Drug Safety: One Step Forward, One Step...

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KEVIN TUMA

Far too many people suffering from an asthma attack or migraine headache have had their misery increased by the very thing that should bring them relief: the government-approved labeling of their medicine. Drug information labels, found on paper inserts dispensed by the pharmacist or in the Physicians' Desk Reference, appear to lack rhyme or reason, with the information that consumers most often need—usage, warnings, and dosing—usually buried far down on the label and in impenetrable small print. This is not only confusing to consumers, but also to their physicians—especially those who need to find the information quickly or who have not used a particular drug previously.

Consider, for example, the antibiotic Cipro, whose labeling in the *Physicians' Desk Reference* runs to five full, large pages of tiny print. The first paragraph of the first section, "Description," contains this gem: "Ciprofloxacin hydrochloride, USP, a fluoroquinolone, is the monohydrochloride monohydrate salt of 1-cyclopropyl-t-fluoro-1, 4-dihydro-4-oxo-7-(piperazinyl)-3-quinolinecarboxylic acid. It is a faintly yellowish to light yellow crystalline substance." Just the information a doctor would need! And the second section, "Pharmacology," is equally unhelpful, discussing absorption, distribution within the body, metabolism, excretion, and so on. It is not until the third page of the labeling that we finally get to critical information, "Indications and Usage." After that follows a series of discrete sections whose contents overlap significantly (and problematically): "Contraindications," "Warnings," "Precautions," and "Adverse Reactions." (Even the regulators cannot explain what goes where.) Later still, we get to "Dosage and Administration."

Although final product labeling is the result of weeks or even months of discussions between a drug's manufacturer and the Food and Drug Administration (which has absolute discretion over the style and substance of labels), the bewildering, unwieldy format prevents efficient communication of essential information about the drug. If it had been up to drug companies or the medical community, we would likely have adopted a standardized and more workable format decades ago.

STEP FORWARD The FDA finally has acted to correct this problem. On Jan. 18, the agency unveiled a new format for prescription drug information, commonly called the patient insert. In addition to reorganizing the label so that information is provided in order of importance, the format includes several new features, including a section called "Highlights" to provide immediate access to the most important prescribing information about benefits and risks; a table of contents for easy reference to detailed safety and efficacy information; the date

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of initial product approval, making it easier to determine how long a product has been on the market; and a toll-free number and Internet reporting information for suspected adverse events, to encourage more widespread reporting of suspected side effects.

Along with the improved format, the FDA also has introduced DailyMed, "an electronic repository of . . . the most current labeling, vetted, approved, the gold standard of drug information." This is a valuable innovation; the *Physician's Desk Reference* on my office bookshelf is the 2004 edition, which means that the data it contains were compiled at least three years ago.

These initiatives offer a marked improvement over the previous, antiquated system of drug labeling and should be a boon to patients and physicians alike.

LESS-CERTAIN STEP I am less excited about another of the FDA's initiatives: the Drug Watch program. The agency has come under intense recent criticism for supposed deficiencies in the surveillance and reporting on the safety of drugs, and I suspect this program is a response to that criticism.

Last May, the FDA announced the program as an effort to "identify drugs for which FDA is actively evaluating early safety signals. The Drug Watch is not intended to be a list of drugs that are particularly risky or dangerous for use; listing of a drug on Drug Watch should not be construed as a statement by FDA that the drug is dangerous or that it is inappropriate for use. Rather, inclusion on the Drug Watch signifies that FDA is attempting to assess the meaning and potential consequences of emerging safety information." The same document went on to say that Drug Watch is intended "to share emerging safety information before we have fully determined its significance or taken final regulatory action so that patients and healthcare professionals will have the most current information concerning the potential risks and benefits of a marketed drug product upon which to make individual treatment choices."

Of course, more information about a drug (or most anything else) is usually better than less information. If patients are to make informed, personal decisions concerning their therapies—especially about what kinds of risk/benefit tradeoffs they will accept—the public availability of safety information about drugs and transparency about regulatory decisions is essential. The kind of "safety information" provided by Drug Watch might be considered to be a "public good"—something that cannot readily be withheld from one individual consumer without withholding them from all, and for which the marginal cost of an additional person consuming it, once it has been produced, is zero.

But with that said, there is reason to be concerned about Drug Watch. Medicines that are listed will not have been shown to be dangerous; they will be FDA-approved drugs that are undergoing further scrutiny because of post-approval concerns about their safety. What should be the proper response of health care providers and consumers to a drug's listing on Drug Watch? Should they take a better-safe-than-sorry approach and avoid using a listed drug—even though the FDA's original approval and labeling may be upheld and the drug's benefits may be significant? Or, given the tentative and preliminary nature of the warning, should they ignore the listing on Drug Watch? Another complicating issue is whether litigation-wary physicians and the keepers of HMO and hospital formularies will avoid drugs listed on Drug Watch, which would result in the under-prescribing of some useful medicines.

These issues raise the question of whether the release of incomplete, preliminary information is really beneficial to the public. As I observed earlier, more information is almost always better than less, but all information is not created equal. Should we not let the quality of information and its context influence our judgments about what to release, and when?

CONCLUSION According to FDA Deputy Commissioner Scott Gottlieb, "Information that could influence clinical medical practice needs to be made available more quickly, and more widely, after it has gone through a deliberative scientific process that firms up its meaning and the magnitude and the veracity of its conclusions." That seems a reasonable standard. DailyMed, which will provide current labeling information to both healthcare professionals and patients, meets those criteria. But Drug Watch does not; indeed, Gottlieb himself described the information that would appear on Drug Watch as data "still unscrubbed by scientific rigor."

More information is better than less, but not all information is created equal.

There is an interesting irony in the FDA's compulsion via Drug Watch to provide information about drugs rapidly. It was not always thus. After the agency approves a new drug for marketing, physicians may prescribe it for indications other than the specific ones for which the FDA has granted marketing approval (and which are included in the labeling). This "off-label" use, which is extremely common in specialties such as oncology, pediatrics, obstetrics, and infectious disease, is vitally important as a source of medical innovation and to bring the benefit of new medical knowledge rapidly to patients. It allows physicians to take advantage of the most current research and experience concerning a drug's properties for the benefit of their patients. But the FDA has tenaciously restricted and interfered with companies' ability to make available information about off-label uses—even if the information has been peer-reviewed and is contained in journal articles and textbooks. For that reason, we must wonder about the extent of the FDA's commitment to protect patients' well-being.

DailyMed is just what the doctor ordered. But the FDA should reconsider Drug Watch in favor of developing an "Off-Label Watch" that would offer current information on successful off-label uses of approved drugs. R

Two Invisible Hands

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The conservative movement in the United States is suffering from a deep intellectual inconsistency in its beliefs. Free market conservatives (such as myself) believe that markets can effectively coordinate economic activity with no central direction. It is a truism to point out that the amount of such coordination needed in the modern world economy is immense. Think of me writing this essay on a computer and then sending it to *Regulation's* editors over the Internet, and then you reading it on a magazine printed on paper and delivered by truck. Literally, millions of people all over the world have been involved in this set of activities. Virtually none of them know each other, and no one has coordinated the process. Every day there are billions of such unplanned and undirected activities.

The beauty and the power of the market, first pointed out by Adam Smith, is that it can coordinate such massively complex activities with no central planning. This is the famous "invisible hand." Conservatives believe that this coordination is powerful and provides innumerable benefits to individuals in society.

But while conservatives accept the invisible hand of the market, many reject the equally powerful invisible hand of biological evolution. The notion of "intelligent design," which received much attention late last year from many conservatives (including, unfortunately, President Bush), is the exact antithesis of the notion of the invisible hand. Intelligent design is the notion that life, and particularly intelligent life, is too complex to be the product of anything but a centrally orchestrated process. But it is inconsistent to reject evolution because of the complexity of living things and at the same time to accept the unplanned complexity of the market.

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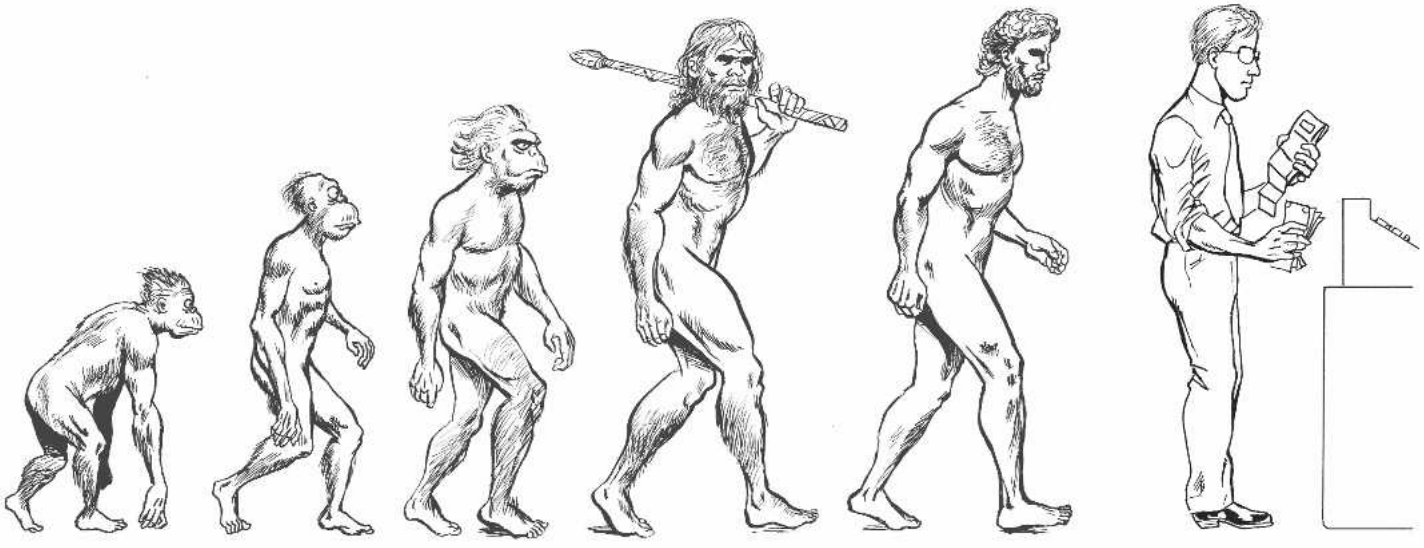
ECONOMIC NATURAL SELECTION Such inconsistency may cost conservatives dearly. One of the reasons for the current intellectual influence of conservatives is their acceptance of the paradigm of the power of the market. Many liberals reject this paradigm in whole or in part, and this lack of a strong rational belief system may explain the apparent intellectual dilemma of the liberal coalition today. Indeed, the triumph of the western democracies over the Soviet Union is due to the belief in the power of the market and the willingness to rely on the market.

But if conservatives reject the theory of evolution—another component of rationality—in favor of alternatives, in the long run we can expect those who have more scientific beliefs to win out. This may seem far-fetched, but consider that, just as the Soviet Union relied on an incorrect model of the economy, it also relied on an incorrect theory of biology: the discredited theory that acquired characteristics could be inherited. This belief was originally proposed by Lamarck, a predecessor of Darwin, and advocated in Russia by Lysenko. It was fostered by Stalin, and use of this incorrect paradigm is a partial explanation for the failure of Soviet agriculture.

If our political system rejects the heart of modern biology and refuses to train our children in the basic science needed for successful biological research and understanding, then we can expect much of the future innovation in the world to move to other countries that accept and understand both the economic and the biological invisible hands. R



KEVIN TUMA (2)

A Collapsing Housing Bubble?

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Anytime there is a consensus about the future, it is probably wise to bet against it. In the past couple of years, predictions about home prices have gone from a sober questioning of future price growth to shrill apocalyptic predictions of an impending market collapse that will trigger a deep recession.

We cannot claim to have a crystal ball that works any better than the commentariat, but we believe a clear look at the available data suggests that the situation is far from dire. While average home prices in the United States have increased smartly in the past decade, that by itself is not sufficient to conclude anything about what future prices will do.

NATIONAL MARKET? The first problem with such prognostications is that it makes little sense to talk about "the" American housing market. Home appreciation rates vary widely across the nation and there is no such thing as a national housing market. While areas in Nevada, Arizona, Hawaii, and California, as well as the metropolitan areas of New York City, Boston, and Washington D.C., have seen housing prices skyrocket in recent years, those places comprise a small portion of the national housing stock (and even in those "hot" markets, the price jumps have not been universal). Elsewhere, home prices have grown at more moderate rates.

Table 1 shows the variation in home price appreciation over the past decade. It reveals that prices in New England and the Pacific regions have risen dramatically over the past decade, but house prices in other parts of the country have increased more modestly.

Also, the context in which the price growth is presented matters quite a bit. A 55 percent real increase in the average price of a house over the course of a decade can seem impressive at first glance, but when broken down to an annual average increase, it translates to just 4.5 percent. That is a healthy gain, but not the stuff of unsustainable bubbles. Compared to stocks, which have had a real average annual increase of 7 percent for the past 70 years, investing in a house is relatively pedestrian.

CHANGING HOUSES The annual rate of growth in house prices seems even less alarming when one discovers that the indexes used to measure home prices likely overstate the actual price appreciation. Homeowners constantly add, fix, improve, and expand their homes, and over an extended period of time a

TABLE 1

Real Home Price Appreciation
1995–2005

AREA	DECADE	ANNUAL
United States	55.80%	4.53%
New England	83.66%	6.27%
Mid-Atlantic	61.54%	4.91%
South Atlantic	61.25%	4.89%
East North Central	31.61%	2.78%
West North Central	42.29%	3.59%
East South Central	21.90%	2.00%
West South Central	22.02%	2.01%
Mountain	51.32%	4.23%
Pacific	99.33%	7.14%

SOURCE: OFHEO

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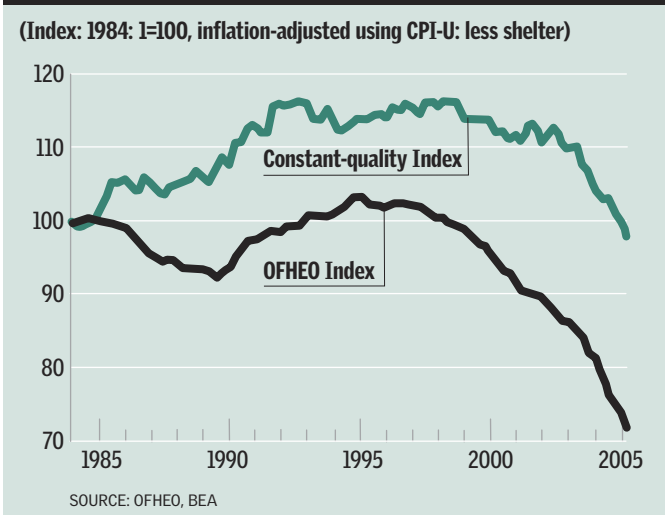
FIGURE 1

Overpriced Housing?

Ratios of owner's equivalent rent to alternative price indexes



SOURCE: OFHEO, BEA

house can morph into an utterly different entity. Harvard's Joint Center for Housing Studies estimates that homeowners spent $233 billion on home improvement projects in 2005 alone.

The House Price Index in Table 1, constructed by the Office of Federal Housing Enterprise Oversight (OFHEO), tracks the same homes and their prices only as they are bought and sold over time. Improvements such as remodeling a kitchen, adding a room, or re-landscaping are not captured by the index. As a result, what often looks like a large jump in a home's price actually has a concrete (or granite, marble, tile) reason behind it.

But it is not just existing homes that are being upgraded. New homes today are not what they were 40 years ago, as home construction has responded to the changing American lifestyle. Strides have been made in the building materials and techniques used in home construction. New homes today are generally built with more square footage and include more features than the homes of yesterday. New homes are more energy efficient and, in some respects, safer than their predecessors. There are also a myriad of options available in homebuilding today that did not exist even a decade ago. The American appetite for home improvement is just as much a driving force in the housing market as anything else out there. Just ask Ty on *Extreme Home Makeover*.

When considering the ratio of owner's equivalent rent to home prices—the standard housing market bubble meter—using the correct measuring stick for home prices puts the market in perspective. The ratio of owner's equivalent rent to home prices compares the rental price a homeowner could get for renting his home to the actual price of homes. A reading well below or above 100 indicates a market that is out of equilibrium: if the reading is below 100, renting is a bargain; if it is above 100, buying is the better deal.

So what does this ratio look like currently? As shown in Figure 1, it depends on which index is used to represent home prices. If the OFHEO index is used, it appears as if houses are overpriced. If the constant-quality new home price index is used, housing has actually been more affordable than renting for a considerable period until very recently, and is now at a "break-even" point. There are still places where the index shows that housing prices are dear relative to rents, such as the San Francisco Bay area, but they are the exception.

'EXOTIC' MORTGAGES If construction is responding to the changing American lifestyle, it makes sense that the mortgage market would also respond and offer new products that appeal to consumers. The long-term, fixed-rate mortgage is still a staple in home financing, but today there is a wider variety of mortgage options available that allows more people than ever to enter the market.

For instance, the oft-derided interest-only mortgage allows families with sufficient earning power to enter a market earlier than they would otherwise. (Interest-only loans made up 28.5 percent of all mortgages in the first half of 2005, according to the mortgage data company Loan Performance.) A generation ago, someone beginning a new career would find buying a house on a typical starting salary to be quite difficult, and would most likely be forced to rent for a number of years. Today, that same person can take out an interest-only loan and buy a house much sooner than before, with increasing mortgage payments being met by the prospect of higher future income.

Similarly, the high transaction costs of buying a house can make it impractical for people with peripatetic careers to buy a house; high closing costs can make it difficult for people who anticipate needing to move in a few short years to afford buying a house. While the relatively uncompetitive real estate services market keeps closing costs high, the ultra-competitive mortgage market makes it easier for this cohort to enter the housing market. Undoubtedly, there are families who use such mortgages to buy houses that are beyond their reach, but that fact alone should not be reason to deter such loans.

NOT JUST A HOME Houses are unique in that they are investment goods as well as consumption goods. There is good reason for people to be willing to pay more for both aspects. With no specter of inflation in our future and a world of relatively low returns, investing more in a house makes perfect sense. A stagnant stock market does not send off the siren song to investors that it did a decade ago. Who is to say that in such an environment a family spending another $100,000 on a nicer house is not making a wise decision? And as Americans become wealthier, it only makes sense that we want to spend more on the consumption aspect of our homes.

The fact that expenditures on homes in the United States outpace incomes is a sign of nothing but the fact that a house is, in effect, a form of luxury good. As people begin to accumulate wealth, they start aspiring to own a house. As they get wealthier, they want a nicer house.

The "speculative froth" in the housing market definitely exists to a degree, and can be seen in the significant proportion of condominiums bought by investors in major markets. But the froth is relatively minor in the ocean of home buyers. We see little reason to think that it is enough to swamp the other forces supporting home prices in this country. R