Social Science & Medicine 75 (2012) 1433–1440

Contents lists available at SciVerse ScienceDirect

Social Science & Medicine

journal homepage: www.elsevier.com/locate/socscimed

# Science, politics, and health in the brave new world of pharmaceutical carcinogenic risk assessment: Technical progress or cycle of regulatory capture?

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ARTICLE INFO

*Article history:*
Available online 28 June 2012

*Keywords:*
Drug testing
Animal models
Pharmaceutical industry
International regulation
Drug safety regulation
Carcinogenic

ABSTRACT

The carcinogenicity (cancer-inducing potential) of pharmaceuticals is an important risk factor for health when considering whether thousands of patients on drug trials or millions/billions of consumers in the marketplace should be exposed to a new drug. Drawing on fieldwork involving over 50 interviews and documentary research spanning 2002–2010 in Europe and the US, and on regulatory capture theory, this article investigates how the techno-regulatory standards for carcinogenicity testing of pharmaceuticals have altered since 1998. It focuses on the replacement of long-term carcinogenicity tests in rodents (especially mice) with shorter-term tests involving genetically-engineered mice (GEM). Based on evidence regarding financial/organizational control, methodological design, and interpretation of the validation and application of these new GEM tests, it is argued that regulatory agencies permitted the drug industry to shape such validation and application in ways that prioritized commercial interests over the need to protect public health. Boundary-work enabling industry scientists to define some standards of public-health policy facilitated such capture. However, as the scientific credibility of GEM tests as tools to protect public health by screening out carcinogens became inescapably problematic, a regulatory resurgence, impelled by reputational concerns, exercised more control over industry's construction and use of the tests, The extensive problems with GEM tests as public-health protective regulatory science raises the spectre that alterations to pharmaceutical carcinogenicity-testing standards since the 1990s may have been boundary-work in which the political project of decreasing the chance that companies' products are defined as carcinogenic has masqueraded as techno-science.



## Introduction

Most social scientists researching pharmaceuticals have devoted attention to clinical trials and post-marketing experiences of medicines, which involve patients/users directly (Abraham & Davis, 2010; Abraham & Sheppard, 1999; Daemmrich, 2004; Epstein, 1996; Fisher, 2009; Healy, 2004; Hedgecoe, 2004; Light, 2010; Pearce, 2007; Petryna, 2009). By contrast, we focus on carcinogenic risk assessment of pharmaceuticals, a branch of animal/cellular toxicology apparently removed from people's use of medicines, but nevertheless relevant to public health (Tomatis & Huff, 2001). Human exposure to pharmaceuticals can cause cancer, so modern societies have assessed the carcinogenicity of new drugs since the 1960s (Marselos & Vainio, 1991; World Health Organization, 1969). Neither clinical trials nor post-marketing monitoring systems of people's medicine-use can assess pharmaceuticals' carcinogenic risks because such risks typically accelerate over the lifespan – 70–90 years for humans – too long for clinical trials, and too late to prevent cancers even if detected by post-marketing monitoring (Schou, 1992, p. 210). Thus, there is considerable need to investigate carcinogenic toxicology beyond clinical trials and patients' medicine-taking.

Previous social science research on chemical and pharmaceutical risk assessment has examined how techno-scientific standards are applied to particular products by government regulators, and then explained those regulatory interpretations by reference to external socio-political factors (Abraham, 1993, 1998; Brickman, Jasanoff, & Ilgen, 1985; Jasanoff, 1990; Van Zwanenberg & Millstone, 2005). Rather, our focus is on the validation and application of new techno-regulatory testing standards, specifically use of genetically-engineered mouse (GEM) models in pharmaceutical carcinogenic risk assessment. Our research takes this social science field into new empirical domains where regulators must make strategic choices about how much control industry should have over the development of standards.

Of crucial importance is whether the introduction of new GEM models provides a higher standard than before of screening out

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0277-9536/$ – see front matter © 2012 Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.socscimed.2012.04.043

pharmaceutical carcinogens in the interests of public health or represents a standard that might enable more pharmaceutical carcinogens to reach the marketplace contrary to public health, though in the commercial interests of industry. For decades, regulatory agencies in Europe and the US have been mandated by law to protect public health (Doern & Wilks, 1998; Majone, 1996). We argue that regulatory agencies permitted the drug industry to shape the validation and use of those new GEM tests as screens for pharmaceutical carcinogenicity in ways that prioritized commercial interests over the need to protect public health. Consequently, the limitations of the new tests as public-health protective regulatory science were sustained longer than necessary, until a crisis in their capability to detect carcinogens became extensive, leading to greater regulatory intervention. We contend that this latest episode in the history of pharmaceutical carcinogenic risk assessment can be understood within regulatory capture theory, though to differing degrees in Europe and the US.

In this context, capture theory refers to regulatory agencies' 'administrative drift' towards industry's commercial interests and away from their mandated regulatory mission to protect public-health interests, together with a cyclical regulatory resurgence when 'administrative drift' produces regulatory 'crises' – classically a well-publicized drug disaster (Abraham, 1995, 2008; Bernstein, 1955; Carpenter, 2004; Lexchin, 2006). Thus, within capture theory, 'administrative drift' (regulatory capture) is not necessarily a permanent state. It might be argued, mistakenly, that deregulatory legislative reforms in the last 15–20 years by EU and US governments have rendered capture theory irrelevant because they have mandated their respective drug regulatory bodies, the European Medicines Agency (EMA) and the Food and Drug Administration (FDA), to facilitate many industry goals.

Certainly, those reforms emphasized regulators' role in *promoting* health *by approving new drugs* on to the market, as well as *protection* of public health *from* unsafe drugs. The official objective of the EMA, formed in 1995, included 'to promote public health by providing safe and effective medicines' (EMA, 1996, p. 9). Meanwhile, a US Congress, committed to increasing pro-business regulation, passed the 1997 FDA Modernization Act, which changed the FDA's mission statement to include 'promoting public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely manner' (Carpenter, 2010, p. 731). Increased emphases on faster approvals brought the missions of regulatory agencies closer to industry's commercial interests, but they did not extinguish regulators' mandate to prioritize health interests. Both EU and US law continued to *require the EMA and the FDA to protect public health*, while faster drug approvals were *conditioned on promotion of health* (Abraham & Lewis, 2000; FDA Modernization Act, 1997). Thus, the possibility and problem of capture remained even during the deregulatory period of the 1990s and 2000s. Indeed, neo-liberal legislative reforms and capture may have reinforced each other.

An alternative view, often put forward by official representatives of drug regulatory agencies and the pharmaceutical industry, is that the introduction, validation, and use of GEM tests was an example of industry and regulators working and learning together in a scientific quest to improve carcinogenic risk assessment. On this view, the trajectory of regulatory agencies' action should be understood as that of a 'learning regulator' in the face of unfolding scientific developments, rather than in terms of capture theory (Carpenter, 2004). However, we argue that, in this context, the 'learning regulator' representation was part of science-politics 'boundary-work', which facilitated regulatory capture of carcinogenic risk assessment by enabling industry scientists to define commercial concerns as matters of techno-scientific progress, and to shape some standards of public-health policy according their institutional priorities (Jasanoff, 1990). Subsequently, the consequent industrial science struggled to meet the task of public interest regulation, so such boundary-work became less feasible as the worrying implications for public health of GEM tests' use in drug development became more compelling among the wider scientific and regulatory communities. Consistent with capture theory, we suggest that the regulatory resurgence, which followed, exhibited reduced concern to accommodate industry interests and was an attempt by regulators to reassert their reputation as guardians of a regulatory science intended to screen out carcinogenic dangers to public health, rather than solely a result of learning more about the science. To examine the interest-politics of the introduction of GEM tests into drug development, and the applicability of capture theory therein, we investigated the financial/organizational control, methodological design, and interpretation of results, of the GEM tests' validation process; and considered the types of GEM tests selected for use by industry, the issues that attended industry use, and the responses by regulators and experts to the outcomes of such use.

## Background

The idea of incorporating GEM models into pharmaceutical carcinogenicity-testing standards was established at the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) during the 1990s (Abraham & Reed, 2003). Formed in 1990, ICH is an organization/network consisting of expert scientists representing the pharmaceutical industry associations and government regulatory agencies of the EU, US and Japan (Abraham, 2009). According to its secretariat, the International Federation of Pharmaceutical Manufacturers' Association (IFPMA), ICH aimed to 'harmonize' different techno-regulatory drug testing requirements across the three regions to increase efficiency in drug development and regulation by eliminating unnecessary duplication in testing without compromising drug safety – a claim uncritically accepted by some scholars (Daemmrich, 2004; pp. 157–160; Vogel, 1998). However, regarding carcinogenicity testing, ICH evidently sought to *reduce*, not '*harmonize*', standards because by the late 1970s, regulatory agencies in North America, Western Europe, and Japan already all had the same standards (Abraham, 1998).

Industry participants and regulators from Europe and Japan at ICH aimed to decrease the number of long-term rodent carcinogenicity tests required before marketing approval from two species (rats and mice) to just one species, the rat (Abraham & Reed, 2003). Typically, lasting 18–24 months, the long-term rodent tests sought to examine drugs' carcinogenic effects over most of the lifespan of the test animals. They were the most expensive and time-consuming aspect of drug testing not involving patients in trials or epidemiological studies. For decades they were central to screening for *non-genotoxic* pharmaceutical carcinogens, which may initiate and promote tumour formation, but do not cause the mutations thought to initiate tumour formation. The long-term studies were particularly important health screens because *non*-genotoxic carcinogens are not detected by the inexpensive battery of quick *in vitro* mutagenicity tests on micro-organisms and disembodied human cells used to identify *genotoxic* carcinogens that cause cancer primarily by damaging DNA.

Initially at ICH, the pharmaceutical industry and European regulators proposed that the long-term carcinogenicity test with mice should be jettisoned by claiming that mouse tumour findings were not relevant to human risk or regulatory decisions about new drugs (Emmerson, 1992; Usui, Griffiths, & Lumley, 1996; Van Oosterhout et al., 1997). (**1**) However, the FDA rejected that claim and the proposal to conduct carcinogenicity testing in only one rodent species, arguing that such tests were required in more than one