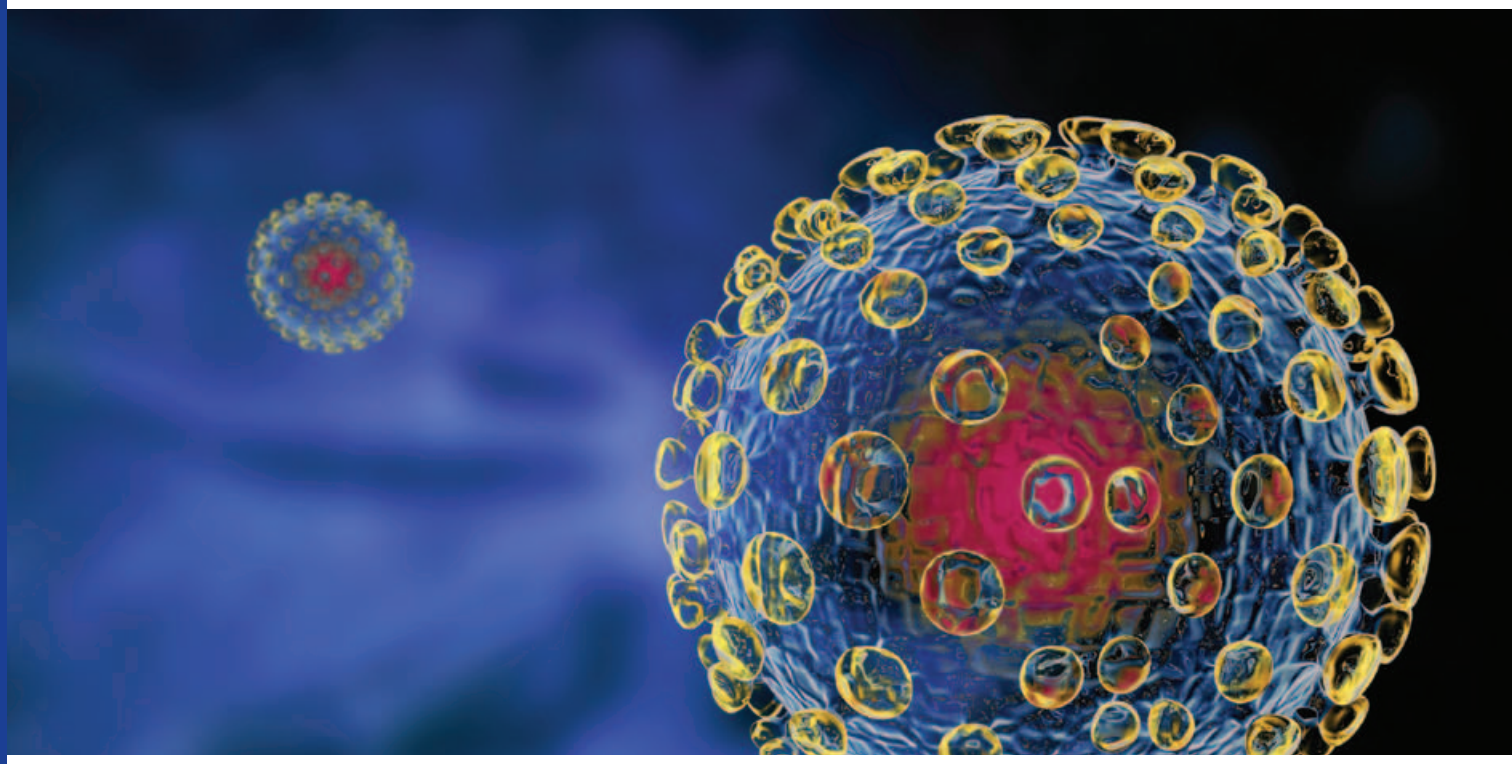
International Federation
of Pharmaceutical
Manufacturers & Associations

The New Frontiers of Biopharmaceutical Innovation



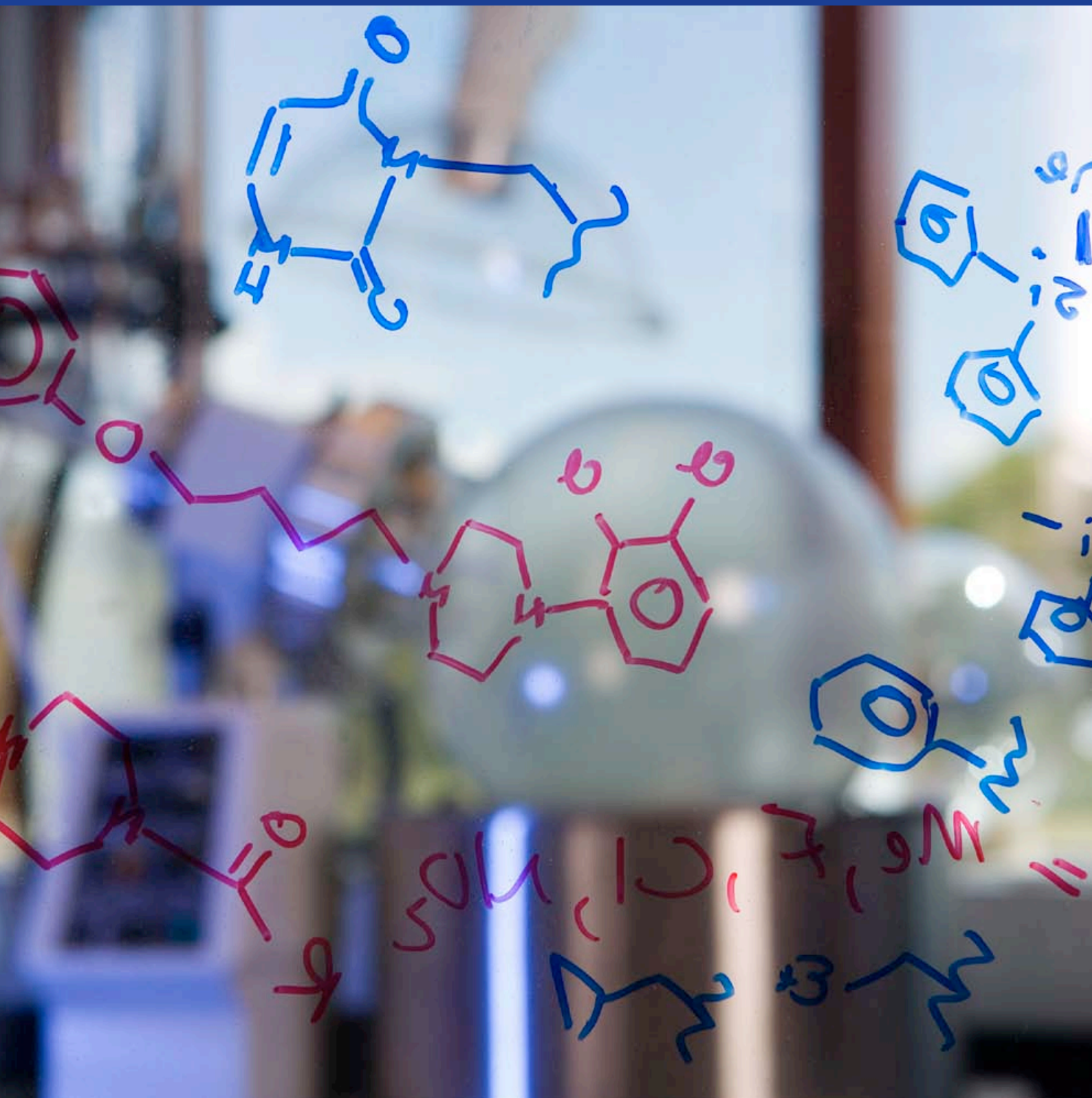
IFPMA

This publication discusses the latest trends affecting innovation in the research-based biopharmaceutical industry. Economic, scientific and regulatory challenges are leading companies to reformulate the way in which they innovate, and to increasingly engage in networked R&D efforts. Even though the pharmaceutical industry is responsible for some of the greatest medical advancements, there are still many health challenges to be addressed in areas like non-communicable diseases, infectious diseases and neglected diseases. Policymakers from across the globe have an important role to play in ensuring that an enabling environment is maintained to support sustainable innovation.

Table of contents

Index of figures, charts and tables

Executive Summary



Executive summary

The research-based pharmaceutical industry is a global leader of innovation and operates at the very frontiers of scientific discovery. In 2011 alone, pharmaceutical companies invested over USD $135 billion[1] on research and development (R&D) of new medicines and vaccines to improve patients' daily lives. Despite the growing scientific and regulatory challenges of the past decade, over 340 new medicines have been introduced since 2002.[2] A large proportion of the global health gains seen over the past century can be attributed to innovative medicines and vaccines.

Perfecting the Art of Innovation

The scientific and technical challenges associated with understanding disease mechanisms have prompted a recent shift to broader collaboration in pharmaceutical R&D. The contemporary, networked approach to health innovation is characterized by extensive sharing of knowledge and joint problem solving between private, academic, and government research groups.

This trend towards iterative collaboration between research teams across the globe is enabling the research-based pharmaceutical industry and other healthcare partners to mitigate the rising costs of innovation associated with modern medicine development. By working toward common goals, researchers are enabled to develop new pharmaceutical products with increased flexibility and efficiency.

The pharmaceutical industry is working to continue to deliver quality, safe, and effective medicines and vaccines to improve global health. Cutting-edge technology and greater understanding of disease mechanisms and biological processes have permitted researchers to explore treatment and prevention options for a range of illnesses and diseases that were once poorly understood and for which no specific treatments were available.

Tools of the Trade

Many of the gains in knowledge in recent decades have been due to a range of high technology tools - including genomic mapping, computational modeling, and molecular imaging - that are replacing the manual trial-and-error approach that researchers used to rely upon to develop new pharmaceuticals.

Computational and imaging technologies have played a critical role by allowing researchers to visualize target protein structures at a molecular level. This information has revolutionized much of the medicine development process by assisting researchers in the molecular design of new medicines. Prior to the introduction of these technologies, researchers faced many scientific hurdles that limited the range and specificity of illnesses that could be treated.

Some of the greatest advances seen today have been in meeting the therapeutic needs of patients with non-communicable diseases, including cancer, diabetes, and heart disease. Researchers are working to fill knowledge gaps about these diseases by using genomics and imaging technologies to identify specific biomarkers that will help them uncover the root causes of the diseases. This in turn will help healthcare practitioners diagnose and monitor these diseases in patients. Researchers are likewise working to stop these diseases in their tracks by developing revolutionary targeted therapies. To date, the global pharmaceutical industry has over 1,500 new medicines in the pipeline.[3]

Researchers are using these same innovative tools to address a greater number of mental and neurological disorders (MNDs), including Alzheimer's disease, depression, autism, bipolar disorder, and attention deficit hyperactivity disorder (ADHD). Significant research challenges in this area remain as scientists train their efforts on better understanding neurological pathways and identifying suitable biomarkers. The end goal is to develop more targeted treatment options to prevent and disrupt MNDs. By the end of 2012, the research-based pharmaceutical industry will have made advances in nearly 200 treatment options for patients with these diseases.[4]

[1]EvaluatePharma, *World Preview 2018 - Embracing the Patent Cliff* (London: EvaluatePharma, June 2012).

[2]PhRMA, 2012 *Pharmaceutical Industry Profile* (Washington DC: Pharmaceutical Research and Manufacturers of America, May 2012), www.phrma.org/sites/default/files/159/profile_2012_final.pdf.

[3]PhRMA, *Medicines in Development for Selected Chronic Diseases* (Washington DC: Pharmaceutical Research and Manufacturers of America, 2010).

[4]PhRMA, "Nearly 200 Medicines in Development for Mental Illnesses," 2012, http://www.phrma.org/media/releases/nearly-200-medicines-development-mental-illnesses.

Infectious disease prevention and treatment research is another core focus of the research-based pharmaceutical industry. Advances in recent years have hinged upon gaining a more sophisticated understanding - at the molecular level - of how pathogens such as viruses, bacteria, and fungi cause illness. At the same time, these pathogens provide a moving target for researchers since they evolve over time and develop resistance to older treatments.

Substantial time and resources have furthermore been directed towards addressing the continued scourge of so-called neglected tropical diseases, such as sleeping sickness or Chagas disease, which affect nearly one billion people in lower-income countries. A growing number of partnerships between industry, philanthropic organizations, and academia are all helping to overcome the unique funding and scientific challenges associated with these complex diseases, whose internal mechanisms remain poorly understood. One of the largest of such initiatives is the London Declaration on Neglected Tropical Diseases, signed in 2012, to target the nine tropical diseases responsible for over 90% of the global NTD burden. To date, 374 medicines and vaccines for these diseases are in the pipeline.[5]

Middle- and low-income countries are well positioned to adopt policies that enable innovation

Historically, the lion's share of pharmaceutical research and development has taken place in higher-income countries. However, in today's globalized world there is a growing need to foster innovative capacity worldwide to meet the varied health challenges faced by different populations.

Governments have a variety of tools available to foster enabling environments for each stage of the R&D process, from basic research to clinical trials. By working hand in hand with academia and the private sector, governments can help introduce appropriate policies that reflect local innovation priorities.

Political Stability, Good Governance and Transparency

At the most basic level, policies to nurture domestic scientific communities and develop stable and transparent legal systems go a long way in encouraging innovation. Stability in industrial and healthcare policy helps reduce the investment risks of innovators in both the public and private sectors by encouraging them to develop the sort of long-term research plans and investment projects that characterize the pharmaceutical industry.

Appropriate Capital Markets

Research and innovation are costly endeavors: developing a new medicine now costs on average USD $1.3 billion and takes 14 years.[6] Innovators require sufficient, stable access to capital markets to finance the long-term investments necessary to embark on lengthy research projects and bring the results to market.

Skilled Workforce

A well-educated workforce with strong scientific and math skills is a necessary condition to contribute to each stage of the pharmaceutical innovation process, from the earliest days of product development to large-scale clinical testing.

Countries with strong education systems contribute to a dynamic workforce that can sustainably replenish research positions over generations. The research-based pharmaceutical sector has played a major role in training researchers and healthcare workers, and building research institutions in lower-income countries.

[5]Elizabeth Ponder and Melinda Moree, *Developing New Drugs and Vaccines for Neglected Diseases of the Poor* (San Francisco: BIO Ventures for Global Health, March 2012), http://www.bvgh.org/LinkClick.aspx?fileticket=h6a0cJK9drg%3d&tabid=91.

[6]Joseph A. DiMasi, Ronald W. Hansen, and Henry G. Grabowski, "The Price of Innovation: New Estimates of Drug Development Costs," *Journal of Health Economics* 22, no. 2 (March 2003): 151–185.

Sound Regulatory Standards

When innovator companies know that regulatory standards are high and predictable, they have greater incentive to invest in that market and test new medicines there. Science-based regulatory standards are important for innovators interested in conducting both basic research and clinical trials.

Regulatory standards provide guidance to innovator pharmaceutical companies about how to carry out clinical trials to assure the safety, quality, and efficacy of medicines before being approved for sale. Clear guidelines and government cooperation provide companies greater certainty when designing clinical trials.

Intellectual Property Protection

The pharmaceutical R&D process is characterized by significant risks and costs because success is never guaranteed. On average, only 1 in 5 pharmaceutical products ever recoup their direct R&D investments.[7] Intellectual property rights, whether patents, copyrights, trademarks, or trade secrets, help innovators to recoup the sunk costs of research that did not materialize in a marketed product. Sound intellectual property protection allows inventors to focus on R&D with the assurance of enjoying the fruits of their labor.

The underlying goal of most intellectual property is twofold: to promote innovation through securing exclusive rights for a limited time, and to disseminate knowledge to the public through incentives for inventors to disclose their inventions. However, regulatory obligations, which apply, for example, to agro-chemicals and pharmaceuticals, often affect intellectual property terms. Thus, intellectual property policies should reflect R&D and regulatory timelines.

Supplemental Policies

Recent years have witnessed growing numbers of initiatives to foster innovation in a range of disease areas with limited treatment options. These initiatives, including open compound databases, research grants, R&D prizes, regulatory incentives and product development partnerships, may complement the existing innovative ecosystem by helping to overcome specific funding and technical challenges unique to each disease. Any individual initiative is rarely employed in isolation because each serves a distinct purpose and is dependent on sound intellectual property policies.

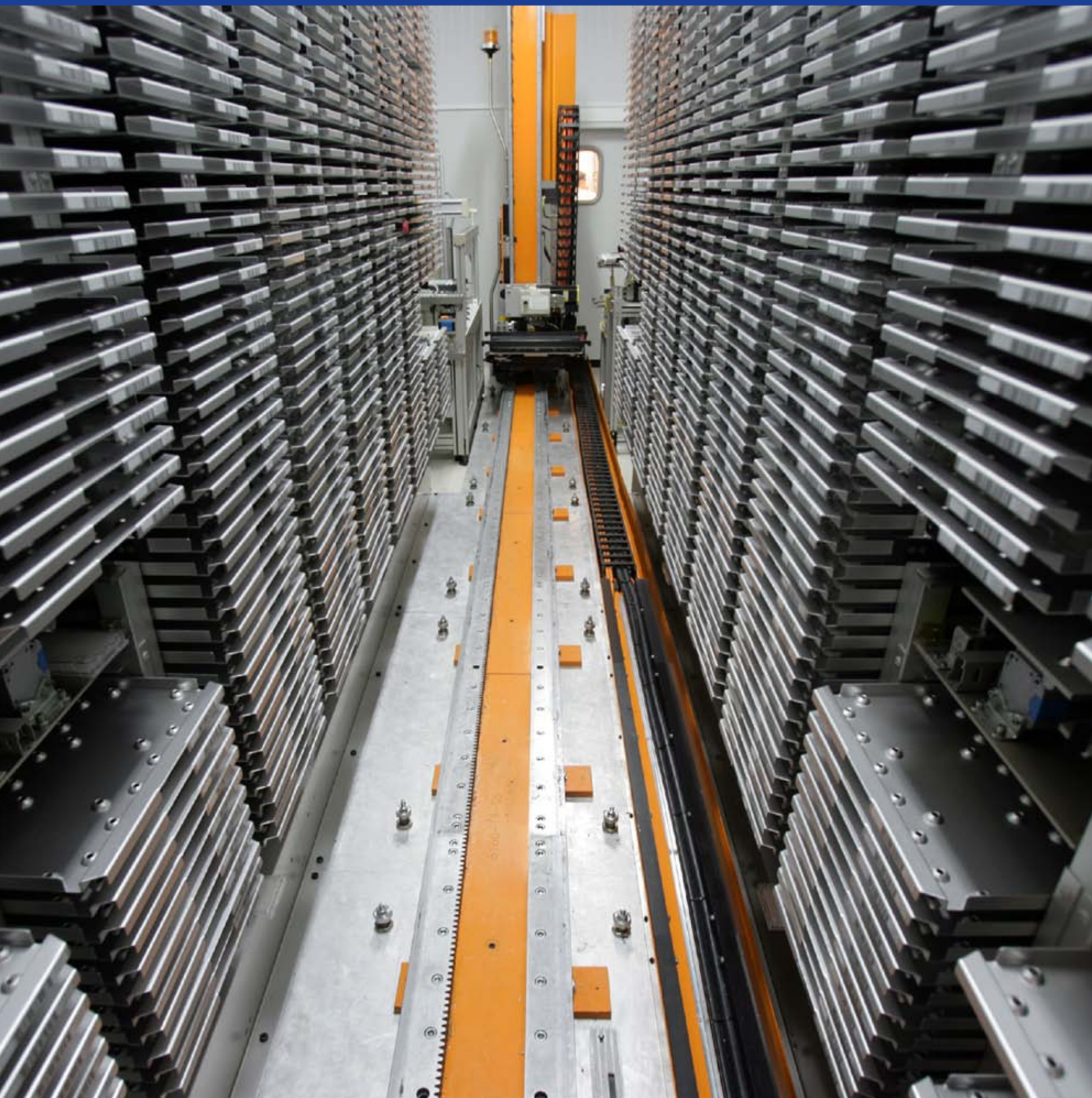
Conclusions

Over the past century, the research-based pharmaceutical industry has played a leading role in health innovation. By investing in human resources and cutting-edge technologies, the industry has developed thousands of new medicines and vaccines to save and enhance patients' lives.

Improved technical capacity and knowledge about disease mechanisms have allowed innovative companies to broaden their research platforms and address a wider selection of disease areas. In the light of growing scientific and regulatory challenges, the industry has repositioned its research model to focus on collaboration with global partners. This network approach to innovation is fostering more extensive knowledge sharing and joint problem solving, while decreasing global research costs.

[7]John A. Vernon, Joseph H. Golec, and Joseph A. DiMasi, "Drug Development Costs When Financial Risk Is Measured Using the Fama-French Three-factor Model," *Health Economics* 19, no. 8 (August 2010): 1002–1005

The Pharmaceutical Innovation Model



The Pharmaceutical Innovation Model

The research-based pharmaceutical industry is a leader of health innovation and operates at the very frontiers of scientific discovery. By continuously developing novel medicines and vaccines, improving formulations and delivery mechanisms, and discovering new compound interactions, the pharmaceutical industry is helping people across the globe live longer and healthier lives. This work requires state-of-the-art equipment and infrastructure; more importantly still, it requires the effective collaboration of leading scientific minds. While the innovation process can take different forms, each presenting its own technical and economic hurdles, the industry continues to deliver new life-saving and life-enhancing medicines year after year. Scientific and technological sophistication has increased over time, but medicine research and development (R&D) remains a highly challenging and risky activity requiring continual evolution of the R&D model.

Perfecting the Art of Innovation

Despite the challenging economic times, the research-based pharmaceutical industry remains one of the largest growth sectors. In 2011, the industry increased its R&D investments by 4.9% over 2010 expenditures, totaling over USD $135 billion.[8] In the same year, four of the top ten global R&D firms across all technology areas were pharmaceutical companies.[9] In practical terms, the industry's investments have materialized in the form of 340 new medicines approved for sale by the US Food and Drug Administration (FDA) since 2002.[10]
During the same period, the industry has faced unprecedented scientific and economic challenges. Largely due to the mapping of the human genome,[11] today's understanding of human biological processes, pathways, and protein structures enables researchers to develop very specific and complex medicines. However, market entry is never guaranteed. In addition, the costs of R&D have increased disproportionately compared to expected returns. This is often attributed to the increasing complexity and length of preclinical and clinical phases, and the relatively long lead-time between initial compound discovery and regulatory approval for marketing the final medicine or vaccine.[12]

Adapting to the times, the research-based pharmaceutical industry is redefining its innovation process. The innovation cycle is shifting from a predominantly in-house only process to a network of discrete research streams. Pre-competitive partnerships, for example, may be used to combine public and private genetic mapping efforts for use in upstream R&D phases. This crosscutting innovation model allows the industry to network research and to recruit world-class experts, thereby distributing R&D costs, reducing possible research redundancies, and ultimately bringing more medicines to market.

[8]EvaluatePharma, *World Preview 2018 – Embracing the Patent Cliff,* op. cit.

[9]European Commission, *Monitoring Industrial Research: The 2011 EU Industrial R&D Investment Scoreboard* (Luxembourg: European Union, 2011), http://iri.jrc.es/research/docs/2011/SB2011.pdf.

[10]PhRMA, *2012 Pharmaceutical Industry Profile,* op. cit.

[11]The Human Genome Project, an international scientific research program, has produced a molecular blueprint of the human genome. This information is critical for understanding medicinal interactions and human physiology at a molecular level. For more information, see National Human Genome Research Institute, http://www.genome.gov/10001772.

[12]European Biopharmaceutical Enterprises, "Clinical Trials," 2008, http://www.ebe-biopharma.org/index.php?option=com_content&task=view&id=43&Itemid=153&lang=en.

The Innovation Backdrop

Regardless of whether a novel compound has the potential to become a hugely successful medicine, its efficacy and safety must be well understood before any patients receive treatment. Health innovation, therefore, is a slow process; unlike in other technological areas, there is little or no room for error as pharmaceutical products are destined for patient use. Bringing one medicine or vaccine to market may take up to 14 years because R&D, regulatory review, and market entry must be carefully planned and orchestrated.[13] In fact, the innovation process has been referred to as an "orchestra" requiring a high level of synchronization.[14] Each part has a unique role to play but all must work together in harmony to produce a masterpiece.

The pharmaceutical industry's R&D cycle can be generally categorized by three scientific "innovation tracks:" discovering new compounds, formulating compounds for effective and safe patient administration, and discovering new therapeutic uses for compounds. Each track may take different forms for particular classes of pharmaceutical products, since small molecule, biotherapeutic, and vaccine R&D exhibit unique scientific issues. For example, biotherapeutic R&D requires increased discovery phase investment because biotherapies, unlike small molecules, utilize living organisms to produce medicinal compounds. Similarly, developing vaccines is often complicated by pathogenic mutations, requiring companies to invest in bioinformatics research to predict future mutations.

The scientific challenges encountered during the R&D process are a backdrop to various economic hurdles encountered during the innovation cycle. Intellectual property, regulatory review, and market entry strategies must be closely coordinated with research phases in order to sustain product pipelines.

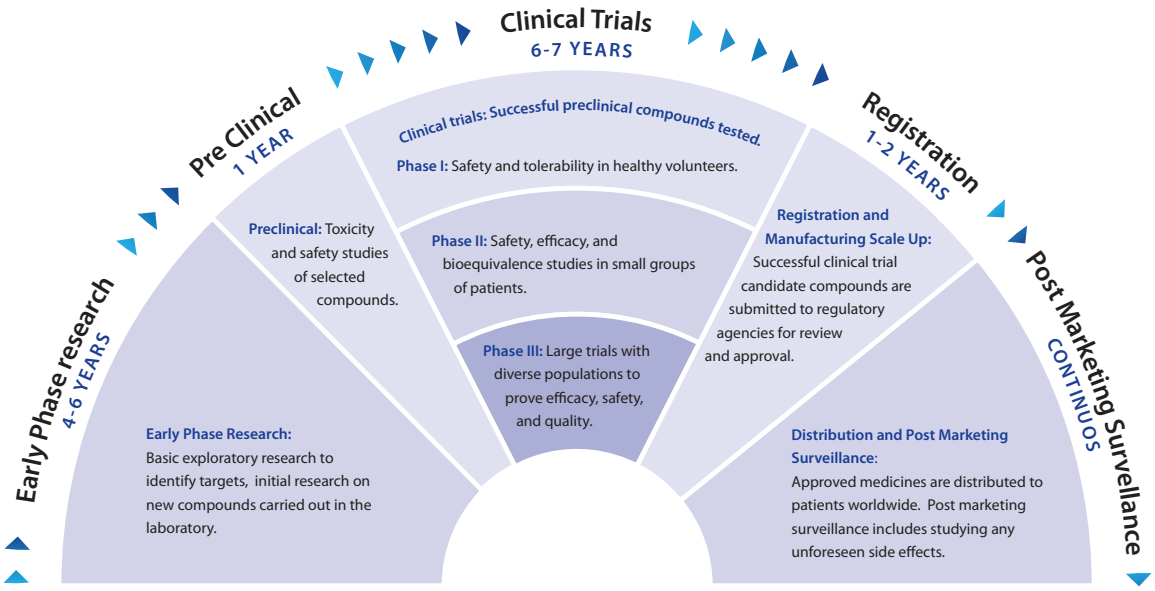


Figure 1: Milestones and activities throughout the biopharmaceutical innovation process.[15]

[13]Eleanor Malone, "Kill, Kill, Kill! The Worrying Mortality of Pharma Pipelines," 2012, http://www.scripintelligence.com/home/Kill-kill-kill-The-worrying-mortality-of-pharma-pipelines-335166

[14]Takeda Pharmaceutical Company, "Drug Discovery Processes," 2012, http://www.takeda.com/research/drug-discovery/article_1050.html

[15]Meir Perez Pugatch, Rachel Chu, and David Torstensson, *Assembling the Pharmaceutical R&D Puzzle for Needs in the Developing World: An Assessment of New and Proposed Delinking Initiatives Aimed at Encouraging R&D into Neglected and Tropical Diseases and Specific Type II Diseases* (Bicester, UK: Pugatch Consilium, May 2012), http://www.ifpma.org/fileadmin/content/Publication/2012/Assembling_the_RD_puzzle_FINAL.pdf..

Scientific Challenges

Apart from specific scientific problems encountered during R&D, different classes of pharmaceuticals, such as small molecules, biotherapeutics, and vaccines, are often characterized by systemic scientific challenges. Solutions applicable to one class may not be applicable to others because the technological focus is fundamentally different.

Small Molecules

Small molecule medicines are relatively low-weight chemically synthesized compounds that can be used to treat or manage diseases. This category of medicines works by exploiting biological pathways to inhibit or induce certain responses. A biological pathway is a series of molecular actions that trigger cellular responses.[16] Overall, small molecule R&D may be segmented into the three general innovation tracks: molecular discovery, formulation, and physiological interaction.

Small molecule discovery is the process of engineering a molecule that may produce a therapeutic effect. The therapeutic classes of small molecules are generally categorized by "functional" groups, reflecting the portion of the molecule that directly interacts with a biological pathway. Each medicine usually contains only a few functional groups, and the remainder of the molecule's atoms serve to position functional groups to maximize therapeutic effect. Once a functional group is associated with a particular disease area, that class of medicine is expanded to cover as many combinations of functional group orientations as possible. Exploring different orientations can lead to optimized molecule interaction, thus increasing overall medicine efficacy.

Formulation is the process of chemically "packaging" a molecule so that it exhibits a therapeutic effect once administered to a patient. This phase is especially important in small molecule R&D because many molecules exhibit therapeutic effects, but often cannot be formulated for safe administration. Lastly, researching physiological interactions is the process of establishing and broadening a molecule's therapeutic uses. Often a molecule is engineered for a particular therapeutic effect, but may be useful for other indications.

In all, approximately 1 in 5000 screened molecules may eventually become available medicines.[17]

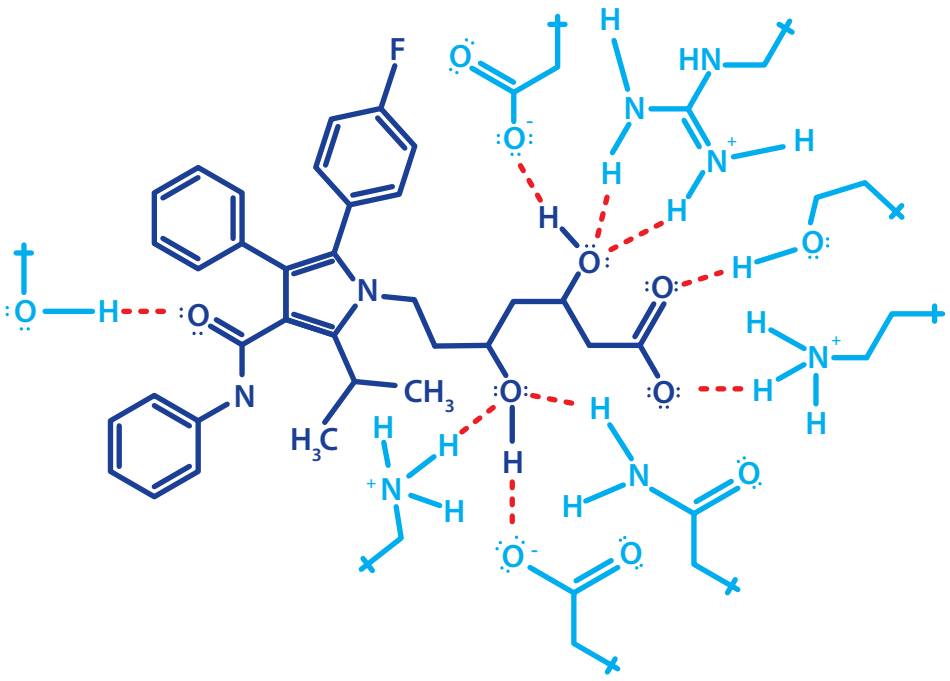


Figure 2: Small molecule, atrovastatin, interacting with HMG-CoA redustase, a human protein that plays a role in cholesterol production.

[16]National Human Genome Research Institute, "Biological Pathways," 2012, http://www.genome.gov/27530687.

[17]Jackie Hunter, "Challenges for Pharmaceutical Industry: New Partnerships for Sustainable Human Health," *Philosophical Transactions of the Royal Society* A: Mathematical, Physical and Engineering Sciences 369, no. 1942 (May 13, 2011): 1820.

Biotherapeutics

Biotherapeutic medicines are derived from proteins and other compounds produced by living organisms, such as cells, viruses and bacteria. Biotherapeutics aim to closely mimic compounds that are naturally produced in the human body. R&D in this area is often more complicated than small molecule research because an underlying organism's genetic and molecular makeup must be fully understood in order to induce production of therapeutic compounds.

Biotherapeutic R&D may be segmented into the same three innovation tracks as small molecule research, but their order is not necessarily linear. Discovery generally involves mapping biotherapeutic interactions. Like small molecules, these interactions involve functional groups. However, a typical protein biotherapeutic has significantly more functional groups that can be oriented in highly complex arrangements due to the protein folding process. Because these compounds are produced by living organisms, protein folding, and thus functional group orientation, is very sensitive to experimental conditions such as temperature or pH. In addition to understanding a biotherapy's biological interaction, researchers must genetically map living organisms to produce therapeutic compounds.

Even when the research is successful, companies face the problem of scaling up production. Unlike small molecules, biotherapeutics are difficult to mass-produce because living organisms are used to make the underlying compounds.

Figure 3: Progression of protein folding.
Primary amino acid sequences (a), secondary alpha coils and beta sheets (b), tertiary protein folding (c), and quaternary polypeptide arrangements (d). Biopharmaceutical R&D generally consists of engineering specific amino acid sequences that eventually correspond to medicinal protein structures.

Vaccines

Vaccines are biological products that improve human immune responses to underlying pathogens. Vaccines are derived from pathogenic organisms' surface proteins, namely antigens. They aim to introduce the right amount of antigens to stimulate antibody production by a patient's immune system. Once antibodies are produced for a particular pathogen, the immune system is equipped to combat future pathogenic infections that exhibit corresponding antigens.

Vaccine R&D generally also follows the three innovation tracks. Vaccine discovery, or the exploratory phase, focuses on identifying pathogenic antigens. This process involves studying a pathogen's surface proteins and identifying possible candidate antigens. Next, antigen safety is studied. Because antigens will eventually be introduced into patients, there is always a risk that the underlying infection may be transmitted. Therefore, safety studies are needed to determine whether immunological responses are proportional to the introduced antigens. For example, viral vaccines, such as influenza, can utilize whole virus, split virus, surface, or live attenuated antigens. There is no "one size fits all" vaccine type; inoculation for a certain pathogen may require introducing only specific surface proteins, whereas another can be safely administered as a whole virus.

Once appropriate and safe antigens and vaccine types are identified, R&D shifts to scaling up antigen production and formulating effective and safe inoculations. Like biotherapeutic R&D, scaling up production is difficult because living organisms are used to produce antigens. Meanwhile, other research focuses on formulating appropriate inoculations. The goal is to produce a preparation that is relatively stable in a variety of "in the field" conditions.

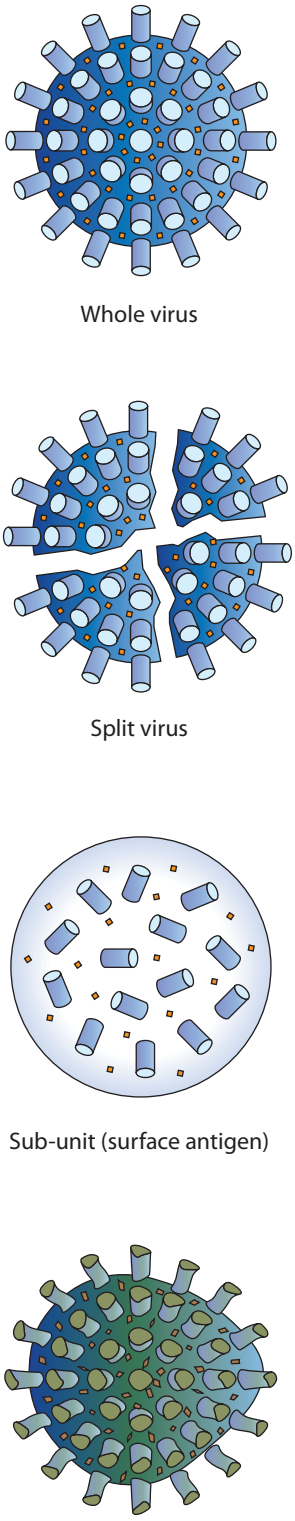


Figure 4: Types of viral vaccines.[18]

[18]IFPMA, "About Influenza Vaccine," http://www.ifpma.org/resources/influenza-vaccines/influenza-vaccines/about-influenza-vaccine.html.

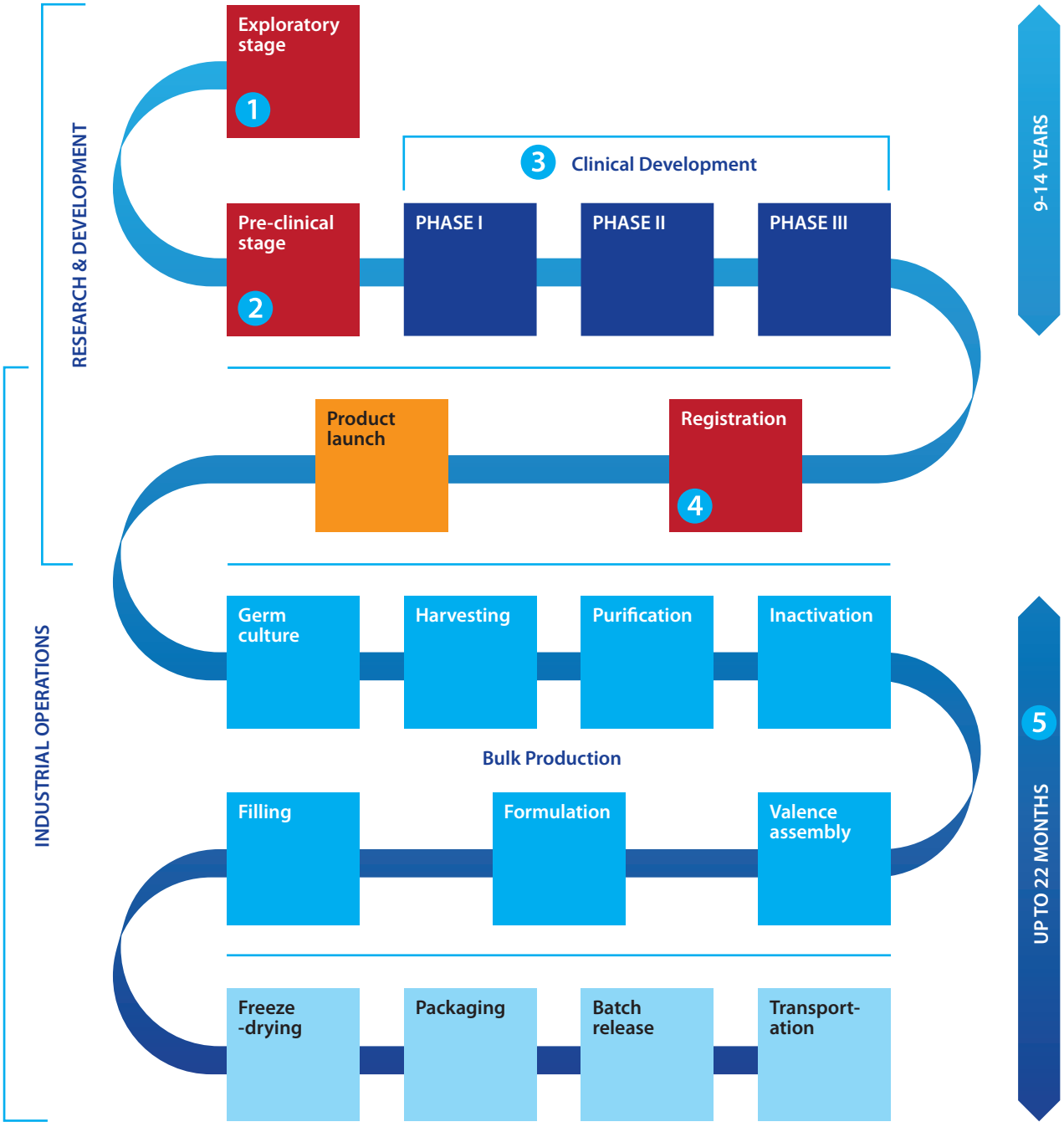


Figure 5: Vaccine development cycle.[19]

1 **Exploratory stage: 2 to 4 years**
Identifying antigens to prevent or treat a disease. Selected candidate vaccines will continue the process.

2 **Pre-clinical stage: 1 to 2 years**
Assessing antigens' safety in animals and selecting the best candidate vaccine to continue the process.

3 **Clinical development: 6 to 7 years**
Testing the candidate vaccine in humans.

Phase I: test of safety on 10 to 100 volunteers.

Phase II: Evaluation of the immune response in 100 to 3,000 volunteers.

Phase III: Large-scale tests of the vaccine's efficacy and tolerance on 3,000 to 40,000 volunteers.

4 **Registration: Synthesis stage from 12 to 18 months**
All of the data that have been collected during the preceding stages are gathered in a file and submitted to the health authorities in order to obtain a marketing authorization.

5 The infectious germs are cultured, harvested and purified. After formulation and freeze-drying (which stabilizes the more fragile vaccines), the vaccines are filled, primarily in vials and syringes and then packed. When the manufacturing process is complete, the cold chain must be constantly maintained during all stages, from distribution to vaccine administration to patients.

[19]Sanofi Pasteur, "The vaccine development cycle," http://www.sanofipasteur.com/sanofi-pasteur4/sp-media/SP_CORP4/EN/63/291/schema-cycle.pdf

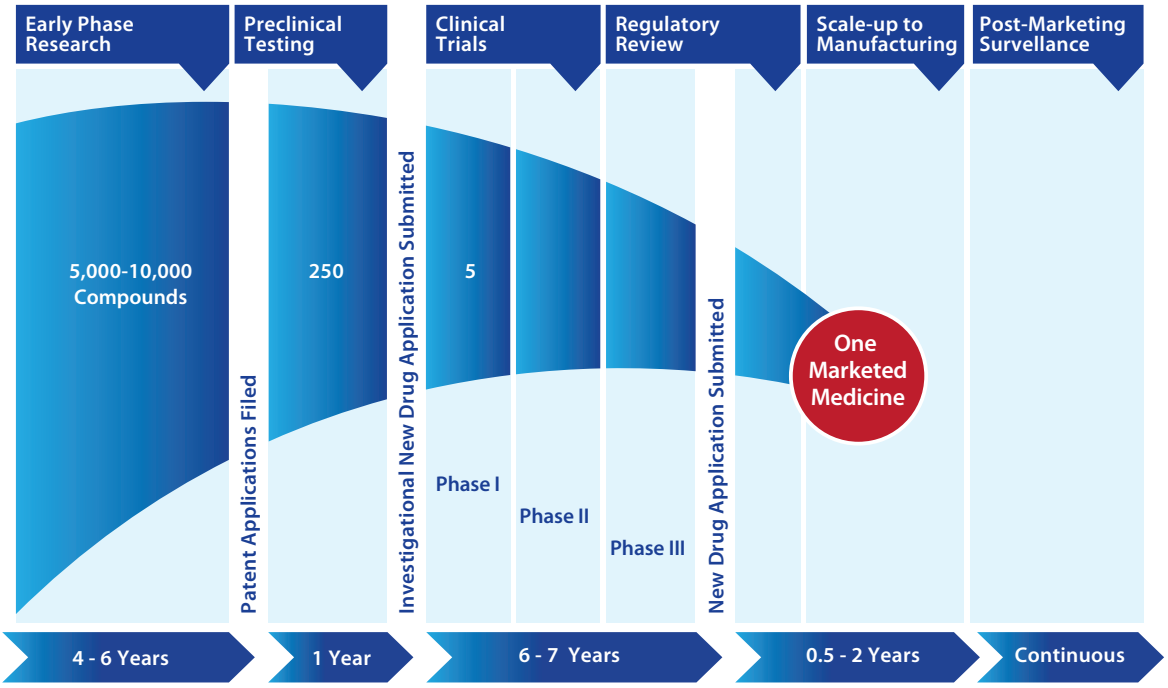


Figure 6: Pharmaceutical regulatory process.[20]

Economic Challenges

Economic challenges tend to parallel the R&D process. Companies often experience sunk R&D costs (i.e. R&D expenditures that do not materialize in a market-approved medicine) because pharmaceutical R&D is marked by high failure rates. An early-phase compound may have a promising outlook, but only preclinical and clinical trials will demonstrate its efficacy, quality, and safety. In addition, sunk costs increase when a failure occurs in upstream R&D phases. A phase III failure is significantly more costly than a preclinical failure because each phase is associated with a certain amount of required investment. In sum, about 4% of investigated compounds become biotherapeutic medicines compared with 14% for small molecules.[21]

In order for the R&D process to be sustainable, each approved medicine or vaccine must cover its own R&D costs, provide funds for reinvestment into other R&D streams, and mitigate sunk costs. For this to be possible, a country's legal system must recognize exclusivity rights in the manufacture and sale of pharmaceutical products for a certain period of time.

The cost of R&D is on the rise. Bringing a medicine to market in 2010 cost approximately USD $1.3 billion, compared with about USD $138 million in 1975.[22] Thus R&D costs have jumped nearly tenfold in 35 years, meaning that a medicine produced in 2010 would need to be ten times more profitable in order to recoup its R&D investment.

Clinical trials are the lengthiest and costliest investments, accounting for more than half of the total R&D expenditures. The clinical phase may take up to six years and cost nearly 60% of the total R&D investment.[23] Both length and costs are related to regulatory requirements aimed at ensuring scientific integrity, efficacy, safety, and quality of medicines. However, regulatory authorities must strike a balance; regulations should minimize costs by removing unnecessary burdens and bureaucracy, while ensuring a high threshold of quality.

[20]PhRMA, "2011 Pharmaceutical Industry Profile," http://www.phrma.org/sites/default/files/159/phrma_profile_2011_final.pdf.

[21]Laura Magazzini, Fabio Pammolli, and Massimo Riccaboni, *Market Structure, Sunk Costs and Scope Economies in Pharmaceutical R&D*, 2010, http://www.webmeets.com/files/papers/EARIE/2010/333/MPR_EARIE.pdf.

[22]Joseph A. DiMasi, Ronald W. Hansen, and Henry G. Grabowski, "The Price of Innovation: New Estimates of Drug Development Costs," *Journal of Health Economics* 22, no. 2 (March 2003): 151–185; Joseph A. DiMasi and Henry G. Grabowski, "The Cost of Biopharmaceutical R&D: Is Biotech Different?" *Managerial and Decision Economics* 28, no. 4–5 (2007): 469–479; Global Health Technologies Coalition and Policy Cures, *Saving Lives and Creating Impact: Why Investing in Global Health Research Works* (Washington DC: GHTC, 2012), http://www.ghtcoalition.org/files/Savinglivesandcreatingimpact.pdf.

[23]EFPIA, *The Pharmaceutical Industry in Figures* (Brussels: European Federation of Pharmaceutical Industries and Associations, 2012), http://www.efpia.eu/pharmaceutical-industry-figures-edition-2012.

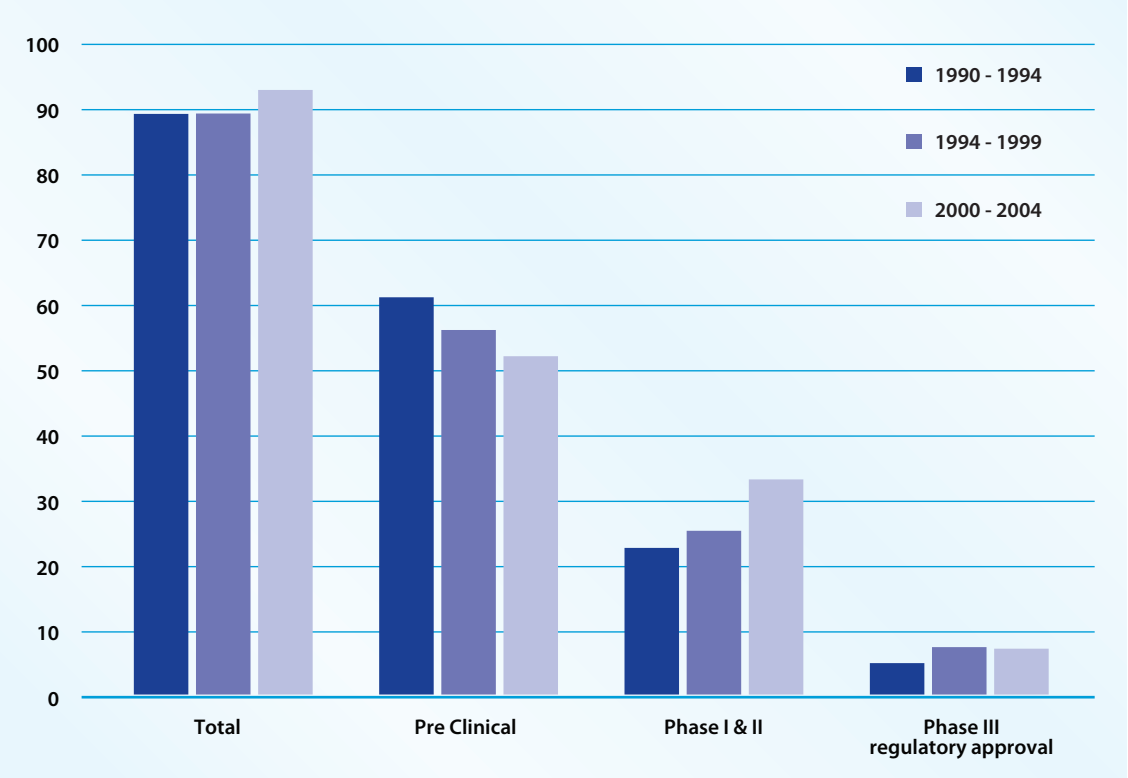


Chart 1. Pharmaceutical R&D failure rates.[24]

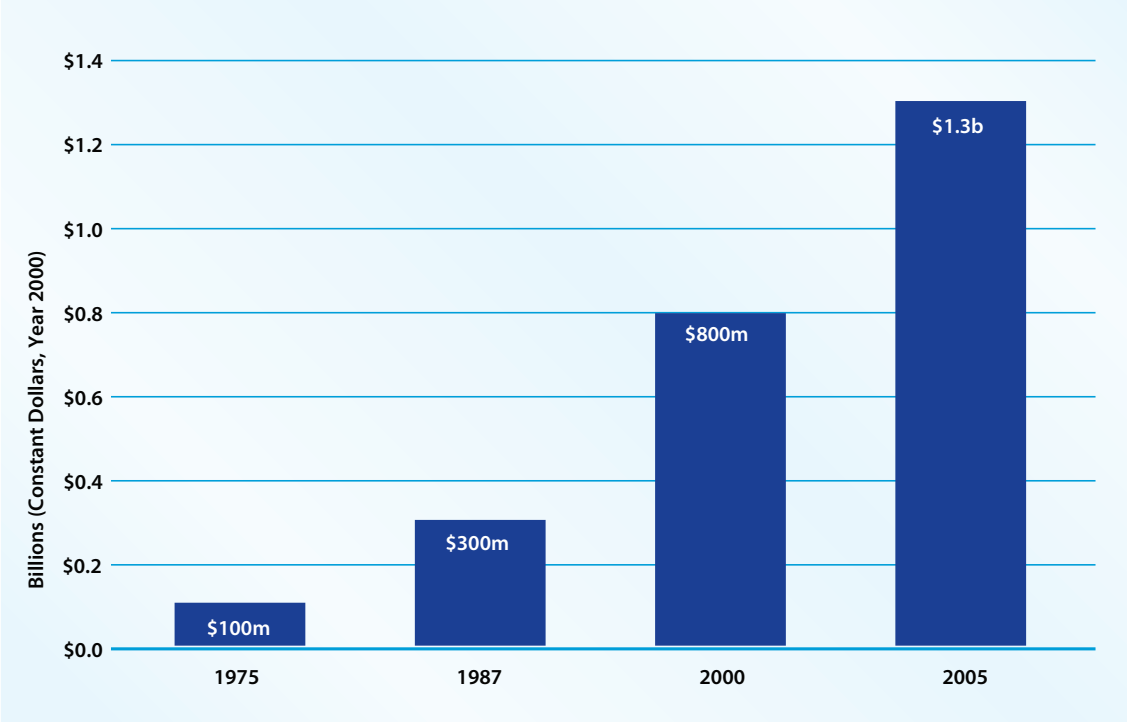


Chart 2. The cost of bringing one medicine to market.[25]

[24]"Market Structure, Sunk Costs and Scope Economies in Pharmaceutical R&D," Magazzini, et al, 2010.

[25]DiMasi et al., 2003, op.cit; DiMasi and Grabowski, 2007, op.cit.

TransCelerate: Cooperating to Speed the Development of New Medicines

Ten of the world's leading biopharmaceutical companies have joined forces to create TransCelerate BioPharma, a non-profit organization that will concentrate on shortening the time it takes to bring new pharmaceuticals to market. The main goal of the initiative is to agree on industry-wide standards to make it easier for practitioners to share and understand clinical trial data.

TransCelerate will initially focus its efforts on five separate projects that improve the efficiency of clinical trials, the most expensive phase of the medicine discovery process. The first projects include standardizing the process of training doctors to work in clinical trials, creating common data notation standards, building a shared web portal for doctors enrolling patients in clinical trials to consult, and standardizing how the risk to patients is measured in studies. By reducing duplication and making it easier for stakeholders to communicate with each other, TransCelerate will help shorten the pharmaceutical development process while simultaneously reducing costs.

Founding companies include Abbott, AstraZeneca, Boehringer Ingelheim, BMS, Eli Lilly, GSK, Johnson & Johnson, Pfizer, Genentech and Sanofi. Membership in TransCelerate is open to all pharmaceutical and biotechnology companies who can contribute to and benefit from these shared solutions.

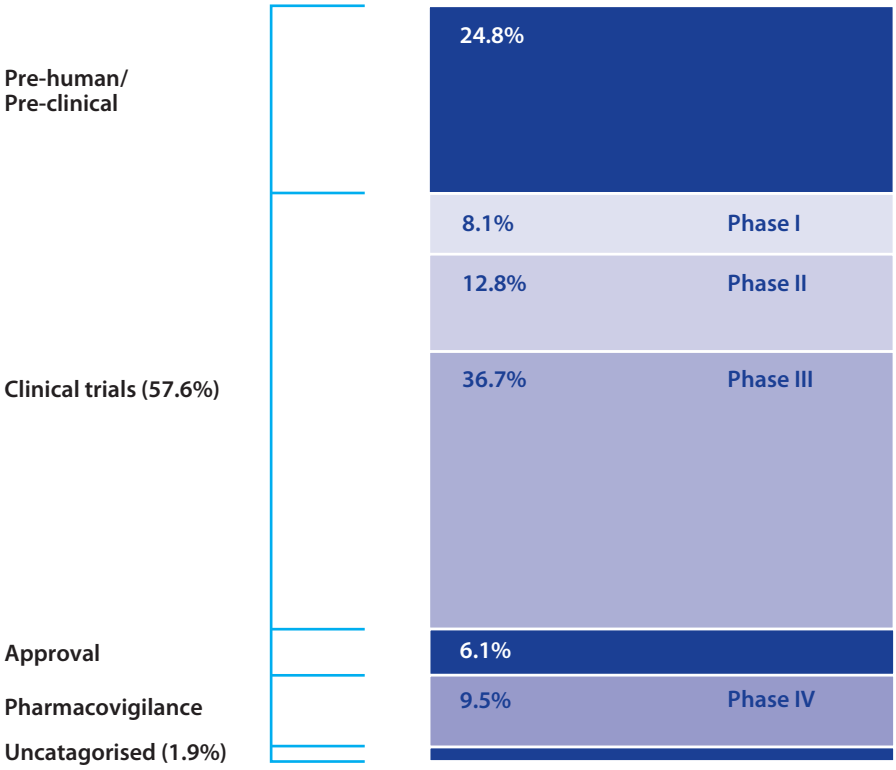


Figure 7: Allocation of R&D investments by function (%).[26]

[26] EFPIA, *The Pharmaceutical Industry in Figures Key Data 2012* (Brussels: European Federation of Pharmaceutical Industries and Associations, 2012), http://www.efpia.eu/sites/www.efpia.eu/files/EFPIA%20Figures%202012%20Final.pdf.

	1999	2005	% Change
Procedures per Trial Protocol (Median) (e.g. bloodwork, routine exams, x-rays, etc.)	96	158	65%
Length of Clinical Trial (Days)	460	780	70%
Clinical Trial-Participant Enrollment Rate (% of volunteers meeting trial criteria)	75%	59%	-21%
Clinical Trial-Participant Retention Rate (% of participants completing trial)	69%	48%	-30%

Table 1. R&D clinical trial phase complexity. [27]

Clinical regulations are nevertheless becoming increasingly strict and difficult to satisfy. By some estimates, the number of clinical procedures grew by 49% between 2000-03 and 2004-07[28] to meet demands by regulatory authorities for additional data to support clinical trial submissions. Stricter regulations are reducing possible volunteer numbers, adding to the cost and complexity of clinical trial design. The success of a clinical trial is highly dependent on patient enrolment and retention; during the same period, the number of eligibility criteria for participation in a clinical trial increased by 51%, leading to lower enrolment and retention rates.[29]

Patent rights for pharmaceuticals do not parallel the innovation and regulatory processes. In most national jurisdictions, patent rights are available for a fixed term from the date of invention. Yet lengthy regulatory and innovation lead times mean that in practice pharmaceutical products benefit from far less than the patent term. For example, candidate small molecules are normally patented during the molecular discovery period. If a patent is granted, the term begins during the very early stages of a molecule's discovery. However, that molecule will not be ready for market entry as a medicine for another 9 to 13 years.[30]

Despite these scientific, economic, and regulatory risks, the research-based pharmaceutical industry is currently developing over 3,000 novel molecules.[31] In addition to scientific innovation, the industry is constantly evolving its business model, for example through partnerships, to respond to greater economic pressure.

[27]Tufts Center for the Study of Drug Development, "Growing protocol design complexity stresses investigators, volunteers," *Impact Report* 10, no. 1 (Jan/Feb 2008), http://csdd.tufts.edu/files/uploads/jan-feb_impact_report_summary.pdf.

[28]Tufts Center for the Study of Drug Development, "Rising Protocol Complexity, Execution Burden Varies Widely by Phase and TA," Impact Report 12, no. 3 (May/June 2010).

[29]Ibid.

[30]See, e.g., supra Figure 6, "Pharmaceutical Regulatory Process."

[31]PhRMA, *2012 Pharmaceutical Industry Profile*, op. cit.

An Innovation Ecosystem

The research-based pharmaceutical industry has addressed the changing innovation landscape by rethinking the way it innovates. In particular, medicine discovery is no longer the linear process that it may have been in the past. Traditional pharmaceutical R&D was largely done by the same entity in a step-by-step fashion, blind to other firms' activity, and largely dependent on downstream and upstream inputs. Inevitably, this process promoted a "boom and bust" innovation model: innovation pipelines were either brimming with promising medicines or trying to fill a void.

Today's innovation is increasingly iterative and networked. Various contributors may enter at any step of the innovation process. For example, early-stage bio-molecular discovery may be done in collaboration with other private firms. Academic work relating to protein mapping may be used to pinpoint additional indications. The goal is simple: to foster an ecosystem to utilize collective knowledge and provide patients with more life-saving medicines.

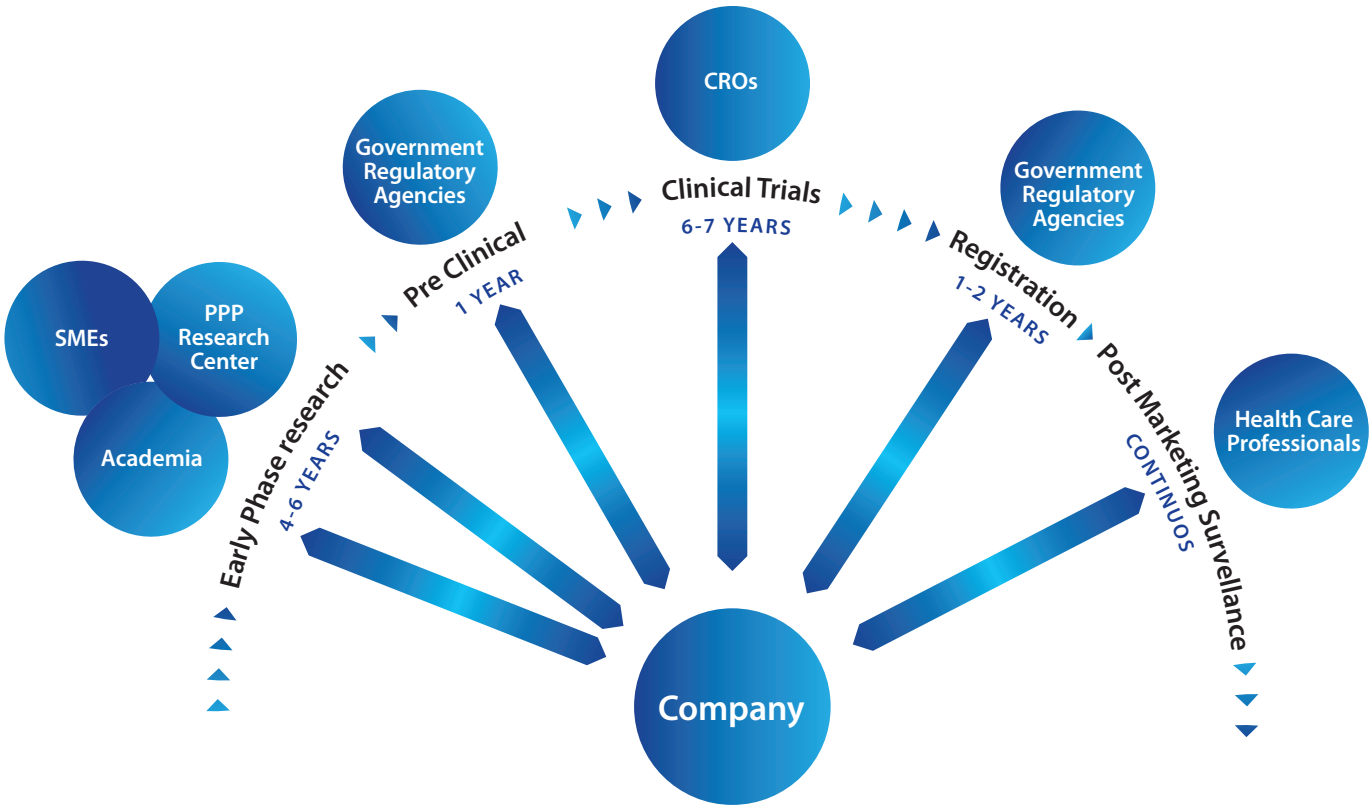


Figure 8: Pharmaceutical R&D networks.

An R&D ecosystem accelerates innovation because R&D can be coordinated to include inputs from various stakeholders. There is a vast amount of research and knowledge inherent in any particular therapeutic area. Yet communication between discrete research groups is often minimal and may result in redundant work. Public institutes, academic research groups, and even competing firms can benefit one another by coordinating research efforts. For example, firms may collaborate through private-public partnerships to pursue joint research into identifying suitable biomarkers to monitor certain therapeutic classes.[32] Likewise, competing firms may be able to collaborate and design a clinical trial that is broadly applicable.[33] In each case, all participants benefit. Costs are generally reduced because they are borne by multiple participants, and knowledge and know-how are transferred.

In addition to creating a network of innovators, ecosystem innovation diversifies R&D contributions. R&D efforts can be separately focused on novel molecules, formulations, and indications. Molecules may be engineered to complement particular proteins, or proteins may be matched to existing molecules. For example, an academic study of protein interactions may suggest that a known molecule exhibits other therapeutic effects. In this situation, the traditional R&D focus is reversed: instead of matching a novel molecule to an indication, a novel indication is researched.

The Structural Genomics Consortium (SGC)

This not-for-profit organization supports the discovery of new medicines by carrying out pre-competitive research in structural and chemical biology. The SGC identifies and maps three-dimensional structures of human proteins, which are the targets for drug discovery. Learning about the precise structure of human proteins provides important clues to discover new therapeutics.

The consortium includes active research facilities at the Universities of Toronto and Oxford and the Karolinska Institutet in Stockholm. Current funders of the SGC include GlaxoSmithKline, Eli Lilly, Takeda Pharmaceutical, Pfizer, the Novartis Research Foundation, the Wellcome Trust, and Canadian granting agencies. More than 200 scientists from academia and industry collaborate within SGC, and all partners make this early-stage research openly available with no patents or restrictions.

More information at: http://www.thesgc.org.

[32]See, e.g., The Biomarkers Consortium, http://www.biomarkersconsortium.org.

[33]See, e.g., Structural Genomics Consortium, http://www.thesgc.org.

New Challenges in Pharmaceutical Innovation

New Challenges in Pharmaceutical Innovation

Major scientific advances are marked by putting theories into practice. The most exciting advances are easily measured and affect our daily lives. From early synthetic organic chemistry experiments to computational genome modeling, the pharmaceutical industry touches the day-to-day lives of almost everyone. The prime measure of the industry's impact is arguably increased human life expectancy. Ever since the discoveries of early pharmaceutical substances, like insulin and penicillin, both longevity and quality of life have significantly improved.

There is still much to be discovered. The research-based pharmaceutical industry uses various technologies and processes to explore promising therapeutic areas. For example, collaborations with public institutes have yielded promising bioinformatics, which may be used to map protein–molecule interactions. Computational methods and collaborations like these make the research and development process more efficient, thereby producing more innovative therapeutics and vaccines available to patients.

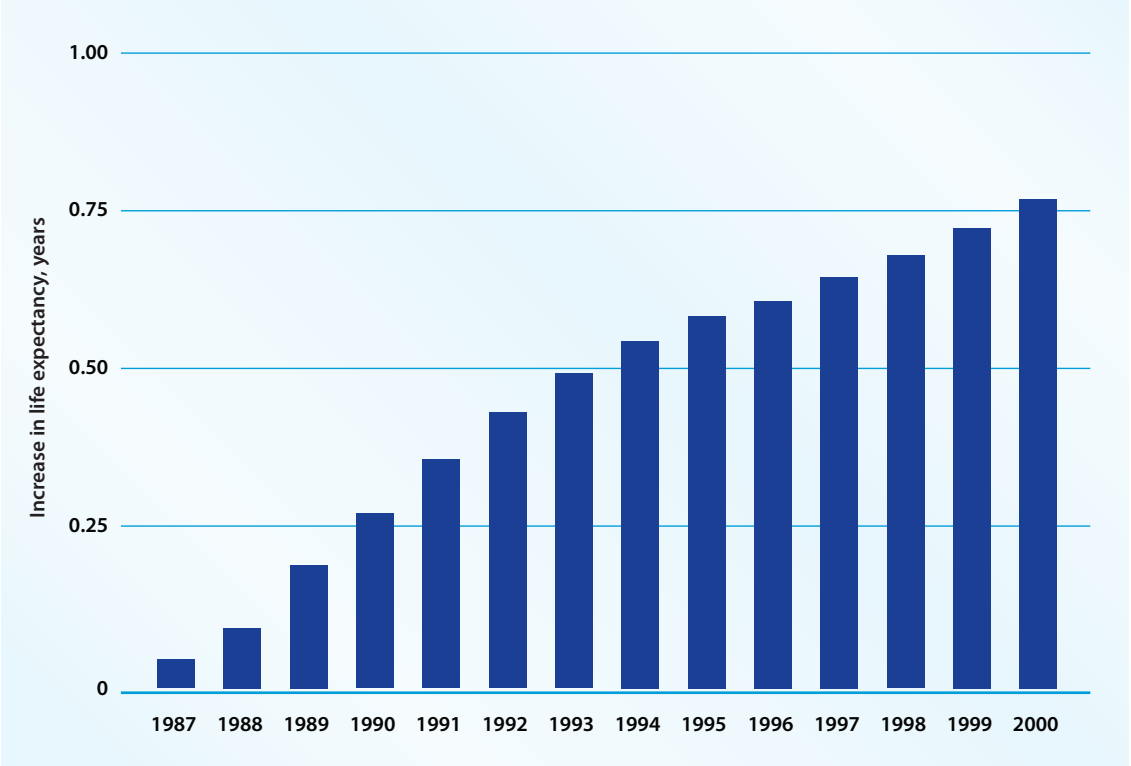


Chart 3: Net increase of human longevity, 1987-2000.[34]

[34] Frank R. Lichtenberg, "The Impact of New Drug Launches on Longevity: Evidence from Longitudinal, Disease-level Data from 52 Countries, 1982-2001," *International Journal of Health Care Finance and Economics* 5, no. 1 (2005): 47-73.

Tools of the Trade

Pharmaceutical innovation depends on a sound understanding of disease mechanisms. Major scientific advances, including the 1953 discovery of the double-helix model of DNA and the 2001 sequencing of the human genome, have revolutionized our understanding of the human body and hereditary disposition to disease. Advances in genomic, proteomic and chemical sciences allow scientists to understand the molecular workings of human disease.

Designing and improving novel therapeutics is like making a key, except that there is no duplicate key to copy and the lock to be opened is not fully understood. The goal of many pharmaceutical products is to interact with a particular human protein. Understanding the molecular structure of target proteins and modeling proposed molecular interactions enable scientists to monitor and address complex relationships between biological pathways and therapeutics. Information relating to a protein's structure provides insight into matching a molecular "key" (a medicinal product) to a protein "lock."

Scientists rely on imaging technologies, including magnetic resonance imaging (MRI) and x-ray crystallography, to generate genetic maps. Applying computational methods to such maps helps to determine protein structures. Gene expression maps identify a particular structure's characteristics at a molecular level. For example, many cholesterol medicines inhibit enzymes (proteins) that are required to produce cholesterol. A gene expression map of the enzyme enables scientists to view possible interaction sites. A molecule may then be engineered, or matched, to complement the identified interaction site.

Early pharmaceutical discovery research was not as technologically refined. Before computational models were developed, researchers proceeded by trial and error. Medicine and protein interactions were studied manually, and results were recorded. If a therapeutic effect was noted, the molecule proceeded to further testing.

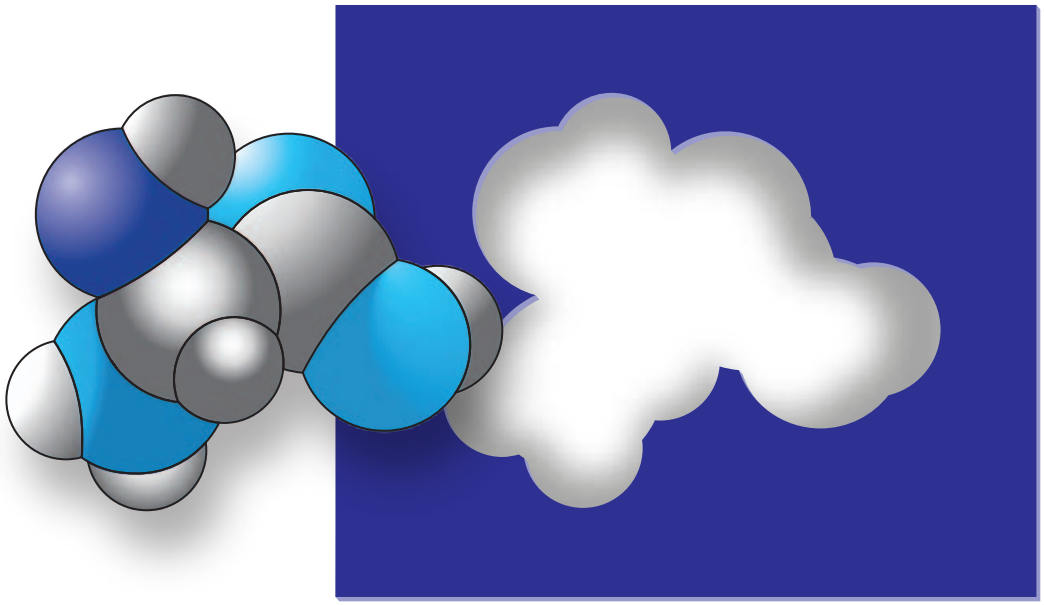


Figure 9: Compounds interact with human proteins like keys fit into a lock.

Computational methods have drastically changed the small molecule discovery process. Researchers consult compound databases that contain potential matches between molecular compounds and proteins, run computer-based predictions about how these molecules will interact with a given protein, and create three-dimensional structures of molecule-protein interactions. These provide a visualization of optimal molecular designs that affect the target protein.[35]

Furthermore, genomics and imaging technologies have helped identify biological markers, or biomarkers. Biomarkers are objective indicators for biological pathways or pathogenic processes, and are especially critical during R&D clinical phases. Identifying a biomarker is important when studying pharmacological responses to therapeutic compounds because biomarkers provide quantifiable results. Biomarkers may be very simple, or extremely complex. For example, blood pressure is a relatively simple biomarker for cardiovascular health. Deviations from normal blood pressure may indicate external stresses on the cardiovascular system. Introduction of a cardiovascular medicine may be validated by stabilized blood pressure. Such biological markers may be used at each stage of the research and development process and can be used to help monitor risk, presence and progression of diseases, and the effectiveness of treatment.[36]

Identifying biomarkers is an important component of pharmaceutical R&D because clinical trials require data for treatment efficacy, quality, and safety. The greater the specificity of a given biomarker to an underlying disease pathway, the better researchers can monitor and quantify the efficacy of treatment.[37] However, identifying biomarkers is a difficult process. There are many diseases, including cancers and systemic diseases, which lack suitable biomarkers. The research-based pharmaceutical industry has focused a large component of its R&D efforts on screening various disease pathways for appropriate biomarkers.[38]

Where challenges exist, innovative solutions follow. The industry's scientific challenges have largely involved understanding therapeutic interactions at molecular level. In other words, before making a key the lock is studied. This sometimes creates scientific and economic bottlenecks because pinpointing biomarkers enables research indirectly: in some circumstances, how to study a therapeutic interaction is understood, but a therapy itself has yet to be developed. Innovation ecosystems aim to avoid such bottlenecks by bringing in various stakeholders at different points in the R&D pipeline. Thus, biomarker research may be executed in partnership with an academic institute, visualizing a target protein may be done through a pre-competitive consortium, and finally a molecule may be designed in-house.

The following is an overview of some of the industry's recent scientific advances.

Innovations Improving Global Health

Technological advances in research and development have opened many avenues of investigation to better prevent and treat diseases. From cancer to mental and neurological disorders, the range of new pharmaceutical products is continuously growing. At the same time, each of these areas is technologically demanding, with researchers confronting new molecular challenges as greater specificity in targeting illness is required. In addition, individual pharmaceutical companies are often becoming specialized in niche therapeutic areas because different diseases require specific expertise and equipment.

[35]Roche, "Innovation and Technologies," 2012, http://www.roche.com/innovation_and_technologies.htm.

[36]Roche, *Biotechnology - New Directions in Medicine* (Basel, Switzerland: F. Hoffman-La Roche, 2008), http://www.roche.com/biotechnology_new_directions_in_medicine.pdf.

[37]Ibid.

[38]Jackie Hunter and Susie Stephens, "Is Open Innovation the Way Forward for Big Pharma?" *Nature Reviews Drug Discovery* 9, no. 2 (February 2010): 87-88.

Non-communicable Diseases

Non-communicable diseases (NCDs) are increasingly burdening patients and healthcare systems worldwide.[39] In economic terms, NCDs are predicted to cost the world economy an estimated USD $35 trillion by 2025.[40] In the United States alone, according to some estimates, cancer has knocked USD $18.2 billion off GDP due to lost productivity from illness, and USD $112 billion due to mortality costs.[41]

Recognizing the growing health and economic burden of these diseases, the research-based pharmaceutical industry has more than 2,400 new medicines in the pipeline to treat cancer, diabetes, heart disease, and asthma.[42] Research strategies are focused on overcoming a number of scientific challenges, particularly at the molecular level, that are associated with non-communicable diseases.

One of the greatest challenges is determining the root causes of NCDs. Especially difficult is identifying specific biomarkers that are uniquely associated with the underlying disease. For example, research on treatments for rheumatoid arthritis, an auto-immune disease where the immune system affects the joints, is at a standstill because there is no biomarker suitable to quantify medicine efficacy. R&D in this area is thus predominantly concerned with identifying a suitable protein that can be used to diagnose and monitor the disease in large patient populations.[43] In addition to searching for biomarkers, the industry has made significant advances in therapies that work either to stop cancer growth or to kill cancer cells. Many companies are using imaging and computational technologies to address the underlying mechanisms of cancers. This has led to several biotherapeutic advances in treating cancer. In fact, some cancers may be managed as chronic diseases.[44] However, cancer remains one of the world's largest healthcare challenges, with an estimated 12 million deaths annually expected by 2030.[45]

Other R&D pipelines are also promising. Substantial benefits are expected from the nearly 300 medicines that are in development to treat heart disease and stroke. In the US, it has been estimated that existing medicines to control blood pressure and cholesterol have already helped reduce the number of deaths attributed to such diseases by 28% between 1997 and 2007.[46] These innovative treatments are significant improvements over invasive cardiac surgeries and wait-and-see "treatments."

	Phase I	Phase II	Phase III	Regulatory Review	Total
Cancer	654	795	208	25	**1682**
COPDs and Asthma	34	68	26	3	**131**
CVDs	117	150	74	16	**357**
Diabetes	91	107	58	20	**276**

Table 2: Medicines in development for NCDs.[43]

[39]A recent study found that 80% of all NCD deaths worldwide occur in low- and middle-income countries. D.E. Bloom et al., *The Global Economic Burden of Non-communicable Diseases* (Geneva: World Economic Forum, 2011), http://www3.weforum.org/docs/WEF_Harvard_HE_GlobalEconomicBurdenNonCommunicableDiseases_2011.pdf

[40]Bruce Heilbruth, "Double Burden," *Development Asia*, no. 11 (December 2011).

[41]Dan Greenberg et al., "When Is Cancer Care Cost-Effective? A Systematic Overview of Cost–Utility Analyses in Oncology," *Journal of the National Cancer Institute* 102, no. 2 (January 2010): 82–88.

[42]IFPMA, *Framework for Action on NCDs – 2011-12 Progress Report* (Geneva: International Federation of Pharmaceutical Manufacturers and Associations, 2012),

[43]Ibid. In certain cases, one molecular compound can serve multiple indications. When the trial phase was not disclosed, compounds were categorized as Phase I. Compounds publicly listed as Phase I / II were considered as Phase II. Compounds publicly listed as Phase II / III were considered as Phase III.

[44]Bayer HealthCare Pharmaceuticals, "Small and Large Molecules: Drugs on a Chemical and Biological Basis," 2012, http://www.bayerpharma.com/en/research-and-development/technologies/small-and-large-molecules/index.php.

[45]AstraZeneca, "Focus on Disease," 2012, http://www.astrazeneca.com/Research/Focus-on-disease.

[46]PhRMA, "Heart Disease and Stroke," 2012, http://www.phrma.org/research/heart-disease-stroke.

[47]IFPMA, *Ending Neglected Tropical Diseases* (Geneva: International Federation of Pharmaceutical Manufacturers and Associations, 2012), http://www.ifpma.org/fileadmin/content/Publication/2012/IFPMA-NTD-NewLogoJUNE2.pdf.

Mental and Neurological Disorders

One of the most pressing therapeutic areas today is mental and neurological disorders (MNDs). These illnesses, including Alzheimer's disease, depression, autism, bipolar disorder, and attention deficit hyperactivity disorder (ADHD), present some of the most difficult R&D challenges because neurological pathways are not well understood and suitable biomarkers have yet to be identified. However, the need for treatments is great. According to the World Health Organization (WHO), one in four individuals will suffer from a mental illness at some point in their life. In the US, it is currently projected that by 2050 Alzheimer's disease alone will affect up to 16 million Americans, up from 5.4 million individuals today, at an annual care cost of USD $1.1 trillion.[49]

The number of MND therapies has grown over the years, but due to the complex nature of mental diseases, most treatments affect physical symptoms[50] and provide little systemic relief. As such, these treatments merely mask patients' symptoms. Development of medicines in this area has been slow because therapeutic mechanisms are usually complex and the incidence of MNDs is drastically under-reported. In addition, significant economic barriers exist when compared to other disease areas. For example, clinical approval success rates are much lower, requiring about 35% more time to receive regulatory approval.[51]

Gathering information about sufferers is one of the biggest challenges to developing therapeutics for MNDs. In many societies, such illnesses are stigmatized, which may prevent sufferers from seeking help. Furthermore, symptoms are often difficult to recognize due to slow disease progression. In the case of Parkinson's disease, for example, the rate of degeneration is quite slow over more than 10 years. Patients may seem asymptomatic because the disease subtly affects motor skills and vision over a prolonged period.[52] Many sufferers dismiss such changes as age- or stress-related, thereby delaying care until very late stages of disease onset. Many MNDs are thought to have genetic origins, but without more information on affected populations, it is difficult to identify at-risk groups and the biomarkers necessary for carrying out clinical studies.

It is also difficult to develop treatments for these diseases because the target organ–the brain–is still poorly understood. Only 50 years ago did scientists begin to understand the biology involved in mental and neurological disorders. Developing medicinal products for these illnesses requires significant inter-disciplinary collaboration because the diagnosis of MNDs often requires clinical practitioners to observe a patient's symptoms, rather than screening and quantifying biomarkers.

[48]World Health Organization, "Mental Disorders Affect One in Four People," 2001, http://www.who.int/whr/2001/media_centre/press_release/en/index.html.

[49]Alzheimer's Association, 2012 *Alzheimer's Disease Facts and Figures* (Chicago: Alzheimer's Association, 2012), http://www.alz.org/downloads/facts_figures_2012.pdf.

[50]PhRMA, "Collaborations Between Public and Private Sector Are Critical to Advance Alzheimer's Research," 2012, http://www.phrma.org/media/releases/collaborations-between-public-and-private-sector-are-critical-to-advance-alzheimers-research.

[51]Tufts Center for the Study of Drug Development, "Pace of CNS Drug Development and FDA Approvals Lags Other Drug Classes," *Impact Report* 14, no. 2 (April 2012), http://csdd.tufts.edu/files/uploads/mar-apr_2012_ir_summary.pdf.

[52]Boehringer-Ingelheim, "Fact Sheet: Parkinson's Disease (PD)," 2012 http://www.boehringer-ingelheim.com/content/dam/internet/opu/com_EN/document/01_news/factsheets/factsheet_parkinsons_disease.pdf.

Advances in the molecular understanding of mental diseases have led to the development of novel therapies and vaccines, including vaccines that may prevent illnesses as varied as Alzheimer's disease and cocaine addiction.[53] Many of these therapies target specific molecular pathways associated with underlying illnesses. One such treatment in development for Attention Deficit Hyperactivity Disorder (ADHD) works by normalizing chemical signaling in the brain to allow neurons to communicate properly. Another therapy in development, for the treatment of major depression, seeks to protect the central nervous system against damage from chronic exposure to stress by recruiting the patient's own neural stem cells.[54] In all, research efforts have produced nearly 200 advance treatment options to prevent and/or disrupt MNDs.[55]

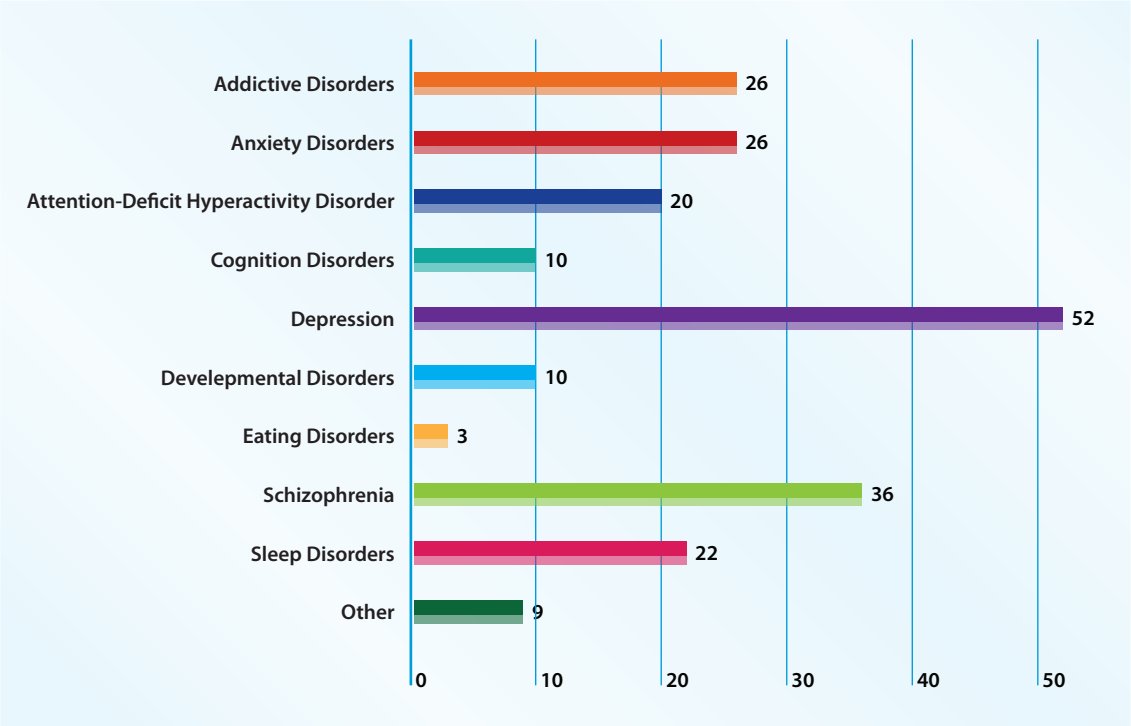


Chart 4: Number of medicines for mental illnesses in clinical trials.[56]

[53]PhRMA, "Medicines in Development for Mental Illnesses," 2010, http://www.phrma.org/sites/default/files/422/mental2010.pdf; PhRMA, "Collaborations Between Public and Private Sector Are Critical to Advance Alzheimer's Research," op. cit.

[54]PhRMA, *Medicines in Development for Mental Illnesses*, op. cit.

[55]PhRMA, "Nearly 200 Medicines in Development for Mental Illnesses," op. cit.

[56]PhRMA, *Medicines in Development for Selected Mental Illnesses and Addictive Disorders* (Washington DC: Pharmaceutical Research and Manufacturers of America, 2012).

Infectious Diseases

By the mid-twentieth century, infectious diseases were thought to be a concern of the past. For the most part, childhood diseases had been eradicated by vaccine campaigns, bacterial infections could be controlled with "miracle drugs" such as penicillin, and living conditions had generally improved due to technological advances of industrialization. However, half a century later, infectious diseases continue to pose significant risk.[57] Seasonal influenza alone is responsible for over 250,000 deaths annually.[58]

The continued prevalence of infectious diseases is largely due to the underlying mechanisms of transmission. Generally, infectious diseases are transmitted by bacterial or viral pathogens. These pathogens wage war against an infected person's immune system. Treatments work either by affecting pathogens or by boosting an individual's immune response. However, pathogens can mutate and become resilient to treatments over time.

In addition to common bacterial infections, other infectious diseases are evolving. Pathogens are becoming resistant to antimicrobial and antiviral treatments, and viruses, such as HIV, pandemic influenza, and severe acute respiratory syndrome (SARS), have demonstrated the need for significant R&D efforts. Generally, there are two treatment options: vaccines and medicines.

Preventatives: Vaccines

Vaccines proactively defend against infectious diseases by "training" an individual's own immune system to protect itself against a particular pathogen. The underlying mechanism of action aims to stimulate the body's immune response to recognize and destroy introduced antigens. Antigens are unique surface proteins of infectious disease-causing pathogens. In response to vaccination, the immune system produces antibodies that match the introduced antigen. When that particular antigen is later reintroduced by disease transmission, the body is already stocked with appropriate antibodies.[59]

Developing effective vaccines is difficult because matching antibodies and antigens requires a high degree of specificity. The process is further complicated by the existence of multiple antigens corresponding to one pathogen and the rapid evolution of pathogen genetics. Through natural mutations, antigen characteristics change and produce new "strains" of pathogens. Existing vaccines that were effective against pre-mutated viruses may be rendered ineffective.

Once strains are identified, industry can mobilize antibody production and begin formulating vaccines. A large part of vaccine R&D is dedicated to formulating multi-strain vaccines, aimed at producing one inoculation that will be effective against multiple pathogenic strains. Extending vaccine shelf-life is also important because biologics tend to degrade quickly. This is especially relevant in remote areas where refrigeration and stable temperature environments are not readily available.

In addition, advances are being made in vaccine delivery and production methods. New technologies are making inoculations less painful and more sanitary. For example, syringe-based delivery of seasonal influenza antigens may be replaced with nasal or subcutaneous administration. This is especially useful for vaccinating children and large numbers of people because nasal or subcutaneous inoculation is minimally invasive.

In all, vaccine R&D involves inputs from many sources; development requires identifying strains, producing strain-specific antigens, formulating and delivering antigens, and preserving vaccines. This is a concerted effort between national health agencies, public academic institutes, and private R&D consortiums.

[57]World Health Organization, World Health Statistics (Geneva: World Health Organization, 2012), http://www.who.int/gho/publications/world_health_statistics/2012/en/index.html.

[58]World Health Organization, "Influenza (Seasonal)," Fact Sheet No. 211, April 2009, http://www.who.int/mediacentre/factsheets/fs211/en/.

[59]College of Physicians of Philadelphia, "The History of Vaccines: The Future of Immunization," 2012, http://www.historyofvaccines.org/content/articles/future-immunization.

Seasonal Influenza Vaccines

Influenza strains correspond to antigens present on the surface of the virus. During any given season, numerous strains may be present and new strains may arise from mutations. Effective vaccines require researchers not only to formulate appropriate antibodies, but also to predict a particular year's influenza strain.

Collaborative innovation helps industry and government health officials to predict influenza trends. About every six months, at least three influenza strains are identified for upcoming vaccination seasons. This process involves gathering information and projections from various national health institutes. Certain pandemic strains may also be identified, based on predicted mutations of existing strains.

More information at: http://www.ifpma.org/global-health/influenza.

Treatments: Medicines

Once a disease is transmitted and contracted, vaccination options may be too late. In fact, vaccines are difficult to produce for many infectious diseases because antigens rapidly mutate, rendering vaccines ineffective. However, other pharmaceutical products, such as small molecules or biotherapeutics, may manage or treat contracted infectious diseases. The major scientific hurdle in this class of medicines is mapping the pathogen's molecular structures. The goal is to destroy the underlying pathogen or to stunt its replication. As with medicine discovery, in order to produce effective treatments, a thorough understanding of the target protein is necessary.

Pathogens are capable of building antimicrobial resistance (AMR). AMR emerges when infectious disease-causing microbes–whether fungal, bacterial, or viral–develop resistance to therapies that were developed to combat them. Therapeutics that were once successful may be completely ineffective against resistant microbes. The immediate impact of resistance is an increased risk of infectious disease mortality.[61]

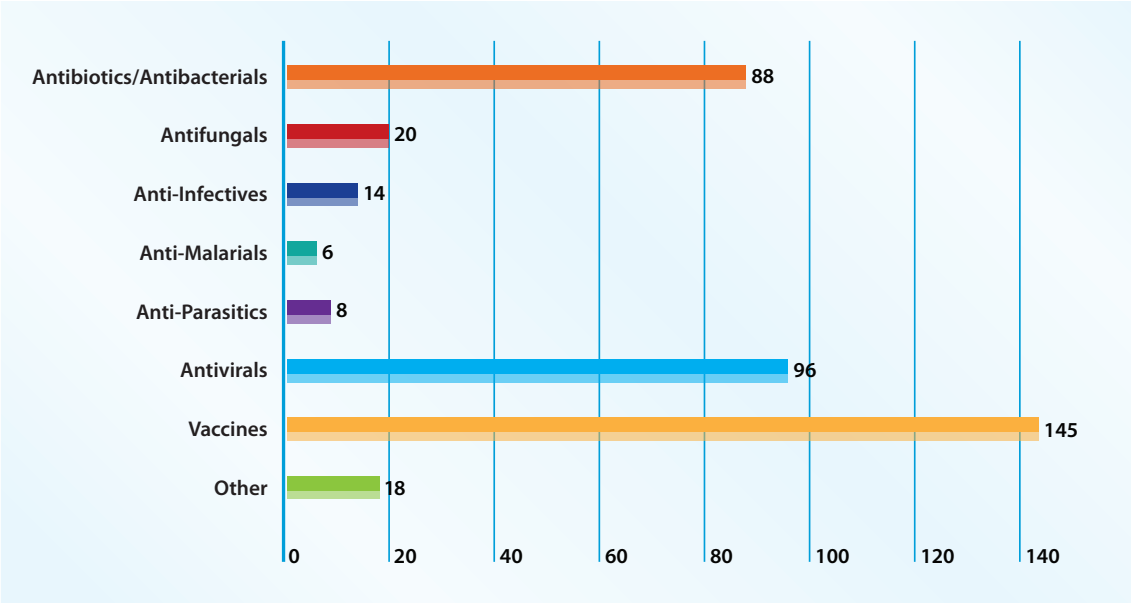


Chart 5: Medicines in development for infectious diseases.[60]

[60]PhRMA, *Medicines in Development for Infectious Diseases*, (Washington DC: Pharmaceutical Research and Manufacturers of America, 2010), http://www.phrma.org/research/medicines-development-infectious-disease.

[61]David Heymann, "Resistance to Anti-Infective Drugs and the Threat to Public Health," *Cell* 124, no. 4 (February 24, 2006): 671–675.

Medical and scientific communities became aware of the AMR risk shortly after penicillin was developed.[62] However, for some time, only the most resilient microbial strains were transmitted because treatments were largely effective against other strains. Growing resistance is due to a number of factors; misdiagnosis, over-treatment, and improper use all contribute to promoting AMR strains of microbes.[63] In other words, improper use of antimicrobials has increased the rate of selective pressure, thereby fostering AMR microbial strains.[64]

The research-based pharmaceutical industry is actively pursuing a variety of solutions to overcome the limitations of earlier antimicrobial therapeutics. R&D efforts have diverged from broad-based antibiotics to narrowly targeted therapeutics. Instead of developing an antibiotic that destroys bacterial cell walls regardless of strain, new medicines target only pathogenic strains.[65] Other R&D approaches are directed at inhibiting key reproductive processes. This approach is inherently less prone to AMR because the microbe is not directly affected, only the environment in which it reproduces.[66] Although these approaches have produced promising laboratory results, clinical trials have been generally difficult to organize due to the relative unavailability of patients with AMR-strain infections.[67]

Another notable area of infectious disease research relates to the development of HIV antiviral therapies. Current treatments permit HIV patients to manage the disease and maintain normal lifestyles. In fact, antiretroviral therapies, which interfere with the replication process of the HIV virus, have been so successful that measurements of HIV concentration in blood samples often return negative results under standard viral load tests.[68] However, despite successfully managing HIV, therapeutics have yet to eradicate the virus. Eradication is complicated because HIV remains dormant in cells, posing an ever-present risk that it may return.

Current HIV research is diverse. Researchers are focusing on treatments and gene therapies that remove or destroy HIV viral particles, maintain virus dormancy, or filter viral particles from infected patients.[69]

Partnerships for AMR Research

The Innovative Medicines Initiative (IMI) is a hub that aims to facilitate private and public R&D collaborations. It is a joint undertaking between the European Union (EU) and the European Federation of Pharmaceutical Industries and Associations (EFPIA) to research and develop medicines against antimicrobial resistance (AMR) microbes. The European Commission's Seventh Framework Programme contributed €1 billion to the IMI research program and that amount will be matched by in-kind contributions from EFPIA member companies, for a total of €2 billion.

IMI is fostering a collaborative innovation ecosystem involving public and private researchers. In 2012, IMI began an AMR R&D program called "Combating Antimicrobial Resistance - NewDrugs4BadBugs (ND4BB)." The program aims to connect various stakeholders to explore existing compounds and develop novel AMR medicines.

More information at: http://www.imi.europa.eu.

[62] Julian Davies and Dorothy Davies, "Origins and Evolution of Antibiotic Resistance," *Microbiology and Molecular Biology Reviews* 74, no. 3 (September 1, 2010): 417–433; Stuart Levy and Bonnie Marshall, "Antibacterial Resistance Worldwide: Causes, Challenges and Responses," Nature Medicine 10 (2004): S122–S129.

[63] Davies and Davies, "Origins and Evolution of Antibiotic Resistance," op. cit.

[64] Heymann, "Resistance to Anti-Infective Drugs and the Threat to Public Health," op. cit.

[65] European Commission, "Antimicrobial Resistance," 2012, http://ec.europa.eu/health/antimicrobial_resistance/policy/index_en.htm.

[66] Levy and Marshall, "Antibacterial Resistance Worldwide," op. cit.

[67] The Economist, "Drugmakers and Antibiotics: The Path of Least Resistance," *The Economist*, May 12, 2012, http://www.economist.com/node/21554542.

[68] AVERT, "A Cure for AIDS," 2011, http://www.avert.org/cure-for-aids.htm.

[69] IFPMA, *Overview of Research-Based Pharmaceutical Industry Contributions to the Health-Related UN MDGs* (Geneva: International Federation of Pharmaceutical Manufacturers and Associations, September 2010),

Neglected Tropical Diseases

Neglected tropical diseases are a major public health problem, affecting nearly one billion people in lower-income countries. Many of these diseases, such as leprosy, lymphatic filariasis, and leishmaniasis, are endemic to rural areas of sub-Saharan Africa and poor urban settings in low-income countries in Asia and Latin America. The effects of these diseases are often severe, causing long-term disability, disfigurement, and impaired childhood growth as well as fatalities. As recently as 2006, an estimated 534,000 annual deaths were attributed to neglected tropical diseases.[70]

Decades-long research bottlenecks and funding deficits have led to a gap in effective treatments and prophylactics. But geographic and disease-specific challenges are pushing the R&D pharmaceutical industry to develop new therapeutics and vaccines.

Many neglected tropical diseases disproportionally affect children, so one research priority is to develop vaccines that give them immunity. There are 11 vaccines in development against diseases of the developing world (DDW); five of these are for malaria,[71] which accounts for over 650,000 deaths each year.[72]

Major scientific breakthroughs in recent years have led to the development of new vaccines that are specifically adapted to diseases and strains dominant in developing countries. One such disease, pneumococcal disease, is responsible for 18% of child deaths in developing countries, killing more than half a million children under the age of five every year through infections like pneumonia, meningitis, or sepsis.[74] There are over 90 strains of bacterium responsible for the disease, and, prior to the 2011 launch of a pneumococcal conjugate vaccine specifically developed to reflect the serotypes circulating in developing countries, the only vaccine available was for strains circulating in developed countries.[75]

An important obstacle to developing vaccines for these diseases is that many are very complex and require significant attention to basic research to understand the disease mechanisms. Malaria, an illness caused by Plasmodium parasites, is a case in point.

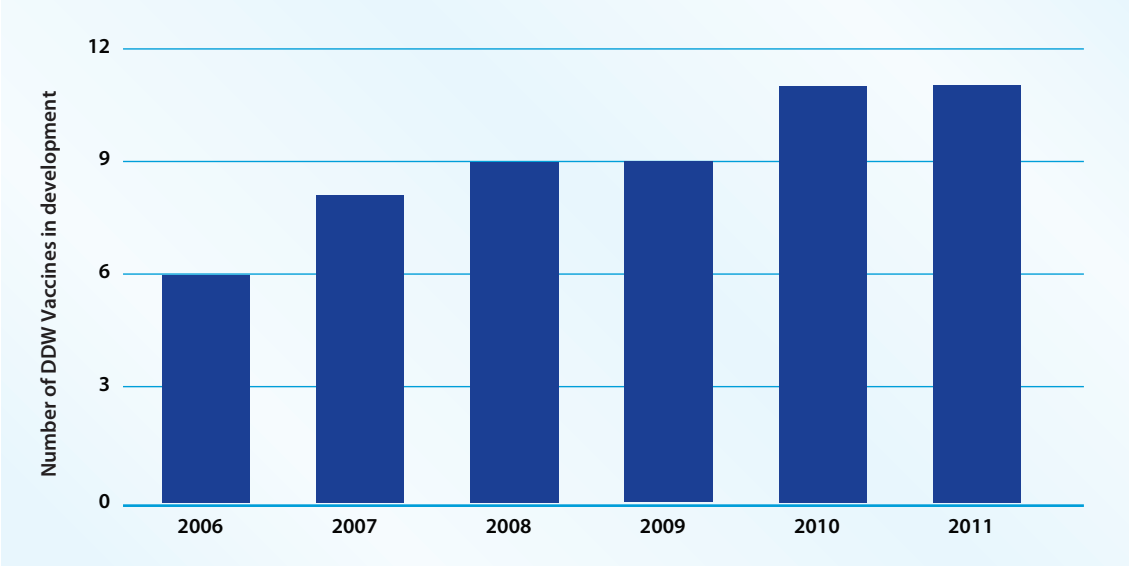


Chart 6: Number of vaccines in development for diseases of the developing world (DDW), 2005-2011.[73]

[70]World Health Organization, *Neglected Tropical Diseases: Hidden Successes, Emerging Opportunities* (Geneva: World Health Organization, 2006).

[71]IFPMA, *Pharmaceutical Industry R&D for Diseases of the Developing World: Status Report* (Geneva: International Federation of Pharmaceutical Manufacturers and Associations, November 2011), http://www.ifpma.org/fileadmin/content/Global%20Health/NTDs/Status_RnD_for_DDW_Nov2011.pdf.

[72]World Health Organization, "Malaria," Fact Sheet No. 94, April 2012, http://www.who.int/mediacentre/factsheets/fs094/en/.

[73]IFPMA, *Pharmaceutical Industry R&D for Diseases of the Developing World: Status Report* (Geneva: International Federation of Pharmaceutical Manufacturers and Associations, November 2011), http://www.ifpma.org/fileadmin/content/Global%20Health/NTDs/Status_RnD_for_DDW_Nov2011.pdf.

[74]Anjali Nayar, "Pneumococcal Vaccine Rolls Out in Developing World," *Nature*, February 11, 2011, http://www.nature.com/news/2011/110211/full/news.2011.89.html.

[75]GAVI Alliance, *Pneumococcal Disease Fact Sheet* (Geneva: GAVI Alliance, 2011), http://www.gavialliance.org/library/publications/gavi-fact-sheets/factsheet--pneumococcal-disease/.

Malaria is preventable through the use of effective control interventions such as bed nets and insecticide spraying. The disease is curable with currently available therapeutics, but developing a vaccine is seen as the only way to provide truly broad-based protection to vulnerable populations by limiting transmission of the parasite.

Until recently, a vaccine had seemed out of reach because the Plasmodium parasite has a complex life cycle and uses a variety of strategies to hide from the immune system by taking shelter inside human cells.[76] However, collaboration between the PATH Malaria Vaccine Initiative and GlaxoSmithKline has helped bring to Phase III of clinical trials a candidate vaccine that uses weakened whole parasites. Contrary to previous attempts to develop malaria vaccines, which were subunit vaccines, the use of whole parasites has allowed researchers to break the cycle of infection.[77]

A number of concurrent challenges exist in the development of therapeutic medicines for neglected tropical diseases. Some diseases, such as dengue, simply lack any kind of treatment, while a host of others – including leishmaniasis and sleeping sickness – have treatments developed many years ago that are characterized by difficulty of administration, severe side-effects, lengthy treatment duration, and parasitic resistance. For example, older treatments for leishmaniasis require 15-30 days of hospital-based parenteral (artificial feeding) or intravenous treatment.[79] Ongoing development of oral treatments is expected to reduce the amount of time patients need to spend away from work and family.

The research-based pharmaceutical industry has been a leader in funding neglected disease R&D, contributing 16.4% of the global research total. The pharmaceutical industry was the only sector in 2010 to not decrease its funding levels.[80]

There are currently 374 medicines and vaccines[81] in the pipeline for diseases disproportionately affecting developing countries.[82] However, three disease areas - malaria, tuberculosis, and HIV – account for 58% of total products in the pipeline. This lopsided funding is expected to change as the research-based pharmaceutical industry has dedicated increased resources to other neglected tropical diseases.

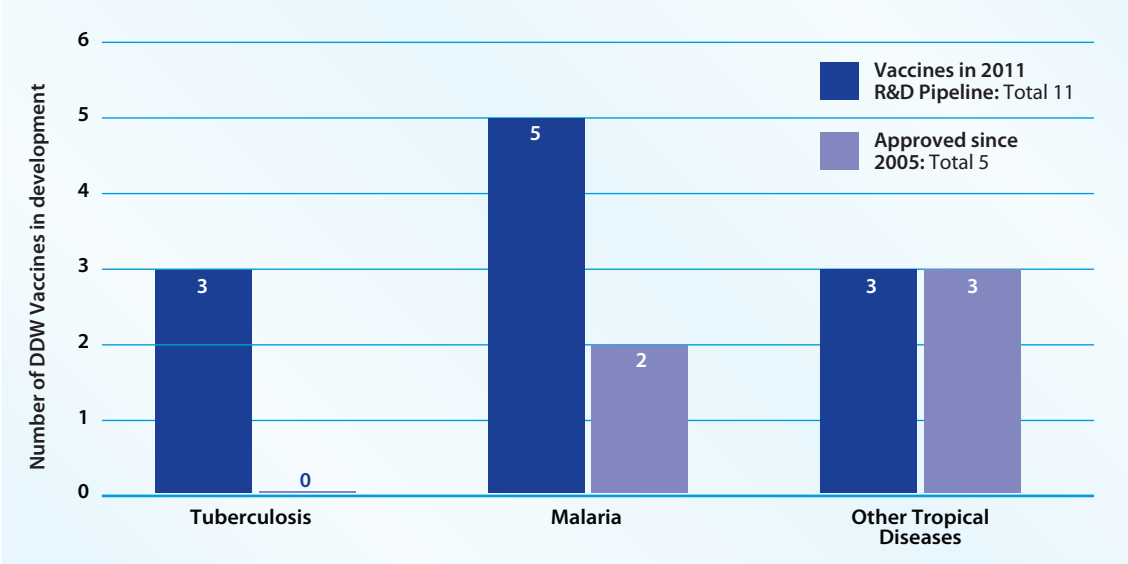


Chart 7: Number of vaccines in development and approved for particular developing world diseases.[78]

[76]Chrissie Giles, "Why Don't We Have a Malaria Vaccine?" Wellcome Trust, 2005, http://malaria.wellcome.ac.uk/doc_WTX033040.html.

[77]GlaxoSmithKline, "First Results from Ongoing Phase III Trial Show Malaria Vaccine Candidate, RTS,S* Reduces the Risk of Malaria by Half in African Children Aged 5 to 17 Months," Press Release, October 18, 2011, http://www.gsk.com/media/pressreleases/2011/2011-pressrelease-676305.htm.

[78]IFPMA, *Pharmaceutical Industry R&D for Diseases of the Developing World Status Report* (Geneva: International Federation of Pharmaceutical Manufacturers and Associations, November 2011).

[79]IFPMA, *Pharmaceutical Industry R&D for Diseases of the Developing World: Status Report*, op. cit.

[80]Mary Moran et al., *Neglected Disease Research and Development: Is Innovation Under Threat?* (London: Policy Cures, December 2011), http://www.policycures.org/downloads/g-finder_2011.pdf?bcsi_scan_9688b637a46568db=0&bcsi_scan_filename=g-finder_2011.pdf.

[81]173 products were medicines (46% of all products) and 201 products were vaccines (54% of all products).

[82]Elizabeth Ponder and Melinda Moree, *Developing New Drugs and Vaccines for Neglected Diseases of the Poor* (San Francisco: BIO Ventures for Global Health, March 2012), http://www.bvgh.org/LinkClick.aspx?fileticket=h6a0cJK9drg%3d&tabid=91.

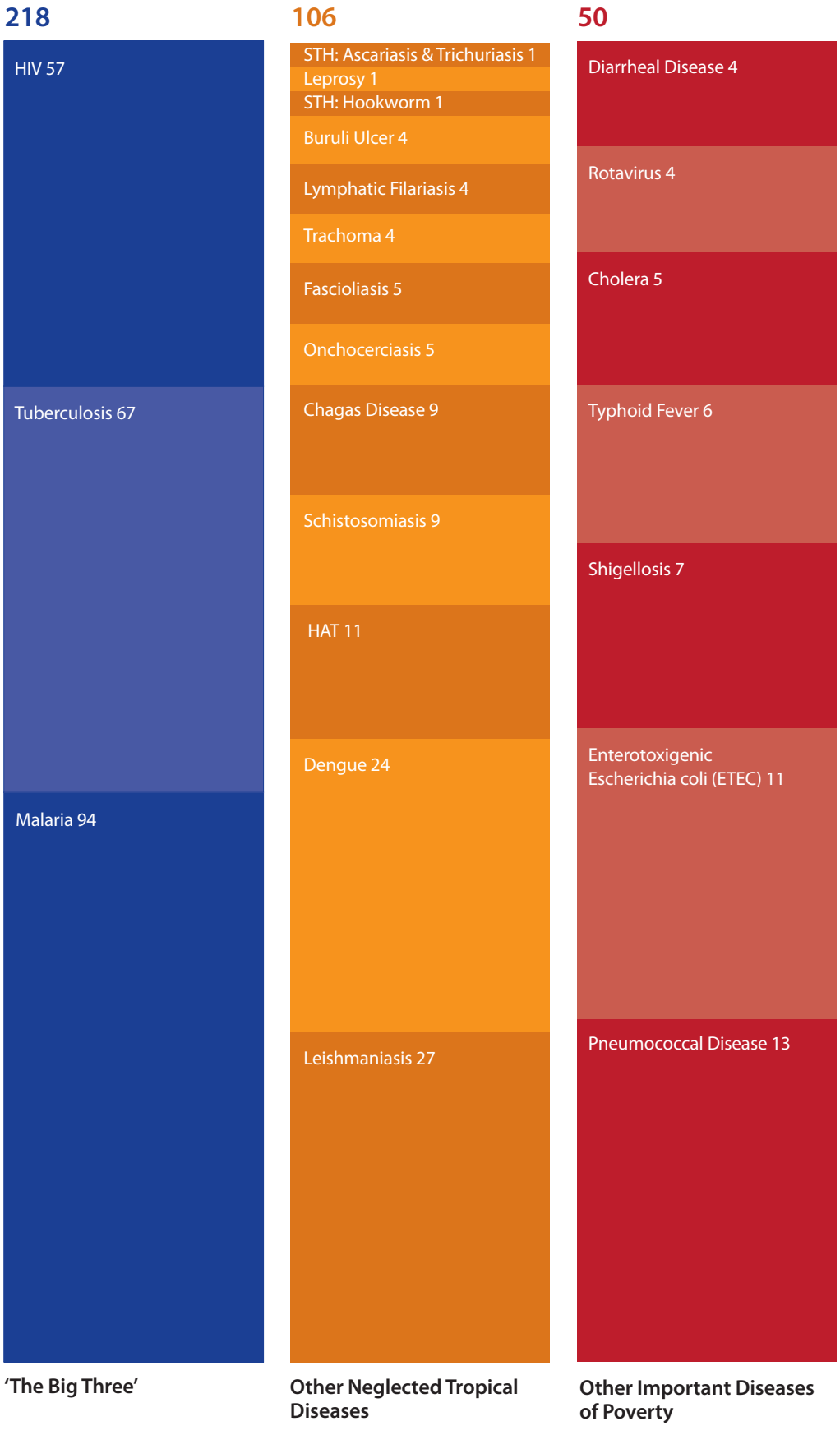


Figure 10: Overview of R&D activity by disease area.[83]

[83]Ibid.

Most notably, the research-based pharmaceutical industry has signed onto the 2012 London Declaration on Neglected Tropical Diseases, which targets the nine neglected tropical diseases[84] that represent over 90% of the global NTD burden. Working in partnership with the Bill & Melinda Gates Foundation, the US and UK governments, international organizations, and endemic countries' national governments, the research-based pharmaceutical industry is allocating substantial resources to tackle these diseases. In addition to its sizeable commitment to donate more than 14 billion treatments over the ten years from 2011to 2020, the industry has pledged to boost partnerships and increase funding to support disease elimination or control.[85]

Further evidence of the industry's commitment is the creation of various research centers targeting neglected tropical diseases. Many centers create R&D interfaces between public and private stakeholders, while other companies integrate such R&D within their own organization.

WIPO Re:Search – a consortium of public and private sector organizations

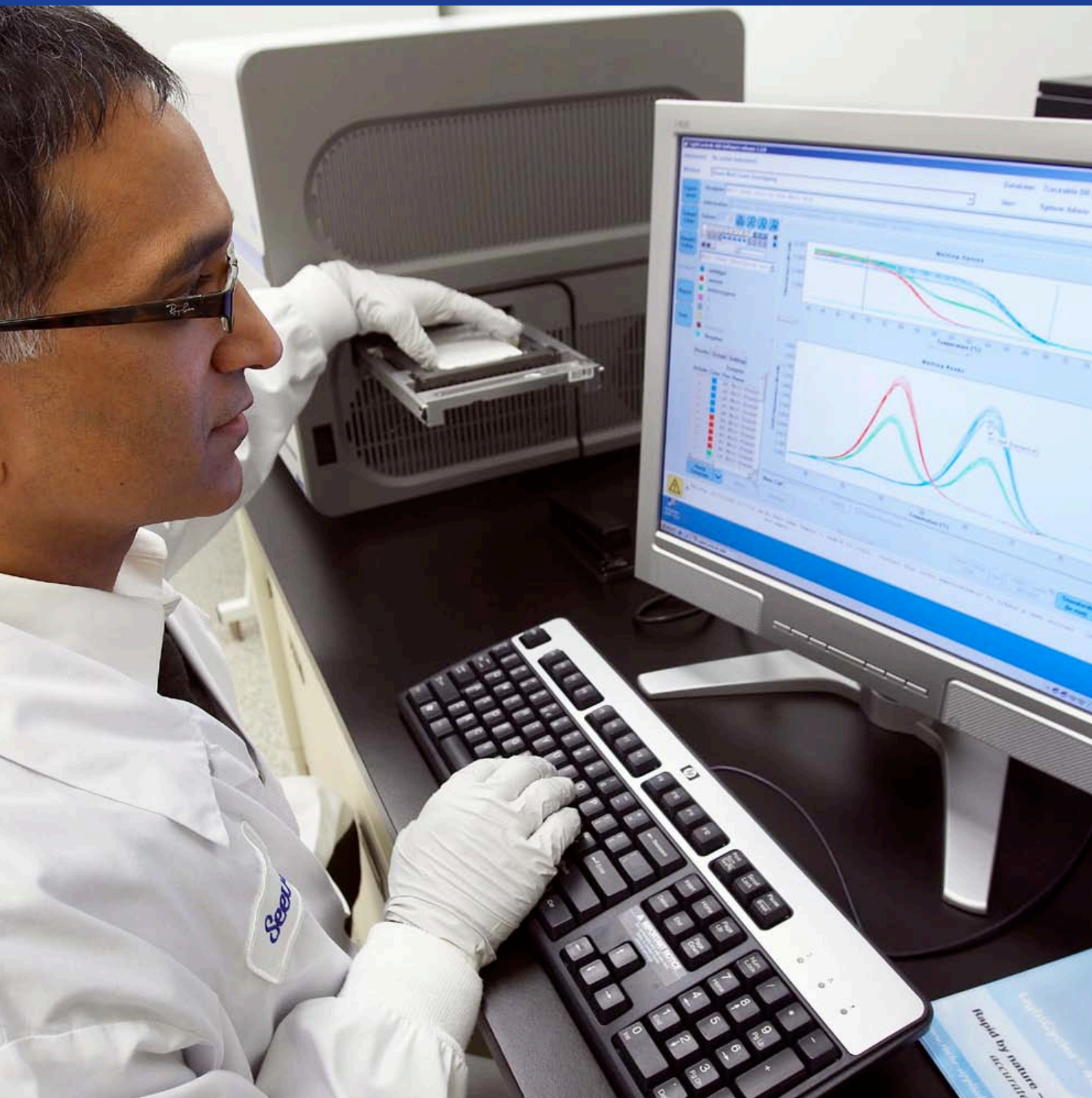
Recognizing the need for more progress in neglected disease research, WIPO Re:Search was formed in 2011 through the efforts of several of the world's leading pharmaceutical companies, the World Intellectual Property Organization (WIPO), and BIO Ventures for Global Health. WIPO Re:Search provides access to intellectual property for pharmaceutical compounds, technologies, and – most importantly – know-how and data available for research and development for neglected tropical diseases, tuberculosis, and malaria. By providing a searchable, public database of available intellectual property assets and resources, WIPO Re:Search is facilitating new partnerships to support organizations that conduct research on treatments for neglected tropical diseases, ultimately improving the lives of those most in need.

More information at: http://www.wipo.int/research/en.

[84]The nine neglected tropical diseases responsible for over 90% of the disease burden are onchocerciasis, human African trypanosomiasis, Chagas disease, lymphatic filariasis, soil-transmitted helminthiases, schistosomiasis, leprosy, fascioliasis, onchocerciasis, and blinding trachoma.

[85]IFPMA, *Research-Based Pharmaceutical Industry Pledges 14 Billion Treatments to Help End Nine Neglected Tropical Diseases* (Geneva: International Federation of Pharmaceutical Manufacturers and Associations, January 2012), http://www.ifpma.org/fileadmin/content/News/2012/IFPMA_Ending_neglected_tropical_diseases_January2012.pdf.

Fostering an Innovating Environment



Fostering an Innovating Environment

Medical advances are the fruit of innovation ecosystems that have helped nurture innovation in a high-risk industry. Innovation cannot happen without a number of enabling conditions, such as access to the best and brightest minds, political and financial stability, and a regulatory framework that protects and rewards innovation. All countries have the potential to foster innovation and improve the functioning of the innovation process.[86]

Governments can help address systemic failures that lead to disadvantages in the R&D process. A recent study suggested that developing countries are well positioned to take action because innovation is stimulated by early institution of national models that link various stakeholders.[87] In fact, four of the top ten countries on the "Global Innovation Index" are lower-middle-income countries.[88]

One way to foster a country's innovation investment potential is to balance "push" and "pull" factors.[89] Push factors are domestic supply-side inputs, such as workforce talent and capital market access. Pull factors include systemic considerations, such as stable political governance, intellectual property systems, and regulatory reviews.[90] Together, a balance of push and pull factors yields an enabling innovation environment.

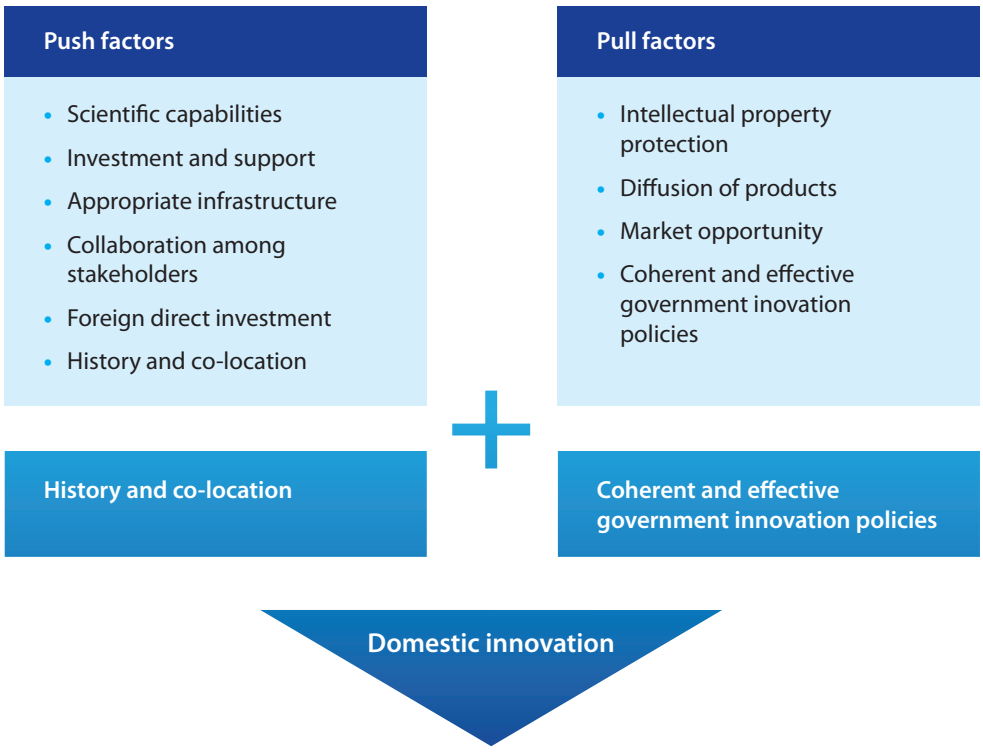


Figure 11: Factors for an enabling innovation environment.[91]

[86]Soumitra Dutta (ed.), The Global Innovation Index 2012: Stronger Innovation Linkages for Global Growth (Fontainebleu, France: INSEAD, 2012), http://www.globalinnovationindex.org/gii/GII%202012%20Report.pdf.

[87]INSEAD, "Release of The Global Innovation Index 2012: Switzerland Retains First-Place Position in Innovation Performance," press release, July 3, 2012, http://insead-global-innovation-index-2012.blogspot.co.uk/p/press-release.html.

[88]Ibid.

[89]Charles River Associates, Policies that encourage innovation in middle-income countries (Boston, MA: Charles River Associates, 2012).

[90]Ibid.

[91]Ibid.

Domestic Innovation Factors

Governments have a range of policy incentives at their disposal to attract, retain, and foster domestic innovation. Effective policies can help bridge private, public, and academic resources by steering research efforts towards particular disease areas. The following are examples of enabling innovation policies.

Political Stability, Good Governance and Transparency

There is a strong correlation between innovation capacity, political stability, and good governance. Predictable policy-making, particularly in relation to industrial and healthcare policy, helps encourage innovative pharmaceutical companies to enter domestic markets by reducing investment risk. Good governance can prepare and facilitate open market entry and create a stable environment for innovation.

Appropriate Capital Markets

Access to adequate capital markets is a major determinant of whether companies will have enough resources to invest in innovation. Research and development in the pharmaceutical industry are particularly expensive and require significant investments over long periods to pay for high standards of quality and safety controls, good manufacturing practices, and sophisticated human capital.

Companies need to know that they can access both domestic and foreign sources of investment. To compensate for the long time-horizons and high risks of pharmaceutical research and development, governments can reduce capital risk by giving incentives, such as tax breaks, reducing or removing tariff barriers for imported materials for medicine manufacture, and instituting clear and consistent rules for both foreign and domestic investors.[92]

Academic Centers and Skilled Workforce

Innovation stems from knowledge; education and human capital are at the heart of all research and development projects. Countries with strong education systems also tend to have strong research and development sectors and high levels of innovation. Germany, for example, became a leader in pharmaceutical innovation in the early twentieth century due to a strong cluster of universities that led in the important fields of organic chemistry, pharmacology and bacteriology.[93]

Investment in education and the capacity to carry out research have become particularly important as research and development have become more globalized. Information and communication technologies enable researchers to collaborate remotely with each other or work on projects in countries other than their own.

Investment in all levels of education can help promote long-term innovation. An exchange of scholars has been particularly important in building knowledge networks. Supportive government policy is crucial in ensuring the free movement of scientists and other experts.

Because of its dependence on access to the best and brightest minds, the research-based pharmaceutical industry has been an important player in building human capital in low- and middle-income countries by supporting research centers, providing scholarships, and training professionals in areas such as international quality control standards.

[92]See, e.g., the "zero-for-zero" initiative in the Uruguay Round of the World Trade Organization, http://www.ustr.gov/trade-topics/industry-manufacturing/industry-initiatives/pharmaceuticals.

[93]Basil Achilladelis and Nicholas Antonakis, "The Dynamics of Technological Innovation: The Case of the Pharmaceutical Industry," *Research Policy* 30, no. 4 (April 2001): 535–588.

The TDR Clinical Research Career Development Professional Program

On-the-job experience is invaluable for students going into biopharmaceutical research and development careers. Aided by the Bill & Melinda Gates Foundation, seven pharmaceutical companies are hosting researchers from low- and middle-income countries on specialized clinical research training programs in diseases as varied as cancer, Chagas, dengue, malaria, and sleeping sickness. After completion of their fellowships, researchers return to their home country equipped to assume leading research roles in the effort to develop new vaccines and therapeutics.

More information at: http://partnerships.ifpma.org.

Sound Regulatory Standards

The research-based pharmaceutical industry is highly regulated throughout its innovation, manufacturing, and distribution pipelines. The goal of such regulations is to ensure the well-being of patients through a high level of safety, quality, and efficacy of the medicines produced. During the R&D phase, governments require innovator companies to regularly submit scientific data sufficient to demonstrate the safety and efficacy of a medicine before it is approved for sale. Once all the information is submitted, appropriate national authorities determine whether the medicine may enter the national market.

Effective regulation should not stunt innovation, but provide guidelines to aid in designing and executing the R&D process. If these guidelines are not clear, innovation and manufacturing processes may be hampered because researchers often do not know in advance whether their efforts will yield a market-ready medicine. Uncertainty is expensive and inefficient. As described in previous sections, the industry is subject to many uncertainties; regulatory ambiguity should not be one of them.

Regulatory capacity is often a factor when determining domestic market-entry options. One way for governments to attract industry investment is to adopt international or stringent regulatory standards. Such standards strive to ensure certainty and efficiency. For example, the US Food and Drug Administration (FDA) oversees all medicine approvals in the United States. Like many national regulatory bodies, it requires predictable data submissions throughout the R&D, manufacturing and distribution processes. In addition, the FDA provides assistance in navigating regulatory requirements by establishing satellite offices in countries with high concentrations of pharmaceutical R&D and manufacturing activity. In fact, foreign companies account for a significant share of the FDA's new drug applications in antiretroviral and anti-malarial therapeutic classes.

Data Exclusivity

In order to determine safety, quality, and efficacy, regulatory authorities rely on data submissions from innovator applicants. Data submissions often parallel the R&D process; research data showing safety and efficacy of new molecules, formulations, and indications are submitted throughout all phases of R&D. Researchers do not know in advance whether their work will result in a marketable medicinal product, but even "unsuccessful" R&D work (that does not lead to a market-ready product) may eventually be rethought and further investigated to produce a new medicine. Thus the R&D data and supporting material submitted to regulatory authorities are a form of intellectual property. Without adequate safeguards, other parties could receive a competitive advantage by using innovator-created regulatory data.

Many governments have regulatory safeguards to give innovators – data-generating applicants – time to recoup R&D expenses. During this period of data exclusivity, non-innovators cannot use these data as a basis for regulatory applications. Data exclusivity relieves innovative companies of some economic risks associated with R&D. In addition, governments can encourage certain research areas through data exclusivity policy, for example, by varying data exclusivity periods according to the underlying indications affected by the innovator's application. In the United States, data exclusivity can be granted for 180 days for abbreviated new drug applications (generic market entry), five years for new chemical entities (innovator market entry), seven years for medicines affecting rare diseases (orphan diseases), and twelve years for biotherapeutic market entry.[94] In this manner, governments can encourage R&D efforts directed at particular diseases or conditions.

United States	Canada	European Union	Chile	Egypt	Japan
5 or 12 years	8 years	10 years	5 years	5 years	8 years[95]

Table 3: Data exclusivity period for innovator products in various countries.[96]

[94]US Food and Drug Administration, "Small Business Assistance," 2012, http://www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/default.htm .

[95]In Japan, data exclusivity is referred to as "re-examination." That period is assigned to medicinal products with new active ingredients based on Pharmaceutical and Food Safety Board (PFSB) Notification No. 0401001, April 1, 2007.

[96]*IFPMA, Data Exclusivity: Encouraging Development of New Medicines* (Geneva: International Federation of Pharmaceutical Manufacturers and Associations, 2011), http://www.ifpma.org/fileadmin/content/Publication/IFPMA_2011_Data_Exclusivity__En_Web.pdf.

Intellectual Property Protection

Intellectual property protection mitigates the scientific, regulatory, and economic risks of pharmaceutical innovation (including discovering new compounds, improving formulations, and discovering new compound interactions) because inventors are afforded time to recoup R&D investments and, more importantly, sunk costs associated with research. Sunk costs are investments for specific R&D stream that do not produce a marketable product. Companies may abandon development of a product for various reasons, such as inadequate regulatory data, scientific hurdles, and commercial viability. As with all endeavors into the unknown, pharmaceutical innovation requires adequate certainty to allow inventors to enjoy the fruits of their labor when their products prove to be successful. Intellectual property rights ensure sustainable innovation in light of considerable risks of failed research attempts.

Both research failures and successes contribute to the progress of science. Industry can overcome great scientific challenges because even though a particular research stream might not produce a marketed product, it nonetheless provides clues for future improvement. Unsuccessful research attempts (not materializing in a marketed product) are the basis of scientific inquiry. The knowledge and know-how acquired is often useful in other R&D projects. Pharmaceutical innovation, in other words, is an iterative process with no guarantees of market success.

Intellectual property rights of a successful product must enable companies to sustain the R&D investments needed for pharmaceutical innovation. The contemporary approach to pharmaceutical research, through networks and partnerships, allows companies to benefit from the expertise developed by various research groups. A specific R&D project can be sourced to a number of teams, working in-house or in other organizations. However, in and out licensing of technologies requires a certain level of economic and legal certainty. Sound intellectual property policies help alleviate some of this uncertainty.

Intellectual property may take several forms, including patents, copyrights, trademarks, and trade secrets. The underlying goal of most intellectual property is twofold: to promote innovation through securing exclusive rights for a limited time, and to disseminate knowledge to the public through incentives for inventors to disclose their inventions. Patent protection, for example, requires inventors to fully disclose their inventions in a manner sufficient to enable others to use the technology. In return, inventors receive exclusive rights relating to that invention for a set period. At the expiration of a patent term, anyone can practice the invention as originally described.

Pharmaceutical patenting activity usually parallels the innovation process. Early phase R&D often leads to filing patent applications relating to novel compounds. As those compounds progress to preclinical and clinical trial phases, patenting activity shifts to formulations and delivery mechanisms. Even after market approval, post marketing surveillance provides opportunities to explore additional formulations to broaden therapeutic classes. As such, domestic patent policies should reflect the varying activities during pharmaceutical R&D, including discovering new compounds, improving formulations and delivery mechanisms, and discovering new compound interactions.

In addition, patent terms should recognize pharmaceutical R&D timelines and regulatory obligations, because time is a costly commodity when preparing for market entry. To a certain extent, data exclusivity alleviates some of this pressure, but in many circumstances a significant lead time between patent filing and regulatory approval still exists. For example, a patented active ingredient may become an approved medicine about 10-15 years after the patent was filed. Recognizing this disparity, some governments have provided mechanisms to retrieve time lost to delays. Restoration of patent terms due to regulatory delay, sometimes referred to as patent term extension (PTE), is one mechanism, applicable only for inventions that are subject to regulatory market approval, like pharmaceuticals and agro-chemicals.[97] In addition to other limitations, a patent term will be extended when regulatory approval is unusually delayed, which would otherwise unfairly cut into a patent term. "Normal" regulatory approval timeframes are determined according to the regulated field.

Similarly, market exclusivity may be affected by delays due to overburdened patent- granting authorities. Some countries have adopted mechanisms to restore patent terms due to granting authority delays, sometimes referred to as patent term adjustment (PTA). Like patent term extension, PTA also extends a patent term, but is only applicable to delays attributed to a patent-granting authority. "Normal" examination timeframes are determined by the appropriate authority.[98]

Harmonized patent laws and rules provide a level of certainty that is useful in planning domestic patenting options. Internationally, the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) of the World Trade Organization (WTO) lays the minimum foundation for sound domestic intellectual property policy.[99] Part II, section 5, of TRIPS outlines WTO members' threshold patenting requirements and obliges them to grant a patent when certain enumerated requirements are met.[100] Thus patents must involve subject matter that is "new, involves an inventive step, and [is] capable of industrial application." Certain patent requirements are left to domestic discretion. For example, TRIPS allows WTO members to exclude from patentability any subject matter where preventing the commercial exploitation of that invention "is necessary to protect public order or morality."[101] However, so long as the subject matter is patent eligible, not subject to any exclusion, and meets patentability requirements, a patent must be granted.

Another consideration in determining an environment's innovation capacity is the ability to enforce intellectual property rights. As with intellectual property protection, enforcement requires easily accessible guidelines on how to seek and what to expect from various enforcement options. For the most part, TRIPS maintains certain enforcement thresholds, but WTO members are free to implement those requirements as they wish, as long as they are complementary to TRIPS. As with intellectual property protection, enforcement seeks to balance two goals, enabling intellectual property owners to enforce their rights against infringing acts while maintaining affordable administrative costs. To this end, enforcement mechanisms should be readily available, predictable, and domestically uniform. Domestic uniformity reduces costs and increases certainty because potential parties can compare the merits of their case to past decisions. In turn, domestic uniformity supports predictable outcomes, weeding out non-meritorious claims early in the enforcement process.

Intellectual property policies should be flexible enough for jurisdictions to proactively anticipate changes in public need. As mentioned earlier in this section, TRIPS lists certain minimum requirements, leaving implementation to WTO member states. In addition, however, TRIPS incorporates considerable flexibility in relation to protection, enforcement, and matters not covered by the agreement. For example, WTO members can include certain limited exceptions to rights conferred by TRIPS. In particular, Article 31 of TRIPS provides that WTO members may permit the use of an invention without the authorization of the right-holder, under certain defined circumstances; such unauthorized use is generally referred to as a "compulsory license."

[97] US Food and Drug Administration, "Small Business Assistance," op. cit.

[98] US Patent and Trademark Office, "Patent Term Adjustment (PTA) Questions and Answers," 2012, http://www.uspto.gov/patents/law/aipa/pta/index.jsp.

[99] Agreement on Trade-Related Aspects of Intellectual Property Rights, http://www.wto.org/english/docs_e/legal_e/27-trips.pdf.

[100] Ibid.

[101] TRIPS, Part II, Section 5, Article 27, Clause 2.

Compulsory licenses are sometimes misunderstood and seen as a solution to problems relating to access to medicines in developing countries. However, while possible under TRIPS, compulsory licenses are an option intended only for use in extraordinary circumstances. They are not a sustainable solution to access problems. Rather, routine use of them could discourage introduction of new medicines to meet patient needs. Moreover, frequent use of compulsory licenses weakens the intellectual property framework and thereby undermines the incentive system that underpins the ability of the private sector to undertake essential R&D. Compulsory licenses are less effective than other access initiatives, including negotiation between the patent holder and licensee. Unlike compulsory licensing, voluntary agreements disseminate not only underlying technologies, but expertise and know-how.

History has demonstrated that compulsory licenses are seldom used because other mechanisms facilitate medicines procurement in a more efficient and sustainable manner.[102] Local manufacturers are always free to approach intellectual property holders to negotiate particular production licenses. If appropriate circumstances exist, voluntary licenses typically include agreements to share information beyond patent coverage and technical experience. Another possible mechanism is a non-assertion declaration of intellectual property rights. This option is similar to voluntary licensing, but instead of active involvement by an innovator company, an agreement is reached that intellectual property rights will not be asserted provided that certain criteria, like product quality and geographical distribution, are met.

Access to medicines in developing countries is also furthered by tiered pricing policies and various product donation programs. Tiered pricing enables companies to deliver medicines at reduced prices in a sustained manner. In part, this model is feasible because pharmaceutical companies can use economies of scale to distribute costs equitably: medicines may be available to low-income countries at a fraction of the price charged in high-income countries. Such a model is also highly dependent on strong enforcement of intellectual property rights, for example, to prevent diversion of products from low-income markets to higher-income markets where such goods command a higher price.

Pharmaceutical companies are also engaged in product donation programs. These programs have proven to be most useful in situations of immediate need or when disease eradication is feasible.[103] For example, in January 2012, 13 pharmaceutical companies pledged to donate an average of more than 14 billion treatments by 2020 to eliminate or control the diseases that represent 90% of the global neglected tropical disease burden.[104]

All of these mechanisms are methods to ensure sustained medicines access, whereas compulsory licenses apply only to very particular and narrow circumstances.

In any event, a sound intellectual property environment attracts innovation because it provides innovators with a level of much-needed certainty. A domestic intellectual property system should include readily accessible laws, rules, and policies relating to procedural and substantive mechanisms for protecting and enforcing intellectual property. Innovators benefit from such transparency because economic and legal risks are much reduced. Domestic jurisdictions benefit from solid innovation environments because they attract investment, knowledge, and know-how to their economies.

[102] Tim Wilsdon et al., *Evidence on Access to Essential Medicines for the Treatment of HIV/AIDS* (London: Charles River Associates, October 2011).

[103] IFPMA, *Ending Neglected Tropical Diseases*, op. cit.

[104] IFPMA, *The Changing Landscape on Access to Medicines* (Geneva: International Federation of Pharmaceutical Manufacturers and Associations, 2012), http://www.ifpma.org/fileadmin/content/Publication/2012/ChangingLandscapes-Web.pdf.

Supplemental Policies

Recently, much attention has been devoted to exploring alternative innovation incentives.[105] Generally, these models build upon existing intellectual property policies and apply to discrete phases within the innovation cycle. Many of these models complement the industry's innovation ecosystem by fostering collaborations with stakeholders in various phases of R&D. For example, open compound databases, research grants, R&D prizes, regulatory incentives and product development partnerships have been explored to incentivize and stimulate early- and late-stage molecular discovery and development. Each model requires a sound intellectual property environment in order to succeed. In fact, any individual model is rarely employed in isolation because each incentive serves a distinct purpose that acts as a springboard for innovation.

Open compound databases provide users with access to proprietary compound databases or libraries within specific technological areas. Such databases are especially useful when research groups seek additional technologies to complement their own work. When a promising technology is identified, a licensing agreement may be entered into with the "donating" user. These agreements are usually royalty-free and are designed to benefit both users.

Research grants are generally sponsored by governments or philanthropic organizations. In many cases, grants are narrowly focused on particular research areas. Most grants aim to provide an early source of R&D start-up capital, thereby enabling innovative discoveries. However, grants generally do not sustain research investment beyond the initial R&D. Grants are most useful in "proving" the commercial feasibility of academic endeavors. If research passes this threshold, other mechanisms can be available for moving into later phases of R&D. For example, researchers may rely on intellectual property assets to attract funding, partners, and commercialization networks.

Historically, the US National Institutes of Health has been the largest global funder of basic research on neglected tropical diseases, providing almost 50% of global discovery and pre-clinical funding.[106] Over the last decade alone, this has totaled USD $12.7 billion.[107] More recently, other philanthropic organizations, including industry-led initiatives, have emerged as major funding sources for neglected disease research. One-third of all funding for tropical disease research comes from industry and philanthropic initiatives.[108]

R&D prizes are almost the opposite of research grants. Instead of providing R&D investment, prizes act as "carrot" mechanisms to incentivize final technology development. The prize is only available when the parameters of the prize are met, in the form of a finished product. This product may be a biomarker, molecule, or fully developed medicine. However, prizes do not address the need for R&D investment. The success of any given prize, therefore, depends on its limitations and requirements.

Regulatory agencies may be a source of innovation incentives. As previously outlined, sound regulations can focus R&D efforts on particular disease areas by providing exclusivity rights, tax incentives, and expedited clinical trial assistance. Two programs–one in the US and the other in the European Union (EU)–have been particularly successful in focusing R&D efforts on areas of rare disease, referred to as "orphan diseases."

[105] See, e.g., World Health Organization's Consultative Expert Working Group on Research and Development: Financing and Coordination (CEWG), http://www.who.int/phi/news/cewg_2011/en/.

[106] Moran et al., *Neglected Disease Research and Development: Is Innovation Under Threat?*, op. cit.

[107] Global Health Technologies Coalition, *Saving Lives and Creating Impact: Why Investing in Global Health Research Works*, op. cit.

[108] Moran et al., *Neglected Disease Research and Development: Is Innovation Under Threat?*, op. cit.; Mary Moran et al., *Neglected Disease Research and Development: Is the Global Financial Crisis Changing R&D?* (London: Policy Cures, 2010), http://policycures.org/downloads/g-finder_2010.pdf.

During the first decade of the EU program 62 treatments have been designated as orphan drugs, whereas only eight orphan drugs were approved before 2001.[109] Before the launch of the US Orphan Drugs Program in 1983, there were only 10 medicines marketed for rare disease indications; between 1983 and 2011, over 392 received marketing approval, representing new treatment options for more than 200 rare diseases.[110] Today, there are over 460 medicines for orphan diseases currently in the development pipeline; in 2011 alone, 11 new medicines were made available for rare diseases such as the genetic defect congenital factor XIII deficiency, several cancers, and scorpion poisoning.[111] The success of these programs has led to proposals that similar incentives be offered for therapies to treat developing world diseases.

Product development partnerships (PDPs) have become the most ubiquitous mechanism for incentivizing research into diseases affecting developing countries. PDPs bring together diverse collaborators from private, public, and non-profit sectors to bridge R&D funding gaps. The goal is to combine industry expertise with local know-how to bring advanced R&D, manufacturing, and distribution capacity to developing countries. Sixteen PDPs were founded between 1999 and 2003, and the Global Funding of Innovation for Neglected Diseases (G-FINDER) survey now counts at least 18 of these partnerships.[112] After little more than 15 years in existence, PDPs are addressing many of the major neglected diseases.

Contrary to many other funding mechanisms, PDPs can operate at all stages of the R&D process. Various PDPs have been instrumental in early-stage molecule discovery, platform and infrastructure capacity building, aiding regulatory approval, and distributing medicines.[113] Like all supplemental incentives, PDP success often relies on an enabling innovation environment.

In all, the research-based pharmaceutical industry has played a leading role in global health innovation. By investing in human resources and cutting-edge technologies, the industry has developed thousands of new medicines and vaccines to improve patients' quality of life.

Improved technical capacity and knowledge about disease mechanisms have allowed innovative companies to broaden their research platforms and address a wider selection of disease areas. In the light of growing scientific and regulatory challenges, the industry has repositioned its research model to focus on collaboration with global partners. This network approach to innovation is fostering more extensive knowledge sharing and joint problem solving, while increasing R&D efficiency and flexibility.

As many commentators have pointed out, low- and middle-income countries are well positioned to promote and foster an innovative industry presence because they are starting from a clean "slate." Domestic policies can be planned and adopted proactively; for example, regulatory provisions may be synchronized with intellectual property rights, and private sector input can help shape academic concentrations.

[109]Meir Perez Pugatch, Rachel Chu, and David Torstensson, *Assembling the Pharmaceutical R&D Puzzle for Needs in the Developing World: An Assessment of New and Proposed Delinking Initiatives Aimed at Encouraging R&D into Neglected and Tropical Diseases and Specific Type II Diseases*, op. cit.

[110]Ibid.

[111]PhRMA, 2012 *Pharmaceutical Industry Profile*, op. cit.

[112]Moran et al., *Neglected Disease Research and Development: Is Innovation Under Threat?*, op. cit.

[113]Perez Pugatch, Chu, and Torstensson, *Assembling the Pharmaceutical R&D Puzzle for Needs in the Developing World*, op. cit.

About the IFPMA

IFPMA represents the research-based pharmaceutical companies and associations across the globe. The research-based pharmaceutical industry's 1.3 million employees research, develop and provide medicines and vaccines that improve the life of patients worldwide. Based in Geneva, IFPMA has official relations with the United Nations and contributes industry expertise to help the global health community find solutions that improve global health.

IFPMA manages global initiatives including: IFPMA Developing World Health Partnerships, which studies and identifies trends for the research-based pharmaceutical industry's long-term partnership programs to improve health in developing countries; IFPMA Code of Practice, which sets standards for ethical promotion of medicines; IFPMA Clinical Trials Portal, which helps patients and health professionals find out about on-going clinical trials and trial results.

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