

Impact of the Crisis in Clinical Research on New Drug Development

Barry Gertz, MD

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Thank you, Dr Buchman and the American Federation for Medical Research, for this invitation today. I have been asked to speak to the crisis in clinical research and its impact on drug development from an industry perspective. I say I am speaking from an industry perspective, but I do not speak for the entire industry.

We Americans are in a rapidly changing environment, and that environment will produce changes that are quite impactful. Notably, drug development, already an unpredictable and expensive undertaking, will take on even greater uncertainty in the future. Because of the difficulty we have in executing clinical trials in the United States, we will experience significant implications for the process of drug development. The net impact will be innovation, and advances in therapeutics, which critically depend on clinical research, are threatened.

We live in extraordinary times from the perspective of the potential for advances in medical research. Indeed, we are just beginning to benefit from new knowledge in genetics, and we are only beginning to explore personalized medicine. Nonetheless, we have already seen tangible rewards, such as safer dosing strategies for some drugs on the basis of genetic testing and targeted therapy for oncology such as Herceptin (Genentech, Inc, San Francisco, Calif). The benefits of these innovations extend beyond the realm of medicine and improved quality of life and extend into the vibrancy of the American economy.

Our ability to meet urgent medical needs is at stake. These needs range from the ability to fight newly emerging, highly virulent infections such as antibiotic-resistant bacteria and highly contagious viral illnesses to the population's increasing afflictions, which include chronic disease requiring long-term therapeutic approaches, and finally, to scourges of the aging—most notably Alzheimer disease. However, clinical research and drug development are experiencing pressures from a multitude of converging forces. From an industry perspective, these forces are making a difficult process even more challenging.

For today's presentation, I will focus on 3 areas. They include the increasing costs of research and development, the deteriorating capacity to execute clinical research and drug development in the United States, and the evolving relationships with our research partners and the regulatory environment.

INCREASING COSTS FOR RESEARCH AND DEVELOPMENT

Rising costs for research and development within the industry have not been met by commensurate output of new drugs. Funding for the biotech sector, which many consider a source of innovation and of novel therapeutics, is deteriorating. Patents are losing their protection, and generic drugs are expanding, which benefits consumers but also requires that new medicines be different and have demonstrable value. However, these demands often require more and larger trials to demonstrate added benefit.

Between 2009 and 2012, nearly US \$125 billion worth of patented drugs will go off patent. These drugs are important medical drugs for the industry. Currently, 65% of prescriptions are for generics in the United States. The industry has responded by making more mergers and acquisitions while also attempting to share risk-taking and narrowing the pipeline focus. This last point is highlighted by Pfizer's recent declaration that it will no longer conduct cardiovascular research.

The cost of research and development is increasing across the biopharmaceuticals industry (Fig. 1), juxtaposed against the output based on Food and Drug Administration–approved drugs, both new molecular entities and biologics. Although this reflects intrinsic factors and environment challenges, this cost increase is not sustainable and will impact the industry's ability to continue to support drug research and development.

The biotech world is frequently viewed as the small, agile, and productive cousin of "Big Pharma"; however, this source of innovation in therapeutics is facing an unprecedented challenge to their funding model. Whether, in these difficult economic times, we look at the amount of money raised to support or sustain start-up companies or at the evaluation of those companies, we can see that this industry is threatened. Many companies will not survive, and the new ideas and frequent challenges that come from start-up companies to the established paradigm of medical treatment will be lost. Because of pressures that the larger pharmaceutical companies have experienced, many companies have consolidated (Fig. 2). According to *The New York Times*, in the past 15 years, 22 companies have contracted to what is expected in this year to total 7.¹ In 1980, we had 30 major pharmaceutical companies. Thus, if 2009 proceeds as expected, we will see a 75% contraction of pharmaceutical companies, and 2009 is not yet over.

DETERIORATING CAPACITY TO EXECUTE US CLINICAL RESEARCH IN DRUG DEVELOPMENT

Only 10% of the eligible population has ever participated in a clinical trial,^{2,3} and in some therapeutic areas, the actual percentage is far less. Clinical-trial execution is facing serious challenges in the United States for a number of reasons. First, clinical researchers lack participants for their studies. The patient may observe frequent negative messages from the media about research; therefore, patients' trust of clinical research is eroding. The patient asks, "Do the physicians and the pharmaceutical industry have my best interests in mind?" Researchers see a

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Reprints: Barry Gertz, MD, 126 E. Lincoln Avenue, RY80-107, Rahway,

New Jersey, 07065. E-mail: barry_gertz@merck.com.

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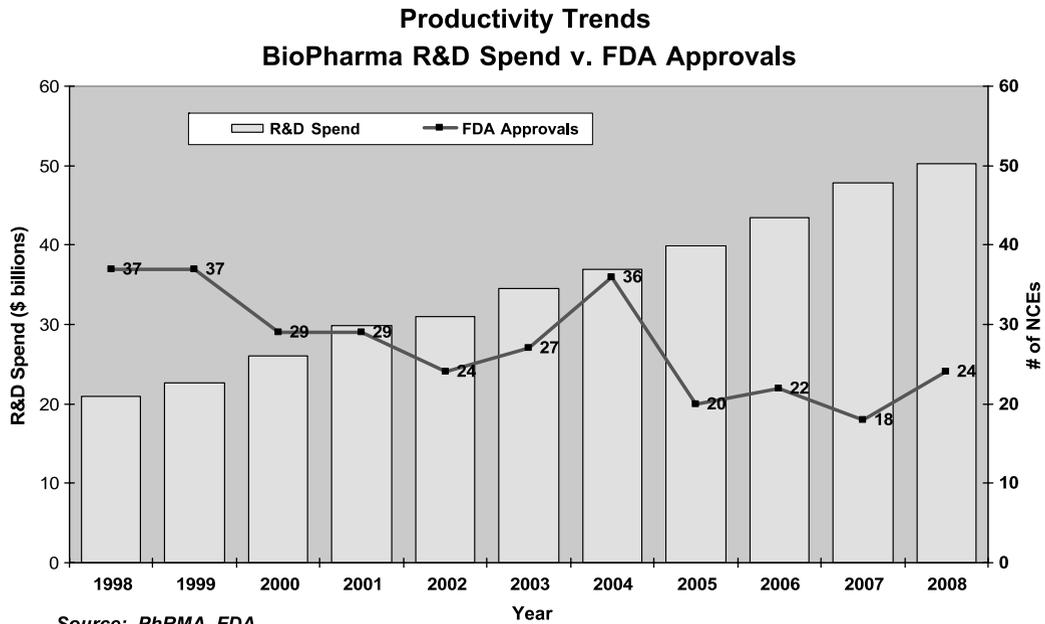


FIGURE 1. The new reality: research and development costs continue to rise, while output falls.

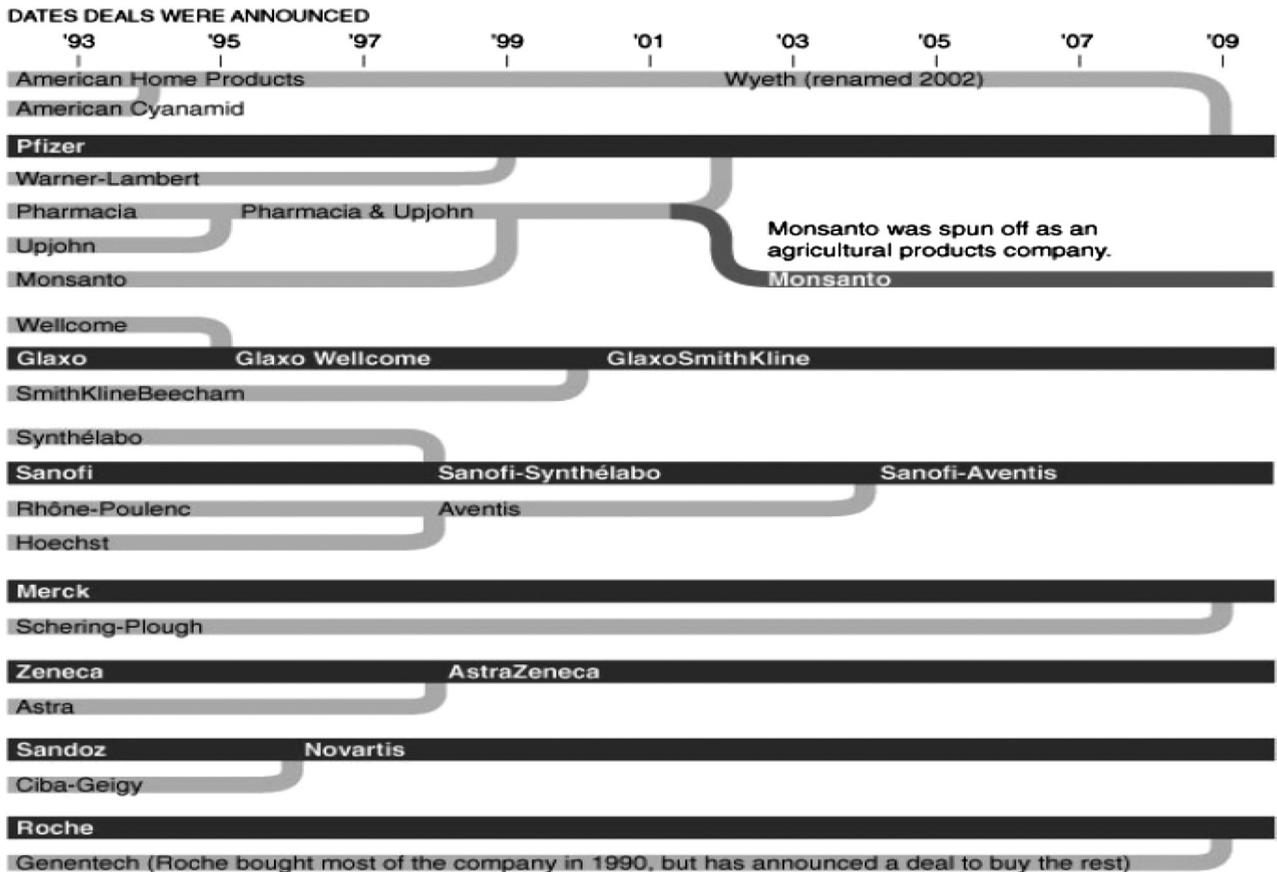


FIGURE 2. Significant drug industry consolidation in the past 15 years.

greater complexity and increased demand related to the protocols, so even with resources such as ClinicalTrials.gov, patients may be unaware of relevant protocols, and the United States has too few patient networks for studies outside oncology and pediatrics. In the future, we may be able to use social networking sites on the Web to inform potential participants. Second, United States physicians have competing demands for time to sustain their practice. Medical facilities do not provide sufficient infrastructure to train clinical researchers and then to support their clinical research. Indeed, physicians are often unaware of relevant protocols. The lack of participants has led to an increase in study costs, slow accrual of patients in the clinical trials, and, as a result, the movement of clinical research outside the United States.

The public's attitudes about health-related research and trust in clinical research present another interesting issue. In the United States, 78% view global leadership and health-related research as important, 90% believe the United States must train medical researchers, and 68% reflect on the substantial value of clinical research. However, 42% distrust the pharmaceutical companies, who are doing much of the research, only 45% trust the Food and Drug Administration to ensure drug safety, and 29% believe that one of the primary motivations for their physician to conduct clinical research is a financial motivation.⁴

In addition, as I noted, clinical trials are becoming increasingly complex, which has increased the burden on both the patient and the physician. The number of procedures per trial protocol for a 6-year period has increased by 65%.⁵ The length of trials and the duration of the studies have increased, meaning that participants must commit to a longer period of time. As a result, enrollment and participation rates and retention rates of patients have significantly decreased. In addition, investigators are frequently failing to meet their timelines. Data⁶ show that 82% of clinical trials experience a delay of more than 1 month, and 42% have major study delays, all because of patient accrual rates.

Because of reduced participation rates in the United States, many pharmaceutical companies have moved research to other countries. Figure 3 provides data about contract research organizations, which pharmaceutical companies often contract to execute clinical trials. Comparing the funds allocated for current

research (left side) with the budget for development in 2010, we see a one-third reduction in what pharmaceutical companies are spending for trials in the United States.

EVOLVING RELATIONSHIPS WITH RESEARCH PARTNERS AND THE REGULATORY ENVIRONMENT

These research partnerships are symbiotic relationships that allow researchers to generate new knowledge: from basic research to full-scale drug development. The partners compliment and depend on each another. However, in these relationships, the partners face a number of demands, which make the research a more difficult process.

The industry-academia-government research relationship has sometimes been referred to as a partnership and sometimes as a parasitic relationship, to suggest that the drug industry benefits from work performed elsewhere. This suggestion is not a helpful way to frame this discussion. Rather, each partner in these relationships provides something unique, which culminates in the difficult process of modern drug development. The industry is constantly scanning for external research relationships that can expedite drug development, and drug-discovery tools that were often pioneered in the industry are now available for translational research outside of the larger pharmaceutical companies.

Increasingly, industry, academia, and government representatives have partnered to explore fundamental issues around drug discovery, development, and safety. As a result, the industry has made major contributions to the current therapeutic armamentarium, as reflected in research and a quote from the Manhattan Institute. The Manhattan Institute notes that 35 of the most important drugs available today "would not have been developed or their development would have been delayed without the scientific or technical contributions of the pharmaceutical firms."⁷ The data in Figure 4 are actually derived from Merck Research Labs, and the facts depict the type of external activities in which the industry is involved.

In 2008, nearly 6000 scientific opportunities were subsequently narrowed through review to 46 signed agreements. These agreements are not what many people consider as part of

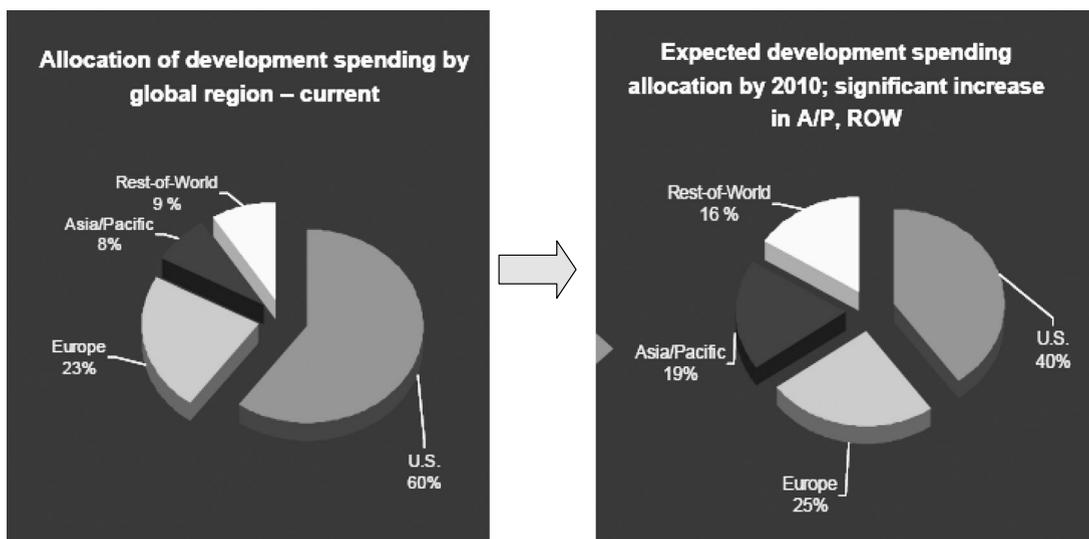


FIGURE 3. Response: increased allocation of development spending and patient accrual outside of the US.

the process to license drugs. Most these agreements involve either basic research collaborations or enabling platforms, and most of the agreements were with academic institutions.

These research relationships must exist under different but arguably improved circumstances than in the past. Of the relationships, the public has demanded that the partners be transparent and disclose any conflicts of interest. Although these relationships are clearly beneficial, we must address other possible consequences. For example, the public may misunderstand if the clinical investigator reports that a drug company is paying for the research without explaining that the payment pays for the investigator's staff and for the protocol-specified procedures. If the disclosures of conflicts of interest are used to question rather than broaden participation in scientific debate, we will all suffer.

Finally, returning to the increasing cost for clinical research, as budgets for all groups become constrained, the partners are negotiating over intellectual property, which narrows the discourse between partners. As a result, researchers focus more on various specific deliverables rather than working with open-ended funding.

We need to upgrade the current clinical-research infrastructure in the United States, or we will further impede drug development. We need to better use standards and methodologies to collect data. Data are frequently gathered for "what-if" scenarios rather than really what is important, which can cause clinical-trial monitoring to be an inefficient process and can result in excessive cost. Clinical investigators lack accreditation and formal training in good clinical practices and in the nuances of conducting a clinical trial. We also need to use electronic health records more for both randomized clinical trials and for pharmacoepidemiology. Public and private efforts, such as the Clinical Trials Transformation Initiative, are beginning to address some of these challenges. If we do not, however, address these challenges, we will see the velocity of medical benefits decrease even more.

REGULATORY ENVIRONMENT

The regulatory environment is also evolving, and risk avoidance is paramount because of understandable reasons from

the past few years. Because of the current environment, regulatory agencies are reexamining previously accepted surrogates for approval, which can delay the approval of new therapies. The broader scientific community is also reexamining past policies. As a result, the pharmaceutical companies have more extensive premarketing and postmarketing requirements, and we have expanded requirements for risk mitigation, such as the risk evaluation and mitigation strategies. These reevaluations contribute to some extent to uncertainty around timelines for agency review. Now, we will have advisory committees for all new chemical entities, and we are focusing more on the therapeutic context of a new drug as compared with other drugs on the market, and we are going beyond studies that demonstrate efficacy, for example, versus placebo.

We are facing other factors from the regulatory environment in the United States. We can compare what is evolving in the United States with what has happened in the European Union in the last several years. In the European Union, after making an application for marketing authorization, the reviewers more consistently adhere to timelines, and there is more opportunity, albeit in a formal question-and-answer mechanism, to dialogue with the regulatory agency during the review process. The review process occurs with less public attention and often results in a drug initial approval, at least in the second-line therapy setting. Nonetheless, the pharmaceutical company may have a clearer path forward, which reduces uncertainty while still acknowledging the importance and ensuring, to the extent possible, the safety of new medicines.

Four regulators from the European Union recently addressed this high-profile debate in an article in the *New England Journal of Medicine*.⁸ They note that this prescription for a better definition of a safe drug includes a shift of the regulatory debate to one of developing a tolerable level of risk rather than declaring something that is safe or not safe.⁸ They asked for the development of methodology that would allow for a more quantitative, transparent benefit-risk assessment and a recognition that as we improve our capabilities at pharmacovigilance, we will generate more safety signals—indeed safety signals that could have existed with older drugs had we had the techniques to recognize them. Just as detecting those signals is important, we need to know how

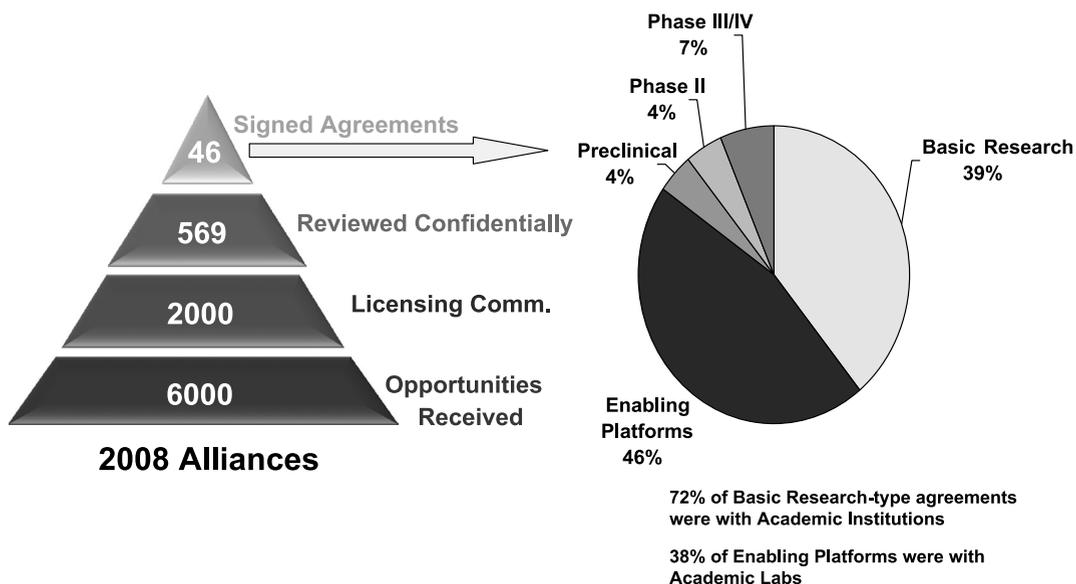


FIGURE 4. Constantly scanning for partnering opportunities.

to communicate that information to the public, and that confirmation of signals is as important as their detection. In addition, the regulators asked that patients be more engaged in assessing the benefit-risk profile.

CONCLUSIONS

In summary, I have noted that drug development is an expensive and increasingly uncertain undertaking; that patient participation in drug development is insufficient for us to expedite the availability of needed new medicines; that research efforts are notably collaborative in nature and are becoming more complex, and we need more collaboration; that we need to modernize our clinical research infrastructure and execute more efficiently if we are to benefit from what we invest; that both the industry and the public would benefit from strong, trusted, and predictable regulatory oversight; and that we need to discuss more and better understand the benefit-risk balance that could change this environment. We must address these challenges if advances in therapeutics are to continue.

Is the sky falling? I will leave that for all of us to ponder and answer for the years ahead.

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