those provisions. This extrapolation of rules (for example, the obligation to ensure product safety) and traditions (for example, risk assessment) may be more difficult to apply where nanotechnologies throw up new and materially different risk, political, social, or ethical concerns.

A further consequence arises from new technologies being 'locked in' to existing regulations and ideas about newness. That is, when a new technology is introduced to a sector in which there is already expansive regulatory coverage, it is difficult to scrutinize existing regulatory provisions because this entails going against the great weight of history and policy expectation. Given that the regulation of nanotechnologies occurs by default, and is inflexibly and unconsciously dependent on prior rules, it becomes all the more difficult to challenge its application and appropriateness. Questioning existing regulations in these terms will also involve asking more fundamental questions about their essential qualities and commitments.

Even where existing regulatory regimes have been amended to include nano-specific provisions, the influence of existing regulatory and policy contexts continues to be felt. The focus of these amendments is on generating information and opening up routes for stakeholder communication (manufacturers-regulators; manufacturers-consumers), however they also place limits on the nature of that information (risk information; the label 'nano'). They are also subject to certain assumptions about how regulatory tools and techniques operate. For example, new nano-labelling requirements are founded on assumptions about the utility and effectiveness of information disclosure via a product's packaging. Labelling a product with a list of its ingredients promotes goals such as openness and transparency, yet it may do little to aid free choice unless meaning can be extracted. Nano-labelling requirements are also based on the assumption that the choice environment into which they are introduced is set up to offer tangible opportunities for free and informed decision-making. What is missing is an accompanying choice infrastructure, such as the provision of other user-information or opportunities for deliberation, on which nano-labelling measures can sit.

Nano-specific amendments are similarly constrained, therefore, by the legislative frameworks into which they are inserted. The interpretation of nanotechnologies as 'new' (politically 'new' for the European Parliament's Environment Committee) has undoubtedly contributed to the momentum behind new nano-specific legislation. Likewise, arguments that nanotechnologies are 'not new enough' have upheld the dominant policy view in the EU that they can be dealt with under existing regulatory regimes. This chapter has started to unpack the many ways in which newness may be construed and contested. It has also sought to remind that, as well as newness, an important determinant of a new technology's regulation is its policy past.

11

Science, Law, and the Medical-Industrial Complex in EU Pharmaceutical Regulation: The Deferiprone Controversy

John Abraham and Courtney Davis

A. Introduction

Logically, the production of pharmaceuticals in a society only makes sense for that society if they benefit health by being safe and effective to treat the illnesses for which they are prescribed. Publicly, at least, this is undisputed by all the major stakeholders, governments, pharmaceutical firms, patient groups, public health advocacy organizations, and the medical profession.[1] However, given that pharmaceutical companies have considerable commercial interests in marketing their drug products, it was gradually realized during the 20th century that industry scientists ought not to be the final arbiters of whether their firms' compounds were safe and effective due to conflict of interests.[2] Consequently, to inspire greater public confidence in the safety and effectiveness of pharmaceuticals, from the 1970s, all modern industrialized societies had established legislative provisions for pharmaceutical regulation. This raised the standards of drug evaluation that the industry had to meet, thereby bringing greater health protection to patients and the public. Yet, it must also be appreciated that such regulation was heavily shaped by consultation with the pharmaceutical industry, whose opposition was minimal. Indeed, the regulation also served to consolidate the hegemony of firms with superior techno-scientific standards of drug testing.[3] That included the European Union (EU) pharmaceutical regulatory system, whose presence gained a new prominence with the creation of the European Medicines Evaluation Agency (EMEA) in 1995, which had changed its name to the European Medicines Agency (EMA) by 2010.[4]

[1] J Abraham and C Davis, 'Interpellative Sociology of Pharmaceuticals: Problems and Challenges for Innovation and Regulation in the 21st Century' (2007) 19 *Technology Analysis & Strategic Management* 387.

[2] J Abraham, *Science, Politics and the Pharmaceutical Industry* (Routledge 1995); J Lexchin, 'The Pharmaceutical Industry and the Pursuit of Profit' in J Clare Cohen, P Illingworth, and U Schuklenk (eds), *The Power of Pills* (Pluto Press 2006) 11.

[3] J Abraham and G Lewis, *Regulating Medicines in Europe: Competition, Expertise and Public Health* (Routledge 2000); AA Daemmrich, *Pharmacopolitics: Drug Regulation in the US and Germany* (University of North Carolina Press 2004). MNG Dukes, *The Effects of Drug Regulation: A Survey Based on the European Studies in Drug Regulation* (MTP Press 1985); L Hancher, 'Regulating for Competition: Government, Law and the Pharmaceutical Industry in the UK and France' (PhD thesis, University of Amsterdam 1989); P Temin, *Taking Your Medicine: Drug Regulation in the US* (Harvard UP 1980).

[4] TK Hervey and JV McHale, *Health Law and the European Union* (CUP 2004).

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[5] AS Relman, 'The New Medical-Indu
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[6] A-M Farrell, 'The Politics of Risk and
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[7] G Majone, *Regulating Europe* (Routl

[8] J Gabe and M Bury, 'Halcion Night
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European Union (CUP 2004).

This chapter is a case study of the controversy surrounding a thalassaemia drug, known as deferiprone, whose approval on to the EU market by the EMA, was appealed to what was then the European Court of Justice (ECJ, now the Court of Justice of the European Union (CJEU)) by one of the key clinical investigators of the drug, on grounds of safety and efficacy. However, perhaps unsurprisingly, given the transnational nature of the pharmaceutical industry, the story of the case takes us across the Atlantic to Canada where the drug was developed, though the legal aspects concerning clinical investigation explored in this chapter are similar in Canada and Europe. The purpose of the case study is to explore some of the interactions between law, science, and what Relman famously called, the 'medical-industrial complex', at various stages of controversy about drug technology.[5] In particular, it highlights the role of the law in constraining professional autonomy. In so doing, it also facilitates an examination of the roles of drug risks in clinical trials, the rights of stakeholders during the drug development process, such as those of pharmaceutical companies and clinical investigators, and the interaction between ethics and markets.

Within the social science and policy literature, discussions about pharmaceuticals and law are dominated by analyses of patenting and intellectual property rights, though political science and socio-legal studies are increasingly turning their attention to health law and the role of law in biomedical technology regulation.[6] In this chapter, we show how the law may be used by industry and what Majone has called 'the regulatory state' (regulatory agencies and the courts) to shape, limit, and close down scientific debate and professional autonomy pertaining to drug technology development.[7] It is a very different, and counter-balancing picture to the one drawn by some analysts of drug injury cases in medical controversy, such as Gabe and Bury, who portray the law as a challenge to scientific and regulatory authority causing amplification of uncertainty, fragmentation of expertise, and plurality of knowledge-claims.[8] Our analysis is also a reminder of the multi-faceted nature of professional autonomy in medicine, which should not be reduced to the view that doctors have too much autonomy, by reference solely to doctor-patient interactions.[9] For instance, the impact of the pharmaceutical industry and government drug regulatory agencies on the autonomy of the medical profession also needs to be considered.

In following the case since 2004 we have reviewed numerous reports and documents from the Canadian Association of University Teachers (CAUT), the College of Physicians and Surgeons of Ontario (CPSO), the then EMEA, the European Commission (Commission), the CJEU, the EU's expert Committee for Proprietary Medicinal Products (CPMP), and the University of Toronto-affiliated Hospital for Sick Children (HSC). In particular, we obtained and analysed the EMEA's European Public Assessment Report for deferiprone, which provided the official, published reasons for approving the drug on to the EU market. The pharmaceutical trade press and publications by the drug's manufacturer, Apotex, were also consulted. When necessary, key

[5] AS Relman, 'The New Medical-Industrial Complex' (1980) 303 *New England Journal of Medicine* 963.

[6] A-M Farrell, 'The Politics of Risk and EU Governance of Human Material' (2009) 16 *Maastricht Journal of European and Comparative Law* 41; ML Flear, 'The EU's Biopolitical Governance of Advanced Therapy Medicinal Products' (2009) 16 *Maastricht Journal of European and Comparative Law* 113.

[7] G Majone, *Regulating Europe* (Routledge 1996).

[8] J Gabe and M Bury, 'Halcion Nights: A Sociological Account of a Medical Controversy' (1996) 30 *Sociology* 447.

[9] E Freidson, *Professionalism* (Polity 2001).

parties to the controversy were interviewed. Our methodological approach is informed by empirical realism, rather than, say, actor-network theory, because our focus is on what institutional interests and politico-legal power do to knowledge-claims, rather than on how actors form beliefs.[10] We define law broadly to include use of litigation (including legal contracts), enforcement of regulations established in law, and the role of the courts in interpreting regulatory law.

B. The Compelling Nature of the Medical-Industrial Complex and its Legal Concomitants in Pharmaceutical Science and Markets

Scientific principles proposing the objective pursuit of truth, tested by open and public scrutiny by other scientists and experts, remain important bases for distinguishing between knowledge and mistaken/false beliefs. However, the assumption that those principles exhaust or are even fundamental to the practical work of scientists may often be an ideology, indeed mythology, of science, as much as a reality. In this section, we explain how the medical-industrial complex, together with its use of legally binding (contractual) agreements with medico-scientific experts involved in sponsored research gradually imposes itself on a biomedical scientific inquiry, initially driven by a desire to improve treatment for a relatively neglected group of patients in society, those with thalassaemia.

Thalassaemia is a blood disorder characterized by faulty production of haemoglobin made in the bone marrow for incorporation into red blood cells. In thalassaemia patients, red blood cells become fragile and break down, leading to severe anaemia without treatment. Thalassaemia is inherited via one or two recessive defective genes, resulting in thalassaemia-minor and thalassaemia-major, respectively. There are about 10,000 people with thalassaemia-major in the EU alone and as many as 30 million sufferers in India.[11]

In this chapter, we are concerned only with thalassaemia-major (hereafter 'thalassaemia'). To prevent thalassaemia patients dying from anaemia, they are treated with blood transfusions. However, successive blood transfusions cause a potentially toxic build-up of iron in the body (known as 'iron-loading') adversely affecting the liver and heart. Consequently, pharmaceuticals, known as chelating agents, are given to help the body to excrete the excess iron. Unfortunately, before the 1990s, the only standard treatment for iron-loading was by subcutaneous or intravenous infusion of the iron-chelating drug, deferoxamine, first introduced in 1963. Although biologically effective and relatively non-toxic, deferoxamine was far from the perfect treatment because patients needed to undergo such infusions for about eight to twelve hours several nights per week, which was unpleasant, costly, and prohibitively expensive for the poor without state health provision or health insurance.[12] Deferoxamine has also been associated with some cases of serious neurotoxicity and growth retardation.[13]

[10] J Abraham, 'Sociology of Pharmaceutical Development and Regulation: A Realist Empirical Research Programme' (2008) 30 *Sociology of Health & Illness* 869.

[11] VP Choudhry, 'Oral Deferiprone—Controversies on its Efficacy and Safety' (1998) 65 *Indian Journal of Pediatrics* 825; EMEA, European Public Assessment Report, CPMP 'Scientific Discussion' Ferriprox (deferiprone).

[12] SK Bichile, PJ Mehta, and SJ Paresh, 'Toxicity of Oral Iron Chelator L1' (1993) 41 *Journal of the Association of Physicians of India* 323; DG Nathan, 'Clinical Research: A Tale of Two Studies' (2003) 114 *Transactions of the American Clinical and Climatological Association* 219.

[13] S Di Vigiliis, M Cangia, and F Fran, 'Deferoxamine-Induced Growth Retardation in Patients with Thalassaemia-Major' (1988) 113 *Journal of Pediatrics* 661; NF Olivieri, JR Buncie, and E Chew,

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Thus, the development of a safe and effective iron chelator that could be taken orally would offer great therapeutic benefit. Deferiprone was first synthesized in the early 1980s at Kings College, London, whose laboratories sold the rights to the UK government-owned British Technology Group. There, the drug showed initial signs that it might serve the desired therapeutic purpose.[14] Consequently, Dr Nancy Olivieri, a specialist in haematology and internal medicine at the HSC, affiliated to the University of Toronto, decided to organize a small trial with deferiprone in her clinic in 1988. After encouraging results from the first two years of a small pilot study, she discussed deferiprone with the US Food and Drug Administration (FDA), the world's largest and best-resourced drug regulatory agency with huge experience of drug development requirements. The FDA advised her that three studies should be performed before the drug could be approved on to markets, including longer term and larger randomized trials, which might necessitate the involvement of a pharmaceutical company.[15]

After designing such trials, Olivieri applied for funding to execute them from the Canadian Medical Research Council (CMRC), who declined to be sole sponsors, but indicated that it would be interested in a re-application under its university-industry programme. These events illustrate the endemic and pervasive presumption of industry involvement in pharmaceutical development, making alternatives to the medical-industrial complex nearly impossible for medical researchers. Evidently, the presumption of the complex in drug development existed in the minds of state-funded regulatory agencies and research councils, even before any actual involvement of pharmaceutical firms. It has also become an accepted convention of pharmaceutical science for many university managers. For instance, in 1997, the President of Johns Hopkins University insisted: 'to move your research forward, you've got to do partnerships with industry'.[16] As the UK Government had done for decades, by the late 1980s, the Canadian Federal Government had come to view transnational pharmaceutical companies as major vehicles for promoting economic growth, while the deficits were partly addressed by cutting federal funding for research.[17]

There is considerable evidence to suggest that academic and health care institutions hosting clinical research have been pursuing ever closer relationships. According to the US-based Pharmaceutical Research and Manufacturer's Association (PhRMA), between 1980 and 2003, overall research and development expenditures by US pharmaceutical companies increased from US$2 billion to US$33 billion.[18] During the 1990s, Canadian pharmaceutical firms' funding of clinical research grew to an annual spend of $624 million in 1998, while CMRC funding declined.[19] By 2001, clinical trial research expenditures in Canada totalled over $800 million.[20] In particular, Bekelman and others found that, between 1980 and 2002, in the USA, a quarter of

'Visual and Auditory Neurotoxicity in Patients receiving Subcutaneous Deferoxamine Infusions' (1986) 314 *New England Journal of Medicine* 869.

[14] Interview with Vice-President for Scientific Affairs, Apotex (12 September 2004).

[15] J Thompson, P Baird, and J Downie, 'The Olivieri Report: Independent Inquiry Commissioned by the Canadian Association of University Teachers' (James Lorimer 2001) 102–3.

[16] A Schafer, 'Biomedical Conflicts of Interest' (2004) 30 *Journal of Medical Ethics* 15.

[17] J Abraham, 'Partial Progress: Governing the Pharmaceutical Industry and the NHS, 1948–2008' (2009) 34 *Journal of Health, Politics, Policy and Law* 943; A Schafer, 'Biomedical Conflicts of Interest' (2004) 30 *Journal of Medical Ethics* 16.

[18] PhRMA, 'Pharmaceutical Industry Profile' (Pharmaceutical Research and Manufacturers of America 2004).

[19] RA Phillips and J Hoey, 'Constraints of Interest: Lessons at the Hospital for Sick Children' (1998) 159 *Canadian Medical Association Journal* 956.

[20] G DuVal, 'Institutional Conflicts of Interest: Protecting Human Subjects, Scientific Integrity, and Institutional Accountability' (2004) 32 *International and Comparative Health, Law and Ethics* 613.

biomedical investigators had industry affiliations.[21] Indeed, in the mid-1990s, the University of Toronto was negotiating a $20 million donation from the pharmaceutical firm, Apotex, towards the construction of a biomedical research centre and $10 million from the company for the university's affiliated hospitals.[22] Moreover, Robert Pritchard, then President of University of Toronto had lobbied the Canadian Government on behalf of Apotex about drug patent laws in a private letter to the Prime Minister.[23]

It was in this wider context of neo-liberalism and institutional relations that Olivieri met with Apotex, whose Vice-President was a former professor at the University of Toronto, to explore the possibility of the company supporting a deferiprone trial programme, in line with the advice she had received from the FDA and the CMRC. After initial concerns about whether deferiprone could be commercially viable, in 1993 Apotex decided that it was a worthwhile endeavour and agreed to co-sponsor the deferiprone trials with the CMRC.[24] The key trials became known as LA-01 (a two-year study comparing deferiprone with deferoxamine), LA-02 (a one-year non-comparative study), and LA-03 (a six-year compassionate use study). The company purchased the patent from the British Technology Group and asked Olivieri to accept a confidentiality clause as part of her contract.[25] This required her to keep secret all trial information up to three years after completion for LA-02, and a ban on publication until one year after completion regarding LA-01, unless disclosure was authorized by the firm

Table 11.1. Chronology of key events

1989	Olivieri synthesizes deferiprone
1993–5	Olivieri signs contract for deferiprone trials with Apotex, including confidentiality clauses
April 1995	Olivieri and others publish paper demonstrating 'favourable effect of deferiprone on iron balance'
July 1995	Some patients in LA-03 exhibit undesirable liver iron concentrations, indicating poor efficacy of deferiprone, so Olivieri requests a separate trial to investigate this, requiring patients to be informed of the negative results
September 1995	Olivieri advises Apotex of her obligation to inform HSC Research Ethics Board (REB) of adverse findings
February 1996	Apotex disputes loss of deferiprone efficacy during trials, refusing Olivieri permission to relay that claim to REB
May 1996	Olivieri informs REB and patients of her findings. Apotex terminates her trials and research sponsorship, telling her that disclosure of trial information without company approval would prompt legal action against her. Olivieri informs Apotex she intends to publish her findings
July 1996	Apotex's expert panel disagrees with Olivieri about deferiprone's efficacy
February–May 1997	Olivieri discovers liver toxicity/fibrosis in patients in LA-03. She informs REB and discontinues deferiprone use due to safety concerns

(*continued*)

[21] JE Bekelman, Y Li, and CP Gross, 'Scope and Impact of Financial Conflicts of Interest in Biomedical Research' (2003) 289 *Journal of the American Medical Association* 454.

[22] E Gibson, F Baylis, and S Lewis, 'Dances with the Pharmaceutical Industry' (2002) 166 *Canadian Medical Association Journal* 448.

[23] J Thompson, P Baird, and J Downie, 'The Olivieri Report: Independent Inquiry Commissioned by the Canadian Association of University Teachers' (James Lorimer 2001) 13. After Pritchard's conduct became public knowledge, he apologized to the university's executive committee for acting inappropriately.

[24] Interview with Vice-President, Scientific Affairs, Apotex (12 September 2004).

[25] Interview (n 24).

Table 11.1. Continued

September 1997	Olivieri expresses co with Apotex
February 1998	Apotex applies to EM LA-01, 02, and 03,
April 1998	Olivieri indicates to
August 1998	Olivieri and others p *Medicine*
January 1999	Olivieri is fired fron affirmed, and she is
May 1999	CPMP recommend her concerns about
June 1999	Marketing authoriz investigation of Oli
August 1999	Marketing authoriz
November 1999	Olivieri files for ann European Court of
March 2000	Commission, EME
April 2000	HSC refers dispute to CPSO
October 2001	CAUT report exon do enough to prote
December 2001	CPSO concludes th complaints against
December 2003	European Court fir decision regarding

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[26] CPSO, 'Complaints Committee

[27] JE Bekelman, Y Li, and CP G Biomedical Research' (2003) 289 *Jou* 'Uneasy Alliance: Clinical Investigato *Journal of Medicine* 1539.

[28] NF Olivieri, GM Brittenham, a Patients with Thalassaemia-Major' (1

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Table 11.1. Continued

September 1997	Olivieri expresses concerns to the University of Toronto about continuing conflict with Apotex
February 1998	Apotex applies to EMEA for marketing authorization in EU, including reports on LA-01, 02, and 03, but without Olivieri's signature
April 1998	Olivieri indicates to HSC that she cannot continue under prevailing conditions
August 1998	Olivieri and others publish findings about liver toxicity in *New England Journal of Medicine*
January 1999	Olivieri is fired from HSC. Later, her position is restored, her academic freedom affirmed, and she is promised legal support against Apotex
May 1999	CPMP recommend deferiprone's marketing authorization. Olivieri sends CPMP her concerns about the drug's safety and efficacy
June 1999	Marketing authorization decision-process is suspended pending CPMP's investigation of Olivieri's concerns
August 1999	Marketing authorization of deferiprone is granted
November 1999	Olivieri files for annulment of deferiprone's marketing authorization with European Court of Justice
March 2000	Commission, EMEA, and Apotex plead that Olivieri's case is inadmissible
April 2000	HSC refers disputes regarding Olivieri's clinical practice with deferiprone patients to CPSO
October 2001	CAUT report exonerates Olivieri, finding that the University of Toronto did not do enough to protect her academic freedom
December 2001	CPSO concludes that Olivieri acted in patients' interests, dismissing HSC's complaints against her
December 2003	European Court finds that Olivieri has no standing to challenge the Commission's decision regarding protection of public health

(see Table 11.1). There was no confidentiality clause pertaining to LA-03.[26] Although such restrictions on publication and data sharing were an assault on the ideals of science, within the medical-industrial complex, they were widespread and frequently passed without comment.[27] Between 1993 and 1995, Olivieri signed the contracts for these trials.

C. Controlling 'Acceptable' Discovery: Industrial Power, Ethics, and Legal Threat

In accordance with the scientific protocols of the deferiprone trials, iron-loading in the thalassaemia patients was assessed and monitored by regular liver biopsies, which were also used to evaluate the safety and efficacy of the iron-chelation therapy. The initial stage of the deferiprone trials conducted by Olivieri and sponsored by Apotex went well. Olivieri and others published early findings that deferiprone had a 'favourable effect' on the iron balance in patients.[28] However, later that year, Olivieri became

[26] CPSO, 'Complaints Committee Decision and Reason' (2001) 5.

[27] JE Bekelman, Y Li, and CP Gross, 'Scope and Impact of Financial Conflicts of Interest in Biomedical Research' (2003) 289 *Journal of the American Medical Association* 454; T Bodenheimer, 'Uneasy Alliance: Clinical Investigators and the Pharmaceutical Industry' (2000) 342 *New England Journal of Medicine* 1539.

[28] NF Olivieri, GM Brittenham, and D Matsui, 'Iron Chelation Therapy with Oral Deferiprone in Patients with Thalassaemia-Major' (1995) 332 *New England Journal of Medicine* 918.

concerned that some of the twenty-one patients on the long-term deferiprone trial, LA-03, were displaying adverse concentrations of iron in the liver. Initially, she deduced that, for six of these patients, deferiprone might be losing its efficacy, putting them at risk of iron overload, but by early 1996 this trend had increased to twelve patients.[29]

Olivieri requested permission from Apotex to establish a 'new' separate trial with patients for whom deferiprone's efficacy seemed to be sub-optimal, and informed the company of her obligation to report the negative efficacy outcomes encountered to both the HSC's Research Ethics Board and the particular patients affected. Upon reviewing the data, scientists at Apotex did not agree with Olivieri that deferiprone had been losing its effectiveness among a significant number of patients, though they accepted that this might be true for a few patients.[30] The firm, therefore, instructed her not to relay her view that the drug was losing efficacy to the Research Ethics Board.[31] While some patients were doing well on deferiprone from both a safety and efficacy point of view,[32] Olivieri reported findings that a significant proportion of trial subjects had iron concentrations in the liver above clinically desirable levels to the Board, who directed her to advise the patients of these risks. However, in May 1996, when she approached the patients to do this, Apotex terminated trials LA-01 and LA-03 and Olivieri's research contracts with the firm, including her involvement with LA-02. Moreover, the company warned her that all information obtained during the trial was to remain secret, otherwise legal action might be taken against her,[33] or as the vice-president of Apotex put it: 'We told her should she present information that is wrong that we are prepared to take action against her.'[34]

Olivieri's trials were terminated because she had broken an unwritten convention of the medical-industrial complex, namely to remain loyal to the sponsoring company. As the vice-president of Apotex put it, 'we had problems with her'.[35] This is clear from the letter sent to Olivieri by Apotex to explain the firm's decision to terminate the trials, which stated that Apotex 'could not justify Nancy as the Principal Investigator in studies of a drug she does not believe works'.[36] The company's vice-president later elaborated this perspective as 'if you [Olivieri] don't even believe that the drug is working, why do you want to even give it to those patients?'[37] Yet the supposed scientific methodology of the 'null hypothesis', with which clinical trials are designed, is precisely to test the validity of the assumption that the new therapy is no better than a placebo-control or an existing therapy as control. While the idealistic rationale of scientific methodology is to use clinical trials to discover whether or not new drugs are efficacious, evidently the convention of the medical-industrial complex is to prove that they are.

Apotex convened an expert panel to review Olivieri's claims about deferiprone and the data underpinning them. The firm reported that its panel unanimously disagreed

[29] J Thompson, P Baird, and J Downie, 'The Olivieri Report: Independent Inquiry Commissioned by the Canadian Association of University Teachers' (James Lorimer 2001) 124–31.

[30] Interview with Vice-President, Scientific Affairs, Apotex (12 September 2004).

[31] A Naimark, BM Knoppers, and FH Lowy, *Clinical Trials of deferiprone at the Hospital for Sick Children* (Hospital for Sick Children 1998).

[32] Interview with Nancy Olivieri, University of Toronto (28 June 2004).

[33] CPSO, 'Complaints Committee Decision and Reasons' (2001) 7; T Koch, 'Absent Virtues: The Poacher becomes Gamekeeper' (2003) 29 *Journal of Medical Ethics* 339.

[34] Despite these remarks, the company subsequently claimed it was 'invalid' to 'characterize the termination of Olivieri's contract as an attempt to stop her divulging her views'. See Correspondence, 'The Olivieri Case' (2003) 348 *New England Journal of Medicine* 861.

[35] Interview with Vice-President, Scientific Affairs, Apotex (12 September 2004).

[36] RA Phillips and J Hoey, 'Constraints of Interest: Lessons at the Hospital for Sick Children' (1998) 159 *Canadian Medical Association Journal* 956.

[37] Interview with Vice-President, Scientific Affairs, Apotex (12 September 2004).

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D. Confronting Risk
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[38] Interview with Medical Director,

[39] Correspondence (seven letters), 'I
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Reasons' (2001) 8; F Tricta, G Sher, an
Active Iron Chelator Deferiprone in Pa
on Thalassaemia and Haemoglobinopa
University of Toronto (28 June 2004).

[40] Correspondence (seven letters), 'I
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P Nielson, 'Liver Iron and Fibrosis du
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[41] Pain in joints and muscle tissue.

[42] SK Bichile, PJ Mehta, and SJ Pare
Association of Physicians of India 323.

[43] Interview with Vice-President, Sc

[44] A Naimark, BM Knoppers, and
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[45] LA Bero and D Rennie, 'Influe
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and Quality' (2003) 326 *British Medic*

on the long-term deferiprone trial,
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Apotex terminated trials LA-01 and
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ems with her'.[35] This is clear from the
firm's decision to terminate the trials,
as the Principal Investigator in studies
mpany's vice-president later elaborated
lieve that the drug is working, why do
the supposed scientific methodology of
designed, is precisely to test the validity
er than a placebo-control or an existing
le of scientific methodology is to use
s are efficacious, evidently the conven-
e that they are.
Olivieri's claims about deferiprone and
l that its panel unanimously disagreed

Report: Independent Inquiry Commissioned
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Apotex (12 September 2004).
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Apotex (12 September 2004).

with her conclusions about the drug's efficacy,[38] as did others researching the drug.[39] Subsequently, however, her interpretation was supported by other specialists and corroborated by research in Switzerland.[40] By that time, Indian medical researchers were also warning that 'due to the high frequency [25 per cent] of serious toxicity [immunologically-based arthralgia[41]] of deferiprone [among patients in Bombay], further trials, if any, should be carried out only in selected patients by applying strict criteria.'[42] Nonetheless, Apotex denied Olivieri consent to submit abstracts of her deferiprone research to the American Society for Haematology. The company also accused her of keeping incomplete trial information records,[43] and notified her that she was being removed from the steering committee of LA-02 for breaching contractual obligations, so denying her access to that trial's data and results.[44]

The underlying conflict between the norms of science publicly to present findings to the medical community and legal commitments to the company sponsoring the drug trials, had become explicit and intense. In this context, legal intervention promoted, and policed, convergence of medical knowledge-claims-making, rather than fostering plurality. Its role was to discourage medical specialists from publicly contesting techno-scientific interpretations that were consistent with the firm's commercial and institutional goals of progressing with development of its product, even if that meant threatening information-flows about drug safety and efficacy to the 'evidence-base' of medicine for the health system.[45]

D. Confronting Risks and Legal Constraint: Institutional Self-Interest versus Professional Autonomy

Despite the objections and legal warnings of Apotex, Olivieri presented her findings from LA-03 at the American Society for Hematology conference in Florida at the end of 1996. During 1997, she concluded that deferiprone was causing liver toxicity and accelerated liver fibrosis in some patients on LA-03, so she informed the patients and Research Ethics Board, and published an abstract in the journal, *Blood*, stating

[38] Interview with Medical Director, Apotex (12 September 2004).

[39] Correspondence (seven letters), 'Iron Chelation with Oral Deferiprone in Patients with Thalassaemia' (1997) 339 *New England Journal of Medicine* 1710; Correspondence, 'The Olivieri Case' (2003) 348 *New England Journal of Medicine* 861; CPSO, 'Complaints Committee Decision and Reasons' (2001) 8; F Tricta, G Sher, and R Loebstein, 'Long-term Chelation Therapy with the Orally Active Iron Chelator Deferiprone in Patients with Thalassaemia-Major' (6th International Conference on Thalassaemia and Haemoglobinopathies, Malta, 5–10 April 1997); Interview with Nancy Olivieri, University of Toronto (28 June 2004).

[40] Correspondence (seven letters), 'Iron Chelation with Oral Deferiprone in Patients with Thalassaemia' (1997) 339 *New England Journal of Medicine* 1710; P Tondury, A Zimmerman, and P Nielson, 'Liver Iron and Fibrosis during Long-term Treatment with Deferiprone in Swiss Thalassaemic Patients' (1998) 101 *British Journal of Haematology* 413.

[41] Pain in joints and muscle tissue.

[42] SK Bichile, PJ Mehta, and SJ Paresh, 'Toxicity of Oral Iron Chelator L1' (1993) 41 *Journal of the Association of Physicians of India* 323.

[43] Interview with Vice-President, Scientific Affairs, Apotex (12 September 2004).

[44] A Naimark, BM Knoppers, and FH Lowy, *Clinical Trials of Deferiprone at the Hospital for Sick Children* (Hospital for Sick Children 1998).

[45] LA Bero and D Rennie, 'Influences on the Quality of Published Drug Studies' (1996) 12 *International Journal of Technology Assessment in Health Care* 209; R DeVries and T Lemmens, 'The Social and Cultural Shaping of Medical Evidence' (2006) 62 *Social Science and Medicine* 2694; J Lexchin, KA Bero, and B Djulbegovic, 'Pharmaceutical Industry Sponsorship and Research Outcome and Quality' (2003) 326 *British Medical Journal* 1167.

that she had discontinued deferiprone in all patients due to safety concerns.[46] Nine months later, Olivieri and others published a major article detailing their findings of liver toxicity in patients taking deferiprone.[47] They reported that five of fourteen patients treated with deferiprone had progression of liver fibrosis, while none of the twelve patients treated with the control, deferoxamine, had such adverse effects.

Meanwhile, Apotex continued to claim that the drug was safe and effective and sought data from the HSC on patients who had received deferiprone on compassionate grounds. The firm also offered to provide new arrangements for Toronto patients to receive deferiprone if they did not wish to return to deferoxamine treatment. However, Olivieri rejected that proposal because she considered the safety monitoring procedures, which did not include liver biopsies, to be inadequate.[48] Subsequently, the firm questioned whether Olivieri had been meeting her obligations to provide data to regulatory authorities, but did not take legal action against her.[49]

Olivieri's determination to publish her work, despite legal threats from a powerful pharmaceutical company that could potentially damage her career, poses conceptual difficulties for over-socialized models of medical professionals as self-interested individuals protecting their status and dominance.[50] It also challenges over-contextualizing models of science in which experts are presented as instrumental creatures of their social context, discarding and adopting values according to what the situation demands.[51] While many scientists are, of course, determined to publish their work, they are often reported to adapt that strategy flexibly to maximize their own interests and career advancement. Olivieri's behaviour cannot be easily accounted for by such models, but reflected instead an 'objective'[52] value-commitment to professional autonomy and patient care, which was stable in the face of a changing context.

This is evident from the extent to which her material self-interest was placed in jeopardy by not relinquishing her value-commitments. From mid-1996 to early 1998, Olivieri sought support from the HSC and the University of Toronto. Initially, the HSC refused to supply her with legal assistance, though the Dean of the University's Faculty of Medicine asked Apotex to refrain from making legal threats.[53] According to Olivieri, neither the hospital nor the University of Toronto, 'both anticipating large donations from Apotex', supported her 'in fulfilling ethical obligations to patients or scientific obligations to the public'.[54] It was not until 1999 that the President of the University intervened directly by stating that 'gag orders' had 'no place in a University'.[55]

Olivieri complained about the close relationship between Apotex and the University of Toronto, including its affiliated hospitals, but was told that her complaints warranted

[46] CPSO, 'Complaints Committee Decision and Reasons' (2001) 9–12.

[47] NF Olivieri, GM Brittenham, and CE McLaren, 'Long-term Safety and Effectiveness of Iron Chelation Therapy with Deferiprone for Thalassemia-Major' (1998) 339 *New England Journal of Medicine* 417.

[48] J Thompson, P Baird, and J Downie, 'The Olivieri Report: Independent Inquiry Commissioned by the Canadian Association of University Teachers' (James Lorimer 2001) 177–204.

[49] A Naimark, BM Knoppers, and FH Lowy, *Clinical Trials of Deferiprone at the Hospital for Sick Children* (Hospital for Sick Children 1998).

[50] E Freidson, *Professionalism* (Polity 2001).

[51] S Jasanoff, *The Fifth Branch: Science Advisers as Policy-Makers* (Harvard UP 1990).

[52] By 'objective' here is meant not solely context-determined.

[53] D Spurgeon, 'Trials Sponsored by Drug Companies' (1998) 316 *British Medical Journal* 618.

[54] D Spurgeon, 'Report clears Researcher who broke Drug Company Agreement' (2001) 323 *British Medical Journal* 1085.

[55] V Di Norcia, 'The Olivieri Report' (2003) 9 *Science and Engineering Ethics* 129.

no action.[56] In April 1998, Olivieri
she could not continue under the
published her concerns about de
New England Journal of Medicine,
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bility for the dispute and included
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Ethics Board.[58] In other words, th
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Initially, at least, that seemed to
entering into confrontation with a

The HSC interpreted Olivieri's
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dismissal. In January 1999, Olivieri
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of the clinical scientist) might c
interests. That calculation is itself

E. The European
of Scientific

While Olivieri was exonerated i
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[56] E Gibson, F Baylis, and S Lew
Canadian Medical Association Journal 4

[57] Subsequently, the HSC admitted
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inquiry dismissed complaints about O
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[58] CPSO, 'Complaints Committee
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Funding' (1999) 318 *British Medical Jo*

[59] J Thompson, P Baird, and J Down
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[60] VP Choudhry, 'Oral Deferiprone
Journal of Pediatrics 825; AV Hoffbran
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1998) 316 *British Medical Journal* 618.
Drug Company Agreement' (2001) 323

d Engineering Ethics 129.

no action.[56] In April 1998, Olivieri indicated by letter to the HSC administration that she could not continue under the prevailing work pressures. One month after Olivieri published her concerns about deferiprone's liver toxicity in some patients in the *New England Journal of Medicine*, the HSC Board of Trustees set up an inquiry into the dispute about Olivieri's deferiprone trials, which absolved the HSC of any responsibility for the dispute and included an investigation into the mistaken[57] notion that she had not reported her concerns about the drug's liver toxicity to the HSC Research Ethics Board.[58] In other words, the initial response of her employers at the HSC and the University of Toronto was to assume that she was the source of the difficulties. Initially, at least, that seemed to be a less costly approach to those institutions than entering into confrontation with a transnational pharmaceutical company.

The HSC interpreted Olivieri's admission of unacceptable pressures from the deferiprone dispute as a letter of resignation—an action regarded by Olivieri as constructive dismissal. In January 1999, Olivieri was fired from her position as Head of the Haemoglobinopathy Research Programme at the HSC, though later in the month, in the aftermath of widespread professional protest receiving media coverage, the HSC agreed to re-instate her, affirmed her academic freedom, and offered financial support if Apotex litigated against her.[59]

This shows the complexity of professional autonomy and how precarious its protection is within the medical-industrial complex, especially when powerful pharmaceutical firms are willing to use the law in ways that constrain such autonomy. It is not simply a matter of pressure from the drug manufacturer on the investigating clinical scientist; the roles of the hospital and/or university are also crucial. When conflict emerges over drug technology development, whether the university/hospital place allegiance with the professional autonomy of its clinical investigator or with the maintenance of a good relationship with the pharmaceutical manufacturer may be a finely balanced judgement based on which political forces (including industrial legal power and the determination of the clinical scientist) might cause least damage to institutional reputations and interests. That calculation is itself determined by where the law stands.

E. The European Regulatory State and the Limits of Scientific Pluralism under the Law

While Olivieri was exonerated in Canada, Apotex continued its plans to market deferiprone outside North America. Between 1987 and 1998, deferiprone was evaluated in seventeen countries at thirty-two clinical centres.[60] From 1994 it was marketed

[56] E Gibson, F Baylis, and S Lewis, 'Dances with the Pharmaceutical Industry' (2002) 166 *Canadian Medical Association Journal* 448.

[57] Subsequently, the HSC admitted it made mistakes. See T Koch, 'Absent Virtues: The Poacher becomes Gamekeeper' (2003) 29 *Journal of Medical Ethics* 337; The external independent CPSO inquiry dismissed complaints about Olivieri, concluding: 'Dr Olivieri ceased to administer [deferiprone] in a timely and expedient way, which was in the best interests of her patients... [and] Dr Olivieri promptly set up meetings with her patients and informed clinical personnel.' See CPSO, 'Complaints Committee Decision and Reasons' (2001) 16.

[58] CPSO, 'Complaints Committee Decision and Reasons' (2001) 12–16; V Di Norcia, 'The Olivieri Report' (2003) 9 *Science and Engineering Ethics* 127; D Spurgeon, 'Canadian Case Questions Funding' (1999) 318 *British Medical Journal* 77.

[59] J Thompson, P Baird, and J Downie, 'The Olivieri Report: Independent Inquiry Commissioned by the Canadian Association of University Teachers' (James Lorimer 2001) 225–70, 505–8.

[60] VP Choudhry, 'Oral Deferiprone—Controversies on its Efficacy and Safety' (1998) 65 *Indian Journal of Pediatrics* 825; AV Hoffbrand and B Wonke, 'Iron Chelation Therapy' (1997) 242 (suppl 740) *Journal of Internal Medicine* 37.

extensively in India by the local pharmaceutical company, Cipla, with the approval of the Indian Department of Health.[61] Indeed, by 2005, the drug had been approved on to the market in twenty-nine countries, mainly in Asia and Europe, but never gained approval in the USA or Canada.[62] In this section we focus on its approval on to the European market. We consider how EU law, in the form of regulations and the courts, weighed the importance of clinical investigators compared with drug manufacturers when in dispute over whether the technology should be approved. That necessitates an understanding of the evidence about deferiprone considered by the regulators.

On 6 February 1998, Apotex submitted an application to the then EMEA for consideration under the supranational centralized procedure to obtain approval to market deferiprone throughout the EU—known as 'marketing authorization'.[63] According to the regulations, 'all information which is relevant to the evaluation of the medicinal product concerned shall be included in the application, whether favourable or unfavourable to the product', including 'the particulars of each clinical trial to allow an objective judgement to be made' and a 'final report signed by the [clinical] investigator'.[64] However, under Article 13(2) of the relevant regulations, in 'exceptional circumstances', when the manufacturer/applicant can show inability to provide comprehensive data, a marketing authorization may be granted if 'in the present state of scientific knowledge comprehensive information cannot be provided'.[65]

The EMEA's expert scientific committee, the CPMP, reviewed the techno-scientific data provided by Apotex. The clinical trial data submitted in support of the efficacy and safety of deferiprone comprised three trials, involving 247 patients in total. These were LA-01, LA-02 (followed up as LA-06), and LA-03. Trial LA-01, for which Olivieri was the principal clinical investigator, was an 'open' (non-blinded), two-year study comparing thirty-five patients taking deferiprone with thirty-six patients receiving deferoxamine. The original hypothesis to be tested in this study was that the efficacy of deferiprone was within 20 per cent of the efficacy of deferoxamine as measured by iron concentration in the liver. However, according to the CPMP, 'this hypothesis could not be tested' partly due to 'poor compliance with study procedures'.[66] Nevertheless, based on measuring serum ferritin,[67] the results of this trial were that, on average, hepatic iron concentrations in deferiprone-treated patients increased more than in deferoxamine-treated patients.[68] In other words, deferiprone was less effective than deferoxamine. As Porter detailed:

> At the end of two years, hepatic iron was in the optimal target range in only 7% of deferiprone-treated patients compared with 64% of those randomized to deferoxamine, even though

[61] EMEA, European Public Assessment Report, CPMP 'Scientific Discussion' Ferriprox (deferiprone).

[62] C Dyer, 'Whistleblower Vows to Fight On' (2004) 328 *British Medical Journal* 187; J Hoey and AM Todkill, 'The Left Atrium' (2005) 173 *Canadian Medical Association Journal* 914.

[63] EMEA, European Public Assessment Report, 'Background Information on the Procedure' Ferriprox (deferiprone) 1.

[64] Council Regulation (EEC) 2309/93 of 22 July 1993 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of medicinal products [1993] OJ L214/1.

[65] Council Regulation (EEC) 2309/93, Annex, part 4.

[66] EMEA, European Public Assessment Report, CPMP 'Scientific Discussion' Ferriprox (deferiprone) 7.

[67] A complex of iron and protein found mainly in the liver and spleen, and the principal form in which iron is stored in the body.

[68] EMEA, European Public Assessment Report, CPMP 'Scientific Discussion' Ferriprox (deferiprone) 7.

treatment compliance in the deferi
group (70%). The study was discor
the clinical investigators.[69]

Trial LA-02 was a one-year, r
deferiprone treatment. The CPI
in hepatic iron concentration du
loading, the drug seemed progre
twenty-five patients had to be wi
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It is to be emphasized that to this
Several investigators remain suppo
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Apotex, however, contended
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At the time of the CPMI
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[69] JB Porter, 'A Risk-benefit As

[70] EMEA, European Public As
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[71] EMEA (n 70).

[72] EMEA (n 70) 10.

[73] DG Nathan, 'Clinical Resear
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[74] Interview with Vice-Presider

[75] AV Hoffbrand and B Won
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Thalassaemic Patients' (1998) 10

[76] EMEA, European Public A
iprone) 10.

[77] A potentially life-threatenin
blood cells to counteract infection

[78] An abnormally low number

[79] EMEA, European Public A
iprone) 8–11.

treatment compliance in the deferiprone group was superior (90%) to that in the deferoxamine group (70%). The study was discontinued in 1996 because of disagreements between Apotex and the clinical investigators.[69]

Trial LA-02 was a one-year, non-comparative study of 187 patients receiving solely deferiprone treatment. The CPMP reported that deferiprone seemed to prevent any rise in hepatic iron concentration during the trial, and that, for patients starting with heavy iron-loading, the drug seemed progressively to decrease the concentration over time. However, twenty-five patients had to be withdrawn from the trial, presumably due to toxicity or lack of efficacy.[70] LA-03 was a long-term, six-year trial based on compassionate use of the drug in just twenty-five patients, which seemed to show some decrease in serum ferritin in the first two years, but not thereafter.[71] The CPMP concluded that 'because of the deficiencies in the comparative study [LA-01], the only data available for assessment of efficacy are uncontrolled.'[72] Indeed, four years later, Nathan confidently asserted:

> It is to be emphasized that to this day, we do not know the actual status of deferiprone in therapy. Several investigators remain supportive of the drug, but a randomized prospective phase 3 trial to compare its efficacy with the standard deferoxamine has never been performed. The published reports of the drug are all uncontrolled and highly suspect.[73]

Apotex, however, contended that in the five years since 1999, evidence showed that deferiprone was 'probably more effective than deferoxamine in removing iron from the heart'.[74]

At the time of the CPMP's review of deferiprone, several studies were already published challenging the firm's view. These suggested that the drug was less effective than deferoxamine or even ineffective in a substantial proportion of patients even at doses above which toxicity might be expected.[75] The Committee was clearly aware of some, if not all, of these studies in reaching its conclusion.[76]

For the CPMP, the most important adverse reactions to deferiprone were agranulocytosis[77] and neutropenia[78] at incidences of 1.2 per cent and 6 per cent, respectively. However, because deferoxamine therapy posed many difficulties, including some of its own toxicities, the Committee decided that deferiprone's risks were acceptable given that the drug would be approved as a second-line treatment only for patients unresponsive to, or intolerant of, deferoxamine therapy.[79]

[69] JB Porter, 'A Risk-benefit Assessment of Iron-chelation Therapy' (1997) 17 *Drug Safety* 417.

[70] EMEA, European Public Assessment Report, CPMP 'Scientific Discussion' Ferriprox (deferiprone) 7.

[71] EMEA (n 70).

[72] EMEA (n 70) 10.

[73] DG Nathan, 'Clinical Research: A Tale of Two Studies' (2003) 114 *Transactions of the American Clinical and Climatological Association* 223.

[74] Interview with Vice-President, Scientific Affairs, Apotex (12 September 2004).

[75] AV Hoffbrand and B Wonke, 'Iron Chelation Therapy' (1997) 242 (suppl. 740) *Journal of Internal Medicine* 37; AV Hoffbrand, F AL-Refaie, and B Davis, 'Long-term Trial of Deferiprone in 51 Transfusion-dependent Iron Overloaded Patients' (1998) 91 *Blood* 295; P Tondury, A Zimmerman, and P Nielson, 'Liver Iron and Fibrosis during Long-term Treatment with Deferiprone in Swiss Thalassaemic Patients' (1998) 101 *British Journal of Haematology* 413.

[76] EMEA, European Public Assessment Report, CPMP 'Scientific Discussion' Ferriprox (deferiprone) 10.

[77] A potentially life-threatening disorder in which bone marrow fails to produce enough white blood cells to counteract infections.

[78] An abnormally low number of white blood cells.

[79] EMEA, European Public Assessment Report, CPMP 'Scientific Discussion' Ferriprox (deferiprone) 8–11.

In January 1999, the CPMP formed the opinion that marketing authorization of deferiprone, under the tradename, Ferriprox, should be approved for marketing within the EU, and advised the EMEA and the Commission accordingly.[80] However, before the Commission translated this advice into a regulatory decision, Olivieri sent letters in April and May 1999 to the EMEA and members of the CPMP. In these letters Olivieri presented scientific grounds on which she based her opinion that marketing of deferiprone would increase the risk of premature death to those taking it, due to the drug's hepatic and cardiac toxicity, especially progression of liver fibrosis. She also presented her finding that, in 32 per cent of patients treated with the drug, iron overload affecting the heart became worse. In those letters she also set out her version of events regarding her dispute with Apotex and the premature termination of LA-01. Consequently, the Commission suspended the normal regulatory process to allow the CPMP to consider the new safety information and to receive further responses from Apotex.[81]

The CPMP formed an expert group to review evidence about deferiprone's safety further. The expert working group acknowledged an unresolved controversy over liver fibrosis associated with deferiprone, but was swayed by the argument that it was to be used as a treatment of last resort for those patients who could not take deferoxamine, and that consequently it was worthwhile to manage the drug's risks.[82] In June 1999, following the recommendation of its expert group, the CPMP recommended that marketing authorization should be granted under 'exceptional circumstances' legislation.[83] Additional measures were demanded, such as labelling informing physicians of inconclusive risks of liver fibrosis and monitoring for it in subpopulations of patients, as well as requiring that Apotex provide detailed sales figures for each Member State to ensure that deferiprone's prescription really was restricted to second-line use.[84] The EMEA also forced the company to investigate further Olivieri's concerns about deferiprone's effect on cardiac function,[85] though she did not consider that the studies conducted on this matter were sufficient.[86]

Nonetheless, the CPMP concluded that 'there is still doubt that deferiprone may worsen hepatic fibrosis' because trial results on the matter conflicted.[87] Four years later, such doubt seemed to remain as Nathan commented that deferiprone's 'toxicity is uncertain and a matter of considerable debate'.[88] The US regulatory agency, the FDA, were also not convinced about the drug's safety, even in 2004, and demanded further toxicity studies before even considering it for approval on to

[80] EMEA, European Public Assessment Report, 'Background Information on the Procedure' Ferriprox (deferiprone) 2.

[81] Case T-326/99 *Fern Olivieri v Commission of the European Communities and the European Agency for the Evaluation of Medicinal Products, supported by Apotex Europe Ltd*, ECR II-06053 paras 24–30, 84.

[82] Interview with Member of Expert Working Group (28 September 2004); Interview with Nancy Olivieri, University of Toronto (28 June 2004).

[83] EMEA, European Public Assessment Report, 'Background Information on the Procedure' Ferriprox (deferiprone) 2.

[84] Case T-326/99 *Fern Olivieri v Commission of the European Communities and the European Agency for the Evaluation of Medicinal Products, supported by Apotex Europe Ltd*, ECR II-06053 paras 32–4.

[85] Interview with Vice-President, Scientific Affairs, Apotex (12 September 2004).

[86] Interview with Nancy Olivieri, University of Toronto (28 June 2004).

[87] EMEA, European Public Assessment Report, CPMP 'Scientific Discussion' Ferriprox (deferiprone) 9–10.

[88] DG Nathan, 'Clinical Research: A Tale of Two Studies' (2003) 114 *Transactions of the American Clinical and Climatological Association* 231.

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[89] Interview with Vice-President
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[92] Case T-326/99 *Fern Olivieri v*
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[93] Case T-326/99 *Fern Olivieri v*
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the US market.[89] This was despite Apotex's claim that post-marketing studies outside North America showed that deferiprone protected the heart more than deferoxamine.[90] In August 1999, the Commission accepted the CPMP's advice, permitting deferiprone marketing across the EU.[91]

In November 1999, Olivieri challenged that regulatory decision in what was then known as the ECJ on the grounds that it was flawed and not in the interests of public health. The Commission and the EMEA, supported by Apotex, asserted that her challenge was inadmissible.[92] Olivieri argued that the regulatory decision-making process was flawed because she was the only person who could guarantee the authenticity of certain clinical trial reports on which the marketing authorization was based, yet those reports did not bear her signature. However, the ECJ found that Olivieri's challenge was inadmissible because the CPMP had taken account of all information she wished to provide about deferiprone within the techno-scientific aspect of the regulatory process. For the ECJ, Olivieri's right to intervene in the process, with respect to the protection of public health, ended after that stage.[93] The ECJ took this view partly because of the narrow design of the EU drug regulatory framework, which created a bilateral procedure between Apotex and the EMEA/Commission regarding marketing authorization.

Consequently, Olivieri's objections to the approval of deferipone on to the EU market could not be tested in court. On the ECJ's ruling, within EU pharmaceutical regulation, only its regulatory apparatus had the authority to decide where the interests of public health lay. Citizens could attempt to influence the regulatory state's determination of the public interest, but once such a determination was made it could not be challenged by citizens, unless the patients themselves wished to claim a violation of their rights. The supranational system permitted no judicial review of substantive techno-scientific issues underpinning regulatory decisions in this context. Regarding medical professional autonomy, the case implied that the regulatory-industrial relationship is privileged to the exclusion of the clinical investigator. In this respect, EU law constrains pluralism of medical expertise and serves to limit fragmentation of scientific knowledge-claims beyond the industry-regulator relationship.

F. Discussion and Conclusion

Our investigation of the deferiprone case shows the almost irresistible nature of pharmaceutical industry involvement in drug technology development in modern industrial societies, even for medical scientists and professionals who are motivated by therapeutic advance for patients and public health, rather than career or commercial goals. The consequent reality of the socio-legal conventions of science in the medical-industrial complex may be far removed from ideal scientific principles. This has been insufficiently appreciated in popular and sociological representations of medical controversies, not least because when they have examined the involvement of the

[89] Interview with Vice-President, Scientific Affairs, Apotex (12 September 2004); Interview with Nancy Olivieri, University of Toronto (28 June 2004).

[90] Interview with Vice-President, Scientific Affairs, Apotex (12 September 2004).

[91] EMEA, European Public Assessment Report, 'Background Information on the Procedure' Ferriprox (deferiprone) 2.

[92] Case T-326/99 *Fern Olivieri v Commission of the European Communities and the European Agency for the Evaluation of Medicinal Products, supported by Apotex Europe Ltd*, ECR II-06053 paras 49–65.

[93] Case T-326/99 *Fern Olivieri v Commission of the European Communities and the European Agency for the Evaluation of Medicinal Products, supported by Apotex Europe Ltd*, ECR II-06053 paras 66–98.

pharmaceutical industry in science, the focus has often been on how actors construct their beliefs, rather than on how those beliefs relate to scientific evidence and decision-making by key institutions, such as regulatory agencies and the courts.

Moreover, loss of professional autonomy in the medical-industrial complex is connected to the politics of how medical science ought to be conducted, together with the extent to which the law reinforces the influence of various stakeholders. It is also important to emphasize the significance of legal *threat* in the context of drug technology development. Even if a firm's legal right to suppress a clinician's knowledge-claims is never tested in court, the mere existence of the threat may shape what is known, or at least when evidence becomes known, to the wider biomedical scientific community. This is a far cry from the classical sociological models of academic science with their preoccupations with 'paradigm' shifts and 'disinterestedness'.[94] Although the existence of legal threat did not prevent Olivieri from pursuing legal and professional avenues open to her, it affected the timing of knowledge-claims, as she had to negotiate its institutional ramifications. Furthermore, it is not difficult to imagine that other less determined individual medical scientists might simply be intimidated into withdrawing from controversy.

Our case study supports the rather depressing findings of Rhodes and Strain that academic establishments may regard medical specialists who conflict with industry as undermining academic institutional interests due to: possible forfeiture of industry support/grants amounting to financial loss; potential decline in prestige from losing industry support; fear of negative publicity; and the threat of industry litigation requiring a costly defence.[95] Consequently, with industry funding, instead of jealously protecting academic freedom and intellectual openness, university administrations may become hospitable to the censorship and non-disclosure found in the commercial sector.[96] As implied by Flear, such neo-liberal developments point to the need for a hitherto neglected political economy of medicine in academic institutions relating them and their medical specialists to the interests of industry and public health, especially in the EU, rather than to abstract normative ideal-types of the academy and scientists.[97]

Many previous discussions of litigation in medicine and pharmaceutical controversies have concentrated on how legal interventions represent challenges to medical expertise and autonomy from increasing consumer/patient rights—challenges which fracture medical expertise.[98] The deferiprone case indicates that a more expansive conceptualization of the role of the law in medical disputes is required. In this case, legal interventions did indeed serve to threaten and limit medical autonomy, but not by fracturing medical expertise and increasing its contestability. On the contrary, legal intervention sought to terminate, ultimately successfully, contestation and to funnel medical expertise into a consensus, first shaped by the drug manufacturer and then by the regulatory apparatus. This implies that while litigation by those outside the

[94] TS Kuhn, *The Structure of Scientific Revolutions* (University of Chicago Press 1962); RK Merton, 'Science and the Social Order' in NW Storer (ed), *The Sociology of Science* (University of Chicago Press 1938); RK Merton, 'The Normative Structure of Science' in NW Storer (ed), *The Sociology of Science* (University of Chicago Press 1942).

[95] R Rhodes and JJ Strain, 'Whistle-blowing in Academic Medicine' (2004) 30 *Journal of Medical Ethics* 35.

[96] A Schafer, 'Biomedical Conflicts of Interest' (2004) 30 *Journal of Medical Ethics* 8.

[97] Flear (n 6).

[98] R Dingwall, P Fenn, and L Quam, *Medical Negligence* (Centre for Socio-Legal Studies 1991); J Gabe and M Bury, 'Halcion Nights: A Sociological Account of a Medical Controversy' (1996) 30 *Sociology* 447.

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[99] J Abraham and G Lewis, 'Citizensh
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practising profession may be legitimately conceptualized as a challenge to medical autonomy, its consequences for medical expertise (for example, fragmentation versus closure) are context-dependent upon the goals of the interests involved. Legal interventions in drug controversies are not necessarily drivers of fragmentation or pluralism of medical expertise, they may be levers of consolidation and marginalization instead, especially if employed by industry and/or the state.

Moreover, the ruling of the then ECJ, previously referred to, asserts that once the decision-making process by the EU's supranational drug regime is complete, no citizens other than the manufacturer have standing to challenge whether the decision was in the interests of public health. In particular, this includes the clinical investigator responsible for the medical management of the trials submitted to the EU drug regulatory agency. EU law presumes that the supranational regulatory regime has the ultimate authority to decide what is in the interests of public health and it need not be publicly accountable in the courts for that decision even if the validity of the underpinning evidence is challenged by the absence of signatures of clinical investigators. A doctor centrally involved in drug development with patients, it seems, may not legitimately launch a legal challenge against a regulatory decision by claiming that the regulator has failed to uphold its legal duty to protect the health interests of those patients. Consistent with 'neo-liberal corporate bias', in this respect, the EU's regulatory regime, in consultation with the drug manufacturer, determines what is in the interests of the clinical investigator's patients and public health, rather than the doctor.[99]

The deferiprone case appears to leave open the possibility in the EU that a pharmaceutical firm could legally terminate trials if it believed that the clinical investigator was going to interpret emerging results in ways not to the company's liking. Evidently, medical autonomy is precarious because of the power of industry and the state. Specifically, in such controversies, the professional autonomy of medical specialists and the interests of public health may be in peril if they are not consistent with the perspective of the regulatory regime both in terms of legal provisions and technical evaluation. Finally, our case study highlights that the production and maintenance of medical knowledge about pharmaceuticals is not merely the outcome of laboratory science, it also involves, to varying degrees, the socio-political and socio-legal dimensions of the 'medical-industrial complex', the regulatory state, and the courts.

Regarding improvements to EU drug law and regulatory measures that might be considered in drawing lessons from this case, it would be desirable to permit more extensive rights to third parties wishing to challenge drug regulatory decisions in the courts, as occurs in the USA. Such third parties may be clinical investigators, but they may also be citizen groups, such as the Public Citizen Health Research Group in the USA. As the United Kingdom and other countries embark on reflective debates about how to limit private funding of political parties in order to protect the integrity of the political process, so a similar high-profile political debate needs to take place regarding commercial funding of biomedical research in relation to its scientific and ethical integrity. We make no specific recommendations in this respect, other than to comment that there is a pressing need for governments to formulate public interest regulation of the medical-industrial complex, so that the law in this field may be deployed in the interests of public health, where it belongs, rather than in threats to clinical scientists or exclusionary judgments.

[99] J Abraham and G Lewis, 'Citizenship, Medical Expertise, and the Capitalist Regulatory State in Europe' (2002) 36 *Sociology* 67.

12

The Governance of Therapeutic Nanoproducts in the European Union—A Model for New Health Technology Regulation?

Bärbel Dorbeck-Jung

A. Introduction

In the past five years nanomedical applications have been promoted worldwide as highly promising new health technologies to cope with unmet causes of mortality and morbidity of the population. Nanomedicine has the goal to provide cost-effective novel therapies and diagnostics using the expanding possibilities of nanotechnologies.[1] Although nanomedicine is still in its infancy, it is advancing rapidly. A growing number of nanomedical products, including nano-pharmaceuticals and diagnostic techniques for the rapid detection of leukemia based on nanotechnologies, have already been granted approval by regulatory agencies such as the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) and have entered the market place in certain jurisdictions.[2] Cancer, Parkinson's, and Alzheimer's are diseases for which therapeutic products are being developed. Research efforts are particularly intensive with regard to new methods and tools for diagnostics, screening and imaging, as well as to drug development, drug delivery, tissue engineering, medical implants, and gene therapy.[3]

Nanomedicine poses a large range of challenges to European medical product regulation. A crucial challenge is the uncertainty about the scientific and technological development and its effects. There is insufficient knowledge about the benefits of nanomedical products and the paths of technological development, and the characteristics and behaviour of nanomaterials, are not well known.[4] Knowledge gaps in relation

[1] European Technology Platform Nanomedicine (ETPN), 'Roadmaps in Nanomedicine Toward 2020' (2009) 6 <www.etp-nanomedicine.eu/public> accessed 10 April 2012.

[2] V Wagner and others 'The Emerging Nanomedicine Landscape' (2006) 24(10) *Nature Biotechnology* 1211; OC Farokhzad and R Langer, 'Nanomedicine: Developing Smarter Therapeutic and Diagnostic Modalities' (2006) 58 *Advanced Drug Delivery Reviews* 1456; EMA, '1st International Workshop on Nanomedicines 2010', Summary Report, EMA/538503 (2010).

[3] M Ferrari and others 'Nanomedicine and Society' (2009) 85 *Clinical Pharmacology & Therapeutics* 466.

[4] European Science Foundation (ESF), 'Forward Look on Nanomedicine', Strasbourg Cedex (2005) <www.esf.org/publications/214/Nanomedicine.pdf> accessed 10 April 2011; European Group of Ethics in Science and New Technologies (EGE), Opinion on the Ethical Aspects of Nanomedicine (Brussels: European Commission 2007); Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR), 'Opinion on the Appropriateness of the Risk Assessment Methodology in Accordance with the Technical Guidance Documents for New and Existing Substances for Assessing the Risks of Nanomaterials' (DG Health and Consumers 2007); Royal Commission on Environmental Pollution (RCEP), Novel Materials in the Environment: The Case of Nanotechnology (2008) <www.rcep.org.uk/reports/27novel%20materials/documents/NovelMaterialsreport_rcep.pdf> accessed 10 April 2012; M van Zijverden and AM Sips (eds), *Nanotechnology in Perspective: Risks for Man and the Environment*

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[5] BR Dorbeck-Jung, 'Governing Na
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[6] R Gaspar, 'Therapeutic Products: r
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[7] BR Dorbeck-Jung and others, 'Go
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