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New Prescription Drugs: A Major Health Risk With Few Offsetting Advantages

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Few people know that new prescription drugs have a **1 in 5 chance** of causing serious reactions after they have been approved. That is why expert physicians recommend not taking new drugs for at least five years unless patients have first tried better-established options, and have the need to do so.

Few know that systematic reviews of hospital charts found that even properly prescribed drugs (aside from misprescribing, overdosing, or self-prescribing) cause about 1.9 million hospitalizations a year. Another 840,000 hospitalized patients are given drugs that cause serious adverse reactions for a total of 2.74 million serious adverse drug reactions. About 128,000 people die from drugs prescribed to them. **This makes prescription drugs a major health risk**, ranking 4th with stroke as a leading cause of death. The European Commission estimates that adverse reactions from prescription drugs cause 200,000 deaths; so together, about 328,000 patients in the U.S. and Europe die from prescription drugs each year. The FDA does not acknowledge these facts and instead gathers a small fraction of the cases.

Perhaps this is “the price of progress”? For example, about 170 million Americans take a prescription drug, and many benefit from the drug. For some, drugs save their life or keep them alive. About 80 percent of them are generic; that is to say, drugs whose benefits and risks are better known. If we suppose they all benefit, then 2.7 million severe reactions is only about 1.5 percent.

But as far as we can tell (very little research is funded on prescription drugs as a health risk compared to less deadly risks like diabetes or Alzheimer’s disease), millions who take new, patented drugs experience only modest benefits over established drugs. Only a small percent of new drugs provide significant advantages for patients to offset these risks of harm. Independent reviews over the past 35 years have found that only 11 to 15 percent of newly approved drugs have significant clinical advantages over existing, better-known drugs. These contribute to the large medicine chest of effective drugs developed over the decades. But the 85 to 89 percent with little or no clinical advantage flood the market.

About four-fifths of the additional $70 billion spent on drugs since 2000 in the U.S. (and another $70 billion abroad) have been spent on these minor new variations rather than on the really innovative drugs.

In a recent decade, between 2002 and 2011, independent reviews by clinical expert teams in France, Canada, and the Netherlands have concluded that only 8 percent of 946 new products were clinically superior, down from 11 to 15 percent in previous decades (see Figure, below). Only 2 were breakthroughs and another 13 represented a real therapeutic advance.

Spokesmen for the pharmaceutical industry point out that therapeutically similar drugs have advantages. First, physicians need some choice within a therapeutic class because some patients do not respond well to a given drug. This is true, but after about three choices, there is little evidence to justify a 4th, 5th, or 6th drug in a class. Second, a sub-group of patients may benefit from new drugs that seem similar. This may be true or not, and we need to identify that sub-group so the effectiveness of the drug can be tested on them. The point of testing drugs for approval is to identify which patients might benefit and see if they do, not to assume that some patients somewhere might. Third, industry spokespersons argue that every incremental development contributes to larger improvements. This might be true, but most significant clinical advances occur through major discoveries. Yet most major scientific discoveries do not significantly improve patients' health and some may prove deadly. Silvio Garattini, a leader in pharmacological research told me, "When a major discovery actually helps patients, we feel very lucky."

The Hidden Business Model of R&D

Flooding the market with hundreds of minor variations seems to be the hidden business model of drug companies, to exploit patent and other IP protections for profits, not for significant advances for patient health. Looking back, Jerry Avorn, an authority on pharmacoepidemiology, wrote that "laws designed to encourage and protect meaningful innovation had been turned into a system that rewarded trivial pseudo-innovation even more profitably than important discoveries."

Despite fewer superior drugs, **Marc-André Gagnon** has shown that sales and profits soared. Net return on revenues (ROR) rose from about 10 percent in the 1970s to 12.5 percent by 1990, then to 16 percent by 2000, and to 19 percent in 2010. Pharmaceutical ROR has increased from about 2.5 times to 3.2 times the return for the Fortune 500 giants, largely as a result of raising prices and getting more physicians to prescribe more drugs.

Risk for the major companies is much less than claimed for several reasons. First, they spread risk over many projects. Second, once inflators and public subsidies are taken out, net research costs are a fraction of the $1 billion to $5 billion per new drug claimed, and big companies largely invest after the public and others have paid for the high risks of research to discover new drugs. As new drugs enter clinical trials, their risks are just 1 in 5. Third, companies cut losses by stopping development of drugs whose profit potential is not as high as they want. We never will know how many beneficial drugs never get approved because companies estimated they would not be profitable enough.

Over the past 35 years, this hidden business model based on marketing power and prowess more than innovation has caused an epidemic of harmful side effects. Given estimates that about 30 adverse reactions occur for every one that leads to hospitalization, about 81 million adverse reactions are experienced by the 170 million Americans taking drugs. The elderly and those taking multiple drugs experience more than others. Most are medically minor, like muscle aches, gastro-intestinal discomforts, slower reactions, or sleepiness. But they reduce productivity and cause many falls and road accidents.

The Trial-Journal Pipeline

The pharmaceutical industry refers constantly to its "R&D pipeline" of new drugs under development. But there is a second, parallel pipeline—the trial-journal pipeline. It consists of randomized clinical trials designed with the marketing departments to produce evidence that their drugs are more effective and safer than unbiased trials would show. Commercially funded clinical trials are at least 2.5 times more likely to favor the sponsor's drug than non-commercially funded trials.

The FDA accepts these biased trials and uses them to approve drugs. Congress strongly supports having companies fund the division that reviews new drugs rather than having the FDA be a publicly funded, independent reviewer and regulator. Financially, the FDA is an extension of the pharmaceutical industry and plays a major role in expanding markets for more people to take more drugs.

Closely coordinated in the trial-journal pipeline, pharmaceutical companies retain teams of statisticians, science editors, and science writers to select which results will go into the medical literature and which will not. They switch end points and other details in the data submitted to the FDA so that physicians read twice-biased medical articles that understate risks of harm and overstate benefits. Negative results are much less likely to be published than positive results, and companies publish positive results more than once, a further bias that distorts clinical practice and guidelines as well the medical knowledge that underlies it. **Marc Rodwin** concludes, "scholarly studies have revealed that drug firms design trials that skew the result and that they distort the evidence by selective reporting or biased interpretation."

This published literature goes into clinical guidelines and protocols, once established to provide an unbiased, evidence-based way to practice good medicine. But **Lisa Cosgrove and Emily Wheeler** document how they have become "essentially marketing tools for drug companies." They create "the potential to expose many patients to harm from unnecessary treatment or from treatment that is not evidence-based." The situation is worse because the evidence is twice-biased and corrupts medical science. Companies then employ what **Sergio Sismondo** describes as "a two-step model of influence by hiring and otherwise enrolling some physicians and researchers who will, in turn influence many others" to prescribe the new, patented drugs.

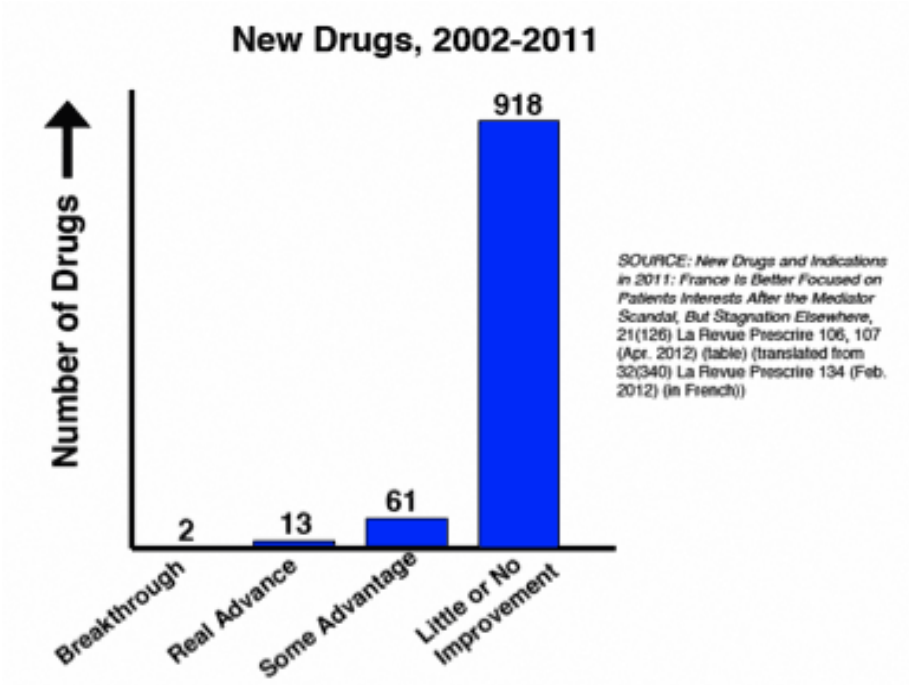
New FDA policies to get more drugs reviewed faster so that they can reach patients sooner in fact mean that drugs are approved with less evidence of being safe or effective. A **systematic study** of shortened reviews found that each 10-month reduction results in an

18 percent increase in serious adverse reactions, an 11 percent increase in hospitalizations, and a 7.2 percent increase in deaths. The risk of serious adverse reactions occurring after approval increases from 1 in 5, to 1 in 3—a huge risk that nobody is telling the public about.

In response to drug disasters like Vioxx, which experts say caused about 120,000 traumatic cardiovascular events and 40,000 deaths, Congress and the FDA have set up monitoring and safety systems. But a **review** of results so far found little evidence they are identifying serious risks or altering prescribing practices.

One key reform that would make new drugs safer and more effective would be to require that the FDA have evidence that new drugs are clinically effective. A **top team** at the London School of Economics concludes that requiring comparative evidence before approval informs all decision makers of the relative merits of new treatments. Also, it "could encourage manufacturers to concentrate on the development of new drugs in therapeutic areas with few or no alternatives." While changing legislation is difficult, the FDA could use its administrative powers and guidelines to get more evidence that new drugs actually help patients before reviewing them.

Figure:



See also: **Public Health**, **Donald Light**