

“NEWDIGS”

NEW
Drug
Development
ParadIGmS

*Catalyzing the Transformation of
Healthcare Innovation*

A working paper from the

MIT
Center for Biomedical Innovation

January 2010

Table of Contents

| | |
|---|-----------|
| Welcome | 3 |
| Introduction | 5 |
| A Systems Re-engineering Approach | 6 |
| The Current State – Historical Context | 7 |
| The Current State – Stakeholder Analysis | 9 |
| The Future State – Closing the Gaps | 12 |
| Future state vision | 12 |
| Market strategies | 13 |
| Operational strategies..... | 14 |
| Product strategies | 17 |
| Policy strategies | 18 |
| Toward a New Model of Drug Development | 20 |
| Product Development Process..... | 20 |
| Enablers | 22 |
| System..... | 23 |
| Conclusion | 25 |
| Appendix | 26 |
| References | 29 |

The MIT Center for Biomedical Innovation (CBI) was established in 2005 to overcome major obstacles to the development and implementation of biomedical innovations. CBI provides a safe haven for collaboration among industry, government, and academia. CBI catalyzes research targeting areas where breakthroughs would have important and immediate impact on healthcare innovation, productivity, regulation and practice.

The following document was developed from discussions involving a number of participants in NEWDIGS workshops between May-November 2009 including individuals from the following organizations:

Aetna
Bayer
Brookings Institution
Centers for Disease Control & Prevention
Eli Lilly
Food and Drug Administration
Johnson & Johnson
Massachusetts Institute of Technology
McDermott, Will, & Emery
Medco
National Institutes of Health
Pfizer
Quintiles
Wellpoint

CBI is grateful for the generous financial and in-kind support provided by Bayer, Eli Lilly, Johnson and Johnson, Pfizer, Quintiles, and Feinstein Kean Healthcare that made it possible to launch and to establish a solid foundation for moving NEWDIGS forward to its demonstration phase, scheduled for launch in early 2010.

Welcome

The NEWDIGS consortium was launched by the Massachusetts Institute of Technology's (MIT) Center for Biomedical Innovation (CBI) in May 2009 following an in-depth future scenario planning exercise involving a number of biopharmaceutical executives. Insights gained from this effort suggested that there is an urgent need to fundamentally re-engineer the current pharmaceutical R&D process in order to reduce the time, cost, and risk of innovation, and to enhance capacity for developing high quality, truly innovative products (rather than “me toos”) that address unmet medical needs.

Building on this foundation, a series of interviews with key stakeholders from the broader healthcare industry (e.g., patients and their advocacy groups, payors, regulators, and others) highlighted a different, but equally pressing, set of needs related the development of new medicines. Target issues identified included a need for better information on the benefits, risks, and relative effectiveness of new therapies to enable better decision-making; greater access to and affordability of treatments; and more effective ways to ensure that innovation is focused on unmet needs.

NEWDIGS is driven not only by the above needs, but also by a range of converging opportunities currently unfolding within the healthcare industry. For example, there is a growing recognition among corporate decision-makers that certain types of data today can have greater value for a company when they are shared and serve as building blocks for collective knowledge generation than when they are tightly held as a proprietary asset. This perspective represents a dramatic shift within an historically highly competitive industry culture, and has opened the door to such important pre-competitive data sharing initiatives as the Biomarkers Consortium, the Serious Adverse Event Consortium, and the National Cancer Institute's (NCI) BIG Health Consortium™, among others.

In addition, there is increasing recognition of the potential value of observational data from everyday clinical encounters to enhance knowledge about benefits, risks, and effectiveness of treatments in real world settings. A number of activities currently underway are helping to drive progress in this arena including the FDA's Sentinel Initiative to improve post launch product safety; the health information technology stimulus funding; and the development of analytic methodologies, supported by the Agency for Health Research and Quality (AHRQ) and Observational Medical Outcomes Partnership (OMOP).

And, at a conceptual level, the Institute of Medicine's Evidence-Based Roundtable has held a series of workshops that have laid out a valuable paradigm-shifting framework for a learning healthcare system characterized by evidence generation and application, rapid cycle learning, and continuous improvement across product innovation and care delivery.

Indeed, there are many individuals and organizations across the healthcare system who recognize the need for change, and the potential to leverage new science, technology, conceptual frameworks, and methods to address problems with the current paradigm of drug development. Many are stepping forward to test potential elements of the bigger solutions. Unfortunately, though, these efforts occur in fragmented ways within silos. There is currently no systematic way to learn from each initiative, avoid duplication of effort, ensure that failures are not repeated, and facilitate the replication and scale up of successes.

NEWDIGS was established to provide an academically-based safe haven for catalyzing transformational change in therapeutic product innovation in healthcare. It provides a neutral environment for collaborative experimentation and learning among industry, academia, government, clinicians and patients. It facilitates new kinds of interactions among key stakeholders. And it enables the evolution of new models, tools and technologies through a unique collaborative test-bed, ensuring that all activities are coordinated and aligned with the overarching vision and objectives of NEWDIGS.

Ultimately, NEWDIGS is a cross-stakeholder community of individuals and organizations who recognize that transformative change is an urgent public health imperative and who are passionately committed to developing a path forward.

This paper provides an introduction to NEWDIGS, a summary of the work completed in Phase I (May-December 2009), and the preliminary plan for launching the initial demonstrations projects in 2010. We look forward to continuing to share the experiences and learnings from our activities along the way in an effort to help catalyze transformational change in pharmaceutical R&D and to contribute more broadly to the evolution of the learning healthcare system.

Gigi Hirsch, MD



Executive Director

MIT Center for Biomedical Innovation

Program Director, NEWDIGS

Introduction

The expectations of the pharmaceutical industry are high. We look to the drug makers to find cures to our diseases, to relieve us from pain or discomfort, to ease the costs and burdens of disease on society. All of this without placing anyone at risk, ensuring the safety of every product. The rapid pace of scientific discovery, especially following the sequencing of the human genome, has led many to believe that a pharmaceutical renaissance is just around the corner. It is perhaps the most frustrating fact of the industry that despite an enormous increase in R&D investment, and historical advances in technology through genomics, automation and computation, the number of new drugs produced each year remains at the same level that existed over 40 years ago (about 20 per year), that many of these new drugs do not match up to the most pressing medical needs we face today, and that serious safety issues still crop up on medicines that have been approved, marketed, and administered to millions of patients.

Can we turn pharmaceutical innovation around? Industries from aerospace to computers and telecommunications have seen their business grow with attention to research and manufacturing efficiencies. Approaches to enterprise transformation such as lean manufacturing, business process re-engineering, systems design and “co-opetition” have all been used to revitalize moribund business models. Can we use these same principles to help create a new paradigm for drug research and development? And can we apply these principles in a way that not only improves productivity, but consistently yields truly transformative products that cure disease?

In 2009, the Massachusetts Institute of Technology (MIT) Center for Biomedical Innovation (CBI) launched the *New Drug Development Paradigms (NEWDIGS)* initiative to provide the answers to those questions, and real solutions for the industry. The MIT Schools of Science and Engineering, and the Sloan School of Management have been at the center of industry transformation for more than one hundred years. Their pioneering efforts have been described and chronicled in “*Made in America*”¹ (1989) which focused on overcoming major weaknesses in industrial productivity in the aerospace and education industries, and “*The Machine that Changed the World*”² (1990) which introduced lean manufacturing principles, based on the Toyota Production System, as a successor to mass production. The book “*Lean Enterprise Value*”³ (2002) translated lean manufacturing principles to the aerospace and enterprise context, extending the concept of *enterprise* to include regulators, suppliers, and other “third-party” players.

Industry restructuring will require new business practices for individual companies, but because of the highly interdependent nature of pharmaceutical research, development, and commercialization, it will also require a cross-industry coalition of stakeholders among government, healthcare providers, insurers and others who are committed to driving change and who are each willing to accept and implement change. NEWDIGS will provide a safe haven for collaborative efforts among all of these stakeholders, and an impartial academic environment in which new models can be evaluated.

Through the NEWDIGS initiative, MIT now turns its attention to the pharmaceutical industry, and together with a consortium of biomedical industry and government stakeholders, seeks to catalyze the development and implementation of a new R&D ecosystem that reduces time, cost and risk of pharmaceutical innovation, while increasing value to industry, patients, and society.

A Systems Re-engineering Approach

NEWDIGS is exploring several key questions as it plots a path to industry-wide transformation: What lessons can we draw from other industries to increase the rate of productivity and value of pharmaceutical innovation? What special considerations are required to make it function optimally within a uniquely complex system of technology, government regulation, and healthcare payment and delivery? How do we structure new incentives to reconfigure old inefficiencies?

Initially drawing from the resources of MIT's *Lean Advancement Initiative (LAI)*, NEWDIGS applied LAI's structured, systems engineering methodology, dubbed "Enterprise Strategic Analysis for Transformation (ESAT)"⁴, to reconfiguring the pharmaceutical industry model. The approach extends the concept of *enterprise transformation* to include not only companies within an industry, but also all third party stakeholders with influence or a vested interest in the ability to create value. For the pharmaceutical industry, that would include insurance payors, regulators, healthcare providers, doctors and patients.

In *Phase I* of transformation planning, research and analysis was conducted by a NEWDIGS team to:

- Complete a *current state assessment* and analysis of the pharmaceutical industry environment through interviews, public sources and data provided by participant organizations. The current state was interpreted from multiple stakeholder perspectives, as determined by an in-depth *stakeholder analysis*.
- Outline a preliminary *blueprint of the desired future state* of the pharmaceutical industry environment, and provide a *gap analysis* between the current and the future state. The gap analysis will help identify high impact research priorities for Phase II of NEWDIGS.

Phase II marks an important transition from a thought exercise to a live application of models and concepts. During this stage, NEWDIGS research teams will *design and evaluate potential future drug development paradigms*. Features of the models will be implemented in a test-bed system including knowledge management, business/research processes, data sharing, tracking and analysis, enabling technologies, and regulatory policy. Where needed, efforts will be combined with those of other initiatives and consortia aimed at improving the productivity and value of pharmaceutical R&D.

The test-bed will consist of a series of *demonstration projects* carrying real drugs through development. The demonstration projects will offer hard, quantifiable evidence on whether the new ideas are working, and whether the systemic changes conceived by the NEWDIGS teams can transform an industry that seems parked in a decades-long holding pattern in productivity.

The Current State – Historical Context

The history of the pharmaceutical industry, as we recognize it today, can be traced back to 1897, the year when Bayer introduced aspirin, a compound that until today remains one of the most commonly used drugs. Since then more than a thousand new medicines have been developed and delivered to patients. The impact on patients and society has been immeasurably large -- insulin preparations became available during the 1920s, greatly extending the length and quality of life for millions of diabetics. The first anti-infective drugs, sulfonamides, were introduced in the 1930s, and penicillin during the 1940s, transforming deadly encounters with infectious diseases into routine treatments with full expectation of a rapid recovery. The success of the early antibiotics led to the formation of many new companies and the discovery of new drugs against major illnesses such as cardiovascular disease with the first anti-hypertensive drugs in the 1950s. Although cardiovascular and infectious diseases remained the largest pharmaceutical markets until the end of the 20th century, the industry shifted its R&D focus to other disease areas, such as cancer, metabolic and neurological diseases. It became clear that many of the “easy” solutions had been discovered, and it was time to turn attention to bigger, more complex challenges.

A major transition occurred in the pharmaceutical industry in the early 1960s, precipitated by the thalidomide crisis when the drug, used to prevent morning sickness in pregnant women, caused severe birth defects in thousands of newborns. In the U.S., this tragedy led to the enactment of the ***Kefauver-Harris Amendments*** to the 1938 U.S. Food, Drug & Cosmetics Act. The legislation considerably tightened the safety regulations of the 1938 Act and, introducing a new precedent in product regulation, required proof of efficacy for all new drugs as a condition to receive market approval in the U.S. In 1971, the U.K. and other countries followed suit.

The impact of the 1962 Amendments on the industry was profound and manifested itself in a ***sharp reduction in the number of new drugs*** introduced to the market, from over 40 per year in the late 1950s to less than 20 per year in the three decades that followed the 1962 legislation. A brief rise to over 30 new drugs per year occurred during the 1990s consequent to passage of the ***Prescription Drug User Fee Act*** (PDUFA) and perhaps reduction of a backlog of applications, yet despite excitement over the potential for genomic and high throughput technologies to vastly increase the number of drugs and disease targets to pursue, the number of new drugs declined once again to around 20 per year from 2000 to 2008.

Much of the decline in productivity was due to the ***increasing number and complexity of clinical trials*** required to demonstrate drug safety and efficacy. Total clinical development times, including US Food and Drug Administration (FDA) regulatory review, increased from an average of about 8 years for drugs introduced during the late 1960s to about 14-15 years in the 1990s.

The decline in pharmaceutical productivity was not for a lack of effort. U.S. companies invest an average of 20% of their annual sales into R&D⁵, about four times the average of all other industries and almost twice as much as the computer industry. Aggregate R&D spending has almost ***quadrupled every ten years***, from less than \$1 billion in 1970 to over ***\$91 billion in 2008***.

There are many inherent difficulties in biomedical research that contribute to the glacial pace of drug discovery and development: we continue to have a poor understanding of underlying disease biology, its variation among individuals, and the effect of drugs on that biology; it is necessary to study the efficacy and safety of drugs in clinical trials with large numbers of subjects to obtain statistical significance; and many of the remaining medical needs are complex in origin, have long term or

difficult to measure endpoints, and include chronic conditions with a wide range of genetic and environmental factors.

Taken together, these factors led to other issues that reduced value and productivity in pharmaceutical innovation. For example, extremely long product development times, and the high cost of R&D, coupled with limited patent duration has led to an industry focus on “blockbusters”, serving only the largest markets with the largest revenue potential. The “swing for the fences” approach has led to a high failure rate in clinical trials.

High stakes also led to a very competitive industry culture, with little interest in cooperative ventures to develop early stage technology tools, establish data standards, share disease target information, etc. Efforts to protect intellectual property have even hindered information flows between groups within the same company.

Historical legacies and the accumulation of many inefficient practices in the pharmaceutical business model have become deeply ingrained by a highly risk averse corporate, legal, and regulatory culture. Many of these industry ills, and the difficulty in resolving them, originate from a lack of alignment between stakeholders.

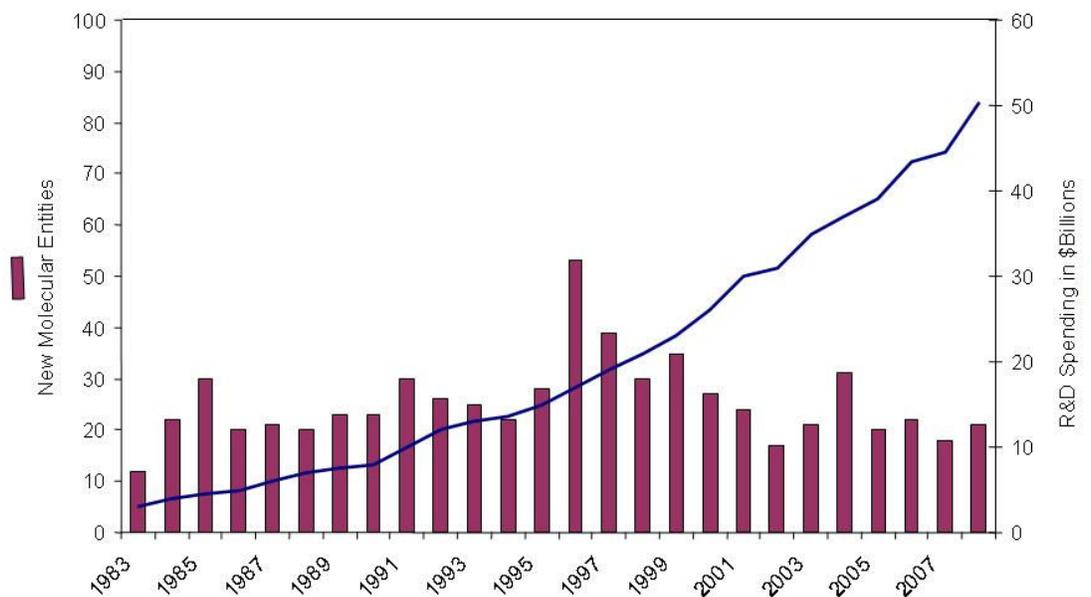


Figure 1: US Pharmaceutical R&D Spending vs. Productivity

The Current State – Stakeholder Analysis

The issues facing pharmaceutical innovation are by now well known, but to better understand the dynamics that have led to persistently weak productivity, NEWDIGS researchers mapped out key interactions of industry players with other stakeholders (Figure 2) including CROs, government regulatory agencies, insurance payors, healthcare providers and patients. This map has become a systems level framework for determining stakeholder requirements, pinpointing key bottlenecks in their interactions with each other as well as missing but potentially valuable interactions, and identifying misaligned incentives. It has also served as a starting point for reconfiguring a model of interactions designed to increase productivity.

The exercise highlighted key challenges faced by each of the stakeholders. For example:

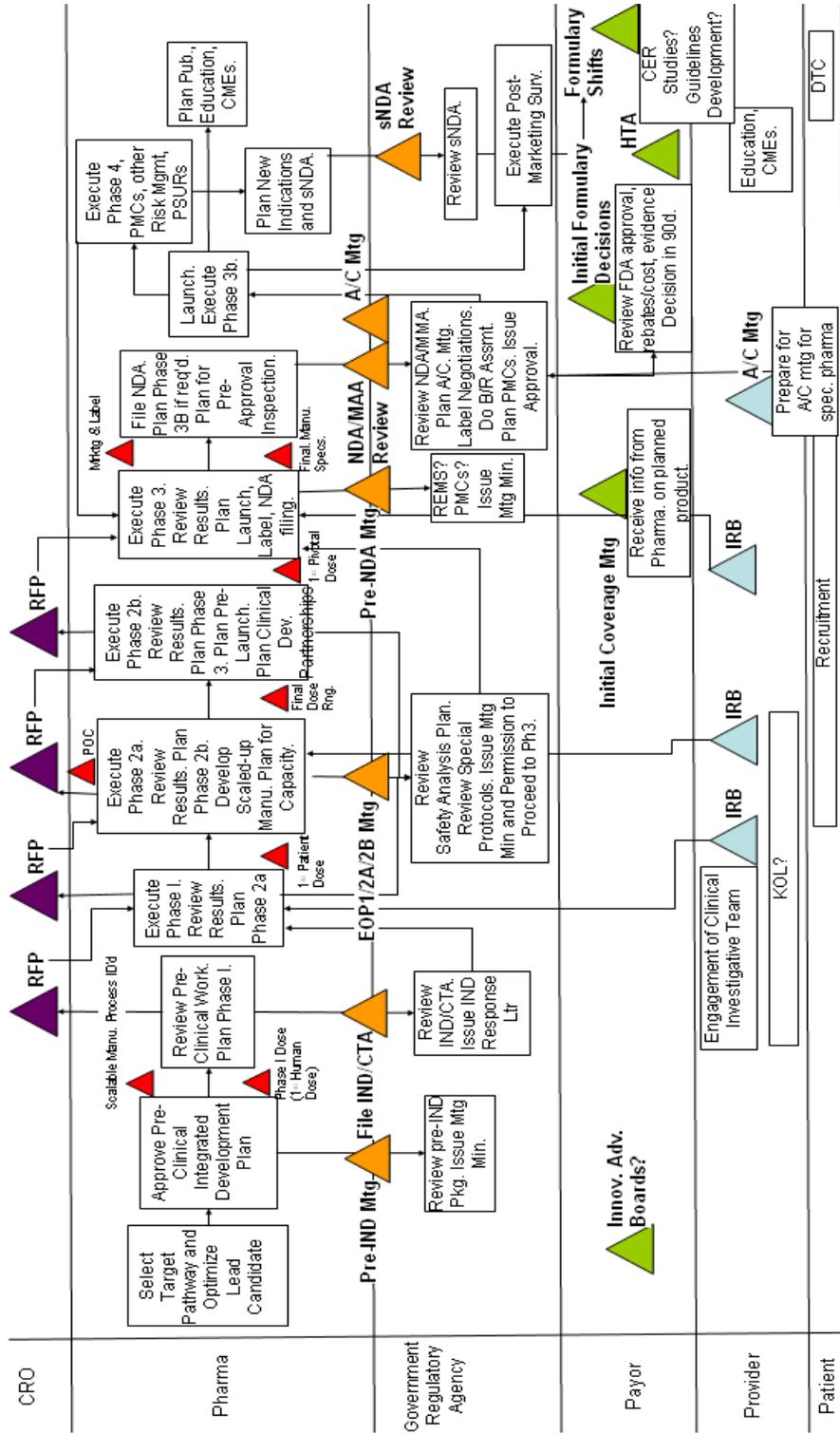
- **Payors:** The pharmaceutical industry has only lately come to the realization of the increasing importance of payors as a key customer, particularly with the rising interest in comparative clinical and cost effectiveness research as part of coverage and reimbursement. One of the most commonly expressed concerns among payors is that when a new drug is introduced to the market, they are not able to determine from the information available where to insert it into the current treatment paradigm. They need better information and clear standards of evidence about the product, its impact on disease, and comparison to other treatments in order to make sound coverage decisions. Current policies on coverage are very inconsistent from one state to the next and from one payor to the next due to this gap, which places a huge burden on the ability of a new drug to become widely prescribed. Consistent coverage decisions will go a long way toward helping to predict and contain spiraling healthcare costs.
- **Regulatory agencies:** The gap between advances in science and product strategies, and the ability of regulatory agencies to adapt their policies to these advances is widening⁶. Combination drugs, multi-indexed arrays, and companion diagnostics all present issues for which the FDA and other international regulatory bodies have been slow to issue new definitive guidelines. That fact alone has hampered innovation since companies tend to be reluctant to venture into areas where the regulatory landscape is uncertain. Regulatory agencies, pharmaceutical and diagnostic companies can help close this gap by *working together* on devising new policies. In addition, educating Congress and the public about the emerging scientific capabilities and their implications for public health is critical for promoting progressive oversight policy.

A second issue that places a drag on the introduction of new products is the lack of harmonization between regulatory requirements in different countries, creating bureaucratic and logistical hurdles that companies must overcome, leading to duplication of work, added costs, and delayed access to treatments for patients.

- **Healthcare providers:** The degree of complexity in diagnosis and treatment options is increasing, but the tools used to handle that complexity have fallen behind. Physicians will need more clinical decision support, particularly as treatments become linked to patients' molecular and genetic profiles in the new paradigm of personalized medicine. Clinicians will also become important gatekeepers of valuable medical data that can be fed back into research through healthcare information technology. Medical education currently does not anticipate these changes, and so will have to be updated to prepare the next generation of physicians to become agents of rather than obstacles to change.

- **Patients:** Many patients have insufficient information on the benefits and risks of new medicines including side effects, drug interactions, and information to help them understand the relationship between the benefits and risks. Since individuals over 65 take an average of 5-10 medications daily⁷, there is a need of better tools for managing medication and the potential for adverse interactions. They have concerns about the rising cost of new treatments, a lower tolerance for safety issues as more therapeutic options become available, and increasing impatience for the development of new options. Patients with less common diseases feel left out as corporate strategies focus on larger markets.

Figure 2: The pharmaceutical industry process map



The Future State – Closing the Gaps

The current state analysis revealed a number of reasons for the inherent difficulty of developing new breakthrough medicines, but also a significant number of misaligned incentives, legacy systems and approaches, and other inefficiencies that have accumulated over decades in the industry. These are the parameters that *can* be changed to improve both performance and value in pharmaceutical development. For example:

- The judicious use of biomarkers and surrogate endpoints can provide a more immediate assessment of drugs in clinical trials, and allow smaller, more targeted populations to be tested, potentially shaving months or years off of the process.
- The channels of communication between industry and regulators can be opened, to allow for more flexibility in introducing new technologies and methods, and to accelerate the development and approval of new drugs and diagnostics without compromising safety.
- Public-private consortia (like CBI) can also play an important role as arbiters of shared industry data, to enable pre-competitive development in areas such as predictive toxicology.
- The risk of commercializing new treatments can be reduced by earlier interactions with insurance companies (payors) and a structured system of health technology assessment, ensuring that better data on benefits, risks and comparative effectiveness will be available for coverage and reimbursement decisions.

Future state vision

While the current state analysis revealed many aspects of the industry that *can* be changed, the question of what *must* be changed was addressed by outlining the desired future state of the biomedical “ecosystem”. The NEWDIGS future state analysis would then permit the creation of a roadmap of transformation between current and future scenarios. The following were the top level elements of the desired future state.

- Reduced time in moving new treatments from discovery to the patient
- Reduced cost of drug development, with lowered costs passed on to the patient
- Success rate of the clinical trial process well above the current 10%
- New products emerge thoroughly vetted for benefits, risks and comparative effectiveness to existing therapies
- Products that meet the most important medical needs – scientifically and medically-driven as opposed to strictly market-driven
- Integration of R&D into the learning healthcare system, with clinical and research data informing each other in real time, leading to optimization of care and acceleration of discovery.

- Scientists and clinicians are not the only participants in R&D. Patients, payors, and regulators play an active role in contributing information to and improving the process of getting new (safe, effective, transformative) medicines to patients as rapidly as possible.

The strategies needed to close the gap between the current and ideal future state of the industry fall into four broad categories: market, operational, product, and policy.

Market strategies

One can shift the focus from “one size fits all” drugs to drugs that are targeted to *defined populations* (stratified by genetic, molecular, imaging and/or biochemical biomarkers). Increasingly, information is becoming available on the genetic variations and molecular signatures that determine whether an individual is susceptible to certain diseases, may benefit from particular treatments, or will suffer side effects from administered drugs. The current system of business models, regulation, organizational structures, and reimbursement reinforces a “blockbuster” product strategy, targeting the largest markets (and not always the most medically important markets) to ensure the greatest return on investment. It is a consequence of the high failure rate of pharmaceutical development that one drug must compensate for the lost investment of several other drugs. It is also a consequence of the long journey through clinical trials and regulatory approval that when a drug product finally makes it to the market, it must bring in all of its revenue within the few years remaining before its patent expires. Under such conditions, big markets become the only option.

A *pharmacogenomic approach* introduces a new model. For the patient, it can offer improved medical outcomes with fewer adverse drug reactions and less time and money spent on ineffective therapies. For pharmaceutical companies, there is the opportunity to reduce the size, cost and duration of clinical trials by focusing on genetically or molecularly defined populations most likely to respond to the investigational drug or least likely to experience adverse reactions. Competitive advantages can be claimed within crowded markets if a particular drug demonstrates superiority in a subset population, and some drugs that have failed clinical trials on a broader population can be revived.

New business models can be implemented that encourage the development of treatments for *orphan diseases* vs. large markets. Such an approach generates tremendous value for patients with rare conditions, and can offer significant value to pharmaceutical companies even if the market is limited to a few hundred or a few thousand individuals. Many of these rare diseases and conditions share molecular pathways with more common diseases, so introducing a drug to a small population with no other treatment options can offer a faster path to regulatory approval, and allow a more rapid extension of the indication to a larger population with a more common, related disease. Such has been the strategy behind the development of the Novartis drug ACZ885 for Muckle Wells syndrome (incidence of 1 in 1 million) – a rare inflammatory condition with similarities to rheumatoid arthritis.

The societal value of the pharmaceutical industry can be significantly enhanced by serving *diseases of poverty in the developing world*. Parasitic, viral and bacterial diseases, such as malaria, tuberculosis, acquired immunodeficiency syndrome (AIDS), African trypanosomiasis and leishmaniasis affect millions of people around the globe each year, more than 90% of whom are from third world, impoverished countries. The expectation of a return on investment is very low for these diseases, despite the magnitude of their societal impact, and discourages investment by companies, venture capitalists, and public investors. Transforming third world diseases into viable markets through public/private partnerships, guaranteed purchase funds, foundation support and other vehicles could serve not only a company’s corporate citizenship goals, but could also score valuable public relations points in an industry inundated with negative public opinion. Risk reducing incentives and guaranteed

funding for third world markets can also provide a useful pathway for emerging biotechnology companies to prove their technology and business models.

Operational strategies

The ability to rapidly adapt *organizational structure* and scale to changes in the environment is a hallmark of thriving in the natural world, and it's no different in the world of drug discovery and development. Yet the majority of large pharmaceutical companies have a highly centralized, hierarchical organization that channels ideas into silos, averts risk to preserve and protect resources, and tends to influence decisions by subjectivity and advocacy rather than having them rooted solely in evidence and merit.

Organizations that are distributed, adaptable, and team based are more adept at dealing with the disease research challenges and the tools available to investigate them in the 21st century. This may involve creating a culture of internal “hypercollaboration” across the organization that convenes targeted expertise and technologies for projects on an as-needed basis. Teams can assemble and disassemble in a highly fluid fashion, while retaining a well defined structure for accountability in decisions. The effective management of external collaborations in a virtual workflow will also be increasingly important for success. Elements of this type of operating model are now being employed in emerging ventures like CollaboRx (http://collabrx.com/for_researchers.php).

A *governance structure* where decisions are pushed down to levels closer to where they are applied, and closer to the teams, and an environment where knowledge is shared freely across disciplines can encourage a level of risk-taking conducive to innovation. This could involve one team pursuing a scientific idea that in a traditional setting might be shot down because it did not fit the model of another group or division, or it could involve a compound being carried over from one disease area to another because of a shared molecular pathway. Governance should enable decisions that support projects on their merits, not feed resources to or preserve a set organizational structure.

By extension, *career rewards and incentives* should align individual performance and decisions with long term, value-building priorities, including recognition for terminating projects early due to identification of potential clinical liabilities. The concept of supporting and incentivizing a “fail fast” philosophy has been put into practice in Eli Lilly’s Chorus drug development model⁸, where minimal scientific experiments are conducted to discharge risk as early as possible in the process.

Clearly defined, transparent, evidence-based decisions can also be supported by implementing a *process-map of research and business activities* with well defined decision points and evidence review. The approach, called business process re-engineering, was introduced by MIT computer scientist and Prof. Michael Hammer and has been successfully implemented in many other industries.

The pharmaceutical industry has a traditionally protective culture around its compounds, disease targets and methods. A more *collaborative, pre-competitive approach* can go a long way toward helping individual companies overcome certain hurdles in drug research and development. The benefits of pre-competitive collaboration are well documented, with examples including the SNP Consortium, the Biomarkers Consortium, the HapMap Consortium, the Serious Adverse Events Consortium, and the Diabetes Genetics Initiative. These efforts have yielded valuable information to the benefit of many commercial and academic research programs. While chemical compounds or biological molecules developed as therapeutic agents will remain proprietary, these consortia and initiatives are demonstrating that data on genetic variation, biomarkers or even disease targets can be

developed through cooperative ventures, then released to the public domain to foster commercial development.

One of the most critical areas of need for “*co-opetition*” is in drug safety and toxicology. The FDA has access to large quantities of data on the safety of various compounds as they move through clinical trials -- data which can be correlated to chemical structures and disease targets. However, due to confidentiality agreements with the pharmaceutical companies, the government agency is not permitted to combine and share the information for the purposes of analysis and generating predictive models. Firewalls on safety data have in some cases led to multiple sponsors encountering similar problems of toxicity or efficacy for similar compounds and targets, which led to repeated, but avoidable failure in clinical trials (see box “Toxicity Déjà vu”). The issue is not simply one of making drug development more effective, but protecting patients as well.

The ability to compile pre-competitive data on compounds from multiple sources will significantly enhance efforts at developing *predictive models* for drug behavior including absorption, distribution, metabolism and elimination, as well as toxicity. Predictive technologies will help eliminate problematic compounds, effectively “pulling risk back” into the earlier stages of preclinical and clinical development, and improving the quality of compounds entering later stage clinical trials.

Drug development works best when it is done in *collaboration with stakeholders*, drawing input from patients, insurance payers, and regulators. Such an approach can inform clinicians and researchers of the most critical medical needs, help gain access to patient populations and biological samples, provide insurers with the evidence needed to make reimbursement decisions, and streamline the regulatory approval process by focusing and adapting clinical trials. The development of a collaborative network will help to improve clarity and transparency in the way each sector operates (payers, regulators, etc) and accelerate the process of having each stakeholder’s needs met by the others.

New models of clinical trial design can overcome significant bottlenecks in drug development. *Adaptive clinical trials* can be reconfigured according to new data collected during the progress of the study. In conventional trials, parameters such as dosage, duration of treatment, and other conditions are fixed until a predetermined end, but adaptive trials can be terminated early based on real time data – either because the drug is determined to be ineffective or unsafe, or because the data indicate it is actually very effective and there is enough information gathered to progress to the next stage. Treatment arms and protocols can be modified to ensure that useful information is obtained on safety and efficacy, and data can be carried over to progressive trial stages in blended Phase II/III studies.

The use of *electronic health records (EHRs)* has implications that extend way beyond efficient healthcare delivery. They also present the opportunity to collect phenotypic data from everyday clinical encounters on millions of patients, and feed that information back into research. The ability to combine and analyze clinical information on a broader population will enable *predictive models of disease* and response to treatment for targeted populations. It will also allow *new models for clinical review* based on post-market analysis to extend traditional models based on randomized clinical trials.

EHRs and health information systems will form the keystone of a *learning healthcare system* that connects clinical care to basic research, enables sharing of information between stakeholders (e.g. patients, physicians, scientists), breaks down barriers across knowledge silos, and creates heuristic opportunities from both successes and failures.

Toxicity Deja Vu

Around 1991, SmithKline Beecham discovered a molecule that, in an *in vitro* screen, had demonstrated a potent anti-inflammatory effect. Working backwards, they identified the target of the compound to be p38, a mitogen-activated protein kinase (MAPK) that is involved in cytokine synthesis. The p38 target has a broad set of biological roles, including involvement in the synthesis of tumor necrosis factor, and induction of enzymes such as cyclooxygenase 2, nitric oxide synthase, metalloproteinases and adhesion molecules. The first iteration of the inhibitor exhibited a fair amount of liver toxicity, enough to warrant termination of the project.

Nevertheless, several other companies jumped in to join the search for a clinical grade p38 inhibitor, including Merck, Novartis, Rhone Poulenc Rorer, and Johnson & Johnson. Using basically the same scaffold and similar chemistry to the original molecule, they found that it was not possible to get rid of the liver toxicity. It was intrinsic to the core structure of the molecule.

In 2001, Boehringer Ingelheim and Vertex pursued a completely different approach using structure-based drug design and came up with a molecule from a different chemical class. Even then, p38 was found to have a direct effect on liver function. The target itself proved problematic. The company Scios (later bought by Johnson & Johnson) developed a p38 inhibitor for rheumatoid arthritis (RA) and moved it into phase II clinical trials, but found issues with toxicity and had to terminate the project. They did not release their data to the public until about 3 years after the clinical studies were concluded.

In the meantime, a number of other companies developed similar compounds, eventually moving them into phase I or phase II clinical trials for the treatment of rheumatoid arthritis, and coming to the same conclusion with the termination of their projects.

The case of p38 presents a strong argument for the sharing of compound and target related safety data across competitors. Had such a resource existed, it would have saved many years, and many millions of dollars of research investment from being spent by numerous companies chasing compounds or targets that clearly had non-resolvable issues of toxicity (see list of discontinued projects below), -- time and money that would have been better spent pursuing other pathways for the treatment of rheumatoid arthritis and related inflammatory conditions.

P38 Targeted Drugs Discontinued

| Drug | Company | Indications | Discontinued |
|-----------|-------------------|-------------------|--------------|
| RWJ 67657 | Johnson & Johnson | Anti-inflammatory | Phase II |
| AMG-548 | Amgen | RA, COPD | Phase I |
| AVE-9940 | Sanofi-Aventis | RA | Phase I |
| SC80036 | Pfizer | RA | Pre-clinical |
| VX-745 | Vertex | RA | Pre-clinical |

Product strategies

Risk and costs in drug development have a profound effect on product strategy. The industry has been criticized for putting forward too many “me too” compounds that differ little from existing drugs (the proliferation of statins are a typical example). The high cost of R&D and a limited window of time to recoup expenses and turn a profit before patent expiration favor risk-averse strategies. New formulations combining already approved agents, or making subtle chemical changes allow a drug a new lease on patent life. In some cases, that incremental innovation can be meaningful to patients, such as permitting one to take a drug once a day rather than twice, improving adherence to treatment. In other cases, drugs in the same class might exhibit an improved profile of safety and effectiveness for one patient subset over another. Nevertheless, the overarching goal of the pharmaceutical industry must remain around the development of **breakthrough treatments** that address significant disease burdens – a bolder product strategy that must be supported by incentives, cost reductions and greater efficiency in research and development.

Very often, product strategies are guided by market and financial forecasts which, like weather forecasts, have some semblance of truth but might be missing key parameters to make them truly predictive. A few companies are exploring the benefits of pursuing more **scientific- and medically-driven product portfolios**, based on the premise that better quality drugs emerge from programs where the scientific basis of mechanism and off-target effects are better understood. The philosophy of: “lead by science and medical need, and the money will follow” is consistent with the idea that providing something of real value to patients is always rewarded.

The long duration of the clinical trial process has led to a product focus on treatments for late stage disease, when it is easier, and faster to demonstrate response. Very few drugs are developed for **prevention of disease, or treatment of early stage disease** to slow progression. Improvements in clinical development processes, incentives in regulatory policy, and the use of biomarkers to get a quick read on a drug’s effects can all support a greater emphasis on prevention and early treatment.

From the third party perspective, new incentives or restructuring of the insurance enrollment system will be necessary to support products with preventive benefits, as current reimbursement strategies look no further than the expected period of enrollment, which may only be a few years.

The pharmaceutical industry can take a page from other industries such as automotive or telecommunications, and see their products as something more than a single deliverable. Automotive manufacturers added value with roadside assistance services, and today, one no longer just buys a cell phone, but considers the entire package of phone and service. Significant value can be added by focusing on **integrated healthcare solutions**. Pharmaceutical companies can offer services, for example, to diabetes patients to help them manage their disease better. Personalized medicine enhances safety or efficacy for genetically defined populations. Bundling the development of a targeted drug with a diagnostic test that identifies the individuals most likely to benefit improves value for all patients, and for the company by securing market share in a targeted group. “Cocktail” strategies of combining drugs with complementary mechanisms can be more effective than single drug formulations, and may require cooperative development with competitors as well as new regulatory pathways.

The standards of evidence for regulatory approval have steadily become more rigorous but are nevertheless predictable. On the other hand, evidence required to secure payment by insurers is inconsistent and not well defined. Future product strategies must take into account that the benefits,

cost effectiveness and comparative effectiveness of new treatments will become an important factor in their adoption, and companies must plan accordingly.

Policy strategies

The future of pharmaceutical innovation will see a *transformation in the relationship between drug developers and regulatory authorities* – a relationship that emphasizes collaboration in addition to strictly statutory obligations. Of course, both real and perceived conflicts of interest must be avoided, but the need to collaborate will be driven by necessity.

Scientific advances that have a potential impact on product regulation have to be dealt with in a timely manner, but the FDA, the Centers for Medicare and Medicaid Services (CMS) and their international counterparts have limited resources to adapt to such developments. Examples include the emergence of *in vitro* diagnostic multiple index arrays (IVDMIA's) that measure the expression of multiple genes with results interpreted through statistical algorithms; the use of companion diagnostic tests to identify patients who will benefit from a particular drug; or drugs formulated in combination for greater effectiveness. Traditional protocols for product review, approval, comparative effectiveness, coverage determination, reimbursement, and introduction to practice do not accommodate these new product concepts very well, so it is imperative for industry and government authorities to work together to define new guidelines for their market utilization.

A collaborative approach will help the FDA to refocus its mission on serving patients and the public good (by finding ways to get safe, effective medicines to market faster) vs. focusing only on public protection.

One approach that could lead to improved safety *and* faster access involves progressive licensing of new drugs⁹. Progressive licensing may allow drug sponsors to conduct clinical trials of more limited scope, followed by continuous evaluation of the benefits and risks of the drug throughout its lifecycle, even as it is being administered to patients. This approach would address a major shortcoming of the current drug development paradigm, where products are tested in homogenous populations in a long series of clinical trials, but evaluation effectively ends after market approval, when they are used in significantly larger heterogeneous populations where the benefits and risks are not well known. Progressive licensing works in an evidence-based decision framework, and as such must be supported by clear decision and evidence standards, an ability to effectively track and analyze data on usage, and an open network for sharing clinical information.

The clarification of evidence standards will also be required for obtaining insurance reimbursement of personalized treatments and diagnostics, or for comparative effectiveness studies, which will help level the playing field for new products to enter the market and gain acceptance based on their real value to patients.

The transition to a more evidence-based approach will not only have to be accompanied by rigorous standards of evidence, but also a strategy for risk communication to both healthcare providers and the public. These steps would be required to help physicians and the public better understand the cost-benefit rationale behind recommendation for certain treatments, particularly when those recommendations go against long held practices or intuitive preferences.

Government support for the implementation of healthcare information technology (health IT) and EHR's are well aligned with the needs of a future pharmaceutical model based on the establishment of a learning healthcare system (including personalized medicine, safety surveillance, and research), yet

more policy changes are required to incentivize and encourage adoption of health IT at all levels. As hospitals and physicians offices go digital, now is the critical time to make sure the new systems are designed to track the right information to be of use along the entire chain of activity from research to patient care.

Toward a New Model of Drug Development

A reconfiguration of pharmaceutical innovation clearly requires a multifaceted approach. In systems engineering, transformation is effected only when every component is accounted for and changes throughout the system are coordinated to be mutually supportive. The NEWDIGS program will focus on transforming the drug discovery and development process, including contributing elements such as regulatory and reimbursement policy. The goal of the program is to improve productivity in the pharmaceutical industry; enhance value for insurers, healthcare providers, regulators; and most importantly, improve patient outcomes. There are three major components of the NEWDIGS initiative:

Product Development Process

A new model for the way products are carried through their entire lifecycle, from preclinical to clinical research and delivered to patient will be refined through a series of live demonstration projects. In these projects, the application of new principals, technologies, methods, and stakeholder interactions will be tested on a small portfolio of drug candidates derived from *active* pharmaceutical company pipelines. Academic research will be associated with these demonstration projects to provide impartial analysis and a laboratory from which new ideas and knowledge can be generated.

A very important aspect of making these demonstration projects work is the ability to conduct them within environments that are flexible and receptive to change and experimentation. Such environments will have cultures that value and reward innovation, and have established operating procedures, policies, and tools that make it easy to test and evaluate new approaches. Essential components of the environment include care delivery systems that have advanced EHR systems with standards in place for interoperability of data; efficient institutional review board (IRB) processes for approving new study designs; and regulatory agencies that value collaboration with key stakeholders and have progressive policies that encourage scientifically and ethically sound innovation. The intention is to assemble, and to learn how to operate effectively within, an innovation ecosystem where critical resources do not have to be in one physical location, but are connected in a virtual network.

NEWDIGS will leverage guiding principles from the evolving concept of a learning healthcare system¹⁰, and incorporate resources and lessons learned from other consortia and initiatives focused on improving and enhancing value in various components of the industry (Table 1), such as NCI's Big Health Consortium™ or the Observational Medical Outcomes Partnership (OMOP). NEWDIGS will focus on what is needed to integrate industry efforts, break down functional silos, improve the flow of knowledge within and between research organizations, and facilitate rapid cycle learning to improve decision-making by all stakeholders, from the research lab to doctor's office.

While many elements of a new drug development paradigm (e.g., biomarkers and surrogate endpoints; adaptive clinical trials; drug safety monitoring; information technology; corporate research re-organization) have been implemented in isolated cases across the industry, there has not yet been a coordinated effort to integrate, evaluate, and refine them from a systems perspective. The NEWDIGS demonstration projects will enable this holistic approach, while at the same time offering hard data on the effectiveness of different models to facilitate adoption in more entrenched systems

Table 1: Sample initiatives for data sharing and re-engineering drug R&D

| Initiative | Capabilities |
|--|--|
| BIG Health Consortium & caBIG | Information systems and initiatives to connect stakeholders, share data, integrate research, coordinate healthcare and deliver consumer information. Establishing a “learning healthcare system” in which formerly independent silos of information are connected and inform each other. |
| Biomarkers Consortium | Identification, development, and validation of biomarkers for use by biomedical researchers, regulators and healthcare providers. Supporting predictive, preventive and personalized medicine through public release of biomarker data. |
| Sage Bionetworks | Building an open access platform and databases to support innovative, dynamic disease modeling that informs laboratory and clinical research. Interconnect scientists contributing to evolving, integrated networks of biological data |
| Cardiac Safety Research Consortium (CSRC) | Improving evaluative sciences specifically in relation to cardiac safety |
| Centers for Education and Research on Therapeutics (CERTs) | Increasing awareness of the uses and risks of new drugs and drug combinations, biological products, and devices, as well as of mechanisms to improve their safe and effective use. |
| Clinical Data Interchange Standards Consortium (CDISC) | Developing and supporting global, platform-independent data standards that enable information system interoperability to improve medical research and related areas of healthcare |
| Clinical Trials Transformation Initiative | Identifying practices that increase the quality and efficiency of clinical trials |
| Critical Path Institute (C-Path) | Building new working relationships among federal regulators and the industries they regulate. Modernize the scientific process through medical products are tested and developed |
| Developing Evidence to Inform Decisions About Effectiveness (DEcIDE) | Gathering new knowledge and information on specific treatments; conducting studies on the outcomes, effectiveness, safety, and usefulness of medical treatments and services |
| FDA – Critical Path Initiative | Collaborating with industry to address specific areas where new technologies could be applied during development to improve the accuracy of predicting safety and efficacy of medical products |
| Predictive Safety Testing Consortium (C-Path) | Identifying improved pre-clinical and clinical safety testing methods and facilitating the development of new regulatory (FDA and EMEA) processes for approving such testing methods |
| FDA – Sentinel Initiative | A national electronic system transforming FDA’s ability to track the safety of drugs, biologics, and medical devices once they reach the market. |
| Health Commons | Creating a virtual marketplace or ecosystem where participants share data, knowledge, materials and services to accelerate |

| | |
|---|---|
| | research. |
| Innovative Medicines Initiative | Overcoming research bottlenecks in the drug development process in the European market |
| Observation Medical Outcomes Partnership (OMOP) | Improving the monitoring of drugs for safety; analyzing existing healthcare databases to identify and evaluate safety and benefit issues of drugs already on the market |
| International Serious Adverse Effects Consortium (SAEC) | Identifying and validating DNA-variants useful in predicting the risk of drug-related serious adverse events |

Enablers

In addition to improved business processes, organizational transformation, regulatory and reimbursement policies, and a collaborative framework, certain technologies, tools, and methodologies will be necessary to make an impact on innovation. NEWDIGS will prioritize the development and implementation of those resources with the highest impact, including knowledge management tools, biorepositories and their management systems, shared databases and analytical software in areas such as predictive toxicology, standards for database interoperability, and electronic health records to link clinical and research information.

The measurement of biological (molecular) markers could serve as surrogate endpoints to accelerate decision-making and evaluation of clinical trials. Such markers could also be used during preclinical testing (in animals) to better correlate results and predict outcomes in humans. The availability of predictive markers (or any predictive technology for that matter) will allow companies to pull risk further upstream into less costly and less time-consuming preclinical and early clinical development stages. While NEWDIGS will not be focused on the search for specific biomarkers, it will combine its efforts with existing initiatives (such as the Biomarker Consortium) to improve supporting technology for biomarker identification and validation, and advocate policies that encourage the use of biomarkers.

It is estimated that during the entire pre-genomics era, the industry worked on a total of about 400 disease targets, mostly receptors, ion channels or enzymes. However, in the post-genomics era, this number is believed to have increased to several thousand druggable targets. Every target selected in R&D has implications for downstream risk in clinical trials. The development of tools and databases that enable sharing of preclinical information on targets can have a significant impact on performance in clinical trials. The greatest challenge in this area is determining what type of information can be shared, while at the same time protecting proprietary preclinical data.

Efforts will be made to catalyze new, targeted interdisciplinary research/innovation among MIT, the Harvard-MIT Division of Health Sciences and Technology, and other academic institutions, in collaboration with external stakeholders, to address these needs. NEWDIGS will support the development of technologies, methods, models, tools, infrastructure and standards that improve the quality and productivity of therapeutic product development.

System

Innovation never works in isolation, but requires an entire system of support to take place. NEWDIGS considers the broad context within which innovation occurs, such as government and private industry policies, statutory frameworks, venues and guidelines for stakeholder interactions. The initiative enables policy and process designs that support a learning healthcare system, puts in place incentives to encourage innovation, shares information to facilitate productivity, removes barriers to new technologies and approaches, fosters risk-sharing business and collaboration models, and channels industry efforts that serve patients' needs for better health and safety.

NEWDIGS seeks to integrate, not duplicate, the substantial efforts of other organizations to improve productivity and value in the pharmaceutical industry and to create a system in which that is possible. Consortia, such as the Personalized Medicine Coalition, standards organizations such as the Clinical Data Interchange Standards Consortium (CDISC) and patient groups such as the Genetic Alliance have already built a substantial network and programs to inform important innovation-enabling policy decisions.

NEWDIGS focuses on complementing these efforts and creating venues in which stakeholders can converge, communicate, and reach consensus. Critical areas of need for system development include helping the FDA to reach clarity on regulatory issues such as the co-development of therapeutic and diagnostic products for personalized medicine applications, or the regulation of biological generics; suggesting standard criteria of evidence for benefit and cost effectiveness studies to facilitate consistent insurance reimbursement decisions; and providing guidelines for comparative effectiveness studies that take into account relative benefits and risks for patient sub-populations.

Changing the system that supports pharmaceutical innovation is not a third party exercise. NEWDIGS is set up as a safe haven for all direct participants in the system to discuss new models of interaction and reach a consensus. Members include:

- Pharmaceutical companies
- Biotechnology companies
- Contract research organizations
- Diagnostics companies
- “Systems integrators” (e.g. Siemens, McKesson)
- Insurance payers
- Healthcare providers
- FDA and other global regulatory agencies
- Patient advocacy groups

The Pharmaceutical Industry at Full Throttle – The HIV Story

It was just a few years after the first reports of the deadly HIV epidemic, but already many in the US had grown frustrated with the slow pace of research into treatments for the disease. This was not an ordinary situation. HIV related AIDS spared no one in its path, and there was nothing available to cure, treat or slow its progress. In June of 1988, a Presidential Commission on the HIV Epidemic issued its final report, declaring that the FDA was "not meeting the needs of people with AIDS". In October of that year, hundreds of ACT-UP demonstrators virtually shut down operations at FDA headquarters

The message was urgent and clear. Just eight days after the ACT-UP demonstration, the FDA announced new regulations that would accelerate the approval of drugs for the treatment of AIDS, easing or lifting many of the hurdles to clinical testing. Community groups participated directly in the research, and by February of 1989, the FDA approved the drug pentamidine for the treatment of AIDS-related pneumonia. The data that led to the approval was collected by the County Community Consortium of San Francisco and the Community Research Initiative of New York

By August 1989, clinical tests showed that the drug AZT could slow progression of AIDS in HIV positive individuals who displayed no symptoms. It was a break in a long string of bad news that finally offered hope. Louis Sullivan, then Secretary of Health and Human Services said: "Today we are witnessing a turning point in the battle to change AIDS from a fatal disease to a treatable one." By October, a second drug, dideoxyinosine (ddI), was made available for the treatment of AIDS, even though clinical trials had not been completed. In 1991, a third antiretroviral dideoxycytidine was approved for patients not able to tolerate AZT. Combinations of these drugs were approved for treatment in 1992 and 1993.

In April 1993, 15 pharmaceutical organizations formed the Inter-Company Collaboration for AIDS Drug Development (ICC) to speed the development of HIV antiviral drugs. The effort would expedite the evaluation and regulatory approval of novel drug combinations, foster independent, direct collaborations between companies, facilitate the exchange of clinical data, and arrange for patients and physicians to have rapid access to promising new treatments.

The history of HIV AIDS serves as an object lesson in rapid, effective drug development. A combination of favorable regulatory policies, community involvement, and industry collaboration led to the availability of new treatment options within months of a change in mindset. Applying similar principles in a broader context may help resolve many of the productivity issues facing the industry today.

Conclusion

The analysis presents one very clear message: the current industry model is not working, and a systemic approach is required to establish a new model in which innovative treatments can be discovered and delivered to patients in a timely fashion, where the rate of production matches expectations set by the genomic era, and the safety and quality of new drugs meet the needs of patients, providers and payers. There is no question that the challenges are formidable. Finding treatments or cures for cancer, AIDS, Alzheimer’s disease or diabetes is a tall order. The complexity of research, regulatory environment, intellectual property issues, and payment systems are significantly greater than any other industry. But there is a strong perception among the public, regulators, insurers, and the pharmaceutical industry itself that we are not extracting the full value of pharmaceutical research and development – that there are myriad inefficiencies and misaligned incentives that are holding us back. In the context of the larger issue of healthcare reform, the timing for reconfiguring pharmaceutical R&D at the system level is ripe.

The NEWDIGS initiative serves as catalyst, convener, and change agent as it provides a safe haven for testing and evaluating new pharmaceutical development paradigms. It provides a vehicle for multiple stakeholders committed to transformation to develop critical knowledge within the healthcare industry about how to operate as a flexible, adaptable, networked innovation ecosystem. Ultimately, NEWDIGS provides a rich and timely opportunity for reconstructing a system that harnesses the full potential of emerging science to cure disease and enhance public health.

Appendix

**MIT Center for Biomedical Innovation
Strategy & Policy Council**

| | |
|---|--|
| <p>Burt Adelman, MD Former Executive VP, Portfolio Strategy Biogen Idec CBI Distinguished Fellow, MIT</p> | <p>Robert Mulroy, MPPM President and CEO Merrimack Pharmaceuticals</p> |
| <p>John Alam, MD, PhD Former Executive VP, Research & Development, Vertex Pharmaceuticals CBI Distinguished Fellow, MIT</p> | <p>Garry Neil, MD Corporate Vice President Office of Science & Technology</p> |
| <p>Tenley Albright, MD Director, Collaborative Initiatives MIT</p> | <p>Steven M. Paul, MD Executive VP, Science and Technology President, Lilly Research Laboratories Lilly and Company</p> |
| <p>Ernst Berndt, PhD Louis E. Seeley Professor of Applied Economics MIT Sloan School of Management Science</p> | <p>Wayne Rosenkrans, PhD President, Personalized Medicine Coalition CBI Distinguished Fellow, MIT</p> |
| <p>G. Steven Burrill Chief Executive Officer Burrill & Company</p> | <p>Ram Sasisekharan, PhD Director & E. H. Taplin Professor, Harvard-MIT Division of Health Sciences & Technology</p> |
| <p>Claude R. Canizares, PhD VP for Research and Associate Provost, MIT</p> | <p>Phillip A. Sharp, PhD Institute Professor, MIT Nobel Laureate</p> |
| <p>Charles Cooney, PhD Robert T. Haslam Professor of Chemical Engineering Faculty Director, Deshpande Center for Technological Innovation, MIT</p> | <p>Anthony J. Sinskey, ScD Faculty Director, CBI Professor of Biology and Health Sciences and Technology, MIT</p> |
| <p>Victor J. Dzau, MD Chancellor Health Affairs and President & CEO, Duke University Medical Services</p> | <p>Matthew W. Strobeck, PhD Senior Security Analyst Westfield Capital Management</p> |
| <p>Peter Farina, PhD Chief Executive of Developing World Cures and Former Senior Vice President of Development, North America, Boehringer-Ingelheim</p> | <p>Steve Tannenbaum, PhD Underwood-Prescott Professor of Toxicology and Chemistry, MIT</p> |
| <p>Fred Frank Vice Chairman Peter J. Solomon Co.</p> | <p>Mark Trusheim President, Co-Bio Consulting, LLC Visiting Scientist, Sloan School of Management, MIT</p> |
| <p>Gigi Hirsch, MD Executive Director MIT Center for Biomedical Innovation</p> | <p>Sheila Walcott Partner, McDermott, Will & Emery, LLP Former Counselor to the Secretary of US Department of Health & Human Services (HHS)</p> |
| <p>Mark B. McClellan, MD, PhD Director, Engelberg Center for Healthcare Reform Senior Fellow, Economic Studies Leonard D. Schaeffer Chair in Health Policy Studies</p> | <p>Janet Woodcock, MD Director, Center for Drug Evaluation and Research Food and Drug Administration (FDA)</p> |

**NEWDIGS – Phase I
Steering Committee**

| | |
|---|--|
| <p>John Alam, MD, PhD Former Executive VP, Research & Development Vertex Pharmaceuticals CBI Distinguished Fellow, MIT</p> | <p>Debbie Nightingale, PhD Professor of the Practice Aeronautics and Astronautics and Engineering Systems Co-Director, Lean Advancement Initiative, MIT</p> |
| <p>Gigi Hirsch, MD Executive Director MIT Center for Biomedical Innovation (CBI)</p> | <p>Wayne Rosenkrans, PhD President, Personalized Medicine Coalition CBI Distinguished Fellow, MIT</p> |
| <p>M. King Jolly, PharmD Senior VP, Quintiles Innovation</p> | <p>Thomas Unger, PhD Executive Director, Strategic Planning, R&D, Pfizer</p> |
| <p>Garry Neil, MD Corporate VP, Corporate Office of Science & Technology (COSAT) Johnson & Johnson</p> | |

Other Contributors

| | |
|--|--|
| <p>Charles Baum, MD, PhD SVP and Chief Medical Officer Biotherapeutics and Bioinnovation Center (BBC)</p> | <p>Shirley Paddock Director of Project Management Operations Eli Lilly</p> |
| <p>Rachel Behrman, MD, MPH Associate Commissioner of Clinical Programs; Director of the Critical Path Programs, US Food & Drug Administration (FDA)</p> | <p>Luis Perez-Breva, PhD Research Scientist and Lecturer, Innovation Teams, School of Engineering, MIT</p> |
| <p>Cherif Benattia, MD VP Pharmacovigilance & Public Health Vertex Pharmaceuticals</p> | <p>Brad Perkins, MD Chief Strategy & Innovation Officer Center for Disease Control & Prevention (CDC)</p> |
| <p>Josh Benner, PharmD Research Director Engelberg Center for Healthcare Reform Brookings Institution</p> | <p>Ed Pezalla, MD National Medical Director & Chief Clinical Officer Aetna Pharmacy Management</p> |
| <p>Deni Deasy Boekell VP for Client Strategy Roger Green & Associates</p> | <p>Judy Racoosin, MD, MPH Sentinel Initiative Scientific Lead Associate Director, Medical Product Safety Programs Office of the Critical Path Program US Food & Drug Administration (FDA)</p> |
| <p>Ken Buetow, PhD Director, Center for Bioinformatics and Information Technology Laboratory Chief, Laboratory of Population Genetics National Cancer Institute (NCI)</p> | <p>Shoshana Reshef, MPH, PhD Deputy Director Global Pharmacoepidemiology Bayer</p> |

NEWDIGS – Catalyzing the Transformation of Healthcare Innovation

| | |
|---|--|
| <p>Felix Freuh, PhD VP of Personalized Medicine R&D Medco Health Solutions, Inc.</p> | <p>Eiry Roberts, MB (Hons) BS, MRCP, FFPM VP, Transitional Phase Development Eli Lilly</p> |
| <p>Daniel Goldsmith, PhD Research Associate Sloan School of Management, MIT</p> | <p>Leonard Sacks, MD Deputy Director, Office of the Critical Path US Food & Drug Administration (FDA)</p> |
| <p>Neil Graham, MBBS, MD, MPH SVP, Program & Portfolio Manager Vertex Pharmaceuticals</p> | <p>Michael Siegel, PhD Principal Research Scientist Sloan School of Management, MIT</p> |
| <p>Marcia Kean CEO, Feinstein Kean Healthcare</p> | <p>Mike Silver, PhD Principal, Synaptix Communications</p> |
| <p>Larry Kocot, MPA, JD Deputy Director, Engelberg Center for Healthcare Reform, Brookings Institution</p> | <p>Sheldon Sloan, MD VP, Policy, Corporate Office of Science & Technology (COSAT) Johnson & Johnson</p> |
| <p>Lance Ladic, PhD Strategic Development Manager of Healthcare Siemens Corporate Research Siemens AG</p> | <p>Kim Slocum President, KDS Consulting</p> |
| <p>Judy Maro PhD Student Engineering Systems Division, MIT</p> | <p>Badhri Srinivasan VP, Enterprise Transformation Quintiles Transnational Corp.</p> |
| <p>Stuart Madnick, PhD John Norris Maguire Professor of Information Technology and Engineering and Engineering Systems Sloan School of Management, MIT</p> | <p>Ernst Terracer Clinical Pharmacy Manager Wellpoint Rx</p> |
| <p>Fiona Murray, PhD Sarofim Family Career Development Professor Associate Professor Management of Technological Innovation & Entrepreneurship Sloan School of Management, MIT</p> | <p>Sheila Walcoff, JD Partner, McDermott, Will, & Emery Former FDA Associate Commissioner & Science/Public Health Counselor to the Secretary of HHS</p> |
| <p>Roy Welsch, PhD Professor of Statistics & Management Sciences and Engineering Systems Sloan School of Management, MIT</p> | |

References

¹ Dertousos ML, Lester RK, Soslow RM. Made in America: Regaining the Productive Edge. MIT Press 1989.

² Womack JP, Jones DT, Roos D. The Machine that Changed the World: The Story of Lean Production – Toyota’s Secret Weapon in the Car Wars that is Now Revolutionizing World Industry. Free Press (Simon and Schuster, Inc.) 1990.

³ Murman E, Allen T, Bozdogan K, *et al.* Lean Enterprise Value: Insights from MIT's Lean Aerospace Initiative. Palgrave Macmillan 2002.

⁴ Nightingale, D,J, Stanke, A, Bryan, T. Enterprise strategic analysis for transformation. MIT Lean Advancement Initiative 2008.

⁵ Pharmaceutical Industry Profile 2009. PhRMA 2009. (Available at: <http://www.phrma.org/files/attachments/PhRMA%202009%20Profile%20FINAL.pdf>)

⁶ FDA Science and Mission at Risk: Report of the Subcommittee on Science and Technology US FDA, November 2007. (Available at: http://www.fda.gov/ohrms/dockets/AC/07/briefing/2007-4329b_02_01_FDA%20Report%20on%20Science%20and%20Technology.pdf#28)

⁷ Kaufman DW, Kelly JP, Rosenberg L, *et al.* Recent patterns of medication use in the ambulatory adult population of the United States: The Slone survey. *JAMA* 2002;287:337-344.

⁸ Bonabeau, E.N., Bodick, N. & Armstrong, R.W. A more rational approach to new-product development *Harv. Bus. Rev.* 2008; 86:96-102

⁹ Progressive Licensing Concept Paper. Health Canada November 2007 (Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/proglic_homprog_concept-eng.pdf).

¹⁰ Olsen L, Aisner D, McGinnis JM. The Learning Healthcare System. Workshop Summary. The National Academies Press 2007. (Available at: http://books.nap.edu/openbook.php?record_id=11903)