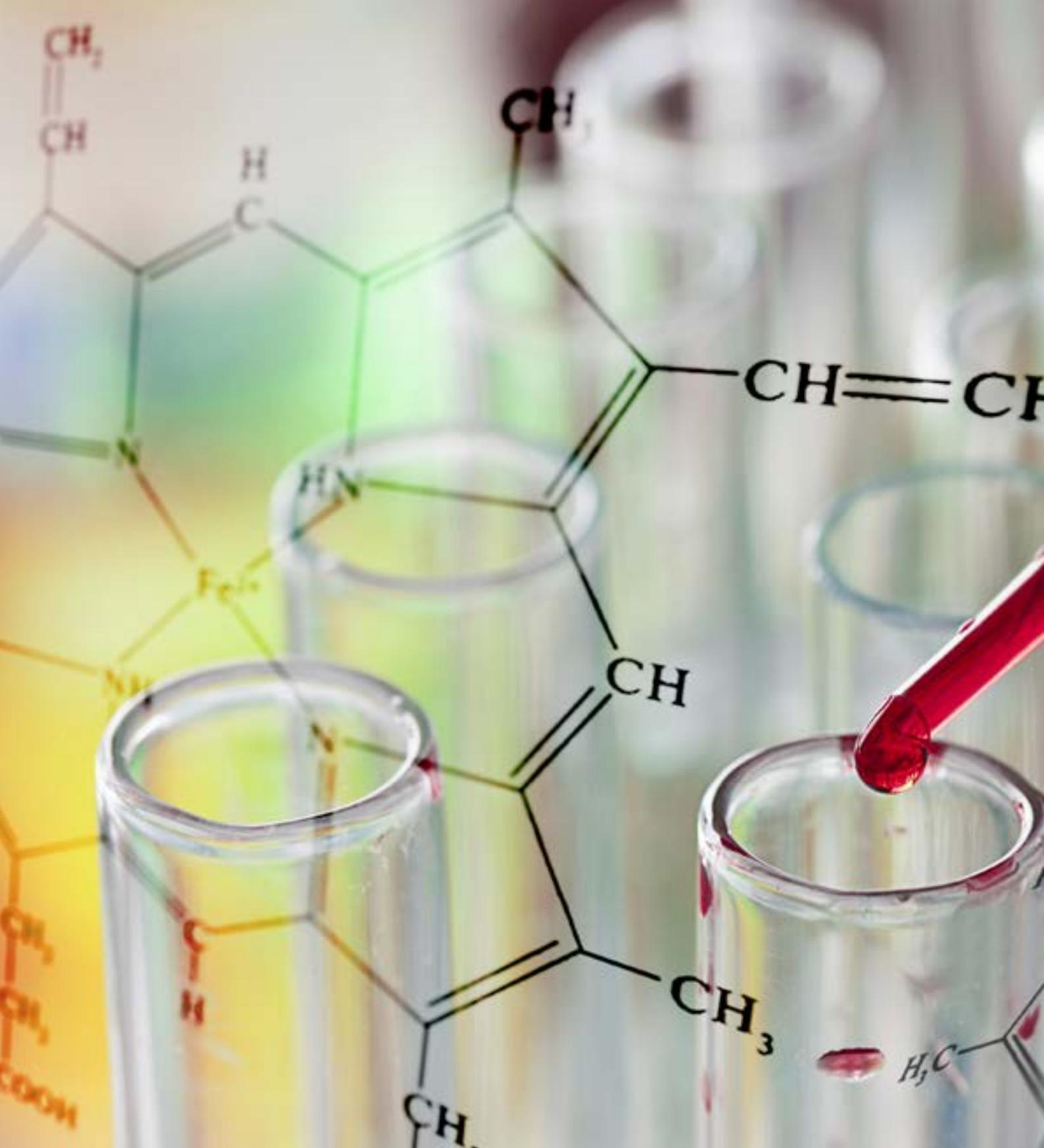


High value, high uncertainty:
Measuring risk in biopharmaceutical
research and other industries
Investing in the future of health





Based on key research delivered by The Deloitte Health Economics Group:

Commissioned by

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Preface



There is no doubt that the biopharmaceutical industry is facing challenging times. We live in a region with a rapidly ageing population, with increasingly stringent regulations and governments struggling to balance health and social expenditures at a sustainable level.

At Janssen, we recognise that because, rather than despite, these challenges we must invest. The uncertainty of investment is outweighed by the growing burden of disease and the need for transformational innovation to tackle diseases of very high complexity. That said, the additional and increasing challenges facing the industry are a very real threat that need to be addressed to safeguard the future and ensure innovative R&D is sustainable.

This report sets the scene for the uncertainty and risk currently facing biopharmaceutical companies in Europe. It places it in the context of comparable industries involved in the development of innovative products. The findings are stark. The biopharmaceutical, automotive and aircraft manufacturing industries spend the most on research and development per product. However, it is the biopharmaceutical industry that reinvests the most revenue into R&D, faces the longest period to market and the greatest risk of failure, the most stringent regulations and the greatest threat of decreasing patent protection periods.

In this high-risk environment, collaboration is the key, together with a higher predictability of external factors. Broad and efficient collaboration is something we strongly advocate, in order to obtain substantial results for our patients and ensure R&D investment can be maximised. Janssen has set the tone by establishing initiatives to increase our collaboration with external private and academic partners. In 2012, we created Janssen Healthcare Innovation, which is responsible for examining new business models, partnership structures and novel concepts of healthcare delivery. We were one of the founding 10 pharmaceutical companies

that formed Transcelerate Biopharma, an organisation focused on advancing innovation in R&D, identifying and solving common R&D challenges and further improving patient safety, with the goal of delivering more high quality medicines to patients. Moreover, last year we launched Johnson & Johnson Innovation Centers with a European office in London, to identify and realise early research partnerships. We are also involved in supporting the Innovative Medicines Initiative, Europe's largest public-private initiative aiming to speed up the development of better and safer medicines for patients.

There are millions of people in Europe whose lives cannot be improved without therapeutic advances. We are driven to continue discovering and developing innovative medicines that ease patients' suffering and give them hope, and which meet the important unmet medical needs of our time. We look for innovation wherever it exists. This drives our relentless search for the best science, and our pursuit of collaborations and partnerships.

Fostering innovation within the biopharmaceutical industry has always been challenging and costly. However, the resulting benefit to patients and society as a whole has generally provided innovators with an investment return that balances the risk. As this report reveals, with additional and increasing challenges facing the industry, more needs to be done to ensure innovation is sustainable by reducing uncertainty and appropriately rewarding innovation. Only by doing this can we ensure patients continue to receive new transformational treatments that can help change lives.

Jane Griffiths
Company Group Chairman
Janssen Pharmaceutical Companies of Johnson & Johnson, Europe, Middle East & Africa

Executive summary

The biopharmaceutical sector provides high societal value to Europe but innovation becomes more challenging over time

- Biopharmaceutical medicines have transformed human health through greater life expectancy and better quality of life. The industry is the most likely source of significant public health benefits for the foreseeable future.
- The biopharmaceutical industry invests a large amount of time and money into improving global public health, employing a highly educated and specialised workforce with a unique mix of strong scientific knowledge, commercial acumen and a strategic mind-set.
- Greater insight into the biopharmaceutical business environment is needed as innovation becomes more challenging for the industry. These changes in business environment, combined with a relative decrease in spending on innovative medicines, have meant that pharmaceutical companies involved in innovative research have had to take higher risks for potentially reduced and decreasing rewards.

In this paper, uncertainty and risk are compared across selected industries

- The main trends in the business environment directed the types of uncertainties and risks have been evaluated, with changes in market access, regulation and R&D challenges being the main features affecting the pharmaceutical industry.
- Other industries were systematically selected to make meaningful comparison possible, then metrics that matched the main trends affecting the pharmaceutical industry were derived so that uncertainties and risks could be quantified. The comparators used in this paper are the automotive manufacturing, commercial aircraft manufacturing, consumer electronics, food manufacturing and generic pharmaceutical industries.

The biopharmaceutical industry encounters a higher level of uncertainty in key areas than comparable industries when developing innovative products

- The pharmaceutical, automotive and aircraft manufacturing industries spend the most on R&D per new product, although these figures do not account for the R&D costs of products which do not make it to the market (which is likely to be highest in the pharmaceutical industry).
- The pharmaceutical industry spends the highest proportion of revenue on R&D (R%D intensity) among comparable industries by a large margin. With an R&D intensity of 14.7%, the pharmaceutical industry has a superior R&D intensity by almost ten percentage points over the closest comparator industry (consumer electronics having the second highest R&D intensity at 5.3%).
- The time period for developing a new product is longest in the pharmaceutical industry and the risk of the product failing to reach the market at the end of that period is still substantial, with a high attrition rate present throughout the R&D process
- The consequences of fragmented and complex regulation appear to have the biggest impact on the pharmaceutical industry. The majority of comparator industries face fragmented regulatory environments on a global level, however these issues seem to be manageable. The exception to fragmented regulation comes from the commercial aircraft manufacturing industry, who have unified regulation across the U.S. and Europe.
- Intellectual property protection seems to be most critical to the pharmaceutical industry as determined by calculation determining the premium afforded by patent protection, however the effective patent protection period can be shorter than for comparable industries due to the long time needed for R&D development prior to launch.
- The pharmaceutical, food, and automotive industries seem to be more competitive than the other comparable industries, as shown by the loss of market share of the largest companies over time in each respective industry.

- The analysis in this paper shows that the biopharmaceutical industry is one of the industries that spends the most on R&D (per new product and as proportion of revenue), takes the longest time to develop a new product, has arguably the most problematic consequences of fragmented and complex regulation, and intellectual property is both most crucial and lasts less time in practice.

The level of uncertainty for the biopharmaceutical industry is high and appears to be increasing, forcing companies to take more risks along the whole value chain

- Scientific advancement increases the complexity of drug discovery, research and development. The evolution of scientific knowledge in therapeutic targeting has increased this complexity, with major breakthroughs increasingly difficult to come by and incremental innovation becoming the main driver of progress.
- Complex and fragmented regulations contribute to the increasing costs of R&D. As a result of this more time and monetary investment are required to bring a product to market, higher uncertainty regarding product success remains present later in the development and following market launch and there is increased uncertainty surrounding length of time taken for processes of approval and access.
- Challenges in obtaining market access increase the uncertainty in securing potential returns on R&D investments. Once market approval has been gained on a regional level, further hurdles must be navigated at a country and local level.

- Increasing risks seem to require substantially higher returns to sustain the level of biopharmaceutical innovation and promote healthcare cost-effectiveness.

The level of biopharmaceutical innovation can be sustainable if collaboration increases, the level of uncertainty is reduced and risks adequately rewarded

- The biopharmaceutical industry deals with a fragmented stakeholder system, each player with different immediate targets. Similar to in other sectors, collaboration between stakeholders in the biopharmaceutical sector can create an environment that fosters innovation.
- The biopharmaceutical industry has already attempted to adapt its business model to the changing environment so it can better address the uncertainties and maintain the level of innovation. Examples of such adaptation include; using large datasets as adjuncts to clinical trials in order to boost value demonstration, exploring a shift from volume-based to value-based contracts and increasing the number of partnership agreements being struck between biopharmaceutical companies and healthcare systems.
- Reducing uncertainty for the industry and maintaining an appropriate level of reward are the two essential and interrelated steps needed to ensure healthcare systems remain sustainable and to continue contributing to improvements in human life. Further alignment between stakeholders and more investment in innovation is crucial for achieving this goal.



The biopharmaceutical sector provides high societal value to Europe but innovation becomes more challenging over time

Biopharmaceutical medicines have a very positive impact on human life

Over recent decades, the biopharmaceutical industry has transformed human health, through both greater life expectancy and better patient quality of life. That industry includes companies which produce innovative pharmaceutical products in addition to mature biotechnology companies (excluding generic pharmaceutical companies). It has been estimated that between 1982 and 2001 new chemical entities were responsible for 40% of the increase in length of life across 52 countries (1). One of the most significant impacts of the biopharmaceutical industry has been the dramatic increase in longevity for patients with acute diseases that were previously difficult or impossible to treat. It has also provided life-changing treatment solutions for patients with chronic diseases, allowing patients actively to participate in society and dramatically improving quality of life. Finally, the biopharmaceutical sector has played a key role in preventing the spread of, and in some cases even eradicating, infectious diseases through treatments, vaccination and education.

Looking ahead, the industry's continuing large investment of time and resources in medical advancement make it the sector most likely to produce significant public health benefits for the foreseeable future.

Improvements in global public health require substantial investments in biopharmaceutical innovation

Developing innovative biopharmaceutical medicines requires a high level of investment throughout the lifecycle of products. In particular, the investment during the later phases of product development can be substantial. Nor does investment end when a product

is launched. For example, the safety monitoring of new products that is required throughout the research and development (R&D) process then also continues into the post-launch phases of a product's lifecycle.

The biopharmaceutical industry employs a highly educated and specialised workforce

The biopharmaceutical industry requires a highly skilled workforce to create innovative medicines. A successful biopharmaceutical company depends on a talent pool of workers who can provide the right balance between strong scientific knowledge, commercial acumen and a strategic mind-set capable of navigating the rapidly changing healthcare environment. This diverse and valuable workforce makes the industry strategically important for the European Economic Area (EEA). Many of the leading biopharmaceutical companies were founded in Europe and a number are still quoted on European stock markets, confirming that Europe is a global force in biopharmaceutical innovation (2).

Greater insight into the biopharmaceutical business environment is needed as innovation becomes more challenging for the industry

The biopharmaceutical industry strives for continuous innovation. However, in the past decades the well-established biological pathways have been targeted for treatment, so innovation becomes more challenging as it will focus on new unexplored pathways. It is now technically and scientifically more difficult to address remaining health needs. For these reasons innovation in the industry nowadays tends to be incremental, rather than providing the major "leaps" in scientific advancement that were achieved in the past.



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Securing recognition and reward for this type of incremental innovation is increasingly difficult for the biopharmaceutical industry in an economic climate where governments are struggling to keep healthcare systems sustainable. This in turn increases the risk the industry needs to take for developing the next generation of innovative medicine.

In recent years, key changes in the business environment in Europe and elsewhere, combined with decreased spending on healthcare, have meant biopharmaceutical companies involved in innovative research have had to take higher risks for potentially reduced and decreasing rewards (3).

The aim of this research paper is to investigate and better understand:

1. How the business environment for the biopharmaceutical industry has changed;
2. How to define and quantify uncertainty and risk across a systematically selected group of comparable industries;
3. The consequences (in terms of uncertainty and risk) for the biopharmaceutical industry of changes in the business environment, compared with other sectors;
4. How these trends affect the sustainability of the biopharmaceutical business model and the future of innovation;
5. What lessons can be learnt from other industries to mitigate the uncertainty and risk for biopharmaceutical firms that result from changes in the business environment.

Uncertainty and risk are compared across selected industries

The main trends in the business environment directed the types of uncertainties and risks have been evaluated, with changes in market access, regulation and R&D challenges being the main features affecting the biopharmaceutical industry.

Risk-taking is an integral part of investment and business. In order to gain adequate returns on investments, risks need to be managed. Not all risks have an immediate impact, with some industries not facing the consequences of certain risks until several years after decisions have been made. Neither are all risks about seeking additional reward: in some areas of business risk-taking is necessary to stay active within the field.

Assessing risk and uncertainty is complex. In order to fully understand the risks involved in different industries, it is important to consider the components that lead to firms in that sector needing to take certain levels of risk. There are three main parameters that contribute towards risk in an industry: the business environment facing companies; uncertainty as a result of unpredictability in that business environment; and the ability of industry members to manage risk (5).

The business environment is defined as the combination of internal and external factors that influence the normal business operations of an industry member. These include factors such as clients, suppliers, competition, technological improvements and laws affecting different sectors.

Uncertainty arises because of an inability to reliably forecast future events. This is caused either by the current state of knowledge being incomplete, the current state of affairs having unpredictable consequences, or an inability to assign credible probabilities to possible outcomes. The business environment and uncertainty, in combination, determine the risks taken by members of an industry.

Finally, **risk management** is the discipline of minimising the likelihood of negative outcomes and the potential losses during uncertain and turbulent financial periods, while also creating value through the successful navigation of opportunities. Calculated risk-taking should be embraced in order to seize opportunities, as only by appropriately managing risk can an enterprise succeed in optimising value and success (5).

The challenge for our leaders is to respond to risk with the right mix of daring and reason... For this we need the best information we can get, the best judgment we can summon, and the best advice we can find.

Madeleine Albright
former U.S. Secretary of State

The risks evaluated during the risk management process are split into three main categories. Firstly, the external challenges faced by a company, which shape the choices and direction taken by industry members, these are considered to be **strategic risks**. Secondly, even if an optimal strategy is followed, **execution risks** arise when strategies are not carried out in an effective manner. Thirdly, influences that affect the ability of a company to operate legally and effectively within an industry represent **operational risks**. For example, an increase in the governmental regulation imposed on a company bringing a new product to market can increase the likelihood of the company being unable to comply with the regulations (6). These categories of risk, although not explicitly applied here, do provide insight in how different risks and uncertainties can impact a company.

When managed well, strategic and executional risks can lead to a positive impact on a business through increasing the success and value of a product. Operational risks, however, rarely offer the scope to secure additional advantage, as compliance with laws and regulations represents a requirement for operating within an industry. Increases in operational risk within an industry thus lead to greater risk-taking, but do not aim to result in additional return.

Changes in market access, regulation and R&D challenges have been the main features of the biopharmaceutical industry

The business environment within which an industry operates can be defined using PESTLE analysis (7), which covers political, economic, social, technological, legal and environmental influences on business.

To carry out a PESTLE analysis for this study, we analysed data from a range of sources in the business literature, including economic and medical journals, news articles and business to business communications. The main trends in the biopharmaceutical industry's business environment were then determined. The analysis demonstrated the breadth of uncertainty faced by members of the sector (Table 1).

Based on the results of the extensive literature review and opinions gained from interviewing experts in the biopharmaceutical industry, the three trends most likely to increase uncertainty in the biopharmaceutical industry are:

1. Market access challenges;
2. Fragmented and increasingly complex regulation;
3. Costs and challenges of scientific advancement.

Table 1: PESTLE analysis of the biopharmaceutical industry

Political	Aging demographic and chronic degenerative diseases are the next challenge. Governments are struggling to keep health and social expenditure sustainable. Health inequalities still exist between and within countries.
Economy	Expenditure on pharmaceutical R&D is stagnating in Europe. There is an increased focus by the global pharmaceutical industry on emerging markets. Large companies are consolidating to ensure pipeline competence in priority diseases.
Social	Patients are more knowledgeable and empowered, within limitations. Social responsibility towards the developing world is increasing.
Technology	New science is required to bring innovative products to the market. Availability of electronic patient data is improving.
Legal	Increasingly stringent and uncertain regulations are imposed, due to risk-aversion (e.g. pharmacovigilance), insufficient trust in industry (e.g. marketing) and new technologies (e.g. biosimilars). Trust is a key issue for this highly regulated sector and is under serious threat.
Environmental	Energy efficiency requirements are stricter. A constant threat exists of global infection outbreak e.g. Ebola.

Other industries were systematically selected to make meaningful comparison possible

According to the Bloomberg Industry Classification System (BICS), more than 60 industries are recognised as distinct from one another (8). From the start of our analysis, we recognised that not all industries were directly comparable because of the differences in the natures of the businesses. A process was therefore adopted to select a reasonable number of suitable industries for comparison against the biopharmaceutical sector.

To render the choice of comparable industries meaningful, a number of inclusion criteria were determined based on the main characteristics of the biopharmaceutical industry. These criteria were applied to a large number of industries defined by the BICS.

To establish comparable metrics for an industry against the biopharmaceutical industry, it was necessary **to have a tangible product** in the market. The biopharmaceutical industry has clearly defined products that can be quantified in terms of units sold, whereas some industries (such as asset management, banking or service industries) rely on a looser definition of a 'product' that is not readily quantifiable in a metric.

Another criterion considered necessary was the **level of R&D investment** made by the industry. An analysis of R&D intensity (as the percentage of revenue reinvested in R&D) was conducted for this purpose and industries with a greater focus on R&D were selected. This criterion reflects the high priority within the biopharmaceutical industry of reinvestment in R&D. By including this criterion, we ensured that comparator industries would be bringing innovation to the market (given the assumption that innovation requires investment in R&D).

The **level of maturity of the industries** was also taken into consideration, ensuring that only market areas as well-established as biopharmaceuticals were selected. Combined with the previous criterion, this also helped to ensure comparability of research intensity across the selected industries because R&D intensity in the early stages of an industry may change materially as the industry matures, hence comparison with mature industries would not be relevant. **Clearly definable industries** were required for the analysis, ensuring there was no ambiguity about the products covered by the industry classification. In some areas, the scope of products included within an industry was unclear. For example, "design, manufacturing and distribution" could incorporate aspects of multiple industries and so would be impossible to investigate the business environment faced by these industries.

Based on this analysis, five industries were chosen as comparable with the biopharmaceutical industry: automotive manufacturing, commercial aircraft manufacturing, consumer electronics, food manufacturing and generic pharmaceuticals.

Once the comparator industries were selected, an analysis to determine the main trends affecting each industry was conducted to enable comparison with the biopharmaceutical industry. In each case, the PESTLE approach was used, based on literature reviews and comparable with the approach taken for the biopharmaceutical industry analysis¹. This showed a significant difference in the uncertainties faced by different industries. (Table 2).

Metrics that matched the main trends were derived so that uncertainties and risks could be quantified

An 'Uncertainty Index' was then developed in order to produce practical outcomes from this study. This index aims to demonstrate how the three main areas of increasing uncertainty faced by the biopharmaceutical industry (market access challenges; fragmented and increasingly complex regulation; costs and challenges of scientific advancement) are affecting the five other industries included in the comparison.

¹ Interviews with Deloitte experts from other industries were carried out for most other industries.

Table 2: Main trends across analysed industries

Industry	Main trends
	Biopharmaceutical industry <ul style="list-style-type: none"> • Market access challenges • Fragmented and increasingly complex regulation • Costs and challenges of scientific advancement
	Automotive industry <ul style="list-style-type: none"> • Consumers looking for alternatives to outright purchasing • Increasing reliance on suppliers to drive R&D • Increasing environmental regulation
	Commercial aircraft manufacturing <ul style="list-style-type: none"> • Accelerating urbanisation increasing demand • Rapid pace of technological advances • Climate change and resource scarcity issues
	Consumer electronics <ul style="list-style-type: none"> • Shift in economic power towards emerging markets • Multiple-focus crossover devices • Value-driven and informed customers
	Food manufacturing <ul style="list-style-type: none"> • Volatility of sourcing raw materials • Shift towards online distribution • Increasing health-related regulation
	Generic pharmaceuticals <ul style="list-style-type: none"> • Regulation of expiration of patents • Shift from developed to emerging markets • Cost containment by Government and healthcare providers

Metrics were derived for these three areas of uncertainty so that their impact on the other industries could be compared with the biopharmaceutical sector². Selecting the right metrics was a combination of finding the best proxies for the uncertainties that need to be assessed and of having the right data available to measure these metrics. Hence, a long list of 15 possible metrics was considered for this analysis, using information derived from the PESTLE analyses. In a second stage, metrics were removed from this list if insufficient data were available to be able to compare all of the industries with one another³. The eight excluded metrics along with the reasons for exclusion are detailed in Table 3.

Table 3: Excluded metrics

Excluded metric	Reason for exclusion
Attrition rate of new products in development	These data are widely published for the biopharmaceutical and generic pharmaceutical industries, however they are not available for the other industries.
Regulatory change	Level of regulation is conceptually difficult to quantify. An industry may face a particularly stringent regulatory process, yet face little uncertainty within this framework. It is therefore difficult to know which aspect of regulation to attempt to analyse.
Patent life	Patents are applicable across the majority of sectors and do not differ between them, therefore are inappropriate for producing a metric.
Variation in sales	An attempt was made to analyse the variation in sales revenue over a one-year period, however this showed little meaningful difference between industries.
Time on market	Data on this metric was unavailable for most industries due to the difficulty in determining the differences between distinct product models and also the exact market removal dates.
Possibility of changing a product once on the market	This metric could not be clearly defined by objective criteria for the changes that can be made once on the market.
Rate of change in product portfolio over time	Data was unavailable for most industries.
Pricing differences across regions	Data was unavailable for most industries within the scope of this project.

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- 2 These metrics represent those factors that we can measure, however they do not capture all important uncertainty factors for the biopharmaceutical industry
 - 3 In some cases there was sufficient data for some of the industries but not for the others. Such metrics were also eliminated.

At the end of this process, seven metrics covering the biopharmaceutical industry's three main areas of growing uncertainty were deemed appropriate for inclusion in the analysis:

1. **The amount of investment required for each product to reach the market.** This was taken from peer-reviewed journals where available; however, for industries for which no data were published, information was taken from case studies⁴. (Scientific advancement.)
2. **R&D intensity**, calculated by averaging the percentage of revenue reinvested in R&D by industry members in 2013 using Bloomberg data. (Scientific advancement.)
3. **The amount of time required to take a product from initial inception to market launch** (or the end of the development period if different to time of launch). (Regulation.)
4. **Possibility of complete product failure late in development**, or if there are processes available to an industry to prevent this occurring. (Regulation.)
5. **Existence of differences in regional regulation**, and if so whether they have a significant impact on the development process of a product. (Regulation.)
6. **The competitive landscape of the industry.** This has been captured by determining the market share of the top 10 companies⁵ in 2007 and again in 2012. The magnitude of loss in market share over this period was taken as an indicator for the volatility of each sector. (Market access.)
7. **The importance of patenting** as a mechanism for protecting intellectual property. A study was utilised (Arora et al (36)) that used survey data from the US manufacturing sector to estimate the increase in the value of innovation that was associated with the use of patents, with a higher value increment indicating a greater importance of patenting for that sector. (Regulation, market access.)

4 The most up-to-date data available were taken for this analysis and all figures were adjusted to year 2013 money using the consumer price index.

5 The commercial aircraft manufacturing industry contains just 12 companies, therefore the change in market share of the top 5 companies was considered to ensure comparability.

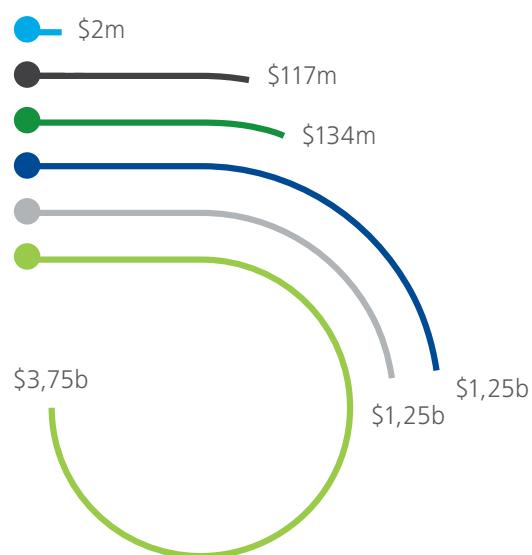
The biopharmaceutical industry encounters a higher level of uncertainty in key areas than comparable industries when developing innovative products

As the analysis in the previous chapter demonstrated, significant differences exist in the uncertainties faced by different industries. In this chapter we provide a detailed breakdown of the results from our analysis.

The biopharmaceutical, automotive and aircraft manufacturing industries spend the most on R&D per new product

The R&D requirement of different industries varies dramatically, due to the different complexities of bringing products to market. The aviation industry spends \$2.5 billion - \$5 billion on a new model of aircraft (9) (10), although this can sometimes be dramatically higher for projects that overspend (for example, in the commercial aircraft manufacturing industry, the development of Concorde is reported to have cost in the region of €1.6 billion by 1976, the equivalent of €8.2 billion in 2013 money (11)). However, after the high initial costs, a single aircraft then sells for hundreds of millions of dollars. The automotive industry also invests a substantial amount of money up front, spending in the region of \$1 billion - \$2 billion for a new model (12). As with the aviation industry, some models require extra investment and there have been cases where up to \$6 billion has been spent (13). However, the high development cost of complex products such as airplanes and cars comes mainly from the engineering investment, including the high costs of setting up manufacturing plants and retaining a large R&D workforce. In comparison, the biopharmaceutical industry will have spent \$500 million - \$2 billion purely on R&D per one new product (14), with developmental manufacturing costs then representing a much smaller proportion of overall R&D costs than in the aviation and car industries (Figure 1). (It should be noted that in one respect these figures are all underestimates in that they do not include the R&D investment written off for products that are abandoned while still in development.)

Figure 1: Estimated average monetary investment required on research and development per one new product (2013)



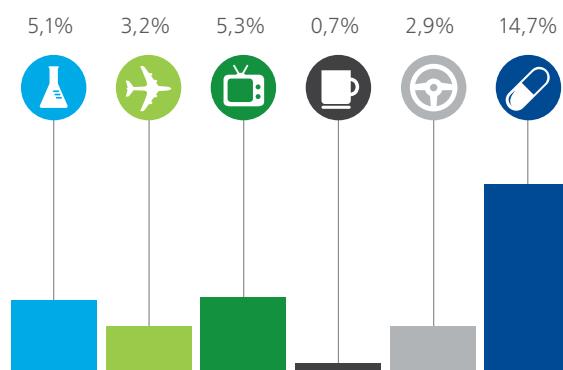
It is difficult to find data on the effort required to research and develop products for the consumer electronics industry due to the secretive nature of the development process. However there have been two widely-reported examples where R&D costs for new and challenging products have cost in the region of \$100 million - \$168 million (15) (16). Food manufacturing has slightly lower R&D costs than the electronics industry, in the region of \$83 million – \$152 million (17) per one new product. Despite this more modest investment, once a strongly branded food product has a hold on the market, it is challenging for competitor companies to capture market share from it.

The generic pharmaceutical industry relies on lower development costs for its business model to work, meaning that to bring a “new” generic to market costs in the region of just \$2 million (18). Thus, as measured by this metric, the generic pharmaceutical industry takes the lowest risk when bringing products to market, despite the need for continued pharmacovigilance once on the market.

The biopharmaceutical industry spends the highest proportion of revenue on R&D among comparable industries

In comparison to the other industries, the biopharmaceutical industry has the highest R&D intensity, with a substantially higher percentage of revenues reinvested. The biopharmaceutical industry reinvests 14.7% of revenue back into R&D, with consumer electronics being the next most research intense industry at 5.3% (Figure 2).

Figure 2: Percentage of revenue reinvested in R&D



When considering the risks taken by industries, it is most relevant to consider R&D investment in terms of intensity as this represents the proportion of annual revenue reinvested. However, it should be noted that the largest overall R&D investment in absolute terms comes from the automotive industry, despite having an R&D intensity of just 2.9%.

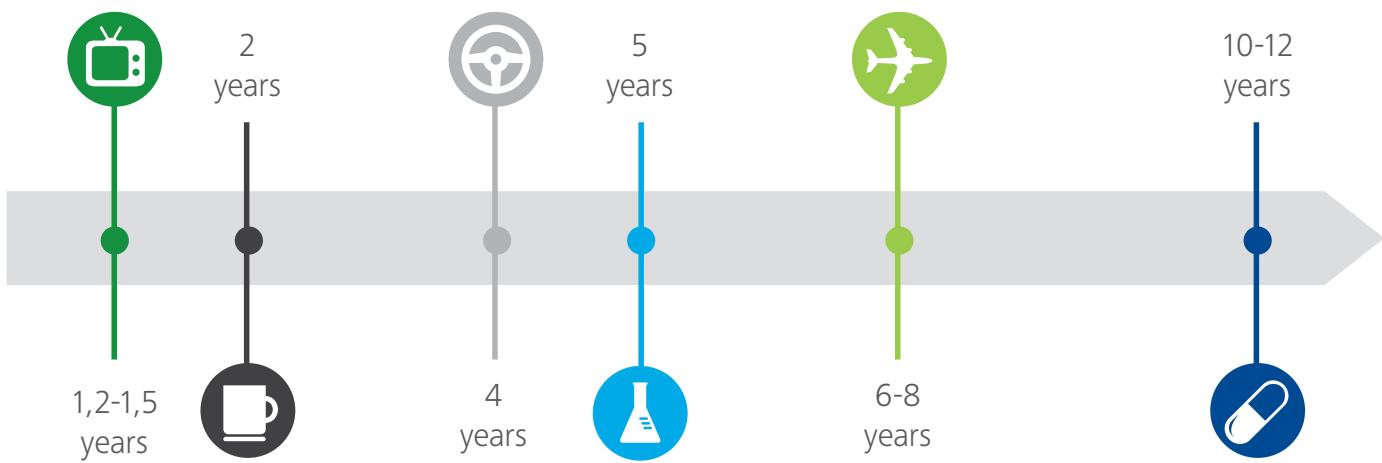
The time period for developing a new product appears longest in the biopharmaceutical industry and the risk of the product failing to reach the market at the end of that period is still substantial

Biopharmaceutical products are difficult to develop and bring to market and there is an extensive literature looking at the long periods of time required for potential chemical, biochemical or biological products to qualify as safe and efficacious for used in clinical practice (14)141 / id}(19). Figure 3 shows how the periods from inception to launch vary between industries in our analysis, and that this period is longest for biopharmaceuticals.

Different industries included in our comparison face different levels of uncertainty over whether a product will ever make it to market and if there is still a serious chance of product failure late in the development process.



Figure 3: Years required to bring a product from inception to launch





In the case of the generic pharmaceutical industry, every product will successfully reach the market (under a chemical name rather than the proprietary version produced by the biopharmaceutical industry) unless there are problems with the overall quality of the manufacturing processes. This means that market launch is predictable, thanks to the past precedent set by the equivalent proprietary drugs, with the exception of a small number of biopharmaceuticals with a complex production process that is very hard to replicate (for example, the process for producing goserelin injections for treating prostate cancer is particularly difficult to replicate (20)).

Industries manufacturing products that are modular in nature face less risk of failure in later stages of development. For this type of product, faulty or

ineffective parts can be readily replaced by more appropriate, working parts. Using the commercial aircraft manufacturing industry as an example, if a failure occurs in a single module of the plane, it does not stop the development of the product as a whole. The concept of modular development is also applicable to the automotive industry, where each project has a pre-defined stage at which a “go or no-go” decision is made as to whether development should be continued. Beyond this point development will be seen through to market launch and the only relevant type of failure is commercial failure.

Despite the modular nature of the consumer electronic products, failure of one component can lead to the failure of an entire project (21), for example if a battery used in a product is found to contain an outlawed toxic chemicals, the whole product may be completely removed from the market. However, this issue could be considered an operational uncertainty as it can be avoided through a good understanding of, and strict adherence to, regional regulation during the R&D process.

In Europe, the European Food Safety Authority (EFSA) provides assessments and advice on all risks associated with the food chain and any food products and ingredients need to satisfy safety regulations prior to being granted market access. It is therefore possible to face failure at any point in the development process, with products being prevented from entering the market (22). This is also the case in the USA, where risk assessment on food products is carried out by the US Food and Drug Administration (FDA), which determines whether certain foods should be allowed to reach the U.S. marketplace (23).

The biopharmaceutical industry faces the risk of complete failure at all stages in the R&D process. There is a large body of work focused on the attrition rate in the pharmaceutical industry, but of particular note is the fact that 31.5% of molecules that make it to phase III clinical trials fail to achieve market access (24). A very significant amount of investment (hundreds of millions of dollars) is lost every time a product fails at a late stage. The cost of these expensive failures has to be accounted for by the sales of the few molecules that successfully reach the market, meaning that the cost of developing a new medicine is in the region of \$5 billion on average if the costs of both failed and successful molecules are taken into consideration (25), compared with \$1.25 billion if the failures are not included in the calculation (Figure 1).

case study

The consequences of fragmented and complex regulation appear to have the biggest impact on the biopharmaceutical industry

The automotive industry faces the challenge of fragmented regulatory regimes, with each market having independent regulation for different aspects of production. For example, rules on environmental factors including emissions, noise control and fuel economy can vary to a large degree between different regulators. This has significant implications for companies in terms of the markets they are able to target and the increased costs associated with targeting markets with divergent regulatory policies (26). Manufacturers are seeking to reach convergence on safety regulations across different regions (27). However, even if this is not achievable, in contrast to the biopharmaceutical industry it is usually possible for automotive companies to produce vehicle models for different markets that differ only slightly, thus avoiding the need to produce completely new products or to withhold a product from a market completely.

The consumer electronics industry similarly faces a divergent range of regulations, and this is recognised as an impediment to free trade at a global level (28). Technical differences between regions also restrict compatibility between some markets. For example, 4G data networks in the USA are different to those in Europe, making many phones incompatible between the two regions and adding to the cost of producing phones for both markets. However, these technical constraints can be addressed through market-specific versions.

In the food manufacturing industry, large differences were observed regionally in the effect of regulation. On genetically modified (GM) foods, for example, Europe has imposed much stricter restrictions on the cultivation and use of GM food crops compared to the USA, with the political climate in Europe seen as the main influence on these decisions (29). Differences in regulation on food products also extend more generally to labelling and the provision of nutritional information, demonstrated by the contrasting approaches by the U.S. Food and Drug Administration (30) and European Commission legislation (31). However, these practical issues are largely surmountable.

The commercial aircraft industry is the only sector included in our analysis that has uniform regulation across the EU and USA (32). Although a number of

Product recalls



When products are tested prior to market launch, all quality and effectiveness standards must be adhered to, as set out in the relevant industry regulations. This is particularly true for the automotive industry, which has one of the largest, most descriptive set of regulations for bringing products to the market.

Once a product has been launched on the market, it is in effect being tested among a much larger proportion of the population, which means that rare defects and side effects are more likely to appear. An example of this was seen in January 2014, when Tesla Motors, a manufacturer of electric cars, initially had to issue a recall action concerning 29,000 charging adaptors in its Model S car, due to the unit overheating and presenting a potential fire hazard. Automotive manufacturers are typically allowed to work behind the scenes with regulators (in this case the US National Highway Traffic Safety Administration) to negotiate the timing and scope of product recalls. This can result in a narrower range of models, or only cars built in certain factories, being recalled, thus lowering the overall cost to the company of the recall. In this particular case, a software update provided by Tesla Motors fixed the faulty units without any actual recall needing to take place.

However, if similar safety worries are present in a large-population use of a biopharmaceutical the biopharmaceutical industry has no choice but to withdraw the product from the market. Whereas other industries can employ "damage limitation" strategies if a product faces safety issues on the market, no such luxury is afforded to the biopharmaceutical sector due to the risk averse nature of the healthcare industry.

other industries appear to be striving towards this type of harmonisation of regulation, the commercial aircraft manufacturing industry appears to be the only sector among those we studied that has achieved this goal. It provides a good example of how harmonisation of regulation can lead to a more transparent relationship between regulatory agencies, allowing for increased efficiency in the R&D process.

As with most other industries, the generic pharmaceuticals industry faces differences in national regulation, in this instance on issues such as proving bioequivalence. In some regions this may necessitate additional testing of bioequivalent products prior to market access approval in order to comply with local requirements. There is, however, a continual process of harmonisation occurring in the industry, meaning the challenges of differences in national regulation should become less of an issue in the future (33).

For the biopharmaceutical industry, the impact of fragmented and complex regulation is felt globally and across all aspects of the business. In Europe, harmonisation of business processes among European Union countries was achieved through the establishment of European Medicines Agency (EMA) in 1995 (known as the European Agency for the Evaluation of Medicinal Products until 2004). However, inconsistencies must still be dealt with at all levels. Globally, there have been a number of cases where the identical biopharmaceutical product has been approved by the Food and Drug Administration (FDA) for use in the US but rejected by EMA. Within the EU itself, significant differences still exist between EU countries, all of which creates additional levels of bureaucracy in the approval process. Similarly some countries outside the EU (for example, Turkey and Russia) can require that individual Good Manufacturing Assessments are carried out prior to approval of biopharmaceutical products, adding further costs and time to the approval process.

After differences in national regulations have been taken into consideration, products in the biopharmaceutical industry can still face further barriers to market availability. National regulatory approval allows for the legal prescribing of a drug within a country, however authorisation to prescribe a drug is most often determined at a local level, meaning access to a drug could be further fragmented by budget prioritisation by local decision-makers. These discrepancies – from global to local level – in the approval of innovative biopharmaceuticals in different regulatory regions inevitably lead to inconsistency of treatment availability (34), even before taking into consideration the length of time needed to set pricing and reimbursement levels and the delays associated with inclusion in local guidelines.

Across the industries in our analysis, the consequences of fragmented and complex regulation appear to have greatest effect on the biopharmaceutical sector, due in part to the nature of the product but also because of the particularly high cost of complying with regulations in different regions. For example, when considering fragmented regulation, the main difference between the generic pharmaceuticals and innovative biopharmaceutical industry is the cost of complying with the regulations in different regions. If an extra bioequivalence study is necessary to allow market access for a generic pharmaceutical, it will cost approximately \$108,000 (35). By comparison, in the biopharmaceutical industry, regulators have the capacity to request a new phase III study to be conducted prior to approving the drug for use, which would cost in the region of \$115 million dollars (14).

The challenge of fragmented and complex regulation also persists throughout the lifecycle of a drug. As mentioned previously, after a product has been launched further assessments on the effectiveness and safety of the technologies may need to be submitted to the authorities to meet requirements for the ongoing collection of pharmacovigilance data and real-world evidence of continued efficacy and cost-effectiveness (36)).

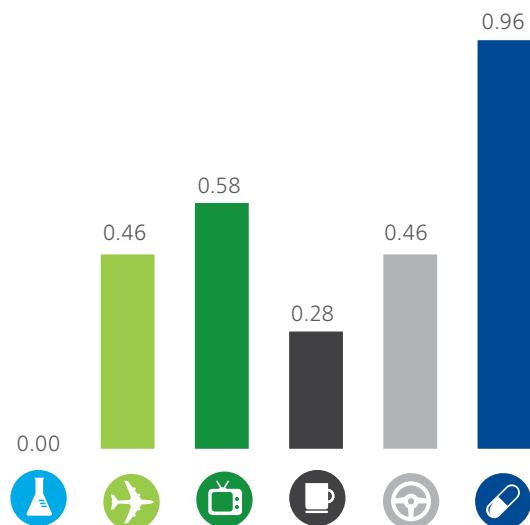
Intellectual property protection seems to be most critical to the biopharmaceutical industry but the effective patent protection period can be shorter than for comparable industries

Protection of intellectual property (IP) has differing levels of importance across industries. A detailed evaluation of the literature was carried out during the preparation of this report to discover methodologies/studies to measure the value of intellectual property rights for different industries. Arora et al (36) carried out a study, using survey data from the US manufacturing sector, to estimate the increase in the value of innovation that was associated with the use of patents (the patent premium); a higher value increment indicated the greater importance of patenting for that sector.

This study was used as the basis for our comparison on this subject. We were able to use the industry sector definitions from Arora et al. (37) as proxies for those in our analysis:

- Drugs and medicines (for the biopharmaceutical industry);
- Other electrical equipment (for consumer electronics);
- Aircraft and missiles (for commercial aircraft manufacturing);
- Transportation, exc. Aircrafts (for automotive);
- Food, kindred and tobacco products (for food manufacturing).

Figure 4: Incremental value of patent protection per industry



The patent premium analysis shows that intellectual property (IP) protection is of greatest importance to the biopharmaceutical industry by some margin (Figure 4)⁶. This analysis can be used as a proxy for the ease with which similar products can enter the market once the patent has expired. All the other comparator industries had far lower patent premiums, with all but that for consumer electronics below half what was seen in the biopharmaceutical industry. (The patent premium in the generics industry was assumed to be zero as by definition the industry is only involved with products that are no longer protected.)

Investors interviewed for this study have also supported this view, stating that without strong IP protection investing in the production of innovative medicines would not be feasible.

⁶ Represents a coefficient quantifying the additional value of returns afforded by a product having patent protection, compared to the returns expected from not having patent protection.

IP protection is the engine of innovation. It is the primary mechanism for ensuring that companies have the right incentives for investing in R&D. The IP protection means that those first filing a patent have guaranteed market exclusivity for a certain period; the term of patent is generally 20 years from the filing date of the application, providing a period during which the company generates profits and has the chance to recoup its investment ((38)).

Patent protection for biopharmaceutical products is especially important compared to other industries as the actual manufacturing process can be copied for a fraction of the investment cost that is required for the research and clinical testing of an innovator product. In addition, given that the approval process for generic products is much simpler and quicker compared to originator products, generic producers can enter the market immediately after loss of exclusivity. The commercial value of an innovator product is thus significantly reduced once the patent protection period comes to an end (39). In some instances this market entry even takes place before expiry date with what are known as 'at risk' launches (40). Biopharmaceutical companies must plan to earn sufficient financial returns to at least recoup the cost of R&D investment before facing a competitive generic product. Since capital investment in the biopharmaceutical industry is disproportionately allocated to laboratory research and clinical trials (rather than the actual manufacture of the final product), patent exclusivity is the most effective way to protect returns on that investment.

As mentioned, the patent protection period is 20 years for innovator products across all industries (41), with the period of protection usually starting from when the patent is granted. However, the effective patent life of a biopharmaceutical is shorter than that of most other products because the comparatively very lengthy process of attaining market approval takes place within the protected period (42). By the time a product is on sale, the number of protected years is often much lower than 20 years. When development and approval periods increase, this issue is further exacerbated.

The importance of patent protection also varies substantially across industries in terms of the extent to which patents define differences between products.

In the consumer electronics industry, for example, the number of patents per single new product is high, particularly in smartphones where even screen unlocking gestures can be patented. Conversely, in the biopharmaceutical industry the patent almost equals the product, hence making its protection even more crucial for any company to operate. As a consequence other industries can rely on multiple patents to protect their product, whereas the biopharmaceutical sector is highly dependent on at most a few patents for a single product.

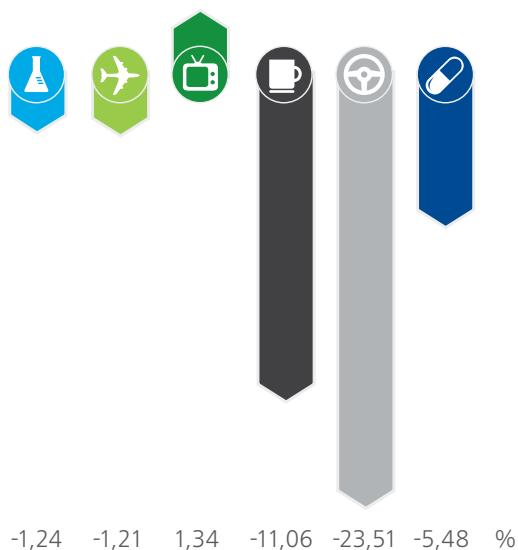
The biopharmaceutical, food, and automotive industries seem to be more competitive than the other comparable industries

Competition is arguably the greatest driver of innovation in a free economy and an optimum level of competition is desirable in every market and industry. However, from an industry perspective high levels of competition also increase uncertainty.

In order to compare the level of competition between industries, the consolidation and change in joint market share of the top 10 companies within a sector was measured using Bloomberg proprietary data (8). The top 10 members of each industry included in the analysis were identified and their total sales calculated for both 2007 and 2012. The overall sales of the entire sector were also calculated in each case, for both of the years in question. The proportion of the market held by the top 10 companies within the sector was determined for the two selected years and the difference calculated. A five year interval was used to give a robust view of the industries over time.

The findings of this assessment indicate that competition in biopharmaceuticals is moderate. The automotive industry is most susceptible to competition, with the 10 largest members of the industry losing 23.51 percentage points of their market share between 2007 and 2012, despite the industry being made up of just 51 members. Food manufacturing also witnessed relatively large loss of market share, showing an 11.06 percentage point decline, but with a much larger number of companies within the industry (n=169) (Figure 5).

Figure 5: Change in joint market share of the 10 leading companies over a five year period



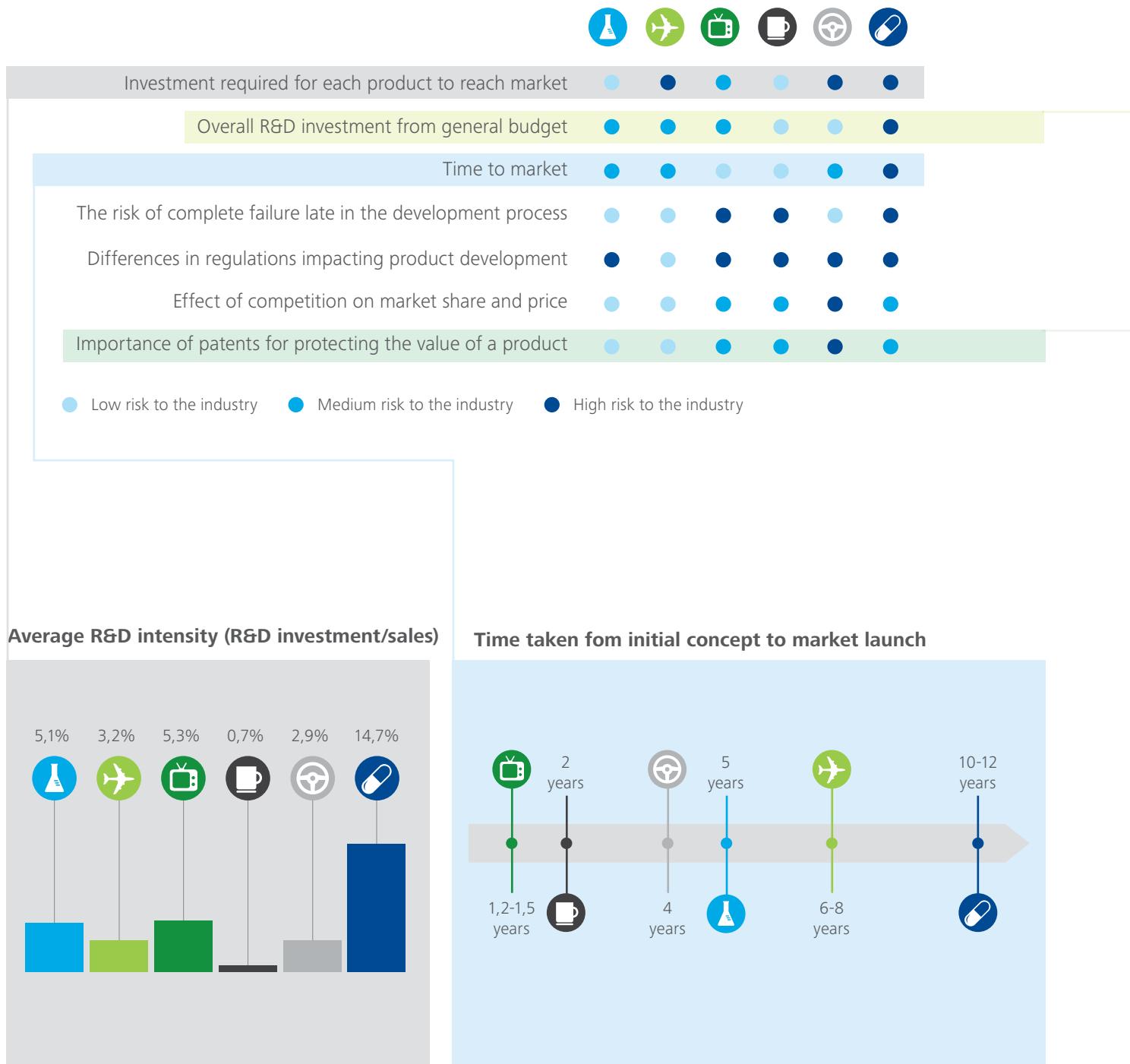
The commercial aircraft manufacturing and generic pharmaceutical industries both show a market share loss of less than 2 percentage points, indicating the stability of this sector. The analysis suggests generic pharmaceutical companies face lower levels of competition in comparison to innovator pharmaceutical companies. The consumer electronics industry showed a consolidation of 1.34 percentage points over the five year period, with the 10 major industry players increasing their share of the market.

The key areas of uncertainty for the biopharmaceutical industry appear to have less impact on other comparable sectors

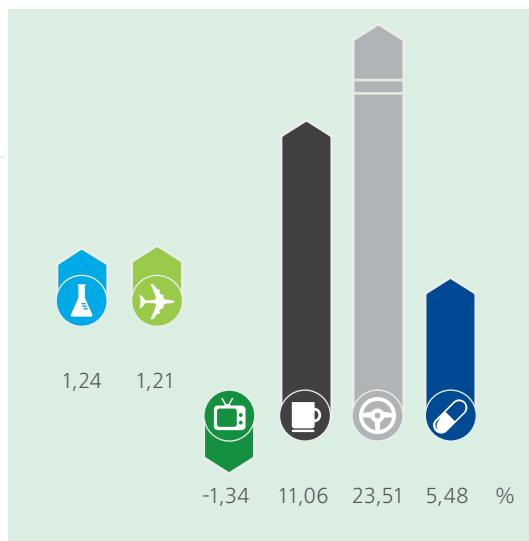
The analysis above used our seven metrics to investigate how the aspects of uncertainty most important to the biopharmaceutical industry impact on the selected five comparator sectors. Overall, as measured by the metrics, the three areas of increasing uncertainty included in the study (market access challenges, fragmented and increasingly complex regulation; costs and challenges of scientific advancement) appear to pose a greater burden for biopharmaceuticals than for the other industries that we reviewed. The analysis showed that the biopharmaceutical industry is one of the industries spending the most on R&D per new product, it spends the highest proportion of revenue on R&D among comparable industries, it takes the longest time to develop a new product, the consequences of fragmented and complex regulation are arguably most problematic, and intellectual property protection is both most crucial and often lasts less time. On only the question of competitiveness within the industry do biopharmaceutical companies face a lower challenge.

It is against this background of uncertainty that innovative biopharmaceutical products make an essential contribution to improvements in population health. Bringing new treatments to patients thus involves managing high levels of risk. However, the value to medical advancement provided by biopharmaceutical innovation can only emerge if it is possible for the industry successfully to negotiate the demands of the business process while also maintaining an appropriate level of reward. It is in this context that the risks along the value chain need to be properly recognised and efforts then made to ameliorate them.

Index of Challenges Facing Industry



Change in total market share held by top 10 companies from 2007 tot 2012



Investment required to launch products in each market



Generic pharmaceuticals



Commercial aircraft manufacturing



Consumer electronics



Food manufacturing



Automotive



Biopharmaceuticals

For a detailed list of the metrics please see the Appendix.

The level of uncertainty for the biopharmaceutical industry is high and appears to be increasing, forcing companies to take more risks along the whole value chain

The uncertainty in the biopharmaceutical industry spans the entire value chain

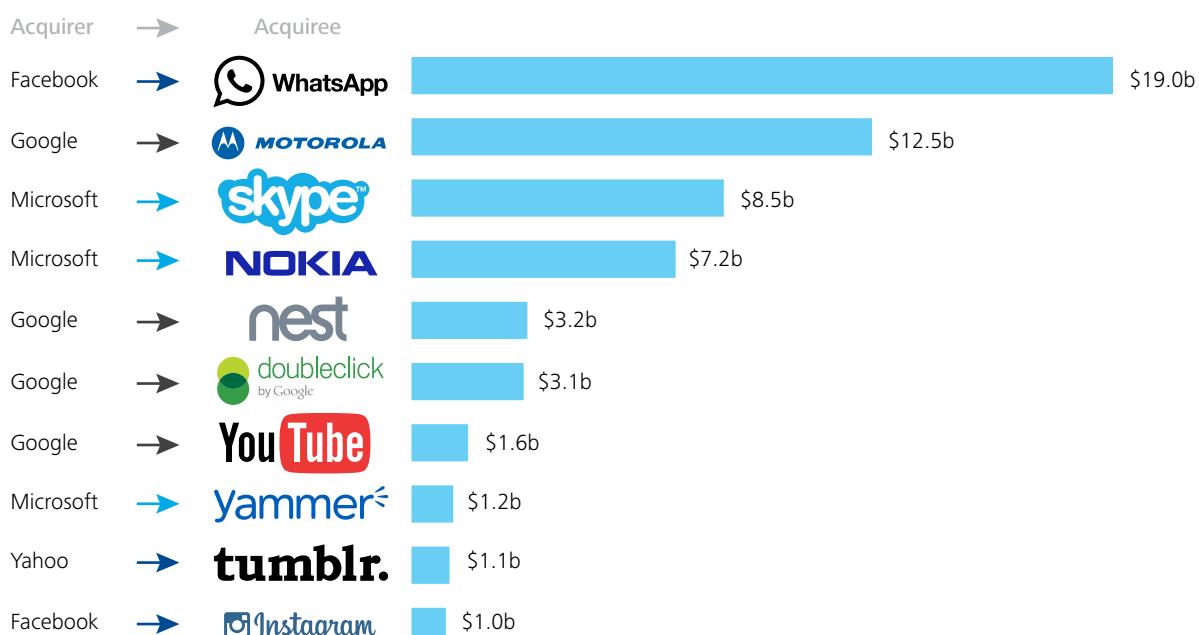
The results of the cross-industry analysis in Chapter 3 demonstrated that the biopharmaceutical industry faces a significant level of uncertainty across the whole value chain, from drug discovery to post-launch pharmacovigilance. From the perspective of industry, the trends identified in the previous chapter are creating an environment where the risks associated with innovation are increasing, while the potential rewards either remain static or decline (43).

The increasing uncertainty falls into the three main categories, as outlined in our original PESTLE analysis in Chapter 2. In this chapter, the implications of growing uncertainty in each of these areas is investigated.

Scientific advancement increases the complexity of drug discovery, research and development, leading companies to adopt new approaches

The evolution of scientific knowledge in therapeutic targeting has made the R&D process substantially more complex than previously experienced in the biopharmaceutical industry. The successes of recent decades has inevitably made it harder for today's researchers to identify major new breakthroughs so progress these days is more often made incrementally, as mentioned in Chapter 2. New areas of interest, such as genetic markers and personalised medicine⁷, show promise but are still at an early stage. Given this increased complexity of identifying new therapeutic biological pathways, the R&D process has become more fragmented as well as carrying a higher risk of failure. However, the scientific advancement holds great promise for new forms of treatment in the future that can result in radical improvements in health outcomes.

Figure 7: High profile takeovers in consumer electronics (45)



⁷ Personalised medicine involves the division of patient populations into sub-groups based on their individual biological genetic and genomic characteristics. It creates the potential for more targeted prescribing of medications, however means that technologies will be further controlled by regulatory agencies at the end of the approval process.

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In this context, the early research stage in the biopharmaceutical industry is becoming more reliant on the acquisition of externally identified target companies and molecules (44) and forging partnerships with public and academic institutions. A similar business model can be seen among large information technology corporations, which are opting to purchase more narrowly-focused companies in order to acquire promising technologies that can be developed using the funding and infrastructure of the larger company (Figure 7). The automotive industry also shows some similarities to adopting an “outsourcing” model, in that it now relies on suppliers to generate the majority of the innovation seen within the industry.

While some large biopharmaceutical companies do still hold the view that internal R&D is important for continuing innovation (46), others are focusing less on internal R&D and more on target acquisition, streamlining their research efforts in an attempt to improve the efficiency of their drug discovery processes (47). For the future of the biopharmaceutical industry, such a shift would represent a major step away from the traditional high level of direct R&D investment. One prominent example of the trend is an emerging biopharmaceutical company, Valeant, which has adopted this approach as its main business strategy, having most recently acquired Medicis Medical Corporation in 2012 and subsequently made over 300 people redundant and implementing a cost-cutting exercise of approximately \$225 million (48;49). This new research model could be sustainable if the smaller innovator entities (i.e. start-up companies and academic spin-offs etc.) were offered appropriate incentives and financial investment to become operational, either from public or private sources. However, an overall decrease in R&D investment by large biopharmaceutical companies could still have negative consequences. Overall growth in R&D healthcare investment in Europe has already been slowing since 2008, with an absolute decline in public health R&D seen in 2011 (50). While this trend clearly coincided with a global economic recession, it illustrates how investment in innovation is always potentially vulnerable to outside factors.

More resistant bacteria, but fewer new antibiotics

The golden age of antibiotic discovery between 1929 and the 1970s saw more than 20 new classes of antibiotic come to market. Since then, only two new classes have been launched. In particular, we have had no new classes of antibiotics to treat Gram-negative bacilli (GNB) for more than 40 years. Meanwhile, antibiotic resistance continues to spread rapidly, particularly among GNB.

There are three principal causes of the antibiotic market failure. The first is scientific: the “low-hanging fruit” in terms of scientific advancement have been taken. Thus, discovery and development of antibiotics has become scientifically more complex, more expensive, and increasingly time consuming. The second cause is economic: antibiotics represent a poor return on investment relative to other classes of drugs due to the absence of appropriate incentives to develop medicines for which use will be restricted. The third cause is regulatory: the attitudes of regulators and payers have discouraged development of so-called “me too” products and have required increasing amount of information to win approval, such as evidence from superiority or non-inferiority trials.

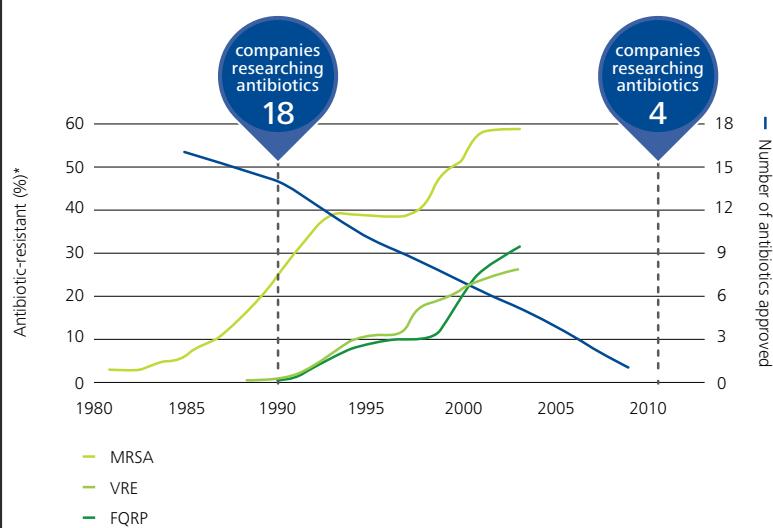
There is a seemingly low societal willingness to pay for antibiotic treatments. In addition, (as with most biopharmaceuticals) R&D costs are substantial and the time commitment is lengthy to bring a new drug to market. This vicious cycle has caused many drug makers to abandon antibiotic R&D programmes in favor of those for chronic diseases that have a greater potential for long-term financial return. Without new antibiotics, doctors and patients are forced to rely on currently available medicines.

As a result of the misalignment between business rewards and the societal value of antibiotics, there has been a significant drop in innovation in this field in recent years despite the increasing need for innovative treatments. There is a severe gap between the burden of infection due to multidrug-resistant bacteria and the development of new antibiotics to tackle the problem (Figure 10), despite the increasing threat that antibiotic resistance represents around the world. In the European Union, for instance, it has been estimated that about 25,000 patients die annually from infections from a selected group of multidrug-resistant bacteria, and that these superbugs account for extra healthcare costs and productivity losses of at least EUR 1.5 billion each year (63).





Figure 10: The declining industry commitment to antibiotic discovery



* Proportion of clinical isolates that are resistant to antibiotic. MRSA, methicillin-resistant *Staphylococcus aureus*. VRE, vancomycin-resistant *Enterococcus*. FQRP, fluoroquinolone-resistant *Pseudomonas aeruginosa*.

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Complex and fragmented regulations contribute to the increasing costs of R&D

The regulatory environment faced by the biopharmaceutical industry is becoming increasingly challenging due to regulators becoming more risk averse and, for example, demanding safety evidence based on real-world data (51). This heightened risk aversion can even lead to biopharmaceutical industries failing to obtain market approval as a result of changes in regulatory requirements that have occurred during product development. In addition, the fragmentation of regulation also creates uncertainty in the industry, as scientific evidence presented by the biopharmaceutical industry is always open to different interpretation by each regulator. For this reason, one regulator may approve an innovative pharmaceutical while another may defer or reject it based on the same evidence; for example, the outcomes of the approval process for gemtuzumab ozogamicin was significantly different across the EMA, US FDA and Japan's Pharmaceuticals and Medical Devices Agency (PMDA) (52)).

In the pharmaceutical industry, changes in regulation have a substantial impact on R&D processes as industry members must quickly adapt and comply in order to ensure their products still meet regulatory requirements. The impact of such regulatory uncertainties are:

1. More time and monetary investment is needed to bring a product to the market.
2. Higher uncertainty regarding success remains present later in the development process and following market launch.
3. Uncertainty is increased surrounding the length of time taken for the processes of approval and access.

These issues are not factored in – either formally or informally – when the value of new technologies is evaluated and rewarding mechanisms set up.

Challenges in obtaining market access increase the uncertainty in securing potential returns on R&D investments

After a molecule has received regulatory approval, there are still a number of market access challenges that need to be successfully negotiated in order to achieve optimal access. Levels of access are usually greatly dependant on the policies in different countries, with EU level standardised pricing only granted when a product's high medical value is acknowledged by the regulatory bodies. A great source of uncertainty comes from the discrepancies in post-launch time to market across different European markets. Time to market varies greatly across European markets: some markets allow instant access to medications (for example UK and Germany), whereas others have a delay period (for example Belgium and Portugal), during which the treatment is evaluated further (53). This delay in allowing access to medication in practice shortens the exclusivity period of a treatment technology and prevents it from rapidly achieving widespread use (53). For example, it may take more than a year after market authorisation for a biopharmaceutical technology to reach patients in Belgium, a country whose economy benefits greatly from direct investment in the area of medical technology (54).

Within countries, different payers may also potentially require different data and ultimately have the autonomy to make their own reimbursement decisions based on the same input (which can take up to two years in some European countries). Such fragmented regulation creates additional data requirements prior to reimbursement being obtainable. These issues are exacerbated by the uncertainty that has accompanied widespread austerity measures across Europe, where there has been a major squeeze on spending on pharmaceuticals, driven by changing prescribing behaviours, headline price cuts, reference pricing calculation alterations, stricter reimbursement controls, smaller distribution margins, introduction of rebates and clawbacks, patient co-payment increases and greater use of tendering to lower prices (55).

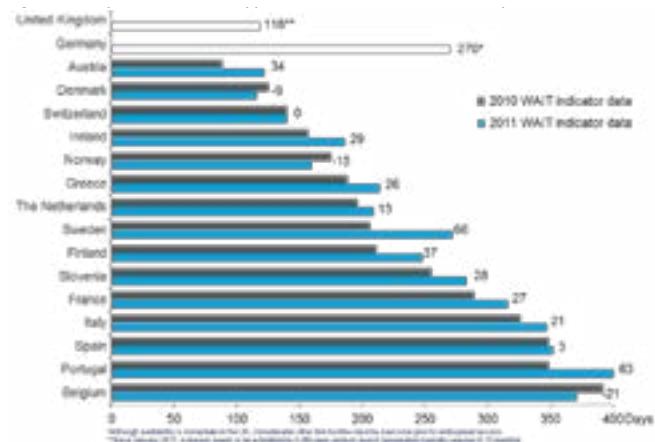
Taken together, these market access challenges are causing the return on investment for biopharmaceutical companies to come under increasing pressure.

Delayed access to treatment for breast cancer increases the risk of death

Women who have a three month delay in breast cancer treatment have a 34% increased risk of breast cancer death. This was the result of a retrospective study among 43,359 female patients diagnosed with breast cancer. Hence the investigators of this study recommended rapid access to treatment for all women with breast cancer (65).

A delay in access to medication is not uncommon. According to data from the EFPIA (Figure 11)(53) (54), the delay between EMA approval and market access is on average 8 months and is increasing in most European countries. This leads to increasing worries that patients are not getting timely access to innovative medicine and will suffer serious consequences from that delay.

Figure 10: The declining industry commitment to antibiotic discovery



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100 new Alzheimer's drugs in development but only 3 Alzheimer's drug wins in 13 years.

Since 1998, there have been 101 failed attempts to develop drugs to treat Alzheimer's. In that time, only three new medicines have been proved to treat the symptoms of Alzheimer's disease; so for every research project that succeeded, 34 failed to yield a new medicine.

The most closely watched experimental treatment for Alzheimer's disease, **bapineuzumab**, proved ineffective in its first large clinical trial, dealing blows to confidence in the field, to a prominent theory about the cause of the disease, and to the three companies behind the drug.

However, in the face of deeply disappointing setbacks, researchers take the findings from unsuccessful projects and use that new information to **move forward**, with the understanding that scientific progress and success can only be built over time, requiring patience and persistence. They know that treatment with new medicines is likely to be our best tool for preventing and fighting Alzheimer's disease, so they continue to work to understand the disease and translate that knowledge into treatments. Dedicated researchers are currently working on **nearly 100 new medicines in development** for dementia.

Alzheimer's currently accounts for an estimated \$200 billion a year globally in healthcare costs. The predicted rapid rise in cases due to the aging population could cause that figure to soar to \$1 trillion by 2050. A breakthrough treatment that delays onset of Alzheimer's by five years could save nearly half that medical cost (64).

Increasing risks seem to require substantially higher returns to sustain the level of biopharmaceutical innovation and promote healthcare cost-effectiveness

The impact of further increases in the levels of uncertainty in the biopharmaceutical industry and healthcare systems can be modelled. Based on this paper's analysis of current and future uncertainties and the characteristics of the business environment, the impact of a number of different scenarios were explored:

1. The Phase III attrition rate increases from 31.5% to 45%.
 2. The Phase III length increases by one year.
 3. Approval is delayed by one year.
 4. Two more phase IV studies are required (cost per trial similar to phase III).
 5. Time to reach peak revenue is delayed by 2 years.
 6. The exclusivity period decreases from 12 to 7 years.
- In the analysis, the increasing attrition rate and length of phase III studies represent the increasing complexity of bringing innovation to market in the biopharmaceutical industry. As already mentioned, therapeutic targets are becoming more difficult and expensive to discover and evaluate effectively, particularly with the focus on personalised medicine, making innovation substantially more complex (56).

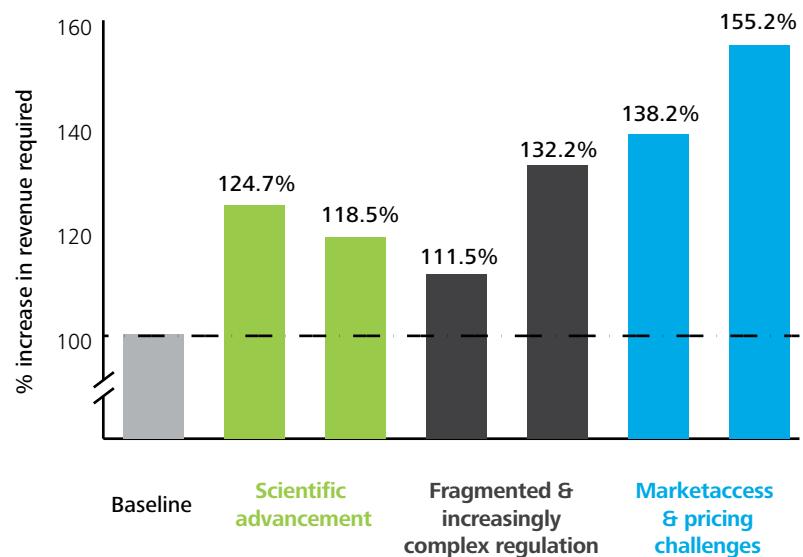
Delayed approval and an increasing number of phase IV studies are indicative of growing complex and fragmented regulation, as lack of transparency in regulation and/or the need for supplementary data in different geographical regions have the potential to result in a substantial increase in the cost of developing an innovative medicine, in addition to lengthening the time before approval.

Delayed time to reach peak revenue and decreasing exclusivity period represent the trend toward more challenging market access conditions. Analysis has shown how access to medicines is currently being delayed, albeit to varying degrees, across European countries, meaning peak revenue is taking longer to achieve. There is also a propensity for healthcare systems to want generic products to reach the market as quickly as possible, with the intention of controlling costs. However, this short-term gain may come at the expense of longer-term efficiencies if the emphasis on generics leads to lower investment by industry in the next generation of cost-effective innovative treatments.

Our modelling looked at the revenue increases that would be required to maintain the internal rate of return constant (baseline case) under the six scenarios outlined earlier. The assumption that the internal rate of return (IRR) of the biopharmaceutical industry needs to remain constant reflect the necessity for the industry of mitigate the increased risks posed by these scenarios and keep innovation sustainable at the current level of investment. The purpose of the model was to test how different realistic scenarios could affect and impair the feasibility of investing in the biopharmaceutical industry due to reduced returns of investment.

The analysis showed that in order for the internal rate of return to be maintained for a new product, revenues would need to increase to mitigate the higher risks faced by the biopharmaceutical companies, depending on which scenario is considered (Figure 8). According to the exercise, an increase in regulation complexity and fragmentation would require revenues to increase by 11.5% in order to maintain the IRR constant, while a less favorable market access scenario would require revenues to increase by 55.2%.

Figure 8: Model showing impact of uncertainty on required revenues per new innovative product (57-59)

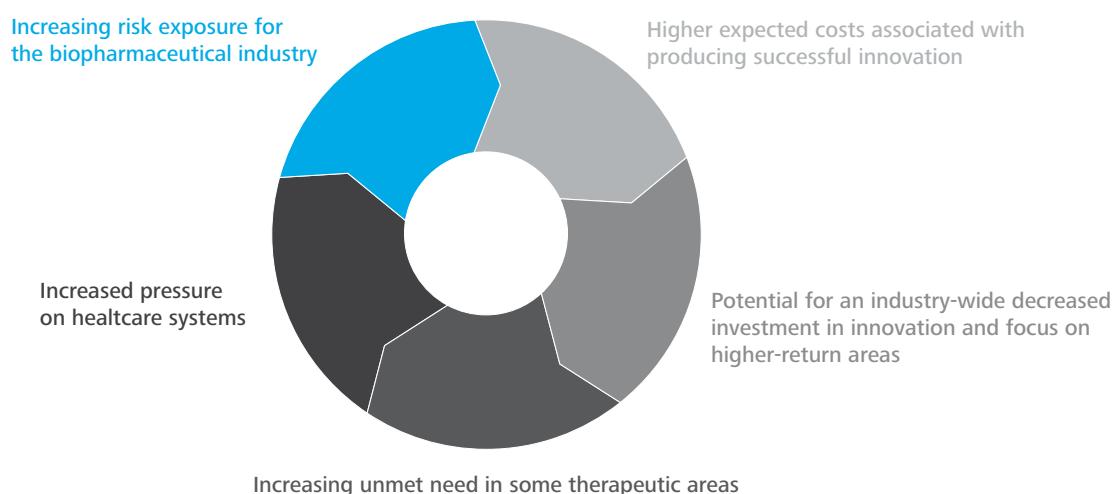


Modelled change in business	Increase in peak revenue necessary to maintain internal rate of return
Phase 3 attrition rate increased from 31.5% to 45%	+24.7%
Phase 3 length increased by one year	+18.5%
Approval delayed by one year	+11.5%
Two more phase IV studies (cost per trial similar to phase III)	+32.2%
Time to reach revenue delayed by 2 years	+38.2%
Exclusivity period decreased from 12 to 7 years	+55.2%

There is need for greater understanding on the role that revenue increases play in safeguarding innovation. Such increases could be managed by recognising the inherent complexities in the biopharmaceutical business model in the rewarding mechanisms, and by re-assessing the market access processes currently in place for biopharmaceuticals. Payers would have to pay a higher price per unit of medication sold, or alternatively commit to allowing access to medication for a larger volume of patients, either through a longer exclusivity period or by no longer restricting authorisations of new drugs to narrowly defined sub-populations. This is the opposite of the trends currently seen in the industry. Under the existing systems, we are seeing increasing pressure on the price of medications in addition to restricted access to new drugs, usually through authorisation being limited to highly selective subsets of populations.

Figure 9 illustrates the vicious circle that will be created if nothing is done to mitigate the increasing risk exposure of the biopharmaceutical industry. In the medium to long-term it will lead to sub-optimal patient outcomes and increased pressure on healthcare systems. It is thus in everyone's interests that all healthcare stakeholders work collaboratively to identify solutions to this challenge.

Figure 9: Potential consequences of increased risk exposure



The level of biopharmaceutical innovation can be sustainable if collaboration increases, the level of uncertainty is reduced and risks adequately rewarded

As in other sectors, collaboration between stakeholders in the biopharmaceutical sector can create an environment that fosters innovation

A vibrant biopharmaceutical industry is key to continued improvements in health, but the uncertainty faced by the industry may impede further innovation. There is therefore a need to create a healthcare ecosystem that places a higher value on better health outcomes while also respecting the need for effective cost-containment. Such a system would widen the scope for innovation, with a resulting positive impact on society through better access to medications and hence improved patient outcomes.

Our comparison with other industries has demonstrated that the biopharmaceutical industry faces a more challenging business environment in the areas of market access hurdles, fragmented and complex regulation and scientific advancement. But there are also positive lessons to be learned from other industries, which could help end and even reverse the trends behind the current increasing uncertainty in the biopharmaceutical industry. Collaboration through harmonisation of regulations is one important goal.

The biopharmaceutical industry deals with a fragmented stakeholder system, each player with different immediate targets but all working towards a common goal of improving quality and length of life while minimising the immediate economic cost of treatment. Against this backdrop, collaborations between stakeholders such as biopharmaceutical companies, regulatory bodies, patient organisations, healthcare providers, reimbursement agencies and academic institutions will be increasingly important for delivering cures and treatments in the future. Bodies already exist that aim to facilitate this type of multi-stakeholder collaboration. For example, with the aim of boosting pharmaceutical innovation in Europe, the Innovative Medicines Initiative (IMI) supports collaborative research projects, builds networks of industrial and academic experts, creates platforms that keep stakeholders informed of changes and advances in specific areas of interest, provides tools to improve R&D productivity and devises innovative approaches for addressing unmet medical needs.

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Harmonisation of regulation in the commercial aircraft and automotive industries

One of the main trends identified in the PESTLE analysis was the fragmented and increasingly complex regulatory environment facing the biopharmaceutical industry.

Harmonisation of regulation is difficult to achieve in any industry, due to differences in the geopolitical landscapes; however there are additional challenges faced by the biopharmaceutical industry due to potentially large differences in the composition of the patient populations.

In the commercial aircraft manufacturing industry, regulatory harmonisation has been achieved between the EU and the USA. It acts to harmonise technical implementation procedures for airworthiness and environmental certification of products between the Federal Aviation Administration (FAA), European Aviation Safety Agency (EASA) and European Union Member State Aviation Authorities (AAs) for importing, exporting and continued support of civil aeronautical products.

The joint regulation relies on similarities between certification systems, so there is a framework for communication of changes to these systems, including changes in: statutory responsibilities, organisational structure, airworthiness standards and procedures, quality control oversight and outsourced functions of the regulatory body (32).

We see a similar goal being shared in the automotive industry. Since 1993, detailed technical requirements for motor vehicles have been set by EU directives and a World Forum for Harmonisation of Vehicle Regulations set up by the United Nations Economic Commission for Europe (UNECE).

case study



Innovative Medicines Initiative (IMI) projects

The Innovative Medicines Initiative (IMI) was launched in 2008 with the goal of speeding up the development of safer and more effective medications through public-private partnerships (PPPs). The IMI encourages open collaboration between academia and industry by providing an effective method of protecting the interests of all project partners while encouraging the sharing and exploitation of knowledge. Thanks to IMI's policy on intellectual property, project partners are sharing compounds, data and knowledge with one another in a more free and open manner.

Up until 2013, a €2 billion budget was available for PPP projects, €1 billion coming from the EU Seventh Framework Programme and €1 billion contributed in kind by biopharmaceutical companies. More than one-third of IMI 1's funding went to research on infectious diseases, tackling issues such as antimicrobial resistance and vaccine safety and efficacy. Other priorities included drug discovery, brain disorders and metabolic disorders. IMI 2's estimated budget is €3.276 billion to 2024. Of this, the EU will contribute up to €1.638 billion from its Horizon 2020 research and innovation programme, matching the in-kind EFPIA commitment of up to €1.425 billion and an additional amount of up to €213 million if other life science industries contribute to individual IMI 2 projects (66).

As discussed earlier, fragmented market access is currently one of the most important factors affecting the biopharmaceutical industry, with different regulations not only at a country level but with access to medications also varying greatly within national health systems. Inconsistencies in the outcomes of health technology assessments (HTAs) are one issue that is starting to be addressed. In Europe, a body known as European Network for Health Technology Assessment (EUNetHTA) has been created to facilitate the development of timely, transparent and transferable information to contribute to HTAs. The ultimate goals are: to allow for the efficient use of resources for HTAs; to create a sustainable system of knowledge sharing; and to promote good practice in HTA methods and practices. Facilitating a unified approach to HTAs could potentially greatly reduce the market access uncertainty facing the biopharmaceutical industry (60).

case study

The biopharmaceutical industry has already attempted to adapt its business model to the changing environment so it can better address the uncertainties and maintain the level of innovation

There are number of ways in which the biopharmaceutical industry is trying to deal with the increasing uncertainty it is facing. To give a few examples:

1. The biopharmaceutical industry is tackling the issue of increasing data requirements by using large datasets as an adjunct to clinical trials to **boost their value demonstration⁸** and provide insight into which population subgroups would most benefit from new treatment options. This will allow biopharmaceutical companies to provide medicines that are more effective and better value for money by targeting treatments at the most appropriate population sub-groups.
2. The industry is also exploring opportunities to **shift from volume-based contracts to value-based contracts** in order to meet market access challenges and pressures. It is often considered that biopharmaceutical products have a monopoly market up until generic competition becomes available. This is not the case, however, with research showing that between the 1960s and 2003, the average exclusivity period a first-to-market drug sees has decreased from an average of 10.6 years to 3.1 years (as illustrated by the cancer treatment delay case study on page xxx). It is therefore important for biopharmaceutical companies to achieve a good return on investment during this period.
3. **Partnership agreements** are being struck between biopharmaceutical companies and healthcare systems to enhance research and provide faster access to innovation treatment and medication. An example of this kind of agreement currently taking place can be seen between Roche and the Manchester Academic Health Service Centre, which is part of the National Health System (NHS) in the UK. The partnership will work on developing biomarker research within six focus areas of cancer, cardiovascular disease, human development, inflammation and repair, mental health and population health. Furthermore, the collaboration will train future researchers and clinicians, while widening access to available new medicines and actively encouraging patients to take part in trials (61).



Collaboration between industry and academia

Collaboration between industry and academia can be a highly efficient way of bringing innovation to the market, but such partnerships have to be planned strategically if they are to be successful. The biopharmaceutical industry is involved in many partnerships with academia, however the calibre of collaborations seen in other industries points the way towards a more successful and efficient system.

Using an example from the commercial aircraft manufacturing industry, Rolls Royce has established a global network of university technology centres (UTCs), each of which is addressing a key technological aspect of the company's strategy. This is a well-developed and successful business model, with the first UTC established in 1990. The strategy of developing long-term relationships with academia has provided close contact with world-renowned institutions, establishing a connection with cutting-edge academic research capability, while providing access to highly skilled people, enabling recruitment and retention of highly qualified and motivated staff. Research projects are supported not only by the collaborating industry partner, but also by research councils and international government agencies.

Following the success of the Rolls Royce collaboration model, suppliers and other companies started to take note of the possibilities available. SKF, a Swedish supplier of Rolls Royce, signed a 5-year UTC partnership agreement with Cambridge University in the UK. The university was given the remit of conducting pure and applied research, with SKF providing funding, technical expertise and practical knowledge.

The close collaboration between Cambridge University and both Rolls Royce and SKF created a platform for the two private companies to innovate together, which is normally difficult to achieve in competitive market places.

The complementary nature of industry and academia is crucial to these partnerships, with academia having a level of freedom to be innovative that may be unrealistic in industry. The biopharmaceutical industry could be encouraged to enter into early close collaboration with academic institutions, rather than continue the current model of purchasing promising technologies after the discovery phase.

⁸ Value demonstration is using evidence (both clinical and economic) to generate a case for the value of medicine, to convince payers and other healthcare stakeholders to utilise and reimburse the product.

Further alignment between stakeholders and more investment in innovation is crucial for keeping healthcare systems sustainable and to improve human life

In conclusion, this paper has illustrated how over the past two decades **market access challenges, fragmented and increasingly complex regulation, and the costs and challenges of scientific advancement have increased uncertainty in the biopharmaceutical industry.** This situation appears to be particularly challenging for the biopharmaceutical sector, as other industries discussed in this study do not appear to carry the same level of risk in these areas when bringing innovation to the market. The severe pressure on healthcare costs has intensified the pressures and biopharmaceuticals are facing a reduced ability to achieve a positive return on investment (62).

Given the complexities of the biopharmaceutical sector, tackling these uncertainties is not straightforward. As a starting point, the current situation must be understood in its entirety. **The growing uncertainty surrounding the process of delivering innovative biopharmaceuticals to healthcare systems is not consistently recognised by policy makers, and therefore not reflected in the reward mechanisms currently in place.** For instance, competition from similar products is important and incremental innovation should be appropriately rewarded if there are benefits from the treatment.

The system is highly fragmented, with different stakeholders responsible for promoting R&D, setting up regulatory requirements, and rewarding innovation when it reaches the market. But there are clearly important interdependencies between the decisions taken in each area, which if ignored will be detrimental to the overall provision of healthcare. This is why **a collaborative approach is important**.

The main aim of this study has been to initiate an objective comparison between a range of industries in order to demonstrate the increasing challenges that biopharmaceutical companies must face to bring a product to market. The disclosure and recognition of this process as a whole is essential, as healthcare systems must function well overall in order to manage complex health problems and diseases. **In order to address priority health areas cost-effectively, a continuous pipeline of innovative technologies needs to be brought to the market.** However, the policy and regulation in this area remain static.

Continued innovation in healthcare is crucial for addressing the upcoming challenges faced by society due to aging populations and the growing number individuals with chronic diseases. But this report has shown that **as industry has continued to innovate, the complexity associated with further innovation has increased dramatically.** In the past, the pharmaceutical industry had the financial freedom to explore disease areas which would not necessarily produce high returns. More recently, a large number of projects have been discontinued at an early stage, despite having the potential to provide a meaningful level of innovation. With increasing pressure for financial returns, there is less interest in innovative projects with a high potential for failure or low potential returns.

Reducing uncertainty for the industry and maintaining an appropriate level of reward are therefore the two essential and interrelated steps for ensuring sustainable innovation and continued improvement in health.

A holistic and collaborative approach can achieve a great deal to improve the situation across the whole value chain, from early drug discovery, IP protection, research, development and regulation, through to reimbursement policies. Transparency and open communication is also important between all stakeholders and at all stages. This would ensure that policies and regulations are more aligned to meet the healthcare goals of better patient outcomes and optimal positive impact for society.

Healthcare represents a large slice of public and private spending and choices will always have to be made to ensure that money is invested wisely. The long-term impact of those decisions is not always straight forward. For instance, it can be argued that an increased reliance on cheaper, generic medicines will in the long-term diminish investment for future innovation and ultimately reduce the efficiency of healthcare systems and have a long-term negative impact on societal health. Only through evidence-based discussion can such issues be explored. **This report has provided relevant new data that support a view that the biopharmaceutical industry is bearing very high levels of uncertainty when assessed against other comparable industries and that this situation threatens to undermine future investment in innovation.** It is hoped our findings will feed into an urgently needed debate on how this uncertainty can be reduced and financial rewards maintained at a level that will safeguard innovation.

Appendix

Comparison of uncertainty across industries

For the main trends biopharma faces the highest level of uncertainty

	Investment required for each product to reach market (\$million)	R&D intensity (R&D investment as % of sales)	Time to market (years)	The risk of complete failure late in the development process	Differences in national regulation impacting product development	Effect of competition on market share & price (% change in market share of top 10)
	500-2000	10.88%	10-15	Yes	Yes	-5.07%
	500-2000	2.59%	4	No	Yes	-13.31%
	2500-5000	3.04%	6-8	No	No	-1.11%
	100-168	4.17%	1.2-1.5	Yes	Yes	-4.57%
	54-100	0.61%	2	Yes	Yes	-5.53%
	2	4.53%	5	No	Yes	-0.99%

-  Scientific advancement
-  Fragmented & increasingly complex regulation
-  Market access & pricing challenges

Comparison of uncertainty across industries

Research & Development	
Research	Clinical development
Investment required	Investment required
<ul style="list-style-type: none"> Increasing average cost of developing an asset Increasing concentration of R&D investments despite risk of failure being high 	<ul style="list-style-type: none"> Increasing average cost of developing an asset
Chance of success	Dependency on external factors
<ul style="list-style-type: none"> Biochemical targets harder and more expensive to discover High failure rate after pre-clinical studies Incremental innovation is discouraged by payers 	<ul style="list-style-type: none"> Dependency on external innovation partners to fill research pipeline Failure in phase 2 and 3 having a strong impact on the stock value of the company
Complexity	Complexity
<ul style="list-style-type: none"> Increasing complexity of disease pathways Increasing dependency on external innovation partners to fill the research pipeline Difficult to recruit appropriately skilled staff 	<ul style="list-style-type: none"> Increasing complexity and costs of clinical trials Increasing number of procedures needed per trial Increasing length of clinical trials Decreasing enrollment rate of clinical trial participants Decreasing retention rate of clinical trial participant Difficulty in recruiting patients Need to run sub-groups analyses and to perform additional studies
Chance of success	Chance of success
	<ul style="list-style-type: none"> Unpredictable effects of biomarkers on clinical outcomes Difficulty to predict safety concerns at development stage High attrition rates remain through phase 3

Main business trends

Scientific advancement
Fragmented & increasingly complex regulation
Market access & pricing challenges



Delayed entry	Competition
<ul style="list-style-type: none"> Delay in launch due to increasing regulatory requirements which may take effect after the clinical trials have been performed Loss of revenue due to delay in receiving approval Unpredictable effects of biomarkers on eligible patient populations 	<ul style="list-style-type: none"> Sales volumes reduced due to principal markets becoming saturated with generics Uncertain effect of biosimilars over the coming few years Decreasing product lifecycle due to "at-risk" launches Substantial reduction in prices due to the cost leadership of new entrants Decreasing sales volume due to increased proportion of spending on generics
Investment required	Demand change
<ul style="list-style-type: none"> Risk of failure to obtain regulatory approval with the required price and patient population Increasing requirements for effectiveness data in addition to efficacy data to obtain reimbursement Increase in costs to get a product reimbursed In the case of outcome based MEAs, increasing resources requirements to implement post-market access studies (Phase 4 studies) Different regulatory agencies require different types of data at the expense of the industry 	<ul style="list-style-type: none"> Decreasing sales volumes because of smaller market size per product Profit erosion due to reduction in prescription drug sales
Financial sustainability	Stakeholder management
<ul style="list-style-type: none"> Increasing weight of direct and indirect national regulation on price controls across different markets Profit erosion due to international price referencing Uncertainty in revenues due to pricing and reimbursement conditions based on post-market access performance (MEAs) In the case of financial MEAs, limited access to the budgets if budget cap is reached 	<ul style="list-style-type: none"> Prices (value) dependent on continuous post-launch data provision Decreasing product lifecycle due to rapidly changing market access rules and regulation when the products are already in the market Shift in stakeholder power which further complicates demonstrating value
Chance of success	
	<ul style="list-style-type: none"> Product failure can occur at any stage based on safety/efficacy issues leading to a total recall of the product from the market

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