# BIOTECHNOLOGY

**BRINGING INNOVATION TO NEGLECTED DISEASE RESEARCH & DEVELOPMENT**

A Joint Report by
BIO Ventures for Global Health (BVGH) &
the Biotechnology Industry Organization (BIO)

JUNE 2012


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# CONTENTS


**Acknowledgments** ..... 1

**Letter of Introduction** ..... 2

**Executive Summary** ..... 3

**Biotechnology and Neglected Diseases** ..... 5

- Global Health Research and Development Goals
- Historic Emphasis on Large, Multinational Pharmaceutical Companies to Fill Neglected Disease R&D Gaps
- Biotechnology Companies Are Contributing Significantly to Neglected Disease R&D

**Biotechnology Companies Drive Innovation in Health R&D** ..... 16

- What Is Biotechnology?
  - What Is a Biotechnology Company?
- Major Contributions by the Biotechnology Sector to Health Care Worldwide
  - Biotechnology Innovation Is an Important Commodity for R&D Success
- Financial Structure of Biotechnology Companies
  - Venture Capital Funding
  - Public Offerings
  - Partnership Funding
  - Government Funding
  - Biotechnology Companies Depend on a Market
- Changing Landscape of Health R&D
  - Translational Science Is Playing a Growing Role in Creating New Drugs
  - Innovative Financing and Partnering Are Replacing Traditional Biotech Business Models

**Barriers to Biotechnology Company Engagement in Global Health R&D** ..... 25

- Some Biotechnology Companies Have Made It Work

**Mechanisms and Motivations for Biotechnology Company Engagement** ..... 28

- Companies Can Benefit from Global Health R&D
- Incentives
- Innovative Collaboration Mechanisms

**An Opportunity to Increase Innovative Biotechnology Leadership in Neglected Disease R&D** ..... 33

Biotechnology Companies Can and Should Grow Their Commitment and Investment in Neglected Disease R&D Through Partnering

Neglected Disease Stakeholders from Academia, Governments, Nonprofits, and Foundations Should Engage Biotechnology Companies Through Both Existing and Novel Mechanisms

**Methodology** ..... 35

**Appendix 1:** Select Private Sector Global Health Initiatives ..... 36

**Appendix 2:** Neglected Tropical Disease Drug Donation Commitments from Multinational Pharmaceutical Companies ..... 38

**Appendix 3:** Biotechnology Companies Participating in Global Health R&D ..... 39

**Appendix 4:** Select Examples of Innovative Financing Mechanisms to Stimulate Global Health R&D ..... 42

**References** ..... 43

## TABLE LIST

Table 1. Neglected Disease Products in Development with at Least One Biotechnology Company Developer ..... 7

Table 2. Industry Participation in Neglected Disease R&D by Organization and Product Type ..... 8

Table 3. 37 Biotechnology Companies Are Working on More Than the Average of 1.4 Neglected Disease Products in Development ..... 9

Table 4. Examples of Biotechnology Products That Fundamentally Changed Health Care ..... 18

## FIGURE LIST

Figure 1. Biotech Companies Participating in Neglected Disease R&D by Country Where Headquarters Are Based ..... 10

Figure 2. Neglected Disease R&D Investment by Small to Medium-Sized Biopharmaceutical Enterprises, 2007–2010 ..... 11

Figure 3. Partnering Among All Neglected Disease R&D Projects Compared to Products with Biotechnology Participation ..... 12

Figure 4. Biotechnology Partners in Neglected Disease R&D Projects ..... 13

Figure 5. Biotechnology Partnering With and Without PDP Involvement by Organization Types ..... 13

Figure 6. Biotechnology-Government Partnership Focus With and Without PDP Involvement by Product Type ..... 14

Figure 7. Biotechnology Companies Work on Tuberculosis and Dengue Fever Independently, While Other Diseases Call for Partnering ..... 15

Figure 8. Barriers to Biotechnology Engagement in Global Health R&D ..... 25

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The majority of data analysis in the first section of this report is based on the BIO Ventures for Global Health *Global Health Primer* and associated database. The *Global Health Primer* is available online at www.globalhealthprimer.org.

# LETTER OF INTRODUCTION

The innovative spirit of biotechnology companies has driven the discovery and development of new approaches to tackling important diseases such as cancer, cardiovascular disease, and diabetes. To reach success, companies must navigate shifting funding environments and tackle scientifically complex questions, but often with the promise of a paying market as a reward for success.

As with these commercially oriented products, neglected disease research and development (R&D) requires that companies possess not only scientific ingenuity, but also financial and organizational flexibility to follow the ever-changing path of new product development. But at the end of this path, very few patients suffering from one or more of the neglected diseases we highlight in this report will have the ability to pay for the drugs, vaccines, and diagnostics that they desperately need—offering companies little or no commercial market to recoup their R&D investment costs and compensate the risk and opportunity cost of this badly needed innovation.

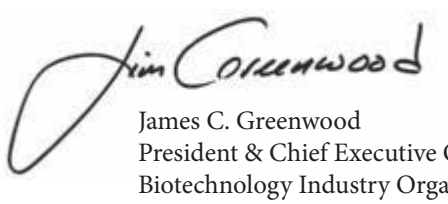
Despite these and other significant hurdles, biotechnology companies are leading the charge in global health R&D. As of March 2012, the *Global Health Primer* dataset, managed by BIO Ventures for Global Health (BVGH), indicated that 134 biotechnology companies globally are involved in 39% of all drugs, vaccines, and diagnostics in development for neglected disease. This illustrates that many biotechnology companies have found successful models that support their desire to solve these complex and important health problems. If only 134—or about 5%—of all biotechnology companies are already participating in neglected disease R&D, this leads us to examine the barriers and potential solutions to getting the other 95% of companies involved. How can the biotechnology industry collaborate with neglected disease stakeholders to advance new biomedical solutions for the world's poorest people?

To answer this and other questions about biotechnology company engagement in neglected disease R&D, BVGH and the Biotechnology Industry Organization (BIO) collaborated to create a report that not only speaks to biotechnology companies, but also to potential public-sector partners on how to better engage innovative biotechnology companies in their global health R&D programs.

Through this report, we offer actionable information for product developers from academia, government agencies, biotechnology companies, and non-profit product development partnership (PDPs) to help spark new partnerships and collaborations with biotechnology innovators to drive new drugs, vaccines, and diagnostics. These new products will help improve the lives of individuals, families, and communities worldwide. Specifically, we hope that our concrete suggestions that conclude this report will stimulate action for innovators in biotechnology to join together with those that possess neglected disease expertise to tackle these tremendous but surmountable challenges.

Sincerely,

Don Joseph
Chief Executive Officer
BIO Ventures for Global Health



James C. Greenwood
President & Chief Executive Officer
Biotechnology Industry Organization

# EXECUTIVE SUMMARY

Research and development (R&D) for new products to prevent, diagnose, and treat neglected diseases of the developing world is both scientifically and financially challenging. Understanding how biotechnology companies function and what they contribute to neglected disease R&D is essential to understanding how we can optimize investments in much-needed new product development. In March 2012, BIO Ventures for Global Health (BVGH) released a report showing for the first time that as of September 2011, small to medium-sized biotechnology companies are participating in 41% of the drug and vaccine projects in development for the neglected diseases. That report, *Developing New Drugs and Vaccines for Neglected Diseases of the Poor: The Product Developer Landscape* (referred to in this report as the *Product Developer Landscape*), identified 104 biotechnology companies participating in the development of 153 separate drugs and vaccines for 16 of the 23 neglected diseases evaluated by BVGH.

Small to medium-sized biotechnology companies lead the innovation charge in developing life-saving drugs, vaccines, and diagnostics in high-income countries, yet the majority of these companies are not profitable and face significant R&D funding challenges—estimates range as high as $1.3 billion to develop a new drug. Thus, the high level of participation of biotechnology companies in development of drugs, vaccines, and diagnostics for diseases of the developing world was unexpected given the financial risks involved in product development for these diseases and the little to no promise of a return on their R&D investment.

These intriguing findings from the *Product Developer Landscape* led us to this new report, *Biotechnology: Bringing Innovation to Neglected Disease Research and Development*—a collaboration between BVGH and the Biotechnology Industry Organization (BIO)—which provides further analysis, based on updated data, of the biotechnology sector's contributions to neglected disease product development across drugs, vaccines, and diagnostics. The report goes on to describe the typical biotechnology business model and identifies some of the challenges facing biotech engagement in global health product development. The report also describes benefits and mechanisms of engagement employed by biotechnology companies working in global health R&D today. We make the case for why small to medium-sized biotechnology companies are critical players in driving critically

needed innovation in neglected disease product development. Finally, we provide a call to action by offering concrete suggestions on how to increase the biotechnology industry's involvement in this effort.

Based on updated data from BVGH's *Global Health Primer*, including the addition of diagnostics products and the analysis of government agencies as a distinct product developer category, several interesting results emerged:

- *Partnering is an important driver for neglected disease R&D.* Sixty-four percent of all products in development by biotechnology companies across the pipeline of drugs, vaccines, and diagnostics for neglected diseases involve partnering. Biotechnology companies have a higher incidence of partnering for vaccines and diagnostics for neglected diseases, for which 75% of projects involve at least one partner, than for drug projects, where only 37% of projects involve partnerships. Biotechnology companies partner most frequently with academic institutions (57% of projects), followed by PDPs (52%), government agencies (30%), other biotechnology companies (16%), and large pharmaceutical companies (7%).

- *Product development partnerships (PDPs) and government agencies are driving biotechnology company partnering for neglected diseases.* PDPs are a unique public-private partnering mechanism designed to increase industry participation in neglected disease R&D. PDPs are involved in 52% of partnered projects. When a PDP is not involved in a project, biotechnology-government partnerships increase (from 23% when a PDP was involved, to 39% when no PDP was involved) especially for vaccines and diagnostics.

- *For tuberculosis and dengue fever, biotechnology companies are often working independently.* Across all neglected diseases, biotechnology companies work without a partner 36% of the time. For tuberculosis (49% of projects alone) and dengue (53% of projects alone), companies have been able to overcome barriers and leverage some market potential to work alone. For the other neglected diseases that have little or no market, biotechnology companies more frequently leverage strategic partnerships to increase their participation. These data suggest that some level of market considerations remain predominant in how biotechnology companies are participating in neglected disease R&D, since tuberculosis and dengue fever have some market potential.

In addition to the financing challenges biotechnology companies face in developing commercially-viable products, participation in neglected disease product development poses additional hurdles. Traditional funding challenges and a lack of familiarity with the science behind developing world diseases are exacerbated for these neglected disease products. Yet we identified 134 biotechnology companies that have overcome these financial, informational, managerial, and regulatory barriers and engaged in global health by seeking creative partnerships, often capitalizing on non-dilutive financing, and realizing strategic benefits to engaging in neglected disease R&D. Although biotechnology company participation is substantial, industry figures provided by BIO reveal that this level represents engagement of 5% of all biotechnology companies worldwide, suggesting far more engagement is possible.

This report examines the current level of biotechnology company engagement, business models that drive innovation in the biotechnology sector, and mechanisms to engage biotechnology companies in neglected disease projects. Based on these factors, we offer concrete recommendations to help biotechnology companies increase their commitment and investment in neglected disease R&D through partnering.

The promise of biotechnology advances has so far been realized through development and approval of important products for cancer, cardiovascular disease, diabetes, neurological, and other diseases for which new products are commercially viable. Biotechnology companies are participating at a surprising overall level in neglected disease R&D. Given their power to innovate, as well as the financial and other barriers that prevent more extensive engagement, more work is needed to build on the significant level of involvement of the biotechnology sector. All stakeholders—government agencies, nongovernmental organizations, disease advocates, policy makers, foundations, donors, and the biotechnology industry itself—must collaborate to address the most pressing unmet health needs of the developing world. Doing so will not only benefit those who need it most, but will inevitably benefit all of us, as global citizens.

# BIOTECHNOLOGY & NEGLECTED DISEASES

## GLOBAL HEALTH RESEARCH AND DEVELOPMENT GOALS

Of the world's poorest 2.7 billion people who live on less than $2 a day, more than 1 billion people are affected each year by neglected diseases, such as malaria, tuberculosis, cholera, and Chagas disease.[1] Each year, ten million people die from neglected diseases. Millions more are so debilitated by disease that they are unable to work, care for themselves, or care for their children. Onchocerciasis and trachoma cause blindness. Deformities caused by leprosy and lymphatic filariasis hinder economic productivity and destroy chances for a normal social life. Human African trypanosomiasis (sleeping sickness) severely incapacitates before it kills, and mortality approaches 100% in untreated cases.[2]

For many of these diseases, safe and effective drugs, vaccines, or diagnostics do not exist. Current tuberculosis drugs, for example, are more than 40 years old and are becoming ineffective due to drug resistance. Other diseases, such as sleeping sickness, are primarily treated with highly toxic compounds and complicated dosing regimens that require hospitalization. Recognizing this lack of effective and acceptable medical tools, the World Health Organization (WHO) issued its first-ever report on neglected tropical diseases in October 2010. Most of the diseases are caused by various protozoan and helminth parasites that are foreign to developed nations, making them unfamiliar targets for many product developers. Research and development (R&D) for new drugs, vaccines, and diagnostics to address these devastating diseases is desperately needed.[3]

The resources dedicated to developing the new drugs, vaccines, and diagnostics that can address health needs in developing countries are insufficient.[4] R&D for neglected tropical diseases receives only $1 out of every $100,000 spent worldwide on biomedical research and product development.[5] Overall, neglected disease R&D funding continues to fall. Total reported funding for R&D of neglected diseases in 2010 was $3.063 billion, marking a decrease of $109.1 million (-3.5%) from 2009 investments.[6] The public sector plays a key role in neglected disease funding, providing about 65% ($2 billion) of global neglected disease funding in 2010, with the vast majority coming from governments of high-income countries (HICs).[7,8] Philanthropic organizations and multinational pharmaceutical companies follow, contributing 18.5% ($568 million) and 14.4% ($442 million), respectively, to global health R&D. Yet even within global health R&D, the 'big three' diseases, HIV/AIDS, tuberculosis, and malaria, collectively receive the majority (71.7%) of global funding, while the remaining neglected diseases such as dengue, sleeping sickness, Chagas disease, leishmaniasis, and helminth infections receive less than 6% of global disease R&D funding each. In fact, leprosy, Buruli ulcer, trachoma, and rheumatic fever received less than $10 million each, or less than 0.5% of global funding collectively.[9]

In addition to funding challenges, new drugs, vaccines, and diagnostics for neglected diseases require new ways of thinking about how to deliver these technologies. Some technologies designed for developed country use are not suitable for use in resource-poor settings, especially in rural areas that may lack infrastructure, electricity, potable water, or trained health care workers. Technologies for the developing world must be robust, able to withstand extremes of temperature and humidity, simple, and easy to administer and store. Shorter treatment times are preferable, as are alternatives to intravenous delivery mechanisms, and pediatric formulations should be included whenever possible. There is great room and need for innovation in new neglected disease products.

### ELIMINATION AND CONTROL OF 10 NEGLECTED DISEASES BY 2020

In January 2012, the Bill & Melinda Gates Foundation convened executives from 13 large pharmaceutical companies and a number of other key stakeholders to announce both new and renewed commitments to accelerate progress toward eliminating or controlling 10 neglected tropical diseases by 2020. The goals are to eradicate Guinea worm disease and to expedite progress toward eliminating lymphatic filariasis, blinding trachoma, sleeping sickness, and leprosy, and controlling soil-transmitted helminths, schistosomiasis, river blindness, Chagas disease, and visceral leishmaniasis by 2020. To achieve this, new and existing tools and strategies are needed. Companies such as GlaxoSmithKline, Merck, Sanofi, Pfizer and Novartis have stepped forward with generous donations of existing medications, but novel drugs, vaccines, and diagnostics are still needed. Commitments from multinational pharmaceutical companies are summarized in Appendix 1. These commitments are the result of efforts to engage top executives of multinational pharmaceutical companies by leading organizations in global health, like the Bill & Melinda Gates Foundation.

## HISTORIC EMPHASIS ON LARGE, MULTINATIONAL PHARMACEUTICAL COMPANIES TO FILL NEGLECTED DISEASE R&D GAPS

Large, multinational pharmaceutical companies are the traditional giants of product development and have historically had a major impact on global health. Merck discovered ivermectin, a drug that cures onchocerciasis, or river blindness, in 1987 and provided the drug free of charge to those in need through a partnership with the WHO. Subsequently, other large pharmaceutical companies have followed suit with drug donations spanning many neglected diseases (see call out box). Drugs and vaccines originating from the pharmaceutical industry have helped to bring several neglected diseases to the brink of elimination and have saved millions of lives over the past two decades.

Given the importance of large pharmaceutical company products to global health programs, increasing engagement of the pharmaceutical industry in R&D for neglected diseases has been a priority of the global health community. Numerous targeted efforts have been developed including activities to increase industry partnerships, engage large companies at the executive level, and provide incentives for successful contributions (see later section on *Mechanisms and Motivations for Biotechnology Company Engagement*.) To date, this emphasis has generally not included biotechnology companies; expanding these efforts to include biotechnology executives could enable the sector to contemplate solutions for the scientific and technological challenges facing neglected disease drug, vaccine, and diagnostics development.

An innovative collaboration model that has increased industry participation in global health R&D is the product development partnership (PDP) model.[10] The PDP model was brought into practice by the Rockefeller Foundation through the creation of the International AIDS Vaccine Initiative (IAVI) in 1996. Subsequently, 16 new PDPs were established with significant support from the Bill & Melinda Gates Foundation between 1999 and 2003.[11] PDPs are now the largest recipients of neglected disease R&D funding and are involved in 40% of all neglected disease drug and vaccine development.[12,13] The majority of industry R&D projects for diseases of the developing world now involve collaboration with PDPs.[14,15]

New programs spearheaded by large pharmaceutical companies point to a continuing trend of increasing collaborations. For example, WIPO Re:Search was launched in October 2011, making hundreds of patents, drug screening datasets, and product development know-how accessible to researchers working on drugs, vaccines, and diagnostics for neglected tropical diseases.

Incentive programs have also been launched to encourage R&D for neglected diseases that lack a market drive, such as the U.S. Food and Drug Administration's (FDA) Priority Review Voucher (PRV) program[16] and the Advance Market Commitment (AMC).[17] Although this AMC was targeted more at incentivizing the building of manufacturing capacity, future AMCs could incentivize the research and development of novel products aimed at the developing world.

The impact of these targeted efforts to engage the pharmaceutical industry is evident in analysis of pharmaceutical company financial contributions to neglected disease R&D. Beyond significant donations of existing products, the aggregate

biopharmaceutical industry is now the second largest funder of neglected disease R&D after the U.S. National Institutes of Health (NIH).[18] Financial contributions from large, multinational pharmaceutical companies have increased consistently over the last four years to a high of $442 million in 2010 and make up more than 85% of contributions from the biopharmaceutical sector.

### DEFINING BIOTECHNOLOGY COMPANIES

BIO Ventures for Global Health's (BVGH) *Global Health Primer* database defines biotechnology companies as small to medium-sized biologics or pharmaceutical companies with annual revenue of less than $10 billion that focus on novel product development. Companies with a primary focus on in-licensing, generics, contract services, or other non-discovery aspects of product development were categorized as "other industry." Biotechnology companies that were purchased by multinational pharmaceutical companies in 2009 or later are still designated as biotechnology companies in this report to reflect the point that products currently in development at these organizations likely originated from the biotechnology company rather than the large pharmaceutical company.

## BIOTECHNOLOGY COMPANIES ARE CONTRIBUTING SIGNIFICANTLY TO NEGLECTED DISEASE R&D

While concerted efforts by the global health community to engage large pharmaceutical companies have resulted in success, the broader landscape of the pharmaceutical industry is changing. Today, large pharmaceutical companies are increasingly purchasing innovation from small biotechnology companies rather than relying primarily on in-house research and development. A study of FDA approvals from 1998-2007 showed that 34% of new drug approvals originated from a biotechnology company or from a university technology transfer to a biotechnology company.[19] The biotechnology sector is contributing

### Table 1: Neglected Disease Products in Development with at Least One Biotechnology Company Developer

| | DRUGS | VACCINES | DIAGNOSTICS | TOTAL PRODUCTS |
|---|---|---|---|---|
| Big Three | | | | |
| Malaria | 18 | 29 | 10 | 57 |
| Human Immuno-deficiency Virus (HIV)* | 0* | 14 | 2 | 16 |
| Tuberculosis (TB) | 23 | 15 | 9 | 47 |
| Other Neglected Tropical Diseases | | | | |
| Buruli ulcer | 0 | 1 | 0 | 1 |
| Chagas disease | 0 | N/A | 0 | 0 |
| Cholera | N/A | 4 | 1 | 5 |
| Dengue fever | 9 | 6 | 0 | 15 |
| Fascioliasis | 0 | 0 | 0 | 0 |
| Human African trypanosomiasis (sleeping sickness) | 2 | N/A | 3 | 5 |
| Leishmaniasis** | 11 | 2 | 3 | 16 |
| Leprosy | N/A | 0 | 1 | 1 |
| Lymphatic filariasis (LF) | 1 | 0 | 0 | 1 |
| Onchocerciasis (River Blindness) | 1 | 0 | 0 | 1 |
| Schistosomiasis | 1 | 0 | 2 | 3 |
| Soil-Transmitted Helminths: Ascariasis, Trichuriasis, and Hookwork | 0 | 0 | 0 | 0 |
| Trachoma | N/A | 0 | 0 | 0 |
| Other Important Diseases of Poverty | | | | |
| Pneumococcal disease | N/A | 4 | 0 | 4 |
| Diarrheal diseases | 5 | N/A | 1 | 6 |
| Enterotoxigenic E. coli (ETEC) | N/A | 6 | 0 | 6 |
| Rotavirus | N/A | 2 | 0 | 2 |
| Shigellosis | 1 | 2 | 0 | 3 |
| Typhoid fever | N/A | 2 | 0 | 2 |
| **Totals** | **72** | **87** | **32** | **191** |

** Only microbicides are tracked for HIV drug development.*

*** Only the visceral leishmaniasis disease forms have been targeted for control*

*The number of products with at least one biotechnology company developer is presented for each of the 18 neglected diseases with active biotechnology company participation in product development. Products designated as N/A are outside the scope of products tracked in the "Global Health Primer". Diseases highlighted in green have been targeted by the WHO for control by 2020; diseases highlighted in yellow have been targeted for elimination by 2020.*

**Table 2. Industry Participation in Neglected Disease R&D by Organization and Product Type**

| | TOTAL PRODUCTS (% OF ALL PRODUCTS) | DRUGS (% OF ALL DRUGS) | VACCINES (% OF ALL VACCINES) | DIAGNOSTICS (% OF ALL DIAGNOSTICS) |
|---|---|---|---|---|
| Biotechnology Companies | **191 (39%)** | 72 (38%) | 87 (40%) | 32 (39%) |
| Large Pharmaceutical Companies [27] | **75 (15%)** | 54 (28%) | 21 (10%) | 0 (0%) |

to 48% of scientifically novel product approvals and 58% of products for orphan diseases.

There is an increasing focus on the biotechnology sector's contributions to new drug, vaccine, and diagnostic development for global health. Historically, the number of biotechnology companies participating in global health R&D has not been systematically tracked. In March 2011, BVGH released the new and expanded *Global Health Primer*, a report and online database of compiled drug, vaccine, and diagnostic development pipelines for neglected diseases.[20] Using this unique dataset, BVGH was able to explore for the first time the extent to which different types of organizations are participating in drug, vaccine, and diagnostic development for a broad range of neglected diseases.

In March 2012, BVGH published an analysis of the types of organizations participating in neglected disease product development.[21] BVGH identified 104 biotechnology companies participating in the development of 153 drugs and vaccines for 16 of the 23 neglected diseases evaluated.[22] When compared to the total number of neglected disease drugs and vaccines in development, biotechnology companies were participating in 41% of neglected disease products (153 out of 374 drugs and vaccines). Following this report, the full *Global Health Primer* dataset was updated and expanded to include diagnostics. The updated and expanded dataset identified 134 biotechnology companies participating in the development of 191 drugs, vaccines, and diagnostics for 18 of the 23 neglected diseases evaluated (Table 1).

When compared to the total number of neglected disease drugs, vaccines, and diagnostics in development, 134 biotechnology companies are participating in 39% of all products (191 out of 489 total products). On average, each participating biotechnology company is engaged in 1.4 neglected disease products. Table 1 summarizes the number of drugs, vaccines, and diagnostics in development that have at least one biotechnology company contributing to the product's research and development.

In Table 1, products in development for HIV, tuberculosis, and malaria—the "big three"—make up the majority of products in development with biotechnology company participation (63%). However, biotechnology companies are also participating in many products in the pipelines for dengue fever (8%), leishmaniasis (8%), sleeping sickness, and other important diseases of poverty such as diarrheal diseases and enterotoxigenic E. coli (ETEC). Malaria, tuberculosis, dengue fever, and leishmaniasis make up 85% of the drugs in development. For vaccines, 76% of products are in development for the 'big three,' dengue fever, and leishmaniasis. Of all the neglected diseases, HIV, malaria, tuberculosis, and dengue fever are suggested to have some market potential.[23,24,25,26] Therefore, these data suggest that some level of market considerations remain predominant in how biotechnology companies are participating in neglected disease R&D.

Table 2 shows that biotechnology companies are contributing to a significant proportion of all drugs (38%), vaccines (40%), and diagnostics (39%), particularly when compared to large pharmaceutical companies. Compared to large pharmaceutical companies, biotechnology companies are participating in the development of more individual neglected disease drugs, vaccines, and diagnostics: 191 total products versus 75 from large pharmaceutical companies.

These quantitative results do not speak to the depth, scope, or nature of involvement of the various developers nor to the quality of the projects. Nevertheless, biotechnology companies are clearly contributing significantly to the vaccine and diagnostics development arena, with respect to the number of products with participation, especially when compared to large pharmaceutical companies.

## Table 3. 37 Biotechnology Companies are Working on More Than the Average of 1.4 Neglected Disease Products in Development [32]

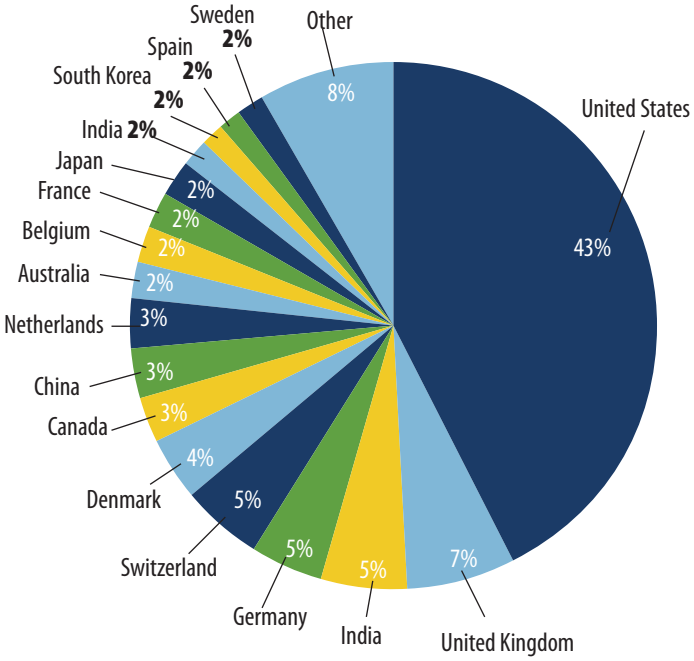
| | COMPANY | # OF NEGLECTED DISEASE PRODUCTS IN ACTIVE DEVELOPMENT | LOCATION OF HEADQUARTERS |
|---|---|---|---|
| DRUGS | Anacor Pharmaceuticals | 9 | United States |
| | NeED Pharma | 5 | Italy |
| | Advinus Therapeutics | 4 | India |
| | Dafra Pharma International | 3 | Belgium |
| | Sequella, Inc. | 3 | United States |
| | DesignMedix | 2 | United States |
| | Galapagos NV | 2 | Belgium |
| | Genzyme *(acquired by Sanofi)* | 2 | United States |
| | Medivir | 2 | Sweden |
| | NanoViricides, Inc. | 2 | United States |
| | Napo Pharmaceuticals, Inc. | 2 | United States |
| | PolyMedix Inc. | 2 | United States |
| | Vichem Chemie Ltd. | 2 | Hungary |
| VACCINES | Okairos Srl | 8 | Italy |
| | Crucell *(acquired by J&J)* | 6 | Netherlands |
| | Statens Serum Institut | 6 | Denmark |
| | Inovio Pharmaceuticals, Inc. | 5 | United States |
| | Celldex Therapeutics Inc. | 4 | United States |
| | GenVec Inc. | 4 | United States |
| | Mucosis B.V. | 4 | Netherlands |
| | Intercell AG | 3 | Austria |
| | Altravax | 2 | United States |
| | Bharat Biotech | 2 | India |
| | Bionor Pharma ASA | 2 | Norway |
| | Finlay Institute | 2 | Cuba |
| | Genocea Biosciences | 2 | United States |
| | Imaxio | 2 | France |
| | Paladin Biosciences division of Paladin Labs Inc. | 2 | Canada |
| | Shantha Biotech *(acquired by Sanofi)* | 2 | India |
| | TD Vaccines A/S | 2 | Denmark |
| | Vakzine Projekt Management GmbH | 2 | Germany |
| DIAGNOSTICS | Chembio Diagnostic Systems Inc. | 4 | United States |
| | Eiken Chemical | 4 | Japan |
| | Claros Diagnostics | 2 | United States |
| | Coris BioConcept | 2 | Belgium |
| | Micronics | 2 | United States |

*There are 37 biotechnology companies working on more than the average of 1.4 drugs, vaccines, and diagnostics for neglected diseases. This table lists the number of active products in development per company, as well as where each company is headquartered. For a full list of biotechnology companies participating in a neglected disease product development program, please see Appendix 3.*

Biotechnology companies also participate in an average of 1.4 products per company (191 products/134 companies) as compared to 5.8 products per pharmaceutical company (75 products/13 companies). Large pharmaceutical companies have considerable capital relative to other organization types, which suggests an ability to participate in a larger number of products per company than smaller biotechnology companies. In fact, the recent BVGH *Product Developer Landscape*, found that just four large pharmaceutical companies—GlaxoSmithKline, Novartis, Sanofi, and AstraZeneca—account for 55 (73%) of the 75 products in the pipeline.[28] Thirty-seven biotechnology companies (see Table 3) are working on more than the average of 1.4 products in development. For example, Anacor Pharmaceuticals,[29] based in the United States, stands out with its participation in nine independent, active drugs in the pipeline for several different neglected diseases, including sleeping sickness, onchocerciasis, lymphatic filariasis, and leishmaniasis. Okairos Srl,[30] based in Italy, is participating in eight independent malaria vaccine development programs, and U.S.-based Chembio Diagnostic Systems Inc.[31] has four preclinical diagnostics programs for tuberculosis, leprosy, malaria, and leishmaniasis.

There are 37 biotechnology companies working on more than the average of 1.4 drugs, vaccines, and diagnostics for neglected diseases. Table 3 lists the number of active products in development per company, as well as where each company is

Figure 1. Biotech Companies Participating in Neglected Disease R&D by Country Where Headquarters are Based




*Countries with only one biotechnology company participating in neglected disease R&D are included in the category "other."*

| COUNTRY WHERE HEADQUARTERS ARE BASED | # OF BIOTECHNOLOGY COMPANIES PARTICIPATING IN NEGLECTED DISEASE R&D |
|---|---|
| United States | 57 |
| United Kingdom | 9 |
| **India** | **7** |
| Switzerland | 7 |
| Germany | 6 |
| Denmark | 5 |
| Canada | 4 |
| **China** | **4** |
| Netherlands | 4 |
| Australia | 3 |
| Belgium | 3 |
| France | 3 |
| Japan | 3 |
| Italy | 2 |
| South Korea | 2 |
| Spain | 2 |
| Sweden | 2 |
| Austria | 1 |
| Cuba | 1 |
| Hong Kong | 1 |
| Hungary | 1 |
| Iceland | 1 |
| Iran | 1 |
| Ireland | 1 |
| Israel | 1 |
| Malaysia | 1 |
| Norway | 1 |
| **South Africa** | **1** |
| **Total** | **134** |

***BRICS countries (Brazil, Russia, India, China, and South Africa) are highlighted***

headquartered. For a full list of biotechnology companies participating in a neglected disease product development program, please see Appendix 3.

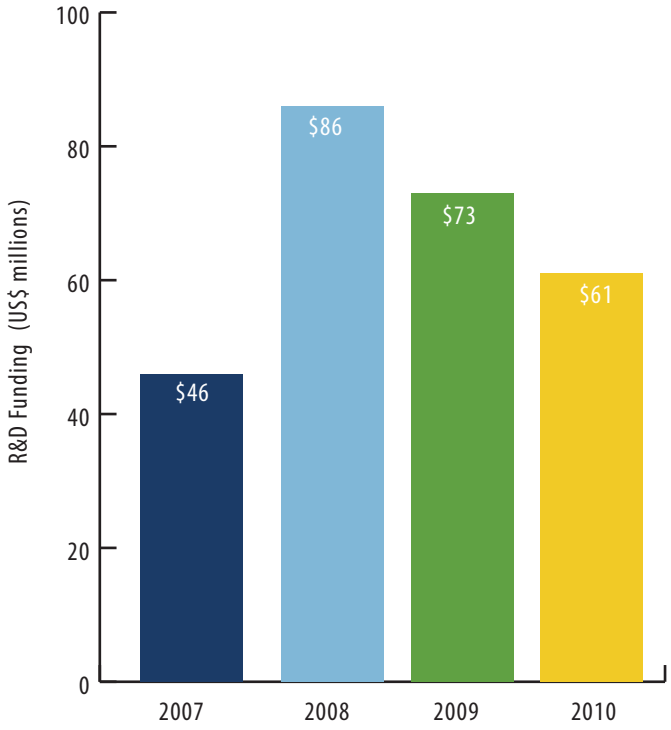
Overall, the 134 active biotechnology companies are headquartered in 28 countries, as summarized in Figure 1. Given that neglected diseases primarily affect populations in middle and low-income countries, it is notable that the United States is home to by far the largest share (43%) of biotechnology companies contributing to the global health drug, vaccine, and diagnostics pipeline. The United Kingdom (at 9%), India, Germany, and Switzerland are home to the next highest concentrations, respectively, of biotechnology companies participating in global health R&D.

Participation by Indian biotechnology companies stands out because the Indian population bears a significant burden of these neglected diseases (e.g., 41% of the global leprosy burden).[33] Drug manufacturers in India, such as Ranbaxy, are well known in the global health community for manufacturing and selling low-cost antimalarial and antiretroviral therapies in Africa.[34,35] Less well known are the products and strategies that the emerging biotech companies in India, like Advinus, can offer toward neglected disease product innovation. Although other emerging markets bear a similarly significant burden of neglected diseases as India, they are not home to as many biotechnology companies participating in the neglected disease R&D space. We did not identify any biotechnology companies in Brazil or Russia that are participating in a neglected disease product development program; we identified four companies in China and one in South Africa that are working in this space. There is a potential opportunity for companies in these emerging market biotechnology sectors to increase their participation.

Despite the significant financial resources flowing into the biotechnology industry—U.S. venture capitalists invested $3.7 billion in biotechnology companies in 2010[36]—only $61 million was invested in neglected disease R&D by small to medium-sized biopharmaceutical companies globally in 2010.[37] The amount of money invested by small to medium-sized biopharmaceutical companies has been steadily decreasing since 2008 (Figure 2) despite the large number of companies active in this space.

The $61 million invested by small to medium-sized biopharmaceutical companies is low relative to the $442 million invested

Figure 2. Neglected Disease R&D Investment by Small to Medium-Sized Biopharmaceutical Enterprises, 2007-2010[38]




by larger multinational pharmaceutical companies.[39]Similarly, estimates in the *Product Developer Landscape* suggest that large multinational pharmaceutical companies spend more on a per product basis—$6 million per product versus the estimated $0.4 million spent per neglected disease drug or vaccine product by a small pharmaceutical or biotechnology company.[40] While these are approximations, the contributions by biotechnology companies to neglected disease R&D are likely less financial and more focused on resource, material, or expertise contributions in preclinical drug and vaccine development. Further analysis of each respective organization type's contribution is needed to better understand *how* these companies are participating in neglected disease R&D.

## Partnering: A Key Element of Neglected Disease Product Development

For all organizations participating in neglected disease product development, partnering is a key activity used to dilute risk and lower the resource burden on individual product developers[41] Biotechnology companies partner at a comparable level to the entire pipeline of drugs, vaccines, and diagnostics for neglected diseases, in that 64% of products in development involve

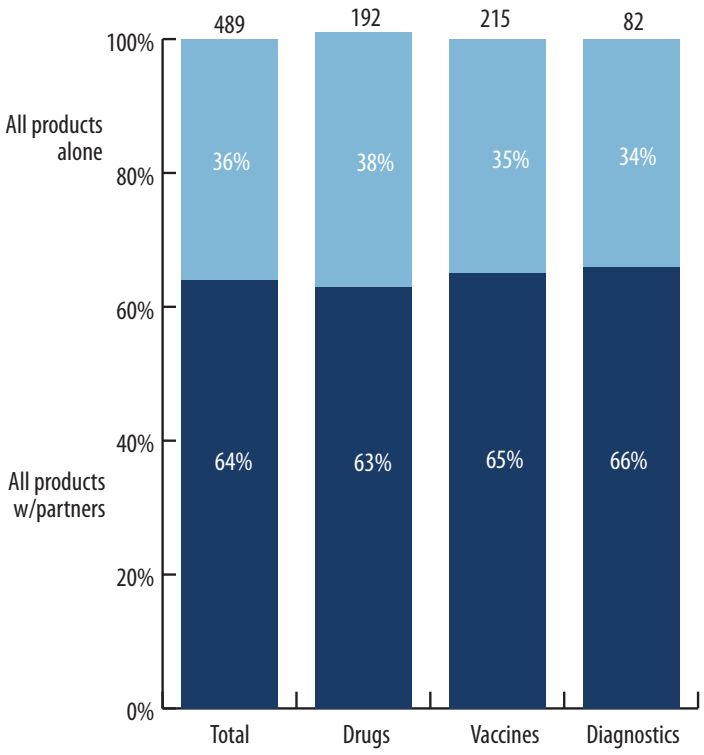
partnering (Figure 3a). While the level of partnering is approximately equal among products types in the composite pipeline, biotech partnering varies by product type (Figure 3b). For drug development projects, a single biotechnology company is independently conducting R&D on 53% of products. In contrast, significantly more biotechnology companies developing vaccines and diagnostics are working with partners (Figure 3b).

Although these data do not permit us to draw conclusions on what is driving differences in the extent of partnering for drugs, versus vaccines and diagnostics in development by biotechnology companies as compared to other developers participating in the overall neglected disease product pipeline, we can speculate that variances in costs of development, technical complexity, or access to funding are contributing factors. In order to explore the nature of biotechnology company partnering for neglected disease product development in more detail, we examined the extent to which different types of organizations are partnering with biotechnology companies. Examining those projects with at least one additional development partner, biotechnology company partnering is highest with academic institutions (57% of projects), which is also the case across all organization types. Besides academic institutions, biotechnology companies partner to the next greatest extent with PDPs (52% of products), then government agencies (30%), other biotechnology companies (16%), and large pharmaceutical companies (7%) (Figure 4).

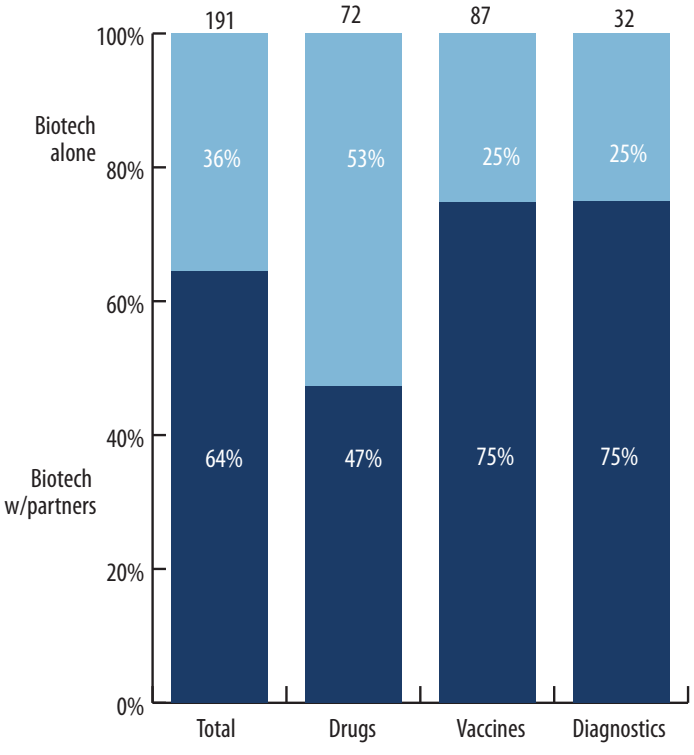
Most biotechnology companies are established by licensing a breakthrough discovered through basic research in an academic setting, and most companies meet major capital requirements by partnering with other organizations. Therefore, the level of biotechnology company partnering with other organization types—and especially academia—for neglected disease product development was not surprising. High rates of partnering with academic institutions were expected given that this is a traditional avenue through which biotechnology companies find their origin.[42]

Figure 3. Partnering Among All Neglected Disease R&D Projects Compared to Products with Biotechnology Participation

*a. Partnering varies slightly by product type for the **overall** neglected disease pipeline.*




*b. Biotechnology companies have a higher incidence of partnering for vaccines and diagnostics for neglected diseases.*

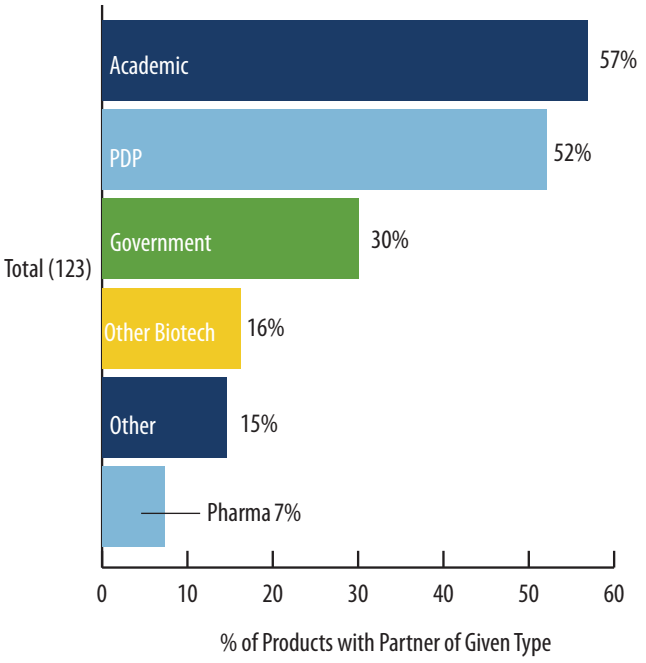


For neglected diseases, PDPs are a key mechanism for R&D investment and were designed to increase partnerships between industry and academic product developers using philanthropic dollars.[43] PDPs provide an important service in neglected diseases by connecting partners across sectors to accelerate and support neglected disease R&D. In addition to funding, PDPs can also provide disease-specific expertise, developing world contacts for research and clinical trials, and important insights into product design appropriate to local cultures. Given the focus on the PDP model in the global health community, these data raised the question as to who is working with biotechnology companies when no PDP is involved. To address this question, biotechnology company partnerships with various organization types were examined for products with and without PDP participation (Figure 5).

PDPs are biotech's second-most frequent partner in neglected disease R&D. Since PDPs are generally recognized as drivers of R&D for neglected diseases and are playing an increasingly major role as managers of R&D funding for neglected diseases, it is unclear how those project partnerships without a PDP developer are funded and operated. In our analysis, we found that when no PDP was involved in a neglected disease R&D project, biotechnology company partnering decreased for all potential partner organization types, with the exception of governments (Figure 5). Government increased to 39% from 23% when no PDP developer was involved in the project (Figure 5). Because the extent of partnering for biotechnology companies differed by product type (Figure 3b) and government partnering with biotech companies increased for projects with no PDP partner, the level of government partnering was examined for drugs, vaccines, and diagnostics with at least one biotechnology company developer (Figure 6).

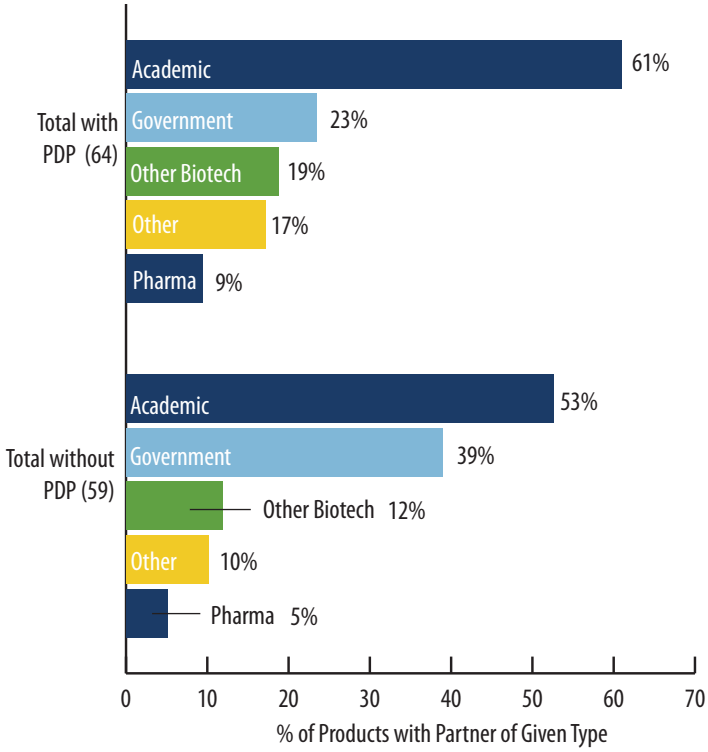
Government research institutes like the NIH are partnering with biotechnology companies to a large extent, and especially when no PDP is involved in a partnership. However, this is primarily the case for vaccines and diagnostics in development.

Figure 4. Biotechnology Partners in Neglected Disease R&D Projects




*Biotechnology companies partner most frequently with academic institutions and product development partnerships (PDPs), and to a lesser extent with government, other biotechnology companies, pharmaceutical companies, and others.*

Figure 5. Biotechnology Companies Partnering With and Without PDP Involvement by Organization Types




*Product development partnerships (PDPs) were developed specifically to advance research and development for neglected diseases through their work funding and managing projects. Without product developer partnership (PDP) involvement, biotechnology is partnering to the greatest extent with government institutions.*

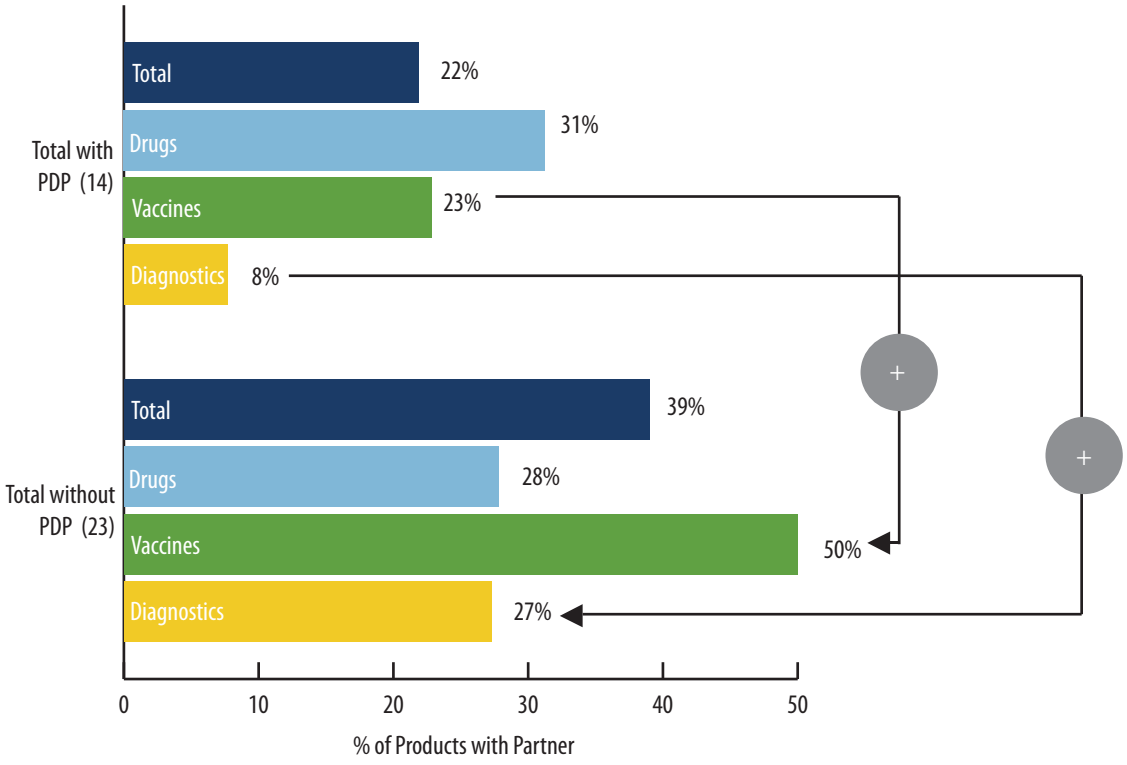
When no PDP is involved, the number of products with both a biotechnology company and government developer is increased for both vaccines and diagnostics. Perhaps for vaccines and diagnostics, government partnering is filling a unique niche not met by PDPs. It is worth considering whether extending government-biotechnology partnerships to drugs might help accelerate R&D in this sector.

As the extent of biotechnology company partnering for neglected disease product development varied by product type, variations in partnering by disease were then examined (Figure 7). Although 36% of biotechnology products are being developed without a partner, the majority of those unpartnered projects are focused on developing products for tuberculosis and dengue fever—diseases for which there is a broader market. Malaria and other diseases of poverty, such as pneumococcal disease and diarrhea, are on par with the average rates of partnering. The remaining neglected disease partnerships across all diseases evaluated have below average numbers of products in development without additional partners (Figure 7).

Variations in biotech partnering by disease may reflect several factors. Tuberculosis and dengue fever both have large numbers of products in development with no biotechnology partner and high number of projects with no additional development partners. Products for these two diseases may have some return on investment, especially in the private sector of emerging market countries, based on demand and market analyses. For example, a 2006 market assessment for tuberculosis vaccines indicated that the peak annual market for a bacille Calmette Guerin (BCG) replacement vaccine would be $450 million and $800 million for the booster, for a combined $1 billion market.[44] The BCG vaccine is the only vaccine available for the prevention of tuberculosis and has been in use for more than 80 years. The vaccine does not prevent primary tuberculosis infection, conversion of disease from latent to active forms, or pulmonary tuberculosis in adolescents or adults in the long-term.

More than 80% of HIV and leishmaniasis products in development by biotechnology companies are being developed with partners. In the case of HIV and leishmaniasis, it is likely that partnering enables greater participation in product development. For the remainder of neglected diseases, variations in

Figure 6. Biotechnology-Government Partnership Focus With and Without PDP Involvement by Product Type




*Biotechnology-government partnerships increase without product developer partnership (PDP) involvement. Products with both a biotechnology company and government developer are increased for both vaccines and diagnostics when a PDP is not involved in the partnership.*

partnering levels make it difficult to draw conclusions. However, the data suggest that a combination of market potential and partnering promote biotechnology company participation in neglected diseases. Future studies are needed to explore if promotion of market factors and/or partnering can increase biotechnology company participation in the future.

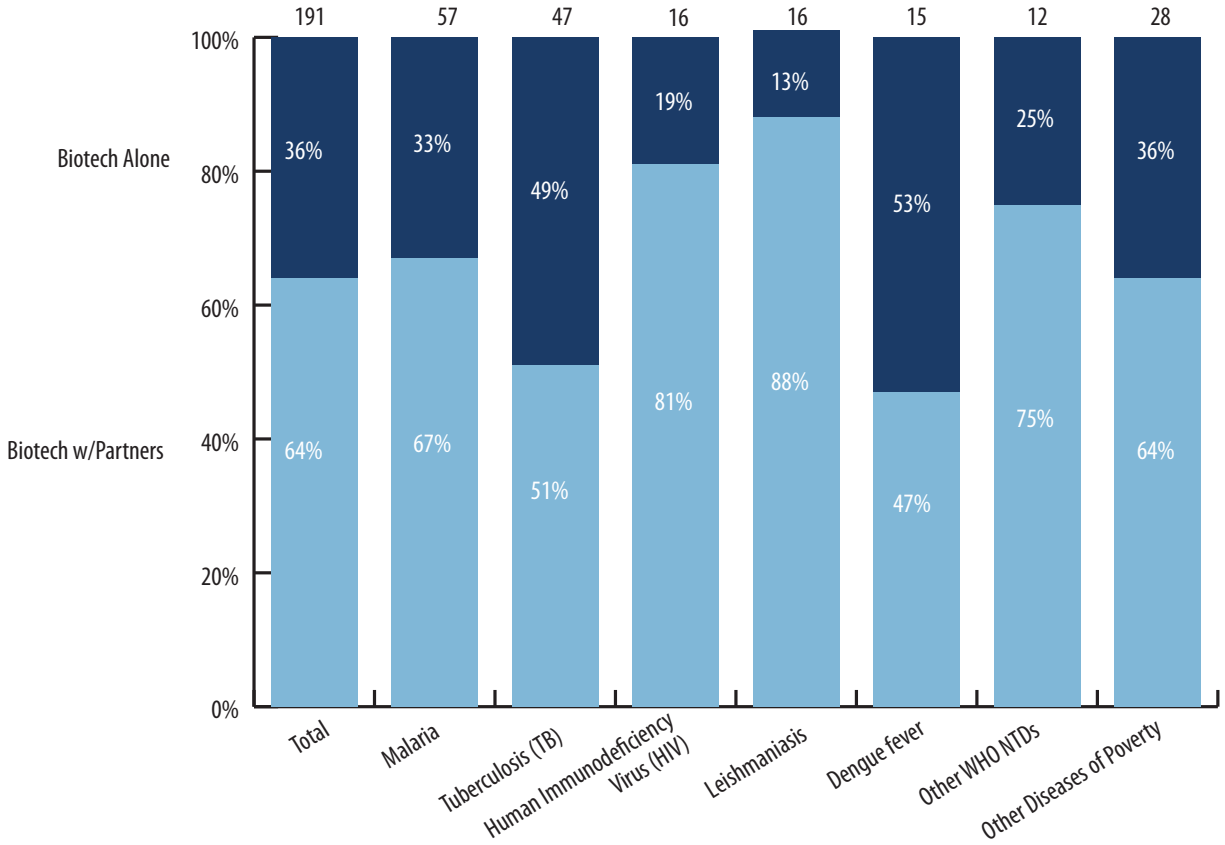
## Biotechnology Companies Are Significantly Engaged, But Only a Small Proportion Are Participating

The number of biotechnology companies involved in global health R&D and their level of participation in product development is high, with 134 companies participating in 39% of all products in development. These numbers are higher than expected given the challenges biotech companies face in riskier product development for global health. Yet those 134 companies represent a very small percentage of the biotechnology sector as a whole. BIO estimates that there are approximately 3,000 public and private biotechnology companies worldwide. At least 90% of these companies focus on health R&D.[45] Using this number of health-focused biotechnology companies (~2,700) as the denominator, this suggests that the 134 biotechnology companies identified as participating in product development for neglected diseases represent 5% of global biotechnology companies.

Biotechnology engagement in neglected disease R&D is significant but has not yet reached its full potential. While biotechnology companies have no doubt benefitted from initiatives to increase pharmaceutical industry participation in neglected disease R&D, specific initiatives targeting the biotechnology sector are needed to reflect the unique needs and challenges faced by this sector relative to the pharmaceutical industry.

In the next section, we will discuss the biotechnology sector, including their major scientific contributions and unique elements of the small to medium-sized company business model in order to better-understand what is needed to further engage the biotechnology industry.

Figure 7. Biotechnology Companies Work on Tuberculosis and Dengue Fever Independently, While Other Diseases Call for Partnering




*More than the average 36% of biotechnology companies are working independently on tuberculosis (49%) and dengue fever (53%), whereas biotechnology companies are partnering more than the average 64% for HIV (microbicides and vaccines only) (81%) and leishmaniasis (88%).*

# BIOTECHNOLOGY COMPANIES DRIVE INNOVATION IN HEALTH R&D

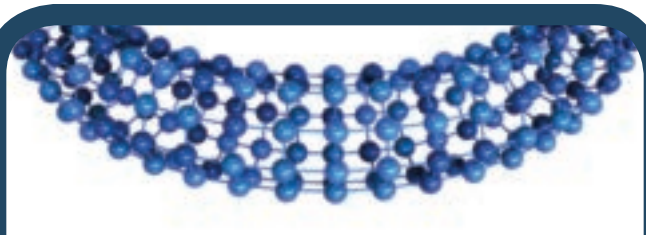
## WHAT IS BIOTECHNOLOGY?

The term "biotechnology" refers to the application of the molecular biology of living organisms to develop novel products. Since the birth of the biotechnology industry, a diverse group of companies has emerged that range widely in size, technologies used, and markets served. The common thread that binds them is their primary mission: to use biological processes to develop products for human health care, agricultural productivity, animal health, food safety and nutrition, industrial processes, energy and environmental improvement.

In the therapeutics field, the biotechnology sector today is categorized more by the structure and size of its companies—small firms and innovative technologies—rather than the type of science behind the products. Biotechnology companies' strong focus on innovation makes them a key partner in achieving global health R&D goals. In fact, BIO estimates 71% of typical biotechnology companies have less than 25 employees, and 90% have less than 100 employees.[46]

## WHAT IS A BIOTECHNOLOGY COMPANY?

The definition of a biotechnology company and how it is distinguished from a pharmaceutical company is one based on historical perspectives. A "biotech" company was, in the early 1980s, identified as a small, relatively young company focused on the discovery of large molecule protein therapeutics, while pharmaceutical companies were generally thought of as large, fully integrated enterprises that relied on medicinal chemistry to discover, refine, and develop small molecule drugs. Over the last two decades this simple definition has become blurred by the rapidly changing business models of pharmaceutical companies. Today, many small molecule developers are considered "biotech." Whether developing small or large molecules,



### ORIGINS

The biotechnology industry first emerged in 1973, when Stanley Cohen of Stanford University and Herbert Boyer of the University of California, San Francisco, were the first scientists to publish their research documenting the discovery of recombinant DNA. Recombinant DNA technology refers to the process of combining two or more different strands of DNA to create a new strand of DNA. With the help of venture capital funding, Boyer founded Genentech, one of the early biotechnology companies, to build a business and develop drugs based on this powerful new discovery.

Although scientists had known about DNA, since the 1950s, the discovery of rDNA allowed scientists to produce and sell human proteins, such as insulin, human growth hormone, and epogen, in large quantities for the first time. This development revolutionized the treatment of certain diseases and provided the opportunity for scientists to make a profit from their research. In 1982, Eli Lilly & Co.'s recombinant human insulin, Humulin, which was originally developed by Genentech, was the first biological therapeutic to gain FDA approval.

The combination of revolutionary scientific developments and promising market opportunities led a number of scientists, backed by venture capital funding, to create new companies in the 1980s, and the biotechnology industry began to grow. The pace of innovation accelerated and in addition to rDNA, biologists discovered and utilized an expanding number of new technologies, including monoclonal antibodies, RNAi, stem cell technology, and nanobiotechnology, among others.

biotechnology companies can be further differentiated by product stage, with those without an approved product defined as "emerging biotech" companies.

Fundamentally, key differences remain between emerging biotechnology, product-driven biotechnology, and large pharmaceutical companies. These distinctions shed light on why many biotechnology companies have been difficult to engage in global health R&D. Understanding the structure of these companies and the motivations of their executives can help global health organizations and policymakers better engage this sector, its resources, innovation, and creativity. It is biotechnology companies' strong focus on innovation and large pharmaceutical companies' increasing acquisition of R&D from biotechnology companies that make them a key partner in achieving global health R&D goals.

## MAJOR CONTRIBUTIONS BY THE BIOTECHNOLOGY SECTOR TO HEALTH CARE WORLDWIDE

Biotechnology companies have produced a variety of new drugs, vaccines, and diagnostics that have saved lives and improved quality of life for patients worldwide. Biotechnology is responsible for many of the protein drugs on the market, and a significant number of small molecule products. Some companies—such as Genzyme, Vertex, and BioMarin—have successfully delivered products to patients with rare and orphan diseases. Table 4 highlights some of the most innovative and successful medicines and novel diagnostics introduced by biotechnology companies.

## BIOTECHNOLOGY INNOVATION IS AN IMPORTANT COMMODITY FOR R&D SUCCESS

Today, large pharmaceutical companies are increasingly acquiring innovative products and projects from small biotechnology companies through collaborations, license agreements, or the purchase of biotechnology companies. This movement of harnessing innovation from the biotechnology sector reaffirms the importance of involving biotechnology in global health R&D. Though policymakers have found it sufficient to work mainly with large pharmaceutical companies, the decreasing emphasis on internal R&D makes reaching these smaller, innovative companies a key strategy to achieving global health research goals.

### *"PHARMADAPTING"*

Large pharmaceutical companies, at the edge of the patent cliff (the term coined for the cumulative patent expirations from 2009-2015 of blockbuster pharmaceutical drugs, and its effects on the pharmaceutical industry), are now operating more like clusters of innovative biotechnology companies either through acquisitions or partnerships with innovative biotechnology companies.
Although conventional business wisdom has often called into question the biotechnology industry's future, it has nevertheless survived and grown to become the truly global enterprise it is today. Product sales and employment have climbed year-over-year. Through the turmoil of change, biotechnology companies have relied on the value of their technology, the entrepreneurial, innovative spirit and skilled scientists to bring revolutionary, life-saving treatments to patients.

While licensing deals and partnering between pharmaceutical and biotechnology companies are not new trends, the extent to which large pharmaceutical companies rely on the biotechnology sector is growing. In July of 2009, Sanofi-Aventis closed eight of its research sites in order to focus on partnerships with biotechnology companies as a source of innovation.[49] Other pharmaceutical companies are seeking to model their research efforts after biotechnology companies. Both Pfizer and GlaxoSmithKline have made significant business changes in order to emulate the innovative nature of biotechnology companies.

Many pharmaceutical companies have launched internal venture capital funds in order to tap into innovation outside of the company, reiterating the strategy of many large pharmaceutical companies of obtaining innovation from the outside. Yvonne Greenstreet, senior vice president and chief of strategy for research and development at GlaxoSmithKline, outlined this tactic in an article for *The Scientist*.[50] "We have been aggressively increasing our outside collaborations, and we believe that as much as 50 percent of our drug discoveries could be obtained from outside the company," she wrote.[51]

## Table 4. Examples of Biotechnology Products That Fundamentally Changed Health Care

| DRUG | COMPANY | DISEASE | NOTES |
|---|---|---|---|
| **ANTIBODIES**: One of the biggest innovations in biotechnology has been the ability to reproduce highly selective antibodies—a type of protein that serves as the native defense for the immune system. To attack specific targets in disease, over the last two decades, biotechnology companies have found ways to optimize these antibodies. Oncology, inflammatory diseases, viral diseases, and osteoporosis have all benefited from antibody products. | | | |
| Avastin | Genentech | Metastic Colorectal Cancer; Non-Small Cell Lung Cancer; Metastic Breast Cancer | An anti-angiogenesis treatment |
| Humira | Cambridge Antibody Technology/Abbott | Rheumatoid Arthritis; Juvenile Idiopathic Arthritis; Psoriatic Arthritis; Chronic Plaque Psoriasis; Ankylosing Spondylitis; Chrohn's Disease | Tumor Necrosis Factor (TNF) blocker |
| Benlysta | Human Genome Sciences/ GlaxoSmithKline | Lupus erythematosus | First new treatment approval in 50 years for Lupus erythematosus (March 2011) |
| Synagis | MedImmune, Inc. | Respiratory syncytial virus (RSV), the most common cause of childhood pneumonia | The world's first monoclonal antibody approved for the treatment of an infectious disease. |
| **SMALL MOLECULES AND PEPTIDES:** Biotechnology has allowed for the identification and isolation of protein targets implicated in various diseases. Once isolated, chemists can design small molecules that bind to these larger proteins and block their biological function. Some examples of small molecules and peptides that biotechnology companies have developed include: | | | |
| Tarceva | OSI Pharmaceuticals and Genentech | Non-Small Cell Lung Cancer; Pancreatic Cancer | Designed to block tumor cell growth by targeting Human Epidermal Growth Factor Receptor 1 (HER1/EGFR). |
| Byetta | Amylin Pharmaceuticals | Type 2 Diabetes | Used to control blood sugar levels, particularly in cases where other medicines have failed. |
| Oseltamivir | Gilead | Influenza (flu) | An antiviral drug, slows the spread of influenza (flu) virus between cells in the body by stopping the virus from chemically cutting ties with its host cell. |
| **ENZYME REPLACEMENT THERAPY:** Certain genetic disorders involve the loss of a single gene function. Biotechnology companies have been able to produce large quantities of the missing gene product and administer them back into patients, extending their survival and quality of life. For example, Genzyme's Cerezyme has saved many people with Gaucher's disease. | | | |
| Cerezyme (previously Ceredase) | Genzyme | Gaucher's disease, a rare disorder that swells internal organs and weakens bones due to the lack of the enzyme glucocerebrosidase | The company's enzyme replacements dramatically improve prognoses for patients with Gaucher's disease. Prior to the introduction of these drugs, physicians could offer patients only palliative measures such as splenectomies and hip replacements.[47] |
| **CANCER VACCINES** | | | |
| Provenge | Dendreon | Prostate cancer | First FDA-approved therapeutic cancer vaccine. |
| **NATIVE & MODIFIED BLOOD PROTEINS** | | | |
| Epogen/ Aranesp | Amgen | Anemia | Epogen was the first biotech blockbuster. This is a recombinant version of erythropoietin (EPO), for the treatment of anemia in kidney and AIDS patients. It makes chemotherapy tolerable and reduces the dependence of oncologists and dangerous blood transfusions.[48] |
| Neupogen/ Nuelasta | Amgen | Chemotherapy and bone marrow transplantation | Spurs bone marrow production of neutrophils that are reduced from chemotherapy and bone marrow transplantation. |
| **ANTISENSE TECHNOLOGY** | | | |
| Vitravene | Isis Pharmaceuticals | cytomegalovirus (CMV) retinitis in patients with AIDS | The first and only antisense drug that has been approved by the U.S. FDA |
| **DIAGNOSTICS** | | | |
| Prostate-Specific Antigen (PSA) Test | Hybritech (acquired by Eli Lilly) | Prostate Cancer | First diagnostic test for prostate cancer |
| AlloMap | XDx | Gene expression test for monitoring acute cellular rejection of post-cardiac transplants | First product to enable a non-invasive way to manage the care of patients after organ transplants, to replace routine invasive biopsies. |
| Oncotype DX | Genomic Health | Breast cancer | A multigene expression test that physicians currently use to predict the likelihood of chemotherapy benefit and recurrence risk for patients with early-stage, estrogen receptor positive (ER+) breast cancer. |

Involving the biotechnology sector in global health product development will protect against a loss in global health R&D as large pharmaceutical companies begin to eliminate internal research programs. The growth of biotechnology investment in global health R&D can lead to a continual feeding of pharmaceutical companies' pipelines with these needed medicines.

## FINANCIAL STRUCTURE OF BIOTECHNOLOGY COMPANIES

Most biotechnology companies in operation owe their origins to the support of one or more investors in an innovative scientific idea and in a leadership team's ability to bring novel products, technologies, and services to the health marketplace.

For both large pharmaceutical companies and small biotechnology start-ups, one fact remains constant: research and development of new drugs, vaccines, and diagnostics is expensive. Estimates show that developing a new biological therapeutic takes 10-15 years, and will cost on average, $1.3 billion.[54] Developing a more traditional small molecule drug is usually a slightly shorter process, with a somewhat reduced cost, but the costs are generally estimated to be around $800 million dollars.[55]

While large pharmaceutical companies can afford to pay for the cost of new R&D with existing product revenue dollars, the reality for biotechnology companies is quite different. Though a few of the early biotechnology companies—such as Genentech (now Roche), Amgen, Genzyme (now Sanofi), Gilead Sciences, and Vertex Pharmaceuticals—grew into significant corporations, the majority of biotechnology companies are still not profitable. Based on 2009 net income, only 17 of 225 (7.5%) public biotechnology companies in the drug development business were profitable, and those companies tended to have three or more products on the market.[56]

Positive net income in biotechnology is a rare luxury, even a couple of years after product approval. Executives of small biotechnology companies often hope to bring a product through the early phases of development and then have the product acquired or partnered by a larger company, or have the company bought out entirely. These licensing deals can be sufficient to recoup the full cost of R&D and make a profit.

### BIOTECHNOLOGY SECTOR BY NUMBERS

In 2011, there were approximately 1,200 U. S. public and private biotechnology companies, according to BIO.[52] A significant number of these companies had made successful initial public offerings. At the end of April 2011, there were 302 public biotechnology companies trading on major US markets with an aggregate market cap of $407 billion.[53] Fifty-eight of these companies have a market cap of greater than $1 billion. Although the economic downturn of 2008 hit the biotechnology sector hard, there was a gradual recovery benefiting from a return of investor confidence in the second half of 2010, particularly the final quarter of the year. These extremes of financial success stories and cash-hungry firms depict the wide range of companies that make up the biotechnology industry.

Even still, small biotechnology companies whose products fail to achieve successful clinical results may face bankruptcy and dissolution. Unable to fund R&D through revenue, biotechnology companies rely on a number of other financing mechanisms to pay for innovation. These include venture capital funding, licensing deals with large pharmaceutical companies or larger biotechnology companies, public offerings, debt financings, private investments in public entities (PIPEs), and government funding. Below, we will provide a brief description of each of these types of funding.

## VENTURE CAPITAL FUNDING

Start-up biotechnology companies are highly dependent on venture capital funding to start their company. Venture capital funding has provided scientists with the means to explore innovative therapies since the early days when Herbert Boyer founded Genentech. In 2007, venture capitalists invested $6.8 billion in the biotechnology sector globally, $5.1 billion in 2009 and $5.6 billion in 2011. As with all venture capital funding,

### TRADITIONAL DRUGS VS. BIOLOGICS

A biologic is manufactured in a living system such as a microorganism, or plant or animal cells. Most biologics are large, complex molecules or mixtures of molecules. A drug is typically manufactured through chemical synthesis, which means that it is made by combining specific chemical ingredients in an ordered process. Drugs generally have well-defined chemical structures, and a finished drug can usually be analyzed to determine all its various components. By contrast, it is difficult, and sometimes impossible, to characterize a complex biologic by testing methods available in the laboratory, and some of the components of a finished biologic may be unknown. Now both biotechnology and pharmaceutical companies engage in a wide range of R&D for both traditional drugs and biologics. Today, a "biotech" company generally refers to a small, innovative company rather than the type of therapeutic that it produces.

biotechnology investors are looking for significant returns on their investment. Many investors hold seats on companies' boards of directors, and biotechnology executives must factor in investors' expectations when fund raising. After its peak in 2007 of $6.8 billion, venture capital funding for biotechnology companies has dropped to $5.6 billion in 2011.[57]

Recent decreasing venture capital funding trends reflect a broader strained financial environment. Since the global economic crisis of 2008, investors have become more risk averse and highly selective in choosing their investments. Venture capital fundraising has decreased by 41% since 2007, leaving investors with less capital to invest overall.[58] As a result, innovative ideas are being turned away, as first round financing is increasingly reserved for only a few innovative companies and for projects with less risk.

More and more, investors are targeting low prevalence orphan diseases rather than high prevalence diseases such as cardiovascular disease, because orphan drugs hold the promise of faster regulatory approvals and an untapped market for desperately needed products.[59] In fact, orphan diseases are one of the few areas where venture capitalists are expected to increase investment over the next three years, compared to cardiovascular disease, diabetes, neurology, and other high prevalence indications where investment decreases are expected.[60] Even large pharmaceutical companies are turning their focus toward orphan/rare diseases. For example, in June 2010 Pfizer created a new research unit focused on rare diseases. This new unit, the company said, will significantly expand its presence in rare disease research with the goal of discovering novel, life-saving medicines for diseases affecting less than 200,000 patients.[61] Earlier that same year, GlaxoSmithKline announced a similar initiative.[62] Nonetheless, these trends illustrate the goals of the venture capital community: minimize risk and maximize return.

## PUBLIC OFFERINGS

Due to the capital-intensive process of developing a new drug, vaccine, or diagnostic technology, biotechnology companies must cultivate a wide range of public and private investors to finance the early stages of development. A successful IPO, a company's first sale of stock to the public, is another way that biotechnology companies seek to raise cash to fuel their product development. When contemplating a public offering, company executives must consider not only the current state of the company and its pipeline, but also the general IPO environment. A favorable IPO environment is critical to achieving financing success.

Since the 2008 crisis, during which there was only one biotech company IPO in the United States, the number of IPOs has slowly grown to 17 in 2010 and 12 in 2011. Still, the IPO picture is generally challenging for biotech fundraising. However, the number of biotech companies entering the public realm is on track with the last US IPO window of 2003-2007. The total number of US IPOs since 2009 is 31, compared to 30 at this time back in 2005.[63] Presently, there are 300 public biotech companies in the US, and 140 in Europe. 167 companies had a market cap of greater than $1 billion, and another 52 companies had a market cap of less than $1 billion.[64]

Increasing access to the public markets is critical to ameliorating the concerns of venture capitalists when they analyze their exit strategy. Offering greater certainty that a company can go public and have the chance to succeed means earlier-stage biotechnology companies face challenges in hitting major milestones and taking steps to de-risk regulatory approval.

## PARTNERSHIP FUNDING

Biotechnology companies also meet major capital requirements by partnering with large pharmaceutical companies or another biotechnology company. A biotechnology company with a promising product might not have enough funds to see that product through clinical trials and marketing. By licensing rights to a partner, a biotechnology company can gain enough additional funding to continue research efforts. In 2011, the biotechnology sector achieved approximately $3 billion in up-front payments in partnering funds for therapeutics in the pipeline alone.[65] In 2011 alone, there were 222 company-to-company alliance deals for therapeutics.[66]

Partnering revenues have now become a staple for many biotechnology companies and this situation is likely to remain, if not accelerate, in the years ahead as drug companies look to broaden product lines, replace revenues lost to patent expiration and expand into emerging markets, where the industry growth rate is much higher in than in the developed nations.

The benefits of partnering with large pharmaceutical companies are substantial. As mentioned earlier, pharmaceutical companies are under substantial pressure to bolster their pipelines, as a number of high-grossing products are scheduled to go off patent in the coming years. Some of these blockbuster products account for a large percentage of a company's total revenue. It has been estimated that 35% to 45% of revenues can come from a single drug. AstraZeneca, for example, currently earns 38% of its total revenue through sales of Symbicort, whose patent is scheduled to expire in 2012. About 41% of Pfizer's revenue comes from sales of Geodon ($1.1 billion), which also goes off patent in 2012.[67] Acquiring new biotechnology products—or, more significantly, acquiring biotechnology companies—can help boost lagging internal pipelines.

### THERAPEUTIC DISCOVERY PROJECT (TDP)

According to the results of a survey released by the Biotechnology Industry Organization (BIO) in October 2010, leading biotechnology innovators say the new Therapeutic Discovery Project (TDP) will have a positive impact on advancing life-saving therapies and cures for patients—and U.S. biotechnology competitiveness—while helping sustain and create jobs.

CEOs of eligible biotechnology companies also say the program increases the likelihood that they will keep their operations in the United States.

As access to private capital for the industry has decreased, the biotechnology industry has shrunk. The sector has shed roughly 100 public companies since fourth-quarter 2007 and today is at least 25 percent smaller in terms of the number of public companies than it was three years ago. Data from the survey show that leaders of small U.S. biotechnology companies anticipate the credit will have a positive impact on job sustainability (75%), on U.S. biotechnology global competitiveness (72%), and on advancing life-saving therapies and cures for patients (76%).

The biotechnology industry leaders surveyed believe that with the tax credit they can create more jobs and hire more people (67%). An additional 30% will be able to maintain current employment levels which would not be possible otherwise.

## GOVERNMENT FUNDING

Biotechnology companies may also take advantage of a variety of U.S. government programs that provide federal or state funds for scientific research. Research!America, a non-profit advocacy group that encourages increased government funding for health research, estimated that in 2010 the U.S. government spent $45.9 billion on health research.[68] The NIH invested the

majority of these federal funds—$34.8 billion. Even though overall health research spending in the U.S. increased by 1%, this fell short of the estimated 2.8% increase in the cost of conducting health research.[69]

Government funds are disbursed through a variety of programs. Government grants, provided in the form of upfront funding, are one option. These are often awarded through the Small Business Innovation Research (SBIR) program, which provides funding for early stage projects. The program addresses a critical juncture in the scientific research project, where there is a general lack of funding to carry forward worthy projects.

Other times, the government will choose to fund specific research aims. For example, the Biomedical Advanced Research and Development Authority (BARDA) provides funding to companies whose drugs, vaccines, and diagnostics are deemed necessary in a public health emergency. These emergency priorities include products that would be effective against chemical, biological, radiological or nuclear agents, as well as medicines to aid in the event of pandemic influenza or other infectious diseases.

Tax credits are another way that biotechnology companies receive government funds. The 2010 Patient Protection and Affordable Care Act in the United States included a major tax credit for qualified small and medium-sized biotechnology companies (firms with less than 250 employees) for tax years 2009 and 2010. Companies that met the requisite medical and job creation criteria could apply for a 50% tax credit, which would be rewarded in the form of a grant to companies that are nontaxable. All of the available $1 billion for the 2009 and 2010 tax years was distributed to 2,923 biotech companies, making this a great opportunity for small, pre-profit companies that had not previously benefited from tax credits.[70,71]

It should also be noted that while a few biotechnology companies are financed primarily by government funds, most biotechnology companies seek government funds to supplement existing sources of cash. Government grants and funds, most often used to advance early stage research, in no way supplant the need for each company to raise hundreds of millions of dollars to bring one product to the market.

## BIOTECHNOLOGY COMPANIES DEPEND ON A MARKET

The above sections outline many of the major funding strategies employed by biotechnology executives. These financing models, for the most part, depend on the existence of a strong consumer market for products and a supportive capital market for public companies. Venture capitalists invest because they seek a reasonable return on their investment, large pharmaceutical companies acquire new drugs based on sales potential, and successful IPOs rely on potential shareholders' expectations of a company's financial success.

For diseases and/or products where there is little to no global market, these traditional financing mechanisms become much tougher to secure. The one exception is government funding. The government can choose to fund the programs or research that it deems worthy, irrespective of potential market value. As a result, the government has a key role to play in bolstering research for neglected diseases, where there is largely no market.

Large pharmaceutical companies are also profit-driven, but it is worth pointing out that these companies' significantly larger sales revenues and operating budgets allow their executives greater latitude to engage in neglected disease research without adversely affecting their bottom lines.

## CHANGING LANDSCAPE OF HEALTH R&D

In the last 10 years, biotechnology has been driven by an increasingly powerful array of technologies, such as genomics, proteomics, high-throughput sequencing, screening, and combinatorial chemistry. These technologies have led to an explosion of biological information that has transformed drug, vaccine, and diagnostic research and development. They are not only accelerating therapeutic R&D, but, at the other end of the spectrum, they are providing the tools to speed up clinical research on biomarkers, antigens, and other biological signatures that can predict probability a patient will respond to a therapeutic or vaccine as well as improve diagnosis. This movement towards individual, customized medicine is more commonly referred to as "personalized medicine." The focus is shifting from disease emergence and treatment, where options to treat and contain disease are difficult to prevent, to

prediction and preemptive treatment, where preventability is high. Biotechnology is leading this charge.

## TRANSLATIONAL SCIENCE IS PLAYING A GROWING ROLE IN CREATING NEW DRUGS

Simultaneously, an increased focus on translational science—from the bench to the bedside —demonstrates recognition of the critical role biotechnology plays in taking innovations from academia and actualizing them. According to a panel of pharmaceutical and biotechnology industry leaders and academics convened by the Tufts Center for the Study of Drug Development (CSDD) in January 2011, biotechnology companies are turning to translational science to make decisions about what targets to pursue and how to allocate resources.

"Traditional drug development approaches still have utility, but they likely won't produce enough new drugs fast enough," said Tufts CSDD Director Kenneth I. Kaitin in a press release. "Translational science offers an important step forward by helping to shorten the time needed to develop solutions in human health and disease based on new, basic research discoveries."[72]

Driving the need to bring new prescription drugs to market faster, according to Kaitin, is the high cost of development—currently about $1.3 billion to develop and gain regulatory approval for each product—as well as the pending expiration of patents on dozens of top-selling drugs in the next few years. Development partnerships, mergers and acquisitions, and in- and out-licensing are viable approaches to driving product development through translational science. Top product development executives, convened by the Tufts CSDD Executive Forum Roundtable, also agreed that:

- Universities and research hospitals will continue to help identify breakthroughs in basic research that may translate into clinical development opportunities, but validating new technologies and identifying specific markets for discoveries made in academic settings remains a key challenge.

- Biomarker development, critical to moving development rapidly from discovery validation to clinical validation, needs to start early in drug development and needs to be actively governed.

- Advances in computers, telecommunication, and imaging technologies hold promise as emerging tools in translational science.

U.S. policymakers are turning their focus to the importance of translational research. For example, the NIH recently launched a National Center for Advancing Translational Science (NCATS), which aims to accelerate development of new therapeutics and includes several special initiatives focusing on neglected diseases, including the Cures Acceleration Network (CAN) and the Therapeutics for Rare and Neglected Diseases (TRND) program. These programs are focused on the process of translating early discovery in academic institutions and government laboratories into real products for the prevention, diagnosis, and treatment of diseases. Specifically, NCATS will manage $700 million of R&D work to also push product development projects through the "valley of death," and enhance early stage research so that it can attract potential industry investment.

## INNOVATIVE FINANCING AND PARTNERING ARE REPLACING TRADITIONAL BIOTECH BUSINESS MODELS

The business models used to create current value will no longer be as effective going forward. Companies must adapt to a risk-averse environment where capital, while still available, has become much more difficult to access.

Investors are now less inclined to invest in biotechnology's hopes and dreams, and companies find themselves in a risk-abated environment. In addition, the traditional business model of pharmaceutical companies is changing in response to patents expirations on top selling drugs. For these reasons, partnering and collaboration among different types of product developers is increasing. In fact, between 2010 and 2011, there was a 25% increase in the number of companies that were merged and acquired, according to data from BIO.

To support early stage innovation and fill the pipelines, large pharmaceutical companies are embracing creative solutions such as working with venture capital firms. The recent announcement of Merck's partnership with Flagship Ventures is one example of this new approach to partnering for large pharmaceutical companies.[73] Likewise, GlaxoSmithKline, Johnson & Johnson, and Index Ventures are jointly managing a $200 million fund to invest in early-stage biotechnology companies.[74] This unprecedented collaboration is among the first where two large pharmaceutical company competitors are working together with a venture capital firm toward investing in R&D.

Governments and foundations are also significantly contributing to novel financing mechanisms, whether it is for developing vaccines for poor people in the developing world, or treatments for people with various rare diseases that investors will not strongly support. These organizations are deploying their focused, targeted scientific advisory boards, as well as their financial resources. Similarly, the NIH supports a lot of early development work at companies as well as at various state and local government agencies around the world.[75]

Unlike large pharmaceutical companies, there is little external pressure for biotechnology companies to participate in global health R&D, and they are able to "fly under the radar." Large pharmaceutical companies, on the other hand, must constantly respond to appeals for donations of intellectual property, medicines, and funds. Small biotechnology companies are under less public scrutiny.

Biotechnology companies face a growing challenge because of the lack of a familiarity with the science behind many of the neglected diseases, and the inadequate market that makes pursuing and R&D program feasible. Yet the wealth of resources, capabilities, and innovation within the biotechnology sector makes these companies a key ally in global health R&D efforts, and policymakers should make a greater effort to engage their executives. Greater biotechnology investment in neglected disease R&D—for therapeutics, diagnostics, and vaccines—will lead to a wider segment of industry engagement overall and could also further increase participation among large pharmaceutical companies.

# BARRIERS TO BIOTECHNOLOGY COMPANY ENGAGEMENT IN GLOBAL HEALTH R&D

The good news is that there is already substantial industry involvement in global health R&D. Large pharmaceutical companies have developed many of the existing products used in mass drug administration (MDA) programs for several of the helminth infections, for example. Despite the greater-than-expected participation of small biotechnology companies in neglected disease R&D, these companies have historically been less involved in global health R&D than large pharmaceutical companies for several reasons. For neglected tropical diseases, the path leading from basic research through product discovery, development, and registration is still being formed. Few companies have either the neglected disease expertise to initiate a program, or the resources to move a promising compound into clinical development. Thus, financial, information, managerial, and regulatory barriers are responsible for hindering biotechnology engagement in neglected disease R&D.[76]

## Financial and Market Barriers

Financing for biotechnology companies generally only allows enough cash to last one to three years before they have to refinance their operations. Unlike large pharmaceutical companies, they do not have a sustainable revenue stream or a corporate social responsibility team to justify the high-risk development of global health products for which there is no profitable market.

### FINANCIAL BARRIERS

**HURDLES**
Companies require market incentives and funding to overcome opportunity costs

**POTENTIAL SOLUTIONS**
Appropriate financial incentives for research, commerialization, and purchase commitments

### INFORMATION BARRIERS

**HURDLES**
Companies lack acces to and experience with neglected disease science

**POTENTIAL SOLUTIONS**
- Establish links between neglected disease-focused academic groups and companies
- Match the right companies to the right science
- BVGH *Global Health Primer*

### MANAGERIAL BARRIERS

**HURDLES**
Companies cannot devote time to non-core activities

**POTENTIAL SOLUTIONS**
External project management and internal champions are needed

### REGULATORY BARRIERS

**HURDLES**
Companies require clarity and transparency around regulatory requirements for neglected tropical diseases

**POTENTIAL SOLUTIONS**
Promote policy initiatives that encourage regulatory bodies to align strategies around neglected tropical diseases

### INTELLECTUAL PROPERTY BARRIERS

**HURDLES**
Ability to obtain or enforce intellectual property rights in country of innovation and distribution

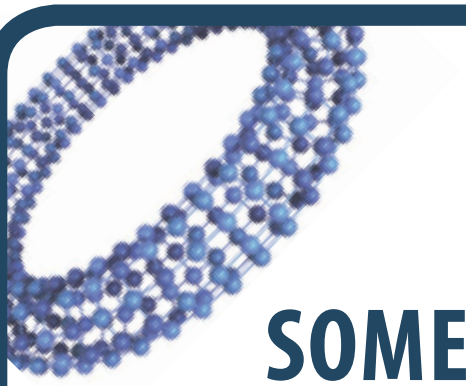
**POTENTIAL SOLUTIONS**
Provide strong and clear patent rights and protect against early entry of generic competition

## Information Barriers

Most biotechnology companies are focused on developing drugs, vaccines and diagnostics for diseases that are prevalent in the developed world markets they operate in, such as cardiovascular disease, diabetes, and cancer. One key barrier to engaging biotechnology companies in neglected disease R&D is their lack of expertise with the diseases and organisms that cause these diseases. This expertise primarily resides within academic institutions and PDPs, yet these organizations often lack a deep familiarity with the proprietary tools of the biotechnology industry.

## Managerial Barriers

Biotechnology companies do not have the resources to devote substantial management time to non-core activities.[77] For biotechnology companies, project management is a significant time and financial investment for a small staff. To manage a neglected disease drug discovery project would likely involve securing initial grant funding, managing staff, linking drug discovery efforts with specific target product profiles, and coordinating with academic and potentially PDP collaborators. Assembling expertise internally would distract from their core business.



# SOME BIOTECHNOLOGY COMPANIES HAVE MADE IT WORK

### ANACOR PHARMACEUTICALS ADVANCES SLEEPING SICKNESS DRUG TO PHASE I

Based in Palo Alto, California, Anacor Pharmaceuticals is a biopharmaceutical company focused on discovering, developing, and commercializing novel small molecule therapeutics derived from its novel boron chemistry platform. Anacor first began global health R&D in 2003 by taking on screening collaborations against human African trypanosomiasis (sleeping sickness) and malaria with the Swiss Tropical Institute in Basel, Switzerland and subsequently with University of California San Francisco Sandler Center. After discovering compounds that cured in the blood-stage of sleeping sickness, Anacor entered into a collaboration with the Drugs for Neglected Diseases *initiative* (DNDi) in 2007 to discover new and better drugs for sleeping sickness, visceral leishmaniasis, and Chagas disease. During the following two years, the early lead series quickly became a promising development candidate, demonstrating safety and efficacy for both blood and central nervous system stage of the disease. Administered orally, once daily for less than a week, the candidate promises to be a great improvement from the current therapies, which are unsafe and costly.

In March 2012, Anacor launched a phase 1 clinical trial for SCYX-7158 (or AN5568), the first new oral drug candidate discovered specifically to combat human sleeping sickness.[81] *"Providing sleeping sickness patients with a safe, effective treatment exemplifies the reason that many of us are in the business of biotech in the first place,"* said Anacor CEO David Perry. *"Anacor is committed to using its boron chemistry to discover and develop potential therapeutics for Neglected Diseases where we think we have the potential to solve a serious problem, but only to the extent we don't use our investors' money. So it is only with the support of our partners … that we are able to fulfill this commitment."*

## Regulatory Barriers

Regulatory barriers are not unique to global health R&D. Given that 70% of the R&D for neglected disease takes place in the United States and Europe, the regulatory barriers that all companies face translate to global health R&D. The pipeline of health products to treat, prevent, or diagnose neglected diseases is fuller than it has been for many years. Late-stage clinical development of these candidate products will be slow and expensive, perhaps prohibitively so. For neglected diseases, clinical trials are conducted with highly vulnerable subjects in environments with limited research and regulatory capacity and, often, across multiple jurisdictions with conflicting rules, standards, and procedures.

## Unclear Intellectual Property Right Barriers

Lack of ability to obtain or enforce intellectual property in both country of innovation and country of distribution creates great risk for the biotechnology companies considering neglected disease R&D. Biotechnology companies rely on strong patent rights to protect against the risk of early entry of generic competition which results in the loss of the large expense of innovation, obtaining regulatory approval, educating doctors, and distribution. Without clear intellectual property rights in neglected disease areas, biotechnology companies will look to other therapeutic areas with less risk.[78,79]

### INVIRAGEN

Founded in 2006, Inviragen seeks to improve global public health through the development of vaccines against existing and emerging infectious diseases. Inviragen's viral vaccines are designed to be safe and induce long-lived antibodies and cell-mediated immunity against the targeted disease agent. Inviragen's pipeline includes two vaccines in clinical testing: a vaccine to protect against dengue fever (DENVax), and a vaccine to protect against Hand, Foot and Mouth Disease (HFMD) due to EV71 infection. Vaccines against chikungunya, Japanese Encephalitis (JE), HPV, influenza and a combination plague/smallpox vaccine are in preclinical development.

In 2009, Inviragen raised $15 million from investors to support international clinical trials of the DENVax and HFMD vaccines. The DENVax vaccine was originally licensed to the firm by the Centers for Disease Control (CDC) and is comprised of a molecular clone of an attenuated DEN-2 virus and three chimeras, each engineered to express DEN-1, DEN-3 or DEN-4 structural genes. DENVax is a four-way (tetravalent) mixture designed to provide overall protection against all four dengue viruses.[82] Work on DENVax was carried out with support from the U.S. National Institutes of Health (NIH), the Pediatric Dengue Vaccine Initiative (PDVI) and Inviragen investors. Inviragen is currently carrying out phase 2 studies of DENVax in dengue-endemic countries on four continents. As part of a new collaboration initiative, Inviragen and International Vaccine Institute (IVI) will work to strengthen regulatory and policy environments to help speed dengue vaccine development and introduction, and to raise funds to help low- and middle-income countries with procuring available vaccine candidates.[84] *"By leveraging funding from investors, grant agencies and global health non-profits we can transition vaccines from the research bench to clinical proof of concept, and from the clinic to global markets, thereby improving public health worldwide,"* said Dr. Dan Stinchcomb, Inviragen CEO.

### CLAROS (NOW OPKO) TACKLES POINT-OF-CARE DIAGNOSTICS FOR RESOURCE-POOR SETTINGS

Claros Diagnostics (now OPKO Diagnostics, LLC) was founded with the goal of developing a point-of-care diagnostic platform suitable for use anywhere, including low-resource settings in the developing world. The founders selected a microfluidics-based approach and identified two critical issues to enable use in the developing world: cost and robustness. Both of these issues have historically impeded the commercialization of microfluidics-based diagnostics. To address these issues, the Claros team pioneered a number of innovations, such as the use of injection molding to fabricate microfluidics components, the use of an approach that uses micro air boluses to enhance the function of the device, the use of robust and inexpensive instrument components such as light-emitting diodes (LEDs) and photodetectors, and the use of inorganic redox chemistry detection to deal with the high heat and humidity in developing world environments, thereby avoiding the problems of enzyme denaturation. The Claros system provides quantitative laboratory-quality results for multiple complex tests simultaneously within 10 minutes on a single finger-stick of whole blood with no preparation or user training necessary. OPKO is commercializing a physician office system for use in urology, general practice, critical care and other fields. Meanwhile, a portable system for simultaneous testing of HIV, syphilis, and hepatitis C has been evaluated in field trials in Rwanda. An offering is planned for screening for infectious disease and anemia among pregnant women in remote areas to prompt early intervention.[84] The market research to support this specific product was funded by a Bill & Melinda Gates Foundation grant to RTI International to assist Claros in understanding the product requirements for various developing world market needs. Michael J. Magliochetti, Ph.D., President and CEO of OPKO Diagnostics, sees alignment and strong business-based motivations in the foundational work for global health: *"The global health aspect of our business forces us to maintain low costs and robust ease-of-use, both of which are important in all of our markets. As a result, the demands of the global health market actually help guide us to optimize the design and functionality of our technology."*[85]

# MECHANISMS & MOTIVATIONS FOR BIOTECHNOLOGY COMPANY ENGAGEMENT

Though there are some very real barriers to the biotechnology sector's participation in neglected diseases R&D, many of them are the same barriers that biotechnology companies face even in developed world markets as they struggle to advance novel therapeutics, vaccines, and diagnostics R&D programs for diseases where a market exists. In fact, "valley of death" obstacles that are all too familiar to biotechnology companies closely mimic the neglected disease barriers companies face. That said, working on a neglected disease R&D program can actually have several benefits, and key incentives have been developed to create an avenue for increased participation by the 95% of biotechnology companies that do not currently have a neglected disease R&D program. Mechanisms to engage companies need to be compatible with the small company business model, must respect intellectual property rights, must have the support of the company's leadership, and must align with a company's scientific and health impact mission.

## COMPANIES CAN BENEFIT FROM GLOBAL HEALTH R&D

In addition to the need for new therapeutics, vaccines, and diagnostics for global health—compelling reasons for investing in their own right—small biotechnology companies can reap other, often unexpected benefits from engaging in global health R&D. Through interviews with biotechnology executives, BVGH learned that many companies gained supplementary advantages through their global health research.[86] These benefits include:

### Accessing Non-Dilutive Financing

Partnering with product development partnerships (PDPs) or other public sector partners on global health programs allows companies to defray the cost of product development without diluting company ownership or the stakes of existing investors. This may also increase the opportunities for a company to earn a reasonable profit on these products. Some examples of non-dilutive funding include foundation grants, government contracts, and strategic alliances.

### Learning to Engage in Emerging Markets

Working in global health has been shown to increase the confidence of government officials in countries such as India and China, and to enable companies to become familiar with patient health seeking behaviors and local clinical practices. This benefits future efforts to bring drugs to market in these countries because it provides a strong starting position and builds local support for the company's brand. For example, 57 of the 473 unique organizations developing a neglected disease drug, vaccine, and diagnostics, are headquartered in a BRICS[87] country.

### Building a Global Network of Partners

Working in global health has been a strong entry point for companies to partner with local partners in countries such as India and China. Working with foreign partners on a common problem has been shown to build trust between groups that otherwise might struggle to work together. For example, Vertex cited the "tactical economic advantage" to working with local partners and identifying credible CROs in emerging markets as part of their involvement with the Global TB Research Network.[88] By seeking out and attending major biotechnology industry events, and reaching out directly to biotechnology companies, neglected disease stakeholders can bring biotech to the table. Biotechnology-targeted events that foster partnering, like the annual BIO International Convention or the Partnering for Global Health Forum,[89] seek to bring neglected disease researchers, policymakers, and key stakeholders together with biotech company leadership to foster relationships and build partnering opportunities.

### Proving the Value and Credibility of Technology Platforms

Young companies may earn credibility through demonstrating their ability to generate clinical candidates for global health applications. In some cases, this has increased the interest of venture capital investors and potential partners who want to explore other applications for the technology outside of neglected diseases.

### Keeping Employees Motivated

Providing employees the opportunity to work on meaningful neglected disease projects has been shown to raise morale and significantly aid recruitment efforts. For example, Genzyme reports that working on projects related to neglected diseases is an important motivator for its most talented scientists, "Working on this is clearly a motivational factor because they see their labors going to some important societal causes. And scientifically, these are extremely interesting problems to try and solve."[90]

### Learning about the Applications of Proprietary Technologies

By allowing the use of proprietary technologies in global health programs, companies can apply the knowledge gained from the global health programs to other more profitable programs.

**"Biotechnology companies have developed many of the cutting edge technologies, innovative scientific expertise, and creative research partnerships that are dedicated to improving human health globally. The biotech industry has unique and powerful capabilities to tackle the greatest scientific and medical challenges of global health."**
*-G. Steven Burrill, chief executive officer of Burrill & Company*

Companies may also gain further validation of their compounds and expand their compound libraries through global health research and development collaborations. For example, Anacor's broad portfolio of funded neglected disease programs on TB, malaria, river blindness, visceral leishmaniasis, Chagas, sleeping sickness, and Shigella are now expanding to the animal health market via a research collaboration with Eli Lilly's Elanco animal health division to discover novel therapeutics.

### Earning a Reputation for Social Responsibility.

Companies may build a global reputation for social responsibility, goodwill, and establish credibility with non-governmental and civil society organizations through global health R&D.

## INCENTIVES

Though there are strategic benefits to engaging in global health research, financial constraints on biotechnology companies create a significant hurdle. Small to medium-sized biotechnology companies often report that they are unable to invest in neglected disease R&D without a compelling potential for financial returns.[91] Traditionally, financial support for innovative research in global health has relied on public research grants or philanthropic dollars. Grants are considered a source of "push" funding, as funding is secured before the work is done thus mitigating risk to the grantee but maximizing risk to the funder. To companies, grants are also a highly desired source of non-dilutive funding.

In contrast, incentives provided by future market sales or other compensation after the work is completed are considered "pull" financing for R&D. These mechanisms create a financial risk to the grantee but mitigate risk of the funder. Policymakers have enacted new incentive mechanisms, such as the Advance Market Commitment (AMC) and the FDA Priority Review Voucher (PRV) mentioned earlier in this report to specifically encourage private sector investment in global health R&D. While these mechanisms provide potential return on investment, they require significant cash investment on the part of the product developer. Thus, these programs are more likely to incentivize large pharmaceutical companies as smaller biotechnology companies do not necessarily have the ongoing cash required to pursue a post-product approval prize. Alone, the PRV is unlikely to incentivize a company to pursue a neglected disease R&D project. For this reason, more proposals and policies need

## THE PRV INCENTIVE IN ACTION

The U.S. Food and Drug Administration's (FDA) Priority Review Voucher (PRV) program, created by legislation in 2007, was designed to incentivize industry to develop new therapeutics for a specified list of neglected tropical diseases, such as malaria, leishmaniasis, dengue fever, and others. Under the program, FDA awards a transferable voucher to a company that receives FDA approval for a new vaccine or drug that prevents or treats a tropical disease, such as malaria, tuberculosis, or intestinal worms. A PRV entitles the bearer to priority review for a future new drug application that would not otherwise qualify for priority review—potentially shaving off four to 12 months from the standard FDA review. This expedited review could potentially be worth $50-$500 million, with an average value of $322 million.

In 2009, Novartis obtained the first and, so far, only PRV issued upon obtaining FDA approval of Coartem (artemether/lumefantrine) for malaria. A year and a half later, Novartis announced that it used the PRV to obtain priority review of a supplemental biologic application (sBLA) for Ilaris (canakinumab), a humanized antibody. To date, no market value for the voucher has been documented. Although FDA achieved a 6-month review, as promised, the long-term impact of the voucher program remains to be seen.

Smaller biotechnology companies are unlikely to use the voucher to expedite review of a product in their own pipeline. Rather, they are likely to leverage the PRV as an asset during acquisition. For investors, having a demonstrated market value for the voucher is an important step towards assessing the success of this incentive program. For the PRV program to succeed, it must demonstrate that sponsors are willing to spend resources to accelerate the review of drugs with potentially high market value by using a voucher. To motivate development of drugs for neglected diseases, the expected value of the PRV must exceed half of the R&D costs to develop the drug, because the other half of the R&D costs would be covered by the Orphan Drug Act tax credits.[95] Although only one company has received a PRV to date, significant growth is forthcoming, as the BVGH *Global Health Primer* pipeline data suggest several vaccine approvals can be expected from 2016-18. So far, the only PRV issued to date has done exactly what it was designed to do: expedite the review of a product not otherwise entitled to that priority review. That said, companies and their investors will determine the ultimate success of this program.

to be brought forth that have the endorsement and buy-in of the biotechnology sector.

One concrete proposal by BVGH aims to engage smaller biotechnology companies with a milestone-based, pay-for-success prize system.[92] A successful pilot of such a milestone-based prize would demonstrate the model's effectiveness in stimulating development of a lifesaving global health products—and could be a new and effective model to stimulate development for other crucial tools for developing countries.

Global health policymakers are focused on innovative mechanisms that combine "push" and "pull" strategies to accelerate global health R&D.[93] While several proposed incentive ideas have been evaluated by global health R&D stakeholders, few stakeholders in global health understand the unique challenges of engaging small, innovative biotechnology companies relative to large pharmaceutical companies. For example, biotechnology companies are likely to endorse advanced purchase commitments that guarantee a market when a product is made, and accelerated pathways for approval for neglected disease drugs, vaccines, and diagnostics. Biotechnology companies would also benefit from an earlier inducement that would come at phase I and II, helping to fund the next stage of product development and de-risking the overall program for the resource-constrained company. Many biotechnology companies would like to be involved in global health R&D—and some companies have even identified promising compounds and/or platforms—but are unable to shoulder the significant financial risk without additional upfront funding. We believe that incentive programs such as the milestone-based *Innovation Quotient Prize for Global Health* proposed by BVGH and new non-dilutive financing options with greater cash outlays earlier in the process would encourage development for both therapeutic and molecular diagnostics within the biotechnology sector.

Appendix 4 outlines incentives and some innovative financing mechanisms that aim to stimulate global health R&D. Some

mechanisms are already operational, while others are still proposals and identified as viable options. A recent report by the Kaiser Family Foundation indicated that the U.S. government was more willing to engage in mechanisms that have private sector elements, or "mixed" mechanisms, rather than purely "public" mechanisms. This reflects a growing trend of the government's willingness to engage the private sector, and an emerging approach among companies to create a shared value for businesses and their shareholders—having positive social impact while also generating the return on investment expected by shareholders.[94]

To encourage biotechnology company participation in neglected disease R&D, policymakers should consider market-based mechanisms—including R&D or flat corporate tax breaks and short patent extensions—for companies that successfully develop a drug or vaccine for a neglected disease. Proposals have suggested that patent extensions and tax credits should also be trade-able, which would benefit small companies or non-profits who sold them to larger firms, seeding additional research into neglected diseases. The key, however, is that these rewards should be made automatic, thus eliminating the uncertainty that investors claim has plagued the FDA PRV system.[96]

Finally, existing incentives such as the Orphan Drug Act are familiar to biotechnology companies and have been widely accepted as a success; having spurred tremendous research and innovation for rare disorders.[97] Companies seeking U.S. FDA approval may not realize that orphan drug benefits are applicable to neglected diseases because most of these diseases affect under 200,000 people domestically. Such existing incentives can also benefit neglected diseases.[98]

## INNOVATIVE COLLABORATION MECHANISMS

Beyond financial incentives, disease-targeted collaborations provide a mechanism to spread the risk and resources associated with neglected disease product development among a group of stakeholders. A recent publication focused on "innovative partnership for drug discovery against neglected diseases" highlighted the fundamental need for innovative collaboration proposals, including a more coordinated collaboration multidisciplinary networks of investigators and partnerships between industry and public sector, in both developed and developing countries.[99] Some neglected disease researchers, especially those based in emerging and developing countries, call for mechanisms that support open and cooperative R&D relationships where information and knowledge are freely shared to support innovation.[100] For any R&D program, engaging in collaborative product development lowers the cost while also building capacity among partners. For Alzheimer's, cardiovascular disease, and breast cancer, several precompetitive mechanisms have emerged in recent years, such as the Biomarkers Consortium, the Innovative Medicines Initiative, the Clinical Trials Transformation Initiative, and the Critical Path Institute.[101] For neglected diseases, similar collaboration models should be

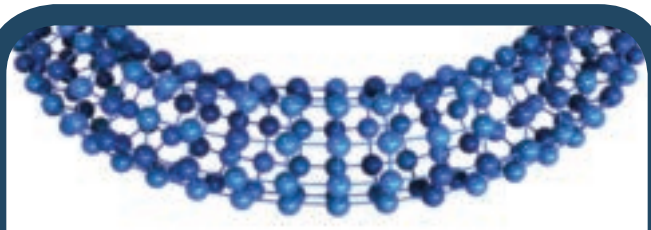
explored. In fact, expanding to collaborate with organizations based in endemic countries offers the additional benefit of leading biotechnology companies into emerging markets where many of these diseases dwell.[102]

In recent years, several approaches to R&D collaboration have emerged to target various parts of the value chain for global health. For example, Collaborative Drug Discovery (CDD) supports neglected diseases drug discovery with a number of technologies for collaboration and drug repositioning which may be helpful for certain projects. A similar initiative from the World Health Organization, the TDR Targets Database is an online resource to facilitate the rapid identification and prioritization of molecular targets for drug development, focusing on pathogens responsible for neglected human diseases. The database integrates pathogen-specific genomic information with functional data (e.g. expression, phylogeny, essentiality) for genes collected from various sources, including literature curation. This information can be browsed and queried using an extensive web interface with functionalities for combining, saving, exporting and sharing the query results.[103]

In Europe, the Innovative Medicines Initiative (IMI) is a collaborative venture between the European Commission (EC) and European pharmaceutical companies, regulators, academia and patient organizations aimed at tackling challenges in pre-competitive drug research and development. Although not focused on neglected diseases, leveraging this successful collaboration model could enable increased participation of companies already involved in this type of initiative.

Based at the United Nations Economic Commission for Africa in Addis Ababa, Ethiopia, the African Network for Drugs and Diagnostics Innovation (ANDI) was established to increase R&D collaboration among African institutions and countries, including through the management of Centres of Excellence in health innovation often based at premier African academic institutions. The ANDI Centres of Excellence offer companies an entry point to potential partners from reputable Africa-based institutions. These researchers are familiar with neglected diseases, as many of them are based in endemic regions.

Finally, the recently-launched WIPO Re:Search program, led by the World Intellectual Property Organization (WIPO) with BIO Ventures for Global Health, encourages innovation through intellectual property and know-how sharing among members that agree to basic licensing terms that are favorable for the world's least-developed countries. WIPO Re:Search facilitates partnerships among neglected disease researchers and companies that voluntarily provide access to their intellectual capital. Biotechnology companies can participate in such collaborative innovation mechanisms to engage in neglected disease R&D. For cash-poor biotechnology companies, shared collaboration mechanisms with financial incentives offer a way to offset the cost of investing in a neglected disease R&D program. Engaging in such initiatives does not distract from a company's principal focus. Rather, participating in such collaborative mechanisms offers a company many opportunities to access the know-how, data, and experience of larger pharmaceutical companies and others. These initiatives further revolve around innovative applications of intellectual property to minimize any IP-related barriers. Mechanisms like WIPO Re:Search were designed as a way to overcome difficulties in early-stage R&D by helping to reduce costs through knowledge and resource exchange, accelerating technology transfer opportunities, reducing duplication of effort in R&D, and widening the collaborative efforts of researchers with the complementary expertise.



**"Industry can contribute its expertise, compound libraries, infrastructure, training, and monetary or other in-kind support; academic institutions can contribute basic research and understanding of pathogens, genomics, and whole cell assays; while governments and non-governmental organizations can contribute resources such as manpower and finance."**
*–Jakobsen et al., Innovative Partnerships for Drug Discovery against Neglected Diseases. PLoS NTDs. (September 2011)*

# AN OPPORTUNITY TO INCREASE INNOVATIVE BIOTECHNOLOGY LEADERSHIP IN NEGLECTED DISEASE R&D

Biotechnology companies lead the innovation charge in developing life-saving drugs, vaccines, and diagnostics for diseases of the developed world. Despite the significant financial, informational, managerial, and regulatory barriers to working in neglected disease R&D, 134 individual biotechnology companies are participating in R&D for neglected diseases, often in partnership with other organizations.

Despite this, current biotechnology sector engagement only represents the work of about 5% of biotechnology companies worldwide. The unrealized potential of increasing participation from these capable innovators is immense. Action should come both from the biotechnology sector and from the global health community. Below we recommend specific, concrete recommendations to make this a reality.

## Biotechnology companies can and should grow their commitment and investment in neglected disease R&D through partnering.

Partnering strategies offer an important way forward in health R&D. For biotechnology companies, partnering provides an important avenue to help offset the barriers to engaging in neglected disease R&D. Strategic partnerships enable access to non-dilutive financing and help companies to build a global network of partners that can support core commercial activities and give companies a foothold in emerging economies that are increasingly important to their commercial strategies. Biotechnology companies can increase commitment and investment in partnering for neglected disease R&D by:

1. Increasing participation in partnering mechanisms and seeking collaboration opportunities to work on new drugs, vaccines, and diagnostics for neglected diseases
2. Pursuing partnerships as a way to access non-dilutive financing to engage in global health R&D
3. Seeking out existing incentives and innovative financing mechanisms that are available to companies working in neglected diseases
4. Expanding R&D efforts beyond HIV, malaria, tuberculosis, dengue fever, and leishmaniasis to other neglected diseases
5. Inviting key global health stakeholders to industry events and meetings to increase the neglected disease dialogue in traditional biotechnology circles

## Neglected disease stakeholders from academia, governments, nonprofits, and foundations should engage biotechnology companies through both existing and novel mechanisms

Engaging biotechnology companies in neglected disease R&D requires astute understanding and tailored solutions to the unique challenges faced by these companies. We encourage neglected disease stakeholders who seek to partner with biotechnology companies to build their understanding of the barriers—particularly financial—that biotechnology companies face, especially in their early stages of identifying investors and in justifying investment in neglected disease R&D. These challenges differ significantly from those of large pharmaceutical

companies. Better understanding the needs, obstacles, and opportunities for biotechnology companies in neglected disease R&D can help those in the global health community to tailor initiatives to address these specialized challenges. Some concrete suggestions include:

1. Actively target small to medium-sized biotechnology companies through existing industry engagement initiatives to increase engagement with the sector
2. Continue funding existing partnering mechanisms, such as PDPs, and increase specific targeting of biotech for participation
3. Bring forth new financial incentive proposals that specifically meet the needs of small to medium-sized biotechnology companies and that have the endorsement and buy-in of the biotechnology sector
4. Continue support of existing incentives and collaboration mechanisms, like the PRV, Orphan Drug Act, and WIPO Re:Search, that are compatible with biotechnology company participation
5. Engage the biotechnology sector leadership at the highest level by involving CEOs and top executives

Calling for biotechnology companies to increase participation in neglected disease R&D promises that innovative solutions will be brought to the neglected diseases that blind, deform, disfigure, pain, and incapacitate the world's poorest people. By providing this resource that explores the biotechnology sector's current involvement in neglected disease R&D, the global health community can understand the value of and considerations for engaging the biotechnology sector. With this report, we hope to encourage action across sectors to increase engagement to accelerate R&D for neglected diseases.

**Engaging biotechnology companies in neglected disease R&D requires astute understanding and tailored solutions to the unique challenges faced by these companies.**

# METHODOLOGY

The analysis presented in the first half of the report was based on data from the BIO Ventures for Global Health (BVGH) *Global Health Primer* database of drugs, vaccines, and diagnostics in development for neglected tropical diseases. The products tracked in the *Global Health Primer* are identified through a variety of sources, including product development partnership websites and reports, interviews with disease experts and organizations actively involved in neglected disease product development, searches of public databases of press releases, scientific literature, and clinical trials databases, and from data presented at scientific and global health meetings and conferences. Products are updated quarterly in the online database. All analyses presented here are based on data exported from the database on March 21, 2012.

Neglected diseases are categorized as a single group due to neglect rather than their biological or medical basis. Therefore, the term "neglected" has been difficult to define and challenging to gain consensus around, even within the global health community. For the purposes of this analysis, 23 diseases were included. The diseases include the so-called "big three" (HIV, malaria, and tuberculosis), the World Health Organization (WHO) list of "neglected tropical diseases," and several major causes of diarrhea and pneumonia. From the WHO list, no products in development were identified for cysticercosis, dracunculiasis (Guinea worm disease), echinococcosis, or yaws. Therefore, these diseases are not included in this analysis. Diarrhea and pneumonia were included as these represent the number one and two leading causes of death in children less than five years of age and disproportionately affect the development world. For HIV, only microbicides are tracked in the "drugs" in development category.

## LIMITATIONS OF THE BVGH *GLOBAL HEALTH PRIMER* DATASET

- Organizations tracked as product developers are identified based on public reporting. Although every effort is made to identify all products in development for neglected diseases, it is difficult to validate the success of this effort. By comparison with a non-public database, we believe the information is fairly complete.
- Projects or products for which public information is not available are not included in the dataset, which may cause underrepresentation of early stage projects or projects conducted entirely in the private sector, although we think this unlikely due to the corporate social responsibility benefits for companies to disclose neglected disease research.
- As product development partnerships (PDPs) have the most comprehensive public pipelines, products with PDP developers may be over represented.
- Organizations may define "participation" in product development differently. For instance, some organizations list funders as development partners while others may list only those organizations actively completing parts of the development process.
- Organizations were listed inclusively as reported by the developers. The organizations analyzed only represent a snapshot of product development known to us as of a given date. Trend data would provide more depth to the analysis and thus allow improved decision making based on changes in direction over time.
- HIV drug development is excluded from both the *Global Health Primer* and this analysis. At present, billions of dollars have been, and are being, invested in the development of HIV drugs and is generally not considered to be "neglected" by the pharmaceutical industry.
- A key limitation to the data is that we have no information as to the role that the various developers play in each project. Thus, we cannot speak to the depth, scope, or nature of involvement of the various developers nor the quality of the projects. For instance, a project where a company may only license a product to another for development is counted the same as a project where a company is committing considerable funds to develop a new drug or vaccine. Thus, the results should not be over-interpreted as to the depth of involvement of the various developers nor the quality of the projects assessed in this study.
- Certain panel assays or monitoring assays that are not specifically designed to diagnose primary neglected diseases are not tracked in the *Global Health Primer*. For instance, liver enzyme function tests, symptomatic fever panels, and CD4 count machines to monitor patients with HIV are not captured in this dataset.

# APPENDIX 1

## SELECT PRIVATE SECTOR GLOBAL HEALTH INITIATIVES

### J&J Partnership with the United Nations' *Every Woman, Every Child*

http://www.everywomaneverychild.org

On September 9, 2010, Johnson & Johnson announced the launch of Every Woman, Every Child, the United Nations' Global Strategy for Women's and Children's Health to reduce mortality in women and children by 2015, by: expanding health information for mothers over mobile phones, helping to increase the number of safe births, doubling donations of treatments for intestinal worms in children, helping to ensure that no child is born with HIV, and furthering research and development of new medicines for HIV and tuberculosis.

### WIPO Re:Search

www.wipoReSearch.org

In October 2011, the World Intellectual Property Organization (WIPO) and BIO Ventures for Global Health (BVGH), in collaboration with several of the world's leading research and development-based pharmaceutical companies and other research and academic institutions launched WIPO Re:Search. The program aims to promote research and development for new drugs, vaccines, and diagnostics for neglected tropical diseases—including tuberculosis and malaria—by voluntarily making available for licensing intellectual property assets and other resources. By providing a searchable, public database of available intellectual property assets and resources, WIPO Re:Search facilitates new partnerships that will support organizations that conduct research on treatments for neglected tropical diseases. The WIPO Re:Search database provides information on the intellectual property available for licensing from  Providers, as well as services and other technologies. Researchers working to advance the development of new drugs, vaccines, or diagnostics for neglected tropical diseases are encouraged to explore the database for any assets that can help advance their work.

### Vertex Global TB Network

http://www.vrtx.com/a-network-of-minds/our-network.html

In mid-2008, Vertex Pharmaceuticals announced the formation of a global collaboration aimed at advancing early-stage research into new approaches for the treatment of tuberculosis. To date, Vertex has engaged the commitment of multiple tuberculosis research organizations and more than 60 researchers around the globe.

## Industry Neglected Disease Discovery Centers

### GLAXOSMITHKLINE (GSK) – TRES CANTOS MEDICINES DEVELOPMENT CAMPUS

www.gsk.com/collaborations/tres-cantos.htm

Focus: Malaria, tuberculosis, leishmaniasis, trypanosomiasis

- Conducts research into global health priorities like malaria, tuberculosis, leishmanaisis, and trypanosomiasis
- Works closely with public-private partnerships, with groups including the Medicines for Malaria Venture (MMV) and the Global Alliance for TB drug Development (TB Alliance)
- In 2010, announced an "open innovation" strategy made up of three parts: greater flexibility around intellectual property; creating new broad-based partnerships by providing access to industrial scale expertise, processes, facilities, and infrastructure; and opening access to GSK's data and knowledge in diseases of the developing world. The "Open Lab" program and GSK's contributions to the Pool for Open Innovation against Neglected Tropical Diseases (now WIPO Re:Search) are concrete examples of this commitment.
- Chemical structures and associated assay data of 13,500 compounds from the Tres Cantos center are now stored on the leading public scientific websites: European Bioinformatics Institute, National Library of Medicine, and Collaborative Drug Discovery

### MSD WELLCOME TRUST HILLEMAN LABORATORIES

www.hillemanlaboratories.in

Focus: Developing affordable vaccines

- Non-profit research facility created in September 2009 through a collaboration between Merck and the Wellcome Trust.
- MSD and the Wellcome Trust pledged up to £90 million to facilitate establishment of the laboratories over the first seven years, with a focus on developing affordable vaccines to prevent diseases that commonly affect low-income countries.

### NOVARTIS INSTITUTE FOR TROPICAL DISEASES (NITD)

www.novartis.com/research/nitd/index.shtml

Focus: Drug development for dengue, malaria, tuberculosis

- Small-molecule drug discovery dedicated to new treatments and prevention methods for dengue, tuberculosis and malaria
- Combines the drug-discovery expertise and cutting-edge technologies of Novartis to fight infectious tropical diseases
- Scope of activities includes target discovery, screen development, compound optimization, pre-clinical development, and proof-of-concept clinical trials
- Works with organizations on early research activities, such as target identification and high-throughput screening, and later stages of drug development and patient outreach

### NOVARTIS VACCINE INSTITUTE FOR GLOBAL HEALTH (NVGH)

www.novartis.com/research/corporate-research/nvgh.shtml

Focus: Vaccines for neglected diseases

- Expands the research and development expertise and assets within Novartis to address the unmet medical need for vaccines to prevent some of the developing world's most prevalent diseases
- Aims to bridge the translational gap where development of promising leads or antigens is halted without being realized into potential vaccines
- Focusing initially on diarrheal diseases
- Actively establishing partnerships with public and private organizations encompassing both the developing and industrialized worlds

# APPENDIX 2

## NEGLECTED TROPICAL DISEASE DRUG DONATION COMMITMENTS FROM MULTINATIONAL PHARMACEUTICAL COMPANIES[104]

| COMPANY | DRUG | DISEASE | COMMITMENTS |
|---|---|---|---|
| Bayer | Nifurtimox | Chagas disease | Double existing donation to 1 million tablets/year through 2010 |
| Sanofi, Eisai, & the Gates Foundation | DEC tablets | Lymphatic filariasis | 120 million DEC tablets to the WHO for its Global Lymphatic Filariasis Elimination programme to ensure sufficient supply from 2012-2020. Eisai will donate 2.2 billion DEC tablets from 2014-2020 |
| Bayer | Suramin and nifurtimox | human African trypanosomiasis (Sleeping sickness) | Extend existing donation to 2020 |
| Gilead | AmBisome | visceral leishmaniasis | Offer Ambisome at cost and invest in technologies and processes that could reduce that cost in resource-limited countries; donation to 50,000 pateitns in South Asia and East Africa from 2012-2017 |
| GlaxoSmithKline (GSK) | Albendazole | soil-transmitted heliminths Lymphatic filariasis | Extend existing donation of 400 million tablets/year to 2020 |
| Johnson & Johnson | mebendazole | soil-transmitted helminthes | Extended existing donation of 200 million tablets/year to 2020 |
| MSD | ivermectin | river blindness (onchocerciasis) & lymphatic filariasis (where co-endemic with river blindness) | Continued unlimited donation |
| Merck KGaA | praziquantel | Schistosomiasis | Significantly increase annual donation of tablets from 25 million to 250 million tablets per year, extending the program indefinitely, and development of child-friendly praziquantel |
| Novartis | multi-drug therapy (rifampicin, clofazimine and dapsone) | Leprosy | Extended commitment patients worldwide in a final push against the disease |
| Pfizer | Azithromycin | Blinding trachoma | Continue donation until at least 2020, as well as donate the drug and placebo to a study on the reduction in mortality of children treated with azithromycin |
| Sanofi | eflornithine, melarsoprol, and pentamidine | human African trypanosomiasis (Sleeping sickness) | Extend its existing donation to 2020, as well as logistical support to ensure that the drugs continue to reach patients at the point of care cost-free |

# APPENDIX 3

## BIOTECHNOLOGY COMPANIES PARTICIPATING IN GLOBAL HEALTH R&D

| | COMPANY | COUNTRY | NEGLECTED DISEASES |
|---|---|---|---|
| DRUGS | Actelion Pharmaceuticals Ltd | Switzerland | Malaria |
| | ActivBiotics Pharma | USA | Tuberculosis |
| | Advinus Therapeutics | India | Leishmaniasis |
| | Akthelia Pharmaceuticals | Iceland | Diarrheal diseases |
| | Amura Therapeutics Ltd. | UK | Malaria |
| | Anacor Pharmaceuticals | USA | Diarrheal diseases, Leishmaniasis, Lymphatic filariasis (LF), Onchocerciasis (River Blindness), Shigellosis, Tuberculosis, Human African Trypanosomiasis (sleeping sickness), Malaria |
| | aRigen Pharmaceuticals, Inc. | Japan | Human African trypanosomiasis |
| | Autoimmune Technologies LLC | USA | Dengue fever |
| | AVI BioPharma | USA | Tuberculosis |
| | Biotron | Australia | Dengue fever |
| | C & O Pharmaceutical Technology (Holdings) Ltd. | Hong Kong | Tuberculosis |
| | Canopus BioPharma | Ireland | Dengue fever |
| | Cempra Pharmaceuticals | USA | Malaria |
| | Dafra Pharma International | Belgium | Tuberculosis, Schistosomiasis, Leishmaniasis |
| | DesignMedix | USA | Malaria |
| | Dilafor | Sweden | Malaria |
| | Galapagos NV | Belgium | Diarrheal diseases, Leishmaniasis |
| | Genzyme (now Sanofi) | USA | Malaria |
| | iCo Therapeutics | Canada | Leishmaniasis |
| | ImCure Therapeutics (formerly JJ Pharma) | USA | Tuberculosis |
| | IOTA Pharmaceuticals | UK | Leishmaniasis |
| | Jomaa Pharma | Germany | Malaria |
| | Lica Pharmaceuticals | Denmark | Leishmaniasis |
| | Luye Pharma | China | Diarrheal diseases |
| | Medisyn Technologies | USA | Tuberculosis |
| | Medivir | Sweden | Dengue fever, Malaria |
| | mondoBIOTECH AG | Switzerland | Tuberculosis |
| | NanoViricides, Inc. | USA | Dengue fever |
| | Napo Pharmaceuticals, Inc. | USA | Diarrheal diseases |
| | NeED Pharma | Italy | Tuberculosis, Malaria |
| | Nycomed | Switzerland | Leishmaniasis |
| | OmniBio | USA | Tuberculosis |
| | ParaQuest, Inc. | USA | Malaria |
| | ParinGenix, Inc. | USA | Malaria |
| | Photopharmica Ltd. | UK | Leishmaniasis |
| | PolyMedix Inc. | USA | Malaria, Tuberculosis |
| | PolyTherics | UK | Leishmaniasis |
| | Quro Science | South Korea | Tuberculosis |
| | Salix Pharmaceuticals | USA | Diarrheal diseases |
| | Sequella, Inc. | USA | Tuberculosis |

| | COMPANY | COUNTRY | NEGLECTED DISEASES |
|---|---|---|---|
| | Siga Technologies, Inc. | USA | Dengue fever |
| | Snowdon Inc. | USA | Tuberculosis |
| | Spirogen Ltd. | UK | Malaria |
| | Summit | UK | Tuberculosis |
| | Synstar Japan Co., Ltd. | Japan | Malaria |
| | Tamir Biotechnology | USA | Dengue fever |
| | TI Pharma | Netherlands | Leishmaniasis |
| | Vertex Pharmaceuticals Inc. | USA | Tuberculosis |
| | Vichem Chemie Ltd. | Hungary | Tuberculosis |
| | Zirus | USA | Dengue fever |
| VACCINES | Affitech A/S | Denmark | HIV |
| | AlphaVax | USA | HIV |
| | Altravax | USA | HIV, Dengue fever |
| | Arbovax | USA | Dengue fever |
| | Archivel Farma SL | Spain | Tuberculosis |
| | Avanti Therapeutics | USA | Malaria |
| | Bavarian Nordic | Denmark | HIV |
| | Bharat Biotech | India | Malaria, Rotavirus |
| | BIOFABRI | Spain | Tuberculosis |
| | Bionor Pharma ASA | Norway | HIV |
| | Bionor Pharma ASA | Norway | HIV |
| | Celldex Therapeutics Inc. | USA | Cholera, ETEC, HIV, Cholera |
| | Crucell | Netherlands | ETEC, HIV, Malaria, Tuberculosis |
| | Cytos Biotechnology | Switzerland | Malaria |
| | Emergent BioSolutions | USA | Tuberculosis |
| | Exir Pharmaceutical Company | Iran | Leishmaniasis |
| | Finlay Institute | Cuba | Tuberculosis, Cholera |
| | Folia Biotech | Canada | Typhoid fever |
| | Genocea Biosciences | USA | Malaria |
| | Genocea Biosciences | USA | Pneumococcal disease |
| | GenPhar | USA | Dengue fever |
| | GenVec Inc. | USA | HIV, Malaria, Dengue fever |
| | GlycoVaxyn | Switzerland | Shigellosis |
| | iBIO | USA | Malaria |
| | Ichor Medical Systems, Inc. | USA | Malaria |
| | Imaxio | France | Tuberculosis, Malaria |
| | Immunitor | USA | Tuberculosis |
| | ImmunoBiology, Ltd. | UK | Tuberculosis |
| | Inovio Pharmaceuticals, Inc. | USA | HIV, Dengue fever, Malaria |
| | Intercell AG | Austria | Tuberculosis |
| | InViragen, Inc. | USA | Dengue fever |
| | ISA Pharmaceuticals | Netherlands | Tuberculosis |
| | LIONEX Diagnostics and Therapeutics | Germany | Buruli ulcer |
| | MOLOGEN AG | Germany | Leishmaniasis |
| | Mucosis B.V. | Netherlands | ETEC, Malaria, Pneumococcal disease, Shigellosis |
| | NasVax | Israel | Pneumococcal disease |
| | Okairos Srl | Italy | Malaria |
| | Oxford-Emergent Tuberculosis Consortium | UK | Tuberculosis |

| | COMPANY | COUNTRY | NEGLECTED DISEASES |
|---|---|---|---|
| | Paladin Biosciences division of Paladin Labs Inc. | Canada | HIV, Malaria |
| | PaxVax | USA | Cholera |
| | Pevion Biotech Ltd. | Switzerland | Malaria |
| | Sanaria, Inc. | USA | Malaria |
| | Selecta Biosciences | USA | Malaria |
| | Sentinext Therapeutics | Malaysia | Malaria |
| | Shanghai H&G Biotechnology | China | Tuberculosis |
| | Shantha Biotech | India | Rotavirus, Typhoid fever |
| | SinoVac Biotech | China | Pneumococcal disease |
| | Statens Serum Institut | Denmark | Malaria, Tuberculosis |
| | Syntiron | USA | ETEC |
| | Targeted Genetics Corp. | USA | HIV |
| | TD Vaccines A/S | Denmark | ETEC |
| | TRANSGENE | France | Tuberculosis |
| | Vaccine Technologies, Inc. | USA | Cholera |
| | Vakzine Projekt Management GmbH | Germany | Malaria, Tuberculosis |
| | VaxOnco | South Korea | Malaria |
| | Vical, Inc. | USA | Malaria |
| | VitamFero | France | Malaria |
| | Wuhan Institute of Biological Products | China | Rotavirus |
| **DIAGNOSTICS** | Access Bio, Inc. | USA | Malaria |
| | AdAlta | Australia | Malaria |
| | Antigen Discovery Inc. | USA | Tuberculosis |
| | BigTec Laboratories | India | Malaria |
| | Carl Zeiss | Germany | sleeping sickness |
| | Cepheid Inc. | USA | Leishmaniasis* |
| | Chembio Diagnostic Systems Inc. | USA | Leishmaniasis, Leprosy, Malaria, Tuberculosis |
| | Claros Diagnostics | USA | HIV, Malaria |
| | Coris BioConcept | Belgium | sleeping sickness, Schistosomiasis |
| | Eiken Chemical | Japan | sleeping sickness , Malaria, Tuberculosis, Leishmaniasis |
| | Epistem | UK | Tuberculosis |
| | Fio | Canada | Malaria |
| | Fyodor Biotechnologies, Inc. | USA | Malaria |
| | Global BioDiagnostics | USA | Tuberculosis |
| | ID-FISH Technology, Inc. | USA | Malaria |
| | mBio Diagnostics | USA | Tuberculosis |
| | Micronics | USA | Malaria, Diarrheal diseases |
| | PortaScience | USA | HIV |
| | Qiagen | Germany | Tuberculosis |
| | Quantaspec | USA | Malaria |
| | Quanterix | USA | Tuberculosis |
| | Rapid Medical Diagnostics | South Africa | Schistosomiasis |
| | SomaLogic | USA | Tuberculosis |
| | Span Diagnostics | India | Cholera |
| | TI Pharma | Netherlands | Leishmaniasis |
| | Tulip Group | India | Malaria |
| | Tyrian Diagnostics | Australia | Tuberculosis |
| | Xcelris Labs | India | Tuberculosis |

**Because Cepheid's GeneXpert® is already in use for tuberculosis, it is not included in the pipeline.*

# APPENDIX 4

## SELECT EXAMPLES OF INNOVATIVE FINANCING MECHANISMS TO STIMULATE GLOBAL HEALTH R&D[105]

| | MECHANISM | PUBLIC/ PRIVATE INVOLVEMENT | STATUS | U.S. GOVERNMENT PARTICIPATION | DESCRIPTION |
|---|---|---|---|---|---|
| "PUSH" MECHANISMS | Patent fees/ "Green IP" | Public | Proposed | No | Proposes an additional fee on patent applications, called an "insurance premium," to finance R&D for neglected disease. In return, patent applicants would be protected against the risk of a compulsory license, face lesser registration fees, and a fee waiver for extending their patents to new regions.[106] |
| | Patent Pools | Mixed | Active | Yes | Agreement between two or more patent owners to license their patents to one another or third parties, to stimulate collaborative R&D.[107] Patent holders can either share patents royalty-free or receive payments from use of their patent(s). |
| | Pooled Funding | Mixed | Proposed | No | Private and public donors collectively fund an investment pool, which is distributed across a range of R&D projects at different stages of the product development continuum.[108] |
| | Product Development Partnerships (PDPs) | Mixed | Active | Yes | Public-private partnerships that facilitate cooperative R&D on products for diseases of the developing world. PDPs partner and fund several biotechnology companies. In 2010, USAID and NIH contributed almost 9% of PDP total funding. |
| | R&D Tax Credits | Public | Active | No[109] | Companies provided tax credits for investments made in neglected tropical disease R&D. H.R 3156 is a 2009 proposal for a 50% non-clinical research tax credit for neglected tropical diseases, which was referred to the U.S. House Ways and Means Committee in 2009.[110] Similar to the Orphan Drug Legislation, tax credits would have to be combined with other grants, prizes, and purchase guarantees incentives to be a viable "pull" mechanism for biotechnology companies. |
| "PULL" MECHANISMS | Advanced Market Commitment (AMC) | Mixed | Active | No | United Kingdom, Italy, Canada, the Netherlands, Sweden, and the Gates Foundation funded the first AMC for a pneumococcal vaccine through GAVI. A future AMC has not been announced. |
| | Medicines Subsidy | Mixed | Active (pilot) | No | Funds that attempt to reduce consumer price and expand access to medicines through subsidizing first-line purchases of drugs from manufacturers. (e.g., the Affordable Medicines Facility for Malaria (AMFm) |
| | Health Impact Fund | Public | Proposed | No | Proposed fund pool that is distributed to innovators of new medicines and vaccines based on their health impact. The recommended initial funding requirement is $6 billion to cover an estimated portfolio of 20 drugs. |
| | Milestone-based R&D prize Incentive(s) | Mixed | Proposed | No | Product developers receive monetary rewards as they complete milestones in the R&D/clinical trial process for target products. |
| | Priority Review Voucher (PRV) | Public | Active | Yes[111] | Developers of a drug or vaccine for a neglected topical disease receive a transferable voucher for priority U.S. Food and Drug Administration review of another product. |
| | End-Product Prizes | Mixed | Active | No | First innovator to develop a product that meets specified guidelines receives a monetary prize (at a set amount or one proportional to impact). |
| | Patent Review Voucher | Public | Active (USPTO Pilot) | Yes[112] | Voucher for 'fast track' patent examination for innovators making a technology available for humanitarian purposes, such as medicine or vaccine development. |

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