

Discovery and Management of Adverse Drug Reactions: The Nomifensine Hypersensitivity Syndrome, 1977–1986

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Summary. Taking the antidepressant, nomifensine, this article focuses on the discovery and management of adverse drug reactions (ADRs) manifested in doctors' spontaneous post-marketing reports. Company-friendly experts, free-lancer research scientists, public servant physicians and regulatory scientists are shown to have made distinct contributions to ADR discovery. However, institutional and international fragmentation delayed synthesis of ADR reports into unambiguous discovery. Qualitative and quantitative interpretative standards of what counted as ADR discovery affected regulatory warning systems and decisions about when to withdraw a drug from the market. The timing and definition of an ADR as 'irreversible' or 'rare' was, in part, a function of the uncertainty and estimation criteria chosen by the party managing the discovery. UK regulators accepted relatively low levels of uncertainty, so the timing of discovery, warnings and regulatory action was relatively late, but US regulators chose higher thresholds of uncertainty about discovery when interpreting the need to warn of suspected serious ADRs. The implications of these practices for the founding ideals of a post-marketing 'early warning system' are considered.

Keywords: drug safety; pharmaceutical industry; regulatory agencies; FDA; CSM

In contrast to the growing literature providing detailed historical accounts of the discovery of pharmaceuticals and their role in combating disease, this paper presents an analysis of the discovery and 'management' of post-marketing adverse reactions to pharmaceuticals.¹ Adverse reactions to pharmaceuticals can occur in pre-market or post-market phases of product development, and they can be detected and regulated via experimental trials, epidemiological surveys (prospective or retrospective), and/or spontaneous case-reports.² Socio-historical research centred specifically on the relationship between the discovery and management of adverse drug reactions (ADRs), on the one hand, and the post-market spontaneous ADR reporting systems established since the mid-1970s, on the other, is rare.

The case studies of practolol, triazolam and fluoxetine by Abraham and Davis, Abraham and Sheppard, and Healy, respectively, give consideration to spontaneous post-

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¹Bud 2007; Lesch 2007; MacFarlane and Worboys 2007; Podolsky 2006; Quirke 2006; Vos 1991; Church and Tansey 2007; Jones 2001; Keating and Cambrosio 2007; Marks 1997; Rasmussen 2002a, 2002b.

²Such reports are known as 'spontaneous' because there is no controlled sampling of patients: doctors simply report (or not) ADRs in their practice.

marketing ADRs, but only as part of wider controversies.³ Greene, Marks, and Moore discuss the adverse effects of drugs to treat diabetes and heart problems, but their analyses pertain to relatively unusual, large post-marketing experimental controlled trials, such as the US University Group Diabetes Program for tolbutamide, and the US National Institutes of Health (NIH) Cardiac Arrhythmia Suppression Mortality Trial (CAST) regarding flecainide acetate.⁴ Apfel and Fisher, Grant, and Watkins recount the accumulations of adverse reactions to diethylstilbestrol (DES), the Dalkon Shield intra-uterine device and oral contraceptives, respectively.⁵ However, the detection and management of adverse reactions to DES and the Pill have been primarily by experimental trials and epidemiological design emerging in the 1960s and beginning of the 1970s, rather than from spontaneous ADR reporting, and (like thalidomide) before the establishment of regulatory systems of spontaneous ADR surveillance.⁶ Grant's account of the Dalkon Shield controversy includes analyses of post-market spontaneous reports of adverse reactions during the 1970s and 1980s, but her discussion is confined entirely to the US, and concerns a medical device, rather than a drug.⁷

Taking the antidepressant, nomifensine, as a case study, this paper focuses specifically on the detection and management of hypersensitivity ADRs which came from spontaneous, post-market reports in clinical practice—the way post-market ADRs are collected for the vast majority of prescription drugs. The relative neglect of spontaneous ADR reporting in the history of medicine means that what counts as a discovery of ADRs, together with the implications of that interpretation for regulators, prescribing doctors, patients and pharmaceutical firms, have not been sufficiently interrogated. Discovery of a new drug capable of treating disease is culturally welcome, and something for which scientists seek public recognition. ADR discovery may be more elusive because it may damage the interests of the manufacturer and convey culturally disappointing news.

By the late 1970s, spontaneous ADR reporting was part of a warning system supposed to protect patients. While regulators encouraged physicians to report all suspected ADRs, suspicion was not necessarily interpreted as a causal link between the drug and an adverse event. By tracing the discovery and management of nomifensine's hypersensitivity syndrome in different countries, we show the fragmented nature of ADR discovery, and how the interpretation of what counts as discovery can affect regulatory warning systems and decisions about when a drug should be withdrawn from the market. We concentrate on the UK, USA and (West) Germany, the drug's three main markets and principal locations of the manufacturer, but for reasons of brevity discuss the regulatory contexts of only the UK and the USA. Understanding more about the discovery and management of ADRs in the 1970s and 1980s may help to illuminate some persistent and present-day concerns about SSRI antidepressants and other drugs. For example, the nomifensine case shows how post-market spontaneous ADR surveillance, which

³Abraham and Davis 2006; Abraham and Sheppard 1999; Healy 2004.

⁴Greene 2007; Marks 1997; Moore 1995.

⁵Apfel and Fisher 1984; Grant 1992; Watkins 1998.

⁶Apfel and Fisher 1984, p. 43; Watkins 1998, pp. 88–90.

⁷Grant 1992, p. 45.

was established, in principle, as an early warning system for doctors and patients based on suspicion, was transformed by UK regulators and the manufacturer, in practice, into a late warning system based on near-certainty.

Locating Nomifensine in the History of Antidepressants

Sedatives, stimulants and amphetamines were used as antidepressants as early as the 1930s and 1940s.⁸ The 1950s saw the introduction of the monoamine oxidase inhibitors (MAOIs) and tricyclics. Scientists theorised that depleted levels of amines in the brain, such as dopamine, noradrenaline and serotonin, affected mood and depression.⁹ MAOIs and tricyclics were thought to have an antidepressant effect by increasing noradrenaline in the brain. Most antidepressants introduced by the pharmaceutical industry in the 1960s and 1970s were close chemical derivatives/analogues of MAOIs or tricyclics.¹⁰ Nomifensine, developed by Hoechst in the 1970s, was part of this industrial effort to market antidepressants, but it was not an MAOI and, unlike the tricyclics, it inhibited re-uptake of dopamine as well as noradrenaline.¹¹ This suggested that low levels of dopamine might also contribute to depression. At a London symposium in January 1977 dedicated to nomifensine, this multi-amine theory of depression and the clinically important role of dopamine were highlighted.¹² The unsatisfactory nature of antidepressants available in the 1970s meant that clinicians were receptive to nomifensine's apparently unique combined dopamine and noradrenaline re-uptake inhibitory antidepressant mechanism. For example, the tricyclics were associated with cardiovascular problems, troublesome sedation and severe/lethal toxicity on overdose.¹³

Nomifensine was first marketed in West Germany in 1976 by Hoechst, a trans-national pharmaceutical manufacturer with headquarters and parent company, Hoechst(AG), in Germany, and major subsidiaries in the UK and the USA, known as Hoechst(UK) and Hoechst-Roussel, respectively. The firm applied to market the drug in the UK on 13 January 1976, an application which the British regulatory authorities, the Department of Health's Medicines Division (DHMD) and expert advisory Committee on Safety of Medicines (CSM), approved on 29 November 1976, assigning to the drug the tradename Merital.¹⁴ It was not until 26 December 1978 that the firm submitted a new drug application to the Food and Drug Administration (FDA) to market nomifensine in the USA. For years, the FDA were not convinced that the drug was efficacious, but eventually approved it on 31 December 1984 noting that it offered little or no therapeutic advance.¹⁵ Thus nomifensine was developed and marketed after modern drug regulatory systems had become established in Europe and North America, but before prozac and other SSRIs would come to dominate the antidepressant drug market.

⁸Moncrieff 2008; Rasmussen 2006.

⁹Healy 1997.

¹⁰Montgomery in Costa and Racagni (eds) 1982, p. 49.

¹¹Hoffman 1977.

¹²Spencer 1977, pp. 585 and 605.

¹³Montgomery *et al.* in Costa and Racagni (eds) 1982.

¹⁴Personal communication 2002.

¹⁵Temple 1984a.

With regulatory approval, nomifensine was recommended to doctors for treatment of a 'wide range of depressive illness', but not approved as more efficacious or safe than other antidepressants.¹⁶ UK regulators did not permit Hoechst to claim on the drug's label (known as the 'data sheet' in the UK) that nomifensine possessed less cardiotoxicity, fewer adverse sedative effects or greater safety in overdose than other antidepressants, although they allowed the firm to state that trials indicated 'a notable lack of cardiovascular effects'.¹⁷ Nomifensine was taken by an estimated 13 million patients world-wide, half a million of whom were in the UK.¹⁸ In January 1986, Hoechst withdrew nomifensine from the market world-wide following numerous reports of severe/fatal allergic (hypersensitivity) reactions in Europe. These included haemolytic anaemia (premature destruction of red blood cells), fever, a flu-like syndrome, immune vasculitis (inflammation of blood vessels), liver toxicity, including jaundice, alveolitis (inflammation of lung passages), interstitial pneumonia and kidney failure. A former member of the CSM recounted: 'When we looked at serious reactions per million prescriptions [for nomifensine] that was awful. It was in the same class as opren [arguably Britain's worst drug disaster since thalidomide]'.¹⁹

By 1980, governments in Western Europe and North America had established regulatory systems of post-marketing surveillance of ADRs.²⁰ Pharmaceutical firms were required by law to report all suspected ADRs in a timely manner to regulatory authorities, while provisions were made encouraging doctors to do the same. The latter, known as the 'yellow card system' in the UK, was (and remains) voluntary. During the 1980s, doctors reported less than 10 per cent of ADRs.²¹ In Germany, the drug regulatory authorities acknowledged that only 20 per cent of ADR reports came directly from doctors—the rest from drug manufacturers, indicating the enormous dependence of the regulatory system on meticulous reporting by industry.²²

According to the US Congress, there were at least 30 deaths associated with nomifensine outside the USA, which were reported to Hoechst, but allegedly not reported to the FDA until after US approval.²³ Consequently, the FDA and the US Attorney's Office launched a four-year investigation of Hoechst and Hoechst-Roussel regarding their compliance with the FDA's ADR reporting regulations. They brought four misdemeanour charges against Hoechst for unintentional failure to make timely reports to the FDA of two fatal haemolytic anaemia reactions to nomifensine that occurred in Europe in 1980 and 1984.²⁴ Hoechst admitted to the charges and was fined \$202,000 by the US District Court of New Jersey.²⁵ This article does not examine the adequacy or legality of Hoechst's ADR

¹⁶Hoechst 1977.

¹⁷*Ibid.*

¹⁸Anon. 1985; Anon. 1986a, p. 23. *Scrip* is a weekly independent publication devoted to reporting current events solely in the pharmaceutical sector.

¹⁹Interview with former member of CSM throughout 1980s, Newcastle, 19 June 2001.

²⁰Abraham 1995; Abraham and Lewis 2000; Daemmerich 2004.

²¹Lumley *et al.* 1986.

²²Anon. 1992.

²³US Congress 1987, p. 18.

²⁴Anon. 1990.

²⁵Anon. 1991.

reporting to regulatory agencies, but against this background, one's historical analysis must always be alert to the possibility that manufacturers have been tardy about reporting ADRs, and that that could affect the timing and management of ADR discovery.

Physician–Industry Interaction: Scientific Testing and Communication

Rasmussen outlines three types of collaboration between physicians and the pharmaceutical industry in clinical trial research during the inter-war period.²⁶ The 'free-lancer', who initiated, designed and published trials independently, was supported by the manufacturer only to the extent that it supplied the drug. By contrast, the 'efficient' collaborator conducted company-funded trials that were mainly/entirely initiated and designed by the manufacturer, who also controlled publication. Between these was the 'friendly expert', who sometimes initiated company-funded trials by proposing them as a way for a firm to advance its own interests, with design, analysis and control of publication being shared between physician and manufacturer. Our case study suggests that, regarding ADR discovery, two further types should be added, namely, the 'public servant' and the 'regulatory scientist'. The 'public servant' is a practising physician, who voluntarily reports ADRs to the company and/or regulators as a potential warning to public health, but does not seek to research those observations or perhaps even publish them. The 'regulatory scientist' is a clinician/physician/psychiatrist employed within a government regulatory agency who analyses ADR reports submitted by physicians or manufacturers.

Dr M. D. Wolf, the chief physician of a district hospital in (West) Germany, was one such 'public servant'. In December 1977, he wrote a letter to Hoechst(AG) entitled 'Haematological side reactions of nomifensine'.²⁷ He reported the death of a 63-year-old woman from thrombocytopenia (reduction of blood platelets), involving evidence of allergy after taking three medications, including nomifensine. Wolf concluded by asking: 'do we know about haematological side reactions leading to thrombocytopenia after intake of nomifensine?' Whether nomifensine was responsible for the death was not known, but Wolf was sufficiently suspicious to pose the question. Hoechst(UK) received three reports of nomifensine-associated haemolytic anaemia in 1978 from which the patients recovered, but required hospitalisation²⁸ (see Table 1). According to the US Congress, the first fatal case of haemolytic anaemia was reported to Hoechst(AG) in 1979, but the patient had leukaemia, and so might have died from that, rather than nomifensine.²⁹ Whatever Hoechst's view of these two fatal cases of thrombocytopenia and haemolytic anaemia, the parent company responded to the non-fatal cases of haemolytic anaemia by instigating a European surveillance programme in France, West Germany and the UK. This involved retrospective studies of blood specimens from some patients taking nomifensine to determine the seriousness of any association between the drug and haemolytic anaemia. In March 1979, Hoechst(AG) told the West German regulatory authorities that the adverse reactions seemed to have an immunological basis, and that the company was investigating the hypothesis that

²⁶Rasmussen 2005.

²⁷Wolf 1977.

²⁸Cole 1980, p. 3.

²⁹US Congress 1987, p. 47.

Table 1. ADRs^a associated with nomifensine and reported to CSM and/or Hoescht(UK), 1977–1986

Year	ADR	Report type	Total no. reports No duplication ^b	Total no. reports Max. duplication ^c
1977	Fever	2 cases to CSM 5 cases to Hoescht(UK)	7 Fever	5 Fever
1978	HA	1 case to CSM 3 cases to Hoescht(UK)	4 HA	3 HA
	Hepatic	3 cases to CSM 3 cases to Hoescht(UK)	6 Hepatic	3 Hepatic
	Fever	3 cases to CSM	3 Fever	3 Fever
1979	HA	1 case to CSM 1 case to Hoescht(UK)	2 HA	1 HA
	Hepatic	3(1) ^d to CSM 5 to Hoescht(UK)	8(1) Hepatic	6(1) Hepatic
	Fever	4 cases to CSM 2 cases to Hoescht(UK)	6 Fever	4 Fever
1980	Hepatic	4 cases to CSM 5 cases to Hoescht(UK)	9 Hepatic	5 Hepatic
	Fever	6 cases to CSM 2 cases to Hoescht(UK)	8 Fever	6 Fever
1981	HA	1 case to CSM	1 HA	1 HA
	Hepatic	4 cases to CSM 6 cases to Hoescht(UK)	10 Hepatic	6 Hepatic
	Fever	6 cases to CSM 2 cases to Hoescht(UK)	8 Fever	6 Fever
1982	HA	2 cases to CSM	2 HA	2 HA
	Hepatic	2 cases to CSM 3 cases to Hoescht(UK)	5 Hepatic	3 Hepatic
	Fever	2 cases to CSM 2 cases to Hoescht	4 Fever	2 Fever
1983	HA	5 cases to CSM 5 cases to Hoescht(UK)	10 HA	5 HA
	Hepatic	8 cases to CSM 4 cases to Hoescht(UK)	12 Hepatic	8 Hepatic
	Fever	1 case to CSM 1 case to Hoescht(UK)	2 Fever	1 Fever
1984	HA	16 cases to CSM 12 cases to Hoescht(UK)	28 HA	16 HA
	Hepatic	10 cases to CSM 10 cases to Hoescht(UK)	20 Hepatic	10 Hepatic
	Fever	14 cases to CSM 5 cases to Hoescht(UK)	19 Fever	14 Fever
1985	HA	33(4) cases to CSM ^e 18 cases to Hoescht(UK)	51(4) HA	33(4) HA

Continued

Table 1. *Continued*

Year	ADR	Report type	Total no. reports No duplication ^b	Total no. reports Max. duplication ^c
	Hepatic	17 cases to CSM 8 cases to Hoescht(UK)	25 Hepatic	17 Hepatic
	Fever	10 cases to CSM 6 cases to Hoescht(UK)	16 Fever	10 Fever

Notes: ^aThe table is not a presentation of all nomifensine-associated ADRs, only haemolytic anaemia (HA), hepatic (liver) reactions and serious fevers.

^bThese totals assume no duplication in ADR reports to CSM and Hoescht(UK).

^cThese totals assume maximum duplication in ADR reports to CSM and Hoescht(UK).

^dFatalities are in brackets.

^eOf which 8(3) were received between January and June 1985 before CSM July 1985 publication of *Current Problems*, regarding nomifensine and HA.

Sources: CSM 1986; Interview with, and Report by, P. Stonier 2001

nomifensine caused immunological adverse effects.³⁰ The firm funded the ‘friendly experts’, Drs Bournierias and Habibi, to conduct blood tests on nomifensine patients. They were French scientists and consultants to Hoechst. Bournierias and Habibi were the first to publish a case of immune haemolytic anaemia ‘induced by nomifensine’, but apart from this case, they found no evidence of antibodies specific to the drug—evidence that would have implied an allergic reaction.³¹

Meanwhile, across the Atlantic, the FDA’s review of the drug was under way. On 15 October 1979, Dr James Cole, the ‘regulatory scientist’ at the FDA responsible for reviewing the drug’s safety, raised the fact that 44 (15 per cent) of the nomifensine patients in clinical trials had eosinophilia (increased number of white blood cells involved in allergic reactions). One of these patients had developed a combination of eosinophilia, abnormally elevated levels of liver enzymes, suggestive of hepatitis, and fever, while eight others combined two of those three signs. At the FDA’s Psychopharmacological Drugs Advisory Committee (PDAC), Cole suggested that, ‘you could speculate whether there is some allergic process going on’.³² In response to a December 1979 request from the FDA to ‘discuss the significance of the high incidence of eosinophilia which occurred in nomifensine patients’ in US trials and ‘the European experience in regard to this laboratory abnormality’, in July 1980, Hoechst informed the FDA of 10 cases of fever with eosinophilia, but advised that the elevated white blood cell counts were ‘generally of doubtful clinical significance’.³³ Apparently reassured, Cole did not pursue the matter.³⁴

About a year later, two free-lancer scientists took an interest in nomifensine’s allergenicity. Drs Neftel and Waelti at the Institute for Clinical Immunology in Switzerland had developed a more sophisticated technique than Habibi’s for detecting drug-specific antibodies in

³⁰US Congress 1987, p. 69.

³¹Bournierias and Habibi 1979.

³²Psychopharmacological Drugs Advisory Committee (hereafter PDAC) 1979, p. 196.

³³Cole 1980, p. 2.

³⁴Cole 1980, p. 3.

patients and hence allergic reactions to drugs. In early 1982, they approached Hoechst(AG) and proposed to apply their technique to patients who had taken nomifensine. Hoechst co-operated and, by May 1982, Waelti had found nomifensine-specific antibodies in the blood of 11 patients, including three who had developed haemolytic anaemia and seven with fever.³⁵ The independent-minded approach of Neftel and Waelti, with respect to Hoechst, combined with their development of more powerful technologies of allergenicity detection were significant steps towards the discovery of nomifensine's hypersensitivity syndrome. Two months later, Habibi acknowledged that his less specific technique explained why he had not had more positive results in 1979.³⁶

In 1983, Neftel and Waelti published findings in a German language journal, *Swiss Medical Weekly*, that nomifensine-specific antibodies were detected in the blood of all 51 nomifensine patients tested, but in none of the 'control' patients who did not take the drug.³⁷ That year the West German labelling for the drug stated that fever and haemolytic anaemia were 'immunologically caused hypersensitivity reactions'.³⁸ Thus by late 1983, Neftel and Waelti had demonstrated the allergenicity of nomifensine. As 'free-lancer' researchers, they were keen to publish how their new method had achieved this, but they did not promote the inference that such allergenicity was producing adverse effects on patients beyond the German-language context.

Indeed, such were the cultural boundaries of institutional and international fragmentation in the clinical science of ADR discovery, that it is unclear whether Hoechst(UK) or the CSM knew about these results contained in German-language publications and labelling. The FDA certainly did not until, on 29 October 1984, Hoechst-Roussel submitted to the agency an acknowledgement that nomifensine-associated haemolytic anaemia, fever, eosinophilia and liver function abnormalities 'probably reflect different target organ sensitivities to a single immunological event'.³⁹ Even then, senior FDA scientists did not assimilate these German-language findings. As late as December 1984, Dr Paul Leber, a psychiatrist and Head of the FDA's Division of Neuropharmacological Drug Products, took the view that 'the eosinophilia is asymptomatic and not linked to any specific clinical syndrome of significance'.⁴⁰ The initial US labelling approved by the FDA in January 1985 stated:

Cases of severe haemolytic anaemia have been reported after treatment with nomifensine. Nomifensine antibodies have been isolated in a few cases and Coombs tests have been positive in a large number but a mechanism has not been established.⁴¹

In summer 1984, other free-lancer scientists, Drs Salama and Mueller-Eckhardt at the Institute of Clinical Immunology and Blood Transfusion at Liebig University in West Germany, detected nomifensine-specific antibodies in blood samples confirming that patients were suffering from nomifensine-induced allergic haemolytic anaemia.⁴²

³⁵Waelti 1982.

³⁶US Congress 1987, p. 63.

³⁷Waelti *et al.* 1983, p. 1865.

³⁸US Congress 1987, p. 90.

³⁹US Congress 1987, pp. 25–6, 64.

⁴⁰Leber 1984a, p. 6.

⁴¹Hoechst-Roussel 1985a.

⁴²Salama and Mueller-Eckhardt 1985, p. 473.

Only after Drs Salama and Mueller-Eckhardt published their findings in the *New England Journal of Medicine* in August 1985, did the FDA relate to the German nomifensine allergenicity research. Consequently, Hoechst and the FDA changed the US label to state that antibodies to nomifensine had been isolated in patients generally, rather than ‘in a few cases’.⁴³

Danger, Suspected Injury and ‘Sound’ Warnings

According to the UK regulatory authorities, the purpose of the yellow card system, when established, was to provide an early warning system about possible dangers of pharmaceuticals based on doctors’ reports of suspected ADRs.⁴⁴ UK regulators used their yellow card data to challenge the safety of nomifensine just before Hoechst’s world-wide withdrawal of the product. The CSM claimed that nomifensine was ‘a prime example of how the yellow card reporting system can provide important information even when a drug has been widely used for several years without causing undue suspicion’.⁴⁵ The CSM and Hoechst(UK) viewed the nomifensine case as evidence that the British warning system for managing ADRs was sound. In this section, we explain what the pharmaceutical industry (specifically Hoechst), the UK regulatory authorities, and the FDA considered sound interpretations of case reports of suspected ADRs to be in this period, and how those interpretations related to the discovery and management of nomifensine ADRs, in terms of labelling changes and maintaining the drug on the market.

As nomifensine entered the UK market, the drug’s initial data sheet, produced by Hoechst(UK) and approved by the DHMD, stated:

All available evidence has indicated that *Merital* is exceptionally well tolerated.... Adverse effects, if they occur, tend to be mild and transient.⁴⁶

According to Dr Peter Stonier, the Medical Director for Hoechst(UK) at the time, the British subsidiary of the company received four reports of haemolytic anaemia during 1978 and 1979, but the CSM recorded only two such cases (Table 1).⁴⁷ Two early cases were published indicating the severity of immune reactions to the drug. Bournierias and Habibi reported a patient who, on taking nomifensine intermittently, had seven identical episodes of ‘malaise, chills, abdominal pain, and fever, each of 2–4 hr duration’ and sometimes ‘slight transient jaundice’.⁴⁸ The other published case involved a UK patient who suffered acute haemolysis and kidney failure in 1978.⁴⁹ Although this case involved an overdose with nomifensine (casting doubt on Hoechst’s claims about the drug’s exceptional safety in overdose), the doctors making the report pointed out that it was similar to the case previously reported by Bournierias and Habibi.⁵⁰ Thus, by the end of 1979,

⁴³Hoechst-Roussel 1985b.

⁴⁴Inman 1999.

⁴⁵Committee on Safety of Medicines (hereafter CSM) 1986.

⁴⁶Hoechst 1977.

⁴⁷CSM 1986; Interview with, and written report by Stonier, Guildford, 20 June 2001.

⁴⁸Bournierias and Habibi 1979.

⁴⁹Prescott *et al.* 1980.

⁵⁰According to US Congress (1987: 18), there were 10 cases of nomifensine-associated suicide and/or fatal overdose before 1985.

doctors had reported strong suspicions of haemolytic anaemia reactions to nomifensine. While such reactions seemed rare, they were known to be serious. In addition, the CSM had received six reports of liver toxicity suspected to be caused by the drug, including one death.⁵¹ Neither these, nor the reports of haemolytic anaemia, were included in the nomifensine data sheet for 1980. Rather, it stated:

Merital has been shown to be exceptionally well tolerated and side-effects, when they occur, tend to be mild and transient. . . . In rare cases a rise in body temperature had been observed which returned to normal when the drug was withdrawn [from the patient].⁵²

Reference to 'rare cases' of 'a rise in body temperature' may be a characterisation of the fever associated with the few allergic haemolytic anaemia reactions reported, but the fever was not put in that context. At this stage, it had not been discovered that these ADRs were all a manifestation of a single hypersensitivity/immunological syndrome.

No mention was made of nomifensine-induced haemolytic anaemia or hepatic injury on the data sheet until January 1981 when Hoechst(UK) and the CSM agreed an addition, which read:

In rare cases, increases in liver enzymes have been observed; haemolytic anaemia had also been reported in rare cases as had a rise in body temperature.⁵³

Presumably, 'increases in liver enzymes' was intended to represent a warning of suspected cases of liver injury, including a fatal one.

By late 1981, the CSM had received 14 reports of liver toxicity associated with the drug and Hoechst(UK) had received 19, including 8 cases of jaundice, and between 1982 and 1984, the CSM received a further 20 reports of liver toxicity (Table 1).⁵⁴ A range of suspected reactions to nomifensine were published by 'public servant' physicians. There were four cases of fever reaching 104°F, including allergic alveolitis and hepatitis;⁵⁵ another nine cases of fever, including two whose causal link to nomifensine was seemingly confirmed by re-challenge, three involving liver problems and two requiring hospitalisation;⁵⁶ two cases of haemolytic anaemia and acute kidney failure in patients who had stopped taking nomifensine and then upon restarting immediately suffered the reactions;⁵⁷ and a further adverse liver reaction.⁵⁸ These constituted a small number of case reports among hundreds of thousands of patients taking the drug. Such reports may have been regarded as idiosyncratic because laboratory research by Waelti *et al.* and Salama and Mueller-Eckhardt had not yet demonstrated widespread allergenicity among samples of patients.⁵⁹ Nevertheless, all of these cases were judged by the authors to

⁵¹CSM 1986.

⁵²Hoechst 1980.

⁵³Hoechst 1981.

⁵⁴US Congress 1986, pp. 454–9.

⁵⁵Hunziker *et al.* 1980.

⁵⁶Dankbaar and Mudde 1980; Nielsen *et al.* 1981; Wiehe *et al.* 1981.

⁵⁷Eckstein *et al.* 1981.

⁵⁸Thomsen *et al.* 1981.

⁵⁹Waelti *et al.* 1983; Salama and Mueller-Eckhardt 1985.

be allergic reactions to the drug, so must be acknowledged as making some contribution to the discovery of nomifensine's hypersensitivity syndrome. According to Bournérias and Habibi, many of the severe cases of haemolytic anaemia followed less serious symptoms, such as fever, in patients using the drug intermittently, so early recognition of the relatively benign adverse effects as hypersensitivity reactions to nomifensine was clinically important.⁶⁰

Hoechst(UK) and the British regulatory authorities interpreted these case reports as rare and insufficient to warrant a warning to doctors during the early 1980s. The data sheets for nomifensine continued to claim that 'all available evidence has indicated that *Merital* is exceptionally well-tolerated' until 1984 when 'clinical jaundice' was first mentioned as a possible side-effect of the drug in addition to rare cases of haemolytic anaemia.⁶¹ Indeed, the data sheet's account of adverse effects remained entirely unchanged from 1982 to 1984, except for the mention of jaundice in 1984. Between 1977 and 1983, the CSM received 24 reports of febrile reactions associated with nomifensine.⁶² In September 1983, another antidepressant, zimeldine, was withdrawn from the UK market following reports of febrile reactions leading, in some cases, to peripheral neuropathies (damage to the nervous system). The UK regulatory authorities recognised these reactions to zimeldine as part of a hypersensitivity syndrome in which the later cases of peripheral neuropathy developed when patients were not withdrawn from the drug after exhibiting earlier signs, such as fever, headache or liver disturbance. In November 1983, the FDA contacted the DHMD to enquire whether the CSM had received reports of a syndrome characterised by fever and/or haemolytic anaemia and/or liver injury associated with nomifensine. Dr John Griffin, then Head of the DHMD, informed Leber that, 'English interest in the syndrome had been piqued by the possibility that it was linked to the recognized syndrome of neurological damage and systemic injury seen with zimeldine'.⁶³

Thus, by the end of 1983, some regulatory scientists in the UK suspected that febrile reactions associated with nomifensine might represent part of a hypersensitivity syndrome—an analogical discovery emerging from their experience of regulating zimeldine. Fourteen additional cases of febrile reactions were reported to the CSM in 1984. Despite suspicions of a hypersensitivity syndrome within the UK regulatory authorities and the publication of Waelti *et al.*'s laboratory discoveries in German, these febrile reactions continued to be described as 'a rise in body temperature' in the data sheets for 1984 and 1985. The only warning given in the UK data sheet regarding the need to discontinue the drug at the first sign of an adverse reaction appeared for the first time in 1985, stating: 'These reactions subside within a short time of discontinuing *Merital* but may recur if it is taken again'.⁶⁴ By contrast, when the FDA were informed by Hoechst-Roussel of the nomifensine-induced fevers of over 40 degrees Celsius in the UK and Europe, senior scientists at the agency interpreted them as having 'serious implications'. In a letter to the company on 1 August 1984, Leber wrote:

⁶⁰Bournérias and Habibi 1979.

⁶¹Hoechst 1982–4.

⁶²CSM 1986.

⁶³Leber 1983, p. 1.

⁶⁴Hoechst 1985.

Your safety update of 7 May 1984 about a previously unappreciated risk of nomifensine, hyperpyrexia, has more serious implications than the low grade temperature elevations of which we were aware. The former may cause brain injury directly.⁶⁵

Leber and his superior, Dr Robert Temple, a physician who was Director of the FDA's Office of Drug Research and Review, agreed that nomifensine should be approved for the US market only as a 'second-line' drug, that is, one recommended for use only when other therapies fail.⁶⁶ This was reflected in the first approval letter to Hoechst-Roussel:

Reports indicating that nomifensine's use has been associated with temperature elevations to 40 degrees Celsius and over have necessitated a re-appraisal of its place in therapy. This newly discovered serious reaction, coupled with the known unusual profile of risks of nomifensine requiring careful monitoring for haemolytic anaemia and liver abnormalities, causes us not to consider nomifensine as a first choice drug in depression. . . . We consider nomifensine to be approvable only for a population of depressed patients unresponsive to, or intolerant of, other agents.⁶⁷

When the firm objected to this restriction and suggested that marketing was not viable with just second-line use, in December 1984, the FDA dropped the restriction and approved nomifensine for first-choice prescription,⁶⁸ but insisted on labelling which stated:

WARNING: hyperpyrexia (fever greater than 40 degrees Celsius) has occurred with *Merital*. All cases who were challenged [took the drug again] after recovery exhibited recurrence of fever. Therefore, *Merital* should be discontinued if hyperpyrexia develops.⁶⁹

Deaths and Regulatory Reinterpretation

As histories of Dalkon Shield in the mid-1970s in the US,⁷⁰ and non-steroidal anti-inflammatory drugs in the UK during the early 1980s show, one cannot assume that the association of deaths with post-market use of a pharmaceutical product must mean a regulatory interpretation that the product is too dangerous to remain on the market.⁷¹ Regarding nomifensine, between January and mid-June 1985 the CSM received eight further reports of haemolytic anaemia, including three fatalities. The first of these cases was published by Sokol *et al.*, who recounted the collapse of a 36-year-old woman within an hour of taking one tablet of nomifensine following acute haemolysis.⁷² Once again, the severe reaction had followed intermittent use of the drug. Blood tests showed antibody presence indicating an allergic reaction to nomifensine.

⁶⁵Leber 1984*b*, p. 1.

⁶⁶Temple 1984*b*, p. 1.

⁶⁷Temple 1984*c*, p. 1.

⁶⁸US Congress 1986, p. 73; US Congress 1987, pp. 92–4.

⁶⁹Hoechst-Roussel 1985*a*.

⁷⁰Grant 1992, pp. 57–65.

⁷¹Abraham and Davis 2007.

⁷²Sokol *et al.* 1985.

In negotiation with the CSM, Hoechst(UK) sent a letter to all UK doctors in September 1985 followed by a revised data sheet in December 1985. In this 'Dear Doctor' letter the firm warned of serious side-effects that could result from taking nomifensine, but Hoechst were also permitted by UK regulators to assert that the drug's benefits outweighed its risks, as follows:

The incidence of adverse reactions must be seen in relation to the 1.25 million prescriptions in the UK (to March 1985) and an estimated world-wide usage by 13 million patients. Experience has shown that nomifensine is an effective agent which is particularly well suited to patients with depression characterised by psychomotor retardation and lack of drive. The choice of such a preparation is limited and few enjoy the good tolerance levels—and therefore also the good compliance and safety in overdosage—of nomifensine. We are therefore convinced that the benefit from nomifensine outweighs the risks associated with its use, despite the fact that serious side-effects have occurred in isolated cases.⁷³

However, three months later, strongly encouraged by the CSM, the company found itself producing a data sheet, which scrapped the statement that 'Merital is exceptionally well-tolerated', and included a new section on hypersensitivity reactions to nomifensine, stating:

A variety of hypersensitivity (allergic) reactions have been observed. Acute intravascular haemolysis has occurred which may be accompanied by renal impairment and may be life-threatening. Fatalities have been reported. This condition may be associated with jaundice. A chronic form of haemolytic anaemia has also been reported in association with nomifensine and this may occur at any time during treatment. An influenza-like syndrome characterised by fever, usually rising rapidly, occasionally above 40 degrees C may develop. . . . Suspected nomifensine-induced inflammation of small blood vessels (immune vasculitis) has been reported in two further cases. All these reactions may occur individually or in varying combinations. *Merital* should be discontinued immediately after the onset of the first signs of a reaction and not used again under any circumstances. . . . Abnormal liver function tests, hepatitis, and jaundice have been reported, and there has been one death from acute hepatic cell necrosis.⁷⁴

At this time, there is clear recognition by the CSM and Hoechst(UK) that many serious reactions to nomifensine are part of a hypersensitivity syndrome. High fevers are no longer interpreted and represented as 'a rise in body temperature', but rather as 'an influenza-like syndrome, usually rising rapidly'. The warning to discontinue the drug after an adverse reaction no longer reassured doctors that such reactions would 'subside within a short time of discontinuing Merital but may recur if it is taken again', but rather now urged immediate discontinuance of the drug at the first sign of an adverse reaction and emphasised that re-use should not even be contemplated.

⁷³Anon. 1985.

⁷⁴Anon. 1986b.

For the first time, the suspected fatal liver reaction to nomifensine reported to the CSM in 1979 was cited in the data sheet as 'one death from acute hepatic cell necrosis'.

On 7 December 1985, the CSM published an 'update' in the *British Medical Journal* providing comparative estimates of the incidence of adverse reactions to three of the newer antidepressants, including nomifensine. This showed that, compared with the other two antidepressants, nomifensine was associated with over 28 times more cases of haemolytic anaemia, 6–26 times more cases of liver toxicity/injury and 2–3 times more ADRs overall.⁷⁵ By November 1985, the CSM had recorded five fatalities associated with nomifensine, including four deaths from haemolytic anaemia.⁷⁶ At the time of US approval, the FDA believed (wrongly) that no one had died from haemolytic anaemia as a result of taking nomifensine. As Temple makes clear, this was particularly important to the FDA's thinking:

in 6 years of marketing [in Europe], whatever the mechanism involved, people had not died of fever, and people had not died of haemolytic anaemia, although a modest number of haemolytic events and quite a large number of febrile events had been reported. The reactions were reversible.⁷⁷

According to Leber, prior to the reports of fatalities from haemolytic anaemia, the first of which the FDA did not learn about until April 1985, 'there was really no appreciation of the seriousness' of it'.⁷⁸ Similarly, Temple testified: 'What impressed us [FDA] was that people were dying of it—that seemed very important'.⁷⁹ Consequently, in November 1985, the FDA forced a major labelling change as follows:

WARNINGS: Immune mediated injury: Illnesses that may be caused by immune mediated injury have been reported in association with use of nomifensine. These include haemolytic anaemia, a syndrome of fever and alveolitis, eosinophilia, necrotising vasculitis and a lupus-like syndrome. Haemolytic anaemia: cases of severe haemolytic anaemia resulting in fatalities have been reported.⁸⁰

When four further cases of haemolytic anaemia, including one fatality, were reported to Hoechst(UK) in January 1986, with encouragement from the CSM and probably from the fact that the US label now cast the drug in such a negative light, Hoechst withdrew the drug world-wide on 22 January 1986.

Quantitative Standards of Risk Management and Market Withdrawal

We have discussed the qualitative interpretations of fatal and non-fatal case reports of suspected ADRs by Hoechst and regulators, with particular reference to discovery of the ADRs and management of a 'sound' warning system via labelling. In this section, we turn to the interpretations of the quantity of serious ADRs deemed necessary to

⁷⁵CSM 1985.

⁷⁶CSM 1986.

⁷⁷US Congress 1986, pp. 16, 41.

⁷⁸US Congress 1986, p. 32.

⁷⁹US Congress 1986, p. 41.

⁸⁰Hoescht-Roussel 1985b.

trigger withdrawal of a drug product in this regulatory period, which also speaks to the question of when ADRs are discovered to be no longer 'rare'.

When Hoechst withdrew nomifensine from the market world-wide, it did so after pressure from the CSM, but before the FDA had reached any conclusion to withdraw the drug in the US market where it had been on sale for just seven months. Hence, our focus is on the UK because the timing of withdrawal from the world market was driven by events there.⁸¹ The CSM have argued that the nomifensine case shows how well the UK drug regulatory system worked because it detected significant increases in the number of ADRs. The Committee acknowledged that there was a 'striking increase in the numbers of reports of haemolytic anaemia and other severe reactions to nomifensine during 1984' (over one year before market withdrawal), but they were unsure about the reason for the increased reporting at that time.⁸² The company described the withdrawal as a 'precautionary measure' prompted by the increasing number of reports of severe ADRs in the UK.⁸³ The medical director of Hoechst(UK) at the time has also argued that the timing of withdrawal was determined by the number of serious ADRs exceeding specific quantitative criteria of rarity.

In the first five years of marketing, from 1977 to 1982, the CSM received just 5 reports of haemolytic anaemia associated with nomifensine.⁸⁴ According to the CSM, they then received five reports of haemolytic anaemia in 1983, 16 in 1984 and 33 in 1985, including four deaths (Table 1). Stonier also wrote an account of ADR reports to Hoechst(UK).⁸⁵ Table 1 summarises the absolute number of serious cases reported to the CSM and Hoechst(UK) based on their own data. According to Dr Ronald Mann, a senior regulator in the UK DHMD when nomifensine was withdrawn, the timing of the CSM's actions was justified as follows:

The risk with nomifensine for the 5 years after its introduction in the UK in 1977 relates to the fact that 990,000 prescriptions were issued by general practitioners yet only 5 reports of haemolytic anaemia were received by the CSM during that time. To suggest that an anti-depressant should be withdrawn for such a risk would be unreasonable. The situation changed substantially in 1984 and 1985.⁸⁶

The use of prescription-based incidence estimates to explain the timing of regulatory action in relation to nomifensine typified both the regulators' and the company's perspective on events.⁸⁷ For instance, Stonier recounted:

Between 1978 and 1979 four reports of acute or chronic anaemia occurring during treatment with nomifensine were received by the manufacturer. . . . Between 1981

⁸¹ West German regulatory authorities were also acting strongly against the drug at this time.

⁸² CSM 1986.

⁸³ Anon. 1986a.

⁸⁴ Mann 1988.

⁸⁵ Interview, Stonier, Guildford, 20 June 2001.

⁸⁶ Mann 1988.

⁸⁷ Our interview (London, 30 May 2001) with senior scientists, employed at DHMD during the 1970s and 1980s, suggests that, for much of this regulatory period, the CSM relied heavily on absolute numbers of yellow card reports, which do not take account of drugs' relative market sizes.

and 1982 there were three more UK reports, to the Department of Health and not referred to the company, of haemolytic anaemia among patients who had received a total of 990,000 prescriptions for nomifensine. This suggested an incidence of only about 1 per 150 000 patients, and thus no regulatory action was considered necessary.⁸⁸

He then contrasted this period with the situation during the second half of 1985, suggesting that it was only during this latter period that a sufficient number of reports of haemolytic anaemia were obtained to justify withdrawal of the drug, by reference to a WHO quantitative standard of rarity:

Between mid-June and the end of November 1985, the UK Department of Health was aware of 25 reports of haemolysis in 96,000 prescriptions (1 : 4,000), and this was the first time that the incidence had increased to a level above 1 : 10,000 (the accepted WHO definition of rare incidence).⁸⁹

However, there are different ways of constructing these estimates. Stonier's account aggregates the years 1983–5. If instead, one disaggregates this period then, in 1984, there was one report of haemolytic anaemia per 16,000 prescriptions and in the first half of 1985 (from January to mid-June 1985), during which time the CSM received eight reports of haemolytic anaemia, there was one per 12,000 prescriptions.⁹⁰

Moreover, Stonier (and the UK regulators) used ADRs per prescription estimates to interpret their standards of 'rarity'. However, the World Health Organization (WHO) definition of 'rarity' appears to be population-based. It could equally well, and perhaps more meaningfully, be interpreted as less than 1 in 10,000 patients, rather than prescriptions.⁹¹ As was clear from the published medical literature, patients taking nomifensine were receiving repeat prescriptions (sometimes for years), so each prescription written did not represent one patient.⁹² Indeed, Hoechst(UK) estimated that the 990,000 prescriptions in the UK since 1977 related to only half a million patients.⁹³ Hence, it is reasonable to assume that, on average, there were two prescriptions per patient.⁹⁴ Thus, taking solely the CSM figures used by Stonier, the number of reports of suspected haemolytic anaemia reactions to nomifensine per patient in 1984, and in the first half of 1985, was 1 in 8,000 and 1 in 6,000, respectively—more common than the threshold for

⁸⁸Interview with, and written report by, Stonier, Guildford, 20 June 2001.

⁸⁹*Ibid.*

⁹⁰*Ibid.* Stonier used CSM figures on the assumption that all reports made to Hoechst(UK) were also made to CSM (maximum duplication). This is reasonable if the CSM figures are records of ADR reports directly from doctors plus those directly from Hoechst(UK). However, as Table 1 shows, for 1978–81, CSM recorded fewer reports of haemolytic anaemia than Hoechst(UK), so CSM figures may relate only to ADRs reported directly to CSM by doctors. Hence, CSM figures alone might under-estimate the total number of serious ADR reports because of less than maximum duplication.

⁹¹Personal communication from Professor Graham Dukes, former WHO expert medical adviser, 21 September 2001.

⁹²Edwards in Hindmarch and Stonier (eds) 1997, p. 217.

⁹³Anon. 1986a, p. 23.

⁹⁴This is confirmed by FDA, who recorded approximately 190,000 nomifensine prescriptions for only 100,000 patients (US Congress 1986, p. 20).

'rarity'.⁹⁵ A different interpretative system based on serious ADRs per patient would have been more precautionary, would have changed the timing of the discovery of non-rarity, and could have triggered an earlier withdrawal of nomifensine from the market, perhaps by as much as a year.

Conclusion

Our case study shows how complex and fragmented ADR discovery can be, involving company-friendly expert scientists, free-lancer research scientists, public servant physicians and regulatory scientists. The company-friendly expert scientists and regulatory scientists at the FDA identified isolated, rare cases of allergic reactions in blood tests, while public servant physicians reported that such cases could be clinically severe. With more advanced laboratory-testing technologies, free-lance researchers revealed that allergic reactions to nomifensine were not so rare, and analogical thinking by regulatory scientists based on experience of regulating other drugs sparked the idea that early, mild allergic reactions to nomifensine might be followed by severe, even life-threatening reactions, if a patient did not discontinue use.

The fragmented nature of ADR reporting in this period, however, delayed any synthesis of warnings from public servant physicians into an unambiguous discovery. For example, the FDA had little insight into the German-language labelling and publications about nomifensine allergenicity until 1985 when such findings were published in the USA. The FDA were also unaware of at least two fatal ADRs associated with nomifensine in Europe due to Hoechst's failure to report them in a timely manner. Nevertheless, even based on what regulators in the UK and USA knew, interpretation of what is meant by 'discovery' in this context seems crucial to understanding how the regulatory/warning systems operated in both countries in this period. While the CSM were certainly aware of the reports and published cases of suspected fatal and non-fatal adverse reactions to nomifensine before 1985, they concluded that they were not sure what was causing these adverse patient events. That uncertainty was magnified by the apparent rarity of those events.

Thus, although the doctors reporting the adverse patient events suspected that nomifensine was their cause, the CSM were not entirely convinced, even by early 1985, that those events could be generalised to conclude that nomifensine caused the reported range of serious ADRs. In this sense, one could say that, as far as the CSM was concerned, nomifensine's hypersensitivity syndrome was not discovered until mid-1985 although, in retrospect, one can say that events reported in the late 1970s were manifestations of the syndrome.

Thus, the timing and definition of an ADR is, in part, a function of the level of uncertainty acceptable to the party claiming the discovery. In this regulatory period, the CSM accepted only a relatively low level of uncertainty, so the timing of discovery was relatively late. Similarly, the product data sheet was not to include stern warnings for prescribing doctors until the CSM and the UK regulatory authorities were sure that nomifensine possessed the capacity to cause serious and life-threatening ADRs more often than 'rarely'.

⁹⁵ Our discussion leaves aside under-estimation due to doctors' extensive under-reporting—possibly as low as 10 per cent at that time, though reporting of fatal ADRs was probably higher (Lumley *et al.* 1986).

By contrast, the FDA interpreted many of the same reports of suspected ADRs as requiring sharp warnings for doctors. The FDA took the view that doctors should be warned about reports of adverse patient events as early as possible, even if the causal link to nomifensine was a suspicion, rather than certainty. Evidently, the FDA accepted a much higher threshold of uncertainty about discovery when interpreting the need to warn of suspected serious ADRs.

The yellow card system was set up in the late 1960s and early 1970s as an early warning system designed to avert another drug disaster in the UK. However, compared with the FDA, one can conclude from the nomifensine case that, by the late 1970s and early 1980s, this system had come to be interpreted, in practice, as a late warning system in which compelling evidence of harm from serious ADRs was deemed necessary to trigger substantial warnings to doctors. This explains why, for example, a fatal liver reaction, reported to the CSM in 1979, first appeared under a list of warnings to doctors in the data sheet in 1985. Regarding the management of ADRs by regulators and pharmaceutical firms in this period, our case study suggests that, not only is the timing of the discovery of serious ADRs important and complex, but so too is the discovery and interpretation of whether or not a serious ADR is 'rare' and/or 'irreversible'. For the UK regulatory authorities, a great deal of weight was given to the rarity (or not) of serious ADRs, when considering whether or not to withdraw a drug. The FDA, on the other hand, placed its emphasis on whether serious ADRs were fatal, and hence irreversible. In the nomifensine case, the interpretation of 'rarity' chosen by Hoechst(UK) and the UK regulatory authorities implied withdrawal of the drug from the market later, rather than sooner. Thus the tendency to delay regulatory action against the drug in the UK was a result of interpretative standards which implied late discovery of the need to warn of dangers and a late judgement that those dangers were not rare.

The FDA's interpretative standards implied early warnings, but an unwillingness to withdraw the drug from the market until fatal reactions were reported. Given that nomifensine was not an especially efficacious antidepressant, this implies that, in this period, fatal, or other serious irreversible, ADRs were required before the FDA would act to remove a drug from the market. Evidently, this sets a high level of injury to patients before removal of a dangerous drug from a market with equally, and more, effective alternatives. Nevertheless, this is a more precautionary approach than the one taken by the FDA towards Dalkon Shield in the mid-1970s, when the agency gave the manufacturer clearance to re-market the contraceptive even after post-market association with at least 12 deaths.⁹⁶ The UK's late warning approach and the FDA's willingness to approve for first-line use a barely efficacious drug with serious adverse reactions were both in the interests of the manufacturer because they helped to maintain the drug on markets. However, it seems unlikely that those regulatory orientations were in the interests of patients or prescribing doctors who remained at risk from, and/or uninformed about, the seriousness of the risks for months/years. Rather than a success story for post-market regulatory systems, the nomifensine case should go down in history as an example of regulatory sluggishness in an effort to maximise patient protection from

⁹⁶Grant 1992, pp. 60–1.

ADRs, reflecting a period in which the founding ideals of the early warning system as a mechanism for quickly withdrawing unsafe drugs lost their way.

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