In 2013, the Food and Drug Administration (FDA) approved 27 new drugs for marketing. Eight of these drugs are for orphan diseases, including six rare cancers. In fact, more than half of the 139 drugs approved by the FDA since 2009 are for orphan diseases and cancers. This disproportion is not solely the result of scientific breakthroughs; the economics of drug development and the business of health care delivery also play large roles. Although these drugs may end up being critically important to patients with the targeted diseases, we believe we must avoid systematically under-investing in drugs in other important areas of medicine.

Bringing a drug from bench to bedside is a risky and expensive proposition. The development of a new drug is estimated to cost many hundreds of millions of dollars; as a result, decisions about funding a drug-development program are based as much on economics as on science and medicine. Decisions to invest and reinvest at all stages of development are driven by the imperative to generate an attractive return on the capital invested, whether by venture-capital and public investors or by pharmaceutical companies.

It is not mysterious why projects get funded. As venture-capital investors, we evaluate projects along four primary dimensions: development costs, selling costs, differentiation of the drug relative to current treatments, and incidence and prevalence of the targeted disease (see table). For a project to be attractive, it needs to be favorably reviewed on at least two of these dimensions. Many drugs designed for orphan diseases and cancers are good investments of scarce capital, since they tend to have relatively low development costs and selling costs and to be strongly differentiated from the current treatment options. Conversely, investors are less likely to fund drugs with much higher development and selling costs (e.g., drugs for type 2 diabetes or psychiatric disorders) and drugs that cannot be strongly differentiated from current treatment options — often because low-cost generics are available to treat the targeted condition — despite the condition’s high incidence and prevalence (e.g., drugs for hypertension or hypercholesterolemia).

Fortunately, much can be done to bring more drugs and a more diverse set of drugs to market. The two economic dimensions — development costs and selling...
costs — can be most easily improved. The most expensive step in creating a new drug is conducting clinical trials. Conducting a trial costs $25,000 or more per patient studied, and phase 3 trial programs consume more than 40% of a sponsoring company’s expenditures.\(^3\) Unfortunately, every patient is not equally valuable when it comes to clinical trials, and many clinical development programs are economically inefficient in that they are excessively large relative to the amount of information they yield, especially in light of the information-technology breakthroughs that have lowered the cost of data acquisition and analysis over the past 20 years. Changing the capacity for differentiation or changing the incidence and prevalence of disease requires break-throughs in science that can be influenced only indirectly through investments in basic science research.

High-frequency, material information about clinical efficacy and safety comes from the first few hundred patients studied in a trial. Unfortunately, most clinical development programs go far past the point of diminishing returns for frequent safety events, but they do not go far enough to permit detection of rare events.\(^4\) Statistically, it is only in the long tail of patient data that reliable signals of rare adverse effects can emerge and comprehensive safety can be established (as demonstrated, for example, by the finding of progressive multifocal leukoencephalopathy in patients taking Tysabri [natalizumab]). Safety is critical, but studying the long tail of adverse events is not feasible from either a time or a capital perspective until after a new drug enters the market, especially if the drug is for a chronic condition.

Redesigning trials to include fewer patients, providing conditional approval of drugs, and requiring postmarketing surveillance could have a profound effect, allowing smaller development programs to achieve greater success. We estimate that development costs for drugs could be reduced by as much as 90%, and the time required by 50%, if the threshold for initial approval were defined in terms of efficacy and fundamental safety. Cutting costs and time, while requiring high-quality and transparent patient registries for independent safety monitoring, would be a

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### Framework for Evaluating Investments in New Drugs.\(^*\)

<table>
<thead>
<tr>
<th>Dimension</th>
<th>Examples of Types of Drugs</th>
<th>Possible Influences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Development cost of drug</td>
<td>Low cost: Orphan drugs or cancer drugs, drugs tested in studies with concrete, short-term end points, and drugs tested in superiority studies</td>
<td>May be influenced through regulatory policy and business-model innovations</td>
</tr>
<tr>
<td></td>
<td>High cost: Drugs for common, chronic, and lower-acuity conditions, drugs tested in long-term noninferiority studies, and drugs tested in outcome studies</td>
<td></td>
</tr>
<tr>
<td>Selling cost of drug</td>
<td>Low cost: Drugs prescribed in hospitals or by specialists</td>
<td>May be influenced through regulatory policy and business-model innovations</td>
</tr>
<tr>
<td></td>
<td>High cost: Drugs prescribed by primary care clinicians</td>
<td></td>
</tr>
<tr>
<td>Differentiation of drug from existing drugs</td>
<td>Low degree of differentiation: Drugs for well-treated conditions and drugs offering incremental improvement over available treatments</td>
<td>May be influenced only indirectly through investments in basic science research</td>
</tr>
<tr>
<td></td>
<td>High degree of differentiation: Drugs for diseases associated with high morbidity or mortality and drugs substantially differentiated from available treatments</td>
<td></td>
</tr>
<tr>
<td>Incidence and prevalence of targeted condition</td>
<td>Low incidence and prevalence: Drugs for rare or infrequent acute conditions</td>
<td>May be influenced only indirectly through investments in basic science research</td>
</tr>
<tr>
<td></td>
<td>High incidence and prevalence: Drugs for common or chronic conditions</td>
<td></td>
</tr>
</tbody>
</table>

\(^*\) Drugs are most favorable for investment when they have low development and selling costs, are highly differentiated from available treatments, and target conditions with a high incidence and prevalence.
more informative and cost-effective approach. With the widespread adoption of electronic health records and the introduction of many low-cost data-analysis tools, it is now feasible to develop mandatory postmarketing surveillance programs that make thousand-patient trials obsolete. Large data sets would also inoculate drug makers against spurious claims such as the false association of pancreatitis with the glucagon-like peptide 1 (GLP-1) and dipeptidyl peptidase 4 (DPP-4) inhibitors. At the same time, it is essential to empower the FDA to quickly remove or restrict the use of drugs when safety signals emerge from the improved data and safety monitoring.

This approach to reducing drug-development costs would have the greatest effect on drugs for chronic conditions such as cardiovascular disease and type 2 diabetes, since such drugs currently require the largest trials. Moreover, our ability to identify rare side effects and take action to protect patients would be substantially improved when many more patients are being followed, albeit in the absence of a control group. We believe this approach would have no adverse effect on the trend in the development of drugs for orphan diseases and cancers, since those drugs will continue to have low development and selling costs and substantial differentiation from existing treatments. Yet, this approach would make it attractive to pursue drug candidates for many more disease conditions and would lower the threshold for financing a drug’s development so that more drugs would be brought forward.

Another major factor is selling costs. It is far more cost-effective to sell a drug when it is either prescribed by specialty physicians or commonly used in hospitals, both of which effectively aggregate patients. Moreover, it is easier to predict the level of adoption by these customers on the basis of the drug’s clinical differentiation and pharmacoconomics. Sales of drugs prescribed by primary care doctors depend on a mixture of expensive sales representatives and advertising and can cost hundreds of millions of dollars annually. Equally important is differentiating such drugs substantially from generic drugs; it is appropriately difficult to develop a successful new antihypertensive or cholesterol-lowering medication, since generic drugs available for those purposes are effective, safe, and cheap.

Although strong differentiation should continue to be required, selling costs for drugs marketed to primary care practitioners and consumers do not necessarily have to remain high. To the extent that more drugs achieve sufficient differentiation, selling costs should fall, since educating clinicians who actively seek out a new drug is cheaper than repeatedly “detailing” clinicians on nuanced differences among drugs. A great deal of sales productivity could also come from applying information technology in ways that reduce the need for in-person sales forces; insofar as in-person interactions continue, their quality could be improved by using data to better segment physician and patient populations, a strategy that has been used in consumer sectors ranging from financial services to airlines to retail and has driven down customer-acquisition costs.

While scientists work hard to increase the rate of scientific discovery, the rest of us should do our part to improve the other variables that figure into the calculus of which cures are brought to market. Such improvement would be good for patients and would represent good economic policy, since drug prices could be lowered even as investors generated the returns necessary to finance more discoveries.

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

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This article was published on February 26, 2014, at NEJM.org.


DOI: 10.1056/NEJMp1400868
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