How Do You Feel Now?

An exploratory analysis of the futures of clinical research regulation amidst the changing landscape of healthcare delivery in the US and Europe

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INTRODUCTION

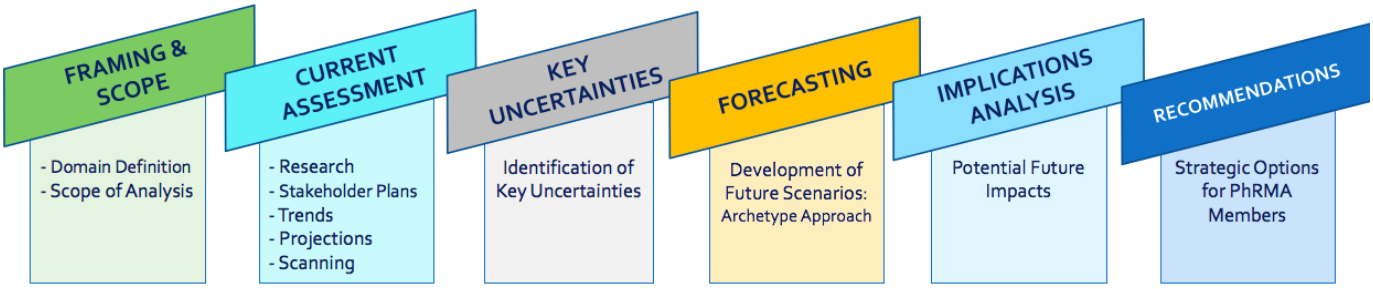
This foresight analysis explores the futures of clinical research regulations amidst the changing landscape of healthcare delivery in the United States and Europe, on behalf of a hypothetical client, the Pharmaceutical Research and Manufacturers of America, a trade organization also known as PhRMA. The group's core mission is to help modernize drug discovery and development, engage and empower consumers, and promote value-driven health care with research, education, and political advocacy. Because PhRMA's members occupy the spectrum from emerging biopharmaceutical start-ups to mature multi-national corporations - with different objectives and with a range of preferred futures - the client's goal for this analysis is to identify potential high impact future disruptions in order to help its members recognize and prepare for the uncertainty inherent in these possible futures.

The work was conducted in partial fulfillment of the requirements of the graduate program in Strategic Foresight at the University of Houston (UH) College of Technology.

FRAMEWORK FORESIGHT ANALYSIS METHOD

The analysis follows the UH Framework Foresight method (Hines and Bishop, 2013), which begins with framing and defining the domain and scope of work and assessing the current state of the ecosystem with focused research, scanning for signals of weak change, and evaluation of historical conditions to recognize important trends and drivers of change. Analysis of this information helped to identify the key uncertainties for the futures of clinical research regulations, which were used to craft plausible future scenarios based on the Houston archetype scenario planning approach.

Once the set of future scenarios was created, the potential future implications were explored to evaluate the potential impact of these futures for PhRMA's member companies. Finally, all of the information and insights were integrated to develop recommendations for strategic options to help PhRMA support its members in developing strategic pathways to identify and achieve their preferred futures.



FRAMING AND SCOPE

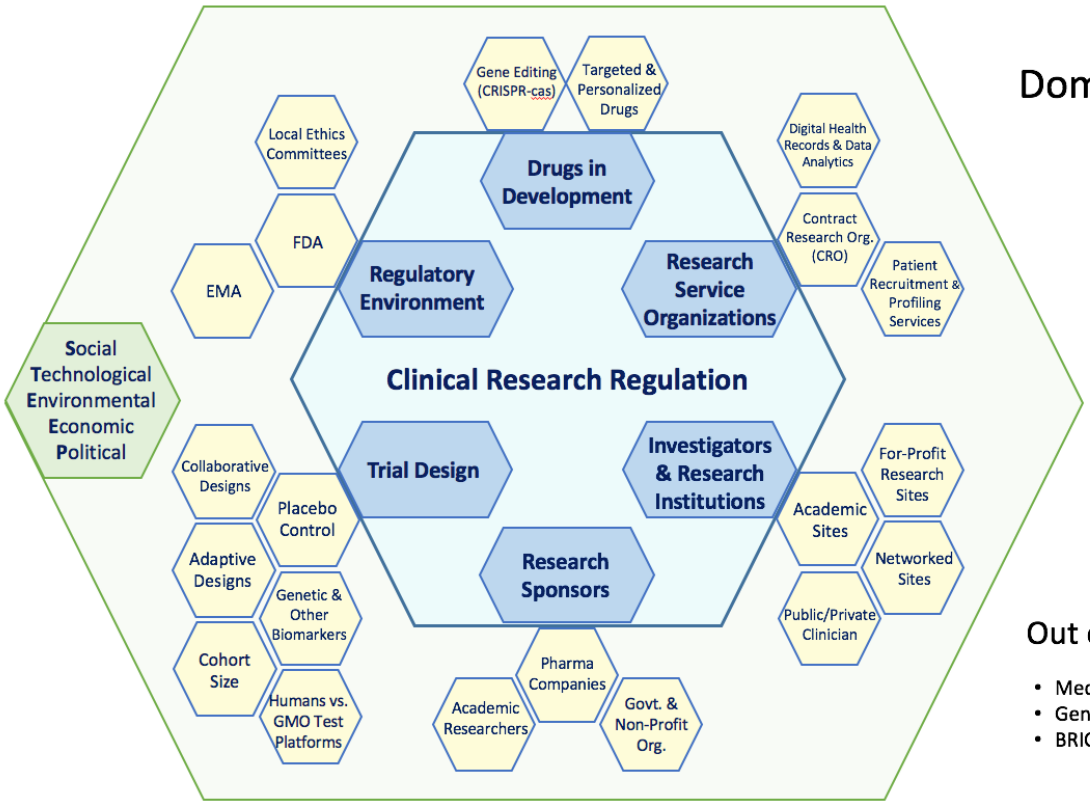
In framing this foresight work, the central question considered was:

> *Can the regulatory systems for pharmaceutical research and development evolve quickly enough to accommodate the rapid changes occurring in drug development and clinical research?*

In defining the domain, it is important to note that multiple tightly-integrated ecosystems interact to influence the futures of clinical research regulations - including healthcare delivery systems, third-party payers such as public and private insurance and pharmacy benefits management companies, the clinical research environment, the pharmaceutical industry, public policy concerns, and the complex regulatory environment itself, which varies by country. Although the current assessment included a broad evaluation of these ecosystems, focused research of the clinical research regulation domain has been limited to the key

areas shown in the domain map below. The scope of this work includes the sponsors of clinical research, innovations in clinical trial design, the regulatory environment, recent trends in drug development, specific aspects of the affiliated research service industry, and clinical investigators and their institutions, as well as evaluation of important drivers of change in the STEEP categories (social, technological, environmental, economic, and political).

The geographic scope of the analysis focused on the United States (US) and European Union (EU) as these are the major pharmaceutical markets and typically the first regions in which companies seek commercial approval from regulatory and marketing authorities: the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Assessment of regulatory affairs for medical devices, generic medications, and biosimilar products was excluded from the analysis, as PhRMA's member focus is on clinical development of new drugs.



Time Horizons

Although three time horizons were considered, this work focuses on Horizon 2 (2025 through 2030).

EXECUTIVE SUMMARY

The Framework Foresight analysis conducted on behalf of PhRMA investigated how current conditions, uncertainties, and drivers of change in the clinical research regulatory system interact to influence the potential futures of this domain. Summarized below are the key findings, as well as recommendations for strategic options to help PhRMA support its membership in preparing for the challenges and opportunities these futures represent.

IMPORTANT TRENDS AND DRIVERS OF CHANGE

Evaluation of the domain and the intersecting ecosystems of healthcare delivery, third-party payers, the pharmaceutical industry, the clinical research environment, and the STEEP categories yielded the following important trends and drivers of change:

- Increasing healthcare costs
- Global population increase and aging populations
- Greater acceptance of value-based reimbursement models
- Growth in targeted and personalized therapies
- Increasing availability of data-driven digital healthcare tools
- Growing use of data analytics and machine learning in drug development and diagnostics
- Increasing competition for clinical research subjects
- Increased use of innovative and adaptive trial designs
- Greater collaboration within pharmaceutical industry

KEY UNCERTAINTIES

The key uncertainties listed below include issues that have been historical challenges as well as emerging concerns that are likely to have impacts in the future. These uncertainties helped guide development of the future scenarios:

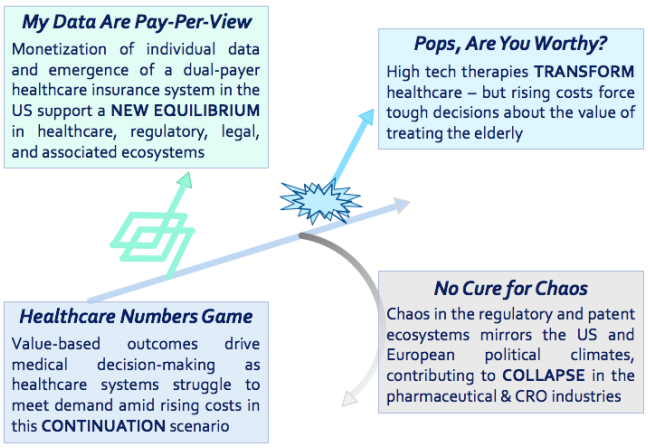
- Structure of US healthcare insurance system
- Rate of uptake of value-based reimbursement models in US
- Federal regulatory authority over artificial intelligence and computer algorithms
- Healthcare as a human right vs. citizen's right
- Availability and cost of personal data to power big data analytics
- Privacy in the age of genomic medicine
- US and EU regulatory structure for individualized genetic engineering therapeutics
- Impact of Brexit on drug development and clinical research in United Kingdom (UK) and EU region

SUMMARY OF FUTURE SCENARIOS

Four future scenarios were developed, based on the Houston archetype method (Hines 2014). The *Continuation* model represents the baseline, or "official" future that would be expected should current trends and conditions continue. The *New Equilibrium* archetype is significantly different from the current system, having arrived at a new balance in response to the challenge of competing forces, but retaining some recognizable features. In the *Transformation* model, the old system is discarded in favor of a new one and the *Collapse* archetype describes a future in which the systems deteriorate to the point of dysfunction.

- In the *Continuation* scenario, called ***Healthcare Numbers Game***, national health systems in the EU countries and payer/provider systems in the US adopt stricter population-based reimbursement policies as rising healthcare

prices, aging populations, and the influx of immigrants strain national healthcare budgets. In this future, regulatory authorities struggle to keep pace with rapid progress of digital health technologies.



- The *New Equilibrium* scenario, called ***My Data Are Pay-Per-View***, features a private non-profit insurance organization that provides low-cost healthcare coverage in the US, effectively creating a dual-payer system. The new company leverages the value of patient data to negotiate favorable prices on drugs and services. The US FDA is split into two agencies: one to regulate food and one to regulate drugs and digital health tools.
- In the vision of the future modeled on the *Transformation* archetype, called ***Pops, Are You Worthy?***, conventional drugs are used mostly in developing regions – while medical care in the advanced economies is focused on gene therapies administered in utero or during early infancy. The FDA streamlines its operations to focus on genetic engineering, leaving other drugs to be regulated by the states, should they so choose. Expensive treatments mean therapies are often reserved for the young or those most likely to contribute value to society.
- The *Collapse* scenario, ***No Cure for Chaos***, has the US FDA in chaos in the post-Trump era after executive orders and political pressure stymie efficient operations of the agency, resulting in dysfunction that leads to delays of new product launches for pharmaceutical companies and subsequent collapse in the industry as generics claim greater market share and research and development innovation stalls. Similar difficulties are faced in Europe as the post-Brexit EMA relocation creates confusion.

Potential High-Impact Implications

Evaluation of the future scenarios informed the implications analysis, in which potential implications of the futures were explored out to the third and fourth order. Some of the more important, provocative, or potentially disruptive implications are summarized below:

- Regulations for digital health products target data analytics and artificial intelligence (AI) processes rather than products
- FDA focus on gene therapy leads to a new regulatory paradigm with simplified compliance practice for biopharma industry
- Requirement for greater confirmation of value from real world data drives new late-phase master protocols and greater collaboration in pharmaceutical industry
- Delays in new product approvals due to regulatory agency chaos leads to failure of small biopharma and rise of mega-corporations with great influence over supply chain and logistics industries
- Value of personal data increases and new markets for consumer data emerge to limit access or increase cost of use for data analytics
- Subject recruitment for clinical research studies becomes difficult due to lack of patients (specificity of eligibility per biomarker or genetic mutation) or lack of motivation (availability of affordable care)
- Loss of health insurance in US leads to greater health disparities and loss of agency for patients of low socioeconomic status when making decisions about their healthcare; wealth becomes a biomarker for health

Recommendations for Strategic Options for PhRMA

PhRMA can best support its member companies to meet future challenges and take advantage of the potential opportunities identified in this analysis by continuing to conduct effective advocacy for public policies that encourage development of new medicines for patients, by communicating with its membership on important issues impacting the future, and by helping to shape public awareness of topics of importance to the pharmaceutical industry via external marketing campaigns:

Political Advocacy

- Limit potential negative impact of new legislation and regulations on AI, machine learning, and data analytics techniques in new drug development

Communication to Membership

- Raise awareness of possible future disruptions in the flow of patient and health outcomes data
- Promote efforts to create and participate in industry-wide data systems and standards to mitigate the risks of potential data access interruptions
- Advocate for creation of industry programs to support new investigators and research-naïve sites in establishing infrastructure to conduct clinical trials
- Prepare for potential delays in new drug approvals and greater consolidation in the pharmaceutical industry
    - Encourage small emerging biopharma companies to partner with multiple firms to co-develop new molecules
- Alert Human Resources leadership to changing employment landscape
    - Regulatory Affairs staffing needs may evolve to require greater scientific and technical expertise
    - Information Technology (IT) teams may need to engage technical and programming talent differently in the future to accommodate the 'open talent' economy models operating in the technology sector

External Marketing

- Raise awareness of importance of clinical trial participation and the value of patients and their data to improving global public health
- Conduct targeted campaign for physicians and clinical providers to highlight the importance of investigators' contributions in advancing medical science and in bringing new medicines to patients
- Promote recent successes of personalized therapies and the important way free access to dynamic data assets contributes to better lives for patients and their families
- Target young programmers and technical talent to demonstrate the value of AI and data analytics in creating better medicines

Current Assessment of the Domain

To make sense of potential disruptive changes on the horizon, it is helpful to understand the systems and driving forces currently in play so that the 'now' can be established as a benchmark before looking forward to the future. In addition, a look back in history helps in understanding the driving factors and events that led to the current systems – to see how we got to 'now.'

The current assessment of the domain (presented below) includes a look at current conditions in the relevant ecosystems, an analysis of key stakeholders and their concerns, evaluation of current trends, and a review of published forecasts and projections, as well as environmental scanning for current innovation and weak signals of potential change in the future.

The information gathered during the current assessment and historical review help set the course for the baseline, or expected future scenario, which is described further in the Futuring/Forecasting section.

Brief Historical Review of Key Events Impacting the Regulatory Ecosystem

In assessing the current state of the clinical research regulatory domain, it is important to appreciate how recent historical events have shaped present conditions to gain perspective on the trajectory of change currently underway. A brief review of important regulatory legislation, establishment of clinical research and regulatory infrastructure, and recent notable events follows.

The **Drug Price Competition and Patent Term Restoration Act** (1984), also known as the Hatch-Waxman act, is US federal legislation that encourages market entry of generic drugs to increase competition and created the modern system of generic drug regulation. A key aspect of the law requires generic drug manufacturers to establish a position of their products with respect to the branded drug's patent protection that can trigger patent challenge litigation for generic drug manufacturers once FDA approval of their product is sought. A summary of the legislation can be found here.

International Conference on Harmonization (ICH) was established in 1990 to harmonize the technical and scientific aspects of drug registration globally so that clinical research conducted across regions can be structured to meet unified standard requirements for regulatory authorities in all participating countries (US, EU, and Japan). The ICH guidance document on Good Clinical Practice (GCP), E6, provides the international ethical and scientific quality standard for the design, conduct, data recording, and reporting of clinical trials that involve human subjects; data that are produced by research studies conducted in strict compliance with ICH GCP standards can be considered by regulatory authorities to be credible in support of an application for marketing approval. A standardized format for compiling all quality, safety, and efficacy data was developed, called the Common Technical Document (CTD), that allows pharmaceutical companies to produce a single document that is acceptable by each of the ICH regulatory authorities.

Prescription Drug User Fee Act (PDUFA) – first instituted in 1992 to collect fees from drug manufacturers to defray the costs associated with new drug approval process as a funding mechanism to accelerate the agency's review, after Congress mandated new responsibilities for the agency (without providing funding for the new mandate) and drug review and approval timelines lagged. The act is reauthorized every five years, most recently in August 2017, and the reauthorizations typically have added conditions, such as the ability to allocate funds to post-marketing safety initiatives and monitoring of direct-to-consumer advertising. Fee rates are posted on the FDA website and are calculated on a line-item basis depending on the number of products and manufacturing locations under review, with a current minimum fee of ~$2.6 million for industry users (pharmaceutical companies).

European Medicines Agency (EMA) was founded in 1995 to harmonize the regulatory approval process for new drugs in the EU and European Economic Area states (including Norway, Iceland, and Liechtenstein). Previously, pharmaceutical companies were required to file separate applications for approvals from each country for which marketing authorization was sought.

FDA Modernization Act of 1997 – legislation designed to align the FDA with current scientific and technological advances; detailed press release from the FDA can be accessed here.

Health Insurance Portability and Accountability Act (HIPAA) was passed in 2003 to regulate privacy and confidentiality of patient medical information, as well as govern transfers of health insurance coverage.

The **#SaveJosh** **social media campaign** in March 2014 created a media sensation and public opinion backlash against a small pharmaceutical company, Chimerix, for denying access under compassionate use rules for 7-year-old Josh Hardy, who suffered a life-threatening infection following a bone marrow transplant. Josh was ineligible to participate in an ongoing clinical trial and Chimerix refused to provide the drug, citing concerns about low supplies that were needed to continue testing for ongoing trials

in support of the marketing approval. Josh's parents launched a social media campaign on Facebook that ultimately led to the FDA approving a small open-label clinical trial conducted at St. Jude's Hospital, with Josh enrolling as the first volunteer. Chimerix' CEO lost his position the following month due to the controversy and Josh Hardy died in September 2016. This event demonstrated the power of social media in influencing access to clinical research and raised new ethical questions for pharmaceutical companies and for the FDA in granting access to potentially life-saving experimental therapies under media and public pressure.

21st Century Cures Act – passed in December 2016 with bipartisan support, authorized funding for National Institutes of Health and made important changes to FDA drug approval processes and requirements for informed consent. https://en.wikipedia.org/wiki/21st_Century_Cures_Act

Brexit - In March 2017, the United Kingdom (UK) notified the European Council of its intention to withdraw from the EU (commonly known as Brexit). It is unknown what the full scope of impact will be for regulatory approval of new drugs in the UK or how legacy marketing authorizations will be handled by the new version of the national regulatory authority. The EMA has provided guidance for marketing authorization holders (pharmaceutical companies) that they must be established in one of the Union member states or transfer their authorization to another entity within the Union. In addition, the EMA headquarters must be moved out of London to a location within one of the EU member states by March 2019. The EMA announced in November 2017 that the headquarters would be relocated to Amsterdam in the Netherlands.

Current Conditions

In evaluating the current state of the domain, research focused on conditions in the regulatory environment, current conditions in healthcare systems, and recent trends in the pharmaceutical industry and the clinical research environment, as well as important technological and demographic drivers of change within the domain. A summary of these findings appears below.

Regulatory Environment

In the US, the FDA is vulnerable to political and other external influence because its Commissioner is appointed by the President and Congressional actions can mandate policies for the agency, without respect to the scientific merits of those policies. Newly-elected President Trump appointed Scott Gottlieb as Commissioner, despite Gottlieb's close pharmaceutical industry ties and his disclosure of at least twenty financial conflicts of interest with pharmaceutical companies, worth millions. Trump issued an executive order to eliminate 75 to 80 percent of FDA regulations, though details on how the FDA would accomplish this have not been announced. The executive order requires that before creating a new rule, the FDA must identify two existing rules that can be eliminated and further requires that the net cost for the new rule must be equal or less than the rules being eliminated – thus effectively limiting the FDA's ability to promulgate new rules and stifling innovation at the agency.

In Europe, the EMA is responsible for protection and promotion of public and veterinary health, serving as a decentralized scientific agency to coordinate evaluation and monitoring of centrally authorized medicinal products for the European Union, allowing harmonized marketing authorizations for products within the EU. The EMA is a *de facto* regulatory organization that operates by committee, with scientific working groups, an administrative Secretariat, and a leadership board with representatives from each of the twenty-eight EU member states, the European Commission and the Parliament all participating in its operation - ensuring fair representation but creating a deliberative and slow decision-making system.

Healthcare Systems

- Publically-funded National Health Systems (NHS) providing universal free healthcare are in place in many EU countries (examples: France, Italy) and hybrid public-private systems operate in other EU countries, such as Germany, where insurance is mandatory with financing provided by employers by "sickness funds" (~90%) and private or voluntary insurance (~10%). National formulary programs (example: NICE in the UK) operate in the EU that regulate the availability, pricing, and reimbursement of pharmaceutical products, with patients having little ability to choose their

therapy. If a preferred treatment is not cost effective, it will not be available under the formulary and patients will not have access. This can motivate some to seek care under the auspices of a clinical trial, especially for those with advanced disease. (Source: *World Health Systems,* Fried and Gaydos)

- The United States health system is evolving following ratification of the Affordable Care Act (ACA) in 2010 from a system of private insurance and government funded programs for poor (Medicaid) and elderly (Medicare) citizens; with the ACA, more citizens have health insurance with prescription drug coverage than in the past, but many are still without insurance. The new Trump administration has vowed to repeal or dismantle the ACA but efforts to do so have not yet fully succeeded. Even patients with healthcare insurance and prescription drug coverage can have difficulty affording the cost of drugs; a study published in *Cancer* (2016) found that breast cancer patients with insurance had median out-of-pocket payments for chemotherapy ranging from $2700 to $5200, with 10% of patients paying from $7000 to more than $11000. High drug co-pays and other treatment costs motivate many patients to volunteer for research studies.
- A "Medicare For All" (single payer US government health care system) policy is attracting more mainstream support among Democrats and will likely be a key issue in the 2020 elections
- Payers have been increasingly demanding real-world evidence demonstrating the value of drug therapies before agreeing to reimburse for these medicines, but recently the FDA is considering allowing the use of real-world data in support of drug approvals, amid some controversy.
- Increasing trend for "medical tourism" for patients seeking expensive treatments outside of their home countries as a way to save money; medical travel concierge companies (examples: Patients Beyond Borders, Overseas Medical) provide support services to patients looking for cost-saving care as medical tourists

Pharmaceutical Industry

Recently, a trend towards greater collaboration among pharmaceutical companies in trial design, data sharing, and other initiatives has gained traction in the industry:

- **TransCelerate** – a consortium of pharmaceutical companies working collaboratively on biopharmaceutical research and development initiatives, including several for more efficient research trial design
- Collaboration on real world data collection for oncology products in Europe among pharmaceutical companies and contract research organizations
- Greater emphasis on partnerships between companies for development of specific compounds

In the area of drug development, the trend towards development of targeted and personalized medicines continues, using biomarkers for research trial eligibility and endpoint analysis; public/private partnerships, such as the Accelerating Medicines Partnership, the Biomarkers Consortium, and the Lung Cancer Master Protocol, are actively working to advance the development of diagnostic and treatment modalities for personalized medicine and biomarkers through research. A 2015 report by the Tufts Center for the Study of Drug Development estimates that 20% of new drug approvals in 2014 were for personalized medicines and projects a nearly 70% increase in development activities for personalized medicines over the next five years. Recent notable events in drug development include:

- In May 2017, the FDA made the first approval of a drug for cancer patients based on a *genetic biomarker profile* – rather than for a specific disease indication, recognizing that the molecular basis of the disease is not limited to the location the patient's tumor was first detected.
- FDA approved the first genetic-engineered drug therapy using CAR-T technology for pediatric use in patients with certain types of leukemia in August 2017. The drug therapy is reported to cost $475,000 – though the manufacturer, Novartis, pledged to provide refunds to patients who do not respond to treatment within the first month.
- Direct-to-Consumer Genetic Health Risk reporting was approved by FDA for 23andMe genotype product in April 2016, marking the first time that consumers could access their genomic data without consulting a physician or genetic counselor. The 23andMe company provides options for customers (2 million genotyped in total) to opt-in to research

projects and estimates that more than 85 percent elect to participate in research – with average individual participation in over 200 different studies.

Emerging trends have recently surfaced in which more collaborative approaches to negotiations with payers in setting fair pricing for new drugs have occurred (example: Regenernon and Sanofi approached payers, pharmacy benefit managers (PBMs), and non-profit value framework groups like the Institute for Clinical and Economic Review (ICER) in advance of determining the price for new drug Dupixent).

Clinical Research Environment

High competition exists for research subjects, as well as clinical investigator sites, especially for oncology trials of drugs targeted to a specific genetic mutation or other biomarker. The scarcity of patients who qualify for trials, combined with a large number of research studies underway, make it challenging for pharmaceutical companies to complete studies on time. Delays are costly, as are strategies to mitigate delays – such as opening additional research sites in new countries in search of eligible subjects. New drugs for targeted therapies are approved after testing on relatively few patients, making the risk of undetected dangerous side effects more likely once the drug is approved and used in the general population.

Innovative Trial Designs – novel approaches to study design to accelerate timelines and reduce subject numbers are gaining in popularity:

- Adaptive trial designs: flexible designs that allow statistically-acceptable, prescribed changes to be made as interim data are analyzed to quickly fine tune the drug dose and eliminate treatment arms that are not effective
- Use of historical placebo control data to reduce the subject count and permit more patients to be exposed to an active treatment arm, especially for therapeutic indications with high placebo response rates
- Collaborative master protocols in which multiple pharmaceutical companies test new drugs within the same research study (example: I-SPY breast cancer trial) and basket trials, in which a drug is tested on patients with multiple disease types to find which are most susceptible to the drug's benefits

Patient-Centric Approaches in Research – emphasis on the value of the patients' experience during participation in clinical trials:

- Direct-to-patient trials, where study procedures and drug treatments are delivered to the research subject's home instead of requiring travel to a clinic or hospital setting
- Digital and virtual trials that are conducted without an associated clinical site or direct interaction with a physician or other healthcare provider (example: VERKKO diabetes trial)
- Trend towards use of social media for patient identification and recruitment to clinical trials
- Greater emphasis on patient reported outcomes (PRO) in clinical research, including acceptance by the FDA of PRO data in support of market approval of new drugs

Digital Tools for Clinical Research – a rising number of companies offer digital trial hosting platforms and other software tools to facilitate clinical research along all stages of the clinical development spectrum – including protocol design, site selection and start-up, patient recruitment and retention, trial administration, and data collection. (See blog post for summary of the current digital clinical research ecosystem.)

Global Research Strategy – most pharmaceutical companies adopt a global approach when conducting clinical trials for cost and subject availability reasons, but this can lead to ethical questions about the risk/benefit calculus for patients in low and middle income countries.

Other Important Drivers of Change

Demographics

- Trend toward global population aging and the impact on healthcare delivery systems, with an increasing burden on resources due to cost of long-term care of the elderly and treatment of chronic diseases; most healthcare systems are designed for treatment of acute illness and must adapt to changing patient populations and their medical needs in the future
- Immigration and forced displacement have put pressure on local and national economies and healthcare systems; in many EU countries, refugees are denied full access to healthcare and are only allowed to access emergency medical services – and often must pay for this care. There are both short- and long-term public health implications to the migrant crisis in Europe that will impact healthcare systems and the clinical research ecosystem in the future.

Technology

- Increase in acceptance of telemedicine, fitness and health-related wearables, smart phone health monitoring apps, and other digital interfaces between patients and healthcare providers is changing the delivery of healthcare and the conduct of clinical research; concerns about data security and limitations on privacy will drive additional changes in research conduct and regulations in the future
- Increase in the use of patients' electronic health records (EHR) and laboratory test values to locate eligible research subjects (example: PatientIP) and facilitate trial feasibility and site selection
- Trend toward greater use of computer-aided diagnosis and machine learning in medicine for rational drug design, identifying potential research subjects based on genomic factors, automated image analysis in radiology, and predictive analytics for epidemiology (among other applications)
- Acceptance of cloud-based solutions for clinical trial data systems (such as electronic data capture, EDC), smart phone apps for patients (example: VitalTrax), and trial matching services that analyze patient health records against open clinical trials to suggest potential eligibility matches (example: Antidote Technologies); all systems must be compliant with applicable regulations and must ensure patient/subject data privacy
- Growing acceptance of digital tools and mobile medical applications for patient treatment: FDA approved a substance use disorder treatment application for mobile devices in September 2017 that delivers cognitive behavioral therapy to patients intended to increase abstinence from substance abuse via a mobile device

Stakeholder Analysis

Because the current assessment evaluated a number of tightly integrated ecosystems that impact and are impacted by the futures of clinical research regulations – including healthcare delivery systems, the regulatory environment, public policy, third-party payers such as public and private insurance systems, and the pharmaceutical industry and affiliated service providers that support new product commercialization as well as research and development efforts – a complete analysis of the associated list of stakeholders operating in these ecosystems is too large for the scope of this project. Thus, evaluation of the most important players is limited to the key stakeholders listed below and includes the prominent concerns for each stakeholder as well as any announced intentions or plans for the future.

Key Stakeholders

- **Regulatory authorities** (FDA, EMA, and national agencies in the EU member states); these institutions evaluate claims of drug safety and efficacy for new medicines seeking marketing approval, monitor and oversee the conduct of clinical research for medical and diagnostic products, and serve as a central clearinghouse for safety recalls
- **Pharmaceutical, medical diagnostics, and other companies** providing healthcare products and services; these companies sponsor the clinical trials required by regulatory authorities for marketing approval of their products and must comply with all regulations
- **Contract research organizations** (CROs) and other **clinical research support service providers**; these organizations are bound by all regulations and often serve as intermediaries between the pharmaceutical companies and regulatory authorities, investigators, and research subjects; as the clinical research environment changes, emergence of specialty

service providers (such as genomic profiling and cataloging services and direct-to-patient research logistics vendors) is expected to increase

- **Government agencies** and **legislative bodies** that create rules, regulations, or legislation to regulate clinical research or pharmaceutical companies; in the US, for example, the Senate must confirm the President's appointment of the FDA Commissioner (chief officer of the administration), which is often politically motivated
- **National health service agencies**, **health insurance companies**, and other **payer institutions for healthcare**; payers control a drug's market uptake and are strong influencers of a product's profitability; availability and/or cost of health insurance can be a factor in motivating patients to participate in clinical trials, especially if treatment of their illness (outside of the research setting) is out of reach due to financial limitations
- **Clinical investigators** and their associated **research institutions**; research is conducted by investigators at public, private, and academic research institutions and must comply with all international, federal, and local rules and regulations
- **Patients** who use the approved drugs, as well as those who volunteer to participate as **research subjects** in clinical trials; these individuals accept the risk of using new medicines in order to benefit in the treatment of their disease

Evaluation of Individual Stakeholders

Regulatory authorities

- FDA
- EMA
- Country-specific authorities

Prominent Concerns

Regulatory authorities are responsible for ensuring the safety and efficacy of new and established drugs to protect and promote the public health. Scientific advancement can move more quickly than agencies are able to keep pace with, leading to delays and inadequate resources available for review and action

Intentions or Announced Plans

- FDA is seeking public comments on which of its existing regulations could be modified, repealed, or replaced – in response to executive order issued in January 2017 to streamline the agency
- FDA has announced its Digital Health Innovation Action Plan. As part of this initiative, the agency is seeking digital health entrepreneurs in residence to help develop a pilot program for software precertification, as well as a centralized Digital Health Unit, to address issues in artificial intelligence, data analytics, cloud-based computing systems, wireless medical devices, telemedicine, and cybersecurity. The Commissioner has stated that the agency understands it needs to become better at using advanced computing tools and sophisticated statistical methods as "almost 100 percent of new drug applications have components of modeling and simulation."
- FDA has promised to modernize and engage earlier with biotechnology companies and researchers working in new technologies such as gene repair, cellular therapies, and regenerative medicine
- FDA intends to streamline the drug regulatory approval process and increase competition through generics as methods to reduce drug prices, per September 2017 comments by the Commissioner
- EMA tends to be slow to act (as this is a coordinating agency for 31 countries) but has announced initiatives on reducing use of antimicrobial agents, developing medicines for elderly patients, revised guidelines for early-phase clinical trials, and personalized treatments and their associated companion diagnostics

Pharmaceutical companies and other sponsors of clinical research

Prominent Concerns

- Maintaining or increasing market share of existing products while keeping an active pipeline of new drugs in development to grow revenues and increase profits
- Complying with global regulatory and legal requirements while maximizing efficiencies of operations, including in the conduct of clinical research
- Ensuring acceptance of product value and pricing by payers, pharmacy benefit managers, healthcare providers, and consumers
- Maintaining a positive public image with patients, healthcare providers, clinical investigators, regulatory and government authorities, and payers

Intentions or Announced Plans

- Some pharmaceutical companies are canceling clinical development programs (GlaxoSmithKline) or cutting staff and operations (Eli Lilly) to save money in the face of competition from generics/biosimilars and tighter cost-control measures by insurers and other payers
- The International Clinical Trials Registry Platform (ICTRP) of the World Health Organization (WHO) established new guidelines for prospective registration of clinical trials and timely public disclosure of study results for trials sponsored by one of twenty major public and philanthropic organizations; it is expected that many pharmaceutical companies will voluntarily comply with the new standard
- Through the TranCelerate initiatives, participating pharmaceutical companies have announced intentions to increase diversity in clinical trials, raise awareness of the benefits of clinical research participation, make trial operational aspects more efficient, increase data transparency, enhance the patient research experience, and share placebo/standard of care data

Contract research organizations (CROs) and other research support service providers

Prominent Concerns

- CROs must stay current with innovations in technology and provide value in their offerings
- CROs have been through a recent period of mergers and acquisitions leaving the market much more consolidated than in the past
- As most pharmaceutical companies need to recruit subjects from the global population in their trials, CROs must be able to meet global operational requirements and accommodate added complexities (translation to patients' native language, e.g.), while ensuring quality meets FDA compliance standards

Intentions or Announced Plans

No specific plans have been announced, though trend is towards acquisition of data and analytics assets.

National Health Systems and associated agencies (EU countries), health insurers, and other payers

Prominent Concerns

- For NHS stakeholders, to ensure healthcare, including safe and cost-effective treatments, is available for citizens; policies must be established to provide funding and administrative services to support the healthcare systems
- Evaluate quality and efficiency of medical treatments (example: Germany's Institute for Quality and Efficiency in Healthcare)
- For private health insurers, ensure business and risk management practices allow sufficient revenue growth

Intentions or Announced Plans

- Optima Health insurance company announced plans to reduce its coverage in the state of Virginia, leaving up to 70,000 people without ACA insurance access through the marketplace; other companies have withdrawn or limited coverage in 29 states in response to changes in the ACA cost structure

- Centers for Medicare & Medicaid Services (CMS) set a goal of bringing at least 50% of Medicare reimbursements toward value-based alternative payment models by the end of 2018
- The EU has proposed new laws for protection of personal data and privacy in the digital age, including healthcare providers and others with access to medical data; these laws are to be applied by the end of May 2018
- German health authorities will roll out new electronic health cards for all residents by July 2018 that include patient medical data, administrative information, personal identification, medication plans, and historical health records

Clinical investigators

Prominent Concerns

- Scientific interest of new treatment modalities
- Opportunity to provide thought leadership in the research community (publications, conferences, advisory boards)
- Ability to offer treatment options to patients who have exhausted other possibilities
- Additional income source from research grants or study fees

Research institutions and clinical study sites

Prominent Concerns

- If research is part of a clinical care setting, ensuring balance between meeting needs of clinical patients and needs of research subjects
- Sites must comply with all applicable rules and regulations to ensure the safety of study participants; significant investment in administrative infrastructure is required to successfully conduct research studies

Patients and research subjects

Prominent Concerns

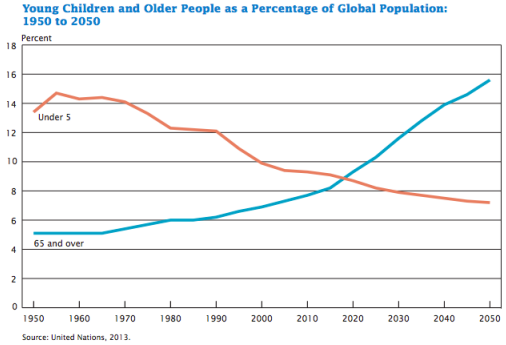
- Access to affordable, safe, and effective treatments
- For those who volunteer to participate in clinical research: to be treated with respect and in an ethical manner, within a scientifically-rigorous study protocol by research investigators and clinical staff who are well-trained, knowledgeable, and compassionate

Trends Identification and Analysis

The important trends described below are examples of parameters or values with clearly identifiable and measurable patterns of change. These trends are recognized as key drivers of the future because they might be expected to continue on the current path without deviating much from their course. Thus, in developing the future scenarios, these are the trends that contributed significantly to the baseline, or expected future.

Will you still feed me, when I'm sixty-four?

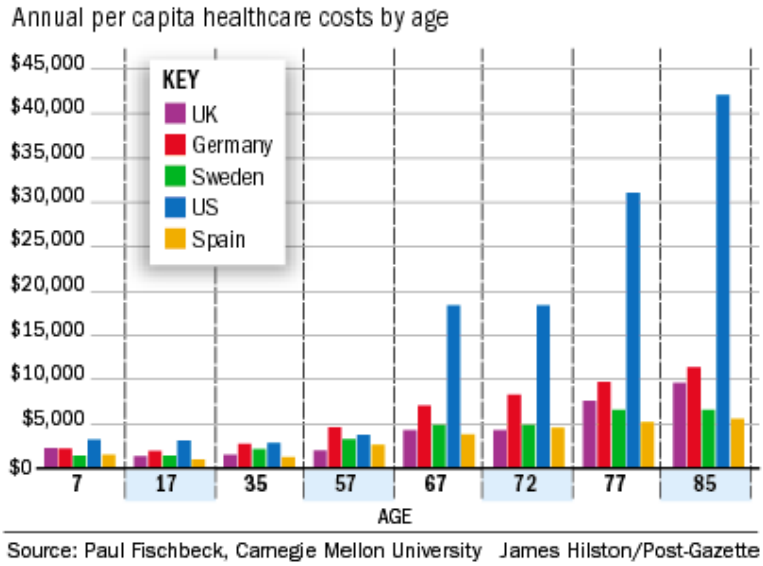
The world is aging – with a greater percentage of elderly in the population - and this trend is projected to continue at an increasing rate through 2050. When combined with decreasing fertility rates, there are concerns about how and who will manage the needs of elder care in the future.



From *An Aging World: 2015*, W. He, et al., US Census report, March 2016 (Figure 2-3) accessed at: https://www.census.gov/content/dam/Census/library/publications/2016/demo/p95-16-1.pdf

Let's retire to Spain!

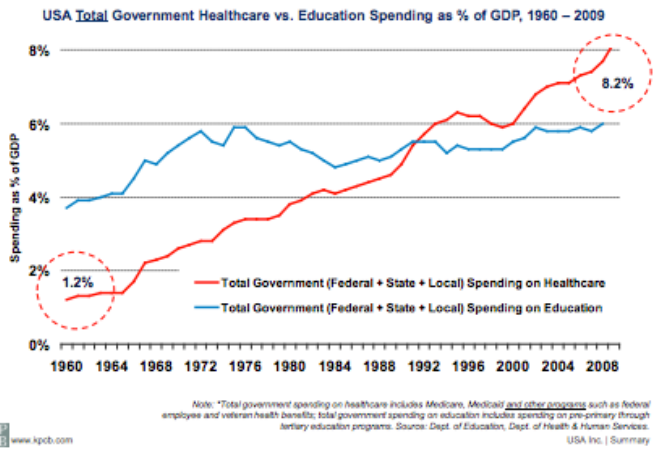
Per capita healthcare costs increase as adult patients age across the globe, but the cost increase is most significant in the US compared with other developed countries with national healthcare systems. Based on 2009 US dollar values, the yearly cost of healthcare for an 85-year-old American is approximately $42,000, compared to about $5000 for a similar patient in Spain.



Graphic from The Denver Post, accessed at: http://blogs.denverpost.com/health/2012/04/23/health-costs-elderly-skyrocket-compared-nations/480/

I hope my doctor went to private school…

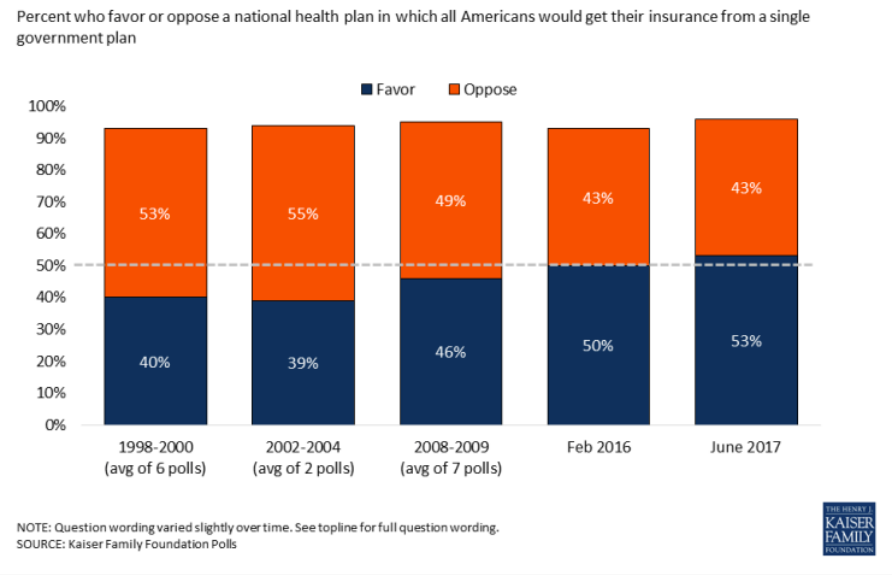
In the US, government healthcare expenditures for Medicare, Medicaid, and other federal health programs are rising relative to the gross domestic product (GDP) since the 1960s, up to 8.2% of the GDP in 2008. Government spending on education programs has remained relatively constant during the same period, ranging from ~4% to 6% of GDP.



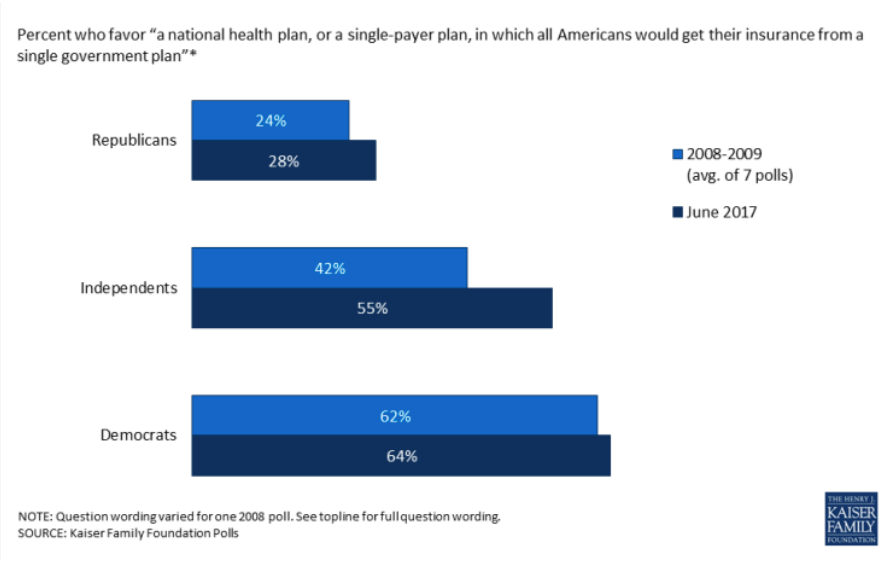
From *USA Inc.* report, published by Kleiner, Perkins, Caufield & Byers, February 2011, accessed at: http://s3.amazonaws.com/kpcbweb/files/USA_Inc.pdf

If single-payer healthcare works for Canada, maybe we should try it here…

Support for single-payer government-funded healthcare insurance in the US is increasing, from 40% in 1998 to a majority of respondents (53%) in favor in a recent poll conducted by Kaiser Family Foundation in June 2017.



The increasing trend of support follows across political affiliation, with independents gaining the greatest ground in acceptance (+13%):

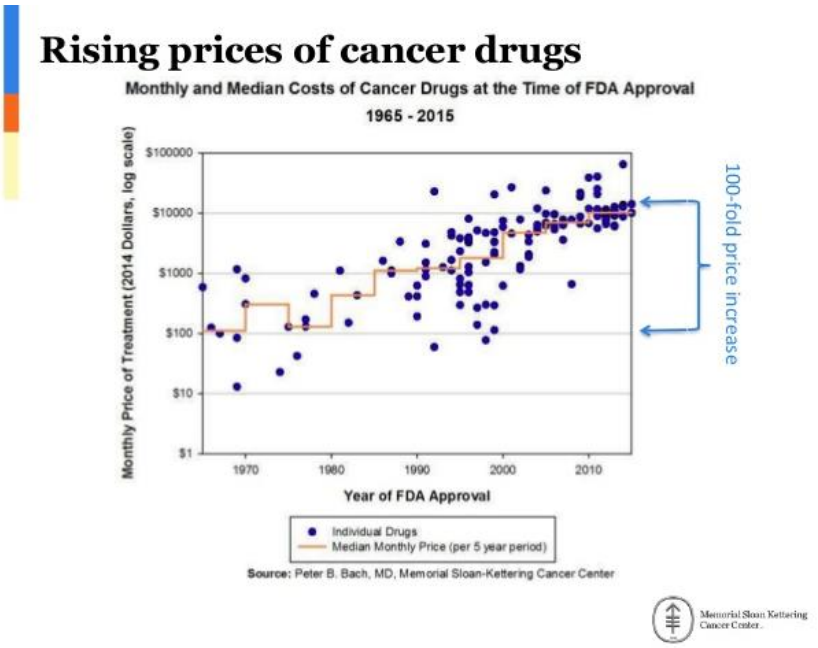


Source: [Kaiser Family Foundation poll data]

I can't afford to be sick

Since the mid-1960s, the median cost of a monthly dose of cancer medication has risen from ~$100 to ~$10,000 in 2015 – a 100-fold increase – based on the initial cost of the drug at the time of FDA approval. Some of this increase reflects the trend toward greater use of new targeted immunotherapies approved for oncology indications.

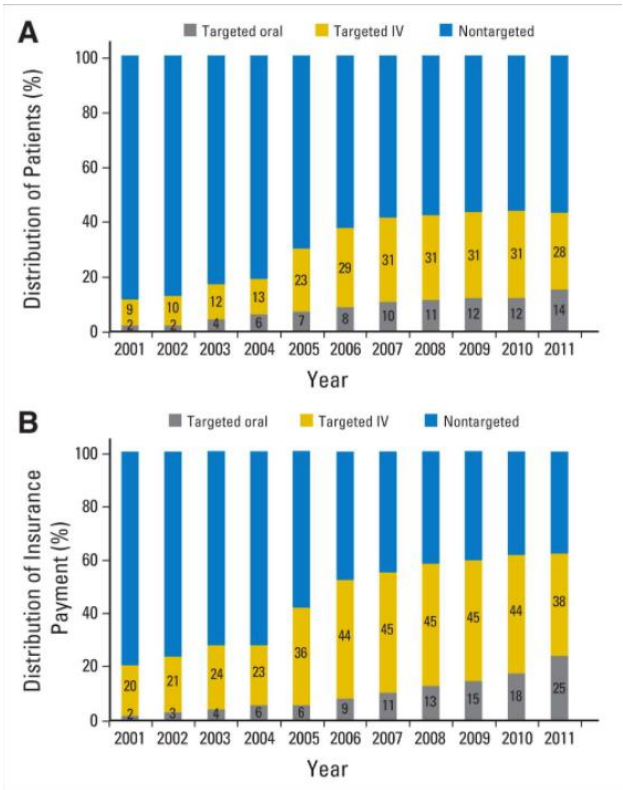
(Note the vertical axis is based on a log scale in the graph below)



From *What Soaring Drug Prices Mean for Patients*, Dr. Peter Bach, Memorial Sloan Kettering Center for Health Policy and Outcomes, September 2015, accessed at: https://www.slideshare.net/reportingonhealth/dr-peter-b-bach-what-soaring-drug-prices-mean-for-patients-9315

Insurers are feeling the pinch of high drug prices

Access to targeted therapies (both oral and intravenous (IV) formulations) for cancer patients in the US held steady from 2007 to 2011 at 41 to 43 percent (graph A, right), but private insurance payments for these therapies consumed an increasing proportion of the insurance resources during the same time period: from 56 percent in 2007 to 63 percent in 2011 (graph B).



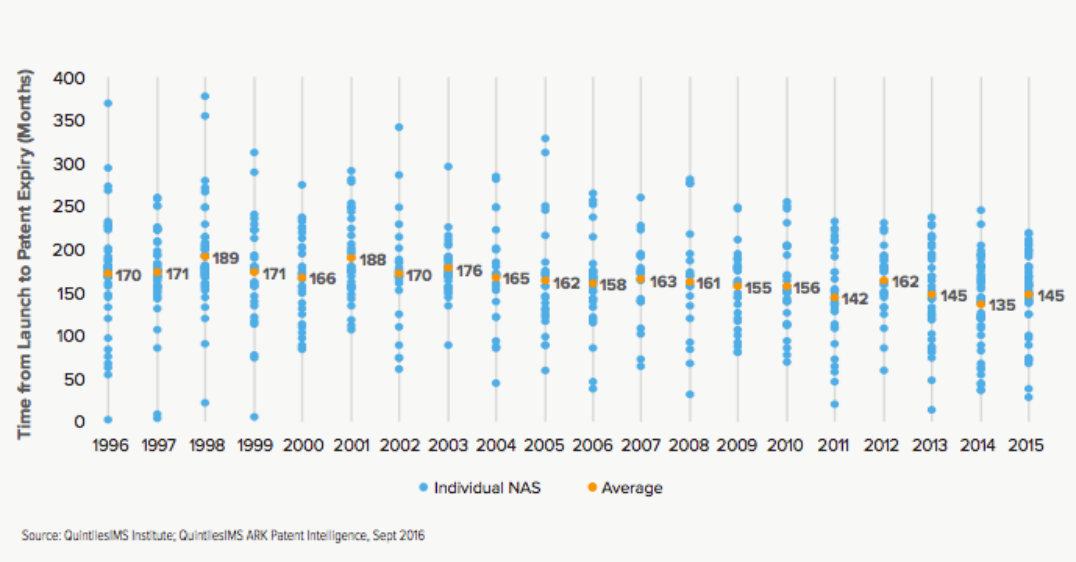
From *Trends in the Cost and Use of Targeted Cancer Therapies for the Privately Insured Nonelderly: 2001 to 2011*, Y. Shih, et al., Journal of the American Society of Clinical Oncology 33, number 19, July 2015, accessed at: http://ascopubs.org/doi/full/10.1200/JCO.2014.58.2320

Time flies while profits evaporate for big pharma

The average time from a new drug launch to the expiration of its patent protection has gradually decreased from 170 months in 1996 to 145 months in 2015. A shorter period of patent exclusivity limits the sales and profit potential of new drugs, which

begins to fall once competition increases when generics and other drugs gain market entry. Factors that influence this patent exclusivity period can be based in lengthy clinical development processes (including clinical trial timelines) and long drug approval review timelines by regulatory authorities, among other influences.

Patents for high value assets (oncology drugs and other blockbusters, e.g.) tend to be defended more aggressively and thus account for longer periods of exclusivity.

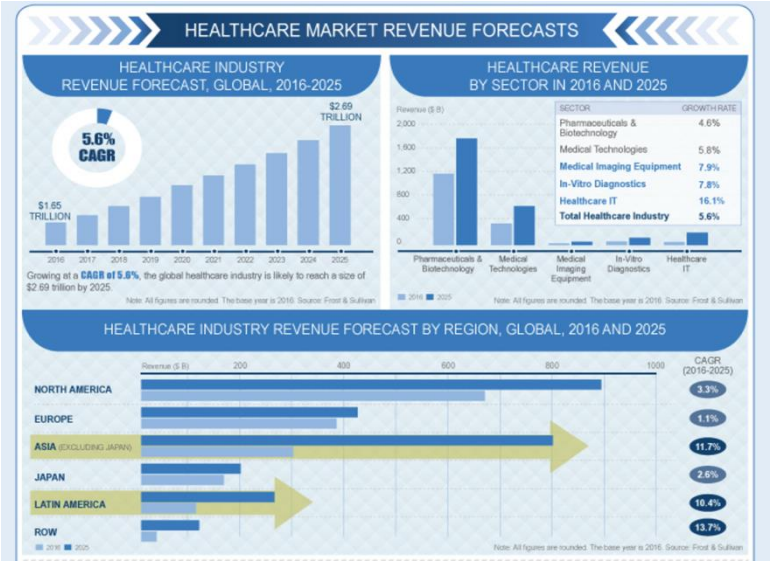


From *Lifetime Trends in Biopharmaceutical Innovation*, QuintilesIMS and STAT News report, January 2017, accessed at: https://tracs.unc.edu/index.php/who-we-are/announcements/723-report-lifetime-trends-in-biopharmaceutical-innovation

Healthcare is big business - and getting bigger

The revenue generated by the healthcare industry is estimated at $1.65 trillion in 2016, led by the pharmaceuticals and biotechnology sector, and is expected to grow - with projections to $2.69 trillion in 2025. Overall, the compound annual growth rate (CAGR) for the industry is projected at 5.6% through 2025.

By region, Asia and Latin America show the greatest potential for revenue growth, with projected CAGRs of 11.7% and 10.4%, respectively, from 2016 through 2025.

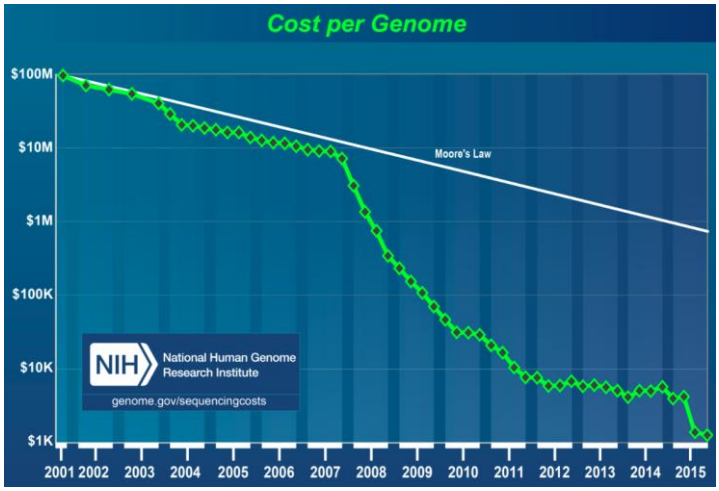


Source: Frost and Sullivan market report: *Vision 2025 – The Future of Healthcare*, November 2016, summary accessed at http://www.frost.com/sublib/display-report.do?id=K0EB-01-00-00-00

Sequencing for a song

The cost for DNA sequencing of an individual's entire genome is decreasing - at a current cost of ~$1000 - with rapid reductions observed since 2008. Recently, direct-to-consumer DNA sequencing services are available that provide ancestry and health information based on analysis of DNA segments for as little as $99. Many consumers purchase these kits without awareness that the sequencing companies can sell their genomic data to third-party companies without their knowledge or specific consent for use.

(Note the vertical axis is based on a log scale in the graph below; the discontinuity seen in 2008 reflects a change in sequencing technology from Sanger-based methods to 'next generation' technology)



Source: *The Cost of Sequencing a Human Genome*, July 2016, NIH National Human Genome Research Institute, accessed at: https://www.genome.gov/sequencingcosts/

Published Projections and Forecasts

To help inform development of the baseline scenario and to better characterize the intersecting ecosystems of clinical research regulation, healthcare delivery, and the pharmaceutical industry, relevant forecasts and future projections of others were explored. A sampling of these forecasts is provided below.

Looking to the Future in Regulatory Affairs

A brief but hopeful forecast from the Regulatory Affairs Professionals Society from 2014 on the future of global drug regulatory affairs that identified four interwoven 'strands' that contribute to the overall ecosystem:

- Global standardization of regulations and greater harmonization of requirements for clinical research in support of drug approvals
- Super (global) regulatory agency with authority across borders
- Priority medicines for underserved populations
- Pharmaceutical frontiers, including personalized drug selection/dosing and new approaches to drug development such as antibody-drug conjugates, will push the technological limits of regulators in the future

From *Looking to the Future in Regulatory Affairs*, O. Cox and S. Schmitt, in **Regulatory Focus** magazine, published by Regulatory Affairs Professionals Society, January 2014

Healthcare Outlook in Five to Fifteen Years

Senior executives and innovation officers from university and private health systems and health insurance providers offered projections in April 2015 to the Healthcare Financial Management Association (professional association) – focusing on four key areas, new care delivery options, changing make up of clinical teams, use of data analytics, and value-based payment models:

- New care delivery models that provide multiple options for home, mobile, and virtual care with greater reliance on technology to connect patients and healthcare providers
- An evolving workforce that will include more affiliated healthcare staff with fewer physician visits
- The role of data analytics will increase with predictive analytics becoming more important in the future delivery of healthcare as the focus shifts towards prevention and the best allocation of resources
- Value-based payment models will continue to grow in importance as resources for healthcare expenditures become more limited; providers will be incentivized for keeping their patients healthy rather than for providing services for sick patients

From *What Will Health Care Look Like in 5-15 Years?*, L. Phillips, in **Leadership+** magazine, published by Healthcare Finance Management Association, April 2015

Six Surprising Trends Shaping the Future of Pharma

Empowered patients, wearables and sensors, artificial intelligence (AI), 3D printed pills, virtual reality, and personalized medicine will drive the future for the pharmaceutical industry, according to a 2015 forecast from The Medical Futurist.

The Fate of Online Trust in the Next Decade

Pew Research conducted an online survey of experts and members of the interested public to assess their expectations about the future of trust in online interactions in the next ten years. Six themes emerged from the opinion data:

- Trust will strengthen because systems will improve, people will adapt, and more broadly embrace them
- The nature of trust will become more fluid as technology embeds itself into human and organizational relationships
- Trust will not grow, but technology usage will continue to rise, as a 'new normal' sets in – driven by convenience and forced compliance
- The impact of blockchain is uncertain, with the potential to help but may have limited value in practice
- The current situation is less than satisfying and is not expected to change much in the next decade
- Trust will diminish because of lack of security and threats to individual rights

As the use of technology in healthcare settings is expected to increase in the future, including virtual tools, services, and other online support platforms for clinical research, this forecast may have implications for the domain.

From *The Fate of Online Trust in the Next Decade*, L. Rainie and J. Anderson, Pew Research Center, August 2017

Environmental Scanning

Throughout the project, scanning of the clinical research, healthcare, and regulatory environments was conducted to keep abreast of innovation and to uncover signals of change occurring in these ecosystems. These scan hits were collected in a Diigo scanning hit library (which can be accessed here), then analyzed for elements of interest that might contribute to creation of a plausible future scenario.

Examples of scanning hit analysis summaries used in the development of the future scenarios can be found in the Addendum section, Scanning Hit Summaries.

Analysis of Key Uncertainties

To develop plausible alternative future scenarios, the data collected during the domain assessment process via ecosystem scanning and focused research were analyzed to identify signals of change, current issues and conflicts with the potential to impact the future, potential breaks in current trends, and possible events or wildcard actions that might lead to new ideas or images of the future. These are described in the following section.

Current Issues and Conflicts

The issues and conflicts identified during the current assessment and summarized in the table below have the potential to develop and/or resolve in many different ways that could influence the future of healthcare delivery, the pharmaceutical industry, and the clinical research regulatory environment. Aspects of these issues led to key uncertainties that helped inform the development of the alternative future scenarios.

Issues & Conflicts	Description
Should immigrants be permitted unrestricted access to healthcare resources? Is healthcare a citizen's right or a human right?	Immigration and forced displacement have strained national healthcare systems in Europe; in many EU countries, refugees are denied full access to healthcare and are only allowed to access emergency medical services – and often must pay for this care (unlike citizens, who enjoy free access via the national system). There are both short- and long-term public health implications to the migrant crisis in Europe that will impact healthcare systems and the clinical research ecosystem in the future. If healthcare is a human right, then refugees must be offered access to the same level of care as citizens – or the healthcare systems must be prepared to manage the public health impact of a large segment of society that cannot access care.
Does an individual's right to privacy protect the confidentiality of information contained in his/her electronic health record (EHR) – including genomic data - and preclude analysis of aggregated data to enable government agencies and insurance companies to make policy decisions at the population level?	Because genomic data are easily linked to an individual, they are nearly impossible to anonymize. The rapid progress of data analytics and the capacity to process large volumes of data have the potential to bring great benefit to healthcare and allow population-based decision making based on observed benefits and trends, especially in the field of genomics. A new definition of "privacy" may emerge in the future, especially with respect to personal data, if the benefit to society in using data for policy decisions outweighs the harm to individuals.
Should the cost of providing a specific therapy to an individual be a factor in deciding how to treat a patient with an illness? Should the value of the patient's potential contribution to society in the future factor in the calculus of a value-based reimbursement system for healthcare?	As value-based reimbursement begins to gain ground in the US, patients with insurance coverage will increasingly face resistance for reimbursement for expensive therapies, especially in last-ditch efforts to buy time for terminal patients. In the future, as healthcare budgets are strained by caring for an increasingly aged population, this has the potential to transform the question from deciding if treatment adds value for the patient into an analysis of whether treating the patient adds value to society.
Should the US adopt a government-funded national healthcare system that provides care for all citizens?	A national or single-payer healthcare system would provide important economic and public health benefits, including keeping healthcare costs in check as much of the cost of providing care to uninsured patients is borne by both the government and privately-insured patients.

Key Potential Trend Breaks

Creating plausible 'breaks' in current trends is an example of a technique to explore and identify potential disruptive changes in the future, using information collected during the current assessment of the domain. Potential trend breaks and the rationale for how they occurred are described in the table below.

Possible Trend Breaks	Description & Rationale
Proportion of elderly population declines significantly in developed nations	The percent of the global population aged 65 and older reached a peak of 8.2% in 2020, then began a gradual decline. A combination of factors led to increased mortality rates in the elderly population: widespread acceptance of value-based reimbursement policies for medical expenses, dissolution of Social Security in 2021, economic pressures on families due to healthcare and long-term care expenses, policy changes to encourage euthanasia and physician-assisted suicide, and impact from influenza pandemics.
US per capita healthcare spending falls in line with that found in EU countries ($5k - $10k per year)	Providing healthcare for elderly patients and subsidizing the under- and uninsured drives rising per capita costs in the US as patients age. Adoption of a single-payer healthcare system or establishment of a low-cost insurance carrier could bring per capita healthcare spending in line with EU rates, especially with a significant reduction in elderly population (see trend break above)
Drug prices fall	Drug prices fall due to greater use of data analytics in the early stages of drug development, combined with reduced cost of clinical trials due to low subject numbers and increased efficiency of technology tools. Pharmaceutical companies are forced to negotiate lower prices based on population health outcomes in the new value framework system.
Pharmaceutical and biotechnology industry annual revenues decline, with negative CAGRs projected through 2030	Economic slow-down in the US and Western Europe, chaos in the regulatory ecosystem that led to critical delays in new drug review and approval, falling drug prices, and greater uptake of value-based reimbursement policies drive declines throughout the pharmaceutical and biotech industries, leading many smaller companies to fail.
The cost of genome sequencing rises	Consolidation in the sequencing instrumentation industry allows a mini-monopoly to form; as the value of genomic data rises, the cost of sequencing rises, as well.

Possible Events or Wildcards

What events are likely to shape the future? Using data and insights from research and scanning, the possible events with high potential for disruption and the rationale for how they might occur were developed and incorporated into the alternative future scenarios. Examples of such potential (yet plausible) events are described below:

Back-to-back years with pandemic influenza or other infectious disease outbreak (such as a 'superbug' drug-resistant pathogen) in which millions of patients die

Pandemic influenza outbreak will cause widespread deaths among the elderly, young, and immunocompromised – the flu vaccine was ineffective in preventing infection with this new variant and natural immunity was low.

Patients previously treated with humanized monoclonal antibodies (mAbs) will be found to be at increased risk for death and serious co-morbidities during the flu outbreak – leading to a sudden decrease in use of this drug class, loss of market share for mAbs, and redirection of research/development efforts to drugs with other mechanisms of action.

Four pandemic flu events have occurred recently; concerns about the possibility of widespread avian flu outbreaks have been in the news since the late 1990s, when infections in people were first detected in Hong Kong.

Production processes of monoclonal antibodies are well defined but involve manufacturing using complex biological systems including cell culture of immortal myeloma cells; unknown long-term risks may emerge, especially for patients using mAb therapies for chronic non-oncological conditions (rheumatoid arthritis, psoriasis, e.g.).

Widespread, high impact data security breaches and ransomware attacks on electronic health records (EHR) systems make patient data unavailable and/or unreliable and reduce patient confidence in electronic platforms for clinical care and research

EHR systems and the data they contain are the currency of communication within and between healthcare providers, third-party payers, government agencies, clinical investigators, and clinical research support service providers. Unlike credit card data that can change frequently when fraudulent activity is suspected, individual health data are a permanent record of personal information, making this a valuable target for cybercriminals.

Recent ransomware attacks on hospitals and healthcare networks forced healthcare providers to revert to paper-based record keeping practices, causing significant disruption to patient care. Were a data security breach to be a widespread or coordinated attack, the clinical research system would be paralyzed.

Billionaire philanthropists establish a non-profit organization to provide healthcare insurance to uninsured, working poor, and underinsured Americans; the new company serves as broker for patient data, establishing a new path for monetizing personal data

Warren Buffett and the Gates Foundation form an insurance company in 2019 to address the uninsured crisis created by the repeal of the Affordable Care Act in 2018. Many with private insurance coverage also switched to policies offered by the Buffett Gates Healthcare for All Foundation, making it the largest non-government insurance agency in the country.

The value of aggregated personal and health outcomes data is widely recognized but privacy concerns have limited its use. As a condition for providing low-cost healthcare insurance, the Buffett Gates Healthcare for All Foundation collects patient data from all members, then cleans, anonymizes, packages, and sells patient datasets to public and private companies to offset operating costs.

Because of the high sales volume of prescription drugs purchased by its members, the Foundation negotiated favorable drug prices from pharmaceutical companies in exchange for access to members' health outcomes data for their products.

Ideas and New Images of the Future

The new ideas and images summarized in the table below were inspired by weak signals found in scanning hits in combination with trends discovered during the focused research process. These ideas and new images of the future were used as elements to create the alternative future scenarios.

Ideas & New Images	Description
In the US, the Patent and Trademark Office (PTO) is the first government agency to adopt artificial intelligence and machine learning for use in evaluating descriptions of technology contained in new patent applications against the catalog of prior art.	The current system at the PTO is structured to allow patents to be issued but enforcement is achieved through litigation after patents are granted. A long-standing backlog of applications and estimates that up to 92% of allowed high value patents are found to be invalid at later review provided convincing evidence that changes were needed and funding for the AI initiative was authorized by Congress in 2021 as part of sweeping reforms of the new administration.
New trends in clinical research emerge: growth of site-less, direct-to-patient clinical trials, virtual trials and collaborative, multi-sponsor, large-scale randomized clinical trials conducted under master protocols designed to collect real world data to support value-based pricing models.	As the trend towards personalized and individualized medicine grows, more efficient clinical trials will be designed with fewer research subjects that will rely on technology to "bring the trial to the patient." This shifting paradigm will require a new regulatory approach to ensure compliance and patient safety. Regulatory authorities in the US have signaled a willingness to accept real world data when reviewing applications for new drugs; in the future, pharmaceutical companies will collaborate to conduct studies under master protocols that randomize patients to approved treatments to evaluate the clinical outcomes under rigorous conditions. Patients who may have difficulty affording treatment can access new drugs within the auspices of these large-scale post-marketing studies in exchange for reduced cost of care.
Native American tribes develop medical tourist centers where patients can access healthcare, receive drug products that are more strictly regulated in other parts of the US, and participate in clinical trials of new treatments – all outside of the jurisdiction of federal laws and FDA regulations	After confirming their sovereign immunity to patent challenges in federal court, Native American tribes expand the pharmaceutical patent stewardship enterprise to establish treatment and research centers for experimental therapies, outside the jurisdiction of FDA enforcement. Patients travel to the reservation clinics to receive care or participate in clinical research for treatments that may not be affordable or available to them through conventional treatment pathways because of insurance or regulatory constraints.
Post-Brexit relocation of EMA headquarters to a new location (in Amsterdam) led to greater than anticipated staff attrition, a long transition period to recover operational capacity, and significant loss of public confidence in the European Commission.	Significant delays in review and approval of new drug applications occurred in the two years preceding and following the EMA's move. A few US-based biopharmaceutical companies withdrew their applications for EU marketing authorization of gene therapies, leaving many European patients with few options for care. The EMA was largely ineffective in managing the flu pandemic of 2020 but established improved communication processes before the second pandemic struck in 2021.

Summary of Key Uncertainties

The following uncertainties emerged as the most important based on their potential for disruptive impact and the degree of uncertainty inherent in each condition; these were incorporated as elements of the alternative future scenarios:

- Structure of US healthcare insurance system
- Rate of uptake of value-based reimbursement models in US
- Healthcare as human right vs. citizen's right

- Availability and cost of personal data to power big data analytics
- Federal regulatory authority over artificial intelligence and computer algorithms
- Privacy in the age of genomic medicine
- US and EU regulatory structure for individualized genetic engineering therapeutics
- Impact of Brexit on drug development and clinical research in UK and EU region

FUTURING/FORECASTING

To assist PhRMA's member companies in understanding and anticipating potential pitfalls and disruptions in the future, as well as to consider uncertainties in the ecosystems that may have been overlooked, four future scenarios were developed based on the Houston archetype method (Hines 2014).

The *Continuation* model represents the baseline, or "official" surprise-free future that would be expected should current trends and conditions continue. This scenario was developed using information collected during the current assessment of the domain, including analysis of recognized trends, announced plans of key stakeholders, and published forecasts and projections, as described in the Current Assessment section.

In addition to the baseline scenario, three alternative future scenarios are presented. Analysis of the key uncertainties found in the domain – from exploring current issues and conflicts, potential trend breaks, possible events or wildcards, and new ideas and images of the future – combined with weak signals discovered during environmental scanning provided the building blocks from which the alternative scenarios were constructed.

The alternative future scenarios are modeled after the New Equilibrium, Transformation, and Collapse futures archetypes. The New Equilibrium archetype represents a future that is significantly different from the current system, having arrived at a new balance in response to perturbations or challenges of competing forces, but retaining some recognizable features. In the Transformation model, the old system is discarded in favor of a new one and the Collapse archetype describes a future in which the systems deteriorate to the point of dysfunction.

BASELINE FUTURE SCENARIO SUMMARY AND NARRATIVE

Continuation Scenario

Healthcare Numbers Game

Value-based outcomes drive medical decision-making as healthcare systems struggle to meet demand amid rising costs in this continuation scenario.

Abstract

Several coalescing trends drive the future of healthcare toward population-based health policies for greater efficiency and cost savings for national health systems in the EU countries, as well as for payer/provider systems in the United States. Broad cost containment measures continue to be needed as the populations in these countries age, the influx of refugees and other immigrant groups strains the healthcare systems, and healthcare costs rise. Participation in clinical research becomes a more accepted treatment path, especially for patients who need expensive care.

The regulatory ecosystem has been challenged by the speed of scientific and technological innovation in the pharmaceutical, biotechnology, and digital healthcare industries, where rapid progress exceeded the agencies' ability to monitor and regulate the new systems adequately.

Pharmaceutical companies must adopt flexible and collaborative business models to maximize the impact of research and development spending and maintain market share as competition grows in the generics/biosimilars sector. Implementing long-range visioning and operational planning for drug development with in-house or out-licensed capabilities for generic and biosimilar versions of successful compounds and biotechnologies will help to prolong product lifecycle and safeguard revenue streams as national health systems and third-party payers adopt stricter cost containment measures including stricter value-based reimbursement policies.

Key Drivers of Change

Pressures from current conditions on healthcare systems

- US: Uncertainty surrounding political efforts to repeal and planned changes to the Affordable Care Act (ACA), combined with recognized need for cost control of healthcare spending
- Europe: strain on national health systems due to refugee influx; in UK, anticipated economic downturn due to Brexit will put further financial pressure on NHS
- Aging populations with increasing need for healthcare services, typically retired or in part-time employment without comprehensive health insurance coverage beyond Medicare (US) or national healthcare coverage (EU); care of chronic conditions of elderly is straining healthcare budgets, especially in the US
- Much of the increasing cost of prescription drugs, diagnostic services, and hospital care is being shifted to the consumer
- Value-based approach to reimbursement of healthcare expenses is well entrenched in Europe and will gain acceptance in the US as a cost control measure
- Increasing use of robots in manufacturing, as personal assistants, and in elder-care companion roles
- Many of the economic drivers in the healthcare system also serve as drivers for participation in clinical trials for patients without access to desired therapies due to financial constraints or lack of insurance or prescription drug coverage

Pressures from current conditions on regulatory systems

- Political pressure from elected officials, lobbyists, and industry ties to reduce review and approval times for new medicines in the US; the opposite dynamic is in effect in Europe, where some countries oppose efforts by the EMA to accelerate approval of new medicines
- Staff vacancies at the US FDA have limited its operational efficiency at a time when technological and scientific advancement is accelerating, leaving the agency without adequate resources; high level vacancies of key leadership positions across government or political appointments of leaders without scientific backgrounds created a void of scientific knowledge and expertise in policy decision making during the Trump era
- Uncertainty due to Brexit issues surrounding updating the drug regulatory system in the UK and the relocation of the European Medicines Agency headquarters from London

Emerging innovations and trends in pharmaceutical development and clinical research

- Trend in pharmaceutical development toward high cost personalized medicine, targeted and cellular therapies, gene therapies, and use of biomarkers and associated genome-based diagnostics
- Sensors and wearables for healthcare and wellness applications, social media, smartphone and internet based communication with healthcare providers and patient advocacy groups; increasing reliance on cloud-based data storage solutions for healthcare and clinical research technology platforms
- Greater use of artificial intelligence and cognitive computing in health care and pharmaceutical research and development leading to improved diagnostic ability of computer algorithms with machine learning capability and improvements in rational design of new pharmaceutical products
- Move towards efficient designs of clinical trials, collaboration and data sharing among pharmaceutical companies to reduce patient risk and speed completion of research studies; trend towards personalized and targeted therapies leads

to clinical trials with very small populations under study in which risks may not be identified until after drugs are approved

Narrative:

The pressure of increasing costs of caring for aging and underserved populations in the US and European countries has been a key driver of changes to healthcare systems since the mid-2010s. Political events in Europe, including the influx of refugees fleeing conflicts and the planned exit of Britain from the EU created a difficult economic and social environment in which to deliver healthcare services. The rapidly changing and politically-charged health insurance system in the US led to uncertainties and the eventual loss of insurance and prescription drug coverage for millions due to executive action, tax cuts, and government program reductions. As a result, stricter population-based value approaches to healthcare delivery – enforced efforts in prevention, wellness, and early detection/diagnosis of disease - emerged as the most cost effective policies, leaving patients who depend solely on government health services with little voice in their personal healthcare decisions, especially those with illnesses that involve expensive therapies. As anticipated, acceptance of the new value-based paradigm has been easier in the EU countries where national health systems were already in place; in the US, where individual agency is highly valued, the shift to population-based, outcome-driven healthcare reimbursement decisions has lagged behind Europe.

Technology has driven development of cost-saving innovations in the manufacturing and service industries, with many job functions replaced by robots; this is true for the healthcare sector, as well. There are increasing opportunities for patients to access healthcare providers remotely using videoconferencing and other virtual platforms and to transmit biometric and symptoms data collected by wearable sensors to personal databases for electronic health records that can be networked across provider facilities. Compared to just a decade ago, today's patients are more knowledgeable about their health status and disease conditions, are more engaged in their healthcare decisions, are connected via social media outlets to others living with similar diseases or conditions, and are being held accountable by insurance companies and healthcare providers for their individual wellness and self-care. Physicians and other healthcare providers must now operate under greater cost containment constraints and have a greater patient care load, but also have a number of new tools and techniques to help with prevention, diagnosis, and treatment of disease to meet their population-based patient health performance goals.

Haya and Luda

We came to Germany from Syria when the weather started turning cold in 2013. I was so afraid for Luda because she was always sick and it was hard for us to get to the doctor in Aleppo. We sold almost everything to pay for the fare to Turkey, where my sister's family lives. They have relatives who moved here to Castrop-Rauxel in the 70's when Turkish people were welcome as Gasterbeiter to work in the coal mines, so we had family to sponsor our visit. It's a small town and I think the authorities forget we are here.

Luda has something called ulcerative colitis that makes it hard for her to work…but we don't get health insurance or any medicine like the German people do, so I have to work two jobs to make enough money for us to have food and medicine. Luda can only use the hospital when she has a bad flare. We live with our family and pay what we can, but it's been hard since my husband died.

Personalized medicine and widespread availability of targeted therapies have allowed treatment of disease at earlier stages to preempt active and chronic symptoms; many standard medical treatments of chronic diseases have been replaced with targeted antibody, cellular, and gene therapies.

Libraries of individual genomic data (from patients who have volunteered to participate through academic and direct-to-consumer genetic testing) have been publically available since 2022 in the US to facilitate analyses of genetic mutations and identify potential targeted treatments for specific diseases. These analyses are done annually by supercomputers powered by machine learning and other AI techniques updated with the latest genome-wide association studies data, but the small dataset limits the practical application. Privacy concerns in the European region have restricted similar efforts to academic research with little translation to clinical application.

Regulatory agency staff vacancies and the chaotic political environment of the second half of the decade from 2010 to 2019 contributed to lengthy review and approval times for new drug applications in the US. Agency plans were announced to update capabilities to meet the needs of the increasing complexity of new healthcare technology, but positions were difficult to fill because of high competition in industry and due to a general lack of confidence in the administration.

Development of new drug and biologic treatments and the conduct of clinical trials have become more dependent on cost-saving strategies as the market for expensive blockbuster drugs becomes increasingly limited due to cost constraints. To stay competitive, pharmaceutical companies have continued to rely on a partnering strategy in development of new compounds, often collaborating to share data and other resources. Greater emphasis on patient-centric approaches in clinical research continues, including master protocols, adaptive study designs with reduced patient exposure to placebo controls, and automated data collection for clinical trials using sensors, wearable devices, and other digital tools to reduce patient visits to the clinic. As in the past, many patients are motivated to seek care within the context of a clinical trial when access to treatment is limited by financial constraints or healthcare coverage. But now, as entry criteria for research studies have become more specialized with genomic biomarkers and physicians look for treatment pathways that move the sickest patients out of their 'performance population' pool, referrals to clinical trials are considered a standard of care in most physician practices.

Generic and biosimilar versions of drugs continue to provide lower cost options for patients and are mandated by the majority of payers; the most successful large pharmaceutical companies incorporate strategies for in-house manufacturing or out-licensing of generics and biosimilars as part of their clinical development plan for new drugs as a path to capture and retain a larger market share throughout the lifecycle of a product.

Alternative Future Scenarios Summary and Narrative

New Equilibrium Scenario

My Data Are Pay-Per-View

Monetization of individual data and emergence of a dual-payer healthcare insurance system in the US support a new equilibrium in healthcare, regulatory, and associated ecosystems.

Abstract

Billionaire philanthropists establish a non-profit organization to provide healthcare insurance to uninsured, working poor, and underinsured Americans, leveraging the value of subscribers' personal and healthcare data to fuel innovation in research and public policy. Access to healthcare is recognized as a human right with wide-reaching economic and societal benefits that can be clearly demonstrated via sophisticated data analyses.

Healthcare costs fall as volume discounts and other efficiencies are built into the system while inefficiencies promoted by political concerns are eliminated. Reorganization of the FDA in 2020 reduced further the effect of external influences that had plagued the agency since the mid-1990s.

Key Differences from the Baseline

- A private, non-profit healthcare insurance organization is formed that provides low cost healthcare coverage to under- and uninsured patients in the US – effectively creating a dual-payer system as the majority of subscribers abandon private insurers in favor of the new model.
- Lower drug prices due to higher negotiation power of two high volume prescription drug consumers in US: the federal government and the Buffett Gates Foundation
- Economic value of personal data is realized as mechanism to monetize individual data emerges

- BYOData - health records and individual data are stored on personal chips to reduce vulnerability to cyberattack and maintain ownership control
- New role emerges for healthcare data guardians for hospitalized patients and those unable to make informed decisions about the use of their data
- US FDA is split into two agencies – one for food and one to manage drugs and digital health tools; new rules are established for Commissioner appointments to reduce external influences on agency activities

Narrative:

Despite increasing public support for establishing a single-payer healthcare system in the US, bitter partisan divisions and the influence of insurance lobbyists led to defeat of the Sanders "Medicare for All" bill when Republicans forced a vote in early 2018, a few months ahead of the mid-term elections. The number of uninsured citizens increased by an estimated 35 million when the Affordable Care Act was subsequently repealed later that year. In response, financed with an $8.8 billion donation from Warren Buffett, the Gates Foundation established a non-profit private health insurance company in 2019 to serve the uninsured, working poor, and underinsured. Market uptake of the Buffett Gates Healthcare for All coverage was more rapid than anticipated and many privately insured patients switched to the non-profit company, making it the largest non-government insurance company and essentially establishing a dual-payer healthcare system in the US.

Adam

Like most folks living on the West Coast, I enjoy an active lifestyle and love to be outdoors. I would wear a fitness tracker anyway, but my health monitor does so much more! It even senses the status of my microbiome and tells me what to eat to improve the environment for my gut microbes to make me healthier – eat more carrots or skip the dairy - that's cool!

It's pretty amazing how quickly the economy turned around in our town once everyone got health insurance. I work as the Marketing Director for a small biodynamic vineyard and winery and we've been running on pretty tight margins most years. Now with the new health insurance system, our company can afford to pay the farmworkers a living wage AND cover almost all of the insurance premiums for them and their families. Most are undocumented and could never have afforded private insurance in the past. We set up a virtual clinic near the greenhouse so the office staff or the field workers can VR with their doctor. It's been a great way to deal with minor injuries or when someone gets sick - we just connect in and save a trip to town.

The Buffett Gates company recognized the value of personal data, especially the value of health outcomes data, and created a mechanism for individuals to join together to realize the monetary value of their aggregated data. As a condition of providing low-cost insurance, the Buffett Gates Healthcare for All Foundation collects patient data from all members, then cleans, anonymizes, packages, and sells patient datasets to public and private companies and researchers to offset operating costs of providing healthcare insurance. The high value of these data assets helps to keep the cost of insurance affordable for policyholders and strict data encryption processes are used to protect the security of the information. In parallel, the Microsoft corporation developed a number of data analytics tools that seamlessly integrate with the Buffett Gates datasets to provide data insights across the spectrum of data collected from its constituents.

As the largest non-government group purchaser of prescription drugs, the company directly negotiated favorable prices from pharmaceutical companies in exchange for access to members' health outcomes data for their products as well as for their competitors' products and generic drugs. In addition, the Buffett Gates company serves as a clearinghouse for research-related patient communication and recruitment of clinical trials conducted by investigators within its network.

The Buffett Gates Foundation used its influence to effect social change in important ways, including providing healthcare coverage to all regardless of citizenship, employment status, age, gender, or current health condition – taking the stand that healthcare is a human right that should be available to all. Long term trend analyses of the population health data confirmed the public health and economic benefits of providing comprehensive vaccination programs, preventative and wellness care, sexual and reproductive healthcare services, and mental health benefits to patients.

Because insurance coverage is provided outside of the employment sphere, patients have become more willing to access care for conditions that were stigmatized in the past, including addiction and mental health services. By demonstrating the value of providing these services with health outcomes data, the Buffett Gates Foundation helped convince policy makers to update and expand coverage for those receiving care under government plans such as Medicaid and Medicare.

The trend toward increasing reliance on technology in healthcare continues, with ubiquitous use of sensors and wearables for healthcare and wellness applications, social media, smartphone and internet-based communication with healthcare providers and patient advocacy groups. Individuals have become savvy to the value of their personal data, however, and no longer willingly give their data away without compensation, leading to implementation of new data security protocols designed to prevent collection of consumer preferences and other market data that previously had been associated to individual users through their internet browser history.

A secondary market arose for personal data for those outside of the Buffett Gates network and in other countries. Because of the high number of companies vying for personal data and fragmentation of the international market, no single player has been able to command sufficient market share to compete effectively. After initial efforts at applying blockchain technology to electronic health records systems failed to protect patient privacy, personal and health data are stored on chips that remain in the possession of the individual owner as security concerns are widespread about storing data on web-connected or cloud-based servers following the US and global data breaches of 2017 and 2018.

Amid the growing complexity of technology in the healthcare sector and after several years of increasing delays in review and approval of new pharmaceutical and healthcare technology products – combined with a number of high-impact recalls of new drugs due to patient deaths and other safety concerns – Congress authorized the US Food and Drug Administration to undergo reorganization in early 2020 to establish two new agencies: the Food and Beverage Administration and the Drug, Biologics, and Digital Health Administration (DBDHA). As part of the reorganization, new rules were enacted for non-partisan, non-political nomination and selection of the Commissioners for each agency to serve five-year terms; for the DBDHA, the rules specify that the selection committee includes a majority representation of members from the National Academy of Sciences, as well as members with public health, public policy, industry, and government backgrounds. Although the intent was to provide a greater focus on expertise in science and technology, increased continuity of leadership, and less external political influences, the reorganization created an agency with many characteristics of an academic organization, including slow and deliberative decision-making processes. Timelines for review and approval of new drug applications have increased slightly, but public confidence in the agency's effectiveness is high.

Transformation Scenario

Pops, Are You Worthy?

Advances in genetic engineering, data analytics, and machine learning transform healthcare and the pharmaceutical industry as gene and cellular therapies supplant conventional drugs, but rising costs of high tech treatments force tough decisions about the value of treating illness in the elderly.

Abstract

Rapid acceleration in gene repair technology quickly transformed medicine in developed countries. Chronic diseases could be cured with cellular therapies and those diseases stemming from inherited mutations or damaged DNA that were most feared during the last century could be prevented or cured with genetic engineering.

These therapeutic advances disrupted the pharmaceutical and clinical research industries, shifting manufacturing and testing of conventional drugs to the BRIC countries with increasing penetration into emerging economies.

The high cost of gene therapies has strained healthcare budgets, leading to adoption of extremely strict value frameworks for reimbursement. Because many gene repair therapies are administered to very young patients, determination of the value calculus is moot but as patients age the potential value they may bring to society is a factor in the decision for an insurance company to reimburse for an expensive treatment. In most cases, aggressive treatment for terminal illness is denied for elderly patients.

Key Differences from the Baseline

- The FDA streamlines its operations to focus on gene therapies and *in vitro* genetic diagnostics as most gene repair is done *in utero* or during the first months of infancy; cellular therapies for adult patients are no longer regulated as drugs and pharma/biotech companies out-license these technologies directly to local clinics
- New trends in clinical research emerge: growth of site-less, direct-to-patient clinical trials, virtual trials and collaborative, multi-sponsor, large-scale randomized clinical trials conducted under master protocols designed to collect real world data to support value-based pricing models
- A new regulatory paradigm and evolution in clinical research practices lead to consolidation in the CRO industry, leaving a few large full service global companies with heavy investments in data and analytics assets
- Artificial intelligence is used at the US Patent and Trademark Office to assist in the review and approval of patent applications; awarded patents are considered ironclad against challenges, leading to an overall reduction in patent litigation
- Biotechnology and genetic engineering have replaced chemical synthesis approaches to rational drug design of the past and large pharmaceutical companies have downsized their staff significantly; bioinformatics tools and AI power research efforts focusing on reducing genetic errors, mutations, and single nucleotide polymorphisms (SNPs) at the population level to improve health and prevent disease
- Individual data are considered part of the public domain, with stem cell collection and genome testing performed for each child born in the US; participation in the public genome database is optional in Europe
- Data analytics software powers diagnostic, patient communication, and clinical research tools to allow healthcare providers to coordinate high volume patient care more efficiently with the expectation that patients will collaborate with their healthcare providers and take greater responsibility in managing their own (and their family's) health and wellness
- China and India manufacture ~80% of global supply of conventional pharmaceuticals, including generics and biosimilars; demand for conventional pharmaceutical products is predominantly restricted to W2 and W3 countries as most chronic disease has been eradicated in W1 through genetic engineering and treatments with targeted and cellular therapies
- Increases in longevity and continuing population growth require a firm commitment to value-based healthcare reimbursement policies – practices that shift responsibility for wellness and preventative care to patients with no provision for medical care of the terminally ill beyond hospice and/or palliative end-of-life care; patients whose families cannot care for them are institutionalized, with many facilities staffed with robot care service companions

Narrative:

The translation of genetic engineering from the research setting to clinical care advanced quickly with a number of companies offering automatic gene editing platforms in the early 2020s. The impact to medical care came swiftly on the heels of the success of targeted immunotherapies to usher in the era of personalized medicine. Germline mutations are identified early, if not anticipated during family planning activities by analyzing parents' genomes, and repaired *in utero* or in early infancy once confirmed by sequencing. The few diseases caused primarily by somatic mutations later in life are managed by periodic screening and patients are evaluated for treatment on an individual basis.

Pharmaceutical companies have moved from filling their pipelines with new compounds discovered in the lab using a predominantly chemical synthetic model of rational drug design to adopt a more theoretical "big data" analytics approach to find disease-related signals in patient health and genomic records. Europe has lagged behind the US in adopting gene editing therapies, especially for pediatric patients, due to data privacy concerns and restrictions on access to patient health data. Targeted immunotherapies (monoclonal antibodies) and cellular therapies (stem cell and CAR-T treatments) continue to hold the major market share in Europe; a majority of these compounds will be replaced with biosimilars by 2030. In Latin American countries, Eastern Europe, Russia, and emerging markets the older conventional 'chemical' drugs are still used in most clinical settings. Because of this regional disparity, the medical tourism industry has flourished and forward-thinking biopharma companies are placing clinical trials in W2 and W3 countries in anticipation of future growth markets in these regions.

Clinical research practices similarly adapted to the new model – moving away from large clinical trials of the past in which patients visited a study site to receive experimental treatments or procedures and provided blood and biopsy samples for analysis of treatment effect. The new paradigm involves interrogation of large health and genomic data sets and genome-wide association studies (GWAS) to find those few individuals with the unique combination of genetic markers required for the clinical study under consideration. Because these patients are typically widely distributed geographically, new clinical trial designs are predominately direct-to-patient, conducted virtually using telemetry and other sensing technology to collect data about the patient's condition and response to treatment. Throughout the duration of most studies, the patient and her physician are never in the same location.

Preclinical phase testing of new gene targets is typically performed in animal models and engineered organ-on-a-chip systems. Once clinical trials begin, early phase studies are limited to very old, sick patients to test for immediate safety issues. Phase II and Phase III trials are limited to patients in the elderly and middle to early adult demographic segments, with testing in pediatric patients restricted to late phase trials only.

Ryan, Lenina, and Scotty

Ryan and I didn't think we would want to have kids because we knew that our family history of cancer meant it was almost certain that our children would inherit mutations for one cancer or another. Both of our moms died of breast cancer and my dad passed when I was little from pancreatic cancer. Ryan's dad is fighting prostate cancer now and having a battle with the insurance company about everything. It's been exhausting for everyone. The co-pay for his antibody treatment is 50%, which means most months he can buy medicine or he can buy food. We help when we can but having a baby is expensive!

We found out that Scotty had BRCA2, PALB2, and CDH1 mutations during my prenatal testing. I was really scared to let the doctor repair his germline DNA while I was still pregnant but we found out at his six-month check-up that his genomic profile looks normal. We can't believe it! We're so happy to have him in our family but it's bittersweet knowing that he will grow up without his grandmas and probably without any grandpas, either.

Regulation of clinical research and approval of new medical treatments has moved exclusively to the realm of gene therapy and associated genetic diagnostic testing in the US after the FDA Commissioner lobbied Congress to revise the agency's remit in 2020. Because the gene editing technique is standardized, there is little risk to the patient in undergoing the procedure itself; the major risk of gene repair lies in selecting the correct DNA base pairs to modify. With the agency reorganization, FDA review of new therapy applications requires analysts to evaluate the biopharma company's bioinformatics data structure, analytics techniques, datasets, and logic algorithms employed in determining the targets for repair.

The agency's departure from enforcement efforts, combined with the rise in site-less, direct-to-patient, virtual study designs, has shifted the responsibility for protection of human subjects to the sponsors of the research – usually the biopharma companies. Instant media access and patient networks have kept bioethics of genetic engineering at the top of most news feeds, which has encouraged compliance with ethical standards among the industry.

Patients in 2025 enjoy better health and are living longer than at any time in history, but face greater pressure to take responsibility for their own wellness and preventative care. Global population growth continues unabated, fueled in W1 countries by increases in longevity as well as a fertility rate rise, hypothesized by population biologists to be driven by hopeful parents inspired to raise perfectly genetically healthy offspring. Value-based healthcare reimbursement policies have taken a hard line, especially with high-cost treatments such as gene therapy. If a patient is not expected to contribute significant value to society in the future, reimbursement for expensive treatment will be denied by health insurance companies. Palliative care and hospice are the only options for elderly or terminally ill patients and those without families or other caregivers are institutionalized. Many of the elder care institutions are staffed with robot care service companions. As a consequence, the rate of elder abuse, homicide, suicide, and euthanasia (where legally permitted) has risen significantly in the past twenty years.

Collapse Scenario

No Cure for Chaos

Chaos in the regulatory and patent ecosystems mirrors the US and European political climates, leading to delays for new product launch that cause reduced earnings and collapse in the pharmaceutical and clinical research support industries.

Abstract

Post-Brexit relocation of EMA headquarters to Amsterdam in 2019 led to greater than anticipated staff attrition, a long transition period to recover operational capacity, and significant loss of public confidence in the European Commission. Similarly, in the US, long-term staff vacancies and agency dysfunction limited the effectiveness of the FDA to provide timely review and approval of new drugs and to adequately enforce current regulations. As delays mounted, some pharmaceutical companies adopted new approaches to clinical research outside the conventional ecosystem such as conducting offshore trials or setting up research studies within the confines of sovereign Native American enterprises, but many companies reduced R&D spending or canceled clinical development programs when mounting costs of the delays became unsustainable.

A coordinated cyberattack on electronic health records in the US, Germany, and France, combined with back-to-back pandemic influenza events led to further disruption in the healthcare and pharmaceutical industries – and contributed to the global economic recession currently underway.

Key Differences from the Baseline

- Executive orders and political pressure stymie efficient operations at FDA, leading to delays in review and approval of new drug applications; EMA is unable to recover from Brexit after extensive staff attrition and resulting budget overspend to hire replacements in the new headquarters location
- New pharmaceutical development stalls, generics claim greater market share, and smaller pharmaceutical companies are consumed in new wave of mergers and acquisitions
- Rise of offshore clinical research centers, with concomitant fall of protection of human research subjects; FDA does not have resources to enforce current regulations or enact new regulations
- After establishing sovereign immunity against patent challenges for pharmaceutical patents transferred to their stewardship, Native American tribes build medical centers and clinical research sites on reservation land where patients can access healthcare and experimental treatments outside of the enforcement jurisdiction of the FDA
- Coordinated cyberattack on electronic health records (EHR) systems in the US and Europe bring healthcare and clinical research systems to standstill
- High cost genome sequencing with monopoly of instrument manufacturers decelerates progress of individualized therapies
- Consecutive pandemic influenza events cause millions of deaths in 2020 and 2021; reduced capacity at EMA limited the effectiveness of the response, and a high proportion of elderly and immigrant patients succumbed

- As healthcare costs continued to rise, national health systems have been unable to sustain care for low income and immigrant populations; the global proportion of elderly patients declined due to increased mortality rates in the elderly population

Narrative:

The regulatory systems in the EU and US are both in chaos, reflecting social and political challenges in these regions in the post-Trump and post-Brexit era. Relocation of the EMA to Amsterdam in 2019 resulted in greater staff attrition than expected and longer and more costly hiring of replacements delayed action on routine activities as well as new initiatives. Ongoing political pressure from external influences continues to promote dysfunctional operations at the FDA, resulting in longer than usual review and approval timelines for new drug applications.

In general, the pharmaceutical industry financial performance deteriorates as long regulatory approval times lead to missed milestones for development activities, investor sell-offs, and depression of stock value. As a result, larger pharma companies adopt a conservative research and development spending approach and many smaller companies fail, are forced to sell their NME assets, or are acquired by larger firms. With fewer second- and third-generation innovator drugs in the development pipeline, biosimilars and generics claim increasingly greater market share as the first-line innovator drugs lose patent exclusivity protections.

Hayden

My emphysema usually gets pretty bad during the wildfire season, and it seems like it lasts longer every year. This year was the worst yet - damned global warming. The doctors don't have anything they think will help me and there aren't any clinical trials that I qualify for. It's hard to believe there haven't been any new medicines for COPD in five years…just my luck.

My buddy went to South Dakota to a treatment center they have on the reservation there where he got an experimental medicine. He said it wasn't FDA approved, but he didn't care! You know what? I'm about to the point where I don't care either…I'm sure not getting any better with what they're giving me here.

Traditional clinical research activity likewise slows as some larger, more established pharma companies scale back their development activities. Greater effort is devoted to study planning, patient identification, and research subject recruitment and retention strategies to ensure successful trial operational outcomes. A coordinated global attack on hospital EHR systems in 2022 brought the healthcare and clinical research systems to a standstill as millions of data records were lost.

Chaos at the regulatory agencies and low staffing resources result in reduced enforcement activities, particularly in the US. Some pharma companies view this as an opportunity to conduct early proof-of-concept studies at offshore research centers without ethics committee oversight or adequate protection of research subjects. Because these subjects are paid for their travel expenses and their participation, questions about the validity of the data and economic coercion of the study participants cloud the scientific results.

In parallel, Native American tribes establish treatment and research centers on reservation lands outside of the enforcement jurisdiction of the federal government. Patients are able to access a range of treatment options, including experimental therapies, at a generally lower cost than would be available off-reservation. This provides another option for care for patients without healthcare insurance or for those for whom coverage for a particular treatment has been denied.

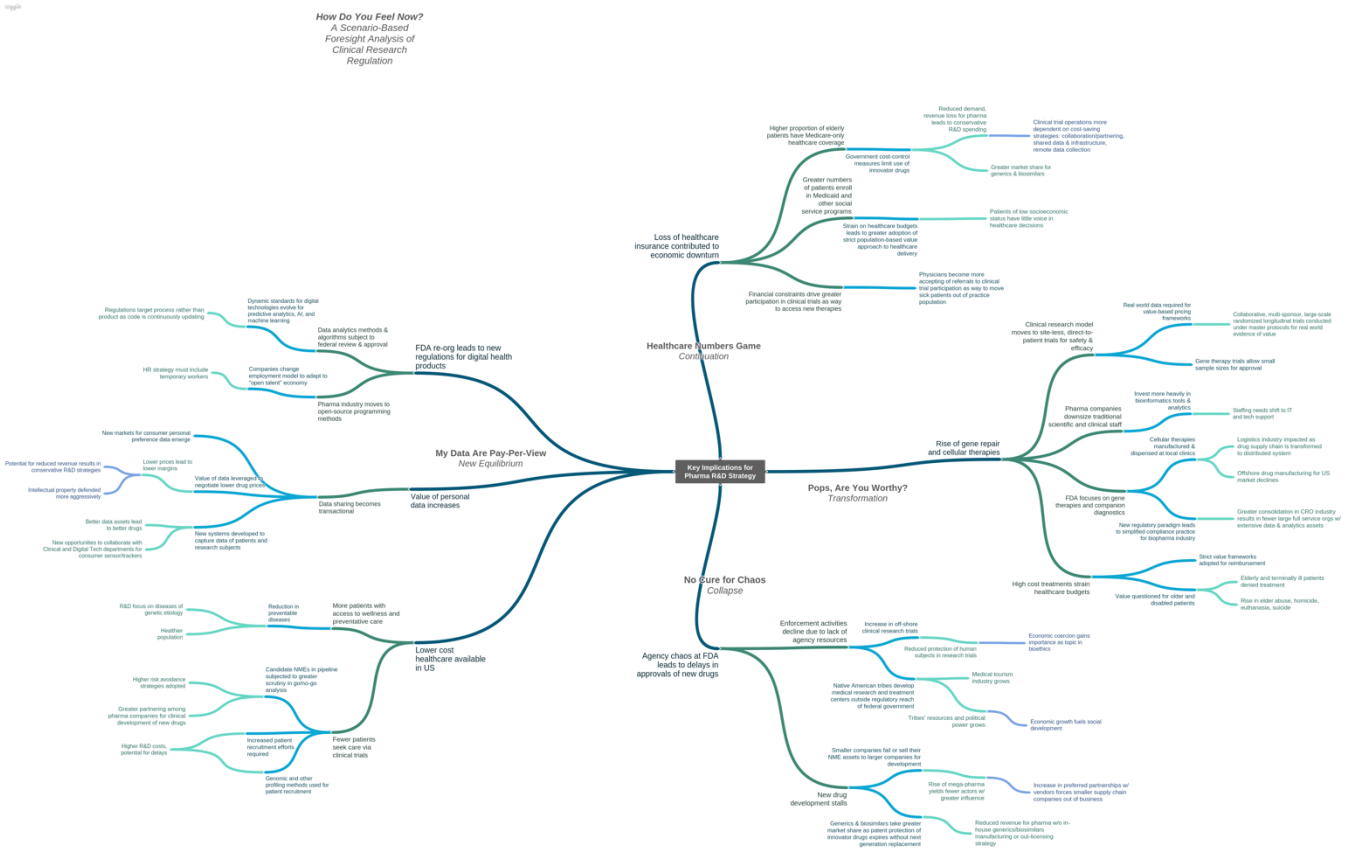
The US Patent and Trademark Office continues to grant virtually all patent applications with the expectation that subsequent litigation will sort out the valid claims from the rest. This policy contributes to high drug costs as pharmaceutical companies must spend hundreds of millions of dollars to defend their assets against patent infringement.

Chaos at the regulatory agencies reflects social and political instability in the US and Europe. Political turmoil and the resulting lack of coherent economic policy has dampened consumer confidence and the US economy is in decline. Unemployment is

rising and the uninsured rate reached a historic peak of 20.4% in 2023. Rising healthcare costs, increased population – including an increase in the number of people enrolled in Medicare and Medicaid in the US - and the impact of an aging population all contributed to a drain on national health systems and their ability to adequately care for their patients. As cost-saving measures, policies that reduce care for immigrants and individuals receiving other social services benefits are enacted, causing outrage and a brief uptick in the number NGO-sponsored charity care providers. The human cost of these policies became apparent after back-to-back flu pandemics in 2020 and 2021 during which mortality events were significantly higher in the elderly, low socioeconomic, and immigrant populations.

IMPLICATIONS ANALYSIS

After the baseline and alternative future scenarios were finalized, their potential impact on clinical research regulations, healthcare delivery, and the larger pharmaceutical industry was investigated. For the scenarios described herein, the analysis of possible implications of importance to PhRMA's member companies focused on pharmaceutical research and development strategy. The implications were mapped out to the third- and fourth-order using the Millennium Project Futures Wheel method (Glenn), constructed with the Coggle online mind-mapping tool, with output shown for illustration (below). To explore the sampling of key implications for the four scenarios in greater detail, access the implications map at the Coggle site here.



The most important implications are those expected to have the potential for significant impact on the pharmaceutical industry in the future – and thus will represent areas of focus for strategic and futures planning. Provocative implications are also identified; while these are considered to be less likely, they may have a high potential for disruption should they occur and are thus worthy of consideration. Evaluation of the important and provocative implications - along with the potential issues they raise for the pharmaceutical industry - helped identify strategic issues for PhRMA to address as actions to help its member companies meet future challenges and take advantage of potential opportunities identified in the foresight analysis.

Most Important Implications

The most important implications of the four scenarios presented are listed below. These implications helped inform identification of potential issues and opportunities for future planning.

- Subject recruitment for clinical research studies becomes difficult due to lack of patients (specificity of eligibility per biomarker or genetic mutation) or lack of motivation (availability of affordable care)
- Loss of health insurance in US leads to greater health disparities and loss of agency for patients of low socioeconomic status when making decisions about their healthcare; wealth becomes a biomarker for health
- Requirement for greater confirmation of value from real world data drives new late-phase master protocols and greater collaboration in pharmaceutical industry
- Delays in new product approvals due to regulatory agency chaos leads to failure of small biopharma and rise of mega-corporations with great influence over supply chain and logistics industries
- Value of personal data increases and new markets for consumer data emerge to limit access or increase cost of use for data analytics

Most Provocative Implications

The most provocative implications described below represent a high potential for disruption to PhRMA members and should remain 'on the radar' when considering strategic challenges and opportunities in the future:

FDA regulations for digital health products target data analytics and AI *processes* rather than products

Current federal regulations are focused primarily on establishing safety and efficacy of products (drugs and devices) that assume little to no change to the final product once marketing approval is granted. Subsequent changes to a product potentially require expensive and time-consuming resubmissions for approval – including new clinical trials – as though the changed product were an entirely new drug or device.

Algorithms that control or inform actions or outputs of products that incorporate AI, predictive analytics, and machine learning constantly change with each iterative cycle as new data are acquired or modified. Because these algorithms are programmed to self-correct and make changes to the code (without direct intervention by the programmer based on human interpretation of new data), the code itself is not easily regulated under the current FDA structure.

At present, the computational chemistry and predictive analytics algorithms used in drug discovery and design are 'behind the curtain' and not subject to FDA review. A re-organization of the FDA to include a new digital health division may broaden the scope of review to include early development activities as well as algorithms used to power sensors, devices, and combination products as proof of safety and efficacy is increasingly provided by clinical trials with small numbers of subjects (making it difficult to find signals of adverse events during testing). Direct knowledge of the algorithms powering the products under review may be required by regulatory authorities in order to assess potential risk to patients.

The agency has demonstrated an understanding that changes are required in the future; a new pilot program was recently introduced to pre-certify companies working to develop digital health technologies, but the full scope of the issue has not yet been addressed.

Regulation of self-modifying computer code represents a new scenario for the FDA as well as for pharmaceutical companies looking to incorporate AI and machine learning technology into new products in the future.

FDA focus on gene therapy leads to a new regulatory paradigm with simplified compliance practice for biopharma industry

The FDA streamlines its operations to focus on gene therapies and *in vitro* genetic diagnostics; most gene repair therapy is administered *in utero* or during the first months of infancy after genomic testing of the fetus or infant has revealed disease-associated germline mutations. Conventional drugs and cellular therapies (such as CAR-T immunotherapy and stem cell treatments) are no longer under federal jurisdiction but may be regulated by individual states.

Although the regulatory affairs profession suffers job losses of administrative staff due to the new simplified regulatory structure, a shift in human resourcing must occur to meet the demands of the highly technical requirements of regulating the safety and efficacy of human genetic engineering. The new regulatory affairs professional must be knowledgeable in the regulations and their application but also be a competent expert in the genomic sciences – a rare combination of education, training, and experience that will be in high demand.

Currently, regulatory compliance activities demand significant resources from biopharmaceutical companies as well as clinical investigator sites. The new regulatory paradigm offers savings opportunity for the industry but also reduces the burden on investigators to participate in clinical research, especially for small clinical practices without the infrastructure to manage the detailed and sometimes onerous administrative regulatory compliance activities for industry-sponsored research studies.

Important and Provocative Issues

The important and provocative issues raised by the implications analysis are presented in the table below. Some of these issues will be familiar to PhRMA's members but some are likely to be emerging issues in the futures represented by the scenarios described above. All are issues that PhRMA's member companies will need to evaluate for potential impact to their organizations as well as for their individual level of preparedness to face such issues in the future.

Issue	Importance
Data access is monetized or interrupted when individuals withdraw permission or exert ownership rights to their data.	Data from patient health records, genetic testing, consumer purchasing preferences and history, demographics, lifestyle choices, and political behavior will be used with greater frequency to power data analytics tools in the future. At present, these data are collected and used to profit by enterprises without compensation to the individual providing the data. As pharmaceutical companies move from the current trend of developing targeted therapies to a greater focus on gene repair for individualized therapies, uninterrupted access to dynamic data assets to power the analytics tools (such as artificial intelligence and predictive analytics) used for drug design and testing in preclinical and clinical research programs will be critical to sustaining success in the future.
In a reorganized FDA with regulatory authority limited to genetic engineering therapies, the regulatory affairs profession in the US will undergo profound change.	With reduced compliance requirements and loss of more administrative functions currently engaged in support of conventional drugs, regulatory affairs professionals of the future will need training and expertise in genomics sciences as well as federal regulations.
As the use of artificial intelligence and other machine learning and data analytics techniques increases in the pharmaceutical industry, greater human and capital resources will be required to manage the complex computer systems and programming needed to keep pace with the rapidly advancing technology. Potential regulatory changes are anticipated in the future that could bring these technologies under the auspices of regulatory authorities	In the past, pharmaceutical companies have not traditionally been at the forefront of computer technology and may not be positioned well to attract top talent in the highly competitive field of AI and data analytics. In addition, recent negative publicity in the media combined with a staid and conservative corporate reputation may leave larger companies struggling to recruit and retain young programmers accustomed to working in the new "open talent" economy. Without fully staffed IT teams, pharmaceutical companies will be ill-prepared to adapt to a quickly changing technological and regulatory environment, leading to delays in the pace of innovation.

when used in the development of new drugs and medical devices, adding an additional layer of complexity to system programming requirements. An emerging trend in the use of short term employees in the computer coding talent arena may present challenges for pharmaceutical companies that have engaged IT employees in more traditional roles previously.	
Long review and approval times at regulatory agencies for new drug applications disadvantage smaller biopharmaceutical companies with limited financing or few assets in the pipeline.	In a scenario of regulatory chaos and with trends towards greater activity in mergers and acquisitions in the pharmaceutical industry, smaller emerging biopharma companies may be vulnerable should project timelines extend beyond forecasts.
Supply of research subjects and clinical investigator sites is insufficient to meet the research needs of the pharmaceutical industry	The increased importance of real world data in establishing the value of a new treatment within the population-based reimbursement value frameworks will put additional pressure on a clinical research system that has faced a dearth of research subjects and investigators in the past.

Recommendations for Strategic Options

The overarching goal of the Framework Foresight method is to assist an organization in linking the potential implications and emerging issues of possible futures to its vision, or preferred future, via strategic actions designed to best position it to meet future challenges and take advantage of future opportunities. As a trade organization for pharmaceutical companies with a diverse membership from small biopharma start-ups to large global corporations, PhRMA's mission is to conduct effective advocacy for public policies that encourage the discovery of important new medicines for patients.

Because PhRMA's membership spans the range from small to large organizations with differing business needs, strategic goals, and preferred futures, a single strategic approach to preparing for future change for PhRMA and its members is not prudent. Thus, the recommendations presented below adopt a three-tiered approach of communication and advocacy for PhRMA's strategic options to best support its member companies: internal communication to PhRMA membership, external marketing to the public, and directed political advocacy.

Communication to Membership

- Raise awareness of possible future disruptions in the flow of patient and health outcomes data
- Promote efforts to create and participate in industry-wide data systems and standards to mitigate the risks of potential data access interruptions
- Advocate for creation of industry programs to support new investigators and research-naïve sites in establishing infrastructure to conduct clinical trials
- Prepare for potential delays in new drug approvals and greater consolidation in pharmaceutical industry
    - Encourage small emerging biopharma companies to partner with multiple firms to co-develop new molecules
- Alert Human Resources leadership to changing employment landscape
    - Regulatory Affairs staffing needs may evolve to require greater scientific and technical expertise
    - IT teams may need to engage technical and programming talent differently in the future to accommodate the 'open talent' economy models operating in the technology sector

External Marketing

- Raise awareness of the importance of clinical trial participation and the value of patients and their data to improving global public health
- Conduct targeted campaign for physicians and clinical providers to highlight the importance of investigators' contributions in advancing medical science and in bringing new medicines to patients
- Promote recent successes of personalized therapies and the important way free access to dynamic data assets contributes to better lives for patients
- Target young programmers and technical talent to demonstrate the value of AI and data analytics in creating better medicines

Political Advocacy

- Limit potential negative impact of new regulations on AI, machine learning, and data analytics techniques in new drug development

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ADDENDUM

SCANNING HIT SUMMARIES

Below are typical scanning hit summaries used in the development of the scenarios presented in this work:

Title	*Offshore Human Testing of Herpes Vaccine Stokes Debate Over U.S. Safety Rules*
Author	Marisa Taylor
Date	28 August 2017
Brief source	Kaiser Health News, published online by Kaiser Family Foundation
URL	http://khn.org/news/offshore-rush-for-herpes-vaccine-roils-debate-over-u-s-safety-rules/
STEEP Category	Social, political
Keywords	Unregulated clinical research, FDA
Type *(bold one)*	**Actual event** New trend New cycle New plan Potential event New information New issue
Brief description of the item	An American university and private financiers (including prominent libertarians and a billionaire supporter of President Trump) sponsored and funded clinical research into a new vaccine for treatment and prevention of genital herpes, conducted on the Caribbean island of St. Kitts without supervision of an Institutional Review Board, the entity charged with protection of the safety of human subjects of clinical research. The clinical trial was conducted outside the realm of review of the US Food and Drug Administration, the government agency charged with determining the safety and efficacy of new drugs seeking marketing approval.
How could the future be different as a result?	Initial review and continuing oversight of clinical research by an independent ethics committee is a key principle in the protection of human subjects participating in clinical research. Testing new medical treatments outside of the accepted ethical parameters allows for doubts about the scientific integrity of the study results. Were new drugs tested under these conditions to become commercially available, outside of the established regulated market systems, a new era of healthcare could emerge in which patients with financial resources could treat themselves without medical supervision using drugs available without an authorizing physician's prescription. In response, the rules concerning ethical oversight of human subjects in medical research could: • Become stricter, making it more difficult to have clinical research approved and leading to fewer (and more expensive) new drugs on the market - OR - • Become more relaxed, as confidence grows within the public and the scientific communities with the successful launch of new drugs outside of FDA's review
What are the potential implications for stakeholders?	**Key stakeholders impacted:** Pharmaceutical companies • Competition from pharmaceutical companies operating outside the regulated environment would put additional pressure on the member companies of PhRMA • Two classes of pharmaceutical companies would emerge: those following established ethical guidelines and rogue companies operating outside the regulatory system • Availability of research subjects for trials conducted under FDA rules might be reduced if companies operating outside the system provide financial inducements or use other coercive measures to recruit subjects, causing 'ethical' research trials to take longer to complete and incurring higher costs than planned for those companies conducting research under the ethical guidelines
Horizon *(bold one)*	H1 Confirming H2 Resolving **H3 Creating**

	(baseline scenario) (between scenarios) (new scenario) A new scenario is created in which drugs can be tested and marketed outside the established regulatory system without human subjects' protections or regulatory oversight
Scan Hit Evaluation (0 – 5 scoring)	Impact – 4, Plausibility – 3, Novelty – 4, Credibility - 5

Title	First Personalized Gene Therapy Approved in US
Author	Jocelyn Kaiser
Date	30 August 2017
Brief source	*Modified T-cells that attack leukemia become first gene therapy approved in the United States* in **Science** magazine; also, NY Times online
URL	http://www.sciencemag.org/news/2017/08/modified-t-cells-attack-leukemia-become-first-gene-therapy-approved-united-states https://www.nytimes.com/2017/08/30/health/gene-therapy-cancer.html?mcubz=0
STEEP Category	Technological, economic
Keywords	Gene therapy, personalized medicine, value-based reimbursement
Type *(bold one)*	**Actual event** New trend New cycle New plan Potential event New information New issue
Brief description of the item	A new type of cancer treatment has been approved for use in pediatric patients with B-cell leukemia, in which the patient's T-cells, a type of lymphocyte (white blood cell) that works with the immune system to locate and attack specific antigen targets, are removed and modified using gene editing techniques and monoclonal antibodies so that they are able to recognize and attack the patient's cancer cells. Once modified in the laboratory to express the appropriate receptors, the patient's altered T-cells are re-implanted in the bloodstream to target and kill the cancer cells. Unlike most cancer therapies that are identical from patient to patient, CAR-T therapies are made by removing the T cells of a patient, modifying them to respond to certain targets expressed on the patient's cancer cells, and then reinfusing the cells. When the T cells come into contact with the relevant target (for instance, CD19 in the case of ALL), they proliferate while secreting a number of programmed substances including inflammatory cytokines that destroy the cancerous cells. Targeted killing of tumor cells by lymphocytes was first suggested by the graft-vs-leukemia effect in bone marrow transplantation, but that effect and the infusion of donor T cells more generally has no effect on solid tumor malignancies or most hematologic cancers. The innovation underlying CAR-T involved exploiting the specificity of antibody-mediated recognition of tumor antigens, and then engineering CAR-T cells to have the relevant antibody fragment fused to the T-cell receptor. Thus, the "living drug" infused into the patient is the patient's own T cells altered to express a receptor that is specific for the target antigen on the tumor. (Peter B. Bach, Sergio A. Giralt and Leonard B. Saltz, JAMA, 9/20) The drug price is high: $475,000 for a single treatment. This cost reflects the difficulty in processing and culturing the patient's cells to produce enough medication for dosing. The manufacturer, Novartis, has pledged that it will not charge patients who do not respond to the

	treatment within a month and will provide financial assistance to families without insurance or with inadequate insurance coverage.
How could the future be different as a result?	This is the first drug brought to commercialization in the US market that employs a truly personalized approach: white blood cells are removed from a patient, modified using gene editing techniques, then re-infused into the patient to treat a life-threatening condition. Each patient's medication is custom-made, using his or her cells modified in a laboratory setting – far outside the usual high-volume manufacturing paradigm used by drug companies for most pharmaceutical products. The company has promised a type of "performance guarantee" as a way to justify the high price of its new drug. This may signal a shift in market expectations in the future in which drug manufacturers take a more vested interest in the outcomes of disease treatments for patients using their products – and demonstrates a willingness to participate in a value-based reimbursement system that pharmaceutical companies have previously resisted.
What are the potential implications for stakeholders?	**Key stakeholders impacted:** Patients, pharmaceutical companies, payers • Clinical research studies in the future will be redesigned for statistical powering with very small cohort sample sizes – as the rise in genomic targeting and gene repair therapeutics will require a new approach to clinical testing of new personalized medicines. Patients will have to accept greater risk when participating in clinical trials, especially in the early stage of the development of new gene therapies, as each individual will be treated with a different medication developed just for them. • Drugs in the future will be created using a bespoke design and manufacturing process to treat the individual patient's disease processes – combining treatments for multiple illnesses into a single immunotherapy that directs the patient's own body to fight his or her disease naturally; pharmaceutical companies will have to adjust their supply chain, logistics, manufacturing, and packaging operations in the future to accommodate a batch size of n=1 • Payers will adopt value-based approaches to qualify personalized therapies for reimbursement. As an example, for the newly-approved Novartis adapted T-cell therapy, despite the expensive cost for a single treatment it is expected that one dose will be curative and will be less expensive than the alternative option for these patients: a bone marrow transplant. Some pharmacy benefit management companies have expressed concerns about the economic viability of such drugs, however.
Horizon *(bold one)*	**H1 Confirming** (baseline scenario) H2 Resolving (between scenarios) H3 Creating (new scenario) Two aspects of the baseline scenario are confirmed in which personalized drugs are manufactured based on the needs of an individual patient and drug manufacturers adopt a value-based approach to reimbursement of their products. This is the first step on the path of widely-accepted commercialized genetic engineering of patients' cells and other organs for therapeutic purposes and the first time a pharmaceutical company publically pledged to refund cost of treatment if the patient's condition doesn't improve.
Scan Hit Evaluation (0 – 5 scoring)	Impact – 4, Plausibility – 4, Novelty – 4, Credibility - 5

Title	*How to Protect a Drug Patent? Give it to a Native American Tribe*
Author	Katie Thomas

Date	08 September 2017
Brief source	New York Times, accessed online
URL	https://www.nytimes.com/2017/09/08/health/allergan-patent-tribe.html?mcubz=0&_r=1 https://www.allergan.com/news/news/thomson-reuters/allergan-and-saint-regis-mohawk-tribe-announce-agr
STEEP Category	Economic, political
Keywords	Pharmaceutical development, patent protection
Type *(bold one)*	**Actual event** New trend New cycle New plan Potential event New information New issue
Brief description of the item	Allergan, a multi-national pharmaceutical company based in Ireland, transferred its patents for a key asset in their portfolio (RESTASIS® eye drops) to the St. Regis Mohawk tribe in New York state to protect the patents from challenges from other companies seeking to market generic versions of the drug in the future. In the deal, the tribe receives the rights to the patents, $13.75 million, and annual royalties of $15 million in exchange for granting exclusive licenses to Allergan and for claiming sovereign immunity to any patent challenge brought in US federal court throughout the lifetime of the patents. An increase in patent challenges and subsequent increased litigation in advance of filing for FDA approval of a generic version of an innovator drug are a consequence of the Drug Price Competition and Patent Term Restoration Act (commonly known as the Hatch-Waxman Act of 1984), which was designed to ease market entry of generic drugs and increase competition. Under this legislation, generic drugs do not have to undergo clinical trials to demonstrate safety and efficacy but must prove bio-equivalency compared to the innovator drug. Advantage is given to the first company to file an Abbreviated New Drug Application (ANDA) with the FDA, announcing their intention to manufacture a generic version of a drug if that manufacturer certifies that their approach to the innovator's patent is to claim it as invalid (one option among four, and one of the most common approaches used in practice). See this summary for a history of Hatch-Waxman, its consequences, and some of the methods used by pharmaceutical companies to 'game the system' by adding new patents to existing products to extend the lifetime of innovator drugs and stave off market entry of generics.
How could the future be different as a result?	In the future, pharmaceutical and other patents cannot be challenged if transferred under the sovereign immunity of Native American tribes, leading to a powerful new stakeholder in the healthcare system. In the event the sovereignty precedent for patent protection is upheld, it could lead to an overall reduction in the level of litigation related to pharmaceutical products, a higher level of scientific integrity in the patents awarded (because pharma companies would need to ensure patents are airtight before transfer to tribes), and a subsequent increased confidence among pharmaceutical companies for investing in new drug development (and clinical trials) if the revenue lifecycles of marketed products were protected through the patent system without the threat of challenge and expensive litigation. A future scenario can be imagined where Native American tribes' claims of sovereign immunity were extended to shield them from federal laws and regulations concerning clinical research, sales and distribution of pharmaceutical products, and delivery of healthcare to establish local regional medical and psychiatric clinics - outside of the review and enforcement jurisdiction of the FDA – where patients could go to receive

	medical care and participate in clinical trials of new medicines. A new 'shadow market' drug and healthcare industry and a new domestic destination for medical tourism in the US would emerge, bringing a new revenue stream to Native American tribes and changing the established healthcare system in the future.
What are the potential implications for stakeholders?	**Key stakeholders impacted:** Pharmaceutical companies, patients, Native American tribes • **Pharmaceutical companies**, manufacturers of both brand and generic drugs, could save money if the drug approval system for generics did not require patent challenges or compliance with federal regulations. By shielding their patents from legal challenges and skirting federal oversight, instead of spending hundreds of millions of dollars on patent litigation and regulatory compliance activities, drug companies could make new investments in research and development of new products or process innovation with some of the savings passed on to the consumer in the form of lower product prices. • **Patients** could access new clinical treatments or research studies only available on Native American reservations, opening new options for healthcare and/or access to clinical trials with less stringent entry criteria due to lack of FDA oversight. Patients would need to be aware of and accept the possibility that the treatments or trials found on the shadow drug market carry higher risks than those available within the conventional healthcare system. • **Patients** might also benefit from reduced drug prices due to reduced litigation activities and reduced cost of new drug development • With a guaranteed revenue stream from patent stewardship, **Native American tribes** could invest in improvements in infrastructure and social services programs for members. Their greater economic power could help generate greater political power, as well, allowing the Native American tribes a stronger voice in North American politics and higher levels of national socioeconomic status.
Horizon *(bold one)*	H1 Confirming (baseline scenario) H2 Resolving (between scenarios) **H3 Creating** (new scenario) A potential new scenario emerges in which Native American tribes create an independent healthcare and clinical research empire, funded by a new patent stewardship industry based on protection and prevention of legal challenges by virtue of the sovereign immunity of the Native American tribes' nation status.
Scan Hit Evaluation (0 – 5 scoring)	Impact – 3, Plausibility – 4, Novelty – 4, Credibility - 5

Title	*EMA Warns of Major Staff Losses in HQ Relocation*
Author	Michael Mezher
Date	26 September 2017
Brief source	Regulatory Affairs Professional Society **Regulatory Focus** newsletter

URL	http://www.raps.org/Regulatory-Focus/News/2017/09/26/28539/EMA-Warns-of-Major-Staff-Losses-in-HQ-Relocation/
STEEP Category	Political, economic, social
Keywords	EMA, Brexit, EU drug/device regulation, patient safety
Type *(bold one)*	**Actual event** New trend New cycle New plan Potential event New information New issue
Brief description of the item	Because of the impending Brexit to be completed in April 2019, in which the UK has announced its intention to leave the European Union, the European Medicines Agency (EMA) must relocate its headquarters from London to one of the EU member states. To date, nineteen EU countries have offered to host the EMA headquarters. To assess the viability of these options, the EMA staff were asked to evaluate the likelihood of staying on in their position if required to relocate to each of the nineteen potential locations. Results of the survey indicated that only four cities were attractive enough to retain sufficient EMA employees to maintain continuity of critical functions, with each of these potential locations requiring significant agency hiring to meet the headcount needs for medium priority public health activities and lower priority administrative activities. EMA has said that the "best case" scenario would involve delays in review and approval of new drugs and slowed progress on health initiatives during the next two to three years. The "worst case" scenario, according to EMA, is that the agency would be unable to operate and emergency measures would have to be implemented to protect the public health.
How could the future be different as a result?	Even in the projected "best case" scenario, major disruptions in the operation of the EU regulatory system are expected that will result in delayed review and approval of new drugs and limited progress in other public health protection initiatives. Because the expiry of the period of patent protection is fixed, any delays in market authorization limit the revenue potential of pharmaceutical products seeking approval in the next five years (during the anticipated disruption), before the onslaught of generic competition begins for these new innovator drugs. In the "worst case" scenario, even a short period of complete dysfunction of the regulatory system would be enough to disrupt the business plans of most pharmaceutical companies, as drugs have long development timelines due to regulatory requirements to complete preclinical research and clinical trials prior to market authorization. Potential additional disruption due to leadership turnover at the US Food and Drug Administration (FDA) is possible as Commissioner Scott Gottlieb is considered a possible candidate for the recently-vacated Secretary of Health and Human Services cabinet position. A leadership vacancy at the FDA would likely exacerbate the existing problems caused by staff vacancies at the agency. Uncertainty in the regulatory system may motivate pharmaceutical companies to revise their strategies in the following possible ways: • Focus on the US market over the next five to ten years and delay applications for approval of new drugs in the EU until the EMA situation has stabilized • Bypass the EMA and seek approval directly from individual European countries • If unable to avoid the European market, reduce R&D spending and look for cost-saving options to increase clinical research efficiencies via protocol design and use of technology in clinical trials • Adopt a more aggressive patent protection strategy for existing marketed products to prolong the period of exclusivity, where possible

	• Identify opportunities to test drugs in 'proof of concept' clinical trials outside of the established regulatory ecosystem to get a fast, inexpensive early read-out of the potential clinical benefit of new drug candidates
What are the potential implications for stakeholders?	**Key stakeholders impacted:** Pharmaceutical companies and their shareholders, patients • Pharmaceutical companies and their shareholders will anticipate reduced revenues which will limit growth and may cause more significant cost-saving measures to be implemented such as staff reductions and reduced investment in R&D – and may initiate shareholder sell-offs for the major corporations leading to lower stock values • In the event of a major public health crisis such as an infectious epidemic, widespread food-borne pathogen, or act of bioterrorism, reduced operational capacity at the EMA will limit the agency's ability to respond quickly – leading to increased risk to patients and healthcare providers • Patients in the EU would not have access to new drugs in the future (and may have to travel for treatment) if pharmaceutical companies bypass the EMA for drugs in development during the period of disruption in operations • Patients may be faced with higher drug prices in the future as competition and innovation are reduced and pharmaceutical companies try to recoup their sunk costs of development
Horizon *(bold one)*	H1 Confirming (baseline scenario) **H2 Resolving** (between scenarios) H3 Creating (new scenario)
Scan Hit Evaluation (0 – 5 scoring)	Impact – 3, Plausibility – 4, Novelty – 3, Credibility - 5