

The New *R&D* PARADIGM

The industry needs to continue developing innovative drugs to address high unmet needs, while addressing the speed and quality of drug discovery, development, and commercialization.

Large and small biopharma companies are seeking to increase the efficiency and productivity of their R&D functions. They are collaborating with nontraditional partners, gathering insights from observational studies, and leveraging analytics to increase throughput of the clinical development process.

Our experts say innovation in R&D is going beyond the science to tools, processes, technologies, and the operating models that result in higher productivity, global collaboration, and better decision-making throughout the R&D cycle. The emergence of new forms of collaboration and open innovation models will be an important part of improving the efficiency of R&D through greater standardization and reduced duplication of efforts. (Editor's Note: see the digital edition for more on open innovation.)

Despite the emergence of many exciting new platform technologies with significant promise, the number of expensive, late-stage development failures, especially in hard-to-treat diseases, continues to rise, says Glen Giovannetti, global life sciences leader, Ernst & Young.

"The cost of failure today is unacceptably high, both to the bottom lines of companies as well as to society overall that must confront an increasing chronic disease burden and aging populations," he says.

For many years, the pharmaceutical industry designed drugs from biological targets that were not always well validated and in areas where the path to clinical proof of concept and ultimate validation on the market was uncertain, says Marc Bonnefoi, D.V.M., Ph.D., head of the North America R&D hub and VP of disposition, safety and animal research scientific core platform at Sanofi.

"We screened scores of molecules to see if they had any effect on different models of many medical conditions that were often incompletely qualified," he says. "There were too many assumptions regarding the biology of



“Our strategy focuses on delivering differentiated, highly effective, and safe medicines that will transform the treatment of chronic, debilitating diseases.”

DR. HUGH DAVIS / Janssen Research & Development

diseases. Today, we seek to begin with an understanding of the underlying cause of a given disease and work to develop a solution to interfere with that process. We are trying to integrate a translational approach to our R&D efforts, applying the knowledge from patient populations and medical experience much earlier in our research and drug development processes and identifying earlier indicators of whether a potential treatment will be successful.”

Dr. Bonnefoi says translational medicine is already changing the face of R&D.

“Boundaries between pipeline stages and disciplines are minimized through the creation of research teams that bridge silos inherent in

traditional R&D,” he says. “Practitioners must be able to communicate across organizational, discipline, and geographic boundaries. Collaboration across industry, academia, and research hospitals will be pivotal to the successful application of translational medicine to projects. The future of medicine will depend on an ability to translate our increasing scientific understanding of the complexities of disease, especially chronic diseases, to effective therapies in the real world.”

Punit Dhillon, co-founder, director, president, and CEO of OncoSec Medical, says the trends impacting R&D are strategic partnerships, availability of funding, and growing reimbursement and regulatory concerns.



“Significantly lower rates of a disease or condition in pediatric patients compared with adult populations pose unique feasibility challenges.”

DR. KAREN WEISS / Janssen Research & Development



“By combining modules against different therapeutic targets into a single therapeutic molecule, it will be possible to tailor these molecules to attack diseased cells while potentially minimizing toxicity and increasing safety by sparing healthy tissue.”

DR. ROB HAYES / Janssen Research & Development

“Driven by decreasing R&D productivity and the desire to strengthen weak pipelines, big pharma is becoming increasingly active in acquisitions and partnerships with biotech companies,” he says. “Meanwhile, ongoing economic challenges in the United States have resulted in reduced funding for biotech companies.”

“Finally, in an effort to control rising health-care costs, payers are beginning to scrutinize treatments, taking into account both comparative effectiveness and cost-effectiveness,” he continues. “At the same time, increasing industry regulation and litigation are forcing life-sciences companies to be more cautious and to increase their focus on product quality.”

FAST FACT

**NEW PRODUCTS WILL ADD
\$100 BILLION TO THE GLOBAL
PHARMACEUTICAL MARKET BY 2016.**

Source: Kalorama Information

Challenges in R&D

The industry has spent \$1.1 trillion over the last 10 years in R&D, according to EvaluatePharma. Additionally, billions are spent by the industry in the potentially aggressive transfer of risky, late-stage, in-process R&D as-

sets in seemingly high-priced and speculative in-licensing deals and company acquisitions.

EvaluatePharma's net present value analyzer finds that the value of the industry's pipeline increased 17% to \$293 billion vs. \$249 billion as calculated in May 2011.

Henry Levy, managing director of research and development in Accenture's Life Sciences practice, says the research and development organizations within pharmaceutical companies are facing increased pressure as they drive for higher performance at a lower cost.

There are several trends impacting the R&D environment that are critical to the future of the pharmaceutical industry and are impacted by a combination of political pressures, economic pressures, sociological pressures, and technological pressures. These trends include: virtualization of research and radical outsourcing of development, focus on precision medi-



“New innovations that can more quickly answer discovery, safety, and efficacy questions are essential to advancing new drugs and lowering development costs.”

KEITH MURPHY / Organovo

cine and targeted therapies, and time to market vs. time to reimbursement.

“As we consider the need to target populations globally — coupled with the need to drive down costs while leveraging a global footprint and workforce — Accenture sees that the ability to seamlessly collaborate across geographies, companies, academic institutions, and governments will become a key core competency for the pharmaceutical industry,” Mr. Levy says. “As the industry reacts to the regulatory pressures and increases the number of trials and patients required for product approval, it will be forced to leverage wider networks and expand external collaboration to fill research pipelines. Further, these organizations will need to establish radical outsourcing relationships to further industrialize clinical and regulatory development activities.”

Mr. Levy says healthcare reform and economic pressures are creating an environment where R&D organizations can no longer focus just on approval to bring a drug to market, but must work collaboratively across the organization to establish a path to reimbursement for products in all critical markets it targets.

“This trend will drive drastic reorganizations within R&D, increase focus on market access data and trials, as well as increase the workload and investment before initial drug launch,” he says. “To drive expected sales volumes from new products from day one, fighting the shorter timelines for patent protection, and the threat of generics and biosimilars, R&D organizations will need to add value vigilance to their current safety and efficacy vigilance activities.”

Shaf Yousaf, chief marketing officer, life-

New Models for Cancer

A new chapter in cancer treatment is unfolding, says Oliver Fetzter, Ph.D., president and CEO of Cerulean Pharma.

“Smart bombs, such as ADCs and nanopharmaceuticals that deliver potent cancer killing agents to tumors while sparing healthy tissue, hold enormous promise,” he says. “These smart bombs should contribute to turning many currently incurable cancers into manageable chronic diseases.”

A lot of attention has recently been focused on multi-specificity of therapeutic molecules, such as bi-specific monoclonal antibodies, multi-specific alternative scaffolds, and small molecule-antibody conjugates, says Rob Hayes, Ph.D., VP and venture leader, Centyrex Venture, Biotechnology Center of Excellence, at Janssen Research & Development, part of the Janssen Pharmaceutical Companies of Johnson & Johnson.

“In oncology, drug combinations are the norm because of the ability of tumor cells to escape the inhibitory effects of a single therapeutic agent,” he says. “These new multi-specific molecules will allow the simultaneous, precise inhibition of two or more receptors or ligands involved in disease, making it much harder for tumor cells to escape treatment. By combining modules against different therapeutic targets into a single therapeutic molecule, it will be possible to tailor these molecules to attack diseased cells while potentially minimizing toxicity and increasing safety by sparing healthy tissue.”

Dr. Hayes says similar combination approaches are likely to expand into other therapeutic areas, including infectious diseases and immune-mediated diseases.

He says Centyrex is working with several academic labs and biotech companies to determine the most efficacious combinations of well-known and novel targets.

“The information from these collaborations will allow a more informed selection of monoclonal antibodies, bi-specific antibodies, alternative scaffolds, and small molecule inhibitors in a range of diseases,” he says. “Advancement of such novel therapeutics has been aided by application of biomarker analyses to many facets of the development process from selecting appropriate patient populations for clinical trials to monitoring efficacy.”

There is now evidence from cancer genome DNA sequencing studies revealing that the extreme genetic diversity of cancer cells (including the major

killers: colon, breast, lung) is far greater than previously hypothesized, says Michael Hanna Jr., Ph.D., president and CEO of Vaccinogen.

“While the pharma industry continues to advocate for more targeted therapies for smaller patient populations, the hundreds and thousands of cancer mutations revealed over the past few years makes this approach impractical,” he says. “We cannot treat a heterogeneous disease with homogeneous drugs.”

Dr. Hanna says there is one evolutionary approach that already exists to address this magnitude of cancer diversity: the immune system.

“The immune system constantly protects humans from a diverse array of deadly foreign pathogens, viruses, and proteins,” he says. “With the exception of safe drinking water, no other modality, not even antibiotics, has had such a major effect on mortality reduction and population growth. Emerging scientific literature continues to support reasoning that cancer immunotherapy can be successful. By finally embracing the heterogeneity of cancer, deploying patient-specific cancer vaccines toward earlier stages of disease, and adapting to lessons learned from 20 years of attempted clinical trials, the cancer immunotherapy field is now on the cusp of a renaissance.”

Another area of research — RNA-based therapies — has the potential to provide clinical benefit for previously difficult-to-address diseases. But Chris Garabedian, CEO of Sarepta, says intense focus on RNA-based drug development in the industry over the last several years has not yet translated into viable treatments.

“Sarepta’s technology matured at a time when we learned a lot about the cause of a particular disease — Duchenne muscular dystrophy (DMD) — and how we could apply our technology to this and other genetic or infectious disease targets,” he says.

Mr. Garabedian says there have been many attempts and some successes of drugs that work at the genetic level by targeting receptors or pathways that are downstream from the true origin of disease.

“By focusing on the underlying cause of diseases at the genetic level, we’ve enabled the rapid discovery and development of promising new therapies for numerous conditions for which there are no current treatment options,” he says. “The potential of RNA-based therapies to reach previously ‘undruggable’ targets and attack previously untreatable diseases could be truly revolutionary.”



“A new chapter in cancer treatment is unfolding. Smart bombs, such as ADCs and nanopharmaceuticals that deliver potent cancer killing agents to tumors while sparing healthy tissue, hold enormous promise.”

DR. OLIVER FETZER / Cerulean Pharma



“There has been a steady decline in the amount of money governments are spending to support the life sciences.”

SHAF YOUSAF / Sigma-Aldrich



“The reality is that pediatric studies are harder to conduct than adult studies. Sponsors may be reluctant to evaluate drugs in children because of economic, legal, and ethical obstacles.”

DR. CHARLI SANDERS / Premier Research

FAST FACT

**GLOBAL PHARMACEUTICAL R&D
SPEND IS FORECAST TO
GROW BY 1.5% PER YEAR
TO \$149 BILLION IN 2018.**

Source: EvaluatePharma

science division at Sigma-Aldrich, says there has been a steady decline in the amount of money governments are spending to support the life sciences.

“This has been occurring all over the world over the course of the last three years because of the economic crisis,” he says. “In fact, as a percent of gross domestic product, spending in the life sciences has been flat and is likely to remain so for quite some time.

“Also, with pharma companies expecting to lose as much as \$50 billion in sales annually once various products go over the patent cliff, we have seen systematic reductions in the amount of money pharmaceutical companies are spending on traditional research and development,” Mr. Yousaf continues.

In fact, EvaluatePharma analysts predict that more than \$290 billion of sales are at risk from patent expirations between 2012 and 2018.

The Road Ahead

The growing interest in biotechnology development has transitioned the industry from pharmaceutical to biopharmaceutical in less than a decade, according to a recent report from Kalorama Information. New products will add \$100 billion to an ailing global pharmaceutical market by 2016.

Kalorama researchers say there are an estimated 724 projects in development from the top 50 pharma companies, and biopharmaceutical products represent a good number of those new products. Cancer treatments represent the highest percentage of new drugs, due to increased cases and favorable reimbursement trends by payers.

Mr. Levy says capitalizing on third-generation ultra-low cost rapid genetic screening technology, widespread biomarker testing, as well as new advances in understanding of human genome switching, will permit the industry to focus on specific populations for targeted therapies.

“This will allow the industry to differentiate itself in the highly competitive promotional market, as well as capitalize on specific growing target populations with unmet needs and in new geographies.”

Chris Bergstrom, chief strategy and commercial officer at WellDoc, says in the future, prescription therapies will include more than just biologics, chemical compounds, or traditional mechanical medical devices.

“Going forward, they will also include therapies whose active ingredients include analytics, behavioral coaching, and clinical decision support,” Mr. Bergstrom says. “These types of therapies are rooted in expert systems and deployed across technologies such as mobile phones, diagnostic devices, and the Internet, and are commonly called mobile health or mHealth.”

Mr. Bergstrom adds mobile health is an emerging industry, as evidenced by the NIH’s

Pediatrics Regulations Updated

Pharmaceutical portfolio management teams have increasingly turned to pediatric extension strategies to extend their brands' life cycles and net a high rate of return, according to a recent study by Cutting Edge Information.

Cutting Edge researchers have found that pediatric indication strategies deliver an average of \$130 for every \$1 spent by surveyed pharma companies. The median return, however, was a more modest \$27 per \$1 spent, still higher than several other life-cycle extension strategy averages, such as new formulations strategies.

A result of the Pediatric Research Equity Act (PREA) — and companion legislation Best Pharmaceuticals for Children Act (BPCA) — is more pediatric research than in the years before the legislation was enacted, says Karen Weiss, M.D., VP, immunology global regulatory affairs, at Janssen Research & Development, part of the Janssen Pharmaceutical companies of Johnson & Johnson.

But, according to a study sponsored by Premier Research, fewer than two in 10 drug company respondents fully understand PREA rules.

The BPCA and PREA Reauthorization Act of 2012 provides for increased reporting on the effectiveness of BPCA and PREA regulations, and it provides the FDA with enforcement tools to ensure that pediatric trials are completed according to stated timelines. Sponsors are now required to submit an initial pediatric plan no later than 60 calendar days after the date of the end-of-Phase II meeting. The FDA can also issue letters to sponsors who fail to meet PREA requirements.

"The growth in pediatric research presents not only issues common to all clinical research, but also its own set of unique challenges," Dr. Weiss says. "First, infants, children, adolescents, and young adults — age varies based on locality — cannot give legal consent to participate in research, although pediatric patients older than about age 7 provide assent."

She says the Office of Human Subjects Protection set forth additional safeguards to protect pediatric research patients that the FDA subsequently codified in regulation. Institutional Review Boards (IRBs) that review pediatric research proposals must only approve the research if it satisfies one of the following criteria: (a) is not more than minimal risk; (b) is greater than minimal risk,

but there is a prospect of direct clinical benefit; (c) poses a minor increase over minimal risk and no prospect for direct benefit but likely to yield generalizable knowledge about subject's disorder or condition.

Studying drugs in children is a scientifically demanding task, says Charlene (Charli) Sanders, M.D., VP of regulatory affairs and pediatric consulting, at Premier Research.

"The reality is that pediatric studies are harder to conduct than adult studies," she says. "Sponsors may be reluctant to evaluate drugs in children because of economic, legal, and ethical obstacles."

Pediatric studies are associated with unique challenges in relation to patient enrollment, study design, formulations, and dosing considerations, Dr. Sanders says.

A recent survey commissioned by Premier Research of 55 biotech and pharma companies in both North America and Europe revealed that almost three-quarters (72%) of U.S. respondents feel that identifying a sufficient number of pediatric patients for PREA studies is a major challenge. Children's hospitals and care facilities as well as clinical practices are being bombarded with requests for pediatric patients to join these studies.

"Additionally, one IRB may reach a different conclusion from another about a particular study and whether — and what — criteria are needed for approving the research," she says. "Added oversight could increase timelines, creating additional pressure and resulting in more study modifications compared with research in adults."

Dr. Weiss says the usually and fortunately significantly lower rates of a disease or condition in pediatric patients compared with adult populations pose unique feasibility challenges.

"Any scenario that reduces the numbers of available patients could make the study impractical," she says. "Different regulatory requirements, for example timing of study initiation or study design, among the health authorities in the U.S., Europe, and other parts of the world could preclude a global trial, severely limiting the pool of available patients to study. Reluctance on the part of investigators or patients/families to enroll in a trial of a marketed product because of widespread off-label use and the perception it is already proven safe and effective for pediatric patients could push out timelines beyond what is feasible."



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CHRIS BERGSTROM / WellDoc

recent decision that mHealth is a science worthy of NIH research funding.

"Several mHealth RCTs have already demonstrated clinical benefits that rival some of the most effective drugs available," he says. "Pharma will need to take advantage of this opportunity before nontraditional healthcare companies with even larger market capitalizations do, e.g. IBM, AT&T, or Google. In fact, merging technology development and science of mHealth and drug discovery could result in a synergistic win with more powerful and efficacious combination products than any industry could achieve on its own."

Jonathan Lewis, M.D., Ph.D., CEO of Ziopharm Oncology, says there will be a revolution in biotech over the next 10 years that will see a dramatic increase in the volume of sequencing data and an improved understanding of its application to human diseases.

"It is critical for the industry to continue developing innovative drugs to address high unmet needs while applying this new insight to optimize the speed, quality, and financial efficiency of drug discovery, development, and commercialization," he says.

Dr. Lewis says at Ziopharm, the science is geared to generate the highest quality data to improve the frequency with which the company identifies drugs that have a stronger likelihood of success in addressing significant unmet medical needs.

"We agree fully with the emphasis of quality over quantity," he says. "It's about data, data, data. The financial crunch on the economy has limited the level of investment available to this industry, so companies have to do more with less and prioritize quality candi-



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CHRIS GARABEDIAN / Sarepta



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HENRY LEVY / Accenture

dates over quantity of candidates. Good innovation will come from this.”

Mr. Giovannetti notes the trend toward increasing the “externalization” of the R&D function by moving from large research campuses to smaller, distributed units closer to academic and biotechnology clusters as one step companies are taking to improve productivity. He says an example is Johnson & Johnson’s recent move to create four global Innovation Centers.

In September 2012, Johnson & Johnson announced plans to establish four regional centers — in California, Boston, London, and China. The centers will serve as regional hubs focused on identifying early-stage innovations and establishing collaborations to invest in and speed development of those innovations to solve unmet needs in patients. Each innovation center will house science and technology experts and have local deal-making capabilities.

At Janssen Research and Development, the company is focused on delivering differentiated, highly effective, and safe medicines that will transform the treatment of chronic, debilitating

diseases, says Hugh Davis, Ph.D., VP and head of biologics clinical pharmacology, Biotechnology Center of Excellence, at Janssen Research & Development, part of the Janssen Pharmaceutical Companies of Johnson & Johnson.

“We have evolved to more aggressively combine our internal capabilities with cutting-edge science and technologies from outside of our labs to advance medicines in our pipeline with an emphasis on quality that evaluates greater potency, improved pharmacokinetic profiles, lower toxicity, and higher target specificity,” he says.

At Sanofi, Dr. Bonnefoi says the company also is evolving its R&D approach to be able to access the best science and people in research.

“This requires a combination of both internal and external research and is implemented through the creation of research and early development hubs in which Sanofi researchers increasingly partner with external teams,” he says. “Geographically focused integrated research hubs have been created in the Boston area, which is part of the North America R&D hub, Germany, and Asia, and a project is being discussed with our social partners for France.

Sanofi is also seeking to make translational research a reality, using the ability to translate to the patient situation as a yardstick to judge the quality of projects. By effectively implementing open innovation and raising the bar for a project to be accepted into development and reach further investment milestones down the road, Sanofi aims create a strong portfolio.”

Dr. Bonnefoi says Sanofi’s R&D aims to tackle therapeutic areas that are in line with the most pressing health needs.

“Chronic diseases, such as diabetes, hypertension, heart disease, stroke, and cancers, are a large and growing burden on the population and healthcare systems, which is why we are focusing on these research areas,” he says.

The North American Hub, Dr. Bonnefoi says, has created a framework to leverage its diversity of expertise across Merial, Pasteur, Genzyme, and Pharma for the benefit of R&D projects and patients.

“We have a vast knowledge within the field of immunology spread across our vaccines division Sanofi Pasteur, our multiple sclerosis franchise within Genzyme, and our Sanofi Oncology group,” he says. “The Hub provides a framework to bring these groups together to share expertise and collaborate on a broad range of potential treatments for patients.”

At bluebird bio, the gene therapy company is setting high expectations for its products, says Faraz Ali, VP, program management and commercial planning.

“We have prioritized tackling rare and very severe disorders precisely because the unmet medical need is high,” he says. “Our vision is

to develop therapies with the potential to transform the lives of such patients, rather than merely offering incremental improvements on existing standards of care.”

Mr. Ali says bluebird bio has built a gene therapy platform to deliver on this vision with early clinical proof of concept in two severe genetic disorders.

“The field of gene therapy has historically been challenged with highly inefficient manu-

facturing processes, so we built a world-class team that hails from disparate disciplines,” he says. “We invested in developing the highest quality gene therapy product through an improved understanding of stem cell biology and industrialized critical manufacturing processes leading to the most pure and potent gene-modified cell therapy product. As a result, bluebird bio can now launch into clinical trials with much higher purity and potency than we could

two years ago, and we can do so at a scale, consistency, and cost of goods that will make our gene therapy platform commercially viable. So the pursuit of high-quality products is also helping us set new standards in the field.” **PV**



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New Science Brings New Targets

Experts say new research avenues and new tools for drug discovery continue to uncover new targets.

A major area for innovation and new technologies is in drug discovery and development, says Keith Murphy, CEO of Organovo.

“The process is heavily dependent on accurate models, analysis, and tools that can give more insight into clinical outcomes,” he says. “For example, the ‘omics’ fields — genomics, proteomics, metabolomics, etc. — are making major advances in improving validation of gene-disease associations and providing new insights and information to analyze the complexities in human physiology.”

Mr. Murphy says these new tools are only as good as the preclinical models that they are used on — namely animal models and traditional cell culture — which are often poor surrogates for human physiology.

“The game changer in disease research, drug discovery, and toxicity testing will be the ability to quickly develop and produce human tissues that can respond to biomechanical and soluble stimuli, resulting in tissue-level responses that encompass multiple cell types and physiologic processes,” he says. “New innovations that can more quickly answer discovery, safety, and efficacy questions are essential to advancing new drugs and lowering development costs. Ultimately, any technologies that can give greater clinical predictive power during drug discovery and preclinical development have the potential to advance the industry and benefit patients with safer, more effective, and more innovative medicines.”

The response rates for many drugs are dismal because too often we don’t understand the biology, says Colin Hill, CEO, president, chairman, and co-founder of GNS Healthcare.

“We don’t understand the disease, we don’t understand how the drugs work, and we don’t understand for whom they work,” he says. “One emerging trend is discovery and development through data-

driven computer models of disease. By collecting high-quality samples from patients, including appropriate measures of disease severity, and doing the appropriate analyses, we can build models that we can use to make connections, draw conclusions, and establish causality. From there we can start to find new targets and NMEs and perhaps repurpose existing medicines.”

Jonathan Lewis, M.D., Ph.D., CEO of Ziopharm Oncology, says synthetic biology and computational biology are two big trends in drug discovery.

“A DNA, cell-based approach to discovery is, in a way, Biotech 2.0,” he says. “With computational biology — a systems-based approach that will drive precision medicine — many older drugs work, but they are less precise. Using models to understand the complex interactions of drugs within the body will enable us to combine old and new drugs to treat patients, not diseases.”

The opportunities for new drug discovery are evolving through uncovering novel biological targets. But the challenges in discovering new medicines continue to be in the area of translational sciences, says Shiv Krishnan, Ph.D., senior director, scouting and partnering, US, Sanofi R&D.

“As new targets are discovered and as biology becomes unraveled, we will need to ask ourselves what is the relevance of these targets in a human disease setting,” Dr. Krishnan says. “Tools, methods, and knowledge that enable this validation are playing an increasingly key role in the making of medicines. Since drug discovery and development is a marathon and not a 100-meter sprint, smart development tactics that allow us to shave off expensive development time will make a big difference. These tactics are not only tied to the availability of technologies but to the availability of unique clinical insights that allow better decision making.”

Mr. Hill says data companies such as his are working with pharma companies to build data-

driven computer models to understand disease, develop biomodels, and to discover biomarkers for patient selection and even to predict the efficacy of drug combinations.

There is significant interest within the industry in novel targets, but the limited experience with these targets results in significantly increased risk of clinical failure because of side effects, lack of efficacy or both, says Arthur Hiller, CEO of SciFluor Life Sciences.

“There is also significant interest in supergenerics because of lower risk and faster approval pathways,” he says. “What is missing is the work that industry researchers have historically done in making iterative advances around validated targets. Today, there are significant opportunities within the industry to apply new technologies to modify chemotypes to address known safety or efficacy liabilities. This approach presents development candidates that are ‘de-risked’ as a result of the valuable insights that have been gained in the nonclinical and clinical development of the established drug.”

Mr. Hiller also points to a paradigm shift based on advances in imaging that are enabling scientists to make more informed decisions. One such advance is the use of fluorine, cesium, gallium, and other radiotracers to determine whether a drug is hitting its intended tumor or biological target and whether the outcome is as expected.

“The applications of precommercialization radiotracers will likely expand,” he says. “But there is currently no precedent in partner transactions that relates compensation for the value of these companion tracers to the revenue potential of the therapeutic. Companies with compounds enabled by companion diagnostics are likely to be increasingly challenged by partners to agree to a value for the development and use of these imaging agents that more closely correlates with the impact these compounds can have on lowering pipeline risk, and ultimately on increasing the likelihood of a compound’s commercial success.”

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The Open *Innovation* MODEL

Industry experts say the companies need to rethink the way they bring new drugs to market.

Ernst & Young researchers suggest what is needed in R&D is a way to glean insights from beyond the life-sciences industry and leverage the strengths of a diverse range of entities. These holistic open learning networks would share data and connect dots across the entire value chain of companies (from early research to marketing) and cycle of care of patients (from prevention to cure).

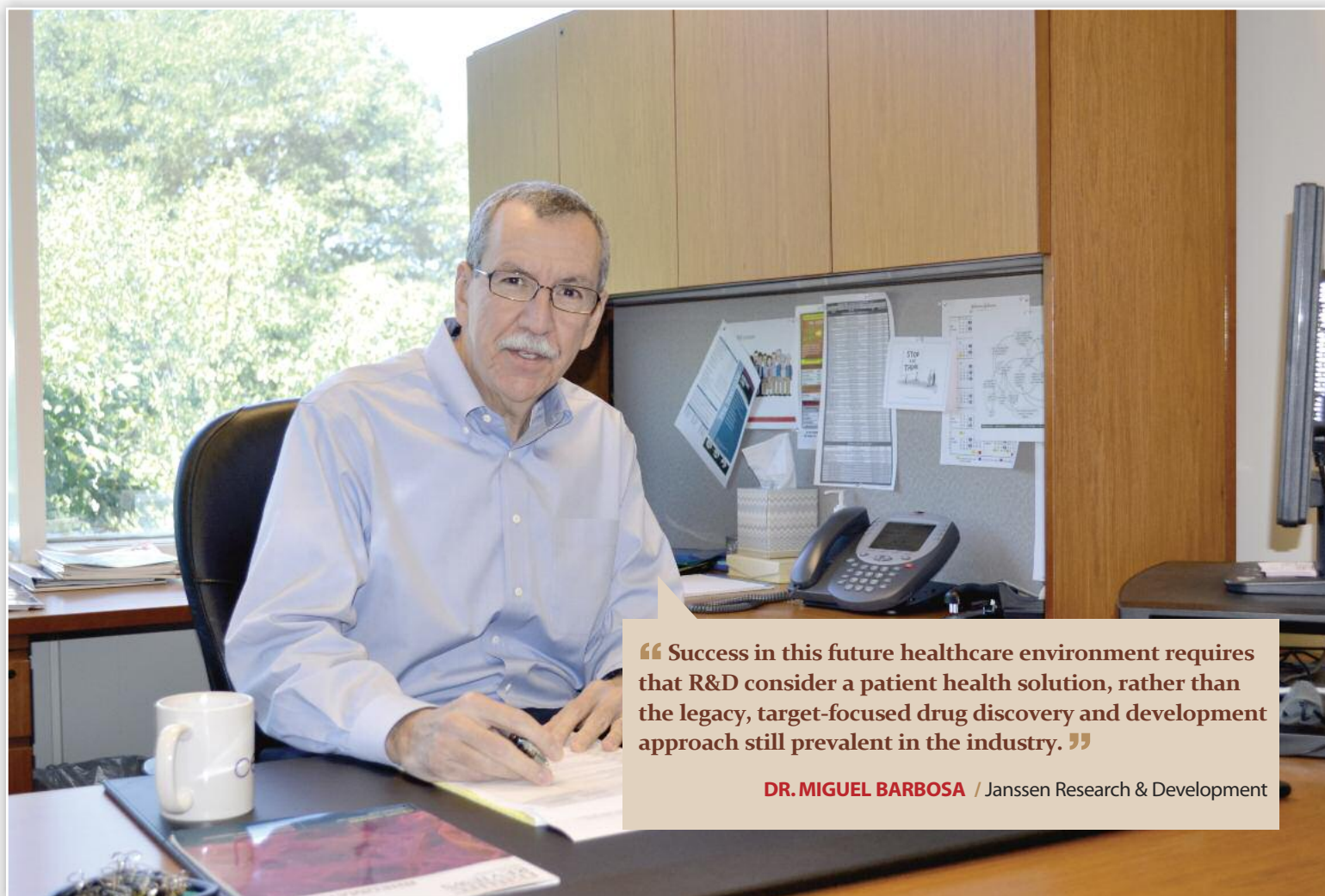
"The emergence of new forms of collaboration and open innovation models will be an

important part of both improving the efficiency of R&D through greater standardization and reduced duplication of efforts, and because of the promise that new insights will emerge through the information shared in these collaborations," says Glen Giovannetti, global life sciences leader, E&Y. "There are many examples of various research consortia that have been formed to address the R&D efficiency and knowledge gap issues, the most recent being TransCelerate BioPharma, a collaboration of 10 global pharmaceutical compa-

nies. Whether such models will be expanded to be inclusive of other actors in the health ecosystem, such as smaller biotech companies, payers, providers and patient groups, remains to be seen."

Mr. Giovannetti says, however, there are myriad challenges to a truly holistic, open innovation model that must be addressed, including intellectual property considerations, regulatory considerations, and changing the measurements and incentives in companies.

"Such models will require companies and



“Success in this future healthcare environment requires that R&D consider a patient health solution, rather than the legacy, target-focused drug discovery and development approach still prevalent in the industry.”

DR. MIGUEL BARBOSA / Janssen Research & Development



“It would be ideal to bring together diverse groups to review, analyze, and critique scientific findings. Realistically, however, it is unlikely that such findings would influence the way the pharmaceutical industry develops new products.”

PUNIT DHILLON / OncoSec Medical

their leaders to think differently in their approach to address difficult unmet medical needs,” he says. “The challenges are more likely to be addressed and overcome when the economic pressure for change builds and a new approach is in the best interest of all of the players involved in the network.”

Holistic, open networks can work as a concept, says Nagaraja Srivatsan, senior VP and head of life sciences, North America, at Cognizant.

“As organizations move toward personalized medicine, one needs to put the patient at the center and then figure out how patient interactions within the ecosystem of payer, providers, pharmacies, life-sciences organizations work in an integrated and cost-effective manner to deliver better care,” he says. “Life-sciences organizations are already exploring how they can leverage longitudinal patient information, claims information, provider-based analytic information, or social media information to figure out how they can better understand personalized care and deliver better outcomes.”

Mr. Srivatsan says the pressure from payers to go from fee-for-service models to fee-for-outcome will only increase the pressure on life-sciences companies to participate more holistically in these open networks.

“The challenge is that there are no standardized models to share information in the network,” he says. “Discussion about disease states and their treatments differ across the ecosystem. Payer information tends to be

more claims-centric, such as how do I pay for this service? Provider information is very personalized but limited to the number of patients the network has access to. The information is not yet aggregated across providers to have a holistic view of that information. Life-sciences companies have a plethora of information both from clinical trial submission but also postmarketed adverse events but they are mostly about safety and not yet correlated to outcomes.”

E&Y’s proposed solution provides an interesting framework to address challenges in a rapidly changing healthcare environment within an industry facing productivity and global economic pressures, says Miguel Barbosa, Ph.D., VP, head, immunology research and external innovation, at Janssen Research & Development.

“As with most high-level frameworks, its probability of success is directly dependent on the effectiveness of its execution,” he says. “A strong feature of the concept is the recognition that all aspects should be patient-centric, since patients have become increasingly educated about their health and treatment options. Success in this future healthcare environment requires that R&D consider a patient-health solution, rather than the legacy, target-focused drug discovery and development approach that is still prevalent in the industry. Further, its recognition of the complexity of the biology, drug discovery and regulatory environment is acutely important. This extreme complexity has resulted in high

A Holistic Open Learning Network Approach to R&D

The four characteristics of HOLNets are a critical requirement for the success of this approach:

- » **Holistic.** The HOLNet approach represents a vastly different and inclusive approach to R&D. The boundaries between drug development, product commercialization, and healthcare delivery are blurred. HOLNets would share data and connect dots across the entire value chain of companies (from early research to marketing) and cycle of care of patients (from prevention to cure).
- » **Open.** One of the biggest changes in the HOLNet approach is openness. While the rules of each HOLNet depend on the needs and preferences of its members, these networks typically require that members pool their strengths and assets (e.g., talent and precompetitive data). They also involve sharing any resulting output (e.g., creating open standards, making insights available to all members and often to nonmembers). This is one of the most powerful aspects of a HOLNet, since it has the potential to make R&D radically more efficient and productive by reducing redundant expenditures and allowing researchers to learn from each other’s insights and mistakes.
- » **Learning.** HOLNets are about learning. But while learning in the drug development process has historically been slow, sequential, and siloed, HOLNets are about learning rapidly, in real time, by connecting data from across the ecosystem. But to learn from big data, we need standards that allow data to be combined as well as sophisticated analytics to mine insights — capabilities that HOLNets will need to enable and foster.
- » **Network.** A HOLNet has to be a network. Radically reinventing R&D and unleashing the transformative potential of big data requires the participation of diverse players from across the ecosystem. The network needs a common goal — a collective intent — around which all its members are aligned.

Source: E&Y. For more information, visit ey.com/beyondborders



“Merely cutting and pasting from other industries is not adequate. Rather, pharma must judiciously adapt and leverage other models as means, not ends, to create significant value for its customers.”

DR. ANAND IYER / WellDoc



“The main challenge of the open innovation model is its unproven return on investment in a period of limited investment funds.”

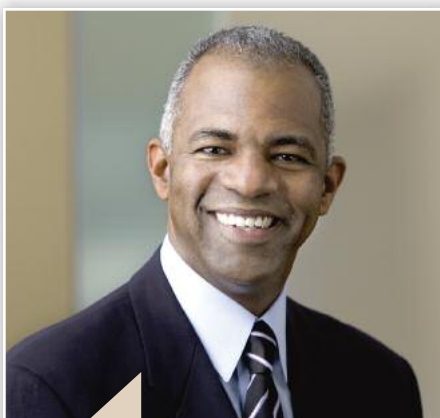
NEIL DE CRESCENZO / Oracle Health Sciences

attrition rates that have remained high due to the ineffective iterative learning and communication barriers put in place to enable competitive position and value control.”

Dr. Barbosa says for an open model to work in the pharmaceutical industry, leaders have to broaden their engagement of the global scientific community proactively con-

necting pharmaceutical and biotech companies with academic laboratories to tackle challenging R&D areas through a collaborative, networked approach that holds tremendous promise for the future of science and medicine.

Pharma needs to learn from other industries and figure out how to apply the strengths of other industries to drug development, says Jay Licther, Ph.D., managing partner of Avalon Ventures.



“An open network model can help transform our traditional model to foster collaboration between companies, academic centers, regulators, patient advocacy, and policymakers.”

DR. N. ANTHONY COLES / Onyx Pharmaceuticals

“The emergence of new forms of collaboration and open innovation models will be an important part of both improving the efficiency of R&D through greater standardization and reduced duplication of efforts.”

GLEN GIOVANNETTI / Ernst & Young



“But this is very difficult because the pharmaceutical industry is so highly regulated and the product development timelines are so different,” he says. “What works for software development or retail or other service industries can’t easily be applied to drug development because it takes 12 to 15 years to go from idea to product in the pharmaceutical industry. In those other industries you can go from idea to product in less

than a year. Additionally, pharma is highly regulated, and the current FDA approval model makes it difficult to innovate in the drug development process because that innovation takes companies outside of what is known to work with the FDA, reducing their already small chances of getting a drug all the way through development to approval.

Neil de Crescenzo, senior VP and general manager, Oracle Health Sciences, says the open model will take investments in new collaborative platforms as well as a long-term commitment from pharmaceutical leaders to establish these relationships and leverage them in a win-win framework.

“The main challenge is its unproven return on investment in a period of limited investment funds, as well as the traditional mindset for investment within the institution versus through external collaborations,” he says.

Punit Dhillon, co-founder, director, president, and CEO of OncoSec Medical, says it would be ideal to bring together diverse groups to review, analyze, and critique scientific findings.

“Realistically, however, it is unlikely that such findings will change the way the pharmaceutical industry develops new products,” he says. “Developers of new drugs must abide by strict guidelines set by the FDA, which puts the safety of the patient above all else. Unless the FDA changes its protocols, little is likely to change.”

Anand Iyer, Ph.D., president and chief operating officer at WellDoc, says several enablers must be in place.

“First, the pharma development paradigm must be open to interact with these networks to establish a true, unfiltered perspective on what they could do,” he says. “That is, they have to identify — working from the patient-provider point backwards — what needs to

happen to drive radical improvements in engagement, compliance, quality measures, and the benefits therein.”

In addition, he says companies must build not just strategies but operational blueprints that systematically address users and value propositions, applications, regulatory environments, medical and communications devices, information services networks and support, integration into mainstream CRM programs and EHR platforms, and open business models.

“Many of these layers are foreign to the historic development culture in pharma,” Dr. Iyer says. “But merely cutting and pasting from other industries is not adequate. Rather, pharma must judiciously adapt and leverage other models as means, not ends, to create significant value for their customers.”

N. Anthony Coles, M.D., president and CEO

of Onyx Pharmaceuticals, says the key question that needs to be answered in order for open innovation to work is: how do you integrate all stakeholders precompetitively to deliver value?

“At Onyx, there’s a real focus on expanding innovation beyond the scientific and medical teams to create a culture of innovators, where all employees feel responsible and accountable for the company’s success,” he says.

Dr. Coles says this innovation model requires a fundamental shift from the traditional pharma approach.

“It relies on the idea of sharing versus owning,” he says. “This mindset of ownership needs to change for us to continue to meet the needs of patients. An open network model can help transform our traditional model to foster collaboration between companies, academic centers, regulators, patient advocacy, and policymakers.” **PV**

Top 20 Most Valuable R&D Projects (WW Product Sales — \$ are in millions)

Rank Product	Company	Phase	Pharmacological Class	Sales 2018
1. GS-7977	Gilead Sciences	Phase III	Hepatitis C polymerase inhibitor	\$5,359
2. BG-12	Biogen Idec	Filed	Fumarate	\$3,400
3. Quad	Gilead Sciences	Filed	NRTI, HIV integrase inhibitor & CYP3A inhibitor	\$2,793
4. RG1273	Roche	Filed	Anti-HER2 MAb	\$2,482
5. AMR101	Undisclosed Partner	Filed	Omega-3 fatty acid	\$2,165
6. Tofacitinib	Pfizer	Filed	JAK-3 inhibitor	\$1,715
7. Trastuzumab-DM1	Roche	Phase III	Anti-HER2 MAb-DM1 conjugate	\$1,102
8. Tresiba	Novo Nordisk	Filed	Insulin	\$1,093
9. Bexsero	Novartis	Filed	Meningococcal B vaccine	\$1,060
10. Alpharadin	Bayer	Phase III	Radiotherapy agent	\$1,038
11. Ryzodeg	Novo Nordisk	Filed	Insulin	\$1,001
12. Qnexa	Vivus	Filed	Adrenoreceptor agonist &	\$983
13. Reolysin	Oncolytics Biotech	Phase III	Oncolytic virus – Ras activated	\$911
14. TMC435	Johnson & Johnson	Phase III	Hepatitis C protease inhibitor	\$900
15. Kyprolis	Onyx Pharmaceuticals	Filed	Proteasome inhibitor	\$897
16. HyperAcute Pancreas	NewLink Genetics	Phase III	Cancer vaccine	\$702
17. AMR101	Amarin	Filed	Omega-3 fatty acid	\$510
18. Relovair	Theravance	Phase III	Beta 2 adrenoreceptor agonist & corticosteroid	—
19. MDV3100	Medivation	Phase III	Androgen receptor antagonist anti-convulsant	—
20. *Bapineuzumab	Elan	Phase III	Anti-beta amyloid MAb	—

* Editor’s Note: Bapineuzumab was discontinued in July 2012 after the product failed to meet endpoints.

Source: EvaluatePharma, May 2012