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In the face of uncertainty: A challenging future for biopharmaceutical innovation

Executive summary

The biopharmaceutical industry is in a precarious position regarding innovation: big bets in bold new areas are fraught with complexity and uncertainty, while success in mature therapeutic areas is becoming increasingly challenging. Sustaining innovation has consistently been difficult, but the resulting benefit to patients has generally provided innovators with an investment return sufficient enough to compensate for the risk. However, the balance of this equation has been shifting and it appears to be getting even tougher for innovators and investors. A recent Deloitte study has shown that the overall rate of return on R&D investment for the 12 largest biopharmaceutical firms has dropped from 10.5 percent in 2010 to 4.8 percent in 2013, and the cost of developing a new medicine has surpassed $1.3 billion.[1] There is little reason to expect this to change because innovators, especially with biologics therapeutics, are facing significant uncertainty:

- **Scientific uncertainty:** Addressing the novel areas of unmet medical need requires innovators to tackle challenging therapeutic areas or emerging biologics modalities.
- **Regulatory uncertainty:** The FDA approval process is associated with a high degree of uncertainty that complicates an innovator's ability to predict review times, pre-approval requirements and post-approval requirements.
- **Coverage uncertainty:** In response to market trends as well as the Affordable Care Act (ACA), health plans have tightened coverage policies and formulary placements, causing significant uncertainty in patient access to new treatments.
- **Policy and implementation uncertainty:** Innovators have to account for future competition from biosimilars, biologic medicines that are developed to be similar to innovator biologics. The ACA created an abbreviated FDA approval pathway for biosimilars; however, the law created a lot of uncertainties and leaves many important areas open to interpretation.

These uncertainties introduce increased volatility into investment projections, which impacts the incentives of the complex network of financiers who support drug development. It is likely that these trends will impact the industry's innovation ecosystem in a permanent way: both venture capital and large biopharmaceutical companies may shift their focus away from challenging innovation opportunities – to the potential detriment of patients and health systems that depend on biopharmaceutical innovation.

This situation may be viewed as an unintended consequence of trying to balance the needs of the many players in the health care ecosystem. There has been a significant emphasis on constraining health care costs to improve patients' access to biopharmaceutical therapeutics today. However, there is also the need to continue cultivating and incentivizing innovation within the industry to develop the new treatments of tomorrow.

This challenge is not easily solved – everyone acknowledges the importance of access to innovation today and the creation of new treatments tomorrow. Sustaining future innovation will require a significant deal of collaboration among stakeholders within the ecosystem. The current approach is not sustainable and an improved process for delivering innovative products is required. The stakes are high, and time is of the essence – but a focused effort to collaborate to reduce the impact of these uncertainties could have a demonstrable impact on R&D returns.

Overview of R&D process and innovation landscape

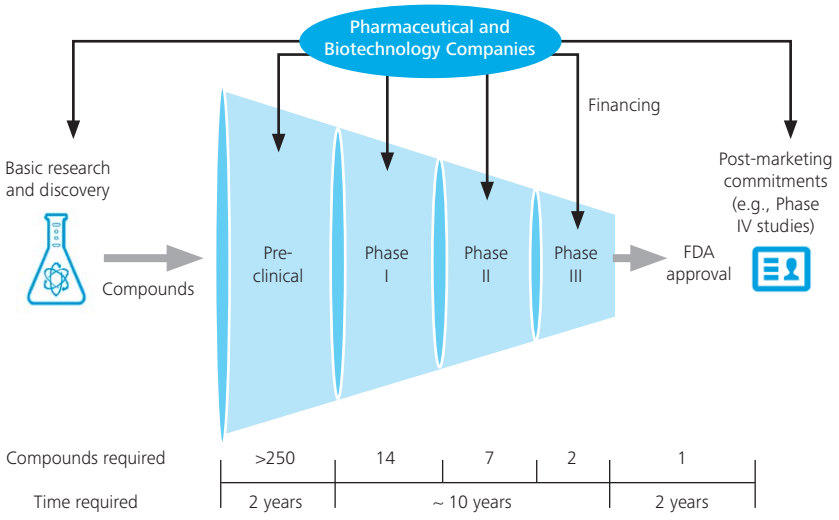
Innovation within the pharmaceutical and biotechnology industry is sustained by a complex business system. In its simplest form, this business system can be summarized by the flow of scientific development and the capital required to finance these activities. As new compounds are discovered in the lab and progress toward approval and launch, they must go through two related sets of stage gates. These scientific (and clinical) gates are often depicted as a funnel – a high volume of early-stage compounds will start the journey but only a few compounds ultimately demonstrate the safety and efficacy required to be approved as therapies.[2] Figure 1 illustrates the attrition rates and durations associated with each stage of the R&D process.[3]

Financing R&D activities is inherently risky because the majority of compounds fail to clear the clinical hurdles required for approval. Investment in early-stage compounds is associated with a high degree of risk because of the attrition rates that occur within these phases. Later-stage compounds generally have a lower probability of failure; however, these phases are extremely expensive and require a significantly larger investment. Throughout the R&D process, financiers must weigh the investment required for each successive stage of R&D against the risk-adjusted commercial market potential of the compounds. This effectively requires compounds to clear two sets of hurdles: scientific/clinical and financial.

Large, publicly-traded corporations have historically generated enough free cash flow to finance innovation and sustain R&D investment. But this is not the case for the hundreds of small, research-focused private biotechnology firms that comprise much of the industry and represent an important source of innovation. These firms are generally focused on a specific technology platform, mechanism of action, or a handful of early-stage compounds, and many of these firms are not profitable or do not have commercial revenue streams (the industry did not become profitable on an aggregate basis until 2009[4]). Venture capitalists (VCs) have traditionally financed these firms because, unlike other investors, they are accustomed to the high risk-to-return profiles of early-stage innovation.

All innovation stakeholders within the ecosystem depend on economic investment returns. At a minimum, each compound must demonstrate an expected rate of return that is greater than the cost of capital to justify investment. This ensures that the few compounds that eventually prove successful can effectively subsidize the high volume of R&D failures. Sustaining innovation has consistently been challenging, but the resulting benefit to patients has generally provided innovators with an investment return sufficient enough to compensate for the risk. However, the balance of this equation has been shifting and it appears to be getting even tougher for innovators and investors. The overall rate of return on R&D investment

Figure 1. Representative Biopharmaceutical System



Source: CMR International 2012 Pharmaceutical R&D Factbook

has dropped from 10.5 percent in 2010 to 4.8 percent in 2013,[5] the cost of developing a new medicine has surpassed $1.3 billion,[6] and only two out of 10 approved drugs ever recoup their investment costs.[7] Within the last 15 years, these challenges have driven a series of fundamental changes to the industry's innovation ecosystem:

- **Industry consolidation:** A series of large-scale M&A transactions has resulted in the consolidation of 58 multi-billion dollar biopharmaceutical firms down to 20.[8] Increasing pressures to foster innovation and replenish R&D pipelines have driven firms to consolidate in order to augment their portfolios and mitigate market risks.

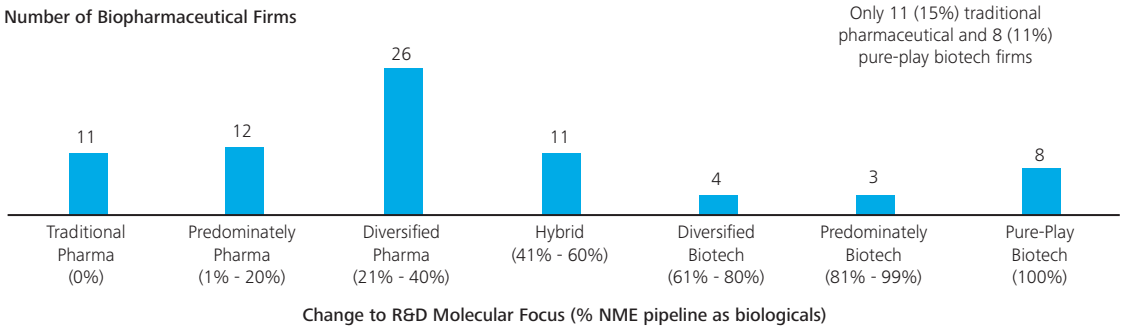
- **Product diversification:** Industry consolidation and strategic priorities have blurred the distinction between pharmaceutical and biotechnology firms. Companies increasingly are diversifying their product portfolios – 56 of the 75 largest biopharmaceutical firms (75 percent) are pursuing both small and large molecules (Figure 2) – and many are also developing companion diagnostics and other products.[9]

- **External innovation:** Large biopharmaceutical corporations' are continuing to expand their R&D portfolios through external licensing and co-development deals with smaller firms (Figure 3). These deals improve larger firms' access to cutting-edge innovation and provide smaller and emerging firms with a valuable source of capital. This is especially pronounced with late-stage assets where small firms struggle to secure the capital required to finance expensive studies.

- **Access to capital:** Given the substantial costs and timelines associated with biopharmaceutical R&D, attracting and sustaining investment remains an ongoing challenge. Patent expirations have significantly impacted large corporations' revenues, resulting in proportionally lower R&D spending and more stringent investment prioritization. Biotechnology venture funding, a critical source of funding for small and emerging firms, has decreased by 29 percent (-6.5 percent CAGR) from 2007 to 2012.[10] Some larger biopharmaceutical firms have actually established their own corporate venture funds to help fill the innovation funding gap.

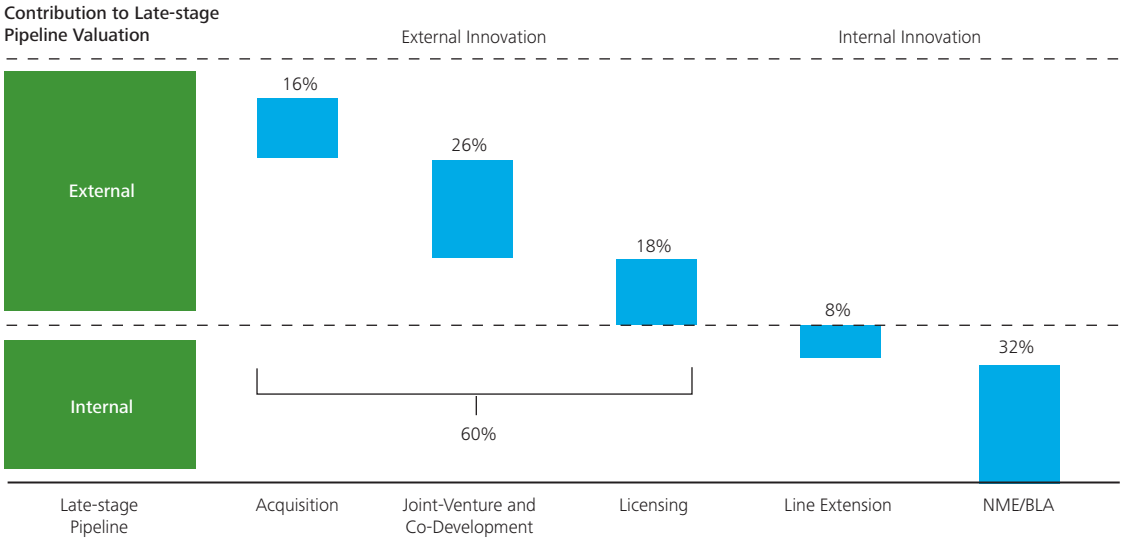
The current innovation ecosystem is drastically different from the life sciences industry of the 1980s. Innovation is increasingly challenging and costly, putting the biopharmaceutical industry in a very precarious position. Big bets in bold new areas are fraught with complexity and uncertainty, while success in mature therapeutic areas is becoming increasingly difficult. As the industry continues to shift toward novel scientific approaches and areas of unmet medical need, the risk profile of R&D investments will continue to increase. How much more risk can the industry absorb before the innovation model breaks?

Figure 2. Distribution of Biopharmaceutical Companies by R&D Pipeline Composition (NME Only)[11]



Source: EvaluatePharma R&D Pipeline Report; Top 75 companies by R&D pipeline size (NMEs only)

Figure 3. Source of Late-stage Pipeline Valuation for Large Biopharmaceutical Cohort (2010 to 2013)[12]



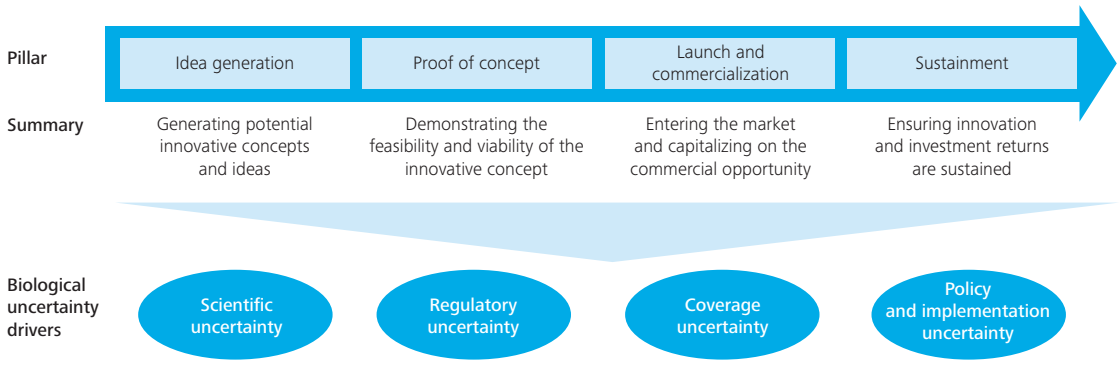
Source: Deloitte UK Centre for Health Solutions, "Measuring the Return from Pharmaceutical Innovation 2013 – Weathering the Storm?"

Assessing the biopharmaceutical industry's future innovation potential first requires an understanding of the factors that influence innovation. Broadly speaking, agnostic of industry, there are four foundational pillars that drive innovation. Each of these pillars – Idea Generation, Proof of Concept, Launch and Commercialization, and Sustainment – represents a different step in the innovation lifecycle. These pillars are critical because they directly affect the risk and return on investment, the primary measure used to assess innovation funding decisions.

Innovation is inherently risky and each investment opportunity has a unique risk profile. Investors incorporate this opportunity-specific risk into individual investment decisions (e.g., attrition, discount rate, etc.) and can mitigate these risks through portfolio diversification. Uncertainty, on the other hand, is not opportunity-specific. In the context of innovation, this uncertainty represents broader, industry-wide risks that are non-diversifiable. Uncertainty can introduce unforeseen volatilities into investment projections and deter financiers from investing in innovation.

Across the biopharmaceutical industry, innovators are encountering uncertainties across each of these pillars which threaten the industry's ability to innovate (Figure 4). They may be broadly categorized into four areas: scientific, regulatory, coverage, and policy and implementation. The aggregation of these uncertainties along a drug's value chain produces a cumulative effect compromising the industry's ability to innovate.

Figure 4. Innovation Pillars and Uncertainty Drivers

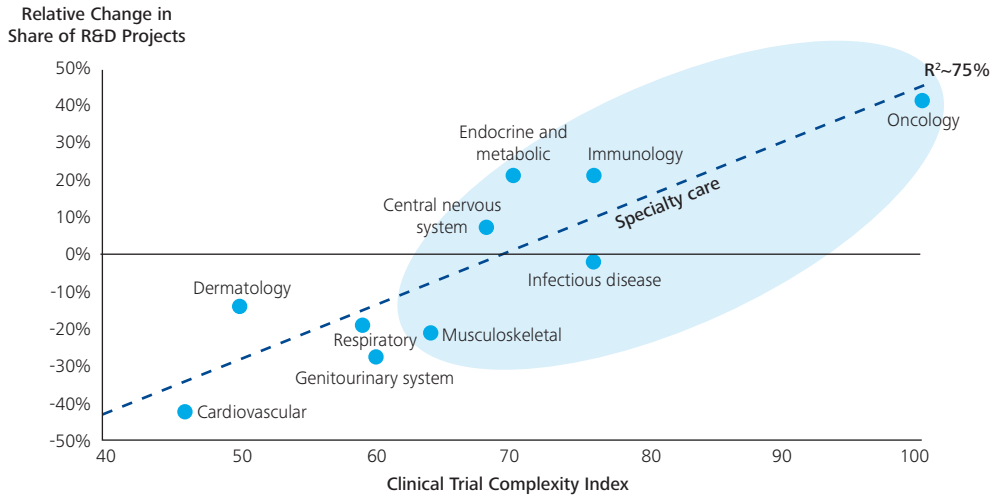


Scientific uncertainty

Progress is a double-edged sword. The biopharmaceutical industry has effectively produced a myriad of breakthrough treatments for primary care disease states and the treatment regimens for many of these therapeutic areas have become mature. This has driven a large shift in the industry's R&D focus towards more complex areas such as Alzheimers, Parkinsons, and rare diseases with limited or no available treatment options (Figure 5). These diseases are proving to be challenging biologically, physiologically and clinically. The identification of attractive targets and potential leads is becoming more difficult, but due to the complexity of these diseases, even promising assets may affect patient sub-groups or those with specific genetic markers differently. At the outset of clinical research, companies are often not aware of the degree to which a potential therapy's effectiveness may be limited to a particular patient population. While the development of more targeted or personalized medicines helps ensure the right medicine is developed for the right patient, it naturally limits the potential market for the medicine. This may result in greater uncertainty within discovery research but also further down the R&D value chain. In addition, the number and complexity of clinical trial protocols has increased, resulting in challenges with patient recruitment and retention.[13] These aspects have made it more difficult to forecast the time and cost of clinical trials.

The R&D pipeline is increasingly focusing on the development of biologics to treat these diseases. Biologics present a unique set of scientific and technical challenges. Compared to small molecule drugs, biologics are more complex and are heterogeneous. These drugs are made by or from living organisms, are highly sensitive to manufacturing process changes, and have immunogenic potential. As part of the Affordable Care Act, the Biologics Price Competition and Innovation Act of 2009 (BPCIA) sanctioned an abbreviated pathway for the approval of biosimilars. Because of the complexities of large molecule biologics, biosimilars cannot be proven to be the "same" as the reference or innovator biologic. Meaningful differences between innovative biologics, biosimilars, and even interchangeable biosimilars could develop over time as each manufacturer implements process changes. These aspects contribute to a number of complexities in terms of building or retrofitting facilities for biologics manufacturing and scale-up of manufacturing. New facilities for biologics manufacturing can require up to a $200M to $500M investment to construct, commission, and qualify (retrofitting existing facilities can cost between $50M to $100M) and necessitate between three to five years.[14]

Figure 5. Shifting of R&D Investment to Increasingly Complex Therapeutic Areas[15]



Source: Nature Reviews Drug Discovery 10, 428-438 (June 2011); Parexel Biopharmaceutical R&D Statistical Sourcebook 2012/2013 (EvaluatePharma Worldwide Prescription and OTC Sales by Therapeutic Category; TTC, GrantPlan® Database); Deloitte Consulting LLP Analysis; Note: Complexity index based on mean number of procedures per patient (Ph I to IV); Y-axis reflects change in the percent of all R&D projects between 1990-2000 and 2000 to 2010

Regulatory uncertainty

Today's biopharmaceutical industry is one of the most highly regulated industries in the world; global regulatory authorities such as the U.S. Food and Drug Administration (FDA) spend considerable time and resources to scrutinize new drug applications to ensure that products are safe and effective. The global regulatory landscape continues to evolve, and while pathways are being created to accelerate this process, there is uncertainty associated with approval timelines and post-marketing commitments.

The time required by the FDA to approve a new molecular entity (NME; abbreviation includes new biologic license applications) can vary significantly. The specific safety and efficacy requirements are different for each combination of disease, drug, and indication, and approval often requires multiple FDA review cycles. Between 2009 and 2012, 50 percent of NME applications that received a Complete Response Letter (CLR) on their first submission were eventually approved.[16] Excluding applications that were not resubmitted – presumably for an ineffective demonstration of safety or efficacy – a startling 96 percent of NMEs resubmissions were approved.[17] The ratio of FDA review cycles to NME approvals averaged about 1.5 during this period,[18] effectively doubling the review time for every other NME approval, and the limited duration of this sample size indicates that these figures are not primarily driven by the need for new clinical trials or patient data. The uncertainty of approval timelines significantly impacts commercial planning, launch activities and projected revenues, particularly for smaller biotechnology firms.

In addition, the proportion of innovative medicines approved with post-marketing requirements or commitments (PMCs) is increasing. Fifty-eight percent of NMEs approved between 2004 and 2006 required PMCs, but this increased to 88 percent for NMEs approved between 2010 and 2012.[19] These commitments frequently require the drug's sponsor to conduct additional clinical trials and can significantly increase post-approval R&D costs. Other commitments may require comprehensive risk management plans that employ ongoing safety measures to monitor the benefits of certain drugs and their risks. These Risk Evaluation and Mitigation Strategies (REMS) may require the sponsor to train and certify physicians before they may prescribe the drug, to restrict their supply chain to a limited number of distributors, or perform ongoing monitoring of patients being treated with the drug. These activities can significantly increase costs, require substantial time commitments, and are not generally considered as R&D or other costs associated with the drug lifecycle, potentially reducing returns on investment.

Coverage uncertainty

The biopharmaceutical industry is facing an insurance landscape that is in the midst of transformation. Pressures to control costs have led to increasing consolidation in the pharmacy benefits management (PBM), provider, and health plan markets. Financial risks are shifting more from payers to providers, with mechanisms such as bundled payment on the rise. Employer-based coverage is beginning to give way to individual coverage, as enrollment grows in the Exchange plans made possible under the ACA.

As health insurance companies' business models evolve, they have adopted aggressive positions with regards to prescription drug coverage.[20] Evidence is growing that the ACA may be accelerating the long-established secular trend toward increased cost sharing for prescription drugs. For example, insurers are increasingly placing certain drugs that they have defined as specialty medicines in a designated fourth tier with higher out-of-pocket co-payments for patients. Between 2008 and 2011, the proportion of drug plans with this fourth tier more than tripled, and in the same period, the proportion of plans with co-insurance (rather than set-dollar co-payments) more than doubled.[21] These trends produce higher out-of-pocket costs for patients, resulting in more limited access to these medicines.

New medicines are facing a much higher burden of proof to receive favorable formulary placement and increasingly must demonstrate both clinical and economic value. Innovating firms' ability to demonstrate sufficient value (as defined by insurers) is inherently uncertain due to the nature of the R&D process and the extent to which evidence of the full value of a medicine evolves over time. Insurers also are increasingly expanding their analytic capabilities to conduct their own value assessments. However, insurers' expectations and evaluation criteria vary, can evolve over time, and are rarely transparent, creating uncertainty for biopharmaceutical companies. For example, in 2010, Wellpoint analyzed data from 26,000 patients on osteoporosis medications and concluded that one particular product was associated with lower patient adherence, higher rates of bone fractures, and higher overall costs relative to two comparators in the same class.[22] As a result, Wellpoint requires patients to use one of the two comparator medications as a first option and U.S. revenues for the product analyzed in the study decreased by 30 percent between 2010 and 2011.[23]

Collectively, these coverage uncertainties significantly impair innovating firms' ability to project the commercial returns from costly R&D investment and can impact future decisions related to R&D pipelines.

Policy and implementation uncertainty

Just as innovators have had to account for increased competition from generic medicines, which now account for 84 percent of all prescriptions in the U.S., innovators must plan for increased competition from biosimilars. As mentioned earlier, the Biologics Price Competition and Innovation Act of 2009 (BPCIA) sanctioned an abbreviated approval pathway for biosimilars. The BPCIA, which was one of the few ACA provisions with widespread bipartisan support in Congress, was intended to strike a balance between the need to promote continued innovation and the desire for increased competition. While the pathway is now law, a number of important guidances have not yet been issued by the FDA, including considerations for demonstrating interchangeability, labeling of biosimilars, and additional clarity around data exclusivity provisions. These guidances are required to inform investment decisions for both innovator and biosimilar manufacturers.

The BPCIA provides 12 years of data exclusivity, also known as data protection, for innovative biologics. During this period of exclusivity, no manufacturer can submit an application for a biosimilar in the first four years and no such application can be approved before 12 years. Some policymakers have continued to advocate for a reduction in the 12-year exclusivity period, and each of the last four Federal Budget proposals issued by the Administration has included a proposed reduction in the data exclusivity period for innovative biologics to seven years.[24] Economic analysis has shown that at least 12 years of data protection is necessary for an established firm to break even and potentially recoup the large upfront R&D investment needed to develop a new biologic.[25] A five-year reduction in the data exclusivity period could dramatically affect innovating firms' ability to recoup their R&D investment.

Data exclusivity is particularly critical for biologics because patents for biologics may provide less clear, less predictable intellectual property (IP) protection than for small molecule drugs, as many biologic patents are process patents or relatively narrowly drawn product patents. These patents may be susceptible to "work-arounds," especially if the regulatory framework permits biosimilars to differ in their structural features from innovator biologics. Furthermore, if a biologic's development time is extended, there may be a very limited period of patent protection remaining once a product is approved. Adding to the uncertainty of achieving returns on investment is the possibility that the few successful biologics will be subject to patent challenges from biosimilars early in their lifecycle but after all of the investments in R&D and manufacturing facilities have been made. This would shift the odds against such large-scale, speculative investment.

Impact of uncertainty on biopharma innovation

As discussed, industry dynamics have changed substantially over time, multiplying uncertainties faced by biopharmaceutical companies. These uncertainties can adversely affect the investment economics associated with biopharmaceutical innovation. To illustrate this effect, an analytical model was constructed to quantify the impact of uncertainty on R&D internal rate of return (IRR). A baseline IRR of 14.8 percent was calculated for a representative new biological entity based upon recent publications and industry benchmarks.[26] The potential impact of individual uncertainty drivers on R&D IRR was analyzed and is summarized in Figure 6 below.

The net reduction in IRR ranges between 0.6 percent and 1.9 percent for each of these uncertainty drivers – a significant impact given the size of the investment required to research, develop and launch a new product (e.g., over one billion dollars). It is also important to evaluate these impacts relative to the underlying cost of capital and not solely the baseline IRR. The analysis assumed a discount rate of 10.5 percent (large biopharmaceutical firms' cost of capital is generally between 8 percent and 13 percent), which implies that the baseline R&D scenario only clears the investment hurdle rate by 4.3 percent. This illustrates the sensitivity of financial returns against these uncertainties – the mean IRR reduction of these examples is 1.3 percent, which accounts for over 30 percent of the value created through the investment (1.3 percent/4.3percent). But more importantly, these uncertainties are not mutually exclusive. The aggregated impact of these same examples produces a compounding effect on investment returns (Figure 7).

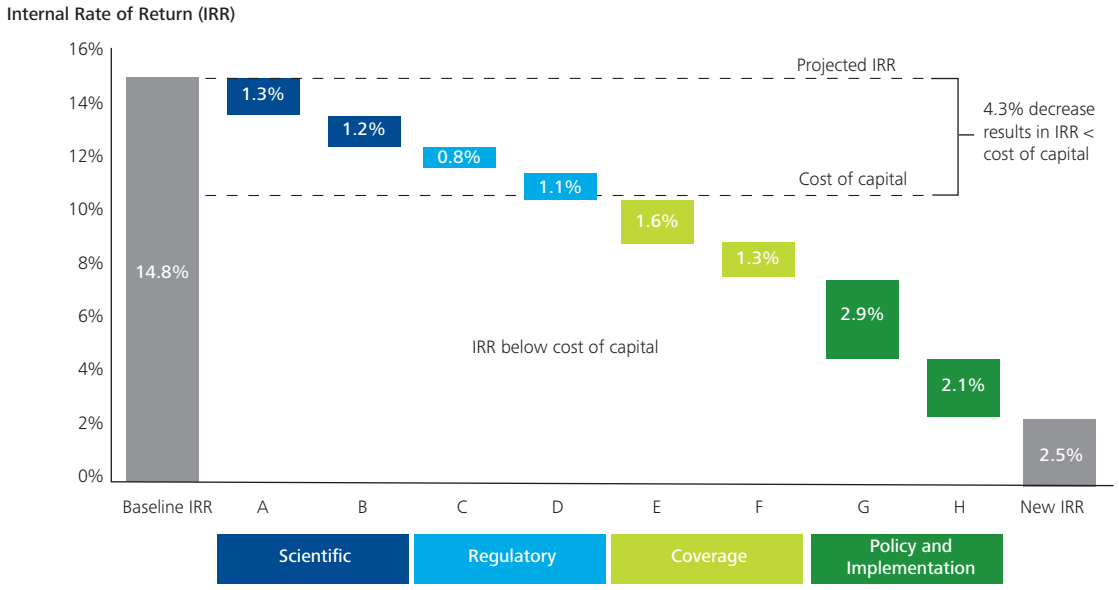
Figure 6. Net Impact of Individual Uncertainty Drivers on R&D IRR

Category	Uncertainty Driver		Example	IRR Impact
Scientific	A	Increased complexity of therapeutic or disease areas may reduce probability of success	Phase III attrition rate increased by 10 percentage points	(1.3%)
	B	Inability to generate clinical trial drug may drive unforeseen delays in study duration	Clinical duration of late-stage study prolonged by one year	(1.3%)
Regulatory	C	Additional FDA review cycles may prolong review time and delay time to approval	FDA approval and launch delayed by one year	(1.0%)
	D	Post-marketing requirements may require significant post-approval investment	Two Phase IV studies required as PMCs	(1.2%)
Coverage	E	Tightening formulary policies may constrain customer access and reduce commercial potential	20% reduction in forecasted peak revenue projections	(1.7%)
	F	Insurer focus on comparative effectiveness may prolong formulary approval and delay market adoption	Time to peak revenue delayed by two years	(1.9%)
Policy and Implementation	G	Unexpected reduction in data exclusivity period may expedite biosimilar market entry	Exclusivity period reduced from 12 to seven years	(1.3%)
	H	Unexpected/unplanned designation of interchangeability may accelerate revenue erosion	Post-exclusivity revenue erosion increased by 20% (YoY)	(0.6%)

The aggregate effect of these uncertainties reduces IRR from 14.8 percent to 2.5 percent. This is admittedly a pessimistic scenario, but each of these uncertainty drivers is already influencing innovation investment today and actual R&D returns are closer to those provided in Figure 7.

Investors have an expectation that their potential financial returns will be commensurate with risk. If an investment opportunity fails to meet this expectation, their capital is more effective if allocated to more promising (i.e., higher returns) or safer (i.e., less risky) investment opportunities. In the case of the biopharmaceutical industry, the risk and uncertainty profile of innovation investment is increasing while the projected financial returns are decreasing. If these trends are sustained it will further encourage financiers to invest their capital elsewhere, and for an industry that heavily relies on small-cap firms and venture capital to fuel innovation, this could negatively impact the ecosystem in a permanent way.

Figure 7. Cumulative Impact of Aggregated Uncertainty Drivers on R&D IRR[27]



Note: Aggregated calculation of uncertainty drivers will result in slight differences to the figures outlined in Figure 6.

Considerations to foster innovation

This precarious situation may be viewed as an unintended consequence of trying to balance the needs of the many players in the health care ecosystem. There has been a significant emphasis on constraining health care costs to improve patients' access to biopharmaceutical therapeutics today. However, there is also the need to continue cultivating and incentivizing innovation within the industry to develop the breakthrough treatments of tomorrow. It is imperative to recognize that these two objectives cannot be viewed in isolation from one another. Policymakers face a huge challenge moving forward – how to protect and incentivize life-saving innovation, while at the same time improving patients' ability to readily access it – but it is unfair to place the responsibility of such a critical dilemma squarely on their shoulders. While approaches to reinvent the innovation engine have been outlined by Deloitte in the past,[28] successfully reinvigorating the industry's ability to foster innovation will likely require contributions from many of the stakeholders in the ecosystem.

Scientific uncertainty remains a core challenge to the biopharmaceutical industry's quest for novel therapies, but the scale of these challenges is shifting from single-receptor diseases to cancers with multiple genotypes, long-term degenerative neurological diseases, and other complex conditions. Addressing challenges on this scale will likely require enhanced collaboration among the biopharmaceutical industry and academic research labs, medical centers, and physicians to gain a better understanding of the underlying disease. This is not a novel concept, but the continued development of innovative partnership models among these stakeholders is paramount to overcoming the excessive costs, misaligned incentives, and lack of commercial emphasis that has historically challenged these agreements. Collaborations between biopharmaceutical firms in the form of pre-competitive partnerships can accelerate the understanding of systems and disease biology and enable firms to more effectively focus on their core competency of drug discovery. Clinically, designing cost-efficient and flexible, adaptive trials will require closer relationships with clinical investigators and key opinion leaders to confirm that studies are executed appropriately and provide efficient insights.

As disease and treatments become more complex, striking the right balance between the products brought forward by innovators and the needs of the regulators for evidence of safety and efficacy is more precarious each year. Reducing the dampening effect of regulatory uncertainty upon innovators will require a series of capability and

Figure 8. Potential Approaches to Overcoming Uncertainty

Category		Uncertainty Driver	Potential Approach
Scientific	A	Increased complexity of therapeutic or disease areas may reduce probability of success	• Enhanced collaboration models with academia, medical centers, and physicians • Pre-competitive partnerships between industry firms • Improved study design and closer relationships with clinical investigators and key opinion leaders
	B	Inability to generate clinical trial drug may drive unforeseen delays in study duration	
Regulatory	C	Additional FDA review cycles may prolong review time and delay time to approval	• Improved regulatory intelligence capabilities • Increased engagement with regulatory agencies throughout development lifecycle • Greater transparency across internal organizations
	D	Post-marketing requirements may require significant post-approval investment	
Coverage	E	Tightening formulary policies may constrain customer access and reduce commercial potential	• Market-driven approach to R&D • Joint input from R&D and commercial organizations for R&D decisions • Commercial resources dedicated to early-stage R&D
	F	Insurer focus on comparative effectiveness may prolong formulary approval and delay market adoption	
Policy and Implementation	G	Unexpected reduction in data exclusivity period may expedite biosimilar market entry	• Proactive education and communication • Fundamentally new approach to drug development
	H	Unexpected/unplanned designation of interchangeability may accelerate revenue erosion	

process-related improvements. Biopharmaceutical companies' Regulatory Affairs departments can become more proficient at detecting and analyzing signals to better understand potential shifts in regulatory agencies' perspectives. Innovating firms will need to proactively engage regulatory authorities regarding the use of real-world evidence from trial populations and bioinformatics to translate clinical phase safety and efficacy signals into the likely effect in larger populations before launch. These actions can be critical to confirming that a program's clinical strategy will provide the data that agencies specifically require for the targeted label.

Overcoming coverage and reimbursement uncertainty will likely require the industry to supplement scientific advancements with stronger market insights to generate commercially viable innovation. Early-stage investment decisions, at both the portfolio and asset level, may require joint input from a company's R&D and commercial departments. The control of decision rights will vary through the development lifecycle, but R&D departments will need to leverage the body of collective insights that are available (e.g., scientific, commercial, reimbursement, etc.) to inform these decisions. Commercial departments will need to allocate both investments and resources to drive these activities on an ongoing basis, and these groups will need to identify how to effectively communicate and convey these insights to early-stage R&D decisions.

Finally, overcoming policy and health care implementation uncertainty is a challenge that is not easily solved. Innovating firms can make concerted efforts to proactively engage and communicate with policymakers and regulators, and, as appropriate, educate these parties on the macroeconomic implications of these uncertainties. However, the harsh reality is that these actions, and to a lesser extent, those described in the preceding paragraphs, likely need to be accompanied by many other actions in order to have a measurable effect on returns. The time, cost, risk and complexity associated with biopharmaceutical innovation has reached a point where the current drug development process may not be sustainable over the longer term. It is possible that the most attractive solution may require a fundamentally different approach for delivering innovative products. An evaluation of the potentially viable alternatives is outside the scope of this paper, but a challenge of this magnitude cannot be taken lightly. The stakes are high, and time is of the essence, because the future of the biopharmaceutical industry's ability to innovate effectively is in question.

Endnotes

[1] Deloitte UK Centre for Health Solutions, "Measuring the Return from Pharmaceutical Innovation 2013 – Weathering the Storm?"
[2] Deloitte Consulting LLP, "Avoiding No Man's Land – Potential unintended consequences of follow-on biologics," 2009
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[9] EvaluatePharma R&D Pipeline Report; Top 75 companies by R&D pipeline size (NMEs only)
[10] National Venture Capital Association; MoneyTree™ Report
[11] EvaluatePharma R&D Pipeline Report; Top 75 companies by R&D pipeline size (NMEs only)
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[16] Datamonitor Healthcare Report, "Complete Response Letter Trends and Influence on Approval Delays," 2013; Deloitte Consulting LLP Analysis; Note: excludes 13 NME resubmissions that remained open (e.g. no FDA decision) at the time of publication
[17] Ibid. 14; Note: figures increase to 66% and 98%, respectively, if analysis expanded to include all New Drug Applications (NDAs)
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