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Peering into the pharmaceutical "pipeline": Investigational drugs, clinical trials, and industry priorities

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ABSTRACT

In spite of a growing literature on pharmaceuticalization, little is known about the pharmaceutical industry's investments in research and development (R&D). Information about the drugs being developed can provide important context for existing case studies detailing the expanding – and often problematic – role of pharmaceuticals in society. To access the pharmaceutical industry's pipeline, we constructed a database of drugs for which pharmaceutical companies reported initiating clinical trials over a five-year period (July 2006–June 2011), capturing 2477 different drugs in 4182 clinical trials. Comparing drugs in the pipeline that target diseases in high-income and low-income countries, we found that the number of drugs for diseases prevalent in high-income countries was 3.46 times higher than drugs for diseases prevalent in low-income countries. We also found that the plurality of drugs in the pipeline was being developed to treat cancers (26.2%). Interpreting our findings through the lens of pharmaceuticalization, we illustrate how investigating the entire drug development pipeline provides important information about patterns of pharmaceuticalization that are invisible when only marketed drugs are considered.

1. Introduction

Within discourses about research and development (R&D), the pharmaceutical industry often represents the process as a pipeline, and a leaky one at that. In these depictions, clinical development – the part of R&D in which investigational drugs are tested on humans – is divided into three phases with some drugs falling out of the pipe at each step as they move toward market approval. Phase I studies primarily rely on healthy volunteers to establish safety profiles for investigational drugs and to help establish appropriate doses that can be given to patients in subsequent clinical trials. A "failed" drug at this stage would be one that produces high rates of serious adverse events (i.e., side effects) in participants. Phase II trials enroll a small number of patients with the target illness in a proof-of-concept trial that aims to collect additional data on the safety of the investigational drug as well as preliminary evidence of its efficacy. Drugs that do not exhibit sufficient promise in treating the targeted illness or are not well tolerated by patients are likely to drop out of the pipeline at this stage. Phase III studies are large-scale clinical trials designed to show the investigational drug's efficacy by comparing the outcomes of several hundred or more patients randomly assigned to receive the drug with a placebo and/or a competitor product. According to industry analysts, the probability that an investigational drug will transition from Phase I to Phase II is 71% and from Phase II to Phase III is 45% (DiMasi et al., 2010). Pharmaceutical companies submit applications to the U.S. Food and Drug Administration (FDA) to market approximately 64% of all drugs that enter Phase III trials (DiMasi et al., 2010) (Fig. 1). Although the FDA subsequently approves 93% of all such applications, these represent only 19% of all drugs that began clinical testing (DiMasi et al., 2010). In other words, more than 80% of all investigational drugs that enter the proverbial pipeline are likely to "leak out" and never make it to market.

The pharmaceutical industry claims that drug development is a high-risk activity, with lengthy and expensive clinical trials on which the success or failure of their products hinge. As part of this framing, the industry lobbying group PhRMA – as well as industry-supported, academic economists – have circulated stunning

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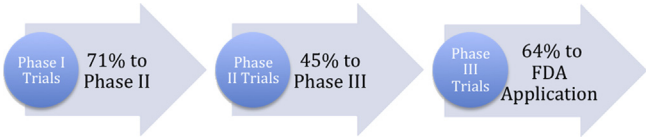

Fig. 1. Visualization of the pharmaceutical pipeline.

estimates of costs associated with bringing new drugs to market (DiMasi et al., 2003; PhRMA, 2004, n.d.). DiMasi et al. (2003) estimated cost based on a sample of 68 self-originated new molecular entities (i.e., the most expensive drugs to develop) and calculated the average investment in a drug brought to market is $802 million. At the same time, consumer advocacy groups and industry critics – within and outside academia – challenge not only this projected average cost of drug development but also the therapeutic value of many new pharmaceuticals (Angell, 2004; Goozner, 2005; Light and Warburton, 2011). On this latter point, for example, Light et al. (2013) have shown that only 8% of drugs approved by the FDA from 2002 to 2011 offer substantial therapeutic benefit for patients over existing products on the market and 15% were deemed to be more harmful than beneficial.

In spite of diverse groups' interest in the process and politics of drug development, the pharmaceutical pipeline itself remains relatively black-boxed. In part, the pipeline metaphor works as a marketing tool for the industry, creating the impression that there is an endless supply of new and innovative products in development. In spite of the powerful imagery, there is much evidence to suggest that the number of investigational drugs is on the decline and those that make it to market offer few therapeutic breakthroughs for patients (Angell, 2004; Light and Lexchin, 2012; Light and Warburton, 2011). In addition, the pharmaceutical industry places understandably more emphasis on promoting information about marketed products than those unable to meet FDA safety and efficacy benchmarks. Within social science and biomedical communities, scholarship has also centered on marketed pharmaceuticals, analyzing physicians' relationships with industry, direct-to-consumer advertising, and industry constructions of illness (e.g., Conrad and Leiter, 2008; Dumit, 2012; Greene, 2007; Kassirer, 2005). This literature often mobilizes the concept of "pharmaceuticalization" to signal the increasing power of the pharmaceutical industry to shape physicians' and patients' engagement with health and illness (Abraham, 2010; Bell and Figert, 2012; Busfield, 2010; Williams et al., 2008a; Williams et al., 2011). Even when this scholarship includes examinations of clinical trials, it often does so retrospectively either for marketed pharmaceuticals or those removed from the market due to safety concerns.

Given the dearth of information about the pharmaceutical pipeline, we constructed a database of drugs for which pharmaceutical companies reported initiating clinical trials over a five-year period (July 2006–June 2011), capturing 2477 drugs being evaluated in 4182 clinical trials. Querying these data, we asked the following questions about drugs in the development pipeline: (1) Including Phase I, II, and III clinical trials, what therapeutic areas are targeted?; (2) To what extent does the distribution of disease categories reflect global disease burden?; and (3) What can be inferred about the pharmaceutical industry's priorities for products they *intend* to market? Interpreting our findings through the lens of pharmaceuticalization, we argue that much of drug development focuses on illnesses prevalent in Western contexts, where drugs have more potential to generate significant revenue for pharmaceutical companies. We also illustrate how investigating the entire drug development pipeline provides important information about patterns of pharmaceuticalization that are invisible when only marketed drugs are considered.

2. Pharmaceuticalization and drug development

Sociological interest in the role of pharmaceuticals in medicine has emerged from a longer-standing research tradition investigating the medicalization of society (Clarke et al., 2003; Conrad, 2007). This broader area of scholarship has shown how the profession of medicine has encroached on and claimed expertise over routine aspects of life from birth to death (e.g., Howarth, 2007; Starr, 1982; Sullivan and Weitz, 1988). Similarly, scholars have shown how pharmaceuticals have extended medicalization such that aging, sex, and sleep have all become problems requiring chemical intervention (Fishman et al., 2010; Fox and Ward, 2008; Healy, 2012; Marshall, 2002; Williams et al., 2008b). Williams et al. (2011) define pharmaceuticalization as "the translation or transformation of human conditions, capabilities and capacities into opportunities for pharmaceutical intervention" (711). They further note that scholars must include in their analyses of pharmaceuticalization "both upstream (macro) level processes concerning the development, testing and regulation of pharmaceuticals and downstream (micro) processes pertaining to the meaning and use of pharmaceuticals in medical practice and everyday life" (711-2). More concretely, increased pharmaceutical use can enable further medicalization, such as the expanded use of drugs developed for depression being used to treat shyness in the form of "social anxiety disorder" and monthly PMS as "premenstrual dysphoric disorder" (Greenslit, 2005; Lane, 2008). In some instances, however, pharmaceuticalization occurs outside of the purview of the medical profession. Examples include increased consumer use of over-the-counter medications and recreational use of prescription drugs for erectile dysfunction and attention deficit hyperactivity disorder (ADHD) for performance enhancement (Abraham, 2010; Loe, 2008; Race, 2009).

Most of the literature frames pharmaceuticalization as a negative trend. By simply watching U.S. television or reading newspapers, it is clear why many scholars are critical. Pharmaceutical companies develop and promote some products that seem to have frivolous uses and unnerving side effects, such as drugs for thickening eyelashes or eastbound travel-induced jet lag (Pollack, 2010; Saint Louis, 2010). Even when the illnesses targeted by pharmaceuticals are relevant to significant morbidity and mortality, aggressive marketing campaigns provide ample fodder for critics to raise concerns about negative social consequences, such as the over-treatment of such conditions (e.g., Applbaum, 2009a; Hart et al., 2006). Feminist scholars have been especially critical of pharmaceutical companies' mobilization of gender norms and stereotypes in order to market diverse products including drugs for sexual dysfunction, cervical cancer, low testosterone (Low "T"), Alzheimer's disease, fibromyalgia, and migraines (Asberg and Lum, 2009; Barker, 2011; Casper and Carpenter, 2008; Fishman, 2004; Kempner, 2006; Watkins, 2013). Additionally, the withdrawal of "dangerous" drugs from the market raises scholarly questions about the harms that accompany pharmaceuticalization (Abraham and Davis, 2005; Prosser, 2008). Adverse drug reactions are now the fourth leading cause of death in the U.S. (Light, 2010). Most notable was Merck's 2004 voluntary withdrawal of Vioxx® from the market when patients taking this arthritis drug experienced severe cardiac side effects, including death. This was a particularly important example of pharmaceuticalization because extensive advertising led to its over-prescription, endangering patients whose arthritis would have benefitted as much or more from over-the-counter naproxen with fewer risks (Biddle, 2007).

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