



Incentives for Drug Development — The Curious Case of Colchicine

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In July 2009, the Food and Drug Administration (FDA) officially announced what physicians have long known — that the drug colchicine can effectively treat acute flares of gouty arthritis. The plant

from which colchicine is derived was first used as a therapeutic agent for gout more than 3000 years ago in ancient Greece, and the tablet form has been widely available as a generic prescription drug in the United States since the 19th century. On the basis of evidence that had built up over the years, numerous consensus guidelines recommended colchicine as an effective second-line treatment for gout — for example, in patients who had adverse effects from nonsteroidal antiinflammatory drugs.¹

It came as a surprise to many patients and physicians that the FDA not only approved the new version of colchicine (Colcrys) but also granted the manufacturer, Philadelphia-based URL Pharma, 3 years of market exclusivity for

this ancient drug. The possibility of such an exclusivity period arose because colchicine, despite its longevity, had never been officially approved by the FDA for a particular indication. The 1938 Food, Drug, and Cosmetic Act required that all new drugs be approved by the FDA for safety before being introduced on the market, but it allowed drugs that were already on the market to remain available. Starting in the 1960s, the FDA began to evaluate the safety and efficacy of older drugs, looking first at drugs that might pose the greatest threat to public health or that appeared to lack effectiveness. Colchicine was one of a number of drugs that the FDA never formally evaluated, although the agency did review and approve

a combination pill containing colchicine and probenecid (Col-Probenecid, Watson Laboratories) for use in gout.

In 2007, URL Pharma organized pharmacokinetic studies testing its version of colchicine in healthy volunteers and a randomized, controlled trial involving 185 patients with acute gout. The combined findings of these studies confirmed the drug's safety and efficacy. The randomized, controlled trial, which followed patients for 1 week, showed that a shortened dosing regimen produced good symptom management in patients with gout while leading to fewer adverse events than a longer regimen.² Its effect size (38% in the group receiving shortened dosing of colchicine vs. 16% in the placebo group) was similar in magnitude to that of a previous randomized, controlled trial of colchicine for the treatment of acute gout (73% vs. 36%).³ According to earlier reports, colchicine's adverse-event

profile included diarrhea and vomiting, and these effects were also reported in the new trial. The reduced rate of side effects in the group receiving the shortened regimen confirmed the usefulness of a dosing adjustment that had been recommended in guidelines from one of the major rheumatology professional societies.¹ On the basis of this new trial, combined with the previously published evidence, the FDA approved Colcris for treatment of acute gout. Because this was technically a new indication for the drug, the Waxman–Hatch Act authorized the FDA to award the company 3 years of market exclusivity — an incentive that the agency believes could encourage voluntary compliance with the drug-approval process.

At the same time, under the Orphan Drug Act, the manufacturer also received 7 years of market exclusivity for the use of Colcris in the treatment of familial Mediterranean fever (FMF), a genetic inflammatory disorder that affects only about 100,000 patients worldwide. The Orphan Drug Act provides federal grant funding and tax credits for clinical trial costs, as well as market exclusivity, to encourage research into rare diseases. The orphan-drug incentive is not restricted to new products: currently available drugs that are approved for a new orphan indication can also be granted exclusivity. For example, thalidomide, a drug designed as an antiemetic agent that fell out of favor in the 1960s after it was linked to birth defects, was approved in 1998 as an orphan product for the treatment of leprosy and in 2006 for the treatment of multiple myeloma. In the case of FMF, the usefulness of colchicine in helping to control debilitating attacks of fever and abdominal pain was

already established, and the orphan indication for Colcris was approved on the basis of a review of previously collected data, along with additional limited safety information from the pharmacokinetic trials.

The implications of market exclusivity for the public health can be substantial. After the FDA approved Colcris, the manufacturer brought a lawsuit seeking to remove any other versions of colchicine from the market and raised the price by a factor of more than 50, from \$0.09 per pill to \$4.85 per pill.⁴ These increased prices directly affect the availability of the drug to patients with gout or FMF who have long been using colchicine safely in an evidence-based manner. Exclusivity can also affect health care delivery more broadly. According to the Centers for Medicare and Medicaid Services, state Medicaid programs filled about 100,000 prescriptions of colchicine in 2007 and paid approximately \$1 million for the drug. Use of the new brand-name colchicine could add as much as \$50 million per year to these insurance programs' budgets at a time when they are addressing the rising costs of health care by reducing some services or raising eligibility thresholds.

The colchicine case demonstrates some important limitations of our current system for rewarding innovation in the pharmaceutical market. Incentive programs like those enacted by the Waxman–Hatch Act and the Orphan Drug Act offer market exclusivity to encourage drug research, but these rewards are not calibrated to the quality or value of the information produced. Although the goals underlying the development of Colcris were sound — few would argue against the need to comply with FDA re-

quirements and the need to ensure the safety and efficacy of all prescription drugs — and the manufacturer seems to have followed FDA guidance, the reward appears to be out of proportion to the level of investment. More important, there is no evidence of any meaningful improvement to the public health. We believe that when creating and implementing incentives for private investment in drug research, policymakers should seek to avoid policies that can lead to such outcomes. An alternative solution, probably much less expensive, would be for the FDA or the National Institutes of Health to fund trials that address outstanding questions related to widely available drugs such as colchicine.

In addition, it is important to remember that the financial burden of market-exclusivity incentives in the United States falls primarily on the patients who are given prescriptions for the drug, or their insurers. Consequently, it seems reasonable to expect that costly new drugs or increases in drug prices would be accompanied by a substantial benefit in disease management to be enjoyed by these patients. This standard is not met by Colcris; in this instance, the public may bear considerable costs for a poorly executed administrative goal.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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1. Zhang W, Doherty M, Bardin T, et al. EULAR evidence based recommendations for gout. II. Management. *Ann Rheum Dis* 2006;65:1312-24.

2. Terkeltaub RA, Furst DE, Bennett K, Kook KA, Crockett RS, Davis MW. High versus low dosing of oral colchicine for early acute gout flare: twenty-four-hour outcome of the first multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-com-

parison colchicine study. *Arthritis Rheum* 2010;62:1060-8.

3. Ahern MJ, Reid C, Gordon TP, McCredie M, Brooks PM, Jones M. Does colchicine work? The results of the first controlled study in acute gout. *Aust N Z J Med* 1987;17:301-4.

4. *Mutual Pharmaceutical Co. v. Watson Pharmaceuticals*, 2009 WL 3401117 (C.D. Calif., Oct. 19, 2009).

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Health Care Reform and Primary Care — The Growing Importance of the Community Health Center

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During the debate over U.S. health care reform, relatively little attention was paid to the long-established network of community health centers (CHCs) in the United States. And yet this unique national asset constitutes a critical element of any reform intent on expanding access to health care through a primary care portal. With an eye toward meeting the primary care needs of an estimated 32 million newly insured Americans, the recently passed Patient Protection and Affordable Care Act underwrites the CHCs and enables them to serve nearly 20 million new patients while adding an estimated 15,000 providers to their staffs by 2015. The “new” CHCs have arrived.

Launched in 1965 by the Office of Economic Opportunity as a component of President Lyndon Johnson’s War on Poverty, the very first CHCs — in urban Columbia Point (Boston) and rural Mound Bayou (Mississippi) — were designed to reduce or eliminate health disparities that affected racial and ethnic minority groups, the poor, and the uninsured. The CHCs were to constitute a key component of the national public safety net, focused simultaneously on the care of individual patients and on the health status of their overall target populations. With their host communities involved in their governance, the centers

were to be “of the people, by the people, for the people.”

Now operating at more than 8000 sites, both urban and rural, in every state and territory (see Fig. 1), run by about 1200 CHC grantees, the centers are the medical home to 20 million Americans, 5% of the current U.S. population (see Fig. 2). Federally funded under the authority of the Public Health Service Act, the non-profit CHCs are administered by the U.S. Health Resources and Services Administration. Support from federal (and frequently state, county, and city) grants notwithstanding, CHCs must meet budget requirements through fees for services rendered to insured patients and “pay-as-you-can” (sliding-scale) collections from the uninsured (who account for 40% of patients served). No one is turned away, regardless of ability to pay. The CHCs are dedicated to the delivery of primary medical, dental, behavioral, and social services to medically underserved populations in medically underserved areas. Marked by a substantial representation of young women and children, the characteristic patient mix includes geographically isolated, migrant, and urban (including homeless) constituencies that are often estranged by linguistic and cultural barriers. Seven of 10 CHC patients live in poverty, and well over half are members of minority groups; the CHC is

often the sole health care provider available to these patients.

Beyond their commitment to the uninsured, the CHCs have always welcomed the insured in need of high-quality primary care. At present, 35% of CHC patients are beneficiaries of Medicaid, and 25% are beneficiaries of Medicare or enrollees in private health plans. With the advent of health care reform, the percentage of insured people frequenting CHCs will undoubtedly grow: the impending expansion of Medicaid and the establishment of health insurance exchanges will see to that. The CHCs are thus likely to further cement their role as the bedrock of primary care for all while remaining the provider of last resort for the uninsured.

Ever since their inception, CHCs have received substantial legislative attention, in a remarkable display of bipartisan harmony. In the face of a national crisis in primary care, sequential legislative initiatives have sought to expand and strengthen the CHC paradigm. The need for such expansion has always been clear. As recently as 2009, the Government Accountability Office reported that 43% of medically underserved areas continue to lack a CHC site.¹ Intent on doubling the number of CHCs, Congress and President George W. Bush doubled the annual appropriation to \$2.1 billion by fiscal year 2008. More recently,