**, MD, PhD, professor of infectious diseases at Federal University of Rio de Janeiro in Brazil, recognized the importance of the study, although he said it had several limitations. He cautioned that the evidence still is mixed about what CD4 cell level to start HAART, but that the guidelines may change with further study data. ■

Oral erythromycin, CYP3A inhibitor combination risky

Patients who took the antibiotic erythromycin with medications that inhibit CYP3A drug enzymes, such as certain calcium-channel blockers, certain antifungal drugs, and some antidepressants, had a five times greater risk of sudden death from cardiac causes than patients who did not take the drugs at the same time, according to a study co-funded by the Agency for Healthcare Research and Quality (AHRQ), the U.S. Food and Drug Administration, and National Institutes of Health. The study was published in the Sept. 9 issue of the *New England Journal of Medicine*

In the study, researchers at AHRQ's Center for Education and Research on Therapeutics (CERTs) at Vanderbilt University in Nashville, TN, did not find the same increased risk for patients who took CYP3A inhibitors with other antibiotics,

such as amoxicillin, or for those who had taken erythromycin in the past. The CERTs program is a national initiative to increase the awareness of the benefits and risks of new, existing, or combined uses of therapeutics and devices.

The researchers reviewed medical records for the Tennessee Medicaid program and identified patients who had experienced sudden death from cardiac causes during the period Jan. 1, 1988, to Dec. 31, 1993. They reviewed prescriptions for erythromycin, amoxicillin, and other medications from computerized Medicaid pharmacy files that included the drug, dose, and total medication dispensed.

The researchers concluded that clinicians should avoid prescribing a combination of erythromycin and CYP3A inhibitors to patients at the same time because there are safer alternatives. ▼

Many patients don't tell docs about medication underuse

A recent study found that two-thirds of chronically ill patients who planned to underuse medication because of the cost did not tell a clinician in advance. Thirty-five percent never discussed it at all.

The researchers conducted a nationwide survey of 660 older adults with chronic illnesses who reported underusing medication in the prior year because of cost. The researchers assessed whether patients discussed cost-related medication underuse with clinicians, reasons that some patients did not talk with clinicians about this problem, how clinicians responded when this issue was raised, and how helpful patients perceived clinicians to be. The study was published in the Sept. 13 issue of the *Archives of Internal Medicine*.

Of those who did not tell a clinician, 66% reported that no one asked them about their ability to pay for prescriptions, and 58% reported that they did not think providers could help them. When patients talked with clinicians about medication costs, 72% found those conversations helpful. However, 31% reported that their medications never were changed to a generic or less expensive alternative, and few patients were given other forms of assistance such as information about programs that help pay drug costs (30%) or where to purchase less expensive medication (28%). Patients were most likely to find clinicians helpful if clinicians provided free samples, asked about problems paying for prescriptions, and offered advice about how to pay for patients' current regimens. ▼

Scientists find potential way to control drug-resistant bacteria

Researchers are reporting that they believe they have discovered a potential new way to control drug-resistant bacteria. The results of the study were published in the Sept. 23 issue of the journal *Nature*.

The new research, funded by the National Institute of Allergy and Infectious Diseases, part of the National Institutes of Health, found that bacteriophages contain genes that allow them to quickly change their proteins to bind to different cell receptors. Researchers at the University of California-Los Angeles made the discovery. They found that the genome of the phage that infects *Bordetella bronchiseptica*, a relative of the bacterium that causes whooping cough, contains a series of genes that change the part of the virus that binds to the bacterial cell.

These genes allow the phage to rapidly evolve new variants that can recognize and attack bacteria that may have become resistant to the previous phage. The researchers believe that this discovery could lead to the use of genetically engineered phages to treat bacterial infections that have become resistant to antibiotics. ▼

Drug shortages negatively affect patient safety, costs of care

A new study finds that ongoing drug shortages are having far-ranging, negative effects on patient care and hospital costs.

The survey, published in the Oct. 1 issue of the *American Journal of Health-System Pharmacy*, polled almost 1,500 pharmacy directors in U.S. health systems. The study revealed that 95% of respondents believe shortages have created roadblocks and hurdles for treating patients with the best medication. Sixty-one percent believe the scarcity of certain drugs has compromised patient care. The American Society of Health-System Pharmacists and pharmacy residents at Johns Hopkins Hospital in Baltimore conducted the survey in March 2003.

Pharmacy directors reported that drug shortages

have affected patients in a number of ways, including contributing to the delay or cancellation of certain medical procedures, prolonged patient stays in hospitals, and serious medication errors.

Shortages also have affected drug prices as pharmacists are forced to buy the same product at higher-than-contracted prices or more expensive alternative products in the same therapeutic class. Survey respondents reported that shortages force their hospitals to spend an annual average of $20,000 more in incremental drug purchasing costs.

According to the survey, pharmacists are spending more time managing shortages, including tracking product availability; identifying therapeutic alternatives; contracting with vendors, manufacturers, and group purchasing organizations to buy therapeutic alternatives; and preparing written communications and training other health care providers on using other medications. ▼

Wyeth: Glass vial breakage of pantoprazole sodium

Wyeth is informing health care professionals about reports of glass vial breakage of pantoprazole sodium (Protonix IV 40 mg vials) for injection during attempts to connect vials to spiked intravenous (IV) system adaptors.

This may be a safety issue for pharmacists when preparing pantoprazole IV vials in combination with spiked IV system adaptors, both during manual assembly and while using mechanical assistance, Wyeth says.

It is recommended that each vial be reconstituted with 10 mL of 0.9% sodium chloride injection, USP. This solution can be administered over a period of at least two minutes or further diluted (admixed) with 100 mL of 5% dextrose injection, USP, 0.9% sodium chloride injection, USP, or lactated ringer's injection, USP. The admixed solution should be administered intravenously over a period of approximately 15 minutes. For more information about the warning, see www.fda.gov/medwatch/SAFETY/2004/safety04.htm#protonix. ■

New FDA Approvals

These drugs were recently approved by the FDA:

• ***Hydromorphone hydrochloride (Palladone) capsules by Purdue Pharma L.P.*** The FDA has approved hydromorphone hydrochloride (Palladone) for the management of persistent moderate-to-severe pain in patients requiring continuous around-the-clock opioid pain relief for an extended period of time.

Hydromorphone is an extended-release formulation that comes in 12, 16, 24, and 32 mg capsules. Hydromorphone must be swallowed whole because chewing, dissolving, or crushing the contents of the capsules leads to the rapid absorption of a potentially fatal dose.

This drug only should be used in patients who are already receiving opioid therapy and who require a total daily dose of at least 12 mg oral hydromorphone or its equivalent. Hydromorphone offers a therapeutic choice for opioid-tolerant patients who might otherwise be candidates for other opioids and who do not achieve satisfactory therapeutic results with these other products.

Hydromorphone currently is a Schedule II controlled substance, the highest level of control for drugs with a recognized medical use. Based on the risks associated with the drug, including the potential for abuse of hydromorphone, the FDA has worked with the sponsor to develop a comprehensive risk management program (RMP). The RMP was designed with three potential risk situations identified. These are the risks posed by improper dosing, indication, or patient selection; the risk posed by accidental pediatric exposure to the drug; and the risk posed by abuse or diversion of hydromorphone capsules.

In addition to the potential for abuse and addiction, respiratory depression is the chief potential risk associated with hydromorphone,

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if not properly dosed. Other common side effects include nausea, vomiting, dry mouth, dizziness, urinary retention, and constipation.

• ***New indication for duloxetine hydrochloride (Cymbalta) by Eli Lilly & Co.*** The FDA has approved duloxetine hydrochloride (Cymbalta) capsules for the management of the pain associated with diabetic peripheral neuropathy. This is the first drug specifically approved for this indication. The drug was previously approved for the treatment of major depressive disorder.

The safety and effectiveness of duloxetine were established in two randomized, controlled studies of approximately 1,074 patients. Although the mechanism of action is unknown, patients treated with duloxetine reported a greater decrease in pain compared to placebo. In these trials, 58% of patients treated with duloxetine reported at least a 30% sustained reduction in pain. In comparison, 34% of patients treated with placebo reported this magnitude of sustained pain reduction.

Duloxetine comes in a capsule and can be taken once a day. The recommended daily dose is 60 mg. (Patients in the studies did not tolerate the 120 mg per day — although still considered safe and effective — as well as the 60 mg dose.) The most commonly reported side effects were nausea, dry mouth, constipation, and diarrhea. In some cases, patients experienced dizziness and hot flashes. ■

United States Postal Service
Statement of Ownership, Management, and Circulation

1. Publication Title	2. Publication No.	3. Filing Date
Drug Formulary Review	1 5 4 8 - 2 7 9 0	10/1/04
4. Issue Frequency	5. Number of Issues Published Annually	6. Annual Subscription Price
Monthly	12	$499

7. Complete Mailing Address of Known Office of Publication *(Not Printer) (Street, city, county, state, and ZIP+4)*
3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, Fulton County, GA 30305
Contact Person: Robin Salet
Telephone: 404/262-5489

8. Complete Mailing Address of Headquarters or General Business Office of Publisher *(Not Printer)*
3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, GA 30305

9. Full Names and Complete Mailing Addresses of Publisher, Editor, and Managing Editor *(Do Not Leave Blank)*
Publisher *(Name and Complete Mailing Address)*
Brenda Mooney, 3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, GA 30305

Editor *(Name and Complete Mailing Address)*
Sue P. Coons, same as above

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PS Form **3526**, September 1998 *See instructions on Reverse)*

13. Publication Name: Drug Formulary Review
14. Issue Date for Circulation Data Below: September 2004

15. Extent and Nature of Circulation			Average No. of Copies Each Issue During Preceding 12 Months	Actual No. Copies of Single Issue Published Nearest to Filing Date
a. Total No. Copies *(Net Press Run)*			417	250
b. Paid and/or Requested Circulation	(1)	Paid/Requested Outside-County Mail Subscriptions Stated on Form 3541. *(Include advertiser's proof and exchange copies)*	161	148
	(2)	Paid In-County Subscriptions *(Include advertiser's proof and exchange copies)*	1	3
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c. Total Paid and/or Requested Circulation *(Sum of 15b(1) and 15b(2)*			193	173
d. Free Distribution by Mail *(Samples, Complimentary and Other Free)*	(1)	Outside-County as Stated on Form 3541	14	14
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g. Total Distribution *(Sum of 15c and 15f)*			232	212
h. Copies Not Distributed			185	38
i. Total *(Sum of 15g, and h.*			417	250
Percent Paid and/or Requested Circulation *(15c divided by 15g times 100)*			83	82

16. Publication of Statement of Ownership
Publication required. Will be printed in the November 2004 issue of this publication. ☐ Publication not required.

17. Signature and Title of Editor, Publisher, Business Manager, or Owner: Brenda L. Mooney Publisher — Date: 9/27/04

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PS Form **3526**, September 1999 *(Reverse)*

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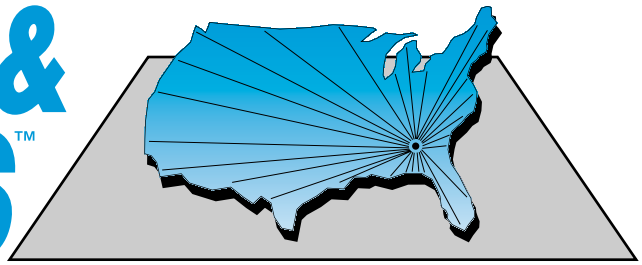

Cinacalcet HCl (Sensipar) Formulary Evaluation

Part 1 of 2: Indications, Mechanism of Action, Pharmacokinetics, Dosing & Administration, Adverse Events, amd Interactions

By **April H. Eubanks**, PharmD Candidate
Harrison School of Pharmacy
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Cinacalcet is the first in a class of calcimimetic agents that increases the sensitivity of the calcium-sensing receptor to activation by extracellular calcium.

Indications

Cinacalcet is indicated for the treatment of:

- Secondary hyperparathyroidism in patients with chronic kidney disease (CKD) on dialysis.
- Hypercalcemia in patients with parathyroid carcinoma.

Background on indications

Secondary hyperparathyroidism in patients with chronic kidney disease on dialysis:

Renal osteodystrophy, also known as renal bone disease, is a major cause of morbidity and mortality in patients with chronic kidney disease on dialysis. As renal failure progresses and glomerular filtration rate (GFR) declines, the kidneys' ability to excrete phosphorus also declines, resulting in hyperphosphatemia. About 70% of all patients with end stage-renal disease (ESRD) have hyperphosphatemia, with approximately 40% having values that exceed 6.5 mg/dL (normal: 2.5-4.5 mg/dL).

High levels of phosphorus directly stimulate the release of parathyroid hormone (PTH). In addition, retention of phosphorus inhibits renal activation of vitamin D, which, in turn, reduces gut absorption of calcium. Low levels of calcium in the blood provide a major stimulus for secretion of PTH.

The parathyroid glands secrete PTH in an attempt to restore the normal balance of phosphorus and calcium. In normal patients, PTH release reduces reabsorption of phosphorus in the renal tubule and promotes its excretion. Thus, phosphorus and calcium levels return to normal. However, as functional renal mass declines, this renal response to PTH declines and hyperphosphatemia is not relieved. The resulting hypocalcemia causes PTH to stimulate the release of calcium through mobilization from bone.

Traditional agents used to treat hyperparathyroidism typically include vitamin D sterols and calcium-containing phosphate binders. These agents, however, put the patient at risk for developing hypercalcemia and may not be efficient at resolving the hyperparathyroidism.

Parathyroid carcinoma:

Hypercalcemia secondary to parathyroid carcinoma occurs as the result of uncontrolled release of PTH.

Mechanism of action

Cinacalcet prevents progression to renal osteodystrophy by decreasing PTH secretion. The calcium-sensing receptor located on the surface of the chief cell of the parathyroid gland is the principle regulator of PTH secretion. Cinacalcet increases the sensitivity of the calcium-sensing receptor to extracellular calcium, and thus, reduces the stimulation of PTH secretion. This reduction of PTH, in turn, reduces mobilization of bone.

Pharmacokinetics

Absorption and distribution

• After oral administration, maximum plasma concentration is achieved in approximately 2-6 hours.

• C_{max} (maximum concentration) and AUC (area under the curve) were increased 82% and 68%, respectively, when cinacalcet was administered with a high-fat meal compared to fasting. C_{max} and AUC were increased 65% and 50%, respectively, when cinacalcet was administered with a low-fat meal compared to fasting.

• Cinacalcet concentrations decline in a biphasic fashion with a terminal half-life of 30-40 hours.

• Steady-state is achieved within seven days.

• Volume of distribution is high (approximately 1,000 L), indicating extensive distribution.

• Cinacalcet is highly plasma-protein bound (93-97%).

Metabolism and excretion

• Primarily metabolized by CYP3A4, CYP2D6, and CYP1A2.

• In healthy volunteers, a 75 mg dose of cinacalcet was rapidly and extensively metabolized via:

— oxidative N-dealkylation;

— oxidation of the naphthalene ring on the parent drug.

• Renal excretion is the primary route of elimination with approximately 80% of the dose recovered in the urine and 5% in the feces.

Recommended dosing and administration

• Cinacalcet should be taken with food or shortly after a meal.

• Cinacalcet tablets should not be divided. There have been no studies with the drug to suggest that it would be safe or that the drug would be efficacious when divided or crushed.

Secondary hyperparathyroidism in patients with CKD on dialysis

• Oral starting dose is 30 mg once daily.

• Serum calcium and phosphorus should be measured within one week.

• PTH should be measured one to four weeks after initiation or dose adjustment.

• Cinacalcet should be titrated no more frequently than every two to four weeks through sequential doses of 60, 90, 120, and 180 mg once daily to target PTH consistent with the NKF-K/DOQI (National Kidney Foundation-Kidney Disease Outcomes Quality Initiative) recommendation for CKD patients on dialysis of 150-300 pg/mL.

• Cinacalcet may be used alone or in combination with vitamin D sterols and/or phosphate binders.

Parathyroid carcinoma

• Oral starting dose is 30 mg twice daily.

• The dose should be titrated every two to four weeks through sequential doses of 60 mg twice daily, 90 mg twice daily, and 90 mg three or four times daily as necessary to normalize serum calcium levels.

Special populations:

• **Hepatic insufficiency:** Patients with moderate-to-severe hepatic impairment (as indicated by the Child-Pugh method) should have PTH and serum calcium levels monitored closely throughout treatment due to higher AUC values (2.4-4.2 times higher) than seen in normal patients.

• **Renal insufficiency:** No dosage adjustments necessary.

• **Geriatric patients:** No dosage adjustments necessary.

• **Pediatric patients:** Not studied in patients younger than 18 years of age.

Monitoring

Serum calcium and phosphorus should be measured within one week, and PTH should be measured one to four weeks after initiation or dose adjustment. Once the maintenance dose has been established, serum calcium and phosphorus should be measured about every month, and PTH every one to three months.

Table 1: Adverse events

Event	Placebo (n = 470)	Cinacalcet (n = 656)
Nausea	19%	31%
Vomiting	15%	27%
Diarrhea	20%	21%
Myalgia	14%	15%
Dizziness	8%	10%
Hypertension	5%	7%
Asthenia	4%	7%
Anorexia	4%	6%
Pain chest, noncardiac	4%	6%
Access infection	4%	5%

Source: Table extrapolated from Sensipar package insert, Amgen.

Table 2: Studied interactions

Drug	Interaction	Management
Ketoconazole	Cinacalcet AUC and C_{max} increased 2.3 and 2.2 times, respectively, when a single 90 mg cinacalcet dose on day 5 was administered to subjects treated with 200 mg ketoconazole twice daily for 7 days compared to 90 mg cinacalcet given alone.	Dose adjustment of cinacalcet may be necessary. PTH and serum calcium concentrations should be monitored closely if a patient initiates or discontinues therapy with a strong CYP3A4 inhibitor such as ketoconazole, erythromycin, or itraconazole.
Amitriptyline	Concurrent administration of 25 mg or 100 mg cinaclacet with 50 mg amitriptyline increased amitriptyline exposure and nortriptyline exposure by approximately 20% in CYP2D6 extensive metabolizers.	Monitor for increased effects/toxicity of tricyclic antidepressants.
Calcium carbonate	No significant interaction.	None needed.
Pantoprazole	No significant interaction.	None needed.
Sevelamer HCl	No significant interaction.	None needed.
S Warfarin and R Warfarin	No significant interaction.	None needed.

Source: Amgen, Sensipar package insert.

Adverse events

The incidence of serious adverse events was similar in the cinacalcet and placebo groups, 29% and 31%, respectively **(see Table 1).**

Drug interactions

Cinacalcet is a strong inhibitor of CYP2D6, but not CYP1A2, CYP2C9, CYP2C19, or CYP3A4. Cinacalcet also is a substrate of CYP1A2, CYP2D6, and CYP3A4 **(see Table 2 for more information on interactions)**.

Potential Interactions:

- *CYP2D6 Substrates*

Haloperidol	Fluoxetine
Metoprolol	Meperidine
Codeine	Oxycodone
Paroxetine	

In addition to these, any inducers or inhibitors of CYP1A2, CYP2D6, or CYP3A4 could potentially affect the metabolism of cinacalcet.

- *Common Inducers:*

Smoking	Rifampin
Phenytoin	Ritonavir
Phenobarbital	Carbamazepine

- *Common Inhibitors:*

Ketoconazole	Fluoxetine
Azole antifungals	Grapefruit Juice
Cimetidine	Macrolides
Cyclosporine	Metronidazole
Amiodarone	

Precautions

- ***Contraindication:*** Cinacalcet is contraindicated in patients with hypersensitivity to any component of the product.
- ***Seizures:*** Because seizure threshold is lowered significantly by reductions in serum calcium levels, patients, particularly those with history of a seizure disorder, should have serum calcium levels monitored closely during treatment.
- ***Hypocalcemia*:** Patients taking cinacalcet should be monitored closely for the occurrence of hypocalcemia. Potential manifestations include paresthesias, myalgias, cramping, tetany, and convulsions.
- ***Adynamic bone disease:*** If PTH levels are suppressed below 100 pg/mL (when assessed using the standard Nichols immunoradiometric assay), patients may develop adynamic bone disease.
- ***Hepatic insufficiency:*** Cinacalcet exposure as assessed by AUC in patients with moderate and severe hepatic impairment were 2.4 and 4.2 times higher, respectively, than that in patients with normal hepatic function. Patients with moderate and severe hepatic impairment should be monitored throughout treatment.
- ***Pregnancy Category C:*** No teratogenicity was observed in female rats when exposed during gestation to doses up to four times those of human exposure (180 mg/day) based on AUC comparison. Decreased fetal body weights were observed at all doses in conjunction with maternal decreased food intake and body weight gain.

Storage

Store at 25°C (77°F); when outside normal storage conditions, keep drug in temperature range of 15-30°C (59-86°F). ■

IN THE PIPELINE

• MediGene AG has initiated a clinical Phase I/II trial of the drug candidate NV1020 for the treatment of **liver metastases developing from colorectal cancer.** NV1020 is a herpes simplex virus, genetically modified for the specific destruction of tumor cells without harming healthy tissue.

• Sangart has initiated a Phase II clinical trial involving MP4 (Hemospan), a hemoglobin-based oxygen carrier designed to serve as an a**lternative for blood transfusions.**

• Corautus Genetics has begun its Phase IIb clinical trial to evaluate the safety and efficacy of Vascular Endothelial Growth Factor-2 (VEGF-2) for the treatment of **severe cardiovascular disease**.

• Encysive Pharmaceuticals has completed enrolling 240 patients in the company's multicenter, Phase III STRIDE-2 (Sitaxsentan To Relieve ImpaireD Exercise) trial to **evaluate the safety and efficacy of sitaxsentan (Thelin) in patients with pulmonary arterial hypertension**.

• Genentech and OSI Pharmaceuticals have initiated a Phase IIIB clinical study of the investigational therapy erlotinib HCl (Tarceva) in **patients with second- and third-line non-small cell lung cancer who have previously received chemotherapy**.

• AstraZeneca is recruiting patients for a new clinical trial for non-small-cell lung cancer. The INTEREST (IRESSA Non-small-cell lung cancer Trial Evaluating REsponse and Survival against Taxotere) trial will **e**valuate the effectiveness of the oral anti-cancer agent gefitinib (IRESSA) tablets vs. docetaxel (Taxotere) in patients with **locally advanced or metastatic non-small-cell lung cancer who have previously received platinum-based chemotherapy**.

• Threshold Pharmaceuticals has received a Special Protocol Assessment from the FDA for a pivotal Phase III clinical trial to evaluate Glufosfamide in patients with **metastatic pancreatic cancer refractory to first-line treatment**. ■

CE *Questions*

Pharmacists participate in this continuing education program by reading the article, using the provided references for further research, and studying the CE questions. Participants should select what they believe to be the correct answers.

Participants must complete a post-test and evaluation form provided at the end of each semester (June and December) and return them in the reply envelopes provided. A certificate of completion requires a passing score of 70% or higher. When a passing test and evaluation form are received, a certificate and answer guide will be mailed to the participant.

This CE program will improve participants' ability to:

- **Compare** the clinical efficacy and safety of one therapeutic agent over another used in the same setting.
- **Assess** clinical trial data and explain how the results influence formulary decision making.
- **Perform** cost-effectiveness analyses.

17. Cinacalcet is the first in a class of calcimimetic agents that increases the sensitivity of the calcium-sensing receptor to activation by extracellular calcium.
    A. True
    B. False

18. Cinacalcet is indicated for the treatment of:
    A. Secondary hyperparathyroidism in patients with chronic kidney disease on dialysis.
    B. Hypercalcemia in patients with parathyroid carcinoma.
    C. Both A and B are correct.

19. The starting dose of cinacalcet for patients with secondary hyperparathyroidism with chronic kidney disease on dialysis and for hypercalcemia in patients with parathyroid carcinoma is:
    A. 30 mg
    B. 60 mg
    C. 90 mg
    D. 120 mg

20. Cinacalcet should be taken on an empty stomach.
    A. True
    B. False

21. Dosage adjustments are necessary for which of the following special populations?
    A. Geriatric patients
    B. Renal insufficiency
    C. Hepatic insufficiency
    D. All of the above

DRUG FORMULARY R•E•V•I•E•W™
Utilization, Criteria and Outcomes

Salary statistics and shortage data give broader picture

Administrator positions are overly burdened with regulations, pharmacists say

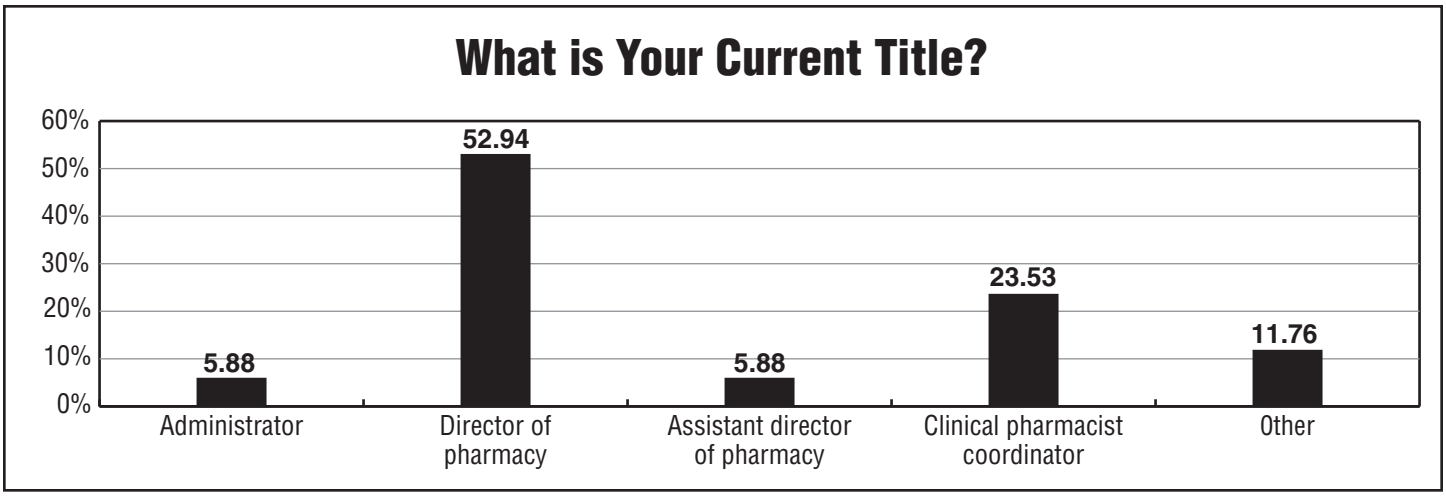
New salary statistics show that hospital pharmacy administrators may make $100,000 or more and work 50 hours a week or fewer. Even so, pharmacy management positions are some of the hardest to fill, according to a second survey.

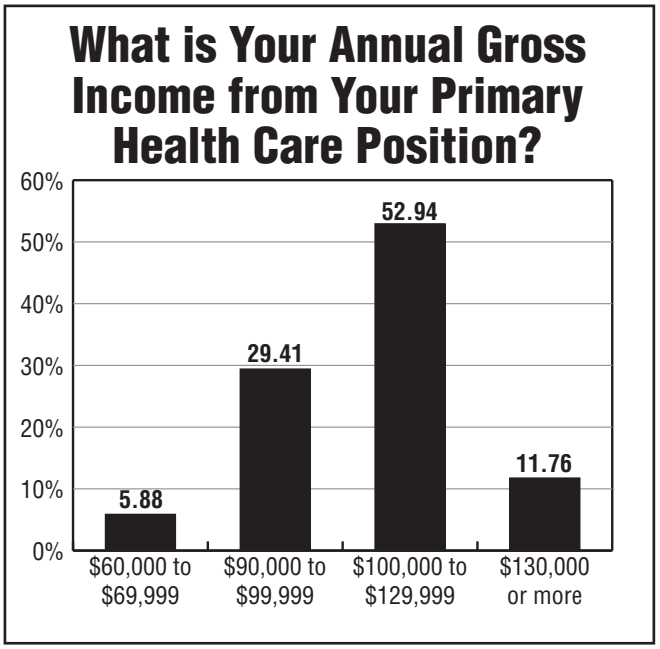
The administrator shortage is directly related to the continued shortage of pharmacists nationwide, pharmacists tell *Drug Formulary Review (DFR)*. The positions also are overly weighed down by regulatory requirements and the pressure to reduce costs.

Responsibilities have become very burdensome by Joint Commissions on Accreditation of Healthcare Organizations surveys, Centers for Medicare & Medicaid Services surveys, and state board of pharmacies across the nation because of the attention given to medication errors and negative outcomes, says **Nadrine K. Balady-Bouziane**, PharmD, director of pharmacy services at High Desert Health System in Lancaster, CA. "Since more regulations are addressing safe medication management, the pharmacy directors at hospitals are receiving the most pressure from administrators, even though the intent of the regulations is meant to be accomplished with a multidisciplinary approach."

A look at the statistics

Pharmacy administrators' salaries at least seem to be moving in a positive direction, according to the 2004 *Drug Formulary Review* Salary Survey. *DFR* recently tabulated the results of its survey to assess





the financial and workplace demographics of its readership. Here are some of the findings:

• The majority of the 2003 respondents (71%) are directors, pharmacy managers, or assistant directors of pharmacy. Other titles include clinical pharmacist or coordinator, and staff pharmacist.

• Ninety-four percent of the 17 respondents report earning more than $90,000 annually. In comparison, 68% of the 2003 survey respondents reported earning more than $90,000 annually.

• Eighty-eight percent of respondents report being older than 40 years old (two did not answer the question), and 77% are men.

• All respondents work in a hospital or clinic; 71% work for a nonprofit facility.

• Thirty-five percent of the respondents work in an urban location, and 65% live in the Northeast or South.

• All but one of the respondents say they have worked in pharmacy for 22 or more years, and 77% of them work 50 hours a week or fewer.

• The number of respondents who have a PharmD degree has decreased (32%) from last year's survey. Last year, 42% of respondents said they had the degree. Other degrees the respondents hold include BS, BSPH, MS, and MBA.

• The 2004 survey shows that about 47% of respondents' salaries increased in the range of 1% to 3%. Thirty-five percent had an increase in the 4% to 6% range. Two respondents report an increase of 7% to 10%, and one reports an increase of 21% or more. The context for the higher increases is not known.

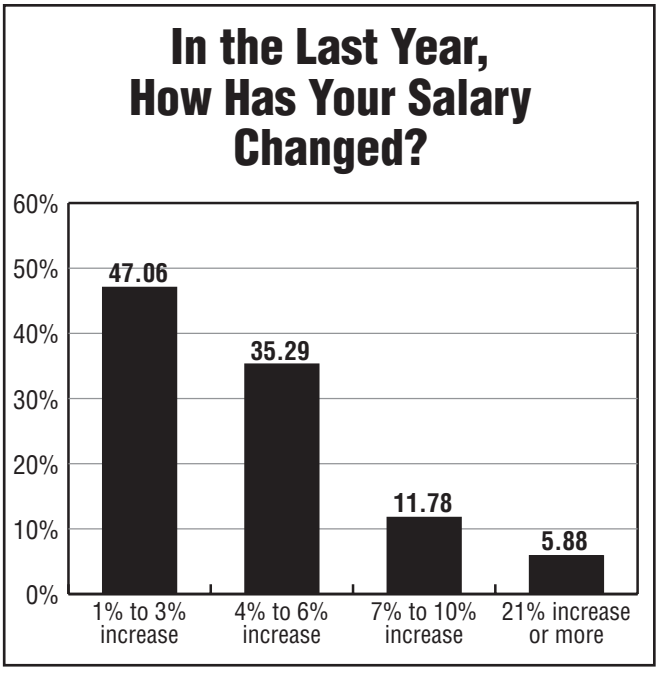
In comparison, the Social Security Administration calculated the latest automatic cost-of-living adjustments (COLAs) to be 2.1%. The COLAs prevent inflation from eroding Social Security and Supplemental Security Income benefits. (To see how COLAs are calculated, see www.ssa.gov/OACT/COLA/COLA.sum.html.)

In addition, the inflation-adjusted income of the nation's median household fell slightly in 2003, from $43,381 to $43,318 (the decline was statistically insignificant), according to the Economic Policy Institute in Washington, DC. Since 2000, the median household income has declined consistently in real terms, down $971, $502, and $63 in 2001, 2002, and 2003, respectively, for a cumulative loss of $1,535 — a 3.4% drop — over these years.

It's not an easy job

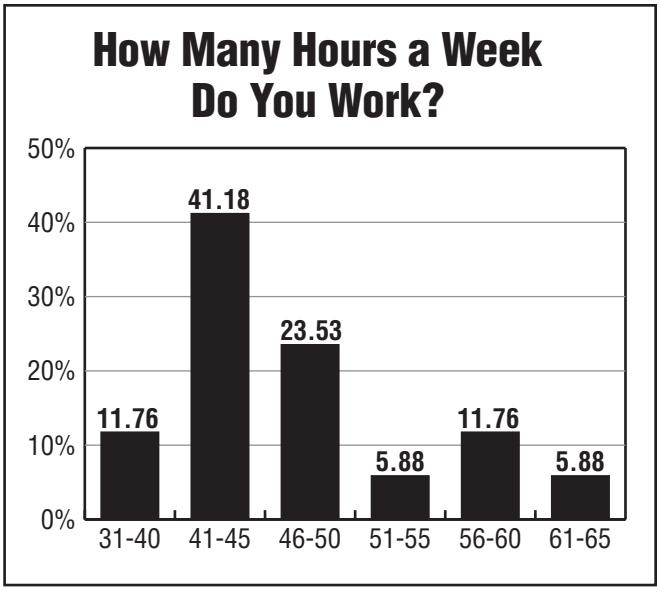
The salaries are much higher than the nation's median, but health systems across the nation are struggling to fill their open pharmacy manager positions, according to the latest staffing survey conducted by the American Society of Health-System Pharmacists in Bethesda, MD. Conducted annually, the study found that 36% of those surveyed believe that there are severe shortages of health system pharmacy directors and assistant directors. Last year, 27% of the respondents perceived this shortage.

A director of pharmacy at a teaching hospital says the position is high stress and high profile. "Typically, drugs are the largest part of a teaching hospital budget, and there is tremendous pressure from administration to reduce costs in pharmacy, either in drugs or in people," reports



Gae M. Ryan, PharmD, director of pharmacy at Oregon Health & Science University Hospitals and Clinics in Portland. "It is sometimes difficult to make the case that reductions are not always the best answer to a financial crisis, and being caught in the middle is part of the stress."

Taking a stand and saying that there are no more reasonable reductions to be made can be hazardous to your job, she says. "There isn't a real sense of job security in this situation. Increasing regulation — both federal and state — pressure to reduce costs, staffing shortages, benchmarking, and increasing demand . . . all of these make survival in this role more difficult than it was in the past."



Recruitment challenges

Younger professionals are not always willing to make the time commitment that is required of a director of pharmacy, she continues. **James Neff**, MS, RPh, director of pharmacy at Holy Cross Hospital in Fort Lauderdale, FL, also sees a lack of pharmacists stepping up to do the job.

"When you have 25- and 30-year people in the business, at what point do you get the new blood? New blood is less willing to step up and face those challenges."

Neff knows why they may hesitate. "You have more regulatory pressures that are out of your control than ever before. You have financial and budgetary constraints that squeeze your resources and your ability to respond to these regulatory rules and regulations.

"You get whipsawed in two different ways," he says. "No. 1, you don't have what you need to get the job done; and No. 2, you are being forced to do things that you don't have the resources to do."

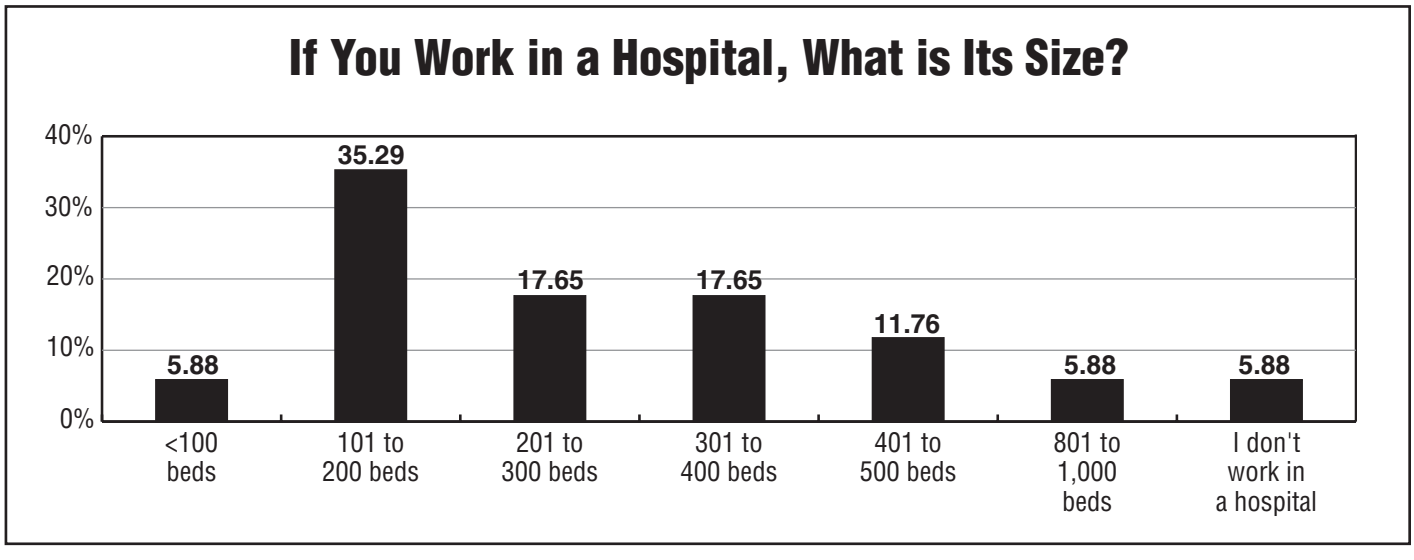
Staff pharmacists might make less money, but they can go home and not worry about everything or have the phone ring in the middle of the night.

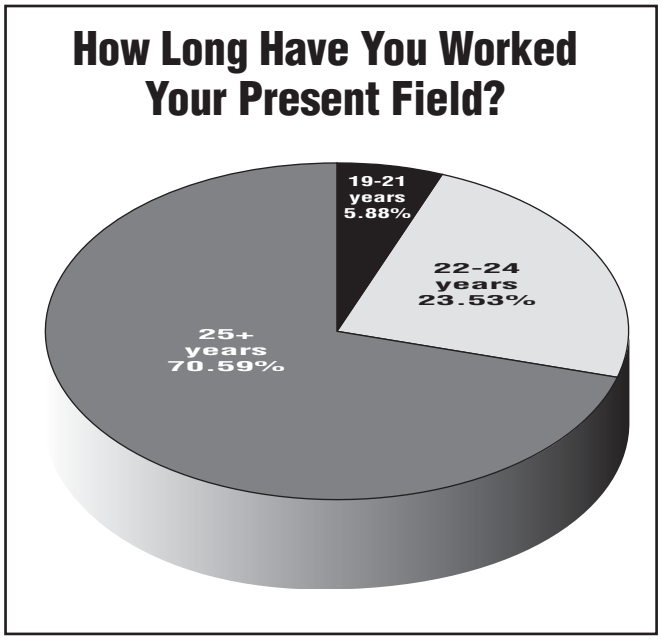
"I wouldn't mind being a staff pharmacist any day of the week, but I happen to love what I am doing," Neff says. "I know there is a challenge even being staff, so I have chosen where I am."

Balady-Bouziane works with per-diem pharmacists (she cannot recruit them full-time) whose hourly rate works out to be more than what she receives as a director. They also can choose day and weekday shifts and not work holidays.

"In addition, they do not have the responsibilities I have. They do not have to manage people problems or deal with making a schedule. Once they leave High Desert at the end of the day, they are free and not responsible for anything."

The salary and flexibility of hours are definitely attractive and would be a strong influence if she





were starting over in her career today. Becoming a staff pharmacist after being a director, however, is a step down.

Even is pharmacy administrators are considering making the change, the anxiety the switch would create can be a major hurdle, Neff says.

"The minute you don't do those day-to-day orders, don't stay up on those latest protocols, don't actually get involved and dirty your hands and mash the calculator buttons on a daily basis in terms of patient care and contact, you lose your skill. If they are directors for 20-something years and have not maintained that frontline mentality in patient care and contact and treatment, they are afraid to move back into that arena. It would be more stressful initially but less stressful in the long run." ■

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