


Biopharmaceutical Research & Development:

The Process Behind New Medicines



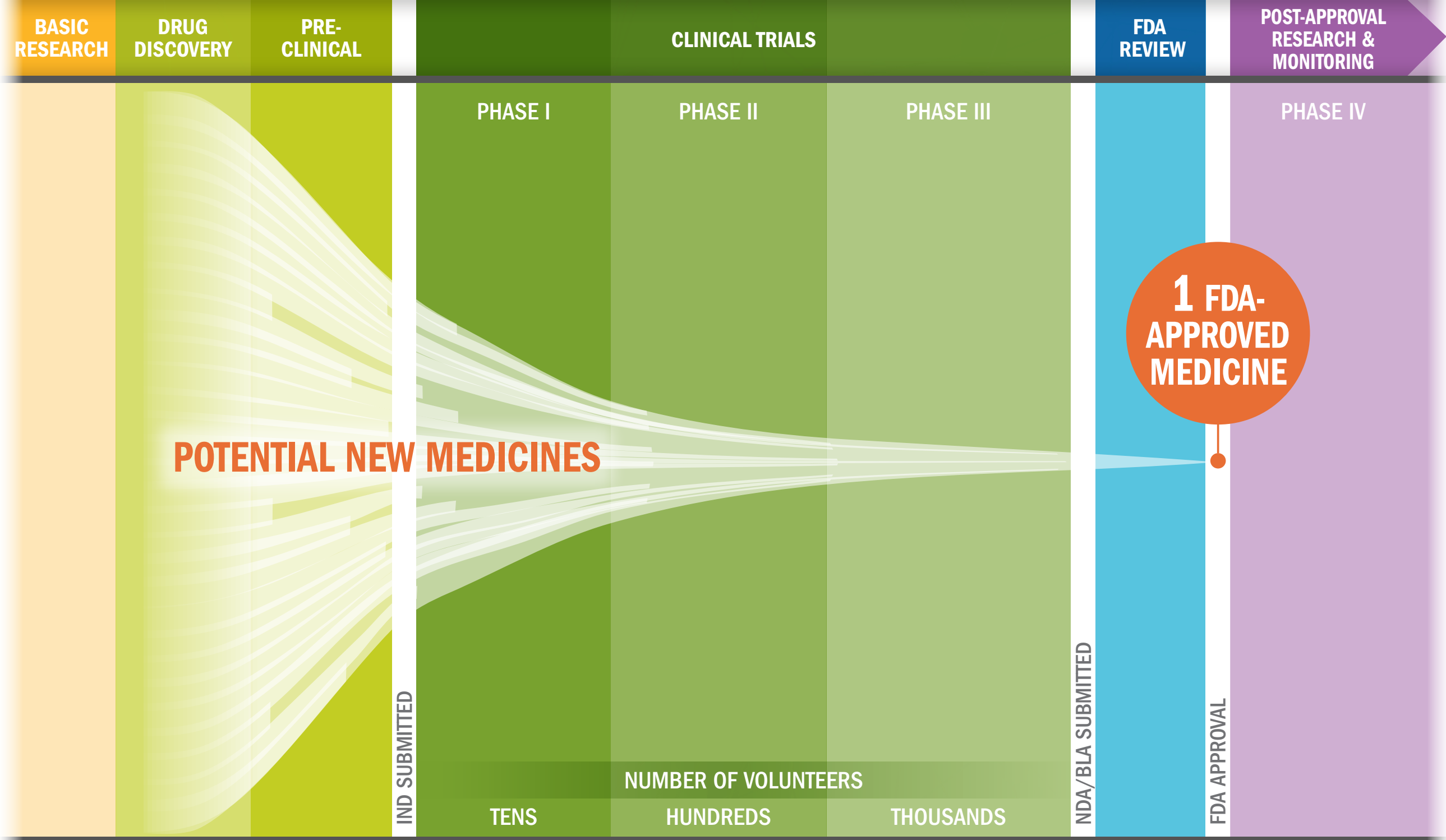


“OUR INDUSTRY IS POISED TO TRANSLATE
OUR MOST PROMISING SCIENTIFIC
BREAKTHROUGHS INTO MEANINGFUL
TREATMENTS CAPABLE OF TACKLING THE MOST
URGENT AND VEXING MEDICAL CHALLENGES
OF OUR TIMES. WE STAND COMMITTED TO
DRIVING PROGRESS FOR PATIENTS TODAY –
AND HOPE FOR TOMORROW.”


- KENNETH C. FRAZIER, CHAIRMAN & CEO, MERCK



THE BIOPHARMACEUTICAL RESEARCH AND DEVELOPMENT PROCESS



Key: IND: Investigational New Drug Application, NDA: New Drug Application, BLA: Biologics License Application



“TODAY, DELIVERING AUTHENTIC HEALTHCARE INNOVATION WORLDWIDE IS MORE CHALLENGING AND COMPLEX THAN EVER. IT DEMANDS A SHARP FOCUS ON WHAT CUSTOMERS NEED. IT REQUIRES THE DEVELOPMENT AND DELIVERY OF DATA, KNOWLEDGE AND PRODUCTS THAT MAKE A DIFFERENCE.”

- CLIVE A. MEANWELL, MD, PHD, CHAIRMAN & CEO,
THE MEDICINES COMPANY

Biopharmaceutical Research and Development

OVERVIEW

For patients, new medicines offer fewer side effects, fewer hospitalizations, improved quality of life, increased productivity, and importantly, extended lives. But developing medicines is a long, complex process.

The rapid pace of scientific advances is enabling a greater understanding of diseases at the molecular level. In turn, scientific, technical, and regulatory challenges related to drug development create complexities as companies often focus their R&D where the science is difficult and the failure risks are higher.

As a result, the process for researching and developing new medicines is growing in difficulty and length. On average, it takes at least ten years for a new medicine to complete the journey from initial discovery to the marketplace, with clinical trials alone taking six to seven years on average. The average cost to research and develop each successful drug is estimated to be **\$2.6 billion**. This number incorporates the cost of failures – of the **thousands and sometimes millions** of compounds that may be screened and assessed early in the R&D process, only a few of which will ultimately receive approval. The overall probability of clinical success (the likelihood that a drug entering clinical testing will eventually be approved) is estimated to be **less than 12%**.

While these numbers are daunting, a deeper understanding of the rigorous R&D process can explain why so many compounds do not make it and why it takes such a large, lengthy effort to get a new medicine to patients. Success requires immense resources – the best scientific minds, highly sophisticated technologies, ever-evolving manufacturing processes, and complex project management. It also takes persistence and, sometimes, luck. Ultimately, though, the process of drug discovery brings hope and relief to millions of patients.

The Discovery Process



The discovery process includes the early phases of research, which are designed to identify an investigational drug and perform initial tests in the lab. This first stage of the process takes approximately three to six years. By the end, researchers hope to identify a promising drug candidate to further study in the lab and in animal models, and then in people.

Pre-Discovery

UNDERSTAND THE DISEASE OR CONDITION

Recent advances in molecular medicine and powerful tools to enhance computational capacity are enabling researchers to better understand the inner workings of human disease at the molecular level. As our knowledge of disease increases, so does the potential of discovering and developing innovative medicines. Biopharmaceutical companies perform basic research independently and in partnership with researchers and others from across the biomedical research ecosystem, including disease foundations and patient groups, venture capital, and pre-competitive consortia.

“THE PROCESS OF MAKING A NEW MEDICINE IS A MARATHON THAT REQUIRES ENDURANCE AND COMMITMENT. WE CANNOT REACH OUR GOALS WITHOUT THE HELP OF PARTNERS FROM INSIDE AND OUTSIDE THE COMPANY.”

- TADATAKA YAMADA, MD, CHIEF MEDICAL & SCIENTIFIC OFFICER, TAKEDA

Personalized Medicine



Advancements in science and technology are changing the way we define disease, develop drugs and prescribe treatments. Armed with a greater understanding of disease biology, it has become evident that a patient's response to treatment—with respect to both safety and efficacy—is greatly dependent upon his or her molecular profile and genetic makeup.

The promise of personalized medicine (or precision medicine) is to get the right treatment to the right patient at the right dose the first time, through the use of molecular diagnostic tests and targeted therapies. Personalized medicines can potentially offer patients faster diagnoses, fewer side effects and better outcomes.

These advances offer great promise, but also add complexity to the R&D process. In order to ensure the safety and efficacy of personalized therapies that are used alongside diagnostics, clinical trial protocols must be modified and enhanced. This may entail the use of additional procedures and resources, as well as new or innovative forms of data collection. Additionally, by their very nature, the patient population identified to respond to targeted therapies is narrower, which makes patient recruitment more difficult.

Despite these challenges, America's biopharmaceutical companies are committed to advancing personalized medicines. In fact, a recent industry survey revealed that 42% of new medicines in the pipeline have the potential to be personalized medicines.

Building on Setbacks



As researchers and scientists investigate new compounds, they are building off of a growing body of evidence that has accumulated over time, illuminating pathways of disease and providing insight into the optimal drug targets.

Along the way, investigators uncover important milestones that may lead to new treatments, but there are also often many dead ends and setbacks, which may lead researchers down a new route, or force them to take a step back. While these stumbling blocks can be disappointing, they are an integral part of a complex research and development process; both the setbacks and successes provide invaluable knowledge that help guide and direct researchers to get one step closer to the next advance.

“THE SCIENTIFIC PROCESS IS THOUGHTFUL, DELIBERATE, AND SOMETIMES SLOW, BUT EACH ADVANCE, WHILE HELPING PATIENTS, NOW ALSO POINTS TOWARD NEW RESEARCH QUESTIONS AND UNEXPLORED OPPORTUNITIES.”

- CLIFFORD A. HUDIS, MD, MEMORIAL SLOAN KETTERING CANCER CENTER

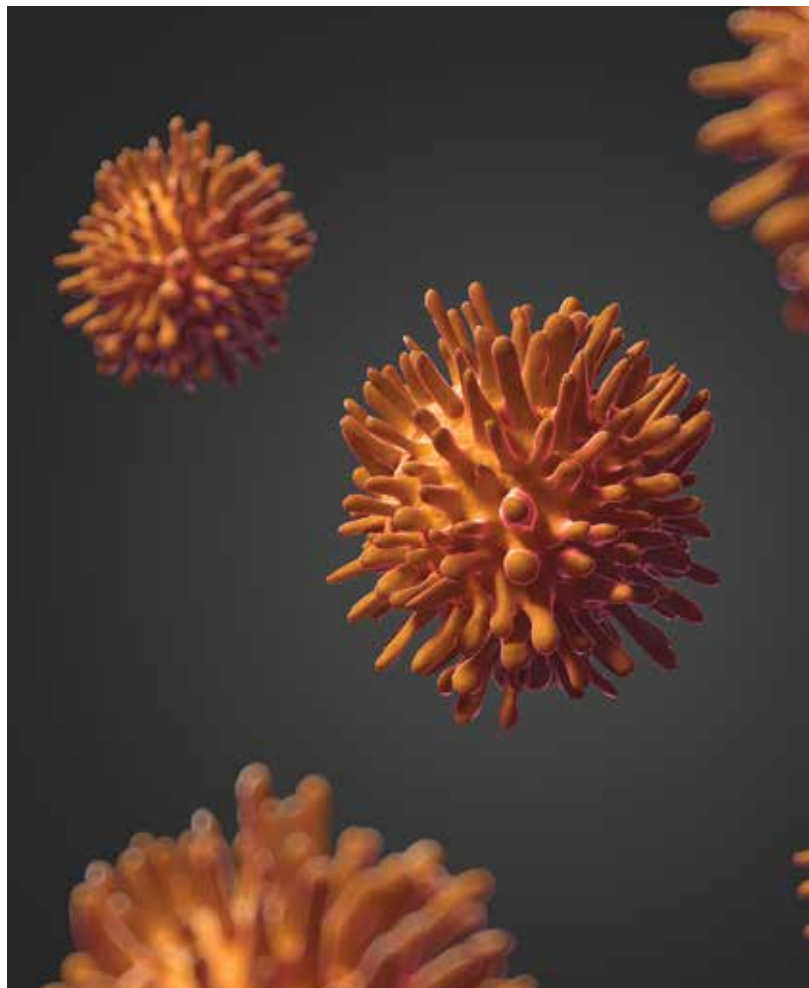
“THE JUXTAPOSITION OF NEW INSIGHTS INTO HUMAN BIOLOGY, COUPLED WITH THE APPLICATION OF NEW TOOLS AND ADVANCED TECHNOLOGIES, HAS THE POTENTIAL TO REVOLUTIONIZE OUR BUSINESS MORE IN THE NEXT DECADE OR TWO THAN IN THE PAST FIVE!”

- JOHN C. LECHLEITER, PHD, CHAIRMAN, PRESIDENT, & CEO, ELI LILLY & COMPANY

Target Identification and Validation

CHOOSE A MOLECULE TO TARGET WITH A DRUG

Armed with an idea, researchers work to identify biological targets for a potential medicine. A drug target is a molecular structure in the body that, when it interacts with a potential drug compound, produces a clinical effect (treatment or prevention of a disease, for example). The investigators conduct studies in cells, tissues and animal models to determine whether the target can be influenced by a medicine. Target validation is crucial to help scientists identify the most promising approaches before going into the laboratory to develop potential drug candidates, increasing the efficiency and effectiveness of the R&D process.



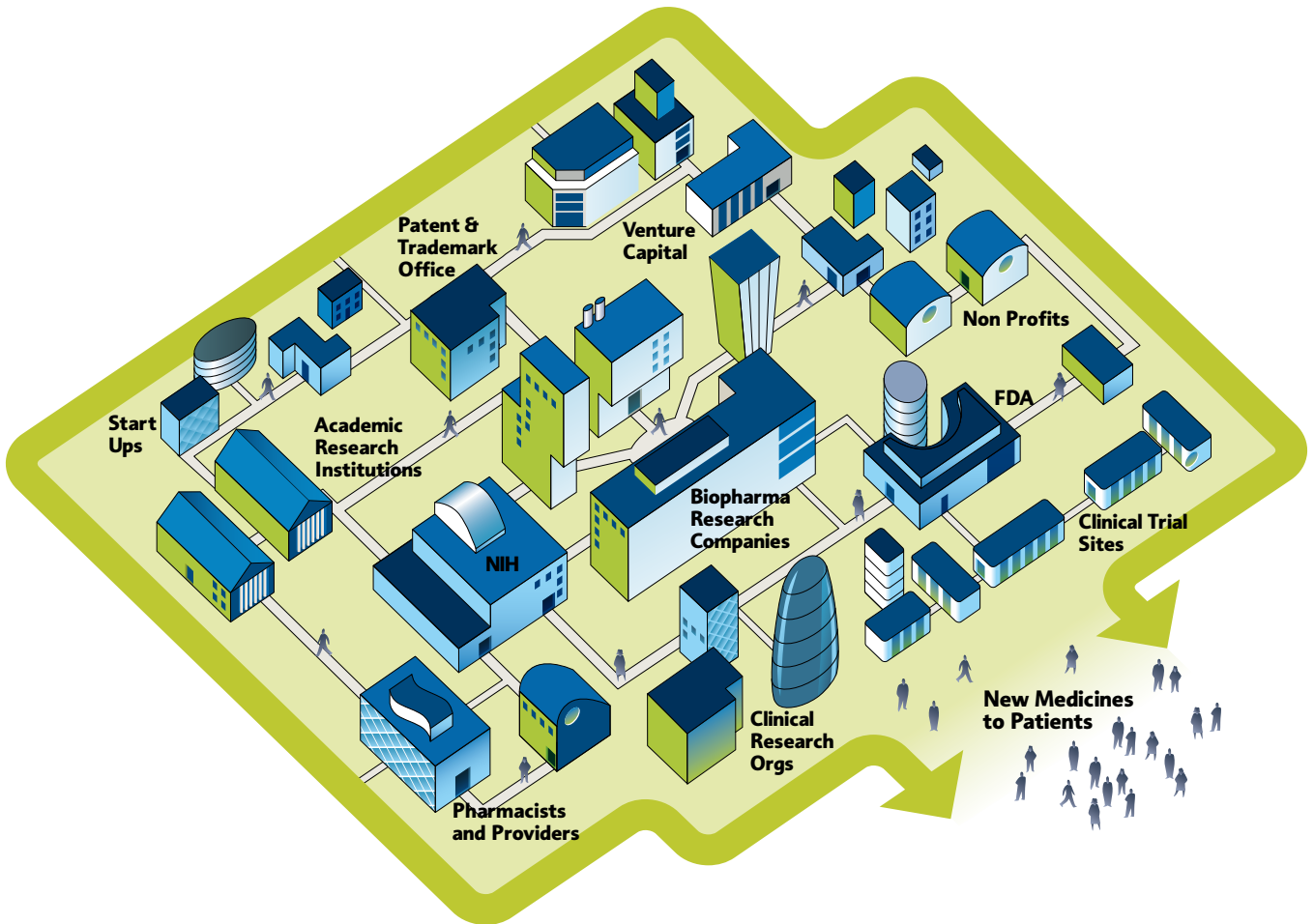
Drug Discovery

FIND A PROMISING MOLECULE (A “LEAD COMPOUND”) THAT COULD BECOME A NEW MEDICINE

After learning more about the underlying disease pathway and identifying potential targets, researchers then seek to narrow the field of compounds to one lead compound – a promising molecule that could influence the target and, potentially, become a medicine. They do this in a variety of ways, including creating a molecule from living or synthetic material, using high-throughput screening techniques to select a few promising possibilities from among thousands of potential candidates, identifying compounds found in nature, and using biotechnology to genetically engineer living systems to produce disease-fighting molecules.

Even at this early stage, investigators are already thinking about the final product, and how it will be administered to patients (for example, whether it is taken in pill form, injected, or inhaled). In turn, they must also consider the formulation (the design of dosage forms) of a medicine and how easily it can be produced and manufactured.

Biopharmaceutical R&D Ecosystem: Delivering New Medicines to Patients



“TODAY, MOST IMPORTANT DEVELOPMENTS IN MEDICAL SCIENCE TYPICALLY BEGIN IN LABORATORIES, SUCH AS THE DISCOVERY OF SPECIFIC NEW BIOLOGICAL MOLECULES, PROCESSES, OR PATHWAYS, OR INNOVATIVE APPLICATIONS OF EXISTING KNOWLEDGE. IN MOST CASES, THESE DISCOVERIES IN AND OF THEMSELVES HAVE LIMITED EFFECT BEYOND MEETING A FAIRLY NARROW RESEARCH GOAL. THEIR REAL IMPACT FOR PUBLIC HEALTH GENERALLY COMES AFTER SEVERAL MORE SIGNIFICANT STEPS - INCLUDING FURTHER R&D, TESTING, APPROVAL BY APPROPRIATE REGULATORY BODIES (SUCH AS THE FDA), MANUFACTURING, AND DISTRIBUTION.”

- NATIONAL INSTITUTES OF HEALTH, OFFICE OF TECHNOLOGY TRANSFER

The Biopharmaceutical Research Ecosystem Drives Innovation



The close and synergistic relationship between sectors in the biopharmaceutical research ecosystem is among our greatest strength in ensuring a robust national biomedical research capacity, making the United States the worldwide leader in biopharmaceutical innovation. Drug discovery and development occurs as a result of many forms of collaboration, with learnings emerging from many disciplines as the result of multiple feedback loops.

Biopharmaceutical companies have formed a growing number of formal and informal partnerships with researchers in government, academic, patient and disease groups, and others in the biomedical ecosystem. Each partner brings different strengths and expertise to the partnership but all have the same goal of improving health outcomes for patients in the United States and around the world. Partnerships range from basic research, to identifying drug targets, to collaborations around innovative clinical trials.

While the basic science providing a foundation to discover and develop drugs is often initiated in academia, industry often partners and contributes to basic research. It is primarily the biopharmaceutical industry where the crucial disciplines of medicinal chemistry, process chemistry and formulation, drug metabolism and pharmacokinetics, and safety sciences are practiced at a scale and level of integration necessary in order to bring a new medicine to the patients that need them. Studies that document the complementary roles of the public and private sectors have demonstrated that between 67% and 97% of drug development is conducted by the private sector.

The Importance of Strong Intellectual Property Protections



Intellectual property (IP) protections provide incentives for companies to make the long, costly investments that lead to medical advances and balances those with the desire for increased competition by timely entry of generics and biosimilars. Strong IP protections, in the form of patents and exclusivity, provide the opportunity for companies to potentially recoup investments made to develop new medicines and to fund future research.

Patents grant inventors the exclusive right with respect to their inventions without others being able to copy and sell it for a set period of time. Data exclusivity (DE)* runs concurrently with patents and prohibits third parties for a set period of time from using or relying upon an innovator's valuable clinical data to obtain FDA approval for their product.

There are also two key targeted incentives:

- Under the Best Pharmaceuticals for Children Act, companies can receive an additional six months of exclusivity upon the completion and submission of pediatric studies that meet the terms of a written request from FDA.
- Under the Orphan Drug Act, seven years of market exclusivity (i.e., another product for same disease or condition cannot be approved during the seven years) is available to the first sponsor obtaining FDA approval of a designated drug to treat a rare disease or condition

*FDA grants five years of DE after initial approval for small molecule drugs (new chemical entities); up to three years for new uses or other conditions of use; and twelve years for biologic medicines.

Early Safety Tests

PERFORM INITIAL TESTS ON PROMISING COMPOUNDS

Establishing the safety of a drug before use in humans begins early in the development process, as lead compounds go through a series of tests to provide a preliminary assessment of safety. Scientists assess how the body processes the investigational compound, also referred to as pharmacokinetics. They also evaluate the impact the investigational compound has on various functions within the body, or the pharmacodynamics.

Successful drugs must be:

- absorbed into the bloodstream,
- distributed to the proper site of action in the body,
- metabolized efficiently and effectively,
- successfully excreted from the body, and
- demonstrated to be not toxic in the tests performed.

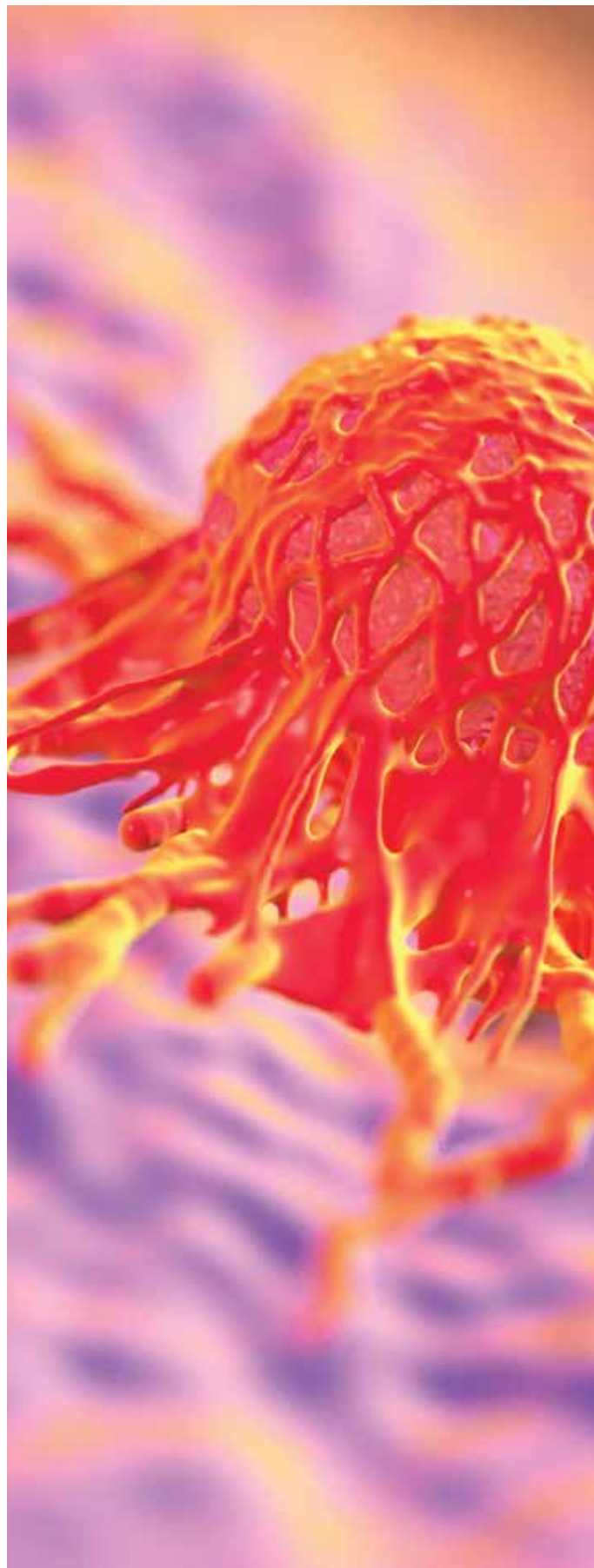
Normally performed in living cells, in animals and via computational models, these studies help researchers prioritize lead compounds early in the discovery process.

Lead Optimization

ALTER THE STRUCTURE OF LEAD CANDIDATES TO IMPROVE PROPERTIES

Lead investigational compounds that survive the initial screening are then “optimized,” or altered to make them more effective and safer. By changing the structure of a compound, scientists can give it different properties. For example, they can make a compound less likely to interact with other chemical pathways in the body, thus reducing the potential for side effects.

Hundreds of different variations or “analogues” of the initial leads are produced and tested. The resulting compound is the candidate drug which will undergo years of further testing and analysis before potentially being reviewed and assessed for approval by the U.S. Food and Drug Administration (FDA).





Preclinical Testing

LAB AND ANIMAL TESTING TO DETERMINE IF THE DRUG IS SAFE FOR HUMAN TESTING

With one or more lead compounds identified, researchers turn their attention to extensive testing to determine if they are ready to be studied in humans.

Scientists carry out both *in vitro* and *in vivo* tests. *In vitro* tests are experiments conducted in the lab (“*vitro*” is “glass” in Latin) and *in vivo* studies are those in living cell and tissue cultures and animal models (“*vivo*” is “life” in Latin). Through these techniques, scientists work to understand how the drug works and what the potential side effects on humans might be. The FDA requires extremely thorough preclinical testing before the candidate drug is allowed to be studied in humans.

During this stage scientists also must determine how to make large enough quantities of the drug to use in clinical trials. Techniques for making a drug on a small scale to use in this preclinical stage may not translate easily to larger production. Production of the medicine will need to be scaled up even more if it is approved for use in the general patient population.

After starting with thousands of candidate compounds, preclinical testing is used to identify one or more lead compounds that will go on to be studied in clinical trials.

“OUR PROGRAMS FOCUS ON INNOVATIONS THAT WILL DELIVER HIGHLY IMPACTFUL THERAPIES, WHETHER IN ORPHAN DISEASES, OR IN SETTINGS WHERE WE CAN DRIVE MAJOR SHIFTS IN THERAPEUTIC BENEFIT IN FAVOR OF PATIENTS. WE ARE APPLYING DISRUPTIVE TECHNOLOGIES, COUPLED WITH DEEP CLINICAL INSIGHTS TO WAGE CAMPAIGNS IN DISEASE SETTINGS WHERE THE UNMET NEED IS GREATEST.” ”

- THOMAS DANIEL, MD, EVP AND PRESIDENT OF GLOBAL RESEARCH AND EARLY DEVELOPMENT, CELGENE

Adapting to Increased Uncertainty



As our scientific understanding advances, revealing the underlying complexities of disease, clinical trials have also become more complex. Planning and executing a clinical trial is an extremely rigorous process, with more procedures required, more data collected, and more numerous eligibility criteria for study enrollment than ever before. For example, the average form used to collect data for each patient expanded in length by 227% between 2000 and 2011, reflecting the growing challenges of conducting clinical trials.

Many factors contribute to the increasing challenges and costs of developing medicines, including:

- Changing science – researchers are targeting more complex diseases where the science is difficult and failure risks higher
- Increasing regulatory requirements
- More testing against comparator drugs
- Increased challenges related to clinical trial recruitment and retention
- Larger clinical trial sizes
- Greater focus on targeting chronic and degenerative diseases

The biopharmaceutical industry is approaching these challenges head on, continually adapting to produce innovative treatments more efficiently. Researchers are exploring ways to reduce development times and increase the odds of success using new research models, new clinical trial designs and methodologies, innovative approaches to patient recruitment, and sophisticated methods of analyzing data.

Clinical Trial Success Depends on Volunteers



An incredible amount of planning goes into the design and conduct of each clinical study. Outlined in the protocol are plans for all aspects of the trial from data collection methods to the timing of dosing to safety measures. None of this plan can go forward, though, without the volunteers who participate in the research studies.

In many early clinical studies, healthy volunteer participants are essential in order for researchers to confirm that the candidate medicine can be safely tolerated.

In later studies, clinical trials enroll patients who have the condition that the medicine is designed to address: their participation is crucial, so researchers can evaluate the effectiveness of the medicine, and understand if adjustments in dosing and timing are needed.

It can take months, or even years, to recruit and enroll volunteers to participate in studies, and recruitment is a particular challenge for trials focused on rare diseases and pediatric indications. It can be difficult to find volunteers for clinical trials, as there are often specific requirements for enrollment, based on the nature of the condition being studied and the patient group that is expected to benefit from the new medicine. Likewise, many people are not aware of the opportunities they might have to participate in a trial. Patients choose to participate for many different reasons, including the desire to get the most cutting edge care available and to help advance science.

The Development Process

A close-up photograph of a male scientist in a white lab coat and safety glasses, looking intently at a piece of laboratory equipment. He is wearing blue gloves. The background is a blurred laboratory setting with various pieces of equipment and containers.

“PATIENTS MAKE AN INCREDIBLE CONTRIBUTION WHEN THEY CHOOSE TO PARTICIPATE IN A CLINICAL TRIAL. WE ARE ACTIVELY FINDING WAYS TO HELP MINIMIZE BURDEN ON THESE PATIENTS AND MAKE OUR STUDIES MORE PATIENT-FRIENDLY, FROM MAKING STUDY PARTICIPATION LOCATIONS MORE CONVENIENT TO USING INNOVATIVE DIGITAL TOOLS TO COLLECT DATA AND SHARE INFORMATION”

- CRAIG LIPSET, HEAD OF CLINICAL INNOVATION, PFIZER

A candidate drug must go through extensive studies in humans and demonstrate that it is safe and effective before receiving approval from the FDA. This process involves three phases of clinical trials, each with its own specific goals and requirements. Companies identify physician researchers to conduct the research and work with them to carry out the procedures of each trial according to a detailed plan, or protocol.

The clinical trials process is both expensive and time-consuming, and ends more often in failure than success. Less than 12% of the candidate medicines that enter clinical testing make it to approval. From start to finish, the clinical development phase takes an average of six to seven years. There are many people involved in the process, including doctors, nurses, lab technicians, clinical trial support team members, and clinical trial managers, among others.

Clinical trials are a significant undertaking, requiring extensive infrastructure, investment, careful regulation, safety measures, and coordinated planning across stakeholders, as well as regulators at the FDA. The biopharmaceutical industry accounts for the vast majority of investment into clinical trials and related activities; in 2013 alone, biopharmaceutical companies sponsored 6,199 trials across the U.S. involving 1.1 million participants.

Investigational New Drug Application and Clinical Trial Planning

FILE IND WITH THE FDA BEFORE CLINICAL TESTING CAN BEGIN; ENSURE SAFETY FOR CLINICAL TRIAL VOLUNTEERS

Before any clinical trial can begin, companies must file an investigational new drug (IND) application with the FDA. The application includes the results of the preclinical work, the candidate drug's molecular structure, details on how the investigational medicine is thought to work in the body, a listing of any potential side effects as indicated by the preclinical studies, and manufacturing information. The IND also provides a detailed clinical trial plan that outlines how, where and by whom the studies will be conducted.

All INDs are submitted to the FDA and proceed after 30 days if there is no additional feedback or restriction given from the agency.

In addition to the IND application, all clinical trials must be reviewed, approved and monitored by the institutional review board (IRB) or ethics committee (EC) at the institutions where the trials will take place. The IRB/EC has the responsibility to protect research participants, and has the right to disapprove the study protocol or require changes before approving the planned clinical trials and allowing any participants to enroll. This process includes the development of appropriate informed consent documents, which will be required from all clinical trial participants.

The clinical trial research team, including the nurses and clinical investigators, continually monitor trial participants and collect data that will be carefully reviewed and tracked by the company supporting the research. Whenever a volunteer in the trial experiences a serious adverse drug reaction, the company sponsoring the research must provide a report of the event to the FDA and the IRB. The FDA or the company can stop the trial at any time if problems arise. In some cases, a study may be stopped because the candidate drug is performing so well that it would be unethical to withhold it from the patients in the trial who are not receiving the candidate drug and the company may accelerate development. Companies also ensure that the trials are conducted correctly and with integrity, and that clinical trial results are publicly disclosed at the appropriate time.



Innovative Trial Designs and Methodologies



Innovative study designs and methodologies are transforming the way clinical research is conducted. In adaptive clinical trials, for example, researchers use accumulating data to modify aspects of the study (e.g., dosing, sample size, patient population) as it is under way, without undermining the validity and integrity of the trial, or having to redo the trial or conduct an additional study.

Many new approaches for clinical trials are using novel drug development tools, such as biomarkers, to identify patients that may respond to a therapy. Basket studies in oncology, for example, identify a common genetic mutation across a variety of cancer types and enroll patients whose tumors have that mutation, regardless of the type of cancer they have, to test the effect of a single medicine. Conversely, umbrella studies test the impact of different medicines on different genetic mutations within a single type of cancer.

Innovative trial designs are capitalizing on the rapid pace of science, providing the possibility for researchers to shorten trials, improve success rates and increase the efficiency of clinical research.

Industry's Clinical Trial Principles



PhRMA member companies have a longstanding commitment to sponsoring clinical research that fully complies with all legal and regulatory requirements, as well as international agreements. In addition, PhRMA has set out voluntary principles reflecting member companies' commitment to the highest standards for ethics and transparency in the conduct of clinical trials.

PhRMA's *Principles on the Conduct of Clinical Trials and Communication of Clinical Trial Results* are designed to help ensure that clinical research conducted by America's biopharmaceutical companies continues to be carefully conducted and analyzed, and that the resulting information is communicated to health care professionals and patients in a way that is informative and meaningful.

“A CRITICAL PART OF THE DISCOVERY PROCESS IS CLINICAL RESEARCH, THE STUDY OF AN INVESTIGATIONAL DRUG OR MEDICAL DEVICE IN HUMAN VOLUNTEERS. IN SPONSORING AND CONDUCTING CLINICAL RESEARCH, PHRMA MEMBERS PLACE GREAT IMPORTANCE ON RESPECTING AND PROTECTING THE SAFETY OF EVERYONE WHO VOLUNTEERS TO PARTICIPATE.”

- WILLIAM CHIN, MD, EVP OF SCIENTIFIC & REGULATORY AFFAIRS, PHRMA

Phase I Clinical Trial

INITIAL SAFETY TESTING IN A SMALL GROUP OF HEALTHY VOLUNTEERS

In Phase I trials the candidate drug is tested in people for the first time. These studies are usually conducted with a small number of healthy volunteers, generally 100 or less. The main goal of a Phase I trial is to assess the safety of the medicine when used in humans. Researchers look at the pharmacokinetics of a drug: How is it absorbed? How is it metabolized and eliminated from the body? They also study the drug's pharmacodynamics: Does it cause side effects? These closely monitored trials are designed to help researchers determine what the safe dosing range is and if the candidate medicine should move on to the next stage of development.

Phase II Clinical Trial

ASSESS SAFETY AND EFFICACY IN A SMALL GROUP OF PATIENTS

In Phase II trials researchers evaluate the candidate drug's effectiveness in 100 to 500 patient volunteers with the disease or condition under study. Many Phase II trials study patients receiving the drug compared with patients receiving a different treatment, either an inactive substance (placebo), or a different drug that is usually considered the standard of care for the disease. Researchers also analyze optimal dose strength and schedules for using the drug and examine the possible short-term side effects (adverse events) and risks associated with the drug. If the drug continues to show promise, they prepare for the much larger Phase III trials.

Phase III Clinical Trial

DEMONSTRATE SAFETY AND EFFICACY IN A LARGE GROUP OF PATIENTS

Phase III trials generate statistically significant data about the safety, efficacy and the overall benefit-risk relationship of the investigational medicine. Phase III trials may enroll 1,000 to 5,000 patients or more across numerous clinical trials sites around the world. This phase of research is essential in determining whether the drug is safe and effective. It also provides the basis for labeling instructions to help ensure proper use of the drug (e.g., information on potential interactions with other medicines, specific dosing instructions, etc.)

Phase III trials are both the costliest and longest trials, often encompassing hundreds of study sites at hospitals and centers both across the U.S. and around the world. Coordinating all the sites and the data coming from the clinical trial sites is a monumental task. Companies must coordinate closely with staff at each trial site, as well as with the IRB/EC that is monitoring the study and the FDA. Often, a clinical research organization (CRO) will work with a company to aid in recruitment and day-to-day operations of the trial.

In addition, the company's manufacturing scientists are working to ensure high quality production of the medicine for use in the trials, as well as planning for the full-scale production of the medicine after approval. Meanwhile, the company is working to assemble and prepare the complex application required for FDA approval.



Regulatory Review and Approval

FDA Review and Approval of Marketing Application

EVALUATION OF COMPLETE DATA SETS AND PROPOSED LABELING AND MANUFACTURING PLANS

After determining that the results of the clinical trials indicate the compound is both safe and effective, the sponsoring company submits a new drug application (NDA) or biologics license application (BLA) to the FDA requesting approval to market the drug. These applications contain the results and data analysis from the entire clinical development program, as well as the earlier preclinical testing and proposals for manufacturing and labeling of the new medicine— which can run 100,000 pages or more.

In order to accelerate the availability of medicines to patients with serious diseases or where there is an unmet medical need, the FDA implements expedited approaches to accelerate the development and review of new medicines, such as:

- **Fast Track:** expedites the review of drugs that treat serious conditions and fill an unmet medical need.
- **Breakthrough Therapy:** expedites the development and review of drugs that may demonstrate substantial improvement over available therapy.
- **Accelerated Approval:** accelerates approval for drugs that address a serious condition or fill an unmet medical, based on a surrogate or an intermediate clinical endpoint.
- **Priority Review:** accelerates FDA evaluation of drugs that, if approved, would be significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions.

Scientists, physicians and statisticians at the FDA review the data from all of the studies on the compound and, after weighing the benefits and risks of the potential medicine, decide whether to grant approval. Occasionally the FDA will ask for additional research before granting approval or convene an independent expert advisory panel to consider data presented by the FDA and the company.

Manufacturing

HIGH QUALITY, LARGE SCALE PRODUCTION OF NEW MEDICINES

Approved medicines may be used by as many as millions of people or by only a very narrow patient population. Biopharmaceutical companies strive to manufacture high quality medicines available to patients for many years.

Manufacturing facilities are constructed to the highest standards to ensure that safety and quality are built into each step of the manufacturing and production process. Companies must adhere to the FDA's good manufacturing practices (GMP) regulations, and they also must constantly update, overhaul, or even rebuild facilities when new medicines are approved, as each new medicine is manufactured differently.



Advanced Manufacturing



Recent advances in science have propelled biopharmaceuticals into a new realm of manufacturing complexity. Biologics, in particular, have created growing challenges for biopharmaceutical companies. These molecules are derived from living cells, and their manufacturing requires multiple steps that use robust technology to ensure purity, consistency and quality.

Companies are implementing advanced manufacturing techniques to keep pace with rapid advances in science and medicine. They use cutting edge materials and emerging science capabilities (e.g., nanotechnology and continuous manufacturing) that are leveraged through close coordination of information, automation, computation, software, sensing, and networking to manufacture these complicated medicines. The scientific, R&D-driven manufacturing capability of the U.S. biopharmaceutical sector will be a crucial part of the health and economic well-being of the U.S. in the future.

“COMPARED TO OTHER CAPITAL-INTENSIVE, ADVANCED MANUFACTURING INDUSTRIES IN THE U.S., THE BIOPHARMACEUTICAL INDUSTRY IS A LEADER IN R&D INVESTMENT, IP GENERATION, VENTURE CAPITAL INVESTMENT, AND R&D EMPLOYMENT.”

- BATTELLE TECHNOLOGY PARTNERSHIP PRACTICE

I'm Not Average: Matt Ellefson



When Matt Ellefson developed a cough, he didn't think much of it. He assumed it was caused by the cold winter air, but as the weeks passed his cough lingered. Then he began coughing up blood. Within hours of going to the emergency room, Matt was diagnosed with advanced non-small cell lung cancer, and the prognosis was not good. With treatment, he faced a 5-year survival rate of less than 5%. His diagnosis in December 2009 was a complete shock. He was a nonsmoker who lived a healthy and fit lifestyle.

Soon after being diagnosed, Matt enrolled in an aggressive clinical trial. After 5 months, his cancer went into remission. One year later, his cancer resurfaced and it had spread. Treatment options were limited. While waiting for his doctor to conduct follow-up testing, he learned about a targeted gene therapy that had been recently approved. However, the odds were still against him. Patients typically developed resistance to the medicine in 8 months. Three years later Matt is living an active, happy life, with his disease under control thanks to advances and innovations in cancer medicines. He runs marathons, participates in cycling competitions, and explores the world with his family. If he does become resistant to his current medicine, there are 3 new drugs that have been approved, so now he has other options. He has hope because of the progress made in cancer research.

Post Approval Research and Monitoring



“INCREMENTAL ADVANCES CAN ADD UP TO TRANSFORMATIVE CHANGES.”

- SIDDHARTHA MUKHERJEE, MD, PHD, COLUMBIA UNIVERSITY MEDICAL CENTER,
AUTHOR OF *THE EMPEROR OF ALL MALADIES*

Research on a new medicine does not end when the discovery and development phases are completed and the medicine is available to patients. On the contrary, companies conduct extensive post-approval research to monitor safety and long-term side effects, and may also pursue research into new indications for the medicine in different disease areas, age groups, or other patient populations.

Safety Monitoring and Research

ONGOING REPORTING AND DATA COLLECTION

The FDA requires that companies monitor approved medicines for as long as they stay on the market and require companies to submit periodic reports on safety and tolerability. Companies must also report any serious and unexpected adverse events that occur from use of the medicine to the FDA in an expedited manner. The FDA sometimes requires companies to conduct Phase IV clinical trials, which evaluate the long-term safety or effects in specific patient subgroups.

The FDA may also require implementation of a risk evaluation and mitigation strategy (REMS) when it determines that it is necessary to ensure, through the accumulation of additional evidence, that the medicine's benefits outweigh its risks over time. A REMS can be required before or after FDA approval and can apply to one drug or a class of drugs. As an example, a REMS may outline specific safety procedures for health care providers before dispensing a drug, such as patient education of warning signs of infection.

Research on Maximizing Therapeutic Value

ADDITIONAL BENEFITS REVEALED OVER TIME

Although FDA approval of a new medicine is a critical milestone, in many cases it is the “starting point,” where data accumulated through ongoing research and the real-world clinical use of the medicine uncovers additional therapeutic value. Additional clinical value of therapies is realized over time through many different pathways, leading to expanded and improved use of a drug, including:

- Greater value in original indication than initially seen in trials
- Earlier use of the medicine
- New indications in other diseases
- Combination use with other treatments
- New formulation or method of delivery
- Use in targeted patient subpopulations

Conclusion

“WE ARE FIRMLY BASED IN SCIENCE, FOCUSED ON PATIENTS AND DETERMINED TO CREATE MEANINGFUL THERAPIES FOR SERIOUS MEDICAL CONDITIONS. I COULDN'T BE MORE OPTIMISTIC ABOUT OUR FUTURE AND I AM PROUD AND HUMBLED TO THINK ABOUT THE POTENTIAL VALUE WE CAN BRING TO PATIENTS AND THEIR LOVED ONES.”

- GEORGE SCANGOS, PHD,
CEO, BIOGEN

The discovery and development of new medicines is a long, complex and rigorous process. Every step is aimed at bringing effective medicines to patients as quickly as possible, while ensuring the highest possible level of safety. It takes an average of ten years to develop a potential new medicine.

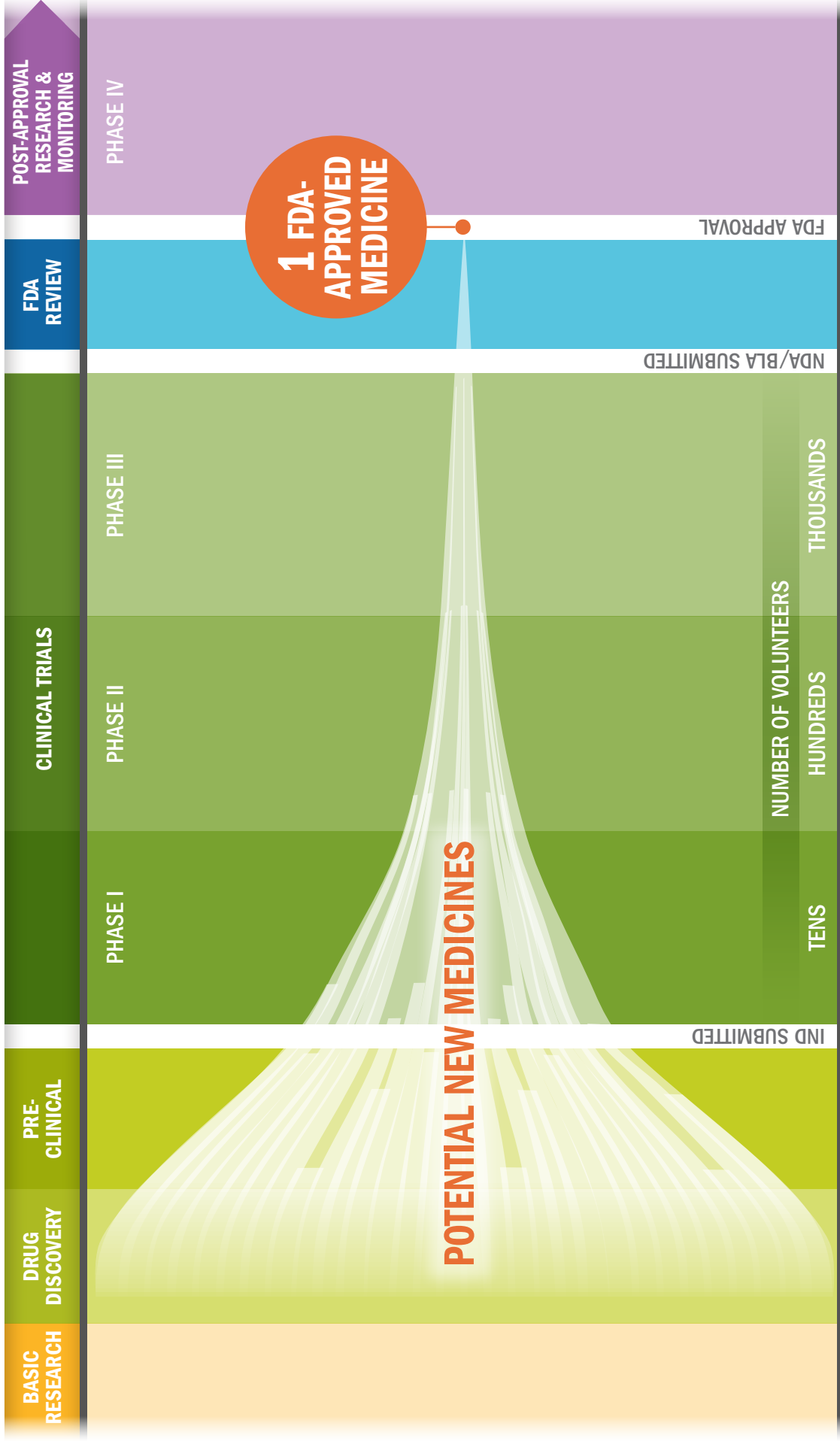
Advances in our understanding of human biology and disease are opening up exciting new possibilities for potential new treatments and cures to meet patient needs. As the complexity of the science increases and R&D challenges mount, researchers are continually adapting and innovating to speed medical advances.

Researchers are working every day in labs across the U.S. and around the world to turn scientific promise into new medicines for patients. Research-based biopharmaceutical companies are committed to advancing science and developing innovative medicines.

Realizing the promise and potential of the pipeline will require increased collaboration and convergence across a range of sectors and fields to harness novel scientific approaches, massive amounts of data and computational capabilities, and a range of new technologies. The scope of scientific and technological challenges and opportunities are heralding a new era of collaborative activity across a range of stakeholders.

Ensuring a favorable policy and regulatory environment is critical to sustaining the vibrant life sciences ecosystem in the U.S. and fostering the development of new medical advances against our most costly and challenging diseases.

THE BIOPHARMACEUTICAL RESEARCH AND DEVELOPMENT PROCESS



Key: IND: Investigational New Drug Application, NDA: New Drug Application, BLA: Biologics License Application

BIOPHARMACEUTICAL RESEARCH & DEVELOPMENT PROCESS

DISCOVERY

BASIC RESEARCH

Scientists in biopharmaceutical research companies, government, academia and for-profit research institutions contribute to understanding of the disease and potential drug targets.

DRUG DISCOVERY

Researchers create a new molecule or select an existing molecule as the starting point, then perform tests on that molecule and optimize it to maximize its effect. They then move forward with one or more drug candidates.

PRECLINICAL

Researchers test extensively to determine if the drug is safe enough for studies in humans using lab and animal models.

CLINICAL DEVELOPMENT

IND SUBMITTED

The company provides FDA with an investigational new drug application (IND), which contains all preclinical testing results and plans for clinical testing, so the FDA can determine if the drug is safe enough to move to human trials.

CLINICAL TRIALS

The candidate drug is assessed for safety and efficacy in three phases of clinical trials, usually beginning with tests in a small group of healthy volunteers, and then moving into larger groups of patients.

NDA/BLA SUBMITTED

The sponsor submits a new drug application (NDA) or biologics license application (BLA) to the FDA requesting approval to market the drug. These applications contain the results and data analysis from the entire clinical development program and earlier preclinical testing, as well as the proposed labeling and manufacturing plans of the new medicine.

FDA REVIEW

The FDA reviews the NDA or BLA submission to determine if the drug can be approved for patients to use. They may solicit the opinion of an independent advisory committee.

FDA APPROVAL

Following comprehensive reviews of the medicine's safety and efficacy, the FDA will either approve the medicine or request additional studies. If the medicine is approved, formulation, scale-up, and manufacturing of the medicine will get underway.

ONGOING STUDY OF THE MEDICINE

POST-APPROVAL RESEARCH AND MONITORING

The company monitors the drug as it is used in the larger population to capture any unexpected serious side effects and to accumulate additional data, both through formal clinical studies and through the collection of real-world evidence, which may reveal greater therapeutic potential in other indications, formulations, combinations, etc.

TOTAL

How much: \$2.6 billion on average*

How long: at least 10 years on average

*In 2015, the average R&D cost required to bring a new, FDA-approved medicine to patients is estimated to be \$2.6 billion over the past decade (in 2013 dollars), including the cost of the many potential medicines that do not make it through to FDA approval.

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