ETHICAL BRIEFING - PHARMACEUTICALS

The pharmaceutical industry poses a dilemma for the responsible investor; it produces both innovative and life-saving medicines and therapies, yet it is also regarded by some as one of the most opaque and controversial of all industry sectors. This briefing outlines the key concerns that are associated with pharmaceuticals, with reference to emerging issues, recent studies, and initiatives to identify and promote best practice within the sector.

PRODUCT RESPONSIBILITY

A standard of living adequate for health and wellbeing, including medical care, is regarded as a fundamental human right under Article 25 of the Universal Declaration of Human Rights (UDHR). It is widely accepted that governments and pharmaceutical companies share the responsibility to ensure access to affordable medicine, particularly for those in developing countries. This position is endorsed in international declarations such as the UN Sustainable Development Goals; by the UN Special Rapporteur on the Right to Health; independent monitoring bodies such as the Access to Medicine Foundation; and medical charities including Médecins Sans Frontières. However, certain practices within the pharmaceutical industry can, rather than promoting health and wellbeing, cause actual harm. These include:

i) Use of unethical marketing practices to overstate the benefits and/or conceal the risks and side effects of drugs;

ii) Stringent patent protection measures to impede the production of cheaper generic versions of medicines, thereby limiting or preventing access to affordable, potentially life-saving medicines;

iii) Manipulation of clinical trial data to downplay the risks and side effects of products.

Unfortunately, such practices are common and companies operating within the sector continue to attract substantial fines for regulatory breaches. The US non-profit organisation, Public Citizen, which represents consumers' interests on a range of issues, has analysed 25 years of pharmaceutical industry criminal and civil penalties imposed by the authorities from 1991 to 2015. This study shows that during the period, a total of 373 settlements totalling $35.7 billion were agreed between federal and state governments, and pharmaceutical manufacturers to resolve allegations of a range of offences. The unlawful promotion of drugs was the issue that resulted in the largest financial penalties, accounting for 25% of all violations. Financial penalties peaked in 2012 at $6,348 million, with a decrease in subsequent years, although the authors caution that it remains to be seen whether this decline represents a longer-term trend.[1]

In the long run, these costs are likely to be passed on to consumers who are paying increasingly high prices for drugs. Historically, the industry has maintained that premium prices are needed to pay for the $1 billion-plus cost of developing a new medicine and bringing it to market, a process which entails absorbing the financial losses from other products which fail to gain regulatory approval. However, comments made in 2013 by Andrew Witty, the CEO of GlaxoSmithKline (GSK), suggest that this figure is misleading. Labelling it "one of the great myths of the industry", he stated that it was "entirely achievable" for companies to make efficiencies in research and development for example, in order to lower drug prices.[2]

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[1] www.citizen.org/sites/default/files/2311.pdf; www.statnews.com/pharmalot/2016/03/31/pharma-fraud-kickbacks/

[2] www.reuters.com/article/us-glaxosmithkline-prices/glaxosmithkline-boss-says-new-drugs-can-be-cheaper-idUSBRE92D0RM20130314; www.economist.com/news/business/21635005-startling-new-cost-estimate-new-medicines-met-scepticism-price-failure

Access to Medicine

Opaque pricing strategies are just one of several barriers which prevent better access to affordable medicine for those who need it most. For example, Médecins Sans Frontières (MSF) recently ran a lengthy campaign ('A Fair Shot') against GSK and Pfizer, to reduce the price of their pneumonia vaccine (PCV). Pneumonia is the single largest infectious cause of death in children worldwide,[3] and these companies currently hold the patent rights to the PCV under a duopoly. This prevents other companies from producing more affordable generic versions of the vaccine. Whilst GSK and Pfizer have made their products available at a reduced cost in lower income countries identified by the GAVI Vaccine Alliance, a public-private partnership, the price in other countries varies significantly.

MSF reported that in 2016, it paid US$68 for one dose of the PCV, 20 times more than the lowest available price elsewhere, in order to vaccinate refugee children in Greece. At these prices, some governments and NGOs including MSF cannot afford to vaccinate vulnerable children in emergency and other situations. In September 2016, following pressure from members of the World Health Assembly, and humanitarian and investor groups, GSK agreed to lower the price of the PCV to around $9 per regimen for humanitarian organisations serving refugee and crisis-affected children. Pfizer followed suit in November of the same year[4]. MSF welcomed these moves but has urged the companies to renew their efforts to reduce the price of the vaccine in the many other countries that are still unable to afford to add it to their standard childhood immunisation packages.

The Access to Medicine Foundation, an independent, non-profit organisation which collects and analyses data from the world's largest pharmaceutical and vaccine companies, publishes the biennial Access to Medicine Index. The Index measures and ranks the top 20 research-based pharmaceutical companies on their efforts to enable access to drugs to treat 51 high-burden diseases in 107 low to middle income countries. Over 80 indicators are used across seven areas of behaviour including Marketing Influence & Compliance; Pricing, Manufacturing & Distribution; Patents & Licensing; and Capacity Building, to evaluate a company's performance. The results of the 2016 Index show that the industry has made moderate progress in its efforts to improve access. However, while most of the companies assessed (17 out of 20) now have a detailed access-to-medicine strategy, good practice in making products affordable and accessible is still limited with the Index finding that in general, companies do not consistently target the populations with the greatest needs in their drug registration, pricing and licensing activities.[5]

Clinical Trial Data Transparency

As innovators of novel products, pharmaceutical companies understandably rely heavily on secrecy but the lack of transparency within the industry can be problematic, particularly regarding the lack of disclosure of clinical trial data. As part of the approval procedure for human medicines, companies routinely submit clinical data to regulatory authorities in order to support their applications. However, there is currently no obligation for them to make this information available publicly. Furthermore, companies can choose to withhold data about clinical trials which have resulted in unfavourable outcomes. The lack of public reporting prevents this information from being shared with others in the industry, potentially resulting in poor treatment decisions and trials being duplicated, thereby adding to the development cost and price of medicines. In 2016, in an effort to increase transparency and restore public trust in the process, the European Medicines Agency implemented a policy under which it publishes clinical trial data submitted as part of the regulatory process, a decision which was opposed by some in the industry. Medical campaign groups such as ALLTrials, have called for much greater disclosure and urged companies themselves to go further by adopting the principles of open research. Such a move would see all clinical trials registered and the results published within one

[3] http://www.who.int/mediacentre/factsheets/fs331/en/

[4] https://shareaction.org/wp-content/uploads/2016/04/PCV-Vaccine-InvestorBriefing.pdf; www.msfaccess.org/about-us/media-room/press-releases/msf-welcomes-gsks-decision-lower-price-pneumonia-vaccine-some; www.msfaccess.org/about-us/media-room/press-releases/msf-welcomes-pfizers-pneumonia-vaccine-price-reduction-children

[5] https://accesstomedicineindex.org/key-findings/good-practice-making-products-affordable-available-limited/

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year of completion, with the data from all past trials of medicines currently in use also made available via public registers.[6]

In July 2017, ALLTrials published the findings of a study in which it systematically assessed the policies and commitments of over 40 pharmaceutical companies regarding access to information about clinical trials, and evaluated how well these corresponded with ethical and professional guidance. The results showed that policies were highly variable. Of 23 companies eligible from the largest 25 companies by revenue, 21 (91%) committed to register all trials and 22 (96%) to sharing summary results. However, policies typically lacked timelines for disclosure so it is unclear when they will be implemented. In addition, trials on unlicensed medicines and off-label uses were only included in six policies (26%). The authors of the study note that at least one company was able to meet all elements of best practice, suggesting that these are not unrealistic goals.[7]

ANIMAL TESTING

The discovery and development of new medicines, vaccines and medical devices is a complex process with a number of stages, some of which involve studies in animal models. National and international regulations require these products to be tested in animals before they are licensed for use. During these studies, animals can suffer pain and distress from the procedures employed, as well as the symptoms of the disease or condition that is being studied. Healthy animals are then used to assess the safety of any new drugs before clinical trials in humans can proceed. Animals are often euthanised at the end of the tests.[8]

Annual statistics published by the UK government regarding the number of scientific procedures performed on living animals show that approximately two million experimental procedures were performed in 2016, with 72% in mice and rats, 14% in fish, 7% in birds, 6% in other species[9], and around 1% in specially protected species (horses, dogs, cats, and non-human primates).[10] Animal welfare organisations such as the Naturewatch Foundation point out that while these statistics reveal certain information, such as the numbers of animals used and their level of suffering, other important details are missing. Very little is revealed about the conditions in which the animals are kept, welfare standards, or the specific justification for each procedure.[11]

The RSPCA strongly advocates that companies performing animal testing, undertake an ethical review, a process which involves evaluating whether projects justify the role of animals, and consideration of practical issues relating to how they will be used. This requires the application of the principles of the 3Rs (Replacement, Reduction and Refinement) regarding the use of laboratory animals.[12] Opinion polls of public attitudes consistently show that support for animal research is conditional on the 3Rs being implemented.[13] As well as adopting these principles, companies can strengthen their support through membership of, or by working with, organisations that promote the 3Rs such as the National Centre for the Replacement Refinement & Reduction of Animals in Research (NC3Rs), or the European Partnership for Alternative Approaches to Animal Testing (EPAA). In addition, best practice involves testing in line with recognised protocols, and undertaking or commissioning studies at accredited facilities, which are subject to regular audits.

[6] www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000629.jsp; www.alltrials.net/find-out-more/all-trials/

[7] www.bmj.com/content/358/bmj.j3334

[8] www.rspca.org.uk/adviceandwelfare/laboratory/medicinesandvaccines

[9] Includes guinea pigs, other rodents, rabbits, ferrets, other carnivores, pigs, goats, sheep, cattle, other mammals, reptiles & amphibians.

[10] www.gov.uk/government/uploads/system/uploads/attachment_data/file/627284/annual-statistics-scientific-procedures-living-animals-2016.pdf

[11] https://naturewatch.org/campaigns/article/animals-used-in-british-experiments-in-2016; www.huffingtonpost.co.uk/joanna-randall/animal-experiments_b_17514236.html; http://nuffieldbioethics.org/blog/animal-research-20052017

[12] https://science.rspca.org.uk/sciencegroup/researchanimals/ethicalreview

[13] https://www.ipsos.com/ipsos-mori/en-uk/attitudes-animal-research-2016

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Use of Transgenic Animals

For some, the widespread use of transgenic (genetically modified) animals in medical research presents further concerns. Since these animals (often mice, rats and fish) can be engineered to carry genetic defects or conditions, many scientists now consider them to be the best models through which they can understand a range of human diseases, and this has led to a dramatic increase in their use in recent years. Transgenic mice in particular, may be used to replace higher orders of mammal in studies.[14] Yet questions remain regarding the ethics of creating diseased animals which are likely to suffer for prolonged periods of time.

In addition, organisations such as the Nuffield Council on Bioethics report that there are a range of wider ethical concerns surrounding biotechnology - the manipulation of living organisms or their components (through genetic engineering for example) which often results in the creation of a commercial product. The use of new and emerging techniques such as the CRISPR-Cas9 system, which are cheaper and more effective, have enabled rapid advances in gene editing to be made. These tools allow unwanted sections of DNA such as those linked to human disease, to be targeted and removed leaving the rest of the genetic code intact.

To date, most uses of genome editing, which has the potential to alter any DNA sequence (bacterial, plant, animal or human) have been in scientific research, but the applications for such technology are wide-ranging. These activities have prompted questions about biosecurity such as the capability to create novel pathogens, and the adequacy of controls governing the supply of gene editing tools (and modified animals) to the scientific community and beyond.[15] Other issues relate to differing moral perspectives on what constitutes an acceptable use for genome editing, which has the potential for transformative health benefits, but also for generating changes which conflict with society's views of what is 'normal'. Disability rights campaigners for example, have argued against selective technologies for many reasons, including the right to life of people with disabilities.

EMBRYO RESEARCH

Human embryonic stem cells (hESC), which have both the potential to differentiate into various cell types and the capacity for continual self-renewal in culture, offer opportunities for modelling human disease and have applications in areas of research such as regenerative medicine and cell-replacement therapies. However, processes which involve the development, use, and destruction of human embryos are highly contentious and are strongly opposed by some on the basis that they violate the sanctity of life.

Current regulations in many countries place tight restrictions on the use of hESC. Over a dozen countries, including the UK, only allow embryo research until the 14th day after fertilisation. The termination of the embryo at this stage was designed to be a compromise between deriving the benefits of research, and alleviating society's ethical concerns. In the UK, the limit was implemented in the early 1980s when research beyond 14 days was not technically possible. However, the results of two recently published studies (2016), which show that embryos can be sustained in vitro for around 13 days (and possibly longer) after fertilisation, have coincided with calls to revise the 14-day limit in order to further scientific understanding.[16]

A number of pharmaceutical companies involved in this activity have committed to only working with hESC obtained from surplus embryos from in vitro fertilisation (IVF) treatment that have been donated

[14] http://ec.europa.eu/research/health/pdf/summary-report-25082010_en.pdf; https://www.genome.gov/12514551/knockout-mice-fact-sheet/; http://www.understandinganimalresearch.org.uk/news/staff-blog/how-refining-animal-research-can-lead-to-more-experiments/

[15] http://nuffieldbioethics.org/wp-content/uploads/Genome-editing-an-ethical-review.pdf

[16] https://stemcells.nih.gov/info/basics/3.htm; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5450057/

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with freely-given informed consent. By law, such embryos are destined to be discarded. Many have also recognised the emerging potential of alternatives to hESC such as induced pluripotent stem cells (iPSC), which can be generated from adult stem cells, since these are genetically and functionally similar to embryonic stem cells. Such advances may eventually enable a move away from hESC, but companies such as Novo Nordisk report that at present, it has not been demonstrated that the same scientific results can be generated by the use of adult stem cells.[17]

SUMMARY

New drugs and therapies can have huge positive impacts on global health, and there is evidence to show that the largest research-based pharmaceutical companies are making progress in addressing the key concerns associated with their activities, by increasing access to essential medicines for those in developing countries, and by committing to greater disclosure of clinical trial data. However, progress is slow, and in some areas the extent to which policies and commitments are being translated into meaningful action appears to be limited. In light of this, regulatory agencies, NGOs and benchmarking projects such as the Access to Medicine Index perform a vital role as drivers of change within the industry, by outlining best practice, measuring corporate performance, and highlighting opportunities for growth and improvement. Continued pressure from civil society and the responsible investment community is also imperative. The operating practices of the pharmaceutical industry need to better reflect the values of these stakeholders if further progress is to be made in overcoming the challenges that it currently faces.

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[17] https://www.novonordisk.com/rnd/inside-r-d/bioethics/stem-cell-ethics/our-position-on-stem-cells.html

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