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ESSAYS ON TRUE DEMOCRACY AND CAPITALISM

# The Pharmaceutical Industry in Contemporary Capitalism

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he pharmaceutical industry has remained near or at the top of the list for profitability for many decades.<sup>1</sup> The myth is that its profits come from producing and selling the many therapeutic advances that industry research has generated, but the reality is far different. In the first place, after tax deductions only about 1.3 percent of the money that the industry spends actually goes into basic research, the type of research that leads to new medications.<sup>2</sup> Second, most of the new medicines that come from the pharmaceutical corporations offer little to nothing in the way of new therapeutic options. For the decade 2005 to 2014, among 1,032 new drugs and new uses for old drugs introduced into the French market, for example, only sixtysix offered a significant advantage, whereas more than half were rated as "nothing new," and 177 were judged "unacceptable" because they came with serious safety issues and no benefits.<sup>3</sup>



Image by Gordon Johnson from Pixabay

The industry also justifies its high level of profits with the claim

that drug development is inherently risky. To this end, the pharmaceutical corporations maintain that only one in every 10,000 molecules actually results in a new drug. Though this may be true, most of the molecules that fall by the wayside do so in the very early stages of development when costs are minimal. The \$2.6 billion figure that is now cited as the cost to bring a new drug to market<sup>4</sup> comes from data that are confidential, and the calculations are based on a set of

<sup>1 +</sup> Harriet Washington, Deadly Monopolies (New York: Anchor, 2011); Richard Anderson, "Pharmaceutical Industry Gets High on Fat Profits," BBC News, November 6, 2014.

<sup>&</sup>lt;sup>2</sup> ↔ Donald W. Light and Joel Lexchin, "Foreign Free Riders and the High Price of US Medicines," BMJ 331 (2005): 958–60.

<sup>&</sup>lt;sup>3</sup> Prescrire Editorial Staff, "New Drugs and Indications in 2014," Prescrire International 24 (2015): 107–10.

<sup>4 +</sup> Joseph A. DiMasi, Henry G. Grabowski, and Ronald W. Hansen, "Innovation in the Pharmaceutical Industry: New Estimates of R&D costs," Journal of Health Economics 47 (2016): 20–33.

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assumptions that have been widely challenged.<sup>5</sup> Were drug development such a risky proposition, then one would expect that from time to time the fortunes of corporations would vary. On the contrary, since 1980, all the large corporations have done well financially. As Stanley Finkelstein, a physician, and Peter Temin, an economist, both based at the Massachusetts Institute of Technology, point out, "No matter how many times industry analysts warn that a patent expiration is going to make this or that company vanish, it hasn't happened."<sup>6</sup>

Despite the continuing impressive level of profit, the industry is undergoing a crisis from a trio of causes: patent expirations that were expected to lead to a loss of revenue in the range of \$75 billion from 2010 to 2015, a poor pipeline of new drugs, and pressure on prices in many countries including, recently, the United States.<sup>7</sup> This crisis reflects the emergence of financialisation, the shift in gravity of economic activity from production to finance as a key feature of modern capitalism. Pedro Cuatrecasas, from the Departments of Pharmacology and Medicine at the University of California, San Diego, argues: "Shareholders, investment bankers, and analysts, who know little about drug discovery, place intense pressures on CEOs and their boards for quick returns."<sup>8</sup>

To maintain its attractiveness to the financial community, the pharmaceutical industry has developed several strategies. With the blockbuster model of development drying up, corporations have shifted to a "nichebuster" model. With fewer potential products in the research and development (R&D) pipeline, it is even more critical to ensure that drugs being

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developed make it through the regulatory process intact, and to do that, industry has deepened its relationship with regulatory agencies to circumvent or corrupt the intent of regulation, often with the collusion of government. Key to the industry's survival is its ability to extend the period during

which it has a monopoly on the sale of products, and that translates into stronger intellectual property rights, both in the developed world and in the developing countries that represent the emerging sites of growth. With the threat of price controls looming, the other way of expanding revenue is to increase the volume of prescriptions for existing and new drugs. The approach to that goal is to control the knowledge about how and when drugs should be prescribed. An exploration of these four points informs the rest of this essay: the development of nichebuster drugs, corrupting the regulatory process, strengthening intellectual property rights, and controlling knowledge about the benefits and harms of pharmaceutical products.

#### From Blockbuster to Nichebuster

Until a few years ago, the pharmaceutical industry operated on what is known as a blockbuster model. The industry targeted drug development for chronic diseases that were common in developed countries, such as heart disease or diabetes, and then heavily marketed those drugs in the hope of reaching \$1 billion annually in sales. Diseases that occurred predominantly or exclusively in developing countries were largely ignored, because the people affected had no meaningful purchasing power. Of 850 new therapeutic products marketed between 2000 and 2011, only thirty-seven (4 percent) were indicated for those types of diseases.<sup>9</sup>

<sup>5 +</sup> Donald W. Light and Rebecca N. Warburton, "Extraordinary Claims Require Extraordinary Evidence," Journal of Health Economics 24 (2005): 1030–33.

<sup>6 ↔</sup> Stanley Finkelstein and Peter Temin, Reasonable Rx: Solving the Drug Price Crisis (Upper Saddle River, NJ: FT, 2008).

<sup>7 +</sup> Greg Miller, "Is Pharma Running Out of Brainy Ideas?" Science 329 (2010): 502–04; David Holmes, "Skies Darken Over Drug Companies," Lancet 379 (2012): 1863–64.

<sup>&</sup>lt;sup>8</sup> ←Pedro Cuatrecasas, "Drug Discovery in Jeopardy," Journal of Clinical Investigation 116 (2006): 2837–42.

<sup>&</sup>lt;sup>9</sup> 
<sup>2</sup>Belen Pedrique, Nathalie Strub-Wourgaft, Claudette Some, Piero Olliaro, Patrice Trouiller, Nathan Ford, Bernard Pécoul, and Jean-Hervé Bradol, "The Drug and Vaccine Landscape for Neglected Diseases (2000–11): A Systematic Assessment," Lancet Global Health 1 (2013): e371–79.

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Recently, since all the easy targets are exhausted, there has been a shift away from the blockbuster model to the "nichebuster" model, whereby corporations target small therapeutic markets with drugs that they can sell for hundreds of

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thousands of dollars per year per patient. In this sense, the challenges experienced by the pharmaceutical industry resemble those of others that operate in a capitalist economy. The exhaustion of markets is an intrinsic condition of capitalism that requires "product differentiation," in this case more and more expensive medications for narrower and narrower markets, assuring requisite growth. In

the United States, the cost of disease-modifying drugs for multiple sclerosis has gone from an average of \$8,000 to \$11,000 per year in the early to mid-1990s to \$60,000 annually.<sup>10</sup> In 2013, 120 cancer specialists from more than fifteen countries came together to denounce prices for new oncology drugs that had reached \$100,000 or more annually.<sup>11</sup> The idea that these prices were justified by the cost of R&D should be put to rest, as confirmed by the former CEO of Pfizer, Hank McKinnell, who said, *It's a fallacy to suggest that our industry, or any industry, prices a product to recapture the R&D budget*.<sup>12</sup> Prices are based on what the market will bear. The more desperate patients become, the higher the price they are willing to pay.

#### Corruption of the Drug Regulatory Process

Before corporations can start making money from the drugs they manufacture, those drugs need to be approved for marketing. This stipulation is merely pro forma in much of the developing world, however, where one-third of countries have no or very little drug regulatory capacity.<sup>13</sup> Even in countries like India, drug regulation is often a sham, as can be seen by a 2011–12 examination of fixed-dose combination (FDC) products, that is, products that contain two or more active ingredients. Research recently found that corporations took advantage of lax regulatory standards to sell *many millions of doses...of FDCs that included drugs restricted, banned, or never approved in other countries owing to their association with serious adverse events including fatality.*<sup>14</sup>

Drug regulation in the United States and the European Union has been corrupted through the influence of the pharmaceutical industry. Courtney Davis and John Abraham, who teach pharmaceutical policy at King's College London, observe that *the last 30 years have seen a raft of deregulatory reforms, ostensibly to promote pharmaceutical innovation deemed to be simultaneously in the commercial interests of industry and the health interests of patients.*<sup>15</sup> An explanation for why this is allowed to take place comes from corporate bias theory.<sup>16</sup> Abraham argues, "Corporate bias theory allows for the possibility of a relatively strong, pro-active state, which may encourage pro-business (de)regulation in collaboration with industry."<sup>17</sup> Abraham contends that industry can drive regulation by influencing not just the regulatory agencies but also the broader government directly through lobbying, financial donations, and other activities

<sup>17</sup> ⇔Davis and Abraham, Unhealthy Pharmaceutical Regulation.

<sup>10 -</sup>Daniel M. Hartung, Dennis N. Bourdette, Sharia M. Ahmed, and Ruth H. Whitham, "The Cost of Multiple Sclerosis Drugs in the US and the Pharmaceutical Industry," Neurology 84 (2015): 2815–22.

Andrew Pollack, "Doctors Denounce Cancer Drug Prices of \$100,000 a Year," New York Times, April 25, 2013.

<sup>12</sup> PHank McKinnell, A Call to Action: Taking Back Healthcare for Future Generations (New York: McGraw Hill, 2005).

<sup>&</sup>lt;sup>13</sup> World Health Organization, The World Medicines Situation (Geneva: WHO, 2004).

<sup>14</sup> Patricia McGettigan, Peter Roderick, Rushikesh Mahajan, Abhay Kadam, and Allyson M. Pollock, "Use of Fixed Dose Combination (FDC) Drugs in India: Central Regulatory Approval and Sales of FDCs Containing Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), Metformin, or Psychotropic Drugs," *PLoS Medicine* 12 (2015): e1001826.

<sup>15 🖓</sup> Courtney Davis and John Abraham, Unhealthy Pharmaceutical Regulation: Innovation, Politics and Promissory Science (Hampshire, UK: Palgrave Macmillan, 2013).

<sup>16 -</sup> John Abraham, "Sociology of Pharmaceuticals Development and Regulation: A Realist Empirical Research Programme," Sociology of Health & Illness 30 (2008): 869–85.

—for example, getting drug company representatives appointed to task forces that help form overall government policy. The ultimate result is that the state actively supports the broad regulatory goals of industry.

The clearest manifestation of corporate bias theory in pharmaceutical regulation is the widespread adoption of corporate-user fees to pay for the functions of drug regulatory authorities such as the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the Medicines and Healthcare Products Regulatory Agency in the United Kingdom (UK MHRA). Resource constraints on the FDA were the major driving force behind the implementation of user fees in the United States. The continuing reluctance of Congress to increase the FDA's budget ultimately led the agency to abandon its previous position in opposition to user fees from the pharmaceutical industry. As part of the Prescription Drug User Fees Act (PDUFA) of 1992, the industry agreed to enter into an arrangement, provided that the fees were supplemental to congressional appropriations and that the money was used exclusively to improve the efficiency and speed of new drug reviews for brand-name drugs. As a result, the majority of fee revenues went to hiring new drug reviewers. It was not until 2007 that the FDA was allowed to use any of this additional money to monitor the safety of the products that it had approved.

PDUFA subsequently has been reauthorised at five-year intervals, with the latest renewal in 2012. One of the key features of PDUFA is that it contains provisions committing the FDA to continual improvements in the percentage of new drug applications approved within set periods of time.<sup>18</sup> With limited patent life, the longer drugs are on the market the greater the return to the corporations marketing them. PDUFA, by getting drugs to the market faster, meant more profits for the corporations.

Prior to 1989, the Medicines Control Agency (the precursor of the MHRA) in the United Kingdom received 65 percent of its funding from user fees and 35 percent via taxes. At that point, funding moved to 100 percent from user fees, a reflection of the philosophy of the Thatcher Conservative government that science should be made "more responsive" to the needs of industry.<sup>19</sup> In the European Union as a whole, the philosophy of user fees seems to have been accepted from the inception of the Agency. The question then becomes: whose priorities are being served, those of the public or those of the industry?

Evidence shows that user fees have had negative consequences for public safety. In the United States, the standard review time for a new drug application is three hundred days, and under PDUFA, the FDA is required to complete 90 percent of applications within that time frame. If this goal is not met, renewal of user fees might be threatened, thereby depriving the agency of a substantial portion of its revenue. In practice, it appears that as the FDA is approaching its deadline for making a decision, it relaxes its standards for evaluating safety. As compared with drugs approved at other times, drugs approved in the two months before their deadlines were over five times more likely to be withdrawn for safety reasons and almost 4.5 times more likely to carry a subsequent black-box warning, the most serious safety warning that the FDA can require.<sup>20</sup>

In the European Union, when a drug application is made to the EMA, the organisation is responsible for choosing what is called the Rapporteur and Co-Rapporteur, that is, the national regulatory agencies that will do the actual evaluation of the new drug application. Since most of the regulatory agencies in EU countries are funded to a considerable extent by

<sup>18 -</sup> James L. Zelenay, Jr. "The Prescription Drug User Fee Act: Is a Faster Food and Drug Administration Always a Better Food and Drug Administration?" Food and Drug Law Journal 60 (2005): 261–338.

<sup>&</sup>lt;sup>19</sup> Pohn Abraham, Science, Politics and the Pharmaceutical Industry: Controversy and Bias in Drug Regulation (London: UCL Press, 1995).

<sup>20 🗝</sup> Daniel Carpenter, Evan James Zucker, and Jerry Avorn, "Drug-Review Deadlines and Safety Problems," New England Journal of Medicine 358 (2008):1354–61.

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user fees, there is often intense competition among them for Rapporteur and Co-Rapporteur status to generate income.<sup>21</sup> This competition puts the national agencies under considerable pressure to conform to or to better the EU's 210-day timeline for drug approvals as corporations look for fast approval rates, one of their key criteria when recommending a

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Rapporteur and Co-Rapporteur. Out of fifteen German, Swedish, and UK regulatory personnel who were interviewed by Abraham and Graham Lewis from the University of York, five agreed that this timeline was a threat to public health, and

an additional five thought that it possibly was.<sup>22</sup> In a similar vein, a British House of Commons Committee looking into the influence of the pharmaceutical industry concluded, *The MHRA*, *like many regulatory organisations, is entirely funded by fees from those it regulates. However, unlike many regulators, it competes with other European agencies for fee income. This situation has led to concerns that it may lose sight of the need to protect and promote public health above all else as it seeks to win fee income from the companies.*<sup>23</sup>

#### Is Intellectual Property a 'Right'?

Intellectual property rights (IPRs) are the key factor in driving revenue and profits for pharmaceutical corporations. In the contemporary pharmaceutical context, the primary IPRs are the patents over the products themselves and the data that the corporations generate when they conduct premarket clinical trials to evaluate the safety and efficacy of their products. The stronger a country's IPRs, the longer the corporations retain a monopoly on their products and the more money they can make from them. Therefore, it should not be any surprise that the pharmaceutical industry goes to great lengths not only to protect IPRs but to strengthen them.

One of the earliest manifestations of this obsession with IPRs was the industry lobbying that led the United States to insist that Canada dismantle its regime of compulsory licensing in return for getting the initial U.S.-Canadian Free Trade Agreement in 1987 and then the North American Free Trade Agreement in 1994. At that time, compulsory licensing was cutting Canada's overall drug spending by about 15 percent.<sup>24</sup> (A compulsory license allows a generic manufacturer to produce a drug even if the patent on the product is still in effect.)

In the United States, the latest victory for stronger IPRs has been the twelve years of market exclusivity for biologic products, that is, those that are made from living cells. These twelve years come courtesy of four years of data protection

Although in developed countries the IPR provisions in trade agreements have a significant impact on drug access, causing delays in generics reaching the market, the consequences in developing countries are much more devastating. and an additional eight years of exclusive use for biological products. This means that the FDA will not approve a "biosimilar," the equivalent of a generic product, during this eight-year period. In some ways, data protection can be even more important to corporations than patents since data protection cannot be challenged in the court system the same

way that patents can. Although biologics represent fewer than 1 percent of prescriptions written in the United States, they account for 28 percent of drug spending, and that figure is only going to increase in the future.<sup>25</sup> For instance, Cerezyme, a treatment for Gaucher disease, a rare inherited enzyme deficiency, costs \$200,000 a year per patient.

 <sup>&</sup>lt;sup>21</sup> Ohn Abraham and Graham Lewis, "Europeanisation of Medicines Regulation," in John Abraham and Helen Lawton Smith, eds., *Regulation of the Pharmaceutical Industry* (Hampshire, UK: Palgrave Macmillan, 2003), 42–81.
 <sup>22</sup> Ohid

 <sup>&</sup>lt;sup>23</sup> House of Commons, Health Committee, The Influence of the Pharmaceutical Industry: Fourth Report of Session 2004–05, vol. 1 (London: Stationery Office Limited, April 5, 2005).
 <sup>24</sup> Poel Lexchin, "Pharmaceuticals, Patents and Politics: Canada and Bill C-22," *International Journal of Health Services* 23 (1993): 147–60.

<sup>25 -</sup> Ameet Sarpatwari, Jerry Avorn, and Aaron S Kesselheim, "Progress and Hurdles for Follow-On Biologics," New England Journal of Medicine 372 (2015): 2380–82.

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Internationally, the U.S. government, with strong backing from the pharmaceutical industry, pushed to make sure that an investor-state dispute settlement (ISDS) mechanism was included in international trade agreements. ISDS allows corporations to sue governments.<sup>26</sup> Eli Lilly has used the ISDS provisions in the North American Free Trade Agreement to

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demand \$500 million from the Canadian government because Canadian courts invalidated patents on two of Lilly's drugs.<sup>27</sup> Although in developed countries the IPR provisions in trade agreements have a significant impact on drug access, causing delays in generics reaching the market, the consequences in developing countries are much more devastating. For instance,

under current patent laws 68 percent of the HIV population in Vietnam receives antiretroviral medications, but under the failed Trans-Pacific Partnership that figure would have dropped to about 30 percent.<sup>28</sup>

The pharmaceutical industry has more than a three-decade history of successfully lobbying for stronger IPRs, beginning with the lead-up to the Uruguay Round of trade talks that ultimately resulted in the World Trade Organization (WTO). Pfizer and its then CEO Edmund Pratt played a key role in convincing the U.S. government to make IPRs a major issue in these talks.<sup>29</sup> The result, in 1994, was the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), which required uniform patent standards for all WTO member countries, meaning product patents for pharmaceuticals of twenty years and limiting the use of compulsory licensing as a tool for accelerating the appearance of generic products. The pharmaceutical industry's goal was to have all countries adopt the same IPRs as those in the United States, regardless of their level of development or ability to deliver drug therapy to their populations at an affordable price. Many developed countries did not adopt full patent protection for pharmaceuticals until the 1970s or later when their gross domestic product (GDP) per capita was in the tens of thousands of dollars. The TRIPS Agreement required developing countries with a GDP in the hundreds or low thousands of dollars to have the equivalent standards.<sup>30</sup>

Due to the strengthening of IPRs, by 2000 many developing countries were confronting a situation where the price of triple therapy for HIV was greater than \$10,000 per person per year, and the ability to access low-cost generics was going to disappear in the near future.<sup>31</sup> Faced with increasing rates of HIV infection and these prices for HIV treatment, the South African government in the late 1990s passed the Medicines and Related Substances Control Amendment Act, which allowed for generic substitution of off-patent medicines and the ability to import a non-counterfeit version of patented medicines from another country without the permission of the intellectual property owners. In response, during 1998, thirty-nine multinational pharmaceutical corporations, with the support of the U.S. government (under the Clinton administration) and the European Commission, took the South African government to court alleging that the legislation violated both the TRIPS Agreement and the country's constitution. Eventually, in the face of widespread public opposition, the U.S. government withdrew its support for the court case, and without the U.S. support the corporations dropped their lawsuit.<sup>32</sup>

<sup>26 -&</sup>gt;James Love, "TPP, Designed to Make Medicine More Expensive, Reforms More Difficult," Medium, June 8, 2015, http://medium.com.

<sup>&</sup>lt;sup>27</sup> →Kazi Stastna, "Eli Lilly Files \$500M NAFTA Suit Against Canada Over Drug Patents," CBC News, September 13, 2013.

<sup>28</sup> Hazel Moir, Deborah H. Gleeson, Brigitte Tenni, and Ruth Lopert, Assessing the Impact of Alternative Patent Systems on the Cost of Health Care: The TPP and HIV Treatment in Vietnam (Sydney: Asia-Pacific Innovation Conference, 2014).

<sup>29 🗝</sup> Peter Drahos, "Expanding Intellectual Property's Empire: The Role of FTAs," International Centre for Trade and Sustainable Development, November 2003, http://ictsd.org.

<sup>30 🕂</sup> Jean O. Lanjouw and William Jack, "Trading Up: How Much Should Poor Countries Pay to Support Pharmaceutical Innovation?" CGD Brief 4 (2004): 1–7.

<sup>31 🖓</sup> Campaign for Access to Essential Medicines, Untangling the Web of Antiretroviral Price Reductions (Geneva: Médecins Sans Frontières, 2010).

<sup>32 🕂</sup> Ellen 't Hoen, "TRIPS, Pharmaceutical Patents, and Access to Essential Medicines: A Long Way from Seattle to Doha," Chicago Journal of International Law 3 (2002): 27–48.

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Since then, the United States and the European Union have used the TRIPS Agreement as a minimum for acceptable IPR standards and have tried to ratchet up their strength with each successive trade deal by incorporating newer and more stringent provisions. Some of the results can be seen in longer periods of patent extension (patents can be extended past twenty years) and in the elimination of objecting to patents before they are granted.<sup>33</sup> Like the consequences for HIV medication access in Vietnam, stronger IPR provisions in free trade agreements significantly decrease access to prescribed medicines.<sup>34</sup>

Thailand provides just one of many examples of how governments and the industry have used IPRs as a tool to bully developing countries. Citing high drug prices and its obligation to provide access to essential medicines, in 2006 Thailand issued a compulsory license for lopinavir/ritonavir, a drug combination used to treat HIV. The EU Trade Commissioner wrote to the Thai Minister of Commerce to complain about Thailand's move. Abbott, the maker of lopinavir/ritonavir, responded by withdrawing all new drug applications from the Thai Food and Drug Administration, including the much needed heat-stable version of lopinavir/ritonavir.<sup>35</sup>

When generic drugs are produced through compulsory licenses, brand-name corporations are quick to denounce this measure. Marijn Dekkers, CEO of Bayer, referred to compulsory licensing as "essentially theft," although it is perfectly legal under the TRIPS Agreement. In addition, when Dekkers was talking about his company's new and highly effective drug sobosbuvir (Sovaldi) for treating hepatitis C, he commented: *We did not develop this product for the Indian market, let's be honest. I mean, you know, we developed this product for Western patients who can afford this product, quite honestly.*<sup>36</sup>

#### SARS-CoV-2, Controlling Knowledge

Clinical trials that fail to demonstrate effectiveness or that raise significant safety concerns can dramatically affect the sale of products. In July 2002, the results of a Women's Health Initiative clinical trial found that the estrogen/progestin combination of hormone replacement therapy (HRT) caused an increased risk of cardiovascular disease and breast cancer in postmenopausal women.<sup>37</sup> By June 2003, prescriptions for Prempro, the most widely sold estrogen/progestin combination, had declined by 66 percent in the United States.<sup>38</sup>

To avoid these scenarios and continue to expand revenue, corporations have evolved from controlling the development of new drugs to controlling the knowledge about those drugs, ensuring that their message is the one that reaches doctors and patients.<sup>39</sup> Pharmaceutical corporations fund almost all pre-market clinical trials, the ones used as the basis for approving a new drug or a new indication for an existing drug. These trials are the foundation of knowledge about a drug and as such their outcome is extremely important. As funders, corporations control all aspects of the trials from

<sup>33 +&</sup>gt; Stephanie Rosenberg, "Comparative Chart of Pharmaceutical Patent and Data Provisions in the TRIPS Agreement, Free Trade Agreements Between Trans-Pacific FTA Negotiating Countries and the U.S., and the U.S. Proposal to the Trans-Pacific FTA," Public Citizen, November 8, 2012, http://citizen.org.

<sup>&</sup>lt;sup>34</sup> • Youn Jung and Soonman Kwon, "The Effects of Intellectual Property Rights on Access to Medicines and Catastrophic Expenditure," International Journal of Health Services 45 (2015): 507–29.

<sup>35 -</sup> Ellen 't Hoen, The Global Politics of Pharmaceutical Monopoly Power: Drug Patents, Access, Innovation and the Application of the WTO Doha Declaration on TRIPS and Public Health (Diemen: AMB, 2009).

<sup>36 - &</sup>quot;"We Didn't Make This Medicine for Indians...We Made It for Western Patients Who Can Afford It': Pharmaceutical Chief Tries to Stop India Replicating Its Cancer Treatment," Daily Mail, January 24, 2014.

<sup>37 •</sup> Writing Group for the Women's Health Initiative Investigators, "Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women: Principal Results from the Women's Health Initiative Randomised Controlled Trial," JAMA 288 (2002): 321–33.

<sup>&</sup>lt;sup>38</sup> Adam L. Hersh, Marcia L. Stefanick, and Randall S. Stafford, "National Use of Postmenopausal Hormone Therapy: Annual Trends and Response to Recent Evidence," JAMA 291 (2004): 47–53.

<sup>&</sup>lt;sup>39</sup> 🖓 Marc-André Gagnon, The Nature of Capital in the Knowledge-Based Economy: The Case of the Global Pharmaceutical Industry (Toronto: York University Press, 2009).

their initial design to the way that they are conducted and analysed, how they are reported to drug regulatory agencies such as the FDA, whether and how they are published, and to a large extent how they are presented to doctors.

Pro-corporate bias starts with the trial design. When the new drug being tested is compared to another drug already on the market, inappropriately low or high doses of the comparator drug may be chosen to either minimise effectiveness or

termination solely on financial grounds can be viewed as a violation of Article 6 of the Declaration of Helsinki, the internationally recognised standard for the conduct of clinical research, that states that "in medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests." maximise side effects.<sup>40</sup> In the 1980s, the most common reason for terminating trials in the late stages of research, including treatments for cancer, cardiovascular disease, and neonatal sepsis, was financial consideration (43 percent), compared to efficacy (31 percent) and safety (21 percent).<sup>41</sup> The financial reasons included a limited commercial market, insufficient anticipated return on investment, and a change in research priorities following drug company mergers. However, termination solely on financial grounds can be viewed as a

violation of Article 6 of the Declaration of Helsinki, the internationally recognised standard for the conduct of clinical research.<sup>42</sup> Article 6 states that "in medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests." Stopping trials before they are completed solely for financial reasons effectively means that the "quarterly business plans or the changing of chief executive officers" takes precedence over "the responsible conduct of medical research [that] involves a social duty and a moral responsibility that transcends quarterly business plans or the changing of chief executive officers."<sup>43</sup>

There is evidence that not all the data from clinical trials is made available to regulatory authorities and that it is presented in a misleading way. Merck failed to provide mortality data in a timely manner to the FDA from two trials involving the use of rofecoxib in patients with Alzheimer's or other cognitive impairment.<sup>44</sup> GlaxoSmithKline presented data to the FDA about its asthma drug, salmeterol, that produced an apparent decrease in the danger associated with the drug.<sup>45</sup>

One of the best-known examples of the way that corporations change the interpretation of trials between the time that they report results to the FDA and when the trials are actually published is the study that examined the effectiveness of celecoxib, a non-steroidal anti-inflammatory drug (NSAID) and pain reliever made by Pfizer. The published trial, based on six months of data, appeared to confirm the protective effect of celecoxib over traditional anti-inflammatories medications in reducing stomach bleeding. However, the two studies combined in the publication actually continued for twelve and sixteen months. At the 12–16-month time there was no difference in gastrointestinal adverse effects between those patients who used celecoxib and those users of the traditional NSAID.<sup>46</sup>

<sup>&</sup>lt;sup>40</sup> Antonio Nieto, Angel Mazon, Rafael Pamies, Juan J. Linana, Amparo Lanuza, Fernando Oliver Jiménez, Alejandra Medina-Hernandez, and Javier Nieto, "Adverse Effects of Inhaled Corticosteroids in Funded and Nonfunded Studies," Archives of Internal Medicine 167 (2007): 2047–53.

<sup>41 -</sup> Joseph A DiMasi, "Success Rates for New Drugs Entering Clinical Testing in the United States," Clinical Pharmacology & Therapeutics 58 (1995): 1–14; Bruce M. Psaty and Drummond Rennie, "Stopping Medical Research to Save Money: A Broken Pact with Researchers and Patients," JAMA 289 (2003): 2128–31.

<sup>42 🖓 &</sup>quot;WMA Declaration of Helsinki: Ethical Principles For Medical Research Involving Human Subjects," World Medical Association, March 29, 2017.

<sup>&</sup>lt;sup>43</sup> ≁Ibid

<sup>44</sup> C Bruce M. Psaty and Richard A. Kronmal, "Reporting Mortality Findings in Trials of Rofecoxib for Alzheimer Disease or Cognitive Impairment: A Case Study Based on Documents from Rofecoxib Litigation," JAMA 299 (2008): 1813–17.

<sup>45</sup> Peter Lurie and Sidney M. Wofle, "Misleading Data Analyses in Salmeterol (SMART) Study," The Lancet 366 (2005): 1261–62.

<sup>46 🖓</sup> James M. Wright, Thomas L. Perry, Kenneth L. Bassett, and G. Keith Chambers, "Reporting of 6-Month vs 12-Month Data in a Clinical Trial of Celecoxib," JAMA 286 (2001):2398–99.

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Ghostwriting in the pharmaceutical industry refers to the practice whereby corporations, or someone working on their behalf, hire medical writers to write a journal article or letter based on company-owned data. The article is then taken to an academic researcher who agrees to sign it, usually for money or the prestige value of having a publication. When the article eventually appears in print, there is no acknowledgement of the role played by the ghostwriter in its production. Wyeth enlisted ghostwriters to defend the \$2 billion in annual sales from Premarin and Prempro, its two HRT products, before and after the publication of the Women's Health Initiative, which showed that the risks from HRT drugs outweighed their benefits. Court documents show that ghostwriters played a major role in producing twenty-six scientific papers that backed the use of HRT. The articles did not disclose Wyeth's role in initiating and paying for the work.<sup>47</sup>

There are numerous examples of selective publication of industry trials with negative results. Out of thirty-seven studies on antidepressants that the FDA viewed as either negative or questionable, twenty-two were never published.<sup>48</sup> Failure to publish data can lead to overestimating the effectiveness of products and underestimating their harm. Published data overestimated the benefit of the antidepressant reboxetine versus placebo by up to 115 percent and also underestimated harm.<sup>49</sup>

Internal documents from GlaxoSmithKline were used to demonstrate differences between the actual results of a study that examined the safety and effectiveness of the antidepressant paroxetine in adolescents and the way the results were presented in published form.<sup>50</sup> The publication claimed that "paroxetine is generally well tolerated and effective for major depression in adolescents."<sup>51</sup> In contrast, based on the protocol-defined primary and secondary outcomes, "there was no significant efficacy difference between paroxetine and placebo on the two primary outcomes or six secondary outcomes," and paroxetine was associated with harm, including an increase in suicidal ideation.<sup>52</sup>

Finally, corporations recognise that there is a credibility gap when they directly present evidence about their products to

Although the pharmaceutical industry seems like an invincible opponent, the Mario Negri Institute in Italy, offers an alternative way for doing pharmacological research. It is willing to accept money from pharmaceutical corporations for research, but it insists on maintaining its independence by designing the trials, conducting them, collecting and analysing the data, and writing up the results without any interference from the funding source. doctors. To get around this problem, they employ doctors and researchers known as "key opinion leaders" (KOLs). It's vital for the corporations to preserve the fiction that KOLs are independent sources of information in order to maintain the trust of doctors who hear the KOLs' presentations. However, it is precisely when KOLs start to act independently and deviate from the messages corporations are cultivating that their value to the corporations starts to be questioned.<sup>53</sup> One KOL wrote a series of case reports about a certain

medication made by a company for which he often spoke that portrayed the product as less favorable than that of a drug

<sup>&</sup>lt;sup>47</sup> Natasha Singer, "Medical Papers by Ghostwriters Pushed Therapy," New York Times, August 5, 2009.

<sup>&</sup>lt;sup>48</sup> Cric H. Turner, Annette M. Matthews, Efthia Linardatos, Robert A. Tell, and Robert Rosenthal, "Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy," New England Journal of Medicine 358 (2008): 252–60.

 <sup>&</sup>lt;sup>49</sup> Dirk Eyding, Monika Lelgemann, Ulrich Grouven, Martin Härter, Mandy Kromp, Thomas Kaiser, Michaela F. Kerekes, Martin Gerken, and Beate Wiseeler, "Reboxetine for Acute Treatment of Major Depression: Systematic Review and Meta-Analysis of Published and Unpublished Placebo and Selective Serotonin Reuptake Inhibitor Controlled Trials," *BMJ* 341 (2010): e4737.
 <sup>50</sup> On Jureidini, Leeman B. McHenry, and Peter R Mansfield, "Clinical Trials and Drug Promotion: Selective Reporting of Study 329," *International Journal of Risk & Safety in Medicine* 20 (2008): 73–81.

<sup>&</sup>lt;sup>51</sup> • Martin B. Keller, Neal D. Ryan, Michael Strober et al., "Efficacy of Paroxetine in the Treatment of Adolescent Major Depression: A Randomised, Controlled Trial," *Journal of the American Academy of Child and Adolescent Psychiatry* 40 (2001): 762–72.

<sup>52 -&</sup>gt;S. Swaroop Vedula, Lisa Bero, Roberta W Scherer, and Kay Dickersin, "Outcome Reporting in Industry-Sponsored Trials of Gabapentin for Off-Label Use," New England Journal of Medicine 361 (2009): 1963–71.

<sup>&</sup>lt;sup>53</sup> Sergio Sismondo, "'You're Not Just a Paid Monkey Reading Slides': How Key Opinion Leaders Explain and Justify Their Work," Edmund J. Safra Working Papers, Harvard University, No. 26 (2013).

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made by a competitor. Once those case reports became public, his invitations to speak dropped from four to six times per month to essentially none.<sup>54</sup>

### A Better World Is Possible

In an unpublished paper, the British economist Alan Maynard notes:

Economic theory predicts that firms will invest in corruption of the evidence base wherever its benefits exceed its costs. If detection is costly for regulators, corruption of the evidence base can be expected to be extensive. Investment in biasing the evidence base, both clinical and economic, in pharmaceuticals is likely to be detailed and comprehensive, covering all aspects of the appraisal process. Such investment is likely to be extensive as the scientific and policy discourses are technical and esoteric, making detection difficult and expensive.<sup>55</sup>

Although the pharmaceutical industry seems like an invincible opponent, the crisis that it is facing also offers the opportunity to advocate for new ways of bringing drugs to the market that are affordable and meet real medical needs rather than maximisation of profits. The Mario Negri Institute in Italy, in existence since the early 1960s, offers an alternative way for doing pharmacological research. It is willing to accept money from pharmaceutical corporations for research, but it insists on maintaining its independence by designing the trials, conducting them, collecting and analysing the data, and writing up the results without any interference from the funding source. In addition, the Institute declines to take out any patents or to demand any other form of IPRs and makes all data freely available. Finally, it rejects any funding when its scientists conclude that the results will not further the interest of public health.<sup>56</sup>

Though it is worth emulating the Mario Negri Institute model on a wider scale, this still leaves the choice of what drugs to focus on and their eventual price in the hands of the pharmaceutical corporations. To deal with these issues, there have been proposals circulating for over a decade to incentivise R&D into products that meet real medical needs rather than just enhancing profits and to base the revenue that corporations earn on the therapeutic value of products rather than their prices. U.S. Senator Bernie Sanders introduced and revised the Medical Innovation Prize Fund bill, which would de-link the incentives for R&D from high drug prices through innovation inducement prizes. "Incentives can target important goals such as products that...address research priorities from a health perspective."<sup>57</sup>

Going further, there is the "sequestration thesis" proposed by Arthur Schafer, Director of the Centre for Professional and Applied Ethics at the University of Manitoba.<sup>58</sup> Under this proposal, an organisation such as the National Institutes of Health or its equivalent in other countries would organise and manage clinical trials and the data that come from them, with funding generated through taxes collected from the pharmaceutical industry and/or general tax revenue.<sup>59</sup> "Drug companies would no longer directly compensate scientists for evaluating their own products; instead, scientists would work for the testing agency."<sup>60</sup> Dean Baker, co-founder of the Center for Economic and Policy Research in Washington, D.C., goes even further in arguing for a system whereby all clinical trials would be publicly financed, with the cost of the

<sup>&</sup>lt;sup>54</sup> John W. Norton, "Is Academic Medicine for Sale?" New England Journal of Medicine 343 (2000): 508.

<sup>&</sup>lt;sup>55</sup> ←Alan Maynard, personal communication with the author, 2001.

<sup>56 🗝</sup> Donald W. Light and Antonio F. Maturo, Good Pharma: The Public-Health Model of the Mario Negri Institute (New York: Palgrave Macmillan, 2015).

<sup>57 🖓</sup> James Love, What's Wrong with Current System of Funding R&D, and What Are Ideas for Reforms? (Washington, D.C.: Knowledge Ecology International, 2015).

<sup>&</sup>lt;sup>58</sup> Arthur Schafer, "Biomedical Conflicts of Interest: A Defence of the Sequestration Thesis—Learning From the Cases of Nancy Olivieri and David Healy," *Journal of Medical Ethics* 30 (2004): 8–24.

<sup>&</sup>lt;sup>59</sup> + Tracy R. Lewis, Jerome H. Reichman, and Anthony Deh-Chuen So, "The Case for Public Funding and Public Oversight of Clinical Trials," *Economists' Voice* 4 (2007): 1–4; Marcia Angell, *The Truth About the Drug Companies: How They Deceive Us and What to Do About It* (New York: Random House, 2004).

<sup>60 ←</sup> Lewis, Reichman, and So, "The Case for Public Funding and Public Oversight of Clinical Trials."

trials in the United States covered through lower drug prices under the Medicare drug program and other public health care programs.<sup>61</sup>

Some national health systems have experienced relative success in controlling overall drug expenditures through a variety of mechanisms. Canada sets a maximum introductory price for new patented medicines.<sup>62</sup> As a result, prices for brand-name drugs are, on average, about 50 percent lower than prices in the United States.<sup>63</sup> However, the benchmark that Canada uses is the median price in seven other countries, some with the highest prices in the world; this is one of the reasons why spending for medications in Canada is \$713 per capita, fourth highest in the world.<sup>64</sup> Australia, with its Pharmaceutical Benefits Scheme that covers the entire population, negotiates prices at a national level. If drugs are not listed on its formulary, sales suffer significantly. Therefore, Australia is able to achieve prices for brand-name drugs that are about 9 to 10 percent lower than Canada's.<sup>65</sup> New Zealand is even more aggressive and uses competitive bidding for generic drugs and reference-based pricing for brand-name drugs. Reference-based pricing groups all drugs that are therapeutically equivalent for a particular problem, and the government then pays only for the lowest-priced drug in the group. Using these two approaches and a few others, instead of spending an expected NZ\$2.34 billion in 2012, based on the rate of rise in drug spending in 2000, New Zealand paid out only \$777 million.<sup>66</sup>

However, despite successes in controlling overall spending, no developed countries have been willing to mount a

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challenge to the current intellectual property regime that grants monopolies for up to twenty years and keeps lower-priced generics off the market. All drug regulatory systems are funded to varying degrees by user fees, thereby embedding a system that makes regulators sensitive to the needs of the pharmaceutical industry when it comes to approving new products. Finally, clinical trials are still under control of pharmaceutical corporations worldwide. Promotion to both health care

practitioners and consumers, even in countries like New Zealand, is poorly regulated, meaning that both prescribers' and patients' knowledge about medications remains limited.

Pharmaceutical corporations are extremely powerful due to their wealth. They achieve this power with the active collusion of regulatory authorities and the governments that oversee these authorities. The introduction of user fees has meant that commercial values are replacing public health as a priority for organisations such as the FDA. In the process, drugs are approved with increasingly weaker evidence, and the result is poor-quality therapy and more safety problems associated with the drugs that are marketed. Ratcheting up the strength of IPRs through international and bilateral trade deals helps protect the profits of the corporations but means that, globally, access to essential medicines is restricted, especially in developing countries.

<sup>61 -&</sup>gt; Dean Baker, "The Benefits and Savings from Publicly Funded Clinical Trials of Prescription Drugs," International Journal of Health Services 38 (2008): 731–50.

<sup>62 -</sup> Patented Medicine Prices Review Board, Annual Report 2016 (Ottawa: PMRPB, 2017), http://pmprb-cepmb.gc.ca.

<sup>&</sup>lt;sup>63</sup> Patented Medicine Prices Review Board, Annual Report 2012 (Ottawa: PMPRB, 2013).

<sup>64</sup> Corganization for Economic Co-operation and Development, Health at a Glance 2015: OECD Indicators (Paris: OECD, 2015).

<sup>65 🖓</sup> Productivity Commission, 2003, Evaluation of the Pharmaceutical Industry Investment Program, Research Report (Canberra: AusInfo, 2003).

<sup>66</sup> Pharmaceutical Management Agency, Annual Review 2012 (Wellington: PHARMAC, 2013), http://pharmac.govt.nz.

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Finally, the industry is able to manipulate knowledge about the value of pharmaceuticals not only to the detriment of what doctors know, but more important, to the detriment of people's health. At the same time as the industry is developing ways of coping with its internal crisis, a crisis that is inherent in the capitalist organisation of pharmaceutical production, there are also serious proposals to curb its power and to ensure that drugs are developed and priced to meet real health needs and not the need for ever larger profits.<sup>67</sup>

#### **Useful links:**

- The Jus Semper Global Alliance
- <u>Monthly Review</u>
- John Bellamy Foster and Intan Suwandi: COVID-19 and Catastrophe Capitalism
- Rob Wallace, Alex Liebman, Luis Fernando Chaves and Rodrick Wallace: <u>COVID -19 and Circuits of Capital</u>
- Nubia Barrera Silva: Capitalism of Dispossession in the Palm Oil Plantations in the Countries of the Global South
- Álvaro J. de Regil: Transitioning to Geocratia the People and Planet and Not the Market Paradigm First Steps
- Adolfo Gilly & Rhina Roux: Capitals, Technologies and the Realms of Life. The Dispossession of the Four Elements

<sup>67 -</sup> As of this writing, two physician organizations, one in the United States (Physicians for a National Health Program) and one in Canada (Canadian Doctors for Medicare), have developed a comprehensive strategy to restrict the power of the pharmaceutical industry and to improve access to medications.

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- About Jus Semper: The Jus Semper Global Alliance aims to contribute to achieving a sustainable ethos of social justice in the world, where all communities live in truly democratic environments that provide full enjoyment of human rights and sustainable living standards in accordance with human dignity. To accomplish this, it contributes to the liberalisation of the democratic institutions of society that have been captured by the owners of the market. With that purpose, it is devoted to research and analysis to provoke the awareness and critical thinking to generate ideas for a transformative vision to materialise the truly democratic and sustainable paradigm of People and Planet and NOT of the market.
- About the author: Joel Lexchin teaches health policy at York University and is an emergency physician with the University Health Network in Toronto.



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