SUSTAINALYTICS

Evaluation: From Policy to Practice

Report commissioned by ASN Bank

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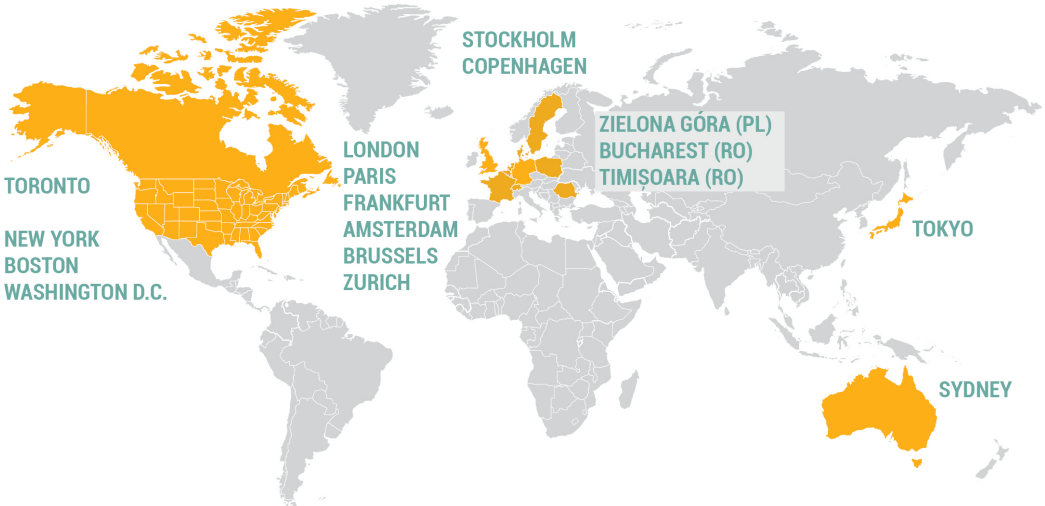

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Preface by ASN Bank:

Towards a Consumer-Focused Pharmaceutical Industry

Almost everybody requires medication at some point in their lives. Pharmaceutical companies produce medicines, which makes them indispensable to people's health and well-being. It follows that the pharmaceutical industry is an essential part of a sustainable society. From this also follows that this industry has an important responsibility to provide for reliable, effective and safe medicines. Subsequent to our investments in this industry our awareness of the frequent cases of ethical misconduct has also grown. Unethical behaviour such as bribing doctors, falsification of test results, and promoting medicines for different uses than is intended (off-label marketing) can result in negative effects on consumers. These unethical practices have occurred despite the sustainability and ethical policies of the pharmaceutical companies. This indicated to us that responsible policy did not guarantee responsible practice.

As an investor in pharmaceutical companies, this reality posed a dilemma for us. Should we divest from these companies although they play such an important role in many people's lives, or should we attempt to change the pharmaceutical industry to generate a greater consumer focus? We decided upon the latter. We believe that by choosing a constructive approach by engaging with the companies we had the potential to change their behaviour. Our goal was to achieve better consumer protection, which additionally positively impacts the risk profile and reputation of pharmaceutical companies. So in the end we could all benefit from a healthy pharmaceutical industry in a sustainable society.

In 2015 we commissioned Sustainalytics to develop the report *From Policy to Practice*, which was published in early 2016. At the same time in partnership with Sustainalytics we developed annual scorecards for each pharmaceutical company in our investment universe. This report and the annual scorecards were initially used in 2015, when we began our practice of engaging with the companies. Four years on and we have evaluated the progress of the companies in our investment universe. For this, we again commissioned Sustainalytics to write a report on the pharmaceutical industry, including developments in the sector and the companies we engaged with. Before we present our conclusion, we first will elaborate a little on the past four years.

As most pharmaceutical companies already had sufficient policies in place, we decided to focus on the implementation and anchoring of these policies as a link between policy and practice and in order to prevent misconduct. We started engagement in 2015 by attending the annual general meetings of the British companies AstraZeneca and GlaxoSmithKline to ask critical questions. Since 2016 we attended the annual general meetings of Novo Nordisk (Denmark) and Novartis (Switzerland). We maintained intensive contact with these four companies. From 2017 we also engaged in dialogue with the six other

pharmaceutical companies in our investment universe: Astellas Pharma, Bristol-Myers Squibb, BTG, Indivior, Merck & Co and Orion. All ten companies received their scorecards accompanied with questions on the components which relate to consumer protection. During this trajectory, we noted that most companies were responsive and cooperative. We have maintained a relationship with all companies, with the exception of Bristol-Myers Squibb.

From our engagement we conclude that although the majority of the companies we engaged with show a moderate improvement in one or several of the indicators used, further progress is yet to be made. Controversies are still widespread in the pharmaceutical industry. This is confirmed by the new report by Sustainalytics.

We also conclude that the companies with which we held an intensive dialogue performed better than companies that we had less contact with. Although a relatively small investor, we were able to accomplish a number of successes. One of which we are particularly proud of is in relation to the promise by AstraZeneca at its annual general meeting (AGM) in 2018. At our request the company announced that they were to become fully transparent worldwide regarding payments to health care professionals and not only in countries where this is a legal requirement. An important step forward. Not only for the company but for the sector as a whole, as this would set a new best practice for the pharmaceutical industry. This was acknowledged in an article written by the Times on AstraZeneca's statement at the AGM. In November last year, the company promised us that in 2019 it will become transparent in an additional eleven countries in Latin-America, North-Africa and the Middle-East.

Another example of a positive result in our endeavours is the progress made by Novo Nordisk in relation to their procedures in the development, manufacturing and distribution of safe and healthy medicines. In the scorecard, we rated each company on several aspects, to systematically track their performance. Novo Nordisk has improved significantly and in the last scorecard of 2018 the company has received the highest score in transparency and accountability. This means that the company has sufficient procedures in place, engages in internal and external audits and also is transparent and responsible for its operations. We compliment Novo Nordisk for adding explanations on its website to clarify that all results of clinical trials are being published, irrespective whether these are negative or positive. This was one of the topics we discussed with the Head of Sustainability of Novo Nordisk.

Unfortunately, in June 2018 we were necessitated to exclude Novartis from our investment universe as it was engaged in serious controversies, including a bribery scandal in Greece. We have been in contact with the company on multiple occasions since then to discuss this matter. Although Novartis was willing to provide us with an extensive explanation, it was not willing to share this publicly. This resulted in the exclusion of the company from our investment universe. Novartis has been very cooperative during our dialogue with the company which led to improvements in the scorecard. As we have held constructive contact with the company since 2016, we continued our engagement with them and produced a scorecard for the company in 2018.

As mentioned before, only Bristol-Myers Squibb has not been responsive to our engagement attempts. This company also shows a deterioration in the scorecard when comparing it to the initial scorecard from 2016 and its most recent one. The company remains involved in many controversies. Therefore, we decided to exclude this company from the investment universe. As was also the case for BTG, Indivior and Merck & Co. These companies showed little or no positive change.

On the positive side, we decided that five companies can remain in the investment universe. GlaxoSmithKline, AstraZeneca and Novo Nordisk score overall sufficiently on the scorecards, although progress can still be made. Unfortunately, these companies are still involved in (serious) controversies, requiring us to continue our dialogue with them. We will do the same with Astellas Pharma and Orion. These companies continue to score insufficiently overall on the scorecards, although they are not involved in any serious controversies. For us this means that at present we will continue to include them in our investment universe and remain in dialogue with them in order to improve their scores. We will monitor this by biannual scorecards.

Furthermore, we added a new pharmaceutical company to our investment universe: Merck KGaA. It has sufficient policies to meet our general sustainability criteria, and it is not involved in any serious controversies. We look forward to starting a dialogue with this company and seeing their results on the scorecard in the coming year.

To optimally monitor progress, we will develop new scorecards in 2020 and 2022 for all the pharmaceutical companies in our investment universe. We will continue to constantly monitor the companies closely for misconduct. For an additional period of four years, we will attend one annual general meeting each year to ask critical questions. By continuing the dialogue with these pharmaceutical companies, albeit less intensively than during the previous four-year period, we aim to further fuel the improvement of the sector as a whole. We encourage others to use our research in their dialogues with pharmaceutical companies as we expect we all will require reliable medicines someday.

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Introduction

Ethical behaviour and consumer protection are of paramount importance in the pharmaceutical industry. The quality and safety of pharmaceutical products have a significant and widespread impact on consumers as well as society at large. This is illustrated by the numerous grave scandals over drug safety and effectiveness, which have harmed hundreds of thousands of consumers over the past decade and which have led to several legal and regulatory interventions. Similarly, ethical business conduct in the marketing of drugs is crucial for both patient health and society at large. Unethical business practices at any stage in a drug's lifecycle have the potential to compromise patient health, jeopardize access to medicine, and inflate the cost of healthcare.

Ensuring product quality and safety does not start and end in the factories where drugs are manufactured. Rather, the way that drugs are designed and tested to a high degree determines their effectiveness and can also entail inherent risks for patients. Furthermore, proper marketing is essential to ensure that doctors and patients are well informed and that drugs are used as intended.

Faulty design, testing and manufacturing or off-label marketing may result in illness, hospitalization or death, caused by, for instance, adverse reactions to a drug, an improper dose, or inappropriately chosen treatment. According to research, 5-7% of all patient hospitalization are due to Adverse Drug Reactions (ADRs), with approximately half of these assessed as to be preventable. Furthermore, 3-6% of ADRs reported are fatal or have serious health consequences[1]. This also has negative consequences for society, as ADRs make up 5-9% of global healthcare costs per year[2].

While ADRs can likely never be eliminated completely, the pharmaceutical industry does have a role to play in ensuring drug safety and clearly disclosing the risk of side effects. For example, 28 drugs were withdrawn from the US market between 1976 and 2007,[3] due to negative, life-threatening reactions. As such, there are grave risks to be dealt with, for which the industry bears at least a partial responsibility.

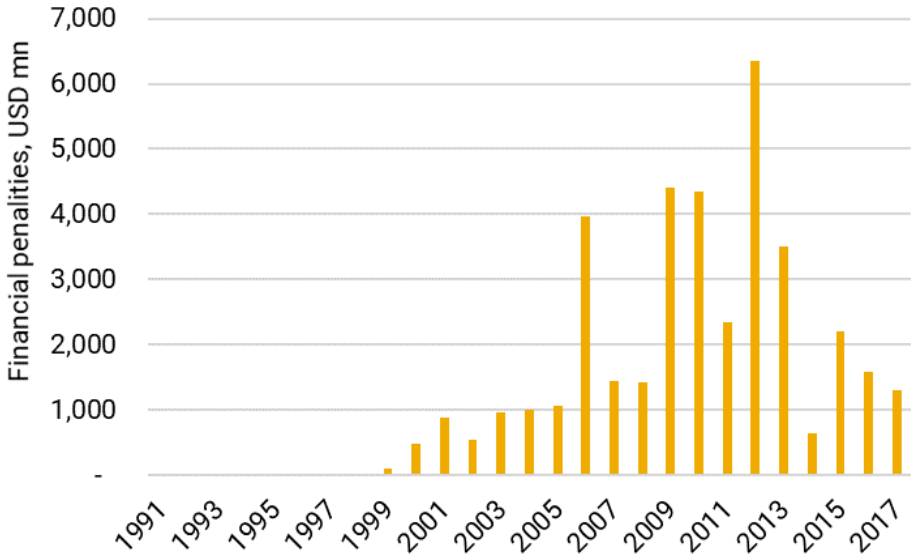
This report is an evaluation from the previous report ''From Policy to Practice'', which was published on February 2016. The previous report examined the implications of unethical business practices in the pharmaceutical industry in relation to product quality and safety. As it showed a gap between policy and practice, its the focus was on what companies can and should do to avoid harming consumers, while zooming in on the area between policy and practice: the internal mechanisms and structures that companies have in place to ensure consumer protection. This report provides an update on and trends in the pharmaceutical industry and the different stages of the product life cycle. Furthermore, this report indicates where we have seen improved and/or deteriorating performances in the ten pharmaceutical companies which were engaged by ASN Bank.

The cost of unethical business practices

Unethical business practices can have severe consequences not only on patients and society, but they can also have a negative impact on companies' enterprise value through resulting fines and settlements.

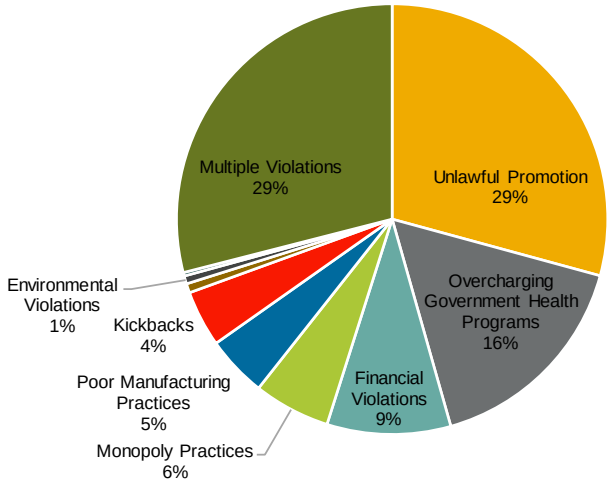
Incidents over product quality and safety and unethical conduct have cost the pharmaceutical industry over USD 30 billion in financial penalties in the past 10 years in the US alone (see Figure 1). **GlaxoSmithKline** (GSK) received the highest financial penalties between 1991 and 2017, accounting for approximately USD 8 billion and representing 20.4% of the financial penalties given to all pharmaceutical companies in that period[4].

Figure 1: Criminal and civil penalties for unethical conduct in the US, 1991-2017[5]



Source: Citizen.org

Figure 2: Financial penalties by type of violation in the US, 1991-2017



Source: Citizen.org

As shown in Figure 2, unlawful promotion of medicines is the main violation in the US, followed by overcharging government and healthcare programmes. Poor manufacturing practices and kickbacks are also common violations.

The figures above suggest that companies may focus on the short-term commercial gains of introducing new products to the markets quickly, rather than focusing on the medium- and long-term benefits of ensuring that medicines are safe and of high quality. The data also suggest that unethical business practices appear to have become common within the pharmaceutical industry, making it more prone involvement in unethical conduct and quality and safety issues.

Impact of unethical business practices on consumers

The potentially severe adverse impacts of unethical business practices and poor quality and safety management on consumers are shown in Figure 3. The events are categorized according to where in the product life cycle a lack of risk management occurred:

- **Research & development**: poor design of products and/or insufficient testing before products are launched to the market.
- **Manufacturing & distribution**: lack of quality control in the factory or during transportation and storage leads to products that have been potentially compromised.
- **Marketing & sales**: provision of false and/or deceptive information on products, off-label marketing, and aggressive marketing tactics, such as bribing doctors.

Figure 3: Adverse consumer impacts from unethical business practices

Company	Stage of Risk Management Failure	Description of Event	Consumer Impact
Merck & Co	Research & Development/ Marketing & Sales	**Vioxx Scandal** In 2012, Merck paid over USD 5 billion in settlements and still faces consumer claims over its painkiller Vioxx. The lawsuits accuse the company of providing unreliable product information, applying deceptive promotional practices and fabricating medical journal studies to enhance Vioxx's credibility.	Studies found a significantly increased likelihood of fatal heart attacks or strokes among patients taking Vioxx. Up to 38,000 people have died from heart attacks or strokes after taking Vioxx, while approximately 160,000 patients have been injured.
GlaxoSmith Kline	Manufacturing & Distribution	**GSK's antidiabetic drug** GSK has faced numerous product liability lawsuits for Avandia, an antidiabetic drug. Avandia was restricted by US regulators and pulled from the European market due to the heightened risk of heart attack.	GSK settled approximately 50,000 consumer lawsuits over injuries related to Avandia.
Novartis	Marketing & Sales	**Bribery and Corruption Allegations** The company faces numerous allegations connected to bribery and corruption of doctors and government officials in several markets. The company's misconduct is widespread and may have affected patients in at least six markets (South Korea, Greece, China, Russia, the US and Romania) over several years.	Prescriptions that are not based on independent clinical considerations can lead to significant health risks for patients. Novartis is accused of inflating Greece's national healthcare spending during the country's financial crisis, which translates into more than EUR 3 billion in losses for the state (or 1.5% of the country's GDP).

Source: Sustainalytics

The structure of this report

This report analyses the adverse effects of unethical business practices and poor quality and safety management on consumers and society at large and is structured as follows.

In Chapter 1, we provide an overview of the product life cycle to clarify in which stages ethical behaviour and consumer protection are particularly important. We analyse each of the stages identified (research & development, manufacturing & distribution, marketing & sales, and post-marketing), highlighting important updates and including main industry trends, new key developments, relevant industry initiatives, and possibly new international legislation.

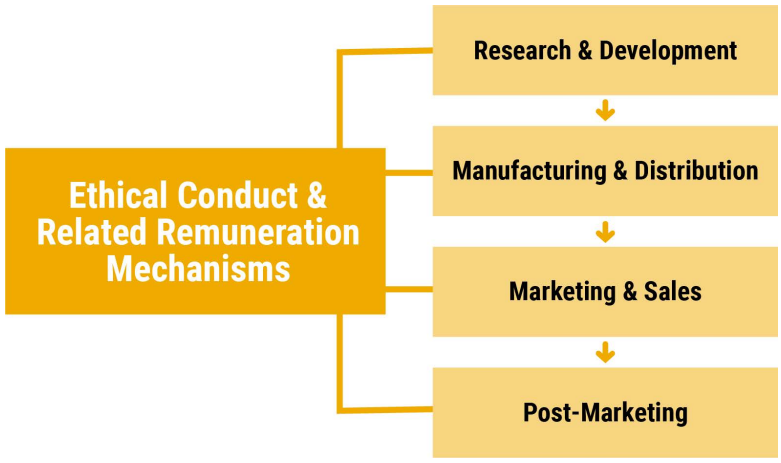
In Chapter 2, we evaluate the performances of ten pharmaceutical companies for each stage of the product's life cycle. This chapter includes a brief overview of the general industry trends for each stage, examples of controversies and evaluates the ten pharmaceutical companies that ASN Bank has engaged with in the last three to four fiscal years. Finally, in the last section, we draw conclusions based on the companies' performance and progress made during their engagement with ASN Bank.

1) Setting the Scene – relevant developments in the sector

Product life cycle

Product quality and safety in medicine are paramount during all phases of the product life cycle. A typical product life cycle is depicted in Figure 4. Research and development (R&D) refer to the research, development, design and testing of new products before they are marketed. Manufacturing and distribution refer to drug production and delivery to the end user. Marketing and sales entail all business activities that are focused on promoting and selling (more) products. Finally, post-marketing refers to the monitoring of products' health effects over the long term. A deeper understanding of the issues will result from analyzing the associated risks and best practices along the product life cycle (see Chapters 1.2-1.5). Ethical conduct (Chapter 1.1) is seen as an overarching topic of importance throughout the product life cycle and throughout a company's operations.

Figure 4: Ethical conduct and consumer protection in the product life cycle



Source: Sustainalytics

1.1 Ethical conduct and related remuneration mechanisms

What are the negative stakeholder impacts and financially material risks for pharmaceutical companies engaging in unethical business practices?

Ethical conduct includes adherence to ethical standards and compliance with local, national and international laws in all business dealings and is therefore crucial to guarantee product quality and safety. Effective ethical conduct management entails strong management of ethical issues, particularly corruption, fraud, anti-competitive practices and conflict of interest. Bribery and corruption, though associated with significant penalties, are relatively common in the pharmaceutical industry, especially bribery of health care professionals in return for prescribing company products. This tends to be the case because companies constantly interact with government officials and are therefore confronted with an "ever-present temptation to cut corners, bend rules and influence decision-makers."[6] Unethical business practices include providing financial inducements (e.g. gifts, hospitality, meals, fees and grants) as part of their interactions with government officials and health care professionals. Such practices are pervasive throughout the industry, in both developed and emerging markets and can ultimately erode consumer trust in the sector.

Historically, pharmaceutical businesses implicated in bribery and corruption have faced high fines (up to USD 500 million), criminal sentences for employees and intense scrutiny from regulators. In December 2016, **Teva** agreed to settle with the US Department of Justice (DOJ) and Securities and Exchange Commission (SEC) to resolve violations of the Foreign Corrupt Practices Act (FCPA). The company paid a total of USD 519 million, the highest settlement recorded in the pharmaceutical sector for bribery and corruption allegations, and the fourth largest FCPA settlement in the private sector[7]. In the US, companies may face exclusion from government health care programmes if they are found

guilty of repeated misconduct, which can result in a loss of market share. For instance, **Novartis** is alleged to have violated the US Corporate Integrity Agreement (CIA), signed by the company's subsidiary, Novartis Pharmaceuticals Corp., with the DOJ in 2010 for off-label marketing of several products. The ongoing bribery investigation by the State of New York is related to events from 2002 to 2011, some of which would have occurred after the CIA was signed and could be considered a violation of the agreement. Theoretically, if substantiated, the violation could exclude the company's drugs from federal health care programmes in the US[8].

In developed countries (e.g. the US and in Europe), pharmaceutical companies' operations are highly regulated. In contrast, emerging markets (e.g. China and India) have weaker regulations related to drugs' quality and safety, promotional marketing practices, as well as bribery and corruption practices. However, the global regulatory environment for ethical business conduct in the pharmaceutical industry is becoming stricter, and governments are increasingly cooperating in information exchanges. Over the few past years, we have also observed increased scrutiny and foreign regulatory attention on companies operating in Asia-Pacific markets. In 2016, the US Department of Justice (DoJ) and Securities and Exchange Commission (SEC) filed a record-breaking number of Foreign Corrupt Practices Act (FCPA) enforcement actions for pharmaceutical companies operating in Asia-Pacific, representing 47% of the DoJ's cases and 65% of the SEC's cases[9].

This increases the risk of engaging in unethical business practices for pharmaceutical companies operating in Asia-Pacific market. Pharmaceutical companies cannot avoid operating in emerging markets, though, as these markets represent a growth opportunity, given the large consumer base. For instance, China has a population of more than 1.4 billion.[10] It is now the world's third-largest pharmaceuticals market[11] [12] and is projected to increase at a 9.1% annual rate to reach USD 167 billion by 2020[13].

While China has less stringent laws regarding corruption than countries in Europe, Chinese regulatory enforcement has been increasing. The Chinese government has been increasingly assertive about punishing unethical behaviour among multinational pharmaceutical companies that sell drugs in China. In 2014, **GlaxoSmithKline** (GSK) paid a USD 489 million fine, the largest fine for a pharmaceutical company in China[14]. Furthermore, US foreign authorities are also increasing their presence in China. In 2016, 40% of the FCPA enforcement actions by US regulators (DOJ and SEC) involved misconduct by companies operating in China. In 2016, GSK settled with the SEC for USD 20 million over claims that it had bribed Chinese officials to boost sales. In 2016, **Novartis** paid more than USD 25 million to settle SEC civil charges that it bribed doctors in China[15]. In the same year, **AstraZeneca** also had to pay the SEC USD 5.5 million for bribing doctors in China[16]. Therefore, pharmaceutical companies must ensure compliance with standards to prevent bribery and implement monitoring mechanisms to ensure that their employees are doing business without becoming involved in corrupt activities, even in countries where regulations have tended to be less stringent.

Therefore, ethical conduct management is expected to go beyond regulatory requirements, and apply to all company operations worldwide, including subsidiaries. Poor ethical conduct is a threat to consumers in a myriad of ways, many of which we explore in subsequent chapters. In our view, the most

significant effect of unethical conduct is that it compromises the integrity and dependability of health systems, and erodes pubic and consumer trust in the industry.

Ethical conduct, however, goes beyond corruption. Anti-competitive practices, for instance, are also a recurring problem in the industry. **Novo Nordisk** faces allegations of collusion with other insulin producers for price fixing. In October 2017, the office of the Attorney General (AG) in Washington, Minnesota and New Mexico issued civil investigative demands (CIDs) related to the company's pricing practices for insulin, a lifesaving drug, as well as its business relationship with other two insulin manufacturers, **Eli Lilly** and **Sanofi**. The company is alleged to have colluded with other insulin manufacturers to increase the price of insulin, which has reached record highs as **Eli Lilly**, **Novo Nordisk** and **Sanofi** raised prices by more than 240% over the past decade[17]. This has had a negative effect on the affordability of those medicines.

According to the WHO, "corruption in the pharmaceutical sector occurs throughout all stages of the medicine chain, from research and development to dispensing and promotion".[18] Hence, ethical conduct is seen as an overarching requirement that spans all phases of the product life cycle and all aspects of companies' operations (see Figure 4).

Implementation and enforcement procedures

A company's implementation of anti-bribery and corruption policies can demonstrate how well it is mitigating risks related to unethical conduct. Pharmaceutical companies must understand local corruption risks, including local industry codes, and consider all stakeholders, including employees, partners and third parties. Furthermore, implementing one global standard that applies to all operations worldwide and goes beyond compliance with local standards can be challenging, but is nevertheless a prerequisite for ethical conduct. As mentioned above, there is increasing scrutiny and foreign regulatory attention toward companies operating in emerging markets, where regulations tend to be less stringent than in developed countries. Therefore, pharmaceutical companies need to make sure that no matter where they operate, high ethical business standards are followed, even in regions where regulations are less stringent.

Companies that work to change their business culture tend to implement policies through regular training, audits, reporting mechanisms for violations and procedures for corrective action. Compliance training should take place on a regular basis and apply to employees, partners and third parties. Effective training should teach behavioural skills and compliance with industry standards, such as the WHO's Ethical Criteria for Medicinal Drug Promotion, provide training feedback, reinforce successful application, and measure training application in the workplace. Pharmaceutical companies should regularly engage in both internal and external audits to examine compliance with ethical standards. Finally, companies need to implement formal mechanisms to collect and investigate complaints by adopting a whistleblower system that includes a global anonymous compliance hotline and a non-retaliation clause against reporters. The adoption of whistleblower mechanisms supports good ethical conduct, permitting disclosure and investigation of unethical practices.

Finally, companies can integrate ethical standards and sustainability practices into their culture by linking part of executive remuneration to environmental,

social and governance (ESG) performance targets, such as ethical or product quality and safety standards.

Relevant indicators to measure individual company performance

The following sub-chapters provide a reflection on the main topics, risks and best practices in product quality and safety management across the product life cycle. As stated previously, ethical conduct should be seen as an overarching part of all product life cycle stages.

1.2 Phase I: Research & development

What does this stage entail and why is product quality and safety an issue at this stage?

The research and development (R&D) stage includes all the steps that take place before a new product receives marketing approval, i.e. before it can be widely sold in the market place. At the R&D stage, companies need to conduct extensive scientific testing to determine the efficacy of a new product, whilst at the same time ensuring that potential side effects and other complications are uncovered. Ultimately, the benefits of a new product should outweigh the risks.

Selective disclosure of test results makes it hard to substantiate companies' health claims about their products and poses various health risks. Specifically, doctors and patients might not be informed of side effects that could outweigh the benefits of pharmaceutical products, they might not be sufficiently aware of the conditions under which a product is (in)effective, or they might mistakenly believe the product to be safer or more effective than alternative treatments.

According to research[19], the average R&D return for pharmaceutical companies was 3.2% in FY2017, compared to 10.1% in FY2010. One of the main reasons for the diminishing R&D return trend is the high cost of releasing a new drug. As of 2017, the average cost to bring a new drug to the market was approximately USD 2.6 billion, if pipeline failures are factored in, compared to USD 1.2 billion in 2010[20]. The main cause of the increased costs is the fact that 90% of the medicines tested do not receive final market approval because they do not satisfy safety and effectiveness tests[21].

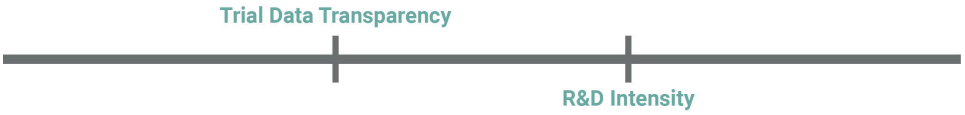
The increased quality and safety criteria for bringing new drugs to the market could improve the quality of the drugs. However, there is also a risk that pharmaceutical companies will lower their R&D spending, given the diminishing returns. Therefore, they may be more likely to focus on developing and marketing drugs that are more lucrative, thus potentially decreasing patients' access to medicine.

Implementation and enforcement procedures

Quality standards that govern product development include Good Laboratory Practice (GLP), Good Clinical Practice (GCP) and Good Manufacturing Practices (GMP). GLP, GMP and GCP standards entail numerous guidelines to ensure that pharmaceutical studies are scientifically accurate and that the clinical properties of new products are properly documented. Adherence to these standards is enforced through frequent inspections by regulatory authorities, and typically a requirement to gain marketing approval for new products. However, due to the generally low transparency of clinical research, regulators and doctors only get part of the picture. Hence, companies should provide fully transparent clinical trial data. Also, companies should go beyond minimum legal requirements by proactively disclosing the results of all their clinical trials, regardless of whether their outcome is favourable to the company, and disclosure should include results from terminated and historical trials.

In addition to R&D transparency, the R&D intensity of companies (i.e. the percentage of revenues invested in R&D) can also be seen as a proxy indicator for the extent to which companies are focused on delivering new high-quality products that meet public health needs. One should be careful, however, when directly comparing companies according to their R&D intensity, as differences can also be explained by variations in business models, the types of R&D conducted, and accounting standards.

Relevant indicators to measure individual company performance



1.3 Phase II: Manufacturing & distribution

What does this stage entail and why is product quality and safety an issue at this stage?

The manufacturing and distribution stage covers all business activities that take place in production plants or in delivering drugs from the factory to the end user. At this stage, companies must ensure that each batch of product that leaves the factory contains the right composition. At the production plant, contamination, incorrect dosages or an improper manufacturing climate are just a few of the risks that could render a product defective. Subsequently, during distribution, products might be further exposed to either the penetration of counterfeit medicines or to improper handling during storage or transportation. For instance, to preserve a medication's properties, some vaccines might require cold storage. The potential health impact of products that have been compromised varies from ineffectiveness to severe adverse reactions. Failure to adhere to extensive regulations and quality management standards has led to expensive recalls, increased regulatory scrutiny and compliance costs, and had a negative effect on customers' trust. In extreme cases, regulators have imposed import bans or halted production until quality issues were resolved.

In developed regions, such as the US and Europe, product quality and safety during manufacturing and distribution are heavily regulated through inspections at factories and storage facilities. However, this is not always sufficient to prevent incidents. For instance, between 2016 and 2017, the annual number of US Food and Drug Administration (FDA)-regulated product recalls increased from 8,305 to 9,199[22]; with product batches being recalled due to, for instance, lack of sterility or potential contamination during the production process. Moreover, the number of Good Manufacturing Practices (GMP) warning letters issued to pharmaceutical companies operating in the US sharply increased by 121% from 2013 to 2017[23]. Therefore, company-wide measures that go beyond legal requirements should be implemented to provide an additional level of quality assurance.

Manufacturing irregularities have occurred mostly in emerging markets, particularly in China and India. Companies exporting products from emerging to developed markets are especially exposed to regulatory scrutiny, particularly due to increased FDA controls and regulatory actions since FY2013. Between FY2013 and FY2017, GMP warning letters issued by the FDA outside the US increased by 65%, with China and India receiving 32% and 28% of the total volume, respectively[24]. In these countries, quality and safety operating standards have tended to be less stringent than in more developed markets; however, pharmaceutical companies are expected to implement strong quality management systems and monitoring mechanisms to ensure quality and safety standards. Foreign enforcement actions are increasing and high-quality medicine is crucial to ensure patient safety.

Implementation and enforcement procedures

Best practices to uphold product quality and safety at the manufacturing stage include implementing quality management systems that consist of regular employee training on product safety, external product safety audits, incident investigation and monitoring of product safety performance. Companies also need to implement standard operating procedures for product recalls in situations where a product may be defective. These procedures should include clear steps to revoke products from the market and to warn doctors, pharmacies and patients. Additional assurance could be provided by seeking external certification of the company's quality management system, beyond the assurance provided by regulatory inspections. Examples of internationally acknowledged standards include ISO 9001 (quality management principles), Good Manufacturing Practice (GMP) or ISO 13485 (quality management systems specifically for medical devices).

Relevant indicators to measure individual company performance

1.4 Phase III: Marketing & sales

What does this stage entail, and why is product quality and safety an issue at this stage?

This stage entails all business activities that are focused on promoting and selling (more) products. Industry spending on product promotion generally outpaces spending on research and development of new treatments. Pharmaceutical companies use a variety of strategies to increase prescription and sales volumes for their products. All of these contain inherent risks of misinformation, potential for conflicts of interest and sometimes corruption, which may negatively impact customers' health. Bribery is arguably the worst outcome of illegal and improper marketing. Some examples of this are inviting health care professionals to lavish events whilst paying for their transportation and accommodation, paying fees to health care professionals for "services" as a financial incentive to boost sales for a certain product, or offering nursing consultants as part of a drug package.

Improper marketing practices can harm society and patients in several ways, such as:

- Over-prescribing expensive patented products when cheaper and equally effective generic products are available, and the prescription of expensive drugs inflate costs within health care systems;
- Prescribing products for which the health risks outweigh the benefits;
- Prescribing products that are not suitable for certain diseases or patient groups;
- Providing biased and unreliable product information to patients;
- Insufficient patient awareness of potential health risks, including side effects.

Prescribing expensive drugs when cheaper and/or generics substitutes are available in the market can ultimately harm patients, as it can inhibit patients' access to a drug. This practice also has a negative effect on society, as it can inflate costs within national health care programmes. For instance, **Novartis** is alleged to have sold overpriced drugs in Greece and, consequently, interfered with Greek patients' ability to receive affordable access to care over a period of nine years. Additionally, Novartis is accused of inflating Greece's national health care spending during the country's financial crisis, which translates into more than EUR 3 billion in losses for the state (or 1.5% of the country's GDP)[25]. According to the OECD, drug purchases in Greece rose from 23.6% of total national health spending in 2006 to 30.7% in 2011[26].

Off-label marketing is an important issue within the pharmaceutical industry. Companies that market pharmaceutical products for unapproved uses or provide misleading product information have faced criminal charges and litigation from patients as well as shareholders. Fines and settlement payments can reach several billion US dollars for a single product and have affected numerous pharmaceutical companies. Business impacts include loss of revenues and returns on a company's R&D investment, if a product must be taken off the market completely, or if regulators impose stricter prescription criteria.

GSK's offence is the most notable. Its much-publicized USD 3 billion settlement with the US government in 2012 is the largest of such settlements in the industry to date. The fine was imposed for various improper marketing practices, including off-label marketing and failure to adequately disclose product safety information for its antidepressant drugs, Paxil, Wellbutrin and Avandia.

Moreover, it can take years to regain trust from patients and doctors. Companies operating in the US, which tends to be a very litigious market, are more exposed to patient litigation. Also, companies operating in markets that allow direct marketing of drugs to patients, like the US and New Zealand, face increased risk exposure in marketing and sales.

Furthermore, over the past year, an increasing number of countries have approved legislation to increase the transparency of payments made from pharmaceutical companies to health care providers (HCPs). For instance, several European countries are signatories of the EFPIA's code of practice, which requires pharmaceutical companies to disclose all payments made to HCPs. As of November 2018, 39 European countries endorse the EFPIA's code of practice[27]. Other countries, such as France, Slovakia, Greece and Romania, have even passed legislation to make disclosures of payments to HCPs mandatory[28].

Implementation and enforcement procedures

To mitigate the aforementioned risks, companies could implement voluntary industry marketing codes, which have been in existence for decades, such as the Code of Pharmaceutical Marketing Practices of the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA)[29]. These industry codes, however, are not as strong as they could be. For instance, the IFPMA code does not cover advertisements and communication to the general public, nor does it address the conduct of pharmaceutical sales representatives. Conversely, the WHO's Ethical Criteria for Medicinal Drug Promotion[30] do cover these issues and generally promote higher standards. Additionally, companies could follow ethical medicine promotion by implementing restrictions on direct payments and other more common forms of unethical promotion, such as providing samples, gifts and hospitality to doctors and patients.

Disclosure of all payments made by pharmaceutical companies to HCPs, doctors and officials, also in countries where it is not legally required, would increase transparency. However, pharmaceutical companies might encounter difficulties in fully disclosing payments made to HCPs, particularly in countries where it is not legally required, as stringent privacy laws could prevent this. Ethical marketing training programmes for sales representatives, mitigation practices, such as an ethical review of promotional materials and sales incentives to reward compliance, should also be encouraged (see the sub-chapter on Sales Incentives).

Relevant Indicators to measure individual company performance

1.4.1 Sales incentives

What do sales incentives entail, and why are they an issue for product quality and safety?

Traditionally, pharmaceutical companies have employed a sales volume-based system to establish rewards for high-performing sales staff and consequences for low-performing sales staff. Sales commissions and bonuses often tie to sales quotas. These sales volume-based systems have been a driving force behind pharmaceutical sales representatives engaging in inappropriate behaviour, such as overly aggressive marketing, including the following:

- Providing financial inducements (e.g. gifts, hospitality, meals, fees and grants) and non-financial inducements (e.g. career opportunities), as part of promotional interactions with health care professionals;
- Providing product information that is unreliable, incomplete or misleading;
- Promoting drugs for unapproved uses or target groups, a practice known as "off-label marketing".

While a volume-based sales model is of little to no concern in many other industries, the principle of "selling as many drugs to as many patients as possible" neglects the concept that a particular treatment might not necessarily be in the best interest of all patients. The provision of incentives to doctors can lead them to prescribe products that are not appropriate for certain patient groups, for which the health risks outweigh the benefits, or for which equally effective (and cheaper) generic versions are available. However, as of FY2018, the vast majority of pharmaceutical companies still have their sales representative compensation connected to sales quotas, increasing the risk that employees would engage in unethical business practices.

Implementation and enforcement procedures

A company's shift away from a "volume-based" sales approach to a more "value-based" one (focused on value creation as the customer defines it) can mitigate unethical marketing practices concerns. Best practices include establishing sales personnel remuneration programmes based on technical knowledge (including expertise on pharmaceutical products, symptoms, and diseases) and quality of service/consumer engagement.

Relevant indicator to measure individual company performance

1.5 Phase IV: Post-marketing (pharmacovigilance)

What does this stage entail, and why is product quality and safety an issue at this stage?

Once its medicine is sold in the market place, the pharmaceutical company's responsibility does not end. If companies do not monitor how their products perform in the wider marketplace, potential problems, such as side effects inherent in the design of the product or defects related to faulty manufacturing,

cannot be signalled early. Such monitoring of a product's health effects is referred to in the industry as pharmacovigilance (PhV), defined by the World Health Organisation as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem"[31].

In other words, PhV entails the monitoring of a product's medium- and long-term effects on consumers. Of course, some of the effects that are inherent in the product design are already known from the clinical trials that are conducted prior to receiving marketing authorization, i.e. during the R&D process. Yet, certain health effects may only become evident during large-scale and long-term use — that is, several years after a product has been launched to the market.

Pharmaceutical companies are largely responsible for collecting and reporting adverse drug events to authorities, an important aspect of PhV. However, recent reports show that pharmaceutical companies are doing a substandard job in reporting adverse drug events to authorities. The FDA has stated that fewer than half of the adverse event reports submitted to the agency by pharmaceutical companies are complete[32], as companies tend to report partial information about post-market safety events. Similarly, in developing countries (e.g. Brazil) there is a tendency to report incomplete information about post-market safety events, preventing the event to be classified as a safety side effect[33]. This is alarming for public health, since it leaves doctors and patients with inadequate information on the risks of certain products. It also means that precious time may be lost before certain (negative) health effects become widely known and corrective measures can be taken.

For instance, **Merck & Co** is facing a significant number of liability lawsuits connected to the negative side effects of its drugs, casting doubts on the effectiveness of its pharmacovigilance programme. The company has several thousand ongoing liability lawsuits related to the safety of its drugs. Specifically, over 1,200 lawsuits regarding its Januvia and Janumet products (which combined accounted for 14.7% of FY2017 revenues) were still pending as of December 2017, with plaintiffs alleging that the type-2 diabetes drugs could cause pancreatitis[34].

Implementation and enforcement procedures

Companies should implement post-marketing surveillance to detect and respond to potential product safety concerns. Best practices include tracking (unanticipated) side effects of all new products, providing mechanisms for adverse events reporting, as well as investigating incidents and taking corrective actions, such as product recalls.

Relevant indicator to measure individual company performance

Product & Service Safety Programme

2) Company evaluation

2.1 Ethical Conduct & Remuneration

General trends insights

Unethical conduct within the pharmaceutical industry has become more frequent over the past years, especially instances of companies bribing health care professionals to increase prescriptions of their products. Moreover, the global regulatory environment for bribery and corruption is becoming stricter, and governments are increasingly cooperating in information exchanges. Asian countries are also strengthening regulation and enforcement. For instance, the Chinese government has given particularly high fines and sentences to pharmaceutical companies and individuals involved in bribery and corruption, and South Korea introduced stricter regulation for alleged bribery of governmental officials in FY2015[35]. Additionally, in developed markets, regulations like the California Sunshine Act are demanding greater transparency from companies on payments made to health care professionals[36].

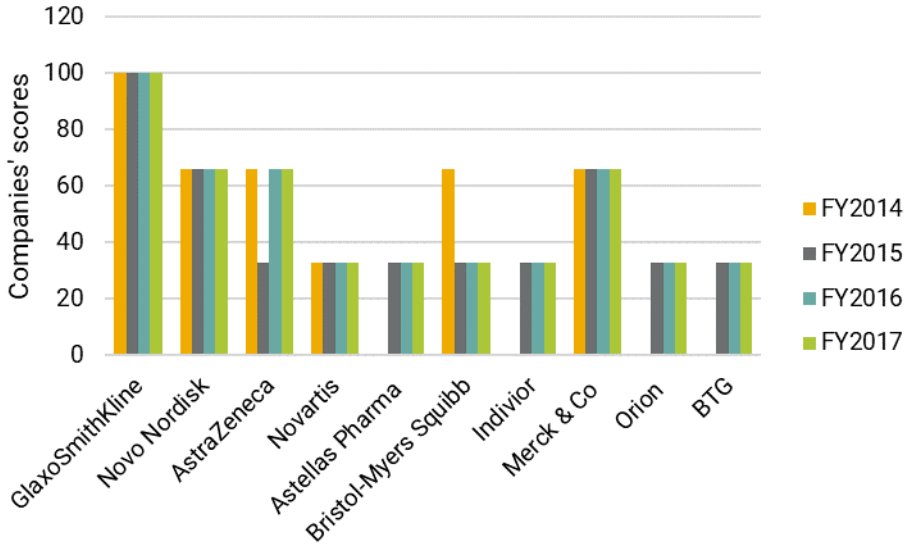
Controversial practices

While many pharmaceutical companies have developed a strong bribery and corruption policy, as part of their commitment to a sustainable business model, in practice, the industry has experienced major gaps between the companies' policy commitments and performance. Examples include pharmaceutical companies that have pledged their commitment to anti-corruption, while also being involved in alleged violations of anti-corruption laws on multiple occasions.

The example of **Novartis** stands out in particular, as the company has a strong and comprehensive bribery and corruption policy in place, and yet the company has faced numerous allegations of bribery in its product sales. In February 2018, Novartis became part of a bribery investigation in Greece for its alleged involvement in an unethical scheme that involved bribing senior Greek officials and thousands of doctors between 2006 and 2015. Meanwhile, in the US, the SEC and DoJ are also looking into Novartis's business practices in Greece and have subpoenaed the company as part of their investigations. At the same time, Novartis also faces an ongoing bribery investigation in the US for allegedly paying kickbacks to doctors at educational events. In 2017, Novartis was fined by South Korea's Fair Trade Commission (FTC), as well as by its Ministry of Health and Welfare, and Ministry of Food and Drug Safety for approximately USD 52 million over kickbacks offered by the company to doctors between 2011 and 2016. The South Korean Ministry of Food and Drug Safety imposed a three-month sales ban on three of Novartis' drugs, including its Alzheimer treatment Exelon. Additional bribery investigations involving Novartis are still pending in Romania, Russia and Asia.

Performance insights from the 10 pharmaceutical companies analyzed

Figure 5: Ethical conduct management trend, FY2014-FY2017

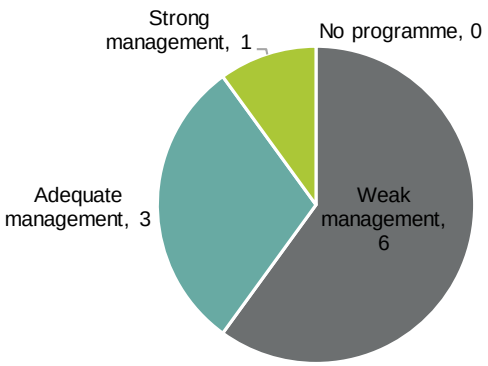


Source: Sustainalytics

Regarding ethical conduct management, the findings from the 10 pharmaceutical companies analyzed (Figure 5), show that over the past three years, the companies' performance on ethical conduct management has been fairly stable. We have not observed any significant improvements over time. **GSK** remains the best-practice example, having implemented a strong bribery and corruption policy, as well as a strong whistleblower programme that enables employees and third parties to report any violations of the code of conduct.

While **Astellas Pharma** still displays a weak ethical conduct management programme, the company's performance over the past three years has seen some improvement, particularly by extending its code of conduct to third parties, adding a stipulation in its bribery and corruption policy to prohibit conflict of interest. The company has also significantly strengthened its whistleblower programme. On the other hand, in FY2016, **Merck & Co** introduced a new code of conduct that provides less detail on corruption than its previous version, as it does not include prohibition of corruption or a definition of what constitutes facilitation payments and conflicts of interest.

Figure 6: Ethical conduct management, FY2017

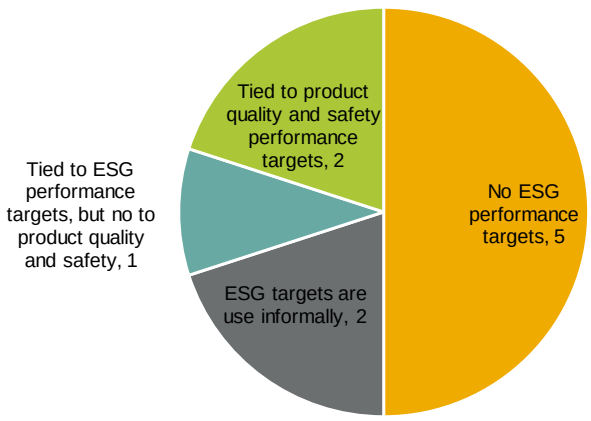


Source: Sustainalytics

As of FY2017, there was still significant room for improvement for pharmaceutical companies in terms of ethical conduct management, as highlighted by the latest performance graph above. Only one of the 10 companies analyzed, **GSK,** has implemented strong mechanisms to manage ethical conduct. These mechanisms entail board and managerial oversight on this topic, formal ethical training at all levels, internal and external compliance audits, corrective action procedures, and the application of the same standards to third parties.

Of the other companies analyzed, we consider **Novo Nordisk**, **AstraZeneca** and **Merck & Co**. to have implemented adequate systems to manage ethical conduct, which include procedures for corrective action and ethical training at the executive level, but tend to lack external audits. Finally, we consider the remaining six companies to have weak mechanisms to manage ethical conduct, showing deficiencies in several of the criteria described above.

Figure 7: Executive remuneration tied to ESG performance targets (FY2017)



Source: Sustainalytics

Regarding executive remuneration, we observed two companies that made progress during the last three years: **Novartis** and **AstraZeneca**. In FY2015, **Novartis** explicitly tied executive compensation to product quality and safety performance targets. Also, while **AstraZeneca**'s executive compensation was previously not attached to any ESG targets, in FY2017, the company developed executive compensation metrics tied to environmental targets, but not specifically to quality and safety targets.

Overall, in last fiscal year (FY2017), most of the pharmaceutical companies analyzed (five) do not show any evidence of anchoring sustainability performance to executive remuneration (Figure 7). This indicates that pharmaceutical companies have room for improvement in this area. Two companies analyzed, **Astellas Pharma** and **AstraZeneca**, indicate that ESG performance targets are used informally to compensate executives, for instance by referring to "company reputation" in relation to remuneration, or by referring to links between remuneration and sustainability performance outside of the formal remuneration policies or annual reporting.

In FY2017, only two companies, **GSK** and **Novartis**, provided evidence that executive compensation is directly linked to product quality and safety. For instance, Novartis's executive compensation is based 60% on financial targets and 40% on individual targets. The latter can include, among others, quality and social initiatives, such as access to medicines and ethical business practices. Also, GSK's CEO is paid for performance, which made up 70.8% of the CEOs FY2017 remuneration, includes financial and non-financial targets, KPIs such as increased access to health care, putting patients and consumers first, and employee engagement.

Best practices for ethical conduct

Overall, GSK stands out for its strong ethical conduct management, which includes training on its code of conduct for all employees, including executives (implemented in FY2014), internal/external audits and procedures for corrective action. Also, the company has implemented a strong bribery and corruption

policy and a strong whistleblower programme that enable employees and third parties to report any violations of GSK's code of conduct. Furthermore, GSK's CEO is paid for performance, which made up 70.8% of the CEO's FY2017 remuneration, including financial and non-financial targets, and KPIs such as increased access to health care, putting patients and consumers first and employee engagement.

2.2 Research & development

General trends insights

When it comes to clinical trials, i.e. the testing of new compounds on humans, transparency is key. In the European Union, all clinical trial results are required by law to be reported within one year of completion. However, as of September 2018, only 51% of clinical trials publicly reported their results[37]. Also, a recent study found that approximately 40% of clinical trial studies allegedly violated US transparency laws[38]. Furthermore, it has been estimated that 64% of drugs' side effects are not mentioned in the published reports on which HCPs and clinicians base their prescription decision[39]. Omitting negative trial outcome and/or failure to report trial outcomes present a distorted picture of the risks and benefits of drugs, which consequently represent a risk for doctors and patients. Furthermore, companies can be exposed to regulatory, litigation and churn risks, should such failures be discovered.

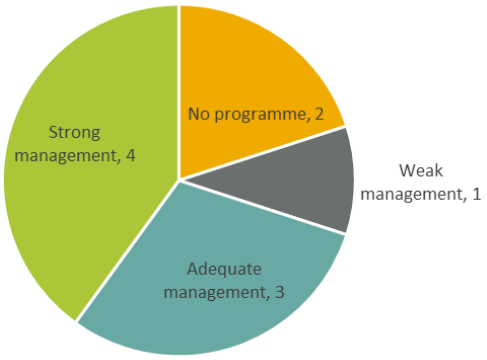
It is also interesting to highlight that in FY2017, only 18% of the drugs in pharmaceutical companies' pipelines received marketing approval from authorities and were launched on the market[40]. This highlights that standards for drug approval are very strict. Generally, out of every 10 drugs in a company's R&D pipeline, only one received marketing approval[41]. Consequently, pharmaceutical companies that invest in researching and developing new drugs, need to make sure that clinical trials are conducted according to quality and safety standards in order to increase the likelihood that their drugs receive regulatory approval for marketing.

Controversial practices

In 2012, **Merck & Co** paid over USD 5 billion in settlements and still faces consumer claims over its painkiller, Vioxx. In January 2016, the company paid an additional USD 830 million to settle a federal class action lawsuit involving allegations related to Vioxx[42]. The lawsuits accused the company of providing unreliable product information, applying deceptive promotional practices and fabricating medical journal studies to enhance Vioxx's credibility.[43] As of November 2018, Merck is still facing around 9,400 product liability claims over some of the company's products, including Vioxx.

Performance insights from the 10 pharmaceutical companies analysed

Figure 8: Clinical trial data transparency programme, FY2017



Source: Sustainalytics

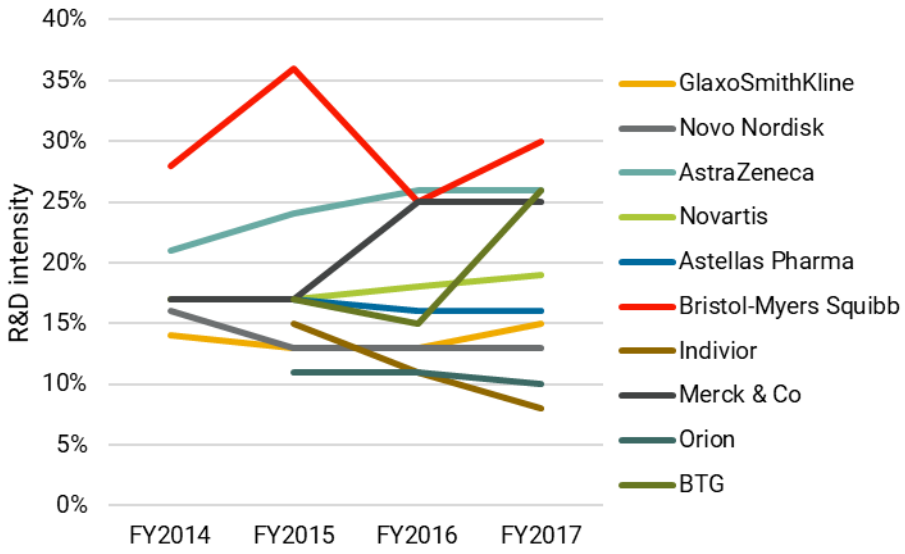
Overall, in the last fiscal year (FY2017), companies' performance on this issue indicates that, while there is still room for improvement, industry players adequately demonstrate a commitment to trial data transparency. Of the 10 companies analyzed, **AstraZeneca, GSK, Novo Nordisk, and Merck & Co.** provide evidence of strong trial data transparency.

GSK stands out for its strong clinical trial transparency programme, in place since FY2013, which includes a commitment to full data transparency across all clinical trial stages. GSK also publishes results from studies of terminated compounds to help inform the scientific community about non-productive areas of research and to reduce unnecessary exposure of study participants to similar compounds in other clinical trials.

AstraZeneca also stands out for its strong position statement on trial data transparency, committing to be fully transparent across clinical trial stages. In addition, the company reports that for some studies, independent external safety data monitoring boards are used to further strengthen the safety evaluation process.

Novartis, Astellas Pharma and Bristol-Myers Squibb (BMS) show adequate trial transparency, with reporting on four of the five relevant criteria requirements. **Orion**, though, has a weak trail data transparency programme in place, as the company states that it publishes clinical trial results, as obliged by the European Medicines Agency (EMA), but it remains unclear whether this comprises all clinical study results of the company. Moreover, two companies, **BTG plc** and **Indivior** do not address the issue in their reporting.

Figure 9: R&D intensity trend, FY2013-FY2017



Source: Sustainalytics

Regarding R&D intensity, we identified some improvement and deterioration of company performance over time. Figure 9 highlights the most interesting changes for six of the 10 companies researched. While **BMS** has the highest R&D intensity (30%), compared to the other nine companies, its performance has worsened over time, having lowered its R&D intensity by 6% from FY2015. On the other hand, **AstraZeneca** increased its R&D intensity by 5% from FY2014, which indicates an improvement in this area. Moreover, **Merck & Co** also greatly improved its performance, by increasing its R&D intensity by 8% from FY2014. **Indivior** remains the worst performer, as its R&D investment has declined from 15% in FY2015, to 11% in FY2016 and to 8% in FY2018.

Best practices

Merck & Co's management of product quality and safety at the R&D stage has always considered strong. The company mentions that all trials on patients are registered in credible databases, such as the US National Institute of Health trials database (clinicaltrials.gov), as well as in medical or scientific journals. Moreover, the company states that all clinical trials are disclosed within 12 months after the patient's last visit providing the primary outcome. For clinical trials that are terminated early for medical reasons, Merck reported medically important information to regulatory authorities and the public, and updated the status on clinicaltrials.gov within 30 days. If clinical trials are terminated early for other reasons, their results are disclosed within 12 months after the patient's last visit. Merck has also implemented an online mechanism for scientific and medical researchers who wish to submit a proposal to access clinical trial data. Furthermore, the company's R&D intensity increased from 17% in FY2015 to 25.44% in FY2017.

2.3 Manufacturing & distribution

General trends insights

The quality and safety of pharmaceutical products directly affects the regulatory approval of products, the scope of approval, a product's competitive advantage and customer trust. Quality and safety risks for pharmaceutical companies at the manufacturing and distribution stage include manufacturing irregularities and unanticipated side effects. Failure to adhere to extensive regulations and quality management standards has led to expensive recalls, increased regulatory scrutiny, compliance costs and a loss of customer trust. In extreme cases, regulators have imposed import bans or halted production until quality issues were resolved.

Manufacturing irregularities have occurred mostly in emerging markets, particularly India, with notable exceptions in developed markets. As of FY2017, the US is the biggest drug importer globally, with 25% of the drugs commercialized in the US imported from other countries, including India and China[44]. Companies exporting products from emerging to developed markets are especially exposed to regulatory scrutiny, particularly because one of the US FDA's mandates is to improve import safety. To do so, the FDA has been increasing its control over overseas manufacturers that supply and export products in the US since 2013. A clear majority of pharmaceutical companies has faced product liability litigation from patients for failing to inform customers or respond to complaints about unanticipated side effects, with costs reaching billions of US dollars. Therefore, the adoption of company-wide quality management system (QMS) certifications can be an indicator of how well pharmaceutical companies are mitigating product quality and safety risks. Examples of internationally acknowledged standards include ISO 9001 (quality management principles), Good Manufacturing Practice (GMP) or ISO 13485 (quality management systems specifically for medical devices).

Controversial practices

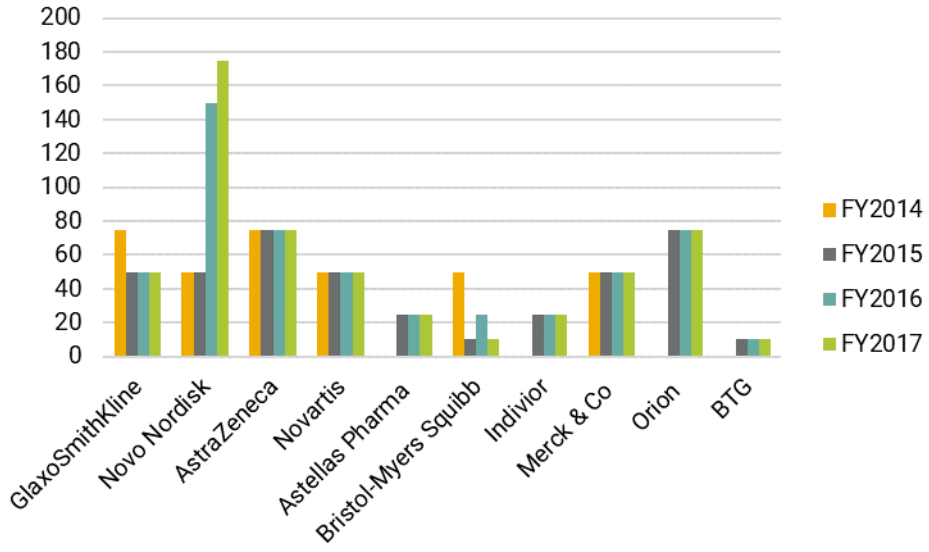
Repeated significant incidents regarding the quality and safety of **Merck & Co's** products have been reported over the past few years. Despite settling the majority of its legal cases, particularly for its high-profile Vioxx product, which has cost the company more than USD 5 billion and allegedly impacted around 160,000 patients, Merck is still facing around 9,400 product liability claims[45]. As of December 2017, 775 lawsuits for its Propecia drug are still pending, alleging that the company failed to warn patients about the medication's sexual and cognitive side effects[46]. Furthermore, over 1,200 lawsuits regarding its Januvia and Janumet products (which combined accounted for 14.7% of FY2017 revenues) were still pending, with plaintiffs alleging that the type-2 diabetes drugs could cause pancreatitis[47]. Similarly, the company is facing more than 4,000 lawsuits for its Fosamax drug, which is used to treat osteoporosis[48]. Plaintiffs allege that Fosamax is linked to an increased risk of bone fractures and osteonecrosis.

GSK has also not been free from quality and safety issues over the years. The company has faced a number of allegations of poor product quality and safety. These incidents have cost the company several billions of US dollars in settlement fees over the past three years. GSK has faced numerous product liability lawsuits for Avandia, antidiabetic drug, and Paxil, drugs for anxiety and depression. Avandia was restricted by US regulators and pulled from the

European market due to the heightened risk of heart attack[49]. GSK has pled guilty to withholding safety data from the FDA and settled approximately 50,000 consumer lawsuits over Avandia related injuries[50]. GSK's Paxil has also been criticized for its numerous side effects, such as birth defects, suicidal tendencies and withdrawal problems.

Performance insights from the 10 pharmaceutical companies analyzed

Figure 10: Overall performance on this dimension, FY2014-FY2017



Source: Sustainalytics

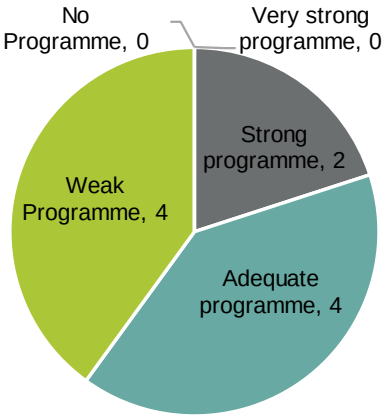
Overall, in the last three fiscal years, we observed some notable improvements in the manufacturing and distribution stage (Figure 10). **Novo Nordisk** deserves a mention for its improvements to both its product and service safety programmes, as well as external QMS certifications. Since FY2016, the company has steadily strengthened its product and safety programme, which now includes a quality management system, reviewed once a year by the board. Novo Nordisk's executive management conducts a quality management review twice a year. The system also includes regular internal and voluntary external (i.e. not by regulatory authorities) quality audits. Novo Nordisk also includes product recalls as a non-financial target in the company's balanced scorecard. Furthermore, any quality-related misconducts will be investigated by the company's audit committee or by the board of directors. In FY2016, the company certified 100% of its sites according to the ISO 9001 standards.

At the same time, **AstraZeneca** has also improved its performance on this dimension. The company has implemented regularly tested emergency response procedures, product/service objectives and targets, and started to report on its product safety audits as of FY2016.

On the other hand, the performance of **BMS's** product safety programme has deteriorated, as the company no longer conducts safety risk assessments. Furthermore, the company is still not publicly disclosing information on quality

management system certifications. Likewise, **GSK**'s performance has deteriorated over time, as the company's product safety programme lacks regularly tested emergency response procedures as well as targets to reduce the number of product recalls, compared to FY2014.

Figure 11: Performance on product and service safety programme, FY2017



Source: Sustainalytics

Looking at specific company performances for the last fiscal year (FY2017), of the 10 pharmaceutical companies researched by Sustainalytics (see Figure 11), two companies – **AstraZeneca** and **Novo Nordisk** – have implemented a strong product safety programme. For instance, Novo Nordisk and AstraZeneca's programmes include several elements, such as managerial responsibility for product quality and safety, regular employee training, and targets for improvement. These programmes do not cover merely manufacturing and distribution of products, but also safety risk assessments during the product development (R&D) stage, as well as during the post-marketing stage (the latter is discussed in chapter 2.5). However, Novo Nordisk and AstraZeneca's programmes still lack certain elements, such as incident investigation and corrective action procedures and voluntary external audits. Therefore, no company in our sample of 10 researched entities has what we consider to be very strong programmes to manage product quality and safety.

Of the remaining companies, four have implemented adequate product safety programmes and the other four have weak programmes. Companies displaying weak programmes – **Indivior**, **Astellas Pharma**, **BMS** and **BTG** – have implemented product quality and safety initiatives, but they have a limited scope (e.g. only cover certain markets), or lack certain key elements, such as regularly tested procedures for product recalls.

Moreover, nine of the 10 pharmaceuticals companies researched do not demonstrate evidence of external certifications according to ISO 9001 or other internationally acknowledged standards, such as Good Manufacturing Practice (GMP) or ISO 13485. This contrasts with the leading company in this area, **Novo Nordisk,** which has a certified QMS for 100% of its operations. Audits and inspections by regulatory authorities are not considered; companies are given credit only for voluntary external certifications.

The fact that most of the companies do not display an adequate safety management system might be explained by the fact that the industry in general does not tend to solicit external assurance of their operations. The argument often used by companies is that additional scrutiny is not necessary, since the industry is already heavily regulated. The large number of product quality and safety incidents in the industry, however, points to a clear need for an additional level of assurance.

Best practices

Novo Nordisk is the best-practice example in the area. In addition to the fact that the company has an overall strong product quality and safety programme, it is the only company that has all of its operations externally certified according to recognized quality standards. As of FY2016, 100% of its sites received ISO 9001 external certifications for their quality management systems, which is still applicable for the last fiscal year (FY2017).

2.4 Marketing & sales (including sales incentives)

General trends insights

The majority of pharmaceutical companies have faced product liability litigation from patients for failing to inform customers or respond to complaints about unanticipated side effects over the past few years, with costs escalating into billions of US dollars. Business impacts include loss of revenues and diminishing returns on R&D investment if a product is removed from the market completely, or if regulators impose stricter prescription criteria. Moreover, it can take years to regain trust from patients and society. Companies operating in the US are more exposed to patient litigation. Companies that market pharmaceutical products for unapproved uses or provide misleading product information have faced criminal charges and litigation from patients, as well as shareholders. Fines and settlement payments can reach several billion US dollars for a single product and have affected numerous pharmaceutical companies.

The marketing intensity indicator (marketing expenditure/company's revenues) identifies companies that may have greater or lower exposure to the risk of improper marketing. Nonetheless, one should take care when comparing these figures directly, as the companies analyzed have different business models and/or geographical focus. For instance, less marketing is needed for specialized, niche drugs than for drugs with a broad potential patient base. For an industry known for its particularly high R&D intensity and the importance of R&D for the long-term viability of its businesses, it is noteworthy that all of the 10 companies analyzed spend more on marketing than on R&D. This difference raises some doubts about the sustainability of the sample companies' business strategies. Investment in R&D, including the development of new products and testing their safety and efficacy, seems to play a less important role than investment in product promotion.

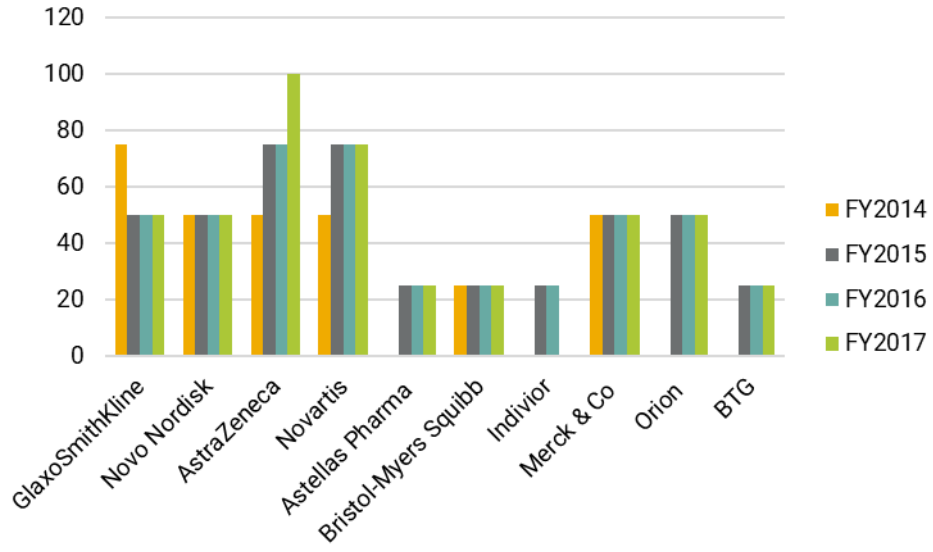
Controversial practices

GSK stands out from its peers for the numerous allegations of false and deceptive marketing it is facing currently. In June 2014, GSK reached a settlement agreement of USD 105 million with 44 US states to resolve

complaints over off-label marketing of three drugs (Paxil, Wellbutrin and Advair). GSK's most notable offence, though, was its much-publicized USD 3 billion settlement with the US government in 2012, representing the largest of such settlements in the industry to date. The fine was imposed for various improper marketing practices, including off-label marketing and failure to adequately disclose product safety information of its antidepressant drugs, Paxil, Wellbutrin and Avandia.

Performance insights from the 10 pharmaceutical companies analyzed

Figure 12: Ethical medicine promotion programme, FY2014-FY2017



Source: Sustainalytics

Regarding ethical medicine promotion, we have found that among the 10 pharmaceutical companies analyzed (Figure 12) performance on ethical medicine promotion has improved over the past three years. For instance, **GSK** is a strong example for its pioneering ethical medicine promotion practices. In 2013, the company rolled out a policy to stop paying health care professionals (HCPs) and moved away from direct sponsorship of individual health care professionals to arm's-length funding, for instance via independent third-party medical organizations. GSK was the first and only company to implement such a policy, at the time. In January 2016, GSK effectively stopped payments to doctors worldwide for promotional activities. However, in 2017, the company decided to change its policy, and allowed payments (at fair market value) to doctors and HCPs, having seen important scientific dialogue with them reduce after the company stopped payments.

On the other hand, **AstraZeneca** has taken a step forward and set the bar for best practices regarding the full disclosure of payments made to HCPs. In May 2018, the company officially stated that it will publicly disclose payments in all

countries in which it has commercial activities, even where it is not legally required to do so. This commitment was made at the company's Annual General Meeting 2018 and was confirmed in an article published by the Times in June 2018.[51] AstraZeneca is the only pharmaceutical company to have made such a strong commitment, and makes the company a pioneer in this space.

Moreover, **Novartis** has committed to fully disclose payments made to HCPs, also where it is not legally required, but only when it is "legally possible". Therefore, this has not led to a higher score. **Indivior**, meanwhile, has shown a visibly worse performance on ethical medicine promotion. In the previous fiscal year (FY2016) the company disclosed standards for employees for ethically interacting with HCPs; however, these standards were not publicly available in FY2017.

Overall in the last fiscal year (FY2017), only two pharmaceutical companies, **AstraZeneca** and **Novartis**, display a strong ethical medicine promotion programme, indicating that pharmaceutical companies have space for improvement. For instance, **AstraZeneca** reports on the number of employees and third parties that have been removed from their roles as a consequence of code of conduct breaches. When working with suppliers, distributors and partners on the sales and marketing of products, the company reports that it conducts company-wide risk assessments.

Most of the companies (40%) have an adequate programme in place. For instance, **Merck & Co** enforces training for its employees who interact with health care professionals and has operating guidelines in place. However, while its compliance programme includes monitoring activities and internal audits, incident investigation and corrective actions, this only covers its US-based activities, which do not represent more than 50% of its operations. Also, there is no evidence that the company has set objectives and targets, conducts external audits, risk assessments or ethical reviews, or publicly discloses payments made to healthcare professionals.

GSK and **Novo Nordisk** also have an adequate ethical medicine promotion programme, with dedicated policies on the promotion of products to health care professionals and consumers. Specifically, **GSK**'s business units adopted an internal control framework to support risk assessment and management related to commercialization. However, the company does not disclose the frequency of related risks assessments conducted.

Moreover, the three companies, **Astellas, BMS, and BTG,** have weak programmes in place, lacking managerial oversight, regular risk assessments, training for sales representatives, objectives, corrective action procedures and regular audits. Lastly, one company, **Indivior,** does not have an ethical marketing promotion programme in place.

Best practices

AstraZeneca's performance over the past few years has seen improvement in the area of ethical medicine promotion. In May 2018, the company committed to publicly disclose payments in all countries in which it has commercial activities, even where it is not legally required to do so. Also, AstraZeneca's marketing expenditure performance has improved over the past few years, as the company has decreased its marketing expenditure.

2.4.1 Sales incentives

General trends highlights

Not rewarding sales staff based on sales volumes, but instead on the quality and objectivity of sales information and technical knowledge, is seen as a solution to incentivize ethical conduct among sales representatives. However, there has been a slow adoption rate from pharmaceutical companies. This may be because a complete shift in the corporate mindset needs to take place, as sustainability should be seen as a factor of growth.

Performance insights from the 10 pharmaceutical companies analyzed

Looking at the specific company performances over the last fiscal year (FY2017), a value-based sales approach could be beneficial for consumers (see chapter 1.4.1). However, only one of the 10 pharmaceutical companies analyzed, **GSK**, has implemented a sales personnel remuneration programme based on non-volume sales targets. The company stopped rewarding sales staff based on prescription volumes and, instead, started rewarding technical knowledge and quality of service. This new approach was implemented globally, in early 2015. These new compliance strategies go beyond those adopted by any of the company's peers and make GSK the undisputed leader in managing and mitigating marketing risks.

Only one company has slightly improved its performance on this topic over the past few years, **Novartis**. In FY2018, **Novartis** changed its sales representatives' compensation scheme, which is now composed of variable and fix parts. The variable part could range from 30-40% of total compensation, depending on the country in which the employee works. However, the company does not specify the individual components that make up the variable compensation. Moreover, most of the pharmaceutical companies analyzed have not expressed any commitment and/or interest to change its sales representatives' compensation structure. Overall, sales incentive programmes are the worst performing indicator analyzed, highlighting a critical weakness within the pharmaceutical industry.

Best practice

Overall, in terms of ethical marketing, GSK stands out for its strong sales personnel remuneration programme, as it is the only pharmaceutical company that has set a goal to eliminate individual sales targets for all sales professionals globally. It has also achieved its goal by completing the roll-out of changes to the way sales teams are compensated worldwide.

2.5 Post-marketing (pharmacovigilance)

General trend insights

According to the World Health Organisation (WHO), pharmacovigilance is "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem". According to research, 30% of the 222 drugs approved by the FDA between 2001 and 2010 were affected by a post-market adverse safety event, as of FY2017[52]. Certain drug side effects may not be identified until a larger number of patients have

used the drug and some side effects can take longer to appear. Therefore, it is crucial that pharmaceutical companies monitor the safety of their drugs after they are commercially available on the market. In the absence of adverse drug event reporting, society and consumers are not adequately informed about medicines' hazards, receive false safety signals, and cannot quantify risk in relation to benefit appropriately. The FDA has stated that fewer than half of the adverse event reports submitted to the agency by pharmaceutical companies are complete,[53] as companies tend to report partial information about post-market safety events. Similarly, in developing countries (e.g. Brazil) there is a tendency to report incomplete information about post-market safety events, preventing the event from being classified as a safety side effect[54].

Controversial practices

The example of **Merck & Co** stands out in particular, as the company has processes in place for monitoring product safety performance, as well as incident investigations and corrective action mechanisms. Nevertheless, the company continues to face a significant number of liability lawsuits connected to the negative side effects of its drugs, casting doubts on the effectiveness of its pharmacovigilance programme. The company has several thousand ongoing liability lawsuits related to the safety of its drugs. Specifically, over 1,200 lawsuits related to its Januvia and Janumet products (which combined accounted for 14.7% of FY2017 revenues) were still pending as of December 2017, with plaintiffs alleging that the type-2 diabetes drugs could cause pancreatitis[55]. To prevent such cases from occurring, companies are expected to implement strong post-marketing control mechanisms.

Performance insights from the 10 pharmaceutical companies analyzed

Figure 13: Post-marketing activities, FY2017

Companies	Monitoring of product safety performance	Incident investigation and corrective action
GlaxoSmithKline	X	X
Novo Nordisk	X	
AstraZeneca	X	X
Novartis	X	X
Astellas Pharma	X	
Bristol-Myers Squibb	X	
Indivior	X	
Merck & Co	X	X
Orion	X	X
BTG	X	

Source: Sustainalytics

The table above (Figure 13) depicts two key elements of a strong

pharmacovigilance system:

- Monitoring of product safety performance: Structural monitoring of product safety performance in the market place should include: post-marketing surveillance to systematically track any side effects and adverse events for several years after a new product is launched. Also, a reporting mechanism for doctors and/or patients to report product safety concerns.

- Incident investigation and corrective actions: Mechanisms in place for investigating reports on drug safety issues such as (unanticipated) side effects, and procedures for corrective action.

As shown in Figure 13, in the last fiscal year (FY2017), all 10 of the pharmaceutical companies that we researched conduct product safety monitoring programmes during the post-marketing stage. **Novo Nordisk** has implemented a reporting system to monitor and address any potential adverse events related to its products. The company also conducts local -driven actions to ensure awareness of product safety, and its dedicated global safety team set up guidance and tools, such as a side effect reporting video. However, there is no evidence that the company has implemented a mechanism to investigate drug safety issues. On the other hand, half of the companies researched have not implemented mechanisms to investigate incidents or take corrective actions if there are adverse events. This highlights room for improvement for the remaining five pharmaceutical companies (**Novo Nordisk, Astellas, BMS, Indivior, BTG**), which still need to develop a mechanism for investigating reports on drug safety issues such as (unanticipated) side effects, and procedures for corrective action.

Conclusion

Our research reveals that it is paramount for pharmaceutical companies to anchor ethical conduct management to their organizations and implement and enforce strong quality management along the product life cycle: from R&D, to manufacturing and distribution, to marketing and sales, to post-marketing. These steps can help reduce the likelihood of negative health outcomes for patients and, in turn, avoid unnecessary costs to society.

It is evident that meeting minimum legal requirements is not sufficient to mitigate adverse impacts on patients and society. Even a moderate adoption of product quality and safety measures, going beyond legal requirements, may not suffice to avoid future harm to consumers. This is demonstrated by the high level and scale of controversy involvement of pharmaceutical companies. In the last 10 years, pharmaceutical companies have paid more than USD 30 billion in financial penalties connected to ethical conduct and quality and safety practices. **GSK**, **Merck & Co**, **Novartis**, **AstraZeneca** and **BMS** together were issued approximately USD 13 billion in financial penalties between 1991 and 2017, with **GSK** representing the highest penalties in the industry. This increases the need to ensure that effective and efficient programmes are in place, in order to avoid involvement in related controversies.

At the corporate level, there is still significant room for improvement among pharmaceutical companies. Only one of the 10 companies analyzed, **GSK**, has implemented strong mechanisms to manage ethical conduct. Most companies have weak mechanisms to manage ethical conduct, showing deficiencies and increasing the risk of being involved in related controversies. Additionally, half of the companies analyzed do not show any evidence that they tie sustainability performance to executive remuneration.

At the R&D stage, the majority of the 10 pharmaceutical companies analyzed implement strong or adequate trial data transparency standards, in response to increased regulation. One achievement of ASN Bank's engagement on this topic is **Novo Nordisk**, which successfully improved its transparency on clinical trial publications. However, in the last decade the average cost to bring a new drug to the market has sharply increased. This points to one of the key problems within the industry, namely the high cost of failure, which is likely to present challenges to pharmaceutical companies during the R&D stage.

At the manufacturing and distribution stage, six of the 10 companies analyzed have implemented adequate product safety programmes. In the last three fiscal years, we have also observed some notable improvements related to this stage. **Novo Nordisk** deserves a mention for its improvements to both its product and service safety programme, as well as external QMS certifications, as it is the only company analyzed that has 100% of its sites certified for ISO 9001 standards. Consequently, nine of the 10 pharmaceutical companies researched do not have external certifications according to ISO 9001 or other internationally acknowledged standards, such as Good Manufacturing Practice (GMP) or ISO 13485.

At the marketing and sales stage, only two pharmaceutical companies, **AstraZeneca** and **Novartis**, report on a strong ethical medicine promotion programme. This indicates that pharmaceutical companies have room for

improvement here. It is important to highlight the positive impact that ASN Bank's active engagement has had on **AstraZeneca**. In May 2018, the company officially stated that it will publicly disclose payments in all countries in which it has commercial activities, even where it is not legally required to do so. AstraZeneca is the only pharmaceutical company to have made such a strong commitment, making it a pioneer in this space. However, very few companies show strong mitigation mechanisms to avoid future improper marketing incidents, indicating a high probability that this will remain a controversial area for the industry in years to come.

At the post-marketing stage, while all 10 of the pharmaceutical companies that we researched conduct product safety monitoring programmes during the post-marketing stage, half of them still need to develop a mechanism for investigating reports on drug safety issues, such as (unanticipated) side effects and procedures for corrective action. Adverse drug reactions (ADRs) remain one of the main causes of patient hospitalization, representing 5-7% of all hospitalizations, and approximately half of are these assessed as preventable. A more diligent pharmacovigilance programme could lower the number of ADRs globally, therefore reducing the negative impacts on patients. More awareness on how patients and doctors can submit information about post-market safety events could improve performance at this stage, highlighting the need for the pharmaceutical sector to raise the bar on it.

Finally, our research confirms that, while some progress has been made in the past few years, the industry still needs to improve standards and raise the bar on best practices in order to avoid putting the health of patients and national health care systems at risk.

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