Massachusetts Institute of Technology

"NEWDIGS"

NEW
Drug
Development
ParadIGmS

A working paper from the

MIT
Center for Biomedical Innovation

May 2009

Center for Biomedical Innovation

Concept Overview

Foreword

How might the myriad forces of change within the healthcare system in the United States converge to reshape the world of drug safety by the year 2020? This was the central question in a recent consortium-based future scenario planning initiative led by the MIT Center for Biomedical Innovation (CBI).

A major finding of the Drug Safety Futures 2020 working group was that in order to meet the needs of the future health care system, the pharmaceutical industry must undergo transformative changes in many, if not nearly all, aspects of how it currently conducts business. What follows is a preliminary overview of a new research program CBI is launching to address the need to fundamentally re-engineer the drug development process, one of the major strategic imperatives that was identified by the working group.

A summary of the methodology and findings from Drug Safety Futures 2020 initiative is available in the attached Appendix.

Introduction

Healthcare reforms currently unfolding in the United States are driving the marketplace toward a more value-based system designed to optimize health outcomes per dollar expended. Such a system has major implications for the pharmaceutical industry.

Companies will face increased pressure to cut development costs as consumers and payers look to rein in the overall costs within the health care system. They will also need to work toward developing novel therapies with clear effectiveness, shifting away from new versions of drugs already on the market.

Increasingly, drug companies will be required to show not only the benefits and the full risk profile of their products, but also their relative effectiveness when compared to other treatment options. This will require more and different data collection and better analysis of drug candidates throughout the development process, well into the post market phase. There will be more emphasis on analytics at all stages of development, with modeling and simulation assuming an increasingly major role in reducing the risk of failure and delays in new product approvals.

The traditional structure of the drug approval process is likely to change significantly with more emphasis on small, micro trials in earlier stages and an emphasis on what is now termed post-market surveillance.

In short, pharmaceutical product innovation for the future healthcare system will require a new development paradigm – one that fully leverages existing data, as well as emerging technologies and processes as a means to optimizing value for all key stakeholders.

Background

The healthcare industry is undergoing rapid and unpredictable change as concerns grow about cost and effectiveness. The public is demanding better and more treatments that are both safe and effective. And yet, there is loud criticism of the pharmaceutical industry over the cost of medications.

There is a growing emphasis in health policy, illustrated by the UK's National Institute for Health and Clinical Effectiveness (NICE), on paying only for what works. This trend is driving increased activity in the U.S. focused on comparative effectiveness research which focuses on evaluating the relative risks and benefits of competing therapies. Although comparative effectiveness is intended to determine the right treatment for the right patient, critics charge that research in this area could lead to a one-size-fits-all approach that discounts individual patient characteristics. Some drug industry leaders acknowledge the potential value of comparative effectiveness but have expressed concern that it could lead to the denial of insurance payments for some necessary treatments.[1]

Meanwhile, the drug industry has failed to live up to the expectations generated by advances and breakthroughs in the laboratory. The full contribution of new technologies (e.g., "-omic" science and RNAi) is still years away. In addition, substantial investments in new high-technology platforms such as high throughput screening systems have yet to pay off in terms of improved productivity.

While R&D investments continue to rise, productivity has not. R&D expenditures have increased by 13% annually since 1970 (a 50-fold increase) while the number of Investigational New Drug (IND) candidates and New Drug Applications (NDA) have remained flat.[2]

Concern over this trend led the FDA to launch its Critical Path Initiative in 2004 in an attempt to spur innovation. Officials were concerned not only about the decline in applications but also over the inefficiency of drug development.

A drug entering Phase 1 trials in 2000 had only an 8% chance of reaching the market, a probability that was no higher than one entering Phase 1 trials in 1985.[3] This, in large part, is due to the poor predictive power of animal toxicity testing. Nearly 90% of drugs that are safe in animals fail in humans. Failures, particularly those that occur in late stage development, are significant cost-drivers for drug development and fuel concerns about the inefficiency of R&D, underscored by FDA officials in a white paper on the Critical Path Initiative:

> Recent biomedical research breakthroughs have not improved the ability to identify successful candidates and bring the most promising products to patients in a timely and affordable manner. We can see a wide range of opportunities to improve the efficiency of product development. But without a concerted focus on the applied science necessary to develop these new approaches, the inefficiencies and unnecessary costs of product development will continue to escalate.[4]

Improving productivity will also require enhanced capabilities in the area of post-launch product safety. Recent recalls of several high profile drugs have fueled concerns about the current surveillance system and led to a public perception of a need for reform. In 2006, the Institute of Medicine issued a report, *The Future of Drug Safety: Promoting and Protecting the Health of the Public,* which was highly critical of the FDA's existing system and contained specific recommendations for improvement.

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[1] Jane Zhang, "Push to Compare Drug Treatments Worries Drug, Device Makers," *Wall Street Journal*, April 15, 2009; http://online.wsj.com/article/SB123967153492015713.html.

[2] B. Booth and R. Zennel, "Prospects for Productivity," *Nature Reviews Drug Discovery*, May 2004, 451-456.

[3] U.S. Food and Drug Administration, Challenge and Opportunity on the Critical Path to New Medical Products, March 2004.

[4] Ibid.

The report led to the creation of the Sentinel Initiative at the FDA, an important effort intended to complement existing systems for identifying adverse safety events once a product is on the market. This new national electronic network will allow the agency to query diverse automated healthcare data holders about potential safety issues quickly and securely. It will, however, require vast amounts of information from numerous data sources.

Following the IOM report, the FDA also established the Reagan-Udall Foundation in 2007. The foundation is designed to work with FDA as an independent organization using mostly private industry and philanthropic funding.[5] Its goal is to conduct research to help the agency modernize drug, medical, veterinary, food and cosmetic product development, accelerate innovation and enhance product safety.[6]

While the pharmaceutical industry has enjoyed many years of robust commercial success, the current challenges in productivity, the growing demand for post-launch data on benefits, risks, and effectiveness, and the ongoing expiration of a significant number of existing blockbuster patents all have major economic implications for the industry.[7] In the 1950's, most major companies invested approximately 5% of sales in R&D; by 2002 the industry average was 16%, with some firms spending more than 20%.[8]

Particularly in the context of decreasing R&D productivity, one has to question whether the drug development process as it currently exists has the capacity for the generation of information about a new drug that the evolving healthcare system is, and will increasingly demand. Even if it were possible, the investment requirements to generate that information using the current paradigm, along with the failure rates, will threaten the ability of the country to develop innovative therapies. For all these reasons, we believe a new paradigm for developing drugs is required.

Addressing the Challenge

All major pharmaceutical companies have undertaken efforts focused on optimizing the efficiency and productivity of their R&D organizations. And while incremental improvements have been realized, many believe that further attempts to optimize the existing drug development model will yield only marginal additional gains.

Industry leaders – increasingly recognizing the urgency and scale of need for change – are pursuing technical solutions within the context of newly formed collaborations with competitors. The growing number of such life science consortia established within the past 3 to 5 years reflects a fundamental change in behavior for this highly competitive culture and underscores the collective level of concern by industry leaders for the sustainability of their current business model.

Despite the challenges inherent to R&D consortia, a number of these collaborations are contributing valuable insights, processes, and technologies to address the challenges targeted by the FDA's Critical Path Initiative.[9] Many of these advancements are focused on narrowly defined technical problems. As a

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[5] Federal Food, Drug and Cosmetics Act, as amended in 2007, Chapter VII, Subchapter 1; http://www.fda.gov/opacom/laws/fdcact/fdctoc.htm

[6] Ibid.

[7] Jason Napodano and Brian Marckx, Big Pharma and Patent Cliffs, Zack's Investment Research, Analyst Blog, March 06, 200; http://www.zacks.com/stock/news/18028/Big+Pharma+and+Patent+Cliffs.

[8] B. Booth and R. Zennel, *Nature Reviews Discovery*.

[9] Elias G. Carayannis and Jeffrey Alexander, Strategy, Structure and Performance Issues of Pre-competitive R&D Consortia: Insights and Lessons Learned from SEMATECH, http://www.uni-klu.ac.at/wiho/downloads/CARAYANNIS_SEMATECH_IEEE_TEM_050503.pdf.

result, much of the progress that is made is fragmented with no systematic mechanism in place to more broadly leverage lessons learned across the industry or to understand the potential implications of the advancement for other elements of the drug development process.

The New Drug Development Paradigms Initiative (NEWDIGS) was conceptualized to address this gap in problem-solving activities in the industry – that is, to provide an industry-wide forum for more fully leveraging new technologies and processes across the product innovation value chain. NEWDIGS will complement the efforts of existing life science consortia by:

- Focusing on drug development as a "system" rather than limiting the scope to a narrowly defined technical problem
- Recognizing the potential to fundamentally "re-engineer" the traditional linear, sequential, siloed model of development from Pre-Clinical through Phase IV
- Building on the evolving concept of a Learning Healthcare System[10] to facilitate a development model that efficiently leverages existing data across silos to drive rapid cycle learning for both product innovation as well as use in clinical care
- Applying a holistic engineering systems model to structure the redesign process
- Actively engaging all key stakeholders in the initiative in the context of a neutral, "safe haven" setting
- Ready access to world class academic researchers across MIT and the Harvard-MIT Division of Health Sciences and Technology with a broad range of expertise across engineering, science, management, and clinical medicine.

The initiative will target significant improvement in the following key areas:

- The benefit/risk profile of new drugs
- The relative effectiveness of new drugs compared with existing treatment options
- The efficiency and productivity of the drug development process.

NEWDIGS will apply the Enterprise Transformation methodology[11] to plan and implement the redesign process. This approach begins with an analysis of the desired values of the future system from each stake holder's perspective, and structures the improvement process to create the defined values. The alignment of the new drug development paradigm with the evolving value-based healthcare marketplace will be key to the success of NEWDIGS.

The scope of NEWDIGS will be refined at the launch meeting for the initiative (May 28, 2009) but is anticipated to be broad in terms of the full innovation lifecycle (Preclinical through Phase IV), the key stakeholders involved, and the potential areas for improvement to be addressed (e.g., technologies, processes, policy, and people).

Participants

NEWDIGS will be structured as a cross-industry coalition led by the CBI. This center was established in 2005 as a collaboration across MIT's schools of Engineering, Science, and Management, as well as the Harvard-MIT Division of Health Sciences and Technology (HST). CBI will provide the overall program management for NEWDIGS.

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[10] The Learning Healthcare System: Workshop Summary, Institute of Medicine, April 2, 2007, *http://www.iom.edu/CMS/28312/RT-EBM/41894.aspx*

[11] E. Murman et al, Lean Enterprise Value: Insights from MIT's Lean Aerospace Initiative, Palgrave, St. Martin's Press, 2002.

Professor Debbie Nightingale, Department of Aeronautics and Astronautics, and Engineering Systems Division, and Co-Director of MIT's Lean Advancement Initiative, will serve as the faculty lead for Phase I of NEWDIGS, along with co-Principal Investigator Gigi Hirsch, M.D., Executive Director of CBI.

The success of NEWDIGS depends upon the active engagement of a broad range of stakeholders. To date, the following organizations have confirmed their commitment to participate:

- Aetna
- Agency for Health Research and Quality (AHRQ)
- Bayer
- Brookings Institution
- Centers for Disease Control and Prevention (CDC)
- Food and Drug Administration (FDA)
- Johnson & Johnson
- Eli Lilly
- Medco
- National Institutes of Health (NIH)
- Pfizer
- Quintiles
- Siemens
- Vertex Pharmaceuticals

Discussions about potential participation are also underway with representatives from other key sectors of the market including providers, diagnostics, information technology, and patient advocacy, among others.

Timeline, Deliverables, and Resources

Phase I (May-September 2009) will focus on completing a high level Current State Assessment and Future Vision for drug development, to be summarized in a white paper and/or publication. In addition, a gap analysis between the Current and Future states will drive the framing of a research plan for Phase II, currently scheduled to begin in October 2009.

Phase I will include 2-3 full day working sessions involving the NEWDIGS coalition and research team.

Funding to date to support Phase I activities has been generously provided by the following participants: Bayer Healthcare, Johnson and Johnson, Eli Lilly, Pfizer, Quintiles, and Vertex Pharmaceuticals.

Phase II (October 2009) will follow the plan defined in Phase I. Fundraising efforts for Phase II have already begun and target a balanced portfolio of public and private sources.

Drug Safety Futures 2020

In the spring of 2008, CBI launched a future scenario exercise in an effort to define the research agenda for its Drug Safety Research Program. This consortium-based initiative, Drug Safety Futures 2020, was designed to meet the following key objectives:

- *To create a shared vision of potential future states of the world of drug safety*
- *To understand the strategic implications of each of these scenarios*
- *To build a research agenda that would help to bridge the current and futures states*

NEWDIGS follows from this important initiative, addressing two of the key strategic imperatives that emerged: the need for a new drug development paradigm, and the need for a fundamentally new benefit/risk "system".

What follows is a high level summary of Drug Safety Futures 2020 – the methodology applied, the process as it unfolded, and key themes that emerged. Further information about this initiative, as well as the parallel future scenario initiative undertaken for our Biomanufacturing Research Program, are available upon request.

Origins of Alternative Futuring

Alternative Futuring, also known as Future Scenarios, was developed by Royal/Dutch Shell Oil in the 1960s. As many other companies adopted the process over the years, it has been further refined and is now a widely used technique to plan for possible future worlds and to mitigate risk associated with those worlds.

It is important to note that the Alternative Futures process does not aim to predict the future, as appealing a thought as that might be. Instead, the process seeks to outline a range of possibilities and then to prepare contingency plans for each of them. By developing several possible pictures of the future, organizations are able to engage in broader, more creative thinking about the direction they should take and specific actions needed to prepare for the future environment. The intent is to anticipate what the future might hold and to identify actions that can be taken today regardless of how the future unfolds.

The Core Question

In any Scenario Analysis process, it is important to avoid trying to "boil the ocean," and instead to focus on a manageable aspect of the future. If the central topic, or core question, is overly broad, the effectiveness of the process will be diluted. Thus, in CBI's case, our first task was for the Working Group (WG)[12] to develop a central question that would guide the process through to completion. We articulated that question as follows:

> Much attention has been paid over the past few years to the topic of diagnostic and therapeutic project safety:
>
> - "Future of Drug Safety in 2007" (IOM report)

[12] See Appendix II for full list of Working Group Participants.

- Establishment of Reagan-Udall Foundation to modernize product development, accelerate innovation, & enhance product safety (2007)

- Launch of FDA's Sentinel Network for post-launch surveillance (2008)

Given these developments, what might the world of product safety look like in 10-15 years across the 'health value chain', and what are the associated strategic implications that we should be addressing?

Driver Ideation

Once the core question was agreed upon, the next step in the process was to think about factors in the environment that are likely to drive changes relative to the world we know today. Drivers are agents of change that have three inherent characteristics:

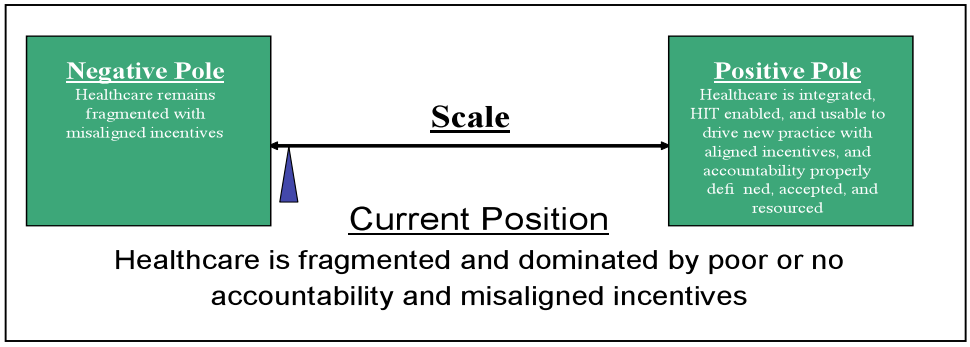
- They are causal
- They are uncertain
- They are impactful

It is important to distinguish drivers from *trends*, which are known and predictable elements of the future. While we took key trends into consideration, we did not use them to create the scenarios. The "graying of America," for example, was not considered as a driver because it is a known area of change that continues to unfold in a very predictable way.

At the Driver Ideation workshop, the WG initially identified dozens of change drivers. We then took that long list of drivers and clustered them into logical highest-order groupings. Because drivers are inherently uncertain, they must be described in terms of a central concept and the possible polar extremes the driver could assume. These are normally described as positive and negative poles, but are not judgments about whether the outcome is good or bad, but simply the extremes of each driver.

In the CBI case, one of the drivers was termed "The Healthcare Delivery System" and reflected the extent to which patients, providers, developers, and payers are appropriately incented[This is a noun and cannot be used in this way. How about "given incentives" ? and recognize/assume appropriate accountability for delivery of quality healthcare and healthcare is integrated as a "Learning Healthcare (HC) System."

The driver looked like this:



After reviewing all of the drivers, the team settled on four as follows:

1. **The Healthcare Delivery System:** The degree to which patients, providers, developers, and payers are appropriately incented [see above] and recognize/assume appropriate accountability for delivery of quality healthcare and healthcare is integrated as a "Learning HC System."
2. **Perception, Ethics, Policy Cycle:** The degree to which patients, providers, and payers, understand the nature of benefit/risk tradeoffs; societal attitudes and beliefs influence HC decisions and policy; and how that is in turn driven by high quality current science.
3. **New Science, Technology, and Engineering:** The degree to which new science, technology and engineering will enable new and more efficient development of diagnostics and therapeutic approaches with more favorable benefit/risk**.**
4. **Global Cultural Disparity:** The degree to which geographic health disparity and circumstance specific risk/benefit lead to varied cultural perceptions of risk and the need for harmonization and standards.

Driver	Defining Concept	Negative Pole	Positive Pole	Current State
The Healthcare Delivery System	The degree to which patients, providers, developers, and payers are appropriately given incentives and recognize/assume appropriate accountability for delivery of quality healthcare and healthcare is integrated as a "Learning HC System."	Healthcare remains fragmented with misaligned incentives	Healthcare is integrated, health information technology (HIT) enabled, and usable to drive new practice with aligned incentives, and accountability properly defined, accepted, and resourced	Healthcare is fragmented and dominated by poor or no accountability and misaligned incentives
Perception, Ethics, Policy Cycle	The degree to which patients, providers, and payers, understand the nature of benefit/risk tradeoffs, societal attitudes and beliefs influence HC decisions and policy and that policy is in turn driven	Public understanding of benefit/risk is limited leading to ethical and legal considerations being mired in political or pseudo-	The public is fully informed and able to balance benefit/risk leading to ethical and legal considerations which are appropriately	Public understanding of risk is variable and suboptimal creating outdated perceptions limiting the ability for forward progress in

	by high quality current science.	scientific thought and policy which is not linked to high quality current scientific thought preventing the advancement of HC	conceived and logically applied and policy which is driven by the best scientific thought in order to advance HC	HC reform while most HHS? agencies are not resourced to integrate best current thinking into policy
New Science, Technology, and Engineering	The degree to which new science, technology and engineering will enable new and more efficient development of diagnostics and therapeutic approaches with more favorable benefit/risk.	Potential contribution from science/ engineering proves illusory	Science/ engineering fully enables the development process and drug safety	Low current ROI from scientific/ technology/engine-ering investment
Global Cultural Disparity	The degree to which geographic health disparity and circumstance specific risk/benefit lead to varied cultural perceptions of risk and the need for harmonization and standards combinations	Regional interests preclude global implementation	Global interests prevail allowing global implementation	Little evidence of real change

Scenario Selection

Generating all of the possible combinations of four drivers with two polar extremes resulted in 16 possible combinations, 16 future scenarios.

Scenario	Delivery System	Perception/ Ethics/Policy	New Science, Technology	Global Cultural Disparity
Able	+	+	-	-
Baker	+	-	-	-
Charlie	+	-	+	-
…..	…	…	…	…

Because 16 scenarios is far too large a number to be manageable or to monitor going forward, the next task was to select the four to six most compelling scenarios--not necessarily the most/least likely, or most/least desirable, but the *most compelling* and the *most challenging*. The chosen scenarios must also be differentiated from each other as much as possible The goal is to select a set of scenarios that effectively bound the future space. At the end of the Scenario Selection Workshop, the team had chosen four scenarios to be more fully developed.

Telling the Stories

The chosen scenarios were better defined through a "characterization" exercise in which a wide range of characteristics were developed for each scenario that took into account the impact each future world would have across varied healthcare stakeholders including:

- Care Delivery Organizations
- Government
- Payers
- Product Developers

Armed with the driver settings that created the scenarios and these characteristics, authors created stories to bring the environment and conditions of each future world to life. Each of the five scenarios is briefly outlined on the following pages, and the full scenario narratives are included in Appendix III.

Scenario 1: "Boutique Care"

DRIVERS	
-	Healthcare remains fragmented with misaligned incentives
-	Public understanding of benefit/risk is limited leading to ethical and legal considerations being mired in political or pseudo-scientific thought and policy which is not linked to high quality current scientific thought preventing the advancement of HC
+	Science/technology/engineering fully enable [science/technology/engineering enable] the development process and drug safety
o	Little evidence of real change in Global Disparity

CHARACTERISTICS

Care Delivery	Government	Payers	Developers
• Global borders crumble • Counterfeiting and offshore medicine • Bifurcation into haves and have nots • Hyper personalized medicine for the rich and famous • Highly complex science impossible for public to understand but available for a price, e.g. oncology targeted therapy	• Bigger footprint for government, redefined benefits • Sentinel system exists by cumbersome [exixts by cumbersome what?]and is not fully leveraged • FDA/EMEA work together	• Global pricing, pricing transparency, increasing price pressures • Bigger footprint for employers, redefined benefits	• Slowly reducing ROI from R&D • Lower margins/consoli d-tion • No money for science, so science driver only slightly positive

SCENARIO HIGHLIGHTS

Congress approved a form of universal healthcare, but failed to change the old incentive structure which continued to reward high cost and high volumes of care – "pay for what works," the mantra of the 2008 election year, was forgotten in the rush to handle the crisis of the under and un-insured. One of the bright points, however, was the FDA's Sentinel system which was steadily expanded and eventually linked with the EU's efforts. However, with the increasing evidence of healthcare product issues, the public became ever more skeptical of biomedical innovation. Those Americans wealthy and desperate enough for new therapies turned to low-cost producers abroad for their medical needs and boutique insurance providers based in Abu Dhabi even began offering foreign medical benefits to supplement the US Universal plans.

Scenario 2: "Healthness[? How about "health" or "healthyness"? Again, this is not a word!] for All"

DRIVERS	
+	Healthcare is integrated, HIT enabled, and usable to drive new practice with aligned incentives, and accountability properly defined, accepted, and resourced
+	The public is fully informed and able to balance benefit/risk leading to ethical and legal considerations which are appropriately conceived and logically applied and policy which is driven by the best scientific thought in order to advance HC
+	Science/technology/engineering fully enable the development process and drug safety
o	Little evidence of real change in Global Disparity

CHARACTERISTICS			
Care Delivery	**Government**	**Payers**	**Developers**
• Healthcare is a right • Life expectancy increases, morbidity declines, productivity/retire-ment age increases to 72 • An "Inconvenient Truth" for healthcare • Providers push for HC Advisors & Specialty clinics • Legal and Tort reform a question mark • Fewer providers and hospitals	• National risk pool managed by CMS or possibly a role for reinsurance to manage the risk pool, perhaps the government • Marshall plan for HIT as critical enabler, link HIT to Medicare reimbursement • HHS agencies work together more closely • FDA more integrated and science based, FDA's job different, but not easier • NIH/CDC work with new Cost effectiveness entity on trials	• Value is the watchword • Consolidation of payers • Economies of Scale • Link provision of EMR data to lower healthcare premiums • This is everybody's second choice which makes it very attractive • Personal responsibility (through incentives) • "Healthness"[see suggestions above]predominate s	• Ultimate Cost Effectiveness World

SCENARIO HIGHLIGHTS
The US healthcare system dodged the bullet of a total system implosion and devised a system that extended insurance coverage to most Americans, maintained the U.S. technological leadership in healthcare, and shifted incentives in the system so that prevention and essential care gained a decisive edge over unnecessary treatment.[Should all be in either past or present tense]

Scenario 3: "Healthplan Nirvana"

DRIVERS	
+	Healthcare is integrated, HIT enabled, and usable to drive new practice with aligned incentives, and accountability properly defined, accepted, and resourced
+	The public is fully informed and able to balance benefit/risk leading to ethical and legal considerations which are appropriately conceived and logically applied and policy which is driven by the best scientific thought in order to advance HC
-	Potential contribution from science/technology/engineering proves illusory.
o	Little evidence of real change in Global Disparity

CHARACTERISTICS			
Care Delivery	**Government**	**Payers**	**Developers**
• Anti-personalized healthcare, population focus • Longevity is nothing without quality of life • Care to the mean rather than to the standard deviation • Prevention trumps treatment • Utilization of OTC/generics goes way up • Retail Clinics prosper • Self treat via Google	• Downstream focus at the expense of basic research • No talent or money for science • Social Ludditeism prevails	• No PBM's in this world • Cost effectiveness rules, Evidence-based HC in its worst form • Cheap HIT-enabled primary care intermediaries, Emergency medical hologram • Figure out how to use the science we have before we invest in new science	• Loss of venture funding and interest • Low levels of innovation • Consolidation of product developers • Lower R&D budgets • Fragmentation of R from D • Outsourcing of R from biotech, D from India/China

SCENARIO HIGHLIGHTS

Virtually every American now has health insurance with their care mediated by a powerful and ubiquitous healthcare information GRID.[Should this whole paragraph be put in present tense?] Enabled by the WEB 2.0 internet, Americans finally take control of their health decisions and start start looking for the best, and most cost-effective, therapies for them. The "Pay for what works" mantra is fully embraced by newly savvy patients who require that providers and hospitals only offer treatment that is proven to be clinically effective. The early experiments at Wal-Mart with hospital-linked redi-clinics to serve most primary care needs are wildly successful and rapidly adopted by other discounters.

Scenario 4: "Global Warming for Healthcare"

DRIVERS	
-	Healthcare remains fragmented with misaligned incentives
-	Public understanding of benefit/risk is limited leading to ethical and legal considerations being mired in political or pseudo-scientific thought and policy which is not linked to high quality current scientific thought preventing the advancement of HC
-	Potential contribution from science/technology/engineering proves illusory.
o	Little evidence of real change in Global Disparity

CHARACTERISTICS			
Care Delivery	**Government**	**Payers**	**Developers**
• Cost increases continue • Heavy bifurcation in haves and havenots • Medical tourism thrives • Healthcare as a financing issue • Ultimately Collapses	• Cost-based HC • Universal healthcare cherry-picks in the developing countries • Government sponsored hamster care for the masses • More conservative FDA with continuing flight of talent • US falls further behind in science, technology and engineering • No funding, or fragmented funding for HIT	• Private Payers cover only the healthy wealthy as a global effect • C in CER stands for cost effective • Forced insurance	• Marketing departments turn the lights off as biopharma fails • Massive offshoring

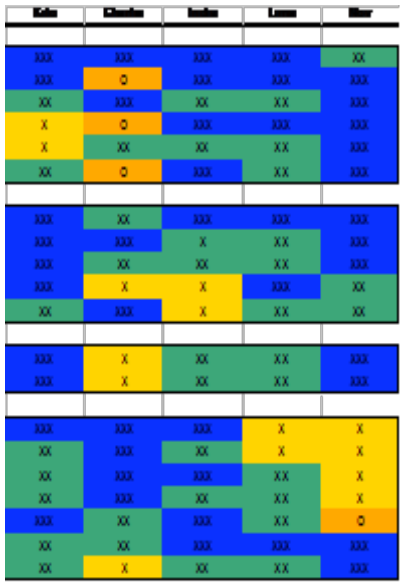
SCENARIO HIGHLIGHTS

Healthcare in America completely bifurcates between the haves and have-nots [However you handle this, do it the same throughout the paper.] of society. The very low levels of coverage provided to all Americans were insufficient to pay for anything but the most rudimentary care, and with the complete failure of the healthcare sectors to agree on common standards for sharing of medical information, there was no hope for the creation of system efficiencies while maintaining medical quality. Patients, already skeptical of the care they were receiving, refused in increasing numbers to even go to the doctor until they were desperate - when they ended up instead flooding emergency rooms.

The future will probably bring some combination of these four scenarios rather than any one of them unfolding exactly as we have characterized it. Nevertheless, the scenarios provide a solid framework to explore the issues that MIT and Drug Safety will face over the coming years.

Identifying Strategic Imperatives

Once the four scenarios had been created, they were used in a Scenario Implications Workshop in which the Core Team engaged in a role-playing exercise. Broken into small groups to deal with each scenario, the teams were asked to answer specific questions wearing several different hats: that of a senior leadership team from a large pharma (type of business and product, financial picture, and core strategy); that of a drug safety leadership team within an organization (focus and strategy, internal and external interactions, research direction/investment, disruptors); that of an entrepreneurial small company working in the space (business model); and that of the FDA Office of the Commissioner (remit for Sentinel, relations to other HHS agencies, define an RFP).



These discussions yielded scores of implications; these are tactics and strategies that would be required to ensure success in each scenario. These were then scored and color coded for relevance across the scenario set, sorted by cross-relevance score, and analyzed for thematic clustering. The result is a matrix where the scenarios are listed horizontally on the chart and each individual implication runs down the rows. Thematic clusters appear as groups of implications.

The objective of the scoring and analysis was to identify those sets of implications that have relevance in most or all of the scenarios (convergent implications), many of the scenarios (semi-convergent implications), some of the scenarios (semi-divergent implications), or only one of the scenarios (divergent implications). The color density running from blue-green to red-orange helps to determine where the break-points are between categories of implications.

Convergent thematic clusters can be viewed as being essentially future independent – potential areas of activity that are essential to future proof strategy, or strategic imperatives. Semi-convergent implications are somewhat dependent on future direction and hence can be acted upon, but require the placing of "bets" on what direction the future takes. Careful monitoring, a process called Strategic Early Warning, is essential if a semi-convergent element is acted upon. Semi-divergent and divergent implications are highly dependent on specific futures occurring and hence should not be considered for action.

The MIT project arrived at the following strategic imperatives:

Imperative	Constituents
New Development Paradigms	Companies will face increased pressure to cut development costs as consumers and payers look to rein in the overall costs within the health care system. They will also need to work toward developing novel therapies with clear effectiveness, shifting away from new versions of drugs already on the markets. Increasingly, drug companies will be required to show not only benefits of their products and the full risk profile, but their relative effectiveness as well. This will require more and different data collection and better analysis of drug candidates across the development process and well into the post market phase. It will also require advancement in the area of modeling to provide better tools for reviewing particular molecules and more emphasis on analytics at all stages of development. The traditional structure of drug approvals is likely to change significantly with more emphasis on small, micro trials in earlier stages and an emphasis on what is now termed post-market surveillance. It is possible that phase III trials could be completed by health care providers or third-party payers who are interested in both economics and safety. While much of this may be driven at the regulatory level, in order for significant change it must be company driven, says MIT Professor Nancy Leveson, Department of Aerospace and Astrospace and Engineering Systems Division, who participated in the exercise: *"In the aerospace industry the companies learned that 'if we want to succeed, our planes can't crash'. As a result, they addressed the critical safety issues. The FAA did not solve this problem. And neither will the FDA. The companies need to manage drug safety in pharma"*
Imperative	**Constituents**
Benefit/Risk Systems	The emphasis around drug safety is shifting toward a complex understanding of the benefits of a drug compared to the risks of taking it. This extends beyond medications to include the broader world of health care delivery overall. This will require better ways of collecting data, tracking information and analyzing outcomes. The way information is collected must be modified so that it will be more useful and there is a critical need to standardize the information collected by various entities so that there will be larger pools of data available. There are ongoing movements within the health care industry that will support and foster the development of better benefit/risk systems such as the FDA's Sentinel Initiative, the push for learning health care systems in which data of ongoing care is used to evaluate best practices, and the Health Information Technology drive by the Department of Health and

	Human Services.
Imperative	**Constituents**
Globalization	There was a consistent theme toward globalization as conditions change in the United States which could move innovation away from the US. Companies will be increasingly looking at markets overseas, especially those in developing areas where there may be development options with fewer regulations and greater access to patients. Conditions may also give rise to smaller, boutique providers that focus their work exclusively off shore and cater to wealthy patients willing to travel to find better health care options.

From Strategy to Action: Next Steps

As of May 2009, MIT CBI is rapidly moving forward to build on the strategic imperatives that emerged from the Drug Safety Futures initiative. Follow-on research activities now underway include:

1) New Drug Development Paradigms ("NEWDIGS") – summarized in this document

2) An Engineering Systems Approach to Risk Management: Many stakeholders across the healthcare industry make daily decisions regarding the relative benefits and risks associated with a given drug. And yet these decision-making processes are typically unstructured, subjective, and lack reproducibility. The lack of any explicit framework to guide benefit/risk assessment and management compromises the quality of decision-making related to the availability and use of medications.

This research project, led by Principal Investigator Professor Nancy Leveson and funded by CBI, focuses on the application of a systems dynamics model for enhancing safety to the drug development process. Her methodology, focused on an expanded model of causality, has been successfully applied and led to major improvements within the aerospace industry. The pilot phase of this project will be completed in the summer of 2009. Interim discussions between Professor Leveson and CBI's Drug Safety working group suggest that this project may lay important groundwork for improving REMS and educating key audiences (e.g., legislators) about the impact of their related decisions on the current system.

APPENDIX I

Drug Safety Futures 2020
Working Group Members

Driver Ideation Team	Scenarios Team	Implications Team
Vikram Dev (AstraZeneca) Gigi Hirsch (MIT) Scott Korn (Merck) Robert Laubacher (MIT) Michael McGinnis (IOM) Gary Neil (J&J) Brad Perkins (CDC) Richard Platt (Harvard) Evelyn Rodriguez (Bayer) Stacy Springs (MIT) Tony Sinskey (MIT) Facilitator: Wayne Rosenkrans (MIT)	Burt Adelman (MIT) Gilbert Burckhart (FDA) Vikram Dev (AstraZeneca) John Ferguson (Novartis) Neil Graham (Vertex) Gigi Hirsch (MIT) Scott Korn (Merck) Robert Laubacher (MIT) Nancy Leveson (MIT) Michael McGinnis (IOM) Garry Neil (J&J) Brad Perkins (CDC) Evelyn Rodriguez (Bayer) Richard Platt (Harvard) Judith Sills (Novartis) Facilitator: Wayne Rosenkrans (MIT)	Cherif Benattia (Vertex) Josh Benner (Brookings) Paul Bleicher (Phase Forward) Rhonda Bohn (HealthCore) John Ferguson (Novartis) Neil Graham (Vertex) Gigi Hirsch (MIT) Scott Korn (Merck) Nancy Leveson (MIT) Larry McCray (MIT) Garry Neil (J&J) Steen Ottosen (Amgen) Ken Oye (MIT) Jennifer Powell (MIT) Shoshana Reshef (Bayer) Judith Sills (Novartis) Marcus Wilson (HealthCore) Neelima Yeddanapudi (MIT) Facilitator: Wayne Rosenkrans (MIT)

Note: CBI is grateful for the generous contribution of its Process Shadow Team, all seasoned futurists and former members of AstraZeneca's Long-range Planning Team for Discovery, Development and Commercial:

- *Deni Boekell (Strategy)*
- *Cathy Bonuccelli (Development)*
- *Nancy Featherstone (Managed Care Markets)*
- *Jim Resch (Discovery)*
- *Kim Slocum (Strategy)*

APPENDIX II

Full Text Scenarios

Boutique Care

Healthcare became an issue in the 2020 elections when a prominent senator revealed that he was receiving an innovative cancer treatment in Singapore thanks to a special insurance policy he had purchased on top of his federal health benefits.

Most Americans thought the healthcare problem had been solved a decade earlier when Congress approved new forms of government-subsidized insurance to make sure that every citizen was covered. Congress failed to change the incentives built into the system, in which providers received higher reimbursements for providing increasing amounts of healthcare, even if the treatment did not do any good. Spending on the new programs did not keep pace with healthcare inflation.

Every year, physicians, hospitals, and pharmaceutical companies engaged in lobbying to increase their share of federal spending. And in most congressional districts, physicians and hospitals had greater clout than the drug companies. By 2013, spending increases on prescription drugs lagged behind those for other forms of care. Pressure on profits and the need to pool resources for research forced mergers throughout the pharmaceutical industry. The 10 leading companies in 2010 were reduced to four by 2019.

Congress further limited spending by confining all recipients of federally supported health insurance, including Medicare, to the drug formulary devised by the Veterans Administration. Patients complained that they were being denied new life-extending therapies as a result. Policy makers were aware that problems of healthcare spending transcended international boundaries and the United States began working with the European Union to devise a common pharmaceutical policy in 2015. The resulting *Common Pricing Agreement* harmonized the price of all prescription drugs, but set up a special category of reimbursement to allow pharmaceutical companies enough profits to continue investing in research.

The flood of retirees in both Europe and North America, however, continued to put enormous pressures on healthcare budgets, and both the United States and the EU continued to tighten price controls.

Government policy was more successful with regard to drug safety. The Sentinel Initiative, unveiled in 2008, allowed the federal government to keep closer track of adverse reactions to medications approved by the Food and Drug Administration. The FDA cooperated with EU regulators to expand the database of patients using a medication so that problems were quickly detected. The Sentinel system, by publicizing problems with new drugs, had the paradoxical effect of making the FDA reluctant to approve high-risk pharmaceuticals without long, stringent testing periods. Even with increased vigilance, a few highly touted drugs occasionally produced adverse reactions, which were heavily publicized by news media. Many Americans grew wary of new medications, and pharmaceutical companies shied away from introducing products that might not meet the FDA's tougher standards.

Americans' suspicions were heightened by a failure in public education. The schools, by and large, did not provide students with the scientific knowledge to make informed assessments about the risks of biomedical innovation. Even with safeguards in place, unexpected and tragic results were inevitable on rare occasions as researchers strove to devise powerful treatments for intractable diseases.

The market for the latest prescription medications, however, was no longer confined to North America and Europe. Citizens of China, India and other newly developed nations now had the knowledge and the money to demand the best treatments. Entrepreneurs and scientists established companies in these countries to do research and supply this

burgeoning market. They recruited scientists from American and European companies to jumpstart their new industry.

A few Americans, despite the suspicion of discoveries, were smart or desperate enough to seek out the best medications and other treatments available, and private insurance companies were willing to provide the financing. The senator had purchased a policy whose principal selling point was that its provider network was not confined to the United States. It steered him to one of the best oncology clinics in the world, where he received medication devised in a research complex nearby that was tailored for his particular genomic variant of liver cancer. Singapore, India and China vied for the high-end business.

Those needing the latest prescription drugs at home, and willing to pay out of pocket, were usually able to get them surreptitiously from lower-cost producers abroad. The FDA and its European counterpart tried to staunch the flow, but this proved to be impossible. Customs agents were more concerned with terrorist threats and many people in North America and the EU thought there was little harm in trying drug regimens that were successful in other countries.

The senator, up for re-election, sought to turn the cancer treatment to his advantage. "Americans shouldn't have to go halfway around the world to get the medicine they need,'' he said. "I want everyone to have the same advantages I have.'' He introduced a bill to mandate that everyone with a federally subsidized insurance policy would receive the best care available anywhere in the world, but he didn't say how he would pay for it.

Healthness[I hate this word! It is really not a word.] for All

After decades of contention and delays, all the participants in the U.S. healthcare industry, the most expensive in the world, finally got it right. They devised a system that extended insurance coverage to most Americans, maintained the U.S. technological leadership in healthcare, and shifted incentives in the system so that prevention and essential care gained a decisive edge over unnecessary treatment.

Movement toward this improved healthcare system began with a sophisticated media campaign by leading news organizations. For once, not relying on isolated anecdotes about medical mistakes or drug overreactions, reporters and commentators focused on systemic problems of the system – lack of coverage for many Americans combined with over-treatment for those who had comprehensive insurance.

The federal government, seeking to cover more people and aware that it would soon be facing an onslaught of Baby Boomers on Medicare, realized it had to get control of the system. It did so through information technology. The Centers for Medicare & Medicaid Services required that every provider who accepted federal money had to connect to the national electronic healthcare network. CMS set the standards and Congress provided the money so that all physicians and other providers could buy the hardware necessary to link to the network.

Once the information network was fully operational, CMS analyzed the data to determine which treatments were most effective. CMS found patterns of over-treatment and under-treatment, and was able to devise a payment schedule that shifted financial incentives to care that promoted health.

Realizing that the government had a handle on costs, Congress and the President devised a public-private plan that provided affordable insurance coverage to just about every American. A national risk pool was established under the aegis of CMS, and Congress provided money to defray the cost of insuring people with chronic or especially expensive ailments. With this money came new rules and payment restriction on private insurers. Many of the smaller insurance companies could not survive, and were consolidated into five large national organizations that could make money on high volumes of business.

Aided by the news media and incentives offered by the insurance industry, Americans got the message that they, on their own, could do much to stay free of disease. Obesity rates plummeted and so did the incidence of Type 2 diabetes and heart disease. The greater emphasis on prevention helped to stabilize the costs of insurance.

Americans still demanded that they get the best medical treatment available anywhere in the word, and the most efficacious medications. The news media embarked on campaigns to make sure people were informed that new drugs and treatments often came with risks that needed to be minimized but could not be avoided. The new electronic medical infrastructure provided quick warnings about adverse reactions from new medications.

The Food and Drug Administration played an important role in this new system of healthcare that minimized cost and maximized effectiveness. It worked with CMS and other federal agencies to make sure that new and already approved prescription drugs and medical devices were not only safe, but also effective and delivered good value for the money. FDA decisions were sometimes controversial but they provided a benchmark by which the government and insurers could determine where their money should be spent.

By 2018, data from the Centers for Disease Control and Prevention were showing an increase in the longevity rate, which had been going up slowly for a century or more. More importantly, nongovernmental researchers reported that the disability rate for older Americans was heading steeply downward. Encouraged by these data, Congress increased the age of eligibility for the full Social Security benefit to 72, and most people seemed to like the idea of working longer in exchange for a healthier old age. [That'll be the day!]

An increase in national well-being meant that there was less work for hospitals and most other medical providers. So Congress initiated a process similar to that applied to closing military bases. A special national commission devised a list of hospitals that were no longer needed. While those that were owned privately or by state or local governments couldn't be forced to close, Congress denied federal healthcare money to any on the list.

Primary care providers were still in demand, and many of them took on new responsibilities as advisers who waded through all the data to offer patients an evidence-based plan for a healthier life. Patients realized that empirical evidence was better than hunches and anecdotes in determining a course of treatment.

Providers still made mistakes occasionally, although public satisfaction with the system minimized malpractice and faulty-product lawsuits. And there were frequent arguments about whether the government was spending enough money on basic research. But the public insisted that new drugs get on the market if they could be proven to enhance the quality of life. And other developed nations began mimicking the American emphasis on information technology as the key to quality in health care. By 2020, the U.S. healthcare system, still the most costly in the world, was offering good value for the money.

Healthplan Nirvana

The decade of the 2010s witnessed a dual transformation of the American healthcare system. Virtually every American had obtained health insurance, and their care was mediated by powerful health information technology. Americans took control of their health records and found the most cost-effective treatments for ordinary problems, but many people on the margins of life found they could not get optimal care.

"No longer do we rely on esoteric prescription drugs, when simpler remedies will suffice, '' one healthcare commentator said. And this was true, for many diseases. Those illnesses that did not affect many people or seemed to defy a cure received little new funding. Research into new pharmaceutical treatments for mental illness, for instance, was at a standstill.

Private companies still provided most of the health insurance for working Americans, and also supplied most of the technology that guided Americans through the system. But the federal government was the arbiter of standards for the nationwide IT network, the kinds of coverage that private insurers offered and the treatments that were provided under the new system. The government had a powerful incentive to control costs. As millions of Baby Boomers became eligible for Medicare, healthcare inflation continued to exceed annual economic growth.

And elderly people stayed alive longer. In 2016, for the first time, the lifespan of the typical American exceeded 80 years. A campaign spearheaded from Washington had blunted the impact of an obesity epidemic that had threatened to diminish the gains in life expectancy.

Expanding coverage to more Americans worsened the nationwide shortage of primary care providers, but this problem was partly alleviated by increased reliance on non-physicians for routine care. The government and private insurance companies demanded that physicians and hospitals only offer treatment that was proven effective through the FMEB (Federal Medical Effectiveness Board created in 2011), and they refused to pay for any mistakes. Providers got the message: The rate of costly medical errors dropped drastically. For minor ailments, costs were further controlled by drop-in clinics at Wal-Mart and other discounters. Use of hospital emergency rooms was held to a minimum.

The IT network was more than just a record of a person's history. They [Who is "they" referring to?] also offered treatment options and a list of recommended hospitals and physicians to treat any health problems, along with the price of each procedure. "Patients are finally aware of the true cost of medical treatment,'' the healthcare commentator noted in 2017.

Americans enjoyed being in charge of their healthcare records, and were usually skillful enough to take advantage of the treatment options presented by the major web sites. The IT web sites encouraged patients to use generic or over-the-counter medications. Some patients went so far as to treat themselves via the *Be Your Own Doctor* site.

The federal emphasis on cost control influenced decision-making at the Food and Drug Administration, which slowed down the approval process for new prescription drugs on the grounds that new medicines were not really needed unless they provided an unambiguous improvement in treatment. The public supported the new approach after two highly publicized cases in which two FDA-approved drugs appeared to increase the incidence of strokes in elderly men. The pharmaceutical companies involved argued unsuccessfully that the results were inconclusive and should not have chilled the climate for drug approval.

The frugal federal government reduced its support for basic research, and with fewer new drugs being approved, private investment in pharmaceutical companies declined. Companies shifted their limited dollars into development work in China and other lower-cost countries. Most new investment money was flowing to biotech companies, which made gains against the symptoms of Parkinson's disease, but had difficulty making similar progress against other illnesses.

The US reliance on information technology to control healthcare spending resonated in Europe and Japan, whose populations were aging faster than that of the United States. Governments in the EU and Japan were stingier than the United States on spending for healthcare research and development. Private investment was nonexistent in these countries.

In the United States, the new healthcare system was working well to get proven treatments and preventative measures to people who needed them. Complaints about inadequate care were increasing, but had not yet reached a critical mass. Those afflicted were either too small a number or, like the mentally ill, lacked political clout.

Many elderly people found that their final years were afflicted with ailments that seemed on the verge of a cure just a few years before. The commentator's mother, for instance developed Alzheimer's disease, but there was little more to do for her than had been done in 2000. "Americans shouldn't face the prospect of disability in their old age,'' he wrote in 2019. In 2020, the AARP began an Internet advertising blitz in an attempt to make increased funding for medical research an issue in the presidential campaign. Neither party was interested in disrupting a system that was keeping the government financially stable.

Global Warming for Healthcare

Americans dreaded getting sick in 2020. Most of them had access to government health insurance but people of modest means almost had to bankrupt themselves to be assured of competent treatment.

The best hospitals and physicians offered outstanding care, but they wanted nothing to do with patients who had stingy insurance. Some insurance plans included the best providers, but they were so expensive that only the

wealthy could afford them. Patients with moderate income either had to settle for inferior care, go deeply into debt to pay for a competently done procedure, or in a few cases go abroad to seek a less expensive treatment

Americans felt the inadequacy of the system most keenly because most of them could remember a time 15 or 20 years earlier when standards were much higher. Even then, the warning signs of declining care were clear. Physicians and hospitals kept performing elaborate and unnecessary procedures. Pharmaceutical companies kept selling high-priced medicines whenever possible, and private payers and the government refused to take sensible steps to control costs without affecting quality. No one could agree on common standards to allow medical information to flow easily across the Internet, which might have allowed insurers and the government to create efficiencies in the system without diminishing quality.

This radical decline of health care began in the United States in 2014, propelled by a coalition of private employers and the federal government. The employers raised co-pays and deductibles on health insurance so much that policies became a shadow of the comprehensive coverage available a decade or so ago. And the federal government, determined not to be bankrupted by Baby Boomers' retirement, did the same for Medicare.

In 2016, a presidential election year, the government stepped in with a supposedly universal plan to replace the employer-based system, but the new program mandated similarly inadequate payments to providers. Hospitals that were once marginally in the black had to close except for the few that received subsidies from local and state governments. Available funding wasn't enough to maintain standards, and few patients went willingly to public hospitals unless they were experiencing a medical emergency.

Pharmaceutical companies were not spared the medical cost cutting of 2016. The Medicare D drug benefit became progressively skimpier. Private insurers and the government's universal insurance plan paid for only minimal amounts of prescription drugs. The government and private insurers agreed on efficacy standards for new drugs that were designed to make low cost the dominant factor. The payers rarely approved reimbursements for new drugs designed to treat diseases that afflicted small numbers of people.

Congress denied the Food and Drug Administration the funds necessary to approve effective medications quickly. As the FDA withered, competent scientists left the agencies. The approval process grew ever longer and more arduous. Federal support for basic research dried up and the biomedical industry was squeezed by the new cost standards. Private investors grew reluctant to invest in biotech start-ups and the industry failed to live up to its promise early in the century. The larger pharmaceutical companies were starved of investment as well, and they struggled to make a profit out of those medications that passed the cost-effectiveness test.

The European Union and Canada were forced to curtail their national health programs as well as the pressure of retiree benefits put unacceptable strains on their government budgets. Economic growth in both Europe and North America was too slow to cope with soaring healthcare expenses.

By 2020, the United States and the European Union were no longer the leaders in pharmaceutical research and development, that role having been assumed by China and India. Companies there had yet to achieve the same level of technological expertise that had been the norm in the United States and the EU in 2000. Most drug production was outsourced from North America and Western Europe. There were more than a few quality control problems as a result, but not even the deaths of several hundred people form tainted medication, made in Bangladesh, were able to reverse this trend.

North America and Europe remained wealthy by the standards of the rest of the world. While most ill people remained close to home to stay near family and friends, a few adventurous and less acutely ill patients sought better options abroad. The country with the greatest number of both US and Canadian patients was Cuba, whose relations with the United States had warmed after the deaths of the Castro brothers in 2011 and 2013. In Cuba, and elsewhere in the developing world, the bulk of the indigenous population rarely had access to the medical institutions that catered to affluent foreigners. Like their neighbors to the north, Cubans had to make do with whatever the government and private payers were willing to make available. Quality healthcare around the world had become synonymous with a patient's wealth.