

*Making Risks Visible:
The Science & Politics of Adverse Drug Reactions*

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Cured yesterday of my disease
I died last night of my physician
*Matthew Prior (1664-1721)*¹

A popular statin used to lower cholesterol is associated with an unusual breakdown of muscle tissue. An analgesic prescribed for arthritic patients is linked to heart attacks. The scenarios involved in the recent cases of Baycol and Vioxx should be familiar. A novel drug passes intense regulatory scrutiny. The drug's makers heavily promote it. Following widespread use, a previously unnoticed side effect is observed. Investigative journalists then trumpet the drug's fall from grace, revealing a "back story" in which the warning signs of harm were ignored or suppressed. The drug's makers defend their product and their integrity while medical reformers and social scientists condemn corporate cupidity. Members of a bewildered public wonder about drug safety while injured patients and outraged politicians call for remedial action.

Psychically gratifying as such "histoires morales" are, they are of limited analytical value. The problem of identifying and regulating "adverse" drug effects is chronic, not acute, long-standing rather than recent.² The drug in such scenarios might be Baycol (2001) or Vioxx (2004), but it might as easily be the antibiotic chloramphenicol (1952), the oral contraceptive Enovid (1962), the diabetes drug Tolbutamide (1969), or various NSAIDs (1980s).³ One might even argue that the problem of adverse drug reactions coincides with the creation of modern therapeutics: the serum sickness associated with diphtheria anti-toxin; the toxicities of Ehrlich's anti-syphilis arsenicals.⁴ Yet if manifestations of drug toxicity appear at the dawn of modern immunotherapy and chemotherapy, the technical and regulatory systems for identifying and managing such toxicities are more recent in origin.

My argument in this paper is two-fold. First, that the handling of adverse drug reactions ultimately derives from a regulatory system which at all costs preserves medical autonomy. For the US case, the problem is ultimately rooted in the statutory language of the 1938 drug law, which authorized the FDA to regulate the claims drug manufacturers could make about the safety and therapeutic uses of their products. With a few notable exceptions,⁵ the FDA regulates drug

1 Cited in RH Moser, *Diseases of medical progress. A study of iatrogenic disease*. 3rd edition, Springfield, Ill: Charles C. Thomas 1969: 267.

2 U.S. Government Accounting Office, *Drug safety. Improvement needed in FDA's postmarket decision-making and oversight process*, GAO-06-402 (2006): 2.

3 T Maeder, *Adverse reactions*. New York: William Morrow 1994; L Marks, "'Not just a statistic': The history of USA and UK policy over thrombotic disease and the oral contraceptive pill, 1960s-1970s," *Social Science & Med* 49 (1999): 1139-1155; HM Marks, *The progress of experiment. Science and therapeutic reform in the United States, 1900-1990*. New York: Cambridge University Press 1997; JA Greene, *The therapeutic transition: Pharmaceuticals and the marketing of chronic disease*. Harvard University PhD thesis 2005; J Abraham, *Science, politics and the pharmaceutical industry*. London, UCL Press, 1995.

4 Marks, 1997.

5 A Daemmrich, "A tale of two experts: Thalidomide and political engagement in the United States and West Germany," *Soc Hist Med* 15 (2002): 137-58; U.S. Government Accounting Office, *FDA drug*

labeling, not drugs. The resulting regulatory system allows for maximum physician autonomy in drug prescribing.

Second: Within such a regulatory system, “making risks visible” poses both technical and political difficulties.¹ Voluntary physician reporting of “unusual” drug reactions is inefficient in all health polities but the highly fragmented US health care system makes detection of adverse effects especially difficult.² Proving a causal link between drug and injury presents further difficulties: a slightly elevated risk for a common medical condition requires studying many more patients than demonstrating an increased risk for an unusual side effect.³ The burden of proof required will vary, according to current notions of evidence and the severity of the contemplated regulatory action. When the prospect looms of adding new warnings to a drug’s labeling, drug companies enter a war of position, seeking – up to a point – to defend the market for their product. While the adversarial character of these negotiations will vary with changes in the political and ideological climate, the result is invariably delay Abraham 1995.⁴

In the following section, I describe the structural premises of the modern drug regulatory system in the US. I follow with a discussion of two paradigmatic cases: chloramphenicol and diethylstilbestrol, drawing on the work of Thomas Maeder and Susan Bell. I then analyze the contested history of administrative and technical efforts in the 1960s, 1970s and 1980s to make drug hazards visible.

A Modern System of Drug Regulation, 1938-2007 5

On June 25, 1938, the U.S. Congress enacted legislation authorizing the U.S. Food and Drug Administration (FDA) to review the safety and composition of new drugs. The new law required drug firms to demonstrate that drugs were “safe for use under the conditions prescribed, recommended or suggested in the proposed labeling thereof [my emphasis].”⁶ This statutory

review. Postapproval risks 1976-1985. GAP/PEMD-90-15 (1990)

- 1 F Chateauraynaud; D Torny, *Les sombres précurseurs. Une sociologie pragmatique de l’alerte et du risque*. Paris: École des Hautes Études en sciences sociales 1999
- 2 DJ Finney, “Statistical aspects of monitoring for dangers in drug therapy,” *Meth. Infor. Med*, 10 (1971): 2-8; EM Tansey; Reynolds, LA, “The Committee on Safety of Drugs,” *Wellcome Witnesses to Twentieth Century Medicine* 1 (1997): 103-132; L Marks, 1999.
- 3 T Brewer; D. Colditz, “Postmarketing surveillance and adverse drug reactions,” *JAMA* 281(1999): 824-829.
- 4 See: HM Marks, “Revisiting ‘The Origins of Compulsory Drug Prescriptions,’” *Amer. J Public Health* 85 (1995): 109-115; Marks, 1997; Maeder, 1994. It is generally argued [A Daemmrich, *Pharmacopolitics. Drug regulation in the United States and Germany*. Chapel Hill: University of North Carolina Press 2004; Abraham, 2002; J. Abraham, C. Davis, “Testing times: The emergence of the practolol disaster and its challenge to drug regulation in the modern period,” *Social History of Medicine* 19 (2006), 127-149] that the US regulatory system is tougher on adverse effects and signs of drug toxicity than other regulatory systems, especially the United Kingdom and Germany. That does not obviate the point I am emphasizing: that the US approach of regulating through labeling is extraordinarily protective in allowing for clinical discretion in the use of drugs.
- 5 This section draws heavily on Marks, 1997, 1995 and HM Marks, “Playing It Safe: Federal Drug Regulation After 1938,” Presented at the Organization of American Historians, 1994 Annual Meeting, Atlanta, GA, April (1994): 14-17. The reader is referred to these publications for additional detail and documentation.
- 6 Federal Food, Drug and Cosmetic Act, chap. 5, sec. 505 (d). This clause sets the standards for new

language incorporated the twin premises of contemporary drug regulation: 1) that drug safety must be defined in risk-benefit terms. A drug that was unsafe for treating colds might be safe for treating pneumonia or influenza; 2) that drug regulation was largely informational in character, intended to instruct but never to command physicians' actions. For the most part, the FDA regulates drug labeling, not drugs or medical practice.⁷

This informational approach to regulation was a product of law, medical culture and politics. By law, most of the FDA's regulatory powers lay in their authority to regulate labeling. This informational approach was characteristic of much New Deal regulation, which sought to improve markets by improving information.⁸ Both the risk-benefit standard for judging drugs and the attempt to direct physician behavior via information were characteristic of the preceding thirty-plus years of professional self-regulation by the American Medical Association's Council on Pharmacy and Chemistry.⁹ J.J. Durrett and Theodore Klumpp, the medical officers in charge of the FDA's drug regulation efforts, were well-acquainted with this professional milieu. Both men were graduates of Harvard Medical School: Durrett was an FDA veteran; Klumpp joined the agency in 1936 from teaching at Yale Medical School, where he maintained many contacts.¹⁰

Klumpp and Durrett worked out the details of the FDA's regulatory approach via their handling of sulfapyridine, the first novel therapeutic compound to come up for review under the new law. Sulfapyridine was the newest of the sulfonamides, anti-infective drugs that had been introduced into medical practice only a few years before.¹¹ The sulfonamides were remarkable drugs, capable both of quelling life-threatening infections and of inducing life-threatening anemias, depressed white-cell counts and other serious blood disorders.¹² Sulfapyridine, the latest sulfonamide, was proposed for use in treating pneumonia, an infection against which sulfanilamide, the original sulfa drug, was useless.

Approving sulfapyridine was a matter of assessing its risks in relation to its clinical benefit. As Durrett put it:

drugs; sec 502 (j) authorized the secretary to treat as misbranded any drug that was dangerous to health when used in the dosage and conditions recommended in the labeling.

7 That the FDA from the onset of the 1938 law sought to regulate claims of therapeutic benefit is clear, despite subsequent political and legal challenges from industry which forced the FDA to get specific statutory authority to examine claims of drug efficacy. See Marks, 1997, 1995; compare P Temin, *Taking your medicine. Drug regulation in the United States*. Cambridge: Harvard University Press 1980, Daemmerich 2002.

8 Legislation creating the Securities and Exchange Commission is the most obvious example of an attempt to fix capital markets by regulating information about those markets. There are elements of a similar approach even in more interventionist economic legislation, such as the National Recovery Administration, so dependent on industry-specific „codes“ for regulating industrial competition.

9 Marks, 1997:22-41.

10 Durrett graduated HMS, 1914, Klumpp, HMS, 1928. See Jacques Cattell, ed., *American Men of Science*, 10th ed. (Tempe, AZ: Jacques Cattell Press, 1960-1962), vol. I, p. 1021; Council on Pharmacy and Chemistry, *Bulletin* 65 (December 4, 1935), 774; "Changes in the Food and Drug Administration," *JAMA* 111 (September 17, 1938), 1116; *Who's Who in America, 1982-1983*, 42nd ed. (Chicago: Marquis Publishing, 1982), vol. I, p. 1838.

11 Daniel Bovet, *Une chimie qui guerit: histoire de la decouverte des sulfamides*. Paris: Payot 1988.

12 PH Long & Bliss, EA, *The Clinical use of sulfanilamide and sulfapyridine and allied compounds*. New York: MacMillan Co 1939; HF Dowling, *Fighting Infection. Conquests of the Twentieth-Century*. Cambridge: Harvard University Press 1977.

If the drug that killed one person in 10,000 was of only minor use therapeutically it might still be judged to be unsafe, whereas the drug which killed one in a thousand persons if it had marked and undisputed therapeutic value, such as the drug under question [sulfapyridine], it would still be a safe and valuable drug.¹³

To evaluate the drug, Klumpp and Durrett reviewed data on over 2,000 clinical cases, along with pre-clinical toxicological studies submitted by the drug's manufacturer, Merck.¹⁴ They interviewed each of the clinical investigators Merck had supplied with the drug, along with an additional forty-five research physicians. Those contacted constituted a virtual who's who of prominent clinical investigators and infectious disease specialists.¹⁵

The researchers consulted agreed that the drug was likely to prove of considerable benefit in treating pneumonias. Questions remained, however, about when and how it was safest to use. Clearly, "the drug was not killing many people" but at the same time, there was "no uniformity of opinion with respect to the harm which the drug might be capable of doing from one investigator to another."¹⁶ The problem was compounded by the existence of serum therapy, a proven therapy for treating pneumonia. While difficult to use in community settings, serum therapy was standard treatment in major hospitals.¹⁷ Some researchers thought that the FDA should delay approval while more data was gathered about the relative risks and benefits of the two treatments. M.A. Blankenhorn (University of Cincinnati), David Rutstein (New York State Health Department) and O.H. Robertson (University of Chicago), fearful that physicians might use the drug casually, each wondered whether the FDA might approve sulfapyridine only for restricted distribution to "qualified clinicians" until more was known about its optimal (and safe) use.¹⁸

On March 9, 1939, the FDA approved sulfapyridine for treating pneumonia, while cautioning manufacturers to warn physicians about the need to closely monitor patients for signs of serious toxicity.¹⁹ The FDA's Klumpp acknowledged academics' concerns that sulfapyridine "will undoubtedly be abused by the unwise and ill-informed whenever it is put on the market." But

13 J. J. Durrett, Memorandum of Interview with Perrin H. Long and E. Kennerly Marshall [Johns Hopkins], December 5, 1938, 88-69A-2099, Box 1, NDA 90, vol. 1, Washington_National Records Center, Suitland, MD [Hereafter W-NRC].

14 Theodore G. Klumpp, Memorandum for Mr. Campbell, February 23, 1939, 88-69A-2099, Box 1, NDA 90, vol. 3, W-NRC.

15 Marks, 1997: 84-91.

16 J. J. Durrett, Memorandum of Interview with Dr. Joseph Rosin [Merck] and D. W. Richards [Columbia University], December 1, 1938; in Durrett's view, "there was no way to dispute the value of this drug." See J. J. Durrett, Memorandum of Interview with Perrin H. Long and E. Kennerly Marshall [Johns Hopkins], December 5, 1938. Both references 88-69A-2099, Box 1, NDA 90, vol. 1, W-NRC.

17 Marks, 1997; SH Podolsky, *Pneumonia before antibiotics. Therapeutic evolution and evaluation in twentieth-century America*. Baltimore: The Johns Hopkins University Press 2006.

18 See the detailed discussion in Marks (1997): pp. 84-92 and M. A. Blankenhorn to W. G. Campbell, February 2, 1939; O. H. Robertson to W. G. Campbell, February 7, 1939; David D. Rutstein to W. G. Campbell, February 7, 1939. See also Hugh Morgan to W. G. Campbell, February 6, 1939; Memorandum of Interview with Harris S. Johnson, February 3, 1939; W. H. Carroll to W. G. Campbell, February 9, 1939; L. H. Schmidt to W. G. Campbell, February 9, 1939. All 88-69A-2099, Box 1, NDA 90, vol. 3, W-NRC.

19 W. G. Campbell to Dr. Joseph Rosin [Merck], March 9, 1939, 88-69A-2099, Box 1, NDA 90, vol. 3, W-NRC. Five additional manufacturers had submitted applications for sulfapyridine since the original Merck filing.

physician misuse had nothing to do with the “intrinsic safety or danger of the drug.” Such misuse was a “problem of medical practice.” Disciplining “unwise” or ignorant practitioners lay outside the FDA’s authority.²⁰ As another agency official would write, the prospect of physicians using drugs “contrary to the recommendations in the labelling is unfortunately a matter which we are not permitted to consider in connection with the new drug applications.”²¹

The philosophy articulated by Durrett and Klumpp rests at the heart of U.S. drug regulation into the twenty-first century. Despite major changes in the FDA’s statutory authority, and in the burden of evidence required to market a new drug, informational labeling remains central to US drug regulation. At various times, academic physicians have suggested that the FDA restrict a drug’s distribution to selected specialist groups.²² For the most part, such suggestions have fallen on deaf ears.²³

Conflicts over drug regulatory policy consequently emerge as conflicts over particular uses of the FDA’s authority to regulate drug labeling. When the FDA has sought to regulate drug claims more aggressively, industry has challenged the FDA in the courts or in Congress. Along with its medical allies, industry has invoked physician autonomy, medical need and freedom from governmental ukases as inviolable principles.²⁴ When, in 1948, the FDA attempted to remove glandular extracts from the market, on the grounds that an inactive and hence ineffective drug could not, by definition, be safe, Abbott Laboratories’ Medical Director, George Hazel, claimed that the ruling

invokes a principle of profound importance in a free society as to whether medical therapeutics should be limited by administrative decrees, or be decided by the physician in charge of the individual case and be based upon his evaluation of the case in the light of his training and experience in clinical medicine.²⁵

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- 20 Theodore G. Klumpp, Memorandum for Mr. Campbell, February 23, 1939, 88-69A-2099, Box 1, NDA 90, vol. 3, W-NRC.
- 21 Hunter F. Kennedy to Perrin H. Long, August 27, 1942, 88-59A-2736, Box 107, F 511.07 (August), W-NRC.
- 22 Marks, 1997: 94-95.
- 23 Recently, in a handful of cases, the FDA has imposed distribution requirements for selected drugs whose unrestricted use might pose particular hazards (CB Karwoski, “Practical experience with risk management plans in the US,” Paper presented at the 42nd annual meeting of the Drug Information Association 2006; PJ Seligman, “Effects on medical practice of regulatory actions. <http://www.fda.gov/cder/Offices/OPaSS/WHORegDec1>. accessed 10/9/2006.). The FDA has required elaborate conditions on physicians who prescribe the drugs thalidomide and accutane and the patients who take them. Both are capable of causing birth defects. For accutane, see SR Shulman, “The broader message of accutane,” *Am J Public Health* 79 (1989): 1565-1568; J Cuzzell, “FDA Approves Mandatory Risk Management Program for Isotretinoin,” *Dermatology Nursing* 17 (2005): 383. The registration system was put into place only after repeated failures of efforts to warn physicians through labeling and medical alerts. For thalidomide, see S Timmermans; Leiter, V, “The redemption of thalidomide: Standardizing the risk of birth defects,” *Social Studies Science* 30 (2000): 41-71.; A Daemmerich; Krücken, G, “Risk versus risk: Decision-making dilemmas of drug regulation in the United States and Germany,” *Science as culture* 9 (2000): 505-534.
- 24 Marks, 1995.
- 25 Hazel, 1949: 37. George W. Calver, Physician to the US Congress, made virtually the same plea on behalf of the Congressional wives he treated: George W. Calver to the Pure Food and Drug Administration, July 1, 1948, 88-59A-2736, Box 582, folder 5126.12, W-NRC.

Industry issued similar legal and political challenges when the FDA attempted to implement efficacy reviews of drugs it had approved prior to the 1962 Drug Amendments.²⁶ More recent FDA officials who have taken a strong regulatory stance on drug claims have had their wrists slapped by Congress and/or the courts. David Kessler, FDA Commissioner from 1990 to 1997, attempted to curtail corporate promotion of so-called “off-label” uses—clinical indications for an existing drug that had not been reviewed by the FDA.²⁷ Congress responded with legislation allowing companies to distribute “scientific” data so long as they ultimately intended to seek regulatory approval for the off-label uses. These generous provisions of the 1997 Food and Drug Modernization Act were not sufficient for some free-market advocates, who successfully challenged the FDA’s new regulations by invoking the First Amendment rights of corporations.²⁸

Although negotiations over the precise wording of new drug labels are routine, some labeling conflicts become deeply politicized. Not surprisingly, such intensified conflicts develop around reports of the adverse effects of previously approved drugs. FDA attempts to add warnings to the labeling for the antibiotic chloramphenicol, the oral hypoglycemic tolbutamide, the oral hypoglycemics, the anti-depressant SSRIs (selective serotonin release uptake inhibitors), various NSAIDs (non-steroidal anti-inflammatory drugs) or the analgesic Darvon have generated lengthy combats over both specific labeling language and regulatory authority.²⁹ Are the effects noted “truly” a product of the drug or of unusual circumstances (individual sensitivity and/or inappropriate usage)? How much attention should be paid to particular effects in revised labeling? How directive should revised labeling be in instructing physicians how to use a particular product?³⁰ What should the agency do about manufacturers who undercut their own warning

26 The 1962 Amendments, which explicitly authorized the FDA to examine the efficacy of new drugs, also required the agency to review the evidence for the efficacy of drugs it had approved between 1938 and 1962 under the „safety“ statute. The FDA, overwhelmed by the task, initially delegated the reviews to expert physician panels convened by the National Academy of Sciences. Industry challenged these initial determinations on the grounds that the FDA had unconstitutionally delegated its regulatory authority to a non-governmental body. The other contested issue was whether the FDA was allowed to insist on evidence from „well-controlled“ clinical trials as a condition of re-approval. See “Drug Efficacy and the 1962 Drug Amendments,” *Georgetown Law Journal* 60 (1971): 185-224; J Gardner, “Supreme Court will decide outcome in FDA, industry drug-effectiveness battle,” *National Journal* (1973a): 519-526; J Gardner, “Supreme Court Rule on ineffective drugs gives FDA sweeping regulatory powers,” *National Journal* (1973b): 963.

27 DA Kessler; Pines, WL, “The Federal Regulation of Prescription Drug Advertising and Promotion,” *JAMA* 264 (1990): 2409-2415; DA Kessler, “Drug Promotion and Scientific Exchange,” *New England J Med* 325 (1991): 201-203

28 Remarkably, neither these aspects of the 1997 law or the subsequent legal challenges have received serious political analysis. For a summary, see AE Blackwell; JM Beck, “Drug manufacturers’ First Amendment right to advertise and promote their products for off-label use: avoiding a pyrrhic victory,” *Food Drug Law Journal* 58 (2003): 439-462.

29 Abraham, 1995; LK Leslie; Newman, TB; Chesney, PJ; Perrin, JM, “The Food and Drug Administration’s deliberations on antidepressant use in pediatric patients,” *Pediatrics* 116 (2005): 195-204; Maeder, 1994; Marks, 1997: 216-229; L Marks, 1999; SB Soumerai; Avorn, J; Gortmaker, S; Hawley, S, “Effect of government and commercial warnings on reducing prescription misuse: The case of propoxyphene,” *Amer J Public Health* 77 (1987): 1518-1523; RJ Smith, “Federal government faces painful decision on darvon,” *Science* 203 (1979): 857-858.

30 In the case of oral contraceptives, Lara Marks emphasizes the FDA’s decision to focus on labeling warning patients, not physicians (L Marks, 1999, HM Marks, “Trust and Mistrust in the Marketplace: Statistics and Clinical Research, 1945-1960,” *History of Science* 38 (2000a): 343-355; HM Marks,

labeling in other promotional activities?³¹ While the FDA has the legal power to order a drug removed from the market, they rarely invoke it. Protracted regulatory conflicts therefore focus on the justification for specific changes in informational labeling.

The moralized histories which accompany the recent episodes of adverse drug reactions (e.g. Vioxx, Baychol, SSRIs) are themselves a product of this regulatory framework. Such accounts focus on the motives of historical actors, judging actions in moralized terms: have FDA guardians relaxed their vigilance? have drug companies suborned the integrity of the scientific process, via misrepresentation or suppression of evidence? have physicians abdicated their professional responsibilities? These narratives reflect a long-enduring conflict within the medical profession itself, between reformers who regard commercial influences as inherently corrupting--"Nearly all abuses arise because someone profits thereby"--and practitioners committed to the conjoined principles of therapeutic innovation and professional autonomy.³² For the latter, the issues at stake in controversies over drug warnings are equally plain: "excessive" regulation endangers the flow of pharmaceutical innovation and threatens the inherent right of physicians to use drugs as they see fit. Both sides invest regulatory language with enormous powers to direct action, yet even reformers seem uncomfortable with more directive regulation which might limit physician autonomy.³³ Given the consistent evidence that many physicians ignore drug warnings and frequently use drugs without regard to their approved indications, such deference to professional autonomy seems indefensible.³⁴ But the core issue here is not individual, corporate or even

"Where Do Ethics Come From? The Role of Disciplines and Institutions," Conference on Ethical Issues and Clinical Trials, University of Alabama at Birmingham, February (2000b): 25-26). See also E Watkins, "Doctor, are you trying to kill me?" Ambivalence about the patient package insert for estrogen," *Bulletin Hist Medicine* 76 (2002): 84-104.

- 31 One or more of these issues arose in each of the examples cited above, and are dealt with in greater detail elsewhere. In the oral hypoglycemic case, the challenges to labeling changes ultimately reached the Supreme Court (Marks, 1997: 216-228). For chloramphenicol, see (Maeder, 1994); for SSRIs, see LK Leslie et al. „The Food and Drug Administration’s deliberations on antidepressant use in pediatric patients,“ *Pediatrics* 116 (2005), 195-204; for Darvon, see Soumerai (1987); for the NSAIDs see Abraham (1995).
- 32 Robert Hatcher to Torald Sollman, November 25, 1936. Torald Sollman papers, Archives, Cleveland Health Science Library, Cleveland Ohio. On the long history of anti-commercialism in therapeutic reform, see Marks (1997, 2000a). For a recent elaborate example of anti-commercialism, see M Angell, *The truth about the drug companies. How they deceive us and what to do about it.* New York: Random House 2004, although the points should be familiar to regular readers of the American press and to Congress-watchers.
- 33 As Nicholas Rasmussen has argued, even "therapeutic reformers" were involved in an extensive network of research and promotion for drug companies as early as the 1930s (N Rasmussen, "Making the first anti-depressant: amphetamine in American medicine, 1929-1950," *J Hist Med Allied Sci* 61 (2006):288-323; N Rasmussen, "The drug industry and clinical research in interwar America: three types of physician collaborator," *Bull Hist Med* 79 (2005):50-80). The proposition that the United States lags behind other countries in drug innovation was key to ideological debates over regulation from the 1970s on; however, the argument can be found much earlier.
- 34 A Melville; Mapes, R, "Anatomy of a disaster: the case of practolol," in Roy Mapes, ed. *Prescribing practice and drug usage.* London: Croom Helm, (1980): 121-144; DC Radley; Finkelstein, SN; Stafford, RS, "Off-label prescribing among office-based physicians," *Archives Internal Medicine* 166 (2006): 1021-1026; KE Lasser; Allen, PD; Woolhandler, SJ; Himmelstein, DU; Wolfe, SM; Bor, DH, "Timing of new black box warnings and withdrawals for prescription medications," *JAMA* 287 (2002): 2215-2220; JK Jones; Fife, D; Curkendall, S; Goehring, E; Guo, JJ; Shannon, MS, "Coprescribing and codispensing of cisapride and contraindicated drugs," *JAMA* 286 (2001): 1607-

regulatory morality, but the structures of drug regulation. Short of removing a drug from the market, the FDA's ability to alter physician practice is limited to written directives transmitted through labeling changes, medical alerts and other forms of information management.

Making Risks Visible

As we all know, thanks to Mary Douglas, in a world full of dangers, only some hazards are certified as "risks." The recognition and interpretation of danger involves cultural work.³⁵ That drugs, ill-used, could cause harm is an ancient proposition. That the therapeutic instruments of modern scientific medicine could cause serious harm was readily acknowledged. Not long after the introduction of diphtheria anti-toxin, clinicians and researchers recognized that some patients reacted badly to the injection of foreign protein. The effects of "serum sickness" and "anaphylaxis" were nonetheless manageable--first, by caution in the initial administration of anti-toxins and vaccines, with the physician advised to look for signs of allergic sensitivity or hyper-reactivity before administering a full dose--and second, by engineering changes in the production of biologics.³⁶ A similar logic was translated to the domain of chemotherapy. Toxic reactions to Paul Ehrlich's salvarsan and its analogues were well known. Physicians were duly cautioned and pharmacologists worked to devise less toxic arsenicals.³⁷ Reports in the 1930s that the early sulfa drugs could engender life-threatening anemias evoked a similar response: physicians using these drugs must be on the look-out for signs of anemias or hepatic damage which were, it was thought, the product of "idiosyncratic" reactions to the drugs.³⁸

The FDA's policies after 1938 on mandatory pre-market toxicological testing did not substantially alter the fundamental premises of regulation. Toxic effects must be identified but they were not necessarily a barrier to drug approval. As Susan Bell has argued, few products were as closely scrutinized as the synthetic hormone diethylstilbestrol (DES). Laboratory researchers had identified some of the drug's side effects: uterine bleeding and possible carcinogenic action. High rates of nausea and vomiting in early clinical tests generated further concern. As with

1609. For an excellent overview and study of prescribing with reference to drug labeling warnings, see AK Wagner; Chan, KA; Dashevsky I et al., FDA drug prescribing warnings: is the black box half empty or half full, *Pharmacoepidemiology and Drug Safety* 15 (2006), 369-386..

35 M Douglas; Wildavsky, A, *Risk and culture. an essay on the selection of technical and environmental dangers*. Berkeley: University of California Press 1982; T Schlich; Tröhler, U, eds. *The risks of medical innovation. Risk perception and assessment in historical context*, London: Routledge 2006.

36 Dowling, 1977: 38-39; AM Moulin, *Le dernier langage de la médecine. Histoire de l'immunologie de Pasteur au Sida*. Paris: Presses Universitaires de la France 1991: 141-145; von Pirquet; Schick, B, *Serum Sickness*. Baltimore: Williams and Wilkins [1905]. [1951 translation of *Die Serumkrankheit*]; Marks, 1997: 60-62. See Wilson (GN Wilson, *The hazards of immunization*. London: Athlone Press 1967) for a fairly thorough survey of earlier reports of reactions to vaccines and other biologics. A more detailed survey of the interplay between the clinical recognition/management of reactions and improvements in vaccine production would be very helpful, as would suggestions to discussions of this topic by historians that I've missed.

37 Marks, 1997: 54-55.

38 Marks, 1997:78-82; Long & Bliss, 1939:266-292. As von Pirquet & Schick [1905] emphasize, these are acquired sensitivities which usually manifest themselves clinically after an initial use. Long & Bliss, though less interested in the biological phenomenon, would agree. The theme of „idiosyncrasy“ in the face of any new adverse reaction would continue to recur.

sulfapyridine, the FDA held protracted discussions with researchers, going beyond the data submitted by the manufacturers. The clinical specialists they surveyed nonetheless considered that the drug's substantial benefits outweighed its risks. The FDA approved the drug for a narrow set of indications, in the hopes that this would discourage inappropriate use.³⁹ The drug was nonetheless widely used for a variety of gynecologic and obstetric complaints, including prevention of miscarriage.⁴⁰ In 1969, Arthur Herbst, an astute clinician working at a referral hospital, noted that he had seen six cases of vaginal adenocarcinoma in adolescent women within the past two years. A mother of one of these patients recalled having used DES during her pregnancy. Herbst and his colleagues followed up with a case-control study which indicated that the mothers of seven of eight cases had taken DES during pregnancy, while no mothers of the thirty-two control cases had used the drug. Vaginal adenocarcinomas were sufficiently rare in young women that the FDA felt justified in warning against using DES during pregnancy.⁴¹ Despite the warning, some physicians continued to use the drug to improve pregnancy outcomes.⁴²

In many ways, the DES story is typical. Evidence of some toxicity is subsumed within a risk-benefit calculus that leads to widespread drug use. Further evidence of substantial and serious harm (cancer in daughters of mothers who took DES during pregnancy) leads to a labeling change specifically warning physicians against the drug's prenatal use. Some physicians nonetheless continue using the drug in such circumstances. Yet DES was unusual in the relative ease with which its effects were detected and verified. As statisticians would later argue, a relatively rare clinical event due to drug use is easier to detect than a drug-related increase in the occurrence of a common condition such as coronary heart disease in middle-aged men.⁴³ It is also much easier to prove: while some DES advocates remained skeptical,⁴⁴ Herbst's careful study of eight patients was sufficient to convince the FDA.

As Thomas Maeder has shown, identifying and remedying the harm done by the antibiotic chloramphenicol (a.k.a. chlormycetin) was far more difficult. Developed and initially tested for its uses against scrub typhus, the drug was approved by the FDA on January 12, 1949.⁴⁵ Parke-

39 SE Bell, *The Synthetic compound diethylstilbestrol (DES) 1938-1941: The social construction of a medical treatment*. Ph.D. thesis, Brandeis University 1980; SE Bell, "From local to global: Resolving uncertainty about the safety of DES in menopause," *Research in the Sociology of Health Care* 11 (1994): 41-56; SE Bell, "Gendered Medical Science; Producing a Drug for Women," *Feminist Studies* 21(1995): 469-500.

40 RJ Apfel, SM Fisher, *To Do No Harm: DES and the Dilemmas of Modern Medicine*. New Haven: Yale University Press 1984.

41 AL Herbst, Scully, RE, "Adenocarcinoma of the vagina in adolescence. A report of 7 cases Including 6 clear-cell carcinomas (So-called mesonephomas)," *Cancer* 25 (1970): 745-757. AL Herbst, Ulfelder H, Pskanzer, DC, "Adenocarcinoma of the vagina. Association of maternal stilbestrol therapy with tumor appearance in young women," *New England J Med* 284 (1971): 878-881; A Langmuir, "New Environmental Factor in Congenital Disease," *New England J Med* 284 (1971): 912-913; DHEW [Department of Health Education & Welfare], "Certain estrogens for oral or parenteral use," *Federal Register* 36 (1971): 21527-21538

42 R Gillam, Bernstein, B, "Doing Harm: The DES Tragedy and Modern American Medicine," *Public Historian* 9 (1987): 57-82.

43 Brewer & Colditz, 1999.

44 DE Reid, "A controversy in fetal ecology," *Am J Obstetrics and Gynecology* 114 (1972): 419-421.

45 Maeder, 1994:73-102.

Davis, the drug's sole manufacturer, promoted the drug heavily as a broad-spectrum antibiotic.⁴⁶ Over the next two years, two physicians described fatal cases of aplastic anemia in patients taking chloramphenicol.⁴⁷ Then, in May, 1952, James Watkins, the nine-year old son of Dr. Albe Watkins died of anemia developed after receiving several courses of antibiotic treatment. His son's illness and death launched Dr. Watkins on a sixteen-year campaign to alert medical groups and the FDA to the dangers of Parke-Davis' drug.⁴⁸

The FDA did not ignore Albe Watkins' concerns. By late Spring, 1952, they were getting reports of blood dyscrasias from hematologists and other physicians around the country. In June the FDA organized a more formal survey, bringing the total number of cases of blood disorders in patients taking the drug to 410.⁴⁹ As with DES, the problem was not in detecting anemias in patients who by all rights should not have them. Rather, the problem lay, first, in interpreting the connection with chloramphenicol and, second, in deciding what to do about the problem.

The FDA's survey was by no means as informative or decisive as Arthur Herbst's case-control study of DES. Of the 410 cases identified, more than half (233) either did not involve chloramphenicol or provided no clear record of its use. In another 116 cases, chloramphenicol was not the only drug being taken. Only in 61 cases was chloramphenicol the only drug involved. Despite these and other methodological limitations, a panel of hematologists and infectious disease specialists convened at the National Research Council was fairly certain that the drug was responsible for producing some anemias.⁵⁰ The problem was in what to do: remove the drug from the market? restrict its use somehow? or modify the labeling to alert physicians to its dangers. Dr. Chester Keefer, who had managed the allocation of penicillin during World War II, summed up the sense of the meeting. Keefer

felt that the evidence was reasonably convincing that chloramphenicol caused blood dyscrasias. He emphasized that it was not known how often these occurred and that a continuing study was needed. In considering the four alternatives proposed by the [Food and Drug] Administration he favored placing a warning on the label. He felt that after such a step had been taken it was the responsibility of each practising physician to familiarize himself with the possible toxic effects of the drug. He felt that it would be impracticable to specify in the labelling that the drug should be used only for typhoid and resistant infections. He believed that each physician would use it as he saw fit. He felt that there was not enough evidence to warrant taking the drug off the market and that a combination of the first and second alternatives under consideration [e.g. to restrict use] ... was impracticable.⁵¹

46 Maeder, 1994.

47 Maeder, 1994:107-109.

48 Maeder, 1994:20-45, 348-349.

49 Maeder, 1994:109-124, 132-143.

50 Maeder, 1994:144-145. Interestingly, a proposal by two National Research Council statisticians to do a case-control study to measure the extent of the damage caused by chloramphenicol was not pursued. See Gilbert W. Beebe and Seymour Jablon, Use of Medical Records Systems of the Army and Veterans Administration in the Study of the Risk of the Production of Aplastic Anemia by the Therapeutic Use of chloramphenicol. 30 July 1952 [MED: Ad Hoc Conference on Chloramphenicol, 1952, National Academy of Sciences Archives, Washington DC. Hereafter NAS archives].

51 Ad Hoc Conference on Chloramphenicol, 6 August 1952. Med: Ad Hoc Conference on Chloramphenicol, 1952, NAS archives.

Several infectious disease specialists on the NRC panel were prominently concerned with the misuse and overuse of antibiotics. Yet none thought the dangers of chloramphenicol justified restricting physicians' ability to use the drug "as they see fit."⁵² Following their panel's advice, the FDA instructed Parke-Davis to issue new labeling warning physicians about the possibility of blood dyscrasias and the need to monitor patients who were taking the drug repeatedly or over long courses of treatment. The warnings were drowned out by the Parke-Davis president's instructions to his sales force:

Chlormycetin has been officially cleared by the FDA and the National Research Council with no restrictions on the number or the range of diseases for which Chlormycetin may be administered.⁵³

Such corporate "spin" enabled the drug to recapture (and increase) its market share by the late 1950s, at which time new adverse effects emerged--in premature neonates given the drug prophylactically. These reports launched another round of efforts to police the drug's use via labeling changes. The NRC's experts rallied in support of the beleaguered drug, if anything more vociferously than before. They emphatically rejected proposals that the drug be restricted to specialist or in-hospital use, a strategy which

would, in fact, be an attempt to regulate the professional activities of physicians. That enormous quantities of chloramphenicol are currently being prescribed is evidence in itself that the drug is being employed unwisely if not unnecessarily in many cases. How can physicians be taught or persuaded to employ this and other drugs properly. [...] The problem is an important one for which some reasonable solution should be sought. However, I doubt that the FDA can or should assume the function of policing physicians.⁵⁴

FDA officials apparently agreed. In a press release announcing the labeling changes, they noted:

52 Only Harvard hematologist William Dameshak seems to have stood strongly for restrictions on the drug's use. Harry Dowling and Maxwell Finland, both critics of the way antibiotics were promoted and used, thought the drug's many benefits outweighed its risks. See Ad Hoc Conference on Chloramphenicol, 1952, NAS archives; Maxwell Finland to Robert Stormont [AMA Council on Pharmacy and Chemistry], August 27, 1953, Box 12, Maxwell Finland papers, Francis Countway Library of Medicine, Harvard Medical School, Boston, MA. Scott Podolsky has emphasized that Finland had other more pressing concerns: the promotion and use of "combination antibiotics" and the related rise of antibiotic resistance (Personal communication, 27 July 2006). For background, see Whorton, J, "Antibiotic abandon': The resurgence of therapeutic rationalism," in John Parascandola, ed. *The History of Antibiotics: A symposium*. Madison: American Institute for the History of Pharmacy (1980): 125-136 and Marks (2000a).

53 Maeder, 1994:160, 208-218.

54 Remarks of C. Lockard Conley (Johns Hopkins) in Replies to Questionnaire on Chlormycetin, 1 December 1960, MED: Requests for Advice Chloramphenicol, 1960-1962, NAS archives. Max Finland again thought that far too much attention was being paid to chloramphenicol--a result, he suggested, of a "very personal and emotional interest of one physician"--presumably a reference to Albe Watkins. See handwritten reply [n.d.] of Maxwell Finland to an inquiry from R. Keith Canaan [NRC], 1 December 1960. Box 4, Finland papers, HMS. I am indebted to Scott Podolsky for calling Finland's remarks to my attention. For similar concerns regarding FDA impingement on the doctor-patient relation, see Food and Drug Administration, Subcommittee on Chloramphenicol of the Medical Advisory Board, Minutes. February 26, 1968, Minutes. February 20, 1969, Box 34, John Adriani papers, National Library of Medicine, hereafter NLM.

Beyond this, there is need for the continuing education of the physician This, of course, is a responsibility of the leaders of medicine and not of the Food and Drug Administration.⁵⁵

Chloramphenicol remained in active use through the 1970s, surviving multiple labeling changes.⁵⁶ The problem of getting physicians to “employ” chloramphenicol or any drug “properly” would continue to vex NRC leaders.⁵⁷

Chloramphenicol’s continued survival was ensured by a confluence of factors: infectious disease specialists, eager to retain a drug they saw as valuable; an academic community reluctant to constrain practitioners’ clinical autonomy; regulators whose principal regulatory tool was drug labeling; and a company willing to take advantage of these circumstances to heavily promote their product. The difficulty of getting reliable, comprehensive estimates of the anemias caused by chloramphenicol was, at best, a minor theme.⁵⁸ It was, however, soon to assume greater importance.

The identification of an adverse drug effect is a complex process. First, an observant physician must notice (and report) an unusual and otherwise inexplicable event: e.g., Arthur Herbst’s run of vaginal adenocarcinomas in adolescent women. Next, the strength of the association between drug use and the event must be measured. If the event is sufficiently unusual, then a very small study (like Herbst’s case-control study) may be enough to securely establish that drug x is producing so many excess cases of condition z. The defects in red blood cell production caused by chloramphenicol are not common, but there are many possible causes of blood dyscrasias. The hematologists consulted in individual chloramphenicol-related cases may have been convinced about those cases, but without an estimate of increases in the rate of chloramphenicol-caused blood disorders, it was difficult to say how much of a public health problem the drug represented. And in the absence of either a disease registry or an adverse-effects surveillance system, such estimates were hard to come by (as the FDA found out).

Methodological excursus. There are multiple strategies for analyzing a putative adverse drug effect. A case-control study like Herbst’s will provide an estimate of relative risk, the increase in the proportion of adverse events associated with a drug exposure. Case-control studies provide

55 FDA Press Release, January 26, 1961. MED: Requests for Advice, Chloramphenicol 1960-1962. NAS archives.

56 Maeder, 1994:184-189, 197-206, 218-224, 292-313, 358-362. Of the specialists consulted by the NRC, only infectious disease specialist Harry Dowling and hematologist Maxwell Wintrobe spoke up for restricting the drug to hospital use. Despite his concerns over the drug’s dangers and misuse, William Dameshak joined the majority in rejecting any moves by the FDA in the direction of restricting the drug’s distribution to hospitals--hospital physicians were equally capable of using the drug inappropriately and/or without proper precautions. Replies to questionnaire on Chlormycetin, 1 December 1960, MED: Requests for Advice Chloramphenicol, 1960-1962, NAS archives. For Dameshek’s concern over the harm done by the drug, see Maeder, 1994: 343. For subsequent discussions of changes in chloramphenicol labeling, see also FDA, Ad Hoc Committee on Chloramphenicol, Minutes, February 26, 1968, February 20, 1969. Box 34, John Adriani papers, NLM.

57 See R. Keith Cannan [NRC] to William S. Middleton, 2 March 1964, 24 March 1964, Drug Efficacy Study: Middleton: Drug Research Board: Correspondence, NAS archives.

58 On the lack of estimates, see the remarks of Gilbert Beebe, Chester Keefer and Harry Dowling in Ad Hoc Conference on Chloramphenicol. 6 August 1952, NAS archives. For proposals to set up registries for chloramphenicol related anemias, see Beebe, *ibid.*; and William Dameshek to John Dingle, September 5, 1952 [MED: Ad Hoc Conference on Chloramphenicol, NAS archives].

prima facie evidence of causation, but without additional information will not tell you much about the extent of the problem. The more common the suspected complication, the larger such a study must be.⁵⁹ Disease registries provide a way of tracking the absolute number of adverse-events, but cannot ensure that these are all drug-related. Herbst and his colleagues set up such a registry for DES-related adenocarcinoma; a similar registry for all suspected cases of drug-related blood dyscrasias was established by the American Medical Association's (AMA) Council on Drugs in 1955.⁶⁰ Finally, one may have an ongoing surveillance system, capable of tracking both drug use and adverse events. In the aftermath of problems with chloramphenicol, thalidomide, and the oral contraceptives, researchers at various institutions began discussing and initiating pilot surveillance programs. Early surveillance programs were established at the Peter Bent Brigham Hospital (1963), the Johns Hopkins Hospital (1964), Philadelphia (1964-66), in Boston (1966), and San Francisco. Other institutions and networks followed their example in the late 1960s and early 1970s (Table 1). The history and operation of these programs remains fragmentary, much like the programs themselves.⁶¹ Some, like the Kaiser-Permanente project, were part of a larger institutional program to computerize medical records.

Others were the initiative of individual researchers interested in the epidemiology of adverse drug reactions: Leighton Cluff at Hopkins and Florida; Hershel Jick in Boston; Sam Shapiro at Boston University. Yet others (e.g. Philadelphia) may have been a response to the anxieties of academic physicians about the growing publicity afforded adverse drug effects.⁶² Most programs were organizationally unstable, dependent on local entrepreneurs and a mixture of local and outside funding. When entrepreneurs moved on or funding dried up, the programs disappeared.⁶³

59 H Jick, "The discovery of drug-induced illness," *New England J Med.* 296 (1977): 481-485.

60 AJ Erslev; Wintrobe, MM, "Detection and Prevention of Drug-Induced Blood Dyscrasias," *JAMA* 181 (1962): 114-119. For methodological criticism of the AMA registry, see Drug Research Board, National Research Council, Report of the international conference on adverse reactions reporting systems. Washington: National Academy of Sciences (1970): 11.

61 This section draws on Anello, C, Identification of adverse drug reactions to marketed drugs in the United States and the United Kingdom. Washington: Biometrics and Epidemiology, Bureau of Drugs, FDA, 1977; A Ruskin; Anello, C, "The United States," in *Monitoring for Drug Safety*, ed. W.H.W. Inman. MTP Press Ltd 1980: 115-128; RB Stewart; Cluff, LE; Philp, JR (1977), *Drug monitoring: A requirement for responsible Drug Use*. Baltimore: Williams & Wilkins; "Meeting the problem," (1966). For the UK, see Finney, DJ, "The design and logic of a monitor of drug use," *Journal of Chronic Disease* 18 (1965), 77-98, Inman, WHW, "The United Kingdom," in Inman, *Monitoring for Drug Safety*, pp. 9-4; Tansey & Reynolds (1997).

62 TM Durant, "Drug Problems and the Philadelphia Plan," *JAMA* 192 (1965): 131-134.

63 The longest-lived of these programs, the Boston Collaborative Drug Surveillance Program (BCDSP) began in 1966 and continues today. The core of the original program was a cooperative effort among Boston-area hospitals to collect data on in-patient adverse drug reactions. The collaborative was especially productive in testing hypotheses about putative drug-linked events via case-control studies. This large data base enabled investigators to routinely explore possible drug effects which smaller institutions could not evaluate (Lawson, 1980). Like several other surveillance programs, the Boston Collaborative Drug Surveillance Program was partially funded by the FDA, which was looking for a way to supplement its principal source of data on adverse reactions: spontaneous reporting from physicians (Anello, 1977). It does not appear, however, that surveillance programs were especially useful in replacing spontaneous reporting as a way of finding new suspected drug effects (GR Venning, "Identification of adverse reactions to new drugs," *BMJ* 286 (1983): 199-202, 289-292, 458-460, 365-368; Rossi, AC; Knapp DE, Anello C, "Discovery of adverse drug reactions. A comparison of selected Phase IV studies with spontaneous reporting methods," *JAMA* 249 (1983), 2226-2228;

Registries, surveillance programs and case-reporting are usually discussed in terms of their methodological properties--how well each performs in identifying and then verifying adverse drug events in various epidemiological circumstances.⁶⁴ Such discussions take place in the open, at professional meetings and in the scientific literature. Yet lurking behind such public discussions were a set of deep, privately held, concerns about how adverse drug effects, if found, should be managed. These behind-the-scenes discussions were conducted in a highly-charged political atmosphere, engendered by the FDA's implementation of the 1962 Drug Amendments. In addition to operationally defining the standards for judging a new drug "effective," this legislation charged the FDA with determining the therapeutic value of the hundreds of drugs evaluated for safety between 1938 and 1962, and with setting the rules for ethical human experimentation.⁶⁵ The FDA's incursions into the previously unregulated terrain of medical research and therapeutic practice were often on the minds of those trying to address the problem of adverse drug reactions.

Medical Ambivalence & Disease Registries: The Hidden Politics of Adverse Drug Reactions, 1960-1975

The reluctance of medical specialists to advocate aggressive intervention in the chloramphenicol case reflects a larger ambivalence within academic medicine towards the federal government which deepened during the 1960s.⁶⁶ Discussions at both the National Research Council and the AMA Council on Drugs regarding adverse drug reporting reflect this ambivalence. With passage of the 1962 Drug Amendments, FDA officials had issued regulations requiring investigators to obtain written informed consent from patient subjects in experimental studies. Drug industry officials proved adept in mobilizing the discontent these regulations provoked in the academic community.⁶⁷ The academic members of the AMA's Council on Drugs saw a clear link between the informed consent issue, and that of managing adverse drug reactions:

Wysowski, DK; Swartz, L, „Adverse drug surveillance and drug withdrawals in the United States, 1969-2002,“ Archives of Internal Medicine 165: 1363-1369.

64 Anello (1977); Brewer & Colditz, 1999; B Strom ed., *Pharmacoepidemiology*. New York: John Wiley & Sons 1989; B Strom ed., *Pharmacoepidemiology*. 2nd edition. New York: John Wiley & Sons 1994; B Strom ed., *Pharmacoepidemiology*. 3rd edition. [electronic book] New York: John Wiley & Sons 2003. See Finney "(1965, 1971). The British biostatistician, David Finney, was the first to take these issues up in a serious way.

65 Marks, 1997; 2000b.

66 See HM Marks, "Leviathan and the Clinic: Academic Physicians and Medical Research Policy, 1945-1955," Paper presented at History of Science Society Meetings, Dec. (1992): 27-30, for a discussion of the longer-range ambivalence of academic researchers towards the federal government.

67 For histories of the informed consent regulations, see WJ Curran, "Governmental Regulation of the Use of Human Subjects in Medical Research: The Approach of Two Federal Agencies," in Paul A. Freund, *Experimentation with Human Subjects*. New York: George Braziller, 1970, pp. 413-414 and Marks (2000b). Examples of the industry organizing campaign against the informed consent regulations include: Walter A. Munns, Smith Kline and French, May 24, 1961 [memorandum on efficacy requirements]; Louis S. Goodman to Maxwell Finland, June 7, 1961; both in A. McGehee Harvey Papers, Chesney archives. Lee van Antwer [Assistant Medical Director, G.D. Searle] to Harry Gold, September 20, 1962; Lawrence B. Hobson, Squibb Institute for Medical Research] to Harry Gold, August 31, 1962; Harold L. Upjohn [??] to Harry Gold, September 19, 1962; all in "FDA

All agreed that the FDA is exceeding the letter of the [1962] law and two examples (‘informed consent now means ‘written consent’ and the proposed restriction of drugs for use according to the specialty of the physician) were offered as proof of this.⁶⁸

These political tensions hampered efforts to create a uniform registry for reporting adverse drug reactions. At issue was the question of who would control the data and how it would be used. At various times, a registry under joint FDA-AMA auspices, an independent AMA managed registry and an adverse drug surveillance system under the auspices of the Joint Commission on the Accreditation of Hospitals (JCAH) were discussed. The fortunes of any one proposal rose and fell with the general relations between organized medicine and the FDA. Academic physicians were crucial intermediaries in this process. Increasingly as the decade wore on, tensions between the staff of the AMA Council on Drugs and academic physicians like John Adriani colored discussions of registry proposals. Adriani, Chair of the Council of Drugs, like other academic researchers, was suspicious of the increasing ties between the AMA and the drug industry. In working on the creation of an adverse drug event monitoring system, Adriani found himself repeatedly undermined by AMA staff, especially Dr. Jean Weston who worked “for” the Council.⁶⁹ Over time, Adriani seems to have put increasing hopes in an adverse events monitoring system to be promoted by the JCAH.⁷⁰

Weston spoke for the rank and file physicians in the AMA’s governing House of Delegates, who objected to FDA attempts to remove from the market various drugs approved prior to 1962. The FDA was required by law to remove such drugs if no substantial evidence of therapeutic efficacy could be found.⁷¹ Medical societies around the country reprinted copies of an article by

Guidelines 1962,” Harry Gold Papers, New York Hospital; Henry K. Beecher to George P. Larrick, December 22, 1964, FDA Docket, Section 130.37, Consent for Use of Investigational New Drugs on Humans. FDA records. I have seen additional examples of this mobilization in the papers of numerous clinical investigators and pharmacologists of the era.

68 AMA Council on Drugs, Minutes. Executive Committee, August 31, 1967. See also Council on Drugs, October 6-8, 1966. Report of Bethesda Conference on Relationship of the Clinical Investigator to the Patient, Pharmaceutical Industry and Federal Agencies. Both in Box 27, John Adriani papers, MS 453, National Library of Medicine. A third friction point was the implementation of the Drug Efficacy Study. The FDA had commissioned the National Academy of Sciences/National Research Council to review the efficacy of all the drugs the FDA had screened for safety between 1938 and 1962. The recommendations of NAS panel were strongly contested both by industry and by the medical rank and file (RJ Bazell, “Drug Efficacy Study: FDA Yields on Fixed Combinations,” *Science* 172 (1971): 1013-1015).

69 On uses and control of adverse reaction data, see: Drug Research Board, Minutes. Sixth Meeting. 11 October 1965, MED: Drug Research Board Minutes, NAS archives; “Meeting the problem,” 1966); various correspondence, Box 30, John Adriani papers, NLM. On tensions between academic physicians and AMA, see R. Keith Canaan to William S Middleton, 30 September 1963, Drug Efficacy Study: Drug Research Board, William Middleton Correspondence, NAS archives; AMA Council on Drugs, Minutes, September 17-19, 1970; John Adriani to John Curry, March 25, 1969, Box 32; Maxwell Wintrobe to Harry Shirkey, February 9, 1967; Adriani to Wintrobe, May 6, 1966; Wintrobe to Adriani, June 7, 1966, Box 34 [all in Adriani papers, NLM]. By comparison with the analysis offered here, Daemmrich (2004: 120-125) offers a relatively bloodless account of these developments.

70 John Adriani to Herbert L. Ley, Jr [FDA] February 24, 1969 provides a good history of the various registry proposals. Box 26, Adriani papers, NLM.

71 Marks, 1997: 218. The FDA delegated this massive assessment task to the National Academy of Sciences/National Research Council, which enlisted specialty panels of academic physicians

Pharmaceutical Manufacturers Association president C. Joseph Stetler, attacking the FDA for interfering in the practice of medicine.⁷² For Weston, regulatory attempts to address adverse drug reactions reflected a similar sort of unnecessary inference in professional territory.⁷³ In an article published after she left the AMA, Weston reviewed the experiences of the various drug registries and surveillance programs established earlier in the decade. According to Weston, only a handful of studies at academic institutions had revealed high rates of adverse drug events, and there was reason to doubt that these were representative of medical practice at large. Perhaps, he suggested, the problem of adverse drug reactions was not, after all, so great.⁷⁴

The AMA did announce a registry for spontaneous drug reporting in 1966, and somewhat less ceremoniously closed it down in 1970. The principal vehicle for spontaneous drug reporting thereafter was provided by the FDA.⁷⁵ The FDA surveillance system, greatly expanded and modernized, remains central to the detection of adverse drug effects.⁷⁶ The FDA's efforts are supplemented by a number of registries run by specialty societies, and by an ever-increasing number of hospital and health care network based systems to detect and evaluate suspected adverse effects.⁷⁷

A detailed analysis of adverse effects surveillance over the past twenty years would require another paper. However, certain broad outlines seem clear. Despite substantial increases in both administrative and computing capacity for adverse drug surveillance, there remains a debate between advocates of such monitoring systems and proponents of more traditional methods for identifying the risks and benefits of drug therapy. Such debates extend to within the FDA

to evaluate the efficacy data on each drug. The reports issued by the Drug Efficacy Study (DES) provided the basis for the FDA's actions in removing these drugs. Now that the DES papers at the National Academy of Sciences are open, there is little excuse for historians continuing to avoid a full analysis of this program, central to understanding the shifting relations between academic medicine, the drug industry, and the medical profession in the 1960s and 1970s.

72 CJ Stetler, "Relative efficacy. When the government decides what drug should be prescribed, is the patient better served?" *Journal of the Mississippi State Medical Association* 13 (1972): 427-432. The article was also printed in the *Ohio State Medical Journal* 68 (1972) and *The Journal of the Medical Association of Alabama* 42 (1972), among others. Not all versions identified Stetler as the source/author of the piece, which attacks the FDA for suggesting that it might require statements of relative efficacy in drug labeling.

73 See Jean K. Weston to James L. Goddard [FDA], March 31, 1966, Box 27, John Adriani papers, NLM.

74 JK Weston, "The Present Status of Adverse Drug Reaction Reporting," *JAMA* 203 (1968): 89-91. Dr. Weston, previously on the staff of the AMA Council on Drugs had moved by 1968 to the National Pharmaceutical Council, a drug industry trade group.

75 Daemmerich, 2004. The starting date is a little ambiguous; some publications from 1966 imply that the registry was already up and running (de Nosaquo, "The American Medical Association Registry on Adverse Reactions," *Annals Internal Med* 64 (1966): 1325-1327).

76 AC Rossi; Knapp, DE; Anello C (1983); LL Leape, "Reporting of adverse events," *New England Journal of Medicine* 347 (2002): 1633-1638; Wysowski DK; Swartz, L (2005). According to Louis Lasagna (L Lasagna, "Discovering adverse drug reactions," *JAMA* 249 (1983): 2224-2225), the FDA began experimenting with formal post-marketing surveillance in 1970, with levodopa. So called Phase IV trials were officially recognized in the 1997 FDA Modernization Act, though the practice by then was well established.

77 The major novelty here are the various European surveillance systems developed in the 1980s and 1990s, which potentially provide another source of information to US regulators. See Strom (1994 and 2003) for a survey.

itself, between members of the Center for Drug Evaluation and Research, responsible for pre-market testing of drugs, and staff in the Office of Drug Safety, responsible for post-approval surveillance.⁷⁸ Similarly, despite some innovations in statistical methods, the basic dilemma remains unchanged: many effects appear only when a drug is used on large numbers of patients, and proving the connection between a drug and an effect is not a straightforward matter. No wonder, then, that there is delay in recognizing and acting on adverse drug effects.⁷⁹

Important as improvements in administrative and analytic capacity for monitoring adverse drug effects may be, they do not in themselves get to the heart of the problem. In writing about the history of adverse drug effects, I have emphasized the centrality accorded to clinical autonomy. The way physicians use drugs is regulated by language--drug labeling.⁸⁰ Since the 1940s (at least), whenever US physicians see the FDA as intruding upon the privilege of clinical autonomy, they have gone on the attack.⁸¹ (Industry has not been slow in exploiting this disposition, to their own advantage). I do not say this to attack the principle of clinical autonomy, but to open a discussion about its justification. As often as it is invoked, rarely is clinical autonomy deliberated.

The central argument for clinical autonomy in recent decades is that such autonomy is crucial in an era of rapid technological innovation.⁸² Only if physicians are allowed to experiment with new, unproven uses of drugs will we arrive at the knowledge of what those drugs can do and how best to use them. How else would we have learned that calcium-channels blockers, approved for treating angina, can be used to treat hypertension?⁸³ Would one really want to shackle those physicians who figured out the precise mix of drugs and drug scheduled to contain drug resistance in immuno-compromised patients? Or, to take a non-drug example, to constrain the clever clogs who made his rabies-infected patient hypothermic so as to inhibit the slow-

78 M Ferris, "Does the FDA adequately protect the public?," *CQ Researcher* 15 (2005): 1-31; US GAO, 2006; Leappe, 2002.

79 Strom, 1994, 2003; RS Stern; Bigby, M, "An expanded profile of cutaneous reactions to nonsteroidal anti-inflammatory drugs," *JAMA* 252 (1984): 1433-1437; Lasser et al. 2002; LA Ladewski; Belnap, SM; Nebeker, JR; Sartor, O; Luons, EA; Kuzel, TC; Tallman, MS; Raisch, DW; Auerbach, AR; Shumock, GT; Kwaan, HC; Bennett, CL, "Dissemination of information on potentially fatal adverse drug reactions for cancer drugs from 2000 to 2002: First results from the research on adverse drug events and reports project," *Journal of clinical oncology* 21 (2003): 3859-2866. See SJW Evans, "Pharmacovigilance: a science or fielding emergencies," *Statistics in Medicine* 19 (2000): 3199-3209; DW Kaufman; Shapiro, S, "Epidemiological assessment of drug-induced disease," *Lancet* 356 (2000): 1339-1343 for discussions of recent methodological advances.

80 I here disagree fundamentally with Peter Temin, who sees the history of drug regulation as moving in the direction of an increasing "command and control" logic (Temin, 1980).

81 Marks, 1995, 1997.

82 In earlier decades, the central argument lay more around the notion of clinical judgment--the physician's capacity to know what is best in treating your individual case. The innovation argument, however, was never absent. I would suggest, speculatively, that they have reversed their relative ideological importance in recent decades. See, for example, the debates in the 1970s about the off-label use of the beta-blocker practolol [Practolol correspondence in *JAMA* (1974) 227: 201-202; *Annals Internal Med* (1973) 79: 752-754; HF Morelli, "Propranolol," *Annals Internal Med* 78 (1973): 913-917; GR Mundy; Fleckenstein, L; Mazzullo, JM; Sundaresan, PR; Weintraub, M; Lasagna, L, "Current medical practice and the Food and Drug Administration. Some evidence for the existing gap," *JAMA* 229 (1974): 1744-1748].

83 AC Gelijns; Rosenberg, N; Moskowitz, AJ, "Capturing the unexpected benefits of medical research," *New England Journal of Medicine* 339 (1998): 693-698.

growing rabies virus from killing her? Against the benefits offered by a culture of innovation are the as-yet-unmeasured costs of clinical autonomy. A great deal depends on whether we think that these costs are down to the handful of physicians who use new drugs promiscuously and seemingly with very little constraint, or rather to far greater numbers of practitioners who use drugs inappropriately and injudiciously, with little appreciation for the sorts of evidence needed to demonstrate the therapeutic value of a new drug. Either argument could be supported from existing socio-medical studies of prescribing, but absent more systematic study of this issue, it would be hard to conclusively prove either.⁸⁴ Yet our continued tolerance for clinical autonomy, for a less directive approach to regulating therapeutic practice, and for the seemingly inevitable delays which accompany the adjudication of newly discovered adverse drug reactions depends on what we think the result of this calculus would be. Has a labeling-oriented approach to drug regulation provided us with a steady stream of innovative and beneficial therapeutic practice, or has it put us at risk for unnecessary exposure to the harmful effects of ill-used drugs? An extended discussion of that question would seem more productive than another round of exchanges about the motives and conduct of drug companies and regulatory authorities.

Table 1

1952-55:	AMA Council on Drugs establishes Registry on Blood Dyscrasias
1963:	Mandatory adverse drug reaction reporting established at Peter Bent Brigham Hospital, Boston
1964:	Leighton Cluff establishes surveillance system at Johns Hopkins Hospital for analysis of adverse drug events
1964-66:	Greater Philadelphia Adverse Reaction Reporting Registry involving five Philadelphia teaching hospitals.
1966:	Hershel Jick establishes drug surveillance program at Lemuel Shattuck Hospital, Boston. Expanded to 22 hospitals later in decade.
1969:	Kaiser-Permanente establishes drug surveillance/adverse effects monitoring for outpatients
1972:	Yale-New Haven Medical Center Outpatient Program
197?:	University of Florida (Leighton Cluff)

84 See AP Jonville-Bera; Bera, F; Autret-Leca, "Are incorrectly used drugs more frequently involved in adverse drug reactions? A prospective study," *European journal of clinical pharmacology* 61 (2005): 231-236; Melville & Mapes (1980); WH Inman; Pearce, G, "Prescriber profile and post-marketing surveillance," *Lancet* 342 (1993): 658-661; D Armstrong, "Clinical autonomy, individual and collective: the problem of changing doctors' behaviour," *Social Science & Medicine* 55 (2002), 1771-1777.