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Investing in sustainability

Health: Pharmaceuticals and Medical Products

Sustainable Development Sector Analysis Framework

March 2021

This is a methodological document aimed at clarifying how Mirova takes into account sustainable development issues in the framework of the environmental, social and governance analysis of each sub-sector of activity.

An affiliate of: NATIXIS INVESTMENT MANAGERS

Companies operating the healthcare sector and, more specifically, those involved in research, manufacturing and distribution of medical products, face complex challenges ahead, such as providing treatment to an aging population, tackling medical conditions arising from changing lifestyle habits and rising urbanization, or fighting the spread of tropical diseases. While medical research and innovation will be essential to tackle these issues in the sector, among others, companies operating in medical research are also posed to benefit from new opportunities arising from the application of modern technologies, such as genomics and sequencing leveraging on the use of big data, as well as an a multiplication of available body of knowledge through improved information sharing mechanisms among the medical community.

As competition in the sector is getting fierce and many blockbuster drugs are no longer patents protected, companies are forced to innovate to remain competitive; However, such competition to preserve market share could also create incentives for adoption of uncompetitive and unfair market practices.

We anticipate and expect that improved disclosure around business practices and the adoption of stricter anti-corruption measures will become standard requirements for a sector that never ceases to be mired in ethical controversies.

This framework has been updated more than a year after the first COVID19 infections thus following a year of pandemic. 2020 has been a major upheaval for all industries, yet, has particularly challenged the pharmaceutical and medical products industry. Indeed, the events and pandemic illustrated how crucial the sector was to ensure global health. Moreover, it highlighted companies' capabilities and responsibility in rapidly gathering R&D and other resources to develop treatments, vaccines, and diagnostics to contain and hopefully eradicate the virus over the long run. Yet, the pandemic also illustrated the complexity of the sector, and somehow its weaknesses, for example in what regard supply chain management.

Sectors: Pharmaceutical companies, biotechnology and life science tools and services, health care distributors.

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The SDGs at the core of an increasingly complex industry

Products offering solutions to the 3rd SDG

Since World War II, global average life expectancy at birth has increased by about 25 years, according to the WHO, from a little less than 50 years to over 70 years today. However, health disparities across regions are growing, with Sub-Saharan Africa experiencing significantly higher probability of premature adult death than more developed, low-mortality regions (WHO, 2017).

Figure 1: Life expectancy at birth (years - both sexes)

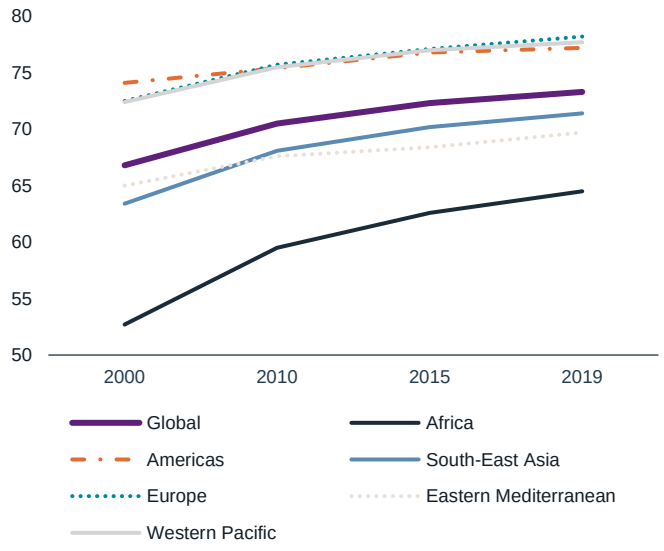
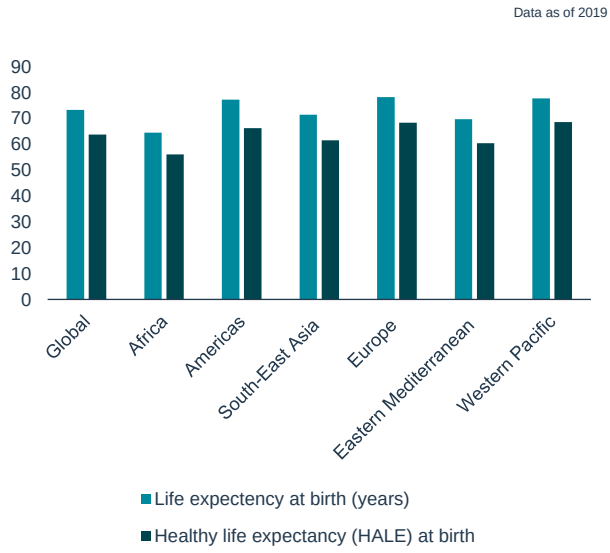


Figure 2: Life expectancy at birth and Healthy Life Expectancy (HALE) at birth per region (years)



Source: Mirova/ (WHO, Global Health Observatory data repository, 2019)

Global health indicators such as life expectancy at birth and healthy life expectancy (HALE) at birth, which reflects the number of years expected to be lived in full health at birth, show modest improvements since the early 2000s. Indeed, global life expectancy at birth rose about 10% since 2000 and the global HALE rose by +9%. Nevertheless, a significant gap across countries persists (Figure 1). For example, the average life expectancy at birth is about 78 years in Europe, yet, 71.4 in South-East Asia, and down 64.5 in Africa. HALE indicators also vary widely across regions and countries: while this is unsurprisingly lower than average in most African countries, the indicator drops below 60 years and may even attain less than 50 years in some African countries. As a result, finding a solution to unmet medical needs remains a global priority, especially in least developed countries.

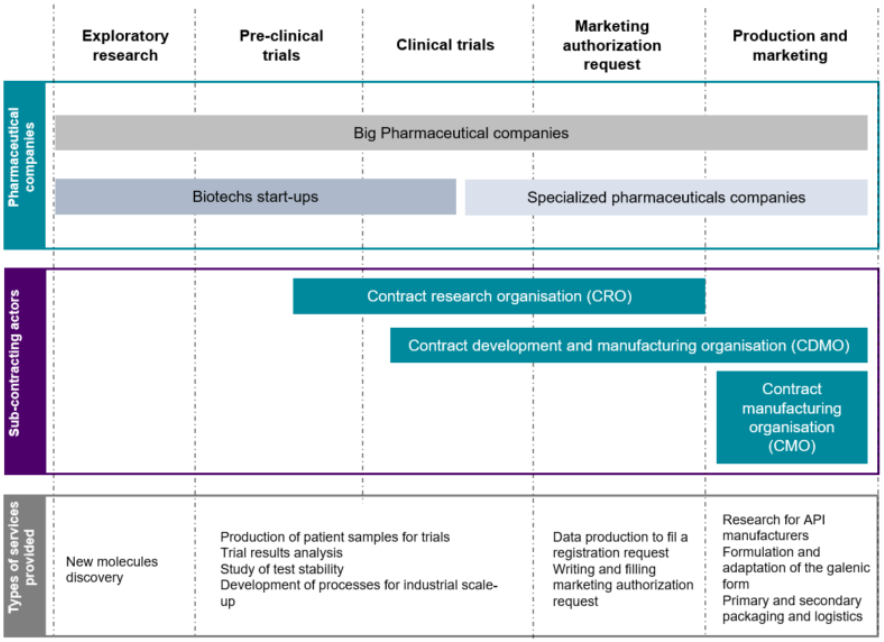
As responsible investors, we thus look at the global healthcare sector as directly addressing the Sustainable Development Goal 3 (i.e. SDG3) - ensure healthy lives and promote wellbeing for all at all ages. In this regard, the United Nations have set a few meaningful goals by 2030 such as the reduction of the global maternal mortality ratio to less than 70 per 100,000 live births, the end preventable deaths of newborns and children under 5 years of age, the end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases and combat hepatitis, water-borne diseases and other communicable diseases etc. Reaching these objectives will undeniably be enabled by a strong public-private relationship, to ensure medical innovations (medicines, vaccines, diagnostics etc), which mainly designed in private

laboratories, are made available to all human beings. Alongside access to medicine, we have identified some key drivers providing high-impact investment opportunities: such as addressing unmet medical needs of vulnerable populations – including tropical and rare diseases – as well as research that responds to the biggest challenges of our times through impactful innovation.

An increasingly complex industry

To be able to adequately analyze companies in the sector from a sustainability point of view, it is crucial to understand the recent evolution of the industry over the last decades. Indeed, while the overall objectives of the sector have not changed, and it continues to positively deliver on social issues, the evolution of the companies' business models have highly increased their exposure to sustainability related risks. Indeed, on the one hand, large pharmaceutical companies have strengthened their focus on R&D and tend to have outsourced certain types of activities resulting in the apparition of CRO, CDMO, CMO (see figure 3 below). This increasingly fragmented industry has led to an increasing risk exposure both on social and environmental perspectives and companies are more and more expected to be able to control the supply chain, to ensure suppliers apply high quality standards. Indeed, Contract Manufacturing Organizations (CMOs) are often located in developing countries, with less stringent regulations. For example, China and India are the world's largest drug manufacturers (API and generics), due to low costs and relatively well-established technical skills in the field. According to a study published in The Lancet in 2020, Indian pharmaceutical companies rely on China for 70% of the active pharmaceutical ingredients (APIs). Indeednn China is the world's leading producer and exporter of APIs by volume.

Figure 3: Different organization models in the pharmaceutical manufacturing highlight the needs for extended transparency



Source: Mirova, (Economie du Médicament, 2016)

Sustainability Opportunities

Access to Medicine

Access to Medicine (ATM) is a serious development challenge as it affects a substantial part of the population in most developing countries. According to the World Health Organization (WHO), underfinancing results into scarce availability of medicines in public sector – on average ~35% - forcing patients to either purchase medicines from the higher-priced private sector or forgo treatment altogether. In addition to developing countries, some low-income patients in developed countries may also have more limited access to some essential treatments when these are not covered by public spending. Both the public and the private sector have a role to play in order to provide equitable and adequate access to essential medicines. As investors, we are primarily concerned with the role of the private sector.

A useful global indicator to understand the global health burden is the Disability-Adjusted Life Year (DALY), which measures a year loss of healthy life. For diseases with high DALY rates one can assume that a high percentage of the population either does not get treated (properly) or that these diseases affect a growing number of people. As Figure 3 shows, some leading causes of DALY have seen a rise in global incidence, while others that are primarily present in developing countries such as HIV, diarrheal diseases and lower respiratory infections show a remarkable decrease, although they still figure within the top 20 according to the WHO figure. Therefore, it is extremely important that access to medicine improves in least-developed countries, while also increasing research into tropical and endemic diseases that continue to claim lives among the most vulnerable populations.

Figure 4: 20 leading causes of Disability-Adjusted Life Year (DALY) globally (in million), 2000 vs 2019

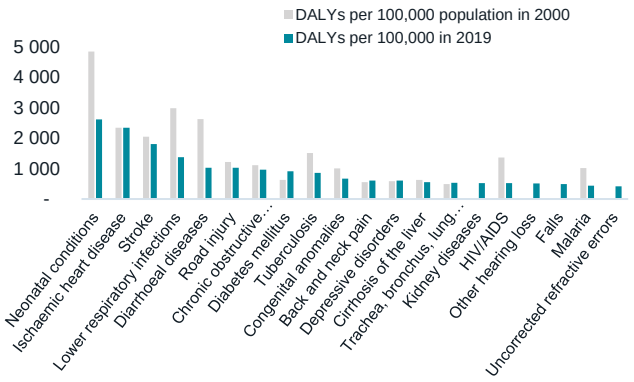
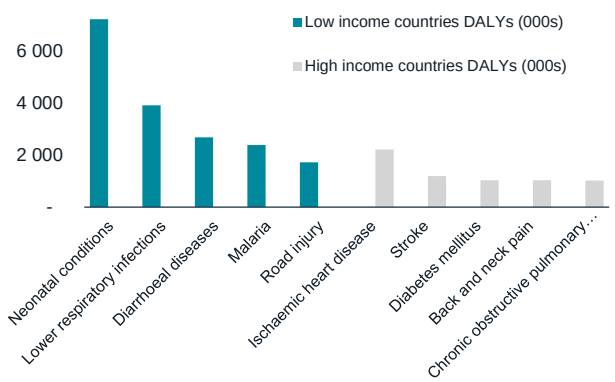


Figure 5: 5 leading causes of Disability-Adjusted Life Year (DALY) in low- and high- income countries (in million), in 2019



Source: Mirova/ (WHO, Health statistics and information systems, 2019)

According to the Access to Medicine index[1], pharmaceutical companies can act on improving drug accessibility in developing countries in several ways, such as differentiated pricing strategies for lower-income patients; research and development (R&D); and intellectual property sharing mechanisms which allow for a broader target base. Indeed, companies have a key role to play in advancing access to medicine through non-exclusive voluntary licensing. A voluntary license is an authorization given by the patent holder to a generic company, allowing it to produce the patented medicine. A non-exclusive voluntary license can be granted to more than one company, thus, enabling increased competition in the drug manufacturing. While the index fundamentally focuses on companies targeting five diseases that are highly

1 The Access to Medicine Foundation is an international not for profit organization dedicated to addressing global healthcare challenges, which publishes an annual Index that ranks pharmaceutical companies with respect to their effort to improve global access to medicine.

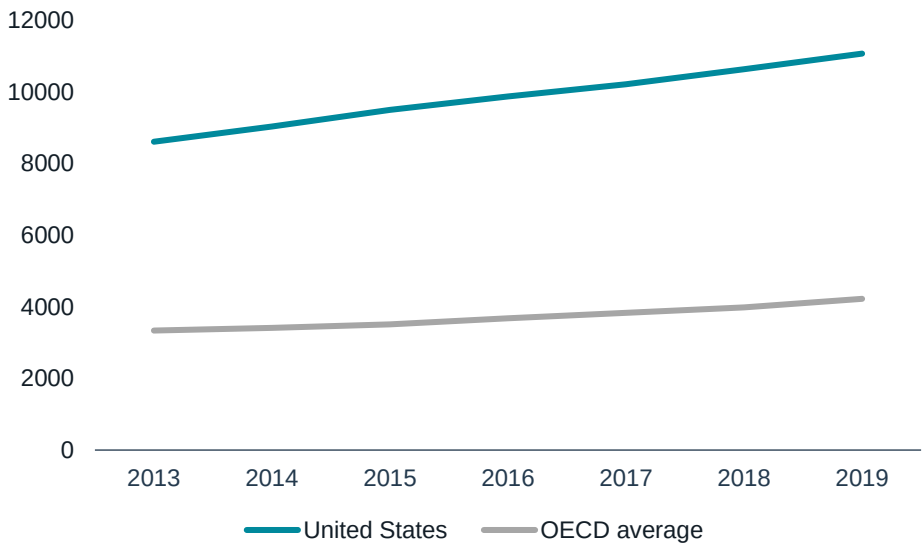
relevant in this area[2], we believe that all medical product companies can strengthen their efforts towards enabling advanced access to medicines among low-income populations. Overall, we consider companies can act towards accessibility through 3 levers: availability, affordability and infrastructure and support.

In addition, generic drugs, which are marketed after a branded drug's patent expires, can also contribute to improve access to medicines for low-income populations, particularly so in developing countries. Biosimilars, which are generic versions of existing complex biologic medicines whose patents have expired or are due to expire soon, bear the same potential social benefits but their regulatory framework is still fragmented.

We believe that access to medicine may have some financial implications to companies involved in the manufacturing and distribution of drugs through first-mover access to new markets and the need to broaden the customer base by also tapping into developing countries where low-income households represent a larger share of the population.

In developed countries, where healthcare systems are usually more mature yet, have also reached an impressive level of complexity, pricing issues needs also to be monitored, and thus, especially in the United States where health spending and drug pricing are known to be way higher than in any other developed market.

Figure 6: Health spending in the United States vs. Average OECD countries (Total, US dollars/capita, 2005 – 2019)



Source: Mirova, OECD

While topics related to infrastructures and availability are considered well tackled, the number of intermediaries (namely PMBs) has obstructed affordability for some patients, with low- or no- health coverage. Of course, private companies cannot be the only one pointed out for the dysfunction of the system, nevertheless they are highly expected to offer affordability solutions for these particularly vulnerable patients.

We expect companies to be significantly involved in providing equitable access to medicine in all markets of operation, especially in developing countries. Access to medicine should be embedded into the strategy of companies operating within the healthcare sector and form an integral part of their core values and profitability drivers. We thus expect medical product companies to adapt their drug prices to the purchasing power of consumers, particularly in least developed countries and also across different socio-economic segments. We also look at initiatives aimed at increasing research collaboration in developing countries; allowing early diagnosis of infants in third-world

2 Lower respiratory infections, diabetes, hepatitis, HIV/AIDS and malaria

countries; and helping build local infrastructure for treatment. Finally, we regard highly companies involved in the marketing of generics (including biosimilars) in low-income countries, due to their positive impact on market access.

KEY INDICATORS

- Transparent pricing policy highlighting strategy for differentiated pricing across countries of operation.
- Quantitative indicators related to the number of people covered by a company's ATM strategy.
- Investment (both Capex and R&D budget) dedicated to ATM.
- Indicators of revenue (either forecasted or realized) from ATM strategies per country of operation.
- Percentage of product portfolio made up of generics and biosimilars sold in low-income countries.

Neglected diseases or unmet medical needs

Another way medical product companies can provide a solution to health issues is by targeting diseases where patients do not currently benefit from a suitable treatment or cure. Among these there are neglected tropical and endemic diseases, where recent outbreaks in developing countries, such as the Zika virus in Latin America and Ebola in Central Africa, have recaptured attention. Such diseases are not yet addressed by current treatments and usually the healthcare sector is less involved due to lower profitability. In addition to such endemic diseases, other illnesses suffer from under-coverage such as rare diseases, i.e. those affecting very few patients around the world. Every country sets its threshold to categories rare diseases; in the EU a rare disease affects fewer than 5 people in 10,000. These range from cystic fibrosis to syndromes such as the Opitz trigonocephaly affecting about one case per million people (Orpha.net, 2007). With such rare incidence, no country can afford offering treatment for the full spectrum of rare diseases, also due to the complexity of conducting research and clinical trials, where critical mass is needed. Therefore, many governmental and non-governmental associations of patients around the world play a pivotal role in promoting international collaboration to develop therapies for rare diseases. Private companies within the pharmaceutical and biotechnology sectors as well as those involved in the full medical research spectrum (e.g. clinical trials, diagnostics) can also play a pivotal role in fostering research and treatment of rare diseases. However, focus on these unmet medical needs requires intense coordination with governments, which reimburse a high share of the expensive treatments (generally over $100,000 per patient), as well as a closer approach with the patients and their representative associations. Therefore, companies involved in treatment of such illnesses need to be especially transparent about their pricing policies and abuse of market dominance (as there is generally little competition) and relationship management with patients and government officials.

We consider medical product companies that focus on rare diseases and unmet medical needs such as tropical and endemic diseases, as offering high value-added investment opportunities from a sustainability point of view by providing treatment to underserved patients.

KEY INDICATORS

- Indicators of revenue from rare diseases treatment or related service offering
- Investment (both Capex and R&D budget) dedicated to rare diseases
- Number of products / Share of the portfolio receiving a "rare" designation (in the US, breakthrough therapy / in the EU, PRIME)

Impactful Innovation

Innovation is a key driver of growth for the pharmaceutical industry and medical product companies, but it is also a large term. By developing new treatments for known diseases, some forms of innovation have the potential to sensibly improve the health outcomes for patients. Within this context, the development of a personalized medicine approach, which aims at customizing therapy based on the genetic composition of each patient, allows for increased effectiveness of treatments and lower development costs and drug time (e.g. time that a treatment passes the research and regulatory burdens to be viable to patients). Such benefits, which contribute towards improving the quality of life of patients, prove to outweigh the high costs involved in developing targeted treatments, although at present they are not yet available to a large share of the affected population. Personalized medicine, also identified as precise medicine, capitalizes on the rise of "-OMICS" technologies which includes genomics (i.e. analysis of the structuring, function and evolution of genomes), transcriptomics (i.e. analysis of the transcriptomes expressed from the genes of an organisms, these transcriptomes are all types of RNA molecules, a synthesized version of DNA), proteomics (i.e. analysis of proteins) and metabolomics (i.e. analysis of the substances necessary for metabolism).

While some drug developers and diagnostic manufacturers have recognized the potential economic opportunity of personalized medicines and have formed partnerships and rising spending in this field, the market for biomarkers (i.e. the proteins in the body that may signal the presence of disease activity) and molecular diagnostics are still at an early stage. Based on the same principles, immuno-oncology also presents a transformative potential for the treatment of many diseases – primarily cancer and rare diseases - although further advances in medical research and cost-reductions are needed to move them to first-line treatment.

At the other end of the spectrum, innovation in the way known molecules are administered to patients both in terms of drug administration, indications and formulation (i.e. the so-called value-added medicine[3]), can address existing inefficiencies in the value chain and improve health outcomes without necessarily finding new treatments. For example, low adherence to treatment of common respiratory diseases in developed countries such as asthma and chronic obstructive pulmonary disease (COPD) contributes to poor patient outcomes and high healthcare costs despite the availability of efficacious drugs (Medicines for Europe). Further innovation is also needed to address existing and potential global health threats such as antimicrobial resistance, which lowers the efficacy of existing antibiotic treatments for several diseases and medical procedures such as management of major surgeries, diabetes management and malaria, to name only a few. Within this context, more efforts are done in research in point-of-care diagnostic technologies that allow the rapid, precise detection of infectious diseases, thus contributing towards a more selective and reduced use of antibiotics. However, further research is needed also to develop new drugs and therapies, while at the same time changing the way certain treatments are carried in various countries so as to reduce the spread of antimicrobial resistance.

Both the pharmaceutical industry as well as biotechnology companies can contribute to the advancement of personalized medicine and genome medicine. However, the prospect of personalized treatments being an integral part of disease prevention and management will depend on medical research progress and cost management. Thus, research advancement remains key, and so does closer collaboration among companies, governments, clinical laboratories and universities. Such collaboration will also be indispensable in order to advance efforts towards the fight against antimicrobial resistance and other global health threats.

From a sustainable investment perspective, we favor investments in companies involved in the development of personalized medicines, genome medicine and more generally disruptive technologies that provide new treatments to known diseases with a significant improvement in patients' health outcomes, as well as value-added medicines that increase efficiencies and reduce the global health burden. We also find

3 http://www.medicinesforeurope.com/value-added-medicines/did-you-know/

opportunities in companies providing products and/or advancing research aimed at fighting antimicrobial resistance and other similar global health challenges.

KEY INDICATORS

- Revenue from medicines and service offering related to personalized medicine and/or genome medicine and/or point-of-care diagnostics and other value-added medicines or diagnostics
- Investment (Capex and R&D budget) dedicated to personalized medicine, value-added medicine and/or technologies preventing antimicrobial resistance

Exposure to Opportunities

	Indicators considered : % of revenue dedicated to providing effective access to medicine, personalised medicines, orphan drugs or endemic and tropical diseases treatments, value-added medicines and treatments % of revenues dedicated to providing generic medicines in low-income countries % of expenditure (both CapEx and R&D) dedicated to the above-mentioned opportunities Number of patients covered by a company's "access to medicine" strategy	
High exposure	Proven, significant involvement in any of the following areas, on the basis of the above-listed indicators, without threshold: • Access to medicine, • Neglected Diseases, • Impactful Innovation	The analysis of CapEx and R&D budget devoted to activities at high opportunity as well as the revenues generated by these activities will also be supported by qualitative indicators such as the presence of a clear strategy toward the development of such solutions.
Significant exposure	All other companies within the medical services sector that are involved in research and development of medical products intended for humans, including testing laboratories within the medical space. The medical conditions targeted by the companies are not discriminant for the rating.	
Low or no exposure	• Healthcare ancillary services (e.g. distribution, marketing, database management) despite a degree of specialisation for the health sector • Diversified Pharmaceutical and Life Science Services companies with >50% revenues in consumer products and/or chemicals	
Negative exposure	n/a	

Environmental and Social Risk

Product Safety

Product safety is a crucial issue for the all actors in the healthcare industry, and especially for drug manufacturers. Similarly to other risks faced by companies in the healthcare sector, regulation enforcing drug safety standards differs across countries: not only the Food and Drug Administration (FDA) in the US and the European Medicines Agency in the European Union have different standards, but also within the Union, countries impose their own requirements. For the rest of the world, the WHO (World Health Organization) has developed a version of Good Manufacturing Practice (GMP) indicators that are less stringent that the European and US ones yet are shared among all actors.

Drug safety incidents range from contamination to mix-ups, deviations, as well as packaging and labelling errors, which represent the highest percentage of incidents. The roots of the incidents can be related to human error as well as to procedures and standards, thus we expect medical product companies to hold diligent control of the track record and quality management process.

In addition, as suspicions around safety prompt drug recalls, both mandatory and voluntary, the safety scrutiny has led over time to an increase in product recall, which can result in drug shortages. Indeed, according to the FDA in 2019, 37% of drug shortage identified were caused by quality manufacturing issues, 27% were also related to quality-related issues generating delays or change in capacity, while 27% related to raw materials availability (the remaining shortages were due to loss of manufacturing site, increased demand and discontinuation issues). Thus, an increase in safety accidents with a few high-profile safety scandals prompted the US to issue the Drug Safety Enhancement Act (2011) to improve FDA-led inspections of foreign drug manufacturing sites.

Product safety constitute a material risk for companies and patients. Alongside, from an operational point of view may lead to drug marketing licenses suspension or withdrawal, substantive fines, reputational risks and, in some cases, share price drop. We therefore expect companies to differentiate their sourcing base to circumvent such risk.

The pharmaceutical industry is also particularly vulnerable to counterfeiting. According to the OECD in 2019, between 2014 and 2016, pharmaceuticals were the 10th most counterfeited type of product (first being apparel, footwear, watches etc). The OECD also discloses that pharmaceutical crime incidents increased by 102% between 2014 and 2018. Of course, the rise is in part due to an improved reporting by a larger number of Pharmaceuticals Security Institute (PSI)[4] member companies over the last five years. With an growing share of sales purchased online, the risk of counterfeiting is becoming a real threat. Of course, private companies are not directly responsible in the development of counterfeiting medicines. Nevertheless, they are expected to join global association and industry coalition in order to partner and better address the topic. Companies are also expected to develop significant tools to track their medicine and integrate specific design in packaging to increase the difficulty in the product to be counterfeited.

We encourage pharmaceutical product companies to disclose and communicate on effective quality management systems that encompass periodical audits of their CMO partners, relevant corrective actions and trainings. Alongside, we foster transparent reporting around the identified causes of product recalls. Additionally, we expect companies to show back-up plans for product recall and drug manufacturing plant

4 The Pharmaceutical Security Institute (PSI) is a not-for-profit, membership organization dedicated to protecting the Public Health Sharing Information on the Counterfeiting of Pharmaceuticals, initiating enforcement actions through the appropriate authorities.

suspension. Alongside, significant efforts to tackle drug counterfeiting products are expected.

KEY INDICATORS

- Track record of product recall and, when available, classification of seriousness in the US (class I, II and III of FDA) and other nation-specific and international classifications of recall seriousness if available.
- CMOs audit mechanisms and transparency on results
- Quality certifications for product manufacturing

Marketing Practices

Marketing practices bear a considerable weight on the overall sustainability risk of companies within the healthcare sector. Although medical products can significantly improve people's quality of life, and thus create investment value-added from a sustainability perspective, such benefits may be counteracted by inappropriate business practices related to the commercialization of treatments. Issues surrounding marketing practices are developed in more detail below.

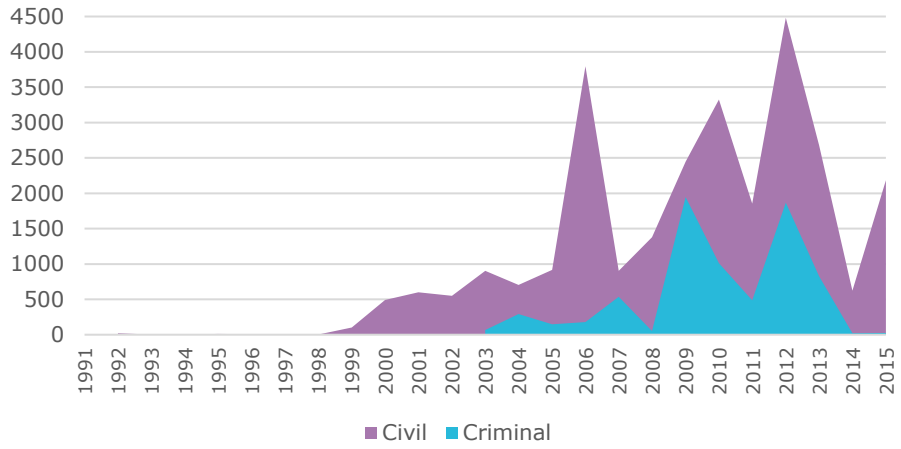
Product pricing: Marketing issues related to product pricing stem from unequal pricing policies across different markets for the same product, to business misconduct related to drug price manipulation and fraud. With regard to "fair" pricing, pricing regulation differs widely across countries, with the US being the only developed country that does not regulate prescription drug prices. Within this complex context, companies currently do not report their pricing policies across different markets, thus making it hard for stakeholders to evaluate the fairness of their approach. In an era of innovative but more expensive treatments, the challenge of balancing access and the cost of care is a focus for the healthcare system. Hence drug pricing will continue to be the center of the debate for medical product companies.

With regard to drug price manipulation, cases have long been reported, especially in the US where prices are negotiated at the state level via intermediaries, usually the pharmacy benefits managers (PBMs). In the US, fraud usually consists of artificially manipulating the amount to be reimbursed to the Medicaid/Medicare systems. In addition, another form of price manipulation also consists of cartels (e.g. price fixing) of over the counter (OTC) drugs, where price regulation is less stringent across countries.

Off-label promotion consists of marketing drugs or treatments for use outside their approved indications. Although off-label use is accepted in most countries, off-label promotion is generally illegal unless information is specifically requested by practitioners. Due to lack of scientific evidence for non-approved product indications, off-label use can result in adverse health impacts with consequent charges for unlawful promotion. Numerous cases of off-label marketing, especially in psychiatry, have led to major fines and settlements over the past years.

Misrepresentation of drug performance and side effects: drug manufacturers involved in research and development of prescription drugs usually direct most of their marketing efforts towards third-party physicians that are responsible for prescribing drugs to patients. Within this context, companies make use of the results of their clinical trials to inform on the efficacy and potential side-effects related to their products. However, there have been cases where companies have failed to appropriately quantify serious health risks and, sometimes, this has led to very high adverse ruling or settlement costs. In addition, since the liberalization on restrictions to broadcast advertising, the amount of Direct-to-Consumer advertising has increased in the US from $ 150M in 1993, to $4.7bn in 2007. Drug advertising, which is still banned in the EU and Japan, focuses primarily on lifestyle-related drugs and on those where consumers can influence physicians. Occasionally this has also led to lawsuits over alleged misleading advertisements to customers.

Figure 7: Pharmaceutical Industry Financial Penalties, 1991 – 2015: Civil vs. Criminal ($Usm)



Source: Mirova, (Public Citizen, 2016)

Together with product safety, issues related to improper marketing practices could lead to serious financial consequences for companies that fail to adopt appropriate practices across their global operations. As Figure 4 shows, between 1991 and 2015 big pharmaceutical companies have accumulated over USD30 billion in settlements in the United States to resolve government allegations, according to Public Citizen, with a spike between 2012 and 2013. However, this represents less 5% of the largest pharmaceuticals' net profits over a similar period, according to the same source. According to the Department of Justice in the United States, DOJ obtained from the Health Care industry (including drug and medical device manufacturers, managed care providers, hospitals, pharmacies, hospice organizations, laboratories, and physicians) more than $1.8 billion in settlements and judgments from civil cases involving fraud and false claims against the government in the fiscal year ending Sept. 30, 2020 (vs. $2.6bn in 2019, $2.5bn in 2018). Recoveries since 1986, when Congress substantially strengthened the civil False Claims Act, now total more than $64 billion.

Although we appreciate that full transparency around a pricing strategy is a sensitive issue for pharmaceutical and medical product companies, we engage with companies to improve disclosure around pricing policies to improve market access. We also encourage improved transparency around the results of clinical trials. In addition, whenever companies have been involved in drug performance and side-effect misrepresentation, or off-label marketing, we seek for improved training of sales representatives and evidence of concrete steps taken to improve marketing practices.

We consider the incentivization of the sales force and other staff using business ethics indicators, the use of self-regulation codes and external certifications on marketing practices with audits of mechanism as keyways to reduce risks. In addition, we look at companies' track records to detect inadequate marketing practices.

KEY INDICATORS

- Training of sales representatives and general staff around responsible marketing
- Qualitative incentive policy for sales representatives, including business ethics indicators
- Average marketing spending vs R&D spending and comparison to industry peers
- Public policy on clinical trials and percentage of product portfolio fully disclosed on public databases with all associated results
- Use of the self-regulation codes on marketing practices such as the PhRMA Code in the US on interaction with healthcare professionals
- External certification of marketing practices and internal/external audit mechanisms

- Track record of involvement in litigations related to product liability and inappropriate marketing practices

Ethical R&D Practices

Research and development (R&D) activities are at the core of pharmaceutical and medical product companies, as innovation is the most important growth driver within the sector. After a drug is discovered, companies need to undertake both pre-clinical tests on animals as well as clinical tests on humans (healthy volunteers) before seeking registration and marketing approval from healthcare authorities.

Pre-clinical trials: these trials are conducted on animals, usually small mammals such as mice, rabbits, monkeys etc to determine the suitability of the new medical compound to become a drug and their safety for continued testing on humans. During this phase, the potential toxicity as well as the effectiveness of the new candidate drug is studied over an average period of two years. Although the actual effectiveness of animal testing is highly debated, no strict regulation banning the use of animals in pharmaceutical testing generally exists, and most of those currently in place in the medical field fail to provide sufficient protection to the animals. Therefore, pharmaceutical and medical product companies should commit to the three Rs (reduction, refinement, replacement) which entail the minimization of experiments on animals whenever substitute tests are possible, the avoidance of animal suffering and a commitment towards finding alternatives to animal testing. Companies are also expected to develop alternatives to animal testing using in vitro methods or advanced computer-modeling techniques.

Clinical trials: once approved for safe testing on humans, new drug applications can pass through up to four clinical trials to determine safety and efficacy of treatment for the specific medical conditions that the drug is targeting. While no globally unified standard exists yet around good practices in clinical trials, the WHO has published the Good Clinical Research Practice (GCP) guidelines in 2002 in order to identify and promote best-practice. Key aspects of the GCP guidelines include: the identification of a trial protocol that includes national regulations, the development of written standard operating procedures, as well as monitoring and auditing procedures, both from the sponsoring company (drug developer) and the contract manufacturing organizations (CMOs). Selection of trial sites and experienced and qualified investigators is also of utmost importance, alongside the review of all studies by an independent ethics committee. Clinical studies have in the past been the cause of controversies surrounding the enrolment of subjects into the trial. Therefore, obtaining written informed consent has become a best-practice standard. Clinical trials should also be conducted according to basic ethical principles, which have their origin in the Declaration of Helsinki, and impact the responsibility of each party in the process.

Transparency on clinical trials is not a requirement, but more and more regarded as a best-practice in the industry: companies wishing to market a new drug application (NDA) for a specific use in humans need to undertake a series of safety tests: both pre-clinical (on animals) and, if these are successful, clinical trials on humans. Although the medical authorities have access to the full results of clinical trials when deciding the approval of a drug, public disclosure of clinical trial results is generally not mandatory. Although a few initiatives and public databases exist (such as clinicaltrials.gov), disclosure around results, especially when these are negative, is still poor (around 20% of registered trials report the results). Such a lack of public information magnifies product liability risk (i.e. risk related to side effect minimization) and also reduces the amount of information available to the scientific community, thus contributing to increasing overall healthcare research costs.

We encourage companies to display high standards of practice when conducting studies and tests both on animals and on individuals. While acknowledging that medical product companies today still rely heavily on pre-clinical trials on animals, we value companies developing alternative tests that do not exploit animals. We also expect companies to abide by the WHO's GCP guidelines and the Declaration of

Helsinki and to be particularly demanding and vigilant toward their contract research organizations (CROs) when externalizing pre-clinical and clinical studies.

KEY INDICATORS

- Use of written protocol for conducting clinical studies according to the Helsinki Declaration as well as the GCP guidelines
- If studies are externalized, presence of an auditing and monitoring mechanism of the contracted external third parties (i.e. the CMOs)
- Commitment to the use of the 3 Rs

Water, biodiversity, and pharmaceuticals in the environment

Medical product companies can have significant environmental impacts through drug manufacturing yet also due to products releases in the environment. Industrial medical waste can cause severe water pollution and consequently profoundly impact local biodiversity. In addition, drug waste from pharmaceutical manufacturing processes contributes to increased antibiotic resistance, which constitutes a serious threat to global health.

Water is essential raw material in the drug manufacturing process. Drug manufacturing processes requires different degrees of water purity. Many pharmaceutical processes require highly pure water that meets strict quality standards, simultaneously these processes generate heavily polluted and toxic wastewaters that require complex and costly treatment. Pharmaceutical factories use a wide range of chemicals and technological processes, such processes may pose major challenges for current waste cleanup technologies. While all these processes are expected to be heavily regulated, some examples have illustrated a lack of control along the supply chain and lack of enforcement of these regulations. As multinational pharmaceutical companies expanded their manufacturing operations abroad, and notably in lower-cost countries such as India and China such risks have become a reality in some cities. For example, dramatic environmental pollution of river effluents has been observed (Larsson, de Pedro, & Paxeus, 2007). Villages located next to major drug manufacturing plants, such as those located in Hyderabad and Visakhapatnam areas in India have reported depleted fish stocks and health problems related to water pollution (Nordea, 2016).

On the one hand, companies are thus expected to ensure they close the loop and to improve their ability to reuse water and limit their dependency on water, especially in areas of water scarcity. On the other hand, companies are expected to define significant process to ensure minimum releases of pharmaceuticals and chemicals products in the environment. They are expected to conduct such due diligence with more scrutiny when most of API or other ingredients productions have been outsourced. As of today, there are limited amount of studies truly identifying the impact of such releases on wildlife and biodiversity. Nevertheless, such levels of water contamination have raised concerns about antibiotic resistance development. Antimicrobial resistance (AMR) is a global health crisis with the potential for enormous health, food security and economic consequences. AMR refers to the ability of a microbe to resist the effects of medication that could once successfully destroy or inhibit the microbe. Drug resistant infections already cause an estimated 700,000 deaths each year globally. The mis- and over-use of antibiotics is an important contributing factor of AMR; up to 50% of the antibiotics prescribed for human use are considered unnecessary. The phenomenon is also stressed by pharmaceuticals releases in the environment.

Without supply-chain engagement and monitoring from multinational pharmaceutical companies, the threat is expected to strengthen as the industry continues to grow. In addition, water contamination also happens on the other side of the value chain, through drug residues after use. In this regard, pharmaceutical and medical product companies still have little levers to reduce the impacts of their products, but further research is required as global access to healthcare treatments is set to increase.

Moreover, the pharmaceutical sector depends heavily on biodiversity resources, which provide a rich and unique source of bioactive lead compounds, especially in the field of anti-cancer and anti-infective agents (i.e. about two-thirds of these agents are derived from natural products). The Convention on Biological Diversity (CBD) in 1992 marked a turning point in the industry, which before used to freely collect plant and microbial sources from around the world for research purposes. Through the CBD, countries maintain sovereignty over their genetic resources and may limit access to these. Hence, pharmaceutical companies, among other users of biological resources, need to pay greater attention to the laws surrounding biodiversity protection and share the benefits derived from their discoveries.

We expect companies to follow the principles of the Convention on Biological Diversity when using natural resources to obtain potential drugs, through publicly acknowledging and incorporating the principles into the company's bioprospecting practices. We also encourage companies to follow best practices that go beyond local regulatory requirements when it comes to hazardous waste management

KEY INDICATORS

- Acknowledgement of Convention on Biological Diversity (CBD) and integration into procurement practices and training mechanisms of relevant personnel
- Use of best-practice standards of medical waste disposal
- Supply-chain environmental policy and audits
- Biodiversity conservation policy and strategy for use of natural resources
- Spending on resource protection and environmental performance improvement

Human Resources

Pharmaceutical and medical product companies rely on highly skilled workers employed across various business areas, from research and development (R&D) through to sales operations. While employees in R&D are key to foster innovation and growth, those involved in commercial roles have a prominent role in driving the ethical conduct and reputation of the companies in the sector, though their marketing practices and ethical conduct. With an increasing fragmentation of the industry, social practices, human rights and human resources are expected to receive higher scrutiny along the supply chain.

In a sector that is exposed to a large number of ethical controversies where big pharmaceutical companies tend to pursue acquisitions strategies, thus integrating different companies and the related cultures, it is thus of particular importance that companies strive to infuse a corporate culture based on transparency and high ethical conduct. This in turn will contribute to retain talent and thus have a positive contribution towards medical research and innovation.

In addition, through external growth strategies, companies within this sector are often exposed to restructuring, which can affect large number of employees.

Facing these risks, companies in this sector can put in place appropriate policies and mechanisms to incentivize employees that interact with physicians and patients to abide by strict ethical standards. These mechanisms can integrate qualitative targets within sales incentives (as opposed to aggressive quantitative targets only) and a larger sensibilization of the workforce towards work ethics. In addition, we expect to see human resources policies aimed at controlling the age pyramid, supporting the development of employees' career paths and their employability, as well as encouraging social dialogue. Companies are encouraged to create optimal working conditions for the well-being of their employees. During restructuring, it is also important to ensure the quality of support (training, compensation, etc.). Transparent communication is also needed to assess performance.

KEY INDICATORS

- Remuneration schemes with incentives that include qualitative indicators
- Strong work ethics, reflected in internal recruitment and training processes, also via the use of an anonymous speak-up line managed by an independent committee and the creation of internal audit committees in charge of enforcing work ethics
- Restructuring: number of people concerned, share of beneficiaries of mitigation measures (early retirement, training and job-search assistance, compensatory measures, etc.)
- Similar standards applied for contractors and other partners in the supply chain

Business Ethics

Besides ethics related to product marketing and clinical trials, which have been dealt with in the previous sections, medical product companies may engage in ethically questionable business practices that range from disease mongering (i.e. the selling of sickness) to highly fraudulent practices such as corruption of healthcare professionals or authorities to boost sales. We examine these practices in detail below.

Corruption: aside from drugs distributed over the counter (e.g. OTC drugs), medical product companies need to market their new drugs to third-party physicians, which increases corruption risk in the sector. Over the past years, international pharmaceutical companies have been systematically involved in high-end corruption scandals whereby their salesforces were systematically engaged in offering kickbacks to medical personnel to promote their products, especially in developing countries. Such issues have highlighted the need to change the way sales representatives are incentivized, with a shift towards a more qualitative approach. In addition, companies need to pay greater attention to training and monitoring of their sales representatives to their code of conduct. Another recurrent form of corruption that receiving scrutiny consists of unduly influencing healthcare professionals via entertainment, expensive gifts, and luxurious travelling arrangements to favor a positive recommendation of the company's new drugs. In addition, sponsoring continued medical education may also lead to an informational bias and is thus increasingly regulated. Finally, distribution of drug samples to medical professionals is also seen as a form of corruption and often regulated.

Disease mongering: is the creation of the need for more drugs, which consists in increasing the scope of illnesses to expand the market of specific drug sales. This practice goes along with the creation of disease awareness campaigns and/or the development "lifestyle drugs" that address conditions that were not previously recognized as actual medical conditions. Some cases also involve misleading statistics about the actual prevalence of the "dysfunction". However, such practices are hard to identify and address, also due to scientific uncertainty or differing expert opinions around some conditions and their treatment.

Anti-competitive practices: generally, drugs' patents expire after 20 years, allowing competitor companies the possibility to file for production and marketing of an equivalent product, marketed with a different brand name (a so-called generic medicine). Increased competition and expiry of several blockbuster drugs over the past years led some companies to engage in fraudulent practices to delay competitors' launch of generic equivalents. This practice consists of abusing government procedures to artificially delay the generic launch, or in some cases it involves "pay-for-delay" arrangements where competitors are paid to hold the launch of a generic product in some markets. These arrangements are generally prosecuted in the EU as anti-competitive practices, while in the US they are more and more challenged but not yet deemed illegal.

Lobbying: although lobbying is perfectly legal in both the EU and the US, some practices are ethically questionable, especially when they are against the interest of consumer groups. For instance, in the US the pharmaceutical industry, which is the second largest lobbying contributor, has focused a lot on safeguarding non-regulation of prices in order to prevent Medicare from negotiating drug prices. Also, corporate inversion tax regulations are among

the key areas of focus for pharmaceutical lobbying in recent times. Lobbying can also be carried indirectly via participation in trade associations. Despite the important role of lobbying in the sector, companies tend to display relatively poor reporting on their lobbying expenditure and spending linked to trade associations. In addition, fewer companies report a policy on lobbying with clearly stated objectives and how these align with the interests of stakeholders.

We expect companies to adopt strict codes of business ethics publicly available and applicable to all employees as well as contractors. We encourage companies to explicitly prohibit anti-competitive and unfair business practices. Oversight and monitoring of the implementation of such practices, as well as appropriate remuneration systems that incentivize good practice, are also recommended. In addition, we look for disclosure of a company's lobbying policy and objectives as well as its expenditures and list of supported trade associations. We also expect companies to put into place whistleblowing mechanisms available to all employees and third parties, and to have a third-party ombudsman. In cases of corruption fraud, we encourage a claw back bonus provision for both management and employees.

KEY INDICATORS

- Code of business ethics applicable to all employees, management and contractors, translated in local languages
- Audit and monitoring systems of ethical business practices
- Incentivization of employees in sales-related functions with qualitative criteria
- Clawback bonus provisions for both management and employees in presence of corruption fraud
- Whistleblowing mechanisms applicable to all employees and third parties and presence of a third-party ombudsman

Sustainable Development Governance

Companies within the medical service sector should integrate the management of social and ethical business issues at the Board-level so as to bring them into the heart of their business strategies: access to medicine, anti-corruption, ethics in research and marketing standards are issues that require concerted effort for companies with global reach and a multitude of stakeholders such as medical product companies. To this regard, we expect companies to integrate key corporate social responsibility (CSR) criteria within the remuneration of their employees with managerial responsibilities, as well as the top management and the executives of the Board. In particular, we expect variable compensation of sales-based representatives to be based less on purely quantitative criteria and increasingly more on qualitative criteria so as to encourage the use of ethical business practices in marketing to healthcare professionals worldwide.

Due to the importance of such issues, companies should also have board representatives with extensive experience in key sustainability issues for the sector, and also when necessary set up a sustainability committee to the board with oversight of environmental and social risks, including business ethics, so as to inform the board of its decision-making.

In addition, business ethics plays a pivotal role in the pharmaceutical sector, due to the sector's value-added role in society through medical innovation. Among the key business ethics challenges that the sector faces, as we described above, there are: unfair product pricing, off-label marketing, kickbacks, disease mongering, anti-competitive practices, transparency and ethics in clinical trials, lobbying, and misrepresentation of drug performance and side-effects.

We encourage companies to set up stretching sustainability targets and reflect these in the variable remuneration of top management and employees with managerial responsibilities so as to incorporate sustainability into business performance. We also look for proactive participation of the Board in such matters via ad hoc sustainability

committees that provide periodical oversight to the Board and the appointment of Directors with expertise in sustainability, including anti-corruption. We also press for transparency around lobbying activities and trade association sponsorship.

KEY INDICATORS

- Presence of sustainability performance indicators and targets within the annual reports
- Presence of measurable CSR criteria within the variable remuneration of the executive Board members and employees with managerial responsibilities
- Presence of qualitative criteria within the remuneration of sales representatives aimed at reducing kickback practices

Risk Assessment

	Criteria
Positive	Not fulfilling the criteria that move the opinion to « risk » AND - Absence of severe and recurrent controversies AND appropriate management of operational H&S topics AND appropriate management of human right issues and human resources issues AND appropriate environmental risk-management
Neutral	All other cases
Risk	- Response of the company to repeated ethical controversies deemed inadequate or inappropriate OR - Inappropriate management of operational H&S topics OR - Inappropriate management of human right issues and human resources issues OR - Inappropriate environmental risk-management

Conclusion

Pharmaceutical and medical product companies can address the Sustainable Development Goal n°3 through the large set of activities and thanks to different levers. Companies addressing unmet medical needs or neglected diseases, alongside companies demonstrating a clear involvement in fostering access to medicines, and/or accelerating the transition towards impactful innovation by tackling global health challenges are considered as highly beneficial for the society. In the context of a global COVID19 outbreak, pharmaceuticals companies have illustrated their role of clear solutions providers, by gathering R&D and human resources and developing in an outstanding timeliness treatments, vaccines, and diagnostics products.

Nevertheless, while companies from the healthcare sectors are de facto unlocking significant or high social opportunities, they are not less prone to sustainability risk issues. The business models' evolution in the past decades, leading to increasingly complex healthcare systems and pharmaceutical industry, have raised investors' expectations from companies to demonstrate superior sustainability management. The complexity of the industry, geographical dependence for raw materials and API have been further highlighted by the COVID19 crisis. Such issues will receive higher scrutiny in the future, to ensure economic and profitability decisions are not interfering global health issues. Business ethics risks with which the sector is riddled: product safety, anti-corruption measures and fair business practices are crucial to determine the eligibility of companies to investment. Pricing related issues are also considered as increasingly material matter and a lack of consideration of access programs and affordability can be detrimental to the overall sustainability analysis of the company. We also expect companies to show extended transparency around lobbying expenditures, trade association or tax policies to meet best-practices. Thus, well-positioned from a sustainability opportunity standpoint, companies that are recurrently involved in malpractice allegations and controversies and with poor risk management systems will not be eligible for investment without a concerted effort to improve business practices and transparency. We will thus continuously engage with companies to ensure adoption of best-practices and periodically evaluate our investment decisions.

Moreover, an increasing scrutiny is made on adverse environmental consequences of medical products and pharmaceuticals activities. Indeed, water pollution and consideration such as antimicrobial resistance are raised at the top of the agenda considering the potential hazards for human health.

Our Approach to sustainability assessment

Acting as a responsible investor requires interpreting the economic world within its social and environmental context. This approach calls for understanding the interactions between different private-public players, small-medium-large companies, developed and developing economies to ensure that each player's growth is consistent with the balance of the rest of the system. It is a long-term approach that guarantees that today's choices will not lead to negative consequences for future generations. Understanding these complex relationships demands:

- Clear understanding of sustainable development issues facing our societies,
- Assessing the possible interactions between the assets of our investment strategies and these sustainability issues.

The SDGs as a Guide

Following the Millennium Development Goals created in 2000, the United Nations set out a new framework for sustainable development in 2015. It contains 17 Sustainable Development Goals (SDGs), broken down into 169 specific targets designed to address the main social and environmental issues between 2015 and 2030. In addition to having been adopted by all members of the United Nations, the SGDs offer several advantages.

First, they establish a comprehensive framework concerning environmental and social issues, applicable to all economies regardless of their level of development. Thus, while some issues such as ending hunger or ensuring access to water for all are often more relevant for low- and middle-income countries, other objectives such as fighting climate change or making cities safe, resilient and sustainable, are applicable at all levels of development.

Moreover, the SDGs can be considered as a frame of reference for sustainable development issues for a variety of actors, from governments to companies and investors. The private sphere is increasingly considering environmental and social issues, illustrating new forms of governance where subjects of general interest are no longer solely the prerogative of the public sphere. Considering the SDGs can help companies to think on how they create environmental, economic, and social value.

Finally, the SDGs help investors to question the long-term resilience of their assets and portfolios to the ongoing transformations. Then, investors can go even further by looking at their exposure to new solutions and economic models that will respond to long-term economic transformations. For example, the targets associated with the SDGs to significantly increase the share of renewable energy and to double energy efficiency by 2030 imply a profound transformation within the energy sector.

We consider the SDGs squarely in line with our mission. As a result, in 2016, Mirova decided to use this framework to define its responsible investment approach.

Figure 8: The 17 Sustainable Development Goals

	End poverty in all its forms everywhere		Reduce inequalities within and among countries
	End hunger, achieve food security and improved nutrition and promote sustainable agriculture		Make cities and human settlements inclusive, safe, resilient and sustainable
	Ensure healthy lives and promote well-being for all at all ages		Ensure sustainable consumption and production patterns
	Ensure inclusive and equitable quality education and promote lifelong learning opportunities for all		Take urgent measures to combat climate change and its impacts
	Achieve gender equality and empower all women and girls		Conserve and sustainably use the oceans, seas and marine resources for sustainable development
	Ensure availability and sustainable management of water and sanitation for all		Protect, restore and promote sustainable use of territorial ecosystems, sustainably manage forests, combat desertification, and halt and reverse land degradation and halt biodiversity loss
	Ensure access to affordable, reliable, sustainable and modern energy for all		Promote peaceful and inclusive societies for sustainable development, provide access to justice for all and build effective, accountable and inclusive institutions at all levels
	Promote sustained, inclusive and sustainable economic growth, full and productive employment and decent work for all		Strengthen the means of implementation and revitalize the global partnership for sustainable development
	Build resilient infrastructure, promote inclusive and sustainable industrialization and foster innovation		

Source: United Nations

Assessing Environmental and Social Quality by the SDGs

We believe that the SDGs will transform the economy as we know it. Acting as a responsible investor starts with taking a broader view of the way investors think about the environmental and social profile of the assets they finance. These interactions can be grouped into two categories:

- **Materiality**: how the current transitions are likely to affect the economic models of the assets financed either positively or negatively.
- **Impact:** how investors can play a role in the emergence of a more sustainable economy

We believe that these two approaches are closely linked. Our evaluation methodology thus seeks to capture the extent to which each asset contributes to the SDGs. From our perspective, this approach provides a relevant vision on both the “Materiality” and “Impact” aspects.

A Five-level Qualitative Analysis

Mirova has based its environmental and social evaluation method on four principles:

A RISK/OPPORTUNITY APPROACH

Achieving the SDGs requires taking two different dimensions into account that often go together.

- Capturing opportunities: when companies center their strategies on innovative business models and technologies focused on technological and societal transformation, they can often capture opportunities related to the SDGs.
- Managing risks: by proactively managing risks related to these transitions, companies can reduce and re-internalize their social and environmental externalities, which often takes the form of general management of sustainability issues.

This analysis structure gives equal importance to opportunities and risks. It is the first prism through which we analyze sustainable development issues.

A LIFE-CYCLE VISION

To identify the issues that could impact an asset, the analysis of environmental and social issues must consider the entire life cycle of products and services, from raw material extraction to end-of-life phase.

TARGETED AND DIFFERENTIATED ISSUES

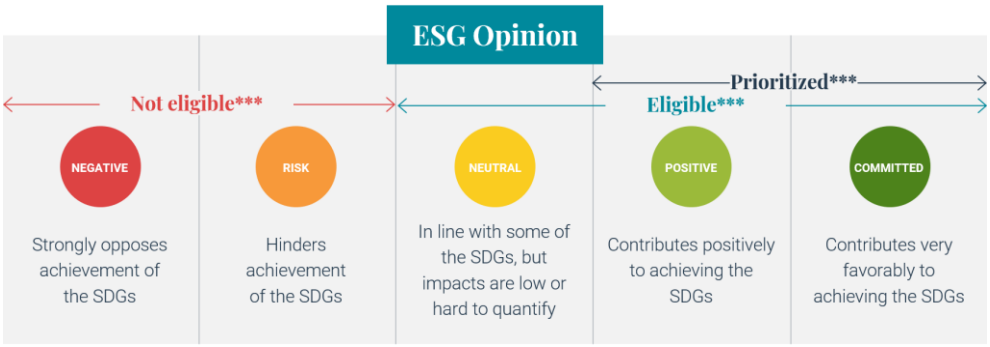
Our risk/opportunity analysis focuses on the elements most likely to have a real impact on the assets studied and on society in general. Additionally, the issues that economic players face

are very different depending on the sector, and can even vary within the same sector[5]. For example, it is important for us to focus on work conditions for suppliers in the textile industry, while for automobile manufacturers, the focus will be more on energy consumption during product use.

So, our analysis focuses on a limited number of issues adapted to the specificities of each asset.

A QUALITATIVE RATING SCALE

Our analyses are summarized through an overall qualitative opinion on five levels. This opinion assesses to what extent an asset contributes to the SDGs.



***[6]

This rating scale is based on the SDGs and their achievement. As a result, opinions are not assigned based on a distribution set in advance: we are not grading on a curve overall or by sector. Mirova does not exclude any industry on principle, and carries out a thorough analysis of the environmental and social impacts of any asset. For some sectors, this analysis may lead to the exclusion of all or some of its actors. For example, companies involved in fossil fuel extraction are considered “Risk” at best, while renewable energy companies are generally well rated.

An indicative grid provides some overall guidelines regarding the links between opportunities, risks and the overall sustainability opinion.

Sustainability Risks Review					
	Positive	Risk	Positive	Positive / Committed	Committed
	Neutral	Negative / Risk	Neutral	Neutral / Positive	Positive / Committed
	Risk	Negative	Negative / Risk	Risk	Risk
		Negative	Low or no	Significant	High
		Sustainability Opportunities Exposure			

5 For every sector, defining key issues is the subject of a specific study. This document is available on Mirova *website.* https://www.mirova.com/fr/recherche/comprendre#vision

6 *** For Mirova’s investments

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